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Note

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Alkyne [2 + 2 + 2]-Cyclotrimerization Approach for Synthesis of 6,7-Cyclopropylallocolchicinoids

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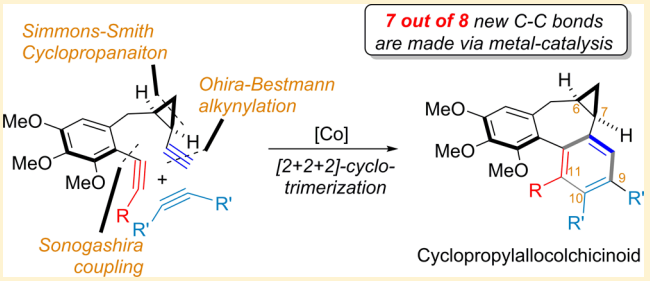
Supporting Information

ABSTRACT: Employing a cobalt-catalyzed [2 + 2 + 2] alkyne cyclotrimerization as the final step, the short and efficient synthesis of cyclopropylallocolchicinoid and its analogues having functional group variations at C9 and/or C10 and C11 of ring C has been accomplished.



Colchicine is one of the oldest known and most studied natural tubulin binding agents that has been used as a drug against acute gout and familial Mediterranean fever.[1,2] It was also identified as a potent antitumor agent (effective in chronic myelocytic leukemia). However, its severe toxicity has limited its therapeutic applications.[3] In this regard, the allocolchicine and related compounds, such as *N*-acetylcolchicinol methyl ether of *N*-acetylcolchicinol (NSC 51046), and dihydrogen phosphate (ZD 6126) having modifications mainly on the ring C have been developed as potential antimitotic agents (Figure 1).[4] These colchicine analogues trivially denoted as allocolchicinoids because of their promising tubulin-binding ability and less toxicity has led to an interest in the development of synthetic protocols to provide the corresponding derivatives by altering the substituents, incorporation of hetero atoms and also annulation of other heterocyclic rings for biological evaluation.[5−9] The structure activity studies indicated that modifications on the ring A are not encouraging while the ring C modifications provided better activity.[5] The role of ring B has been found to be very crucial as it functions as the handle for ring A and ring C.[6] This suppresses the free rotation of biphenyls and leads to equilibrium mixtures of axially chiral diastereomers. Therefore, synthesizing B- and C-ring modified allocolchicinoids is of great interest.[6−8] The cyclopropylallocolchicinoid **1** introduced by Boyer's group is an important development in this regard as its tubulin-binding affinity is as good as that of colchicine despite the fact that the carboxylate group is positioned at C10 and that there is no acetamide substituent (Figure 1).[9] Thus, this disclosure revealed new possibilities in allocolchicinoid design. However, an examination of the synthesis of **1** revealed that the adopted route evolved after several initial setbacks and warranted a practical and flexible approach for the synthesis of **1** and its derivatives. In this note, we document a simple approach for the synthesis of **1** having the flexibility to modulate the functional groups on the ring C at the final stage.

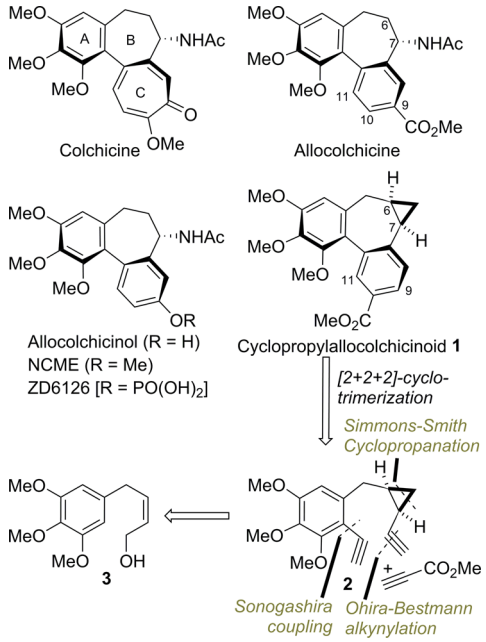


Figure 1. Structures of colchicine and selected allocolchicinoids and the intended approach for the cyclopropyl allocolchicinoid **1**.

As a part of our ongoing project on the synthesis of focused small molecule libraries by employing the [2 + 2 + 2]-cyclotrimerization reaction,[10] the cyclopropylallocolchicinoid **1** has been identified as an interesting synthetic target considering its potential tubulin binding affinity and the need for a unified approach that addresses the analogue synthesis as well. As shown in Figure 1, we realized that both the B- and C-rings can be disconnected by invoking the cyclotrimerization and

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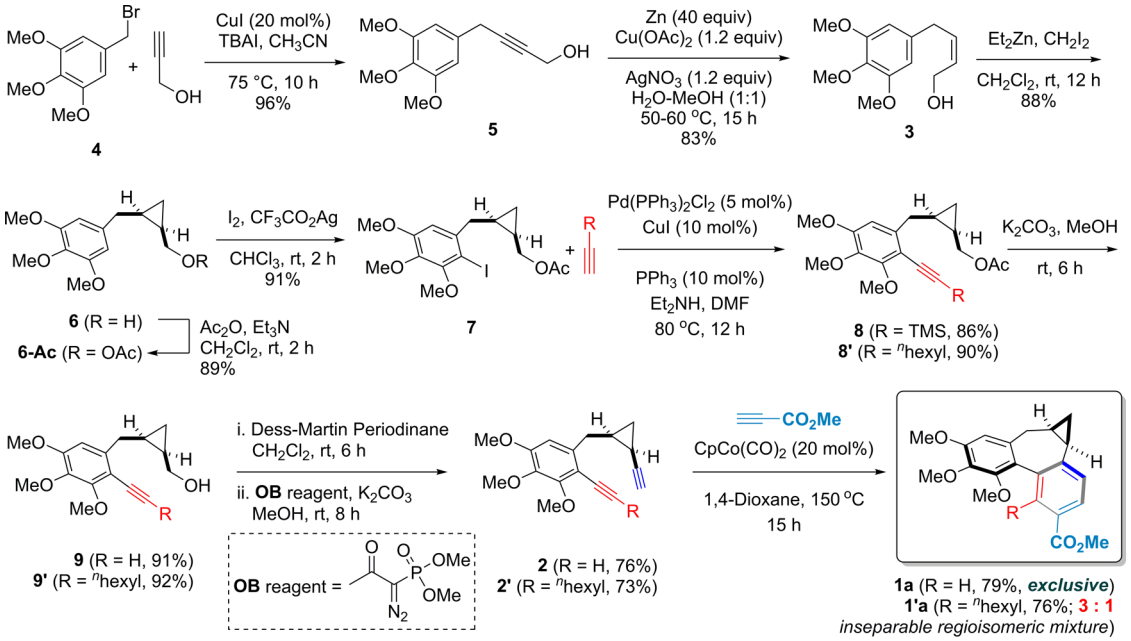
Scheme 1. Total Synthesis of Cyclopropylallocolchinoid 1 and Its 11-Hexyl Derivative 1′



identified the diyne **2** as the key building block. The feasibility of constructing rings B and C using [2 + 2 + 2]-cyclotrimerization was previously established in the synthesis of modified 6-oxa-allocolchicinoids.[11,12] Interestingly, the stability of the alkynylcyclopropane moiety, especially under the harsh cyclotrimerization reaction conditions that are required for the medium-ring construction, was an important concern. Importantly, the cyclotrimerization of the diyne **2** with a terminal alkyne such as methyl propiolate is expected without any regioselectivity and thus delivers both C9 and the reported C10-modified cyclopropylallocolchicinoid **1**. For the synthesis of the diyne **2**, keeping the Ohira–Bestmann reaction for introducing the alkyne unit attached to cyclopropyl group, Sonogashira cross-coupling for introducing the aryl alkyne unit, and a Simmons–Smith cyclopropanation, the *Z*-allyl alcohol **3** was identified as the key intermediate (Figure 1).

The synthesis of *Z*-allyl alcohol **3** was intended from the coupling of the known 3,4,5-trimethoxybenzyl bromide (**4**)[13] with propargyl alcohol followed by *cis*-selective controlled reduction of the internal alkyne unit. After several possibilities were explored, the successful coupling of **4** and propargyl alcohol could be realized in excellent yields by employing Wulff's Cu-mediated coupling protocol.[14] Thus, the treatment of the benzyl bromide with propargyl alcohol in the presence of CuI (20 mol %) and K_2CO_3 (1.5 equiv) in CH_3CN at 75 °C gave the coupled product **5** in 96% yield. Subsequently, the alkynol **5** was subjected to the partial reduction employing the Zn–Cu couple together with $AgNO_3$ in the H_2O–MeOH system.[15] The required *Z*-allylic alcohol **3** was obtained in 83% yield without any olefin isomerization as well as without any traces of saturated alkane. Subsequently, the cyclopropanation of olefin **3** was carried out under Furukawa's modified Simmons–Smith cyclopropanation conditions (Et_2Zn + CH_2I_2) to obtain **6**.[16] The next concern was about the sequential installation of the two alkyne units to arrive at the penultimate intermediate **2**. In this direction, the free hydroxyl group in **6** was protected as its acetate **6-Ac** and then subjected to iodination with molecular I_2 in the presence of Ag(I) salt. The Sonogashira coupling of the resulting iodo derivative **7** with (trimethylsilyl)acetylene was carried out by employing $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), PPh_3 (10 mol %), and Et_2NH in DMF solvent at 80 °C in a sealed tube to obtain **8** in good yields. We next attempted the installation of the second alkyne unit. Treatment of **8** with K_2CO_3 in methanol resulted in the deprotection of both acetate as well as the alkynyl-TMS groups, giving the alcohol **9** in 91% yield. The oxidation of alcohol **9** with Dess–Martin periodinane followed by treatment of the resulting aldehyde with Ohira–Bestmann reagent[17] in the presence of K_2CO_3 in methanol gave the diyne **2** in 76% yield over two steps. In order to increase the library scope of the present cyclotrimerization reaction, we have selected 1-octyne as one of the coupling partners in the Sonogashira cross-coupling reaction to add an additional substituent at the C11 position. In this direction, the intermediate **7** was subjected to the same sequence of reactions to deliver another advanced precursor for the [2 + 2 + 2]-cyclotrimerization reaction. The diyne **2′** was obtained in four steps with 61% overall yield (Scheme 1).

With the fully elaborated diyne frameworks **2** and **2′** in place, first, the cyclotrimerization was attempted with methyl propiolate by employing the $Co(CO)_2Cp$ catalyst that has been found to be better suited for medium-ring construction.[11,18] The optimized conditions for this reaction involve the heating of the diyne with the methyl propiolate in 1,4-dioxane at 150 °C for 15–20 h. The reactions are smooth and yielded the tetracyclic derivative **1a** in 79% yield with exclusive regioselectivity (Scheme 1). The spectral data of **1a** were superimposable with those reported by Boyer's group,[9a,19] suggesting that the high regioselectivity that has been seen during their Diels–Alder cycloaddition was indeed in operation during the cyclotrimerization process, too. In the case of cyclotrimerization of **1a′**, a 3:1 regioisomeric mixture favoring the more crowded *o*-isomer was obtained. This observed regioselectivity in the cyclotrimerization of both diynes with propiolate is unusual and needs a detailed investigation.[7a,11b]

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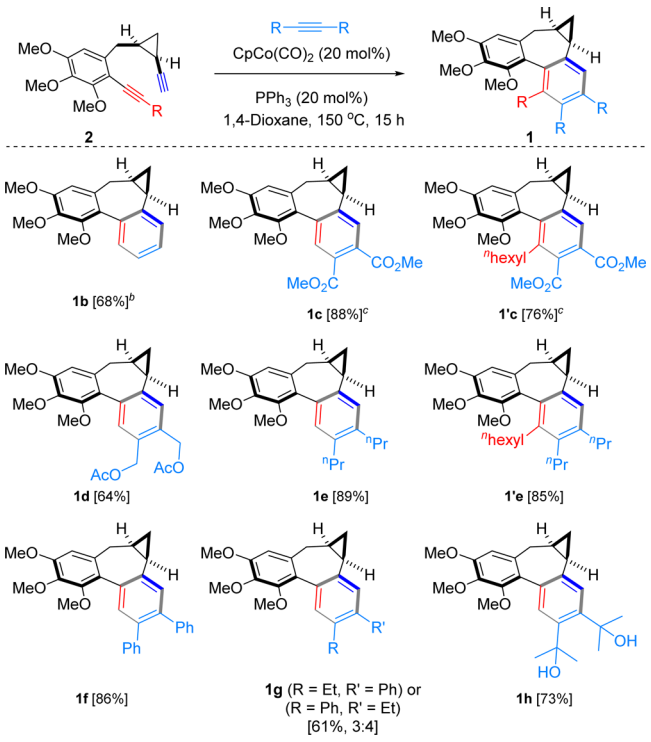
Nonetheless, the inherent stability of cyclopropane moiety under these conditions is quite interesting.[20]

Having synthesized the target cyclopropylallocolchicinoid **1**, we next moved toward the synthesis of analogues. The diynes **2** and **2′** were subjected to [Co]-catalyzed [2 + 2 + 2]-cyclotrimerization employing symmetric and unsymmetrical alkynes that are easily available. The results are summarized in Table 1.[19] Leaving the propiolate, in the case of other alkynes,

Table 1. [Co]-Catalyzed [2 + 2 + 2]-Cyclotrimerization Reaction of Diynes 2/2′ with Various Alkynes[a]



[a]Reaction conditions: **2** (1 mmol), alkyne (3 mmol), $Co(CO)_2Cp$ (0.2 mmol), PPh_3 (0.2 mmol), 1,4-dioxane (3 mL), 150 °C, 15 h, under argon. Yield refers to isolated yield. [b]*hν*, 200 W bulb. [c]Reactions carried out without any additional triphenylphosphine.

the cyclotrimerization reactions were carried out in the presence of 20 mol % of triphenylphosphine as an additive. In the case of propiolates, the added phosphine ligand seems to promote the decomposition of propiolates. With acetylene, the cyclotrimerization reaction of diyne **2** proceeded effectively under light in a sealed tube to afford **1b** in 68%. Other symmetrical alkynes such as the diacetate of 2-butyne-1,4-diol, 4-octyne, diphenylacetylene, and 2,5-dimethylhex-3-yne-2,5-diol were used, while unsymmetrical diynes such as 1-phenylbut-1-yne gave inseparable regioisomeric mixtures (3:4) in moderate to good yields.

In conclusion, a simple and highly modular approach has been developed for the synthesis of the known 6,7-cyclopropylallocolchicinoid **1** having tubulin-binding ability comparable to that of colchicine. The Co-catalyzed [2 + 2 + 2]-cyclotrimerization reaction has been applied as the key reaction for the A → ABC ring construction and importantly as the final event in this synthetic endeavor. This has allowed for the synthesis of several cyclopropylallocolchicinoids having variation of the substituents on the C ring. The adopted route for the construction of the key diynes also comprises several metal-catalyzed or mediated reactions for the key C−C bond formations. The unusual stability of the cyclopropane moiety and limited use of protecting groups in this pathway holds promise as a useful synthetic route to allocolchicinoids.

EXPERIMENTAL SECTION

General Methods. Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2, CH_3OH from Mg cake, THF on Na/benzophenone, and Et_3N over KOH. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60−120, 100−200, 230−400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-*d* (δ = 7.25) or TMS, and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations have been used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded as films on KBr plates.

4-(3,4,5-Trimethoxyphenyl)but-2-yn-1-ol (5). To a suspension of 3,4,5-trimethoxybenzyl bromide **4** (10.0 g, 38.3 mmol), CuI (1.46 g, 7.66 mmol), K_2CO_3 (7.94 g, 57.5 mmol), and tetra-*n*-butylammonium iodide (18.4 mg, 49.8 mmol) in dry CH_3CN (150 mL) was added propargyl alcohol (2.65 mL, 46.0 mmol) dropwise. The mixture was stirred at 75 °C for 10 h. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the resulting crude by silica gel column chromatography (30 → 60% EtOAc in petroleum ether) gave **5** (8.70 g, 96%) as a yellow syrup: R_f 0.6 (2:3 v/v EtOAc/petroleum ether); ^1H NMR (200 MHz, $CDCl_3$) δ 6.54 (s, 2H), 4.31 (t, *J* = 2.3 Hz, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 3.57 (t, *J* = 2.3 Hz, 2H), 1.71 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.3 (s, 2C), 136.7 (s), 132.1 (s), 105.0 (d, 2C), 83.8 (s), 80.5 (s), 60.8 (t), 56.1 (q, 2C), 51.4 (q), 25.4 (t) ppm; HRMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{16}NaO_4$ 259.0941, found 259.0941.

(*Z*)-4-(3,4,5-Trimethoxyphenyl)but-2-en-1-ol (3). To an aqueous suspension of Zn (55.3 g, 0.85 mol) and $Cu(OAc)_2$ (5.1 g, 25.4 mmol) was added $AgNO_3$ (4.3 g, 25.4 mmol), and the solution was stirred for 30 min. The mixture was then filtered and washed successively with H_2O, MeOH, acetone, and then Et_2O before it was transferred to a flask containing the reaction solvents (MeOH−H_2O, 1:1, 150 mL). A solution of alkyne **5** (5.0 g, 21.2 mmol) in MeOH (20 mL) was added, and the mixture was stirred at 50−60 °C in the dark. After 15 h, the reaction mixture was filtered through a Celite pad and washed with EtOAc. Water was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 100 mL), and the combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **3** (4.20 g, 83%) as a yellow syrup: R_f 0.5 (2:3 v/v EtOAc/petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 5.63−5.83 (m, 2H), 4.31 (dd, *J* = 5.2, 2.9 Hz, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 3.38 (dd, *J* = 5.4, 3.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (s, 2C), 136.3 (s), 135.9 (s), 131.0 (d), 129.5 (d), 105.1 (d, 2C), 60.8 (q), 58.5 (t), 56.0 (q, 2C), 33.8 (t) ppm; HRMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_4$ 261.1097, found 261.1095.

2-(3,4,5-Trimethoxybenzyl)cyclopropyl)methanol (6). At 0 °C, a solution of *cis*-alkene **3** (3.0 g, 12.6 mmol) in anhydrous CH_2Cl_2 (50 mL) was treated with Et_2Zn (1 M in CH_2Cl_2, 18.9 mL, 18.9 mmol) dropwise over 15 min. The reaction mixture was stirred for 15 min, and then a solution of CH_2I_2 (1.22 mL, 15.1 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 15 min. The reaction mixture was allowed to warm to rt and stirred for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to 0 °C, and satd aq NH_4Cl (30 mL) was added slowly to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layer was dried (Na_2SO_4) and

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concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **6** (2.80 g, 88%) as a yellow syrup: R_f 0.3 (2:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.51 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.78 (dd, J = 9.8, 6.8 Hz, 1H), 3.56 (dd, J = 10.0, 7.1 Hz, 1H), 2.66 (dd, J = 10.0, 6.7 Hz, 2H), 1.10−1.34 (m, 3H), 0.85 (dt, J = 13.1, 4.8 Hz, 1H), 0.17 (q, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (s, 2C), 137.8 (s), 135.9 (s), 105.1 (d, 2C), 64.2 (t), 61.0 (q), 56.2 (q, 2C), 34.6 (t), 17.7 (d), 17.0 (d), 10.1 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_4$ 275.1254, found 275.1252.

(2-(3,4,5-Trimethoxybenzyl)cyclopropyl)methyl Acetate (6-Ac). To a solution of alcohol **6** (5.0 g, 19.8 mmol), Et_3N (5.5 mL, 39.6 mmol), and DMAP (240 mg, 2 mmol) in CH_2Cl_2 (100 mL) was added Ac_2O (2.81 mL, 29.7 mmol) at rt. After 2 h of stirring, water was added to the reaction mixture, which was then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **6-Ac** (5.2 g, 89%) as a yellow syrup: R_f 0.4 (1:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.49 (s, 2H), 4.27 (dd, J = 11.9, 6.7 Hz, 1H), 4.02 (dd, J = 11.8, 1.0 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.48−2.81 (m, 2H), 2.03 (s, 3H), 1.13−1.41 (m, 2H), 0.91 (td, J = 8.4, 5.0 Hz, 1H), 0.25 (q, J = 5.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2 (s), 153.1 (s, 2C), 137.5 (s, 2C), 105.1 (d, 2C), 65.1 (t), 60.8 (q), 56.0 (q, 2C), 34.6 (t), 21.0 (q), 16.8 (d), 14.5 (d), 10.1 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{16}H_{22}NaO_5$ 317.1359, found 317.1360.

2-(2-Iodo-3,4,5-trimethoxybenzyl)cyclopropyl)methyl Acetate (7). To a stirred suspension of acetate **6-Ac** (5.0 g, 17.0 mmol), $NaHCO_3$ (2.15 g, 25.5 mmol), and silver trifluoroacetate (3.4 g, 20.4 mmol) in $CHCl_3$ (125 mL) was added dropwise a solution of iodine (4.74 g, 18.7 mmol) in $CHCl_3$ (25 mL) over a period of 1 h at 0 °C. After being stirred for an additional 1 h, the mixture was filtered and the precipitate was washed thoroughly with $CHCl_3$ (30 mL). The combined organic layer was washed with satd $Na_2S_2O_3$ solution (2 × 25 mL) and brine (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **7** (6.5 g, 91%) as a yellow syrup: R_f 0.6 (1:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.27 (dd, J = 11.8, 6.6 Hz, 1H), 4.02 (dd, J = 11.8, 7.8 Hz, 1H), 3.89 (s, 6H), 3.87 (s, 3H), 2.84 (dd, J = 15.6, 6.7 Hz, 1H), 2.69 (dd, J = 15.6, 7.3 Hz, 1H), 2.04 (s, 3H), 1.27−1.33 (m, 2H), 0.88−0.96 (m, 1H), 0.35 (q, J = 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2 (s), 153.5 (s), 153.0 (s), 140.4 (s), 139.9 (s), 108.6 (d), 88.3 (s), 65.1 (t), 61.0 (q), 60.7 (q), 56.1 (q), 39.4 (t), 21.0 (d), 16.1 (d), 14.6 (d), 9.9 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{16}H_{21}INaO_5$ 443.0326, found 443.0323..

2-(3,4,5-Trimethoxy-2-((trimethylsilyl)ethynyl)benzyl)-cyclopropyl)methyl Acetate (8). To a solution of iodo compound **7** (3.50 g, 8.3 mmol) in Et_2NH (20 mL) and DMF (20 mL) were added $Pd(PPh_3)_2Cl_2$ (170 mg, 0.42 mmol), CuI (160 mg, 0.83 mmol), and PPh_3 (220 mg, 0.83 mmol). The reaction mixture was flushed with argon for 30 min. To this was added (trimethylsilyl)acetylene (5.3 mL, 37.5 mmol), and the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered, and the precipitate was washed thoroughly with CH_2Cl_2 (300 mL). The combined organic layer was washed with brine (3 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **8** (2.8 g, 86%) as a yellow syrup: R_f 0.4 (2:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.64 (s, 1H), 4.32 (dd, J = 11.7, 6.6 Hz, 1H), 4.02 (dd, J = 11.7, 8.1 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.89 (dd, J = 14.9, 5.4 Hz, 1H), 2.69 (dd, J = 14.9, 7.9 Hz, 1H), 2.04 (s, 3H), 1.27−1.33 (m, 2H), 0.84−0.88 (m, 1H), 0.34 (q, J = 5.4 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1 (s), 155.1 (s), 153.8 (s), 141.1 (s), 129.2 (s), 109.9 (s), 107.5 (d), 101.3 (s), 99.9 (s), 65.3 (t), 61.1 (q), 61.1 (q), 56.0 (q), 32.8 (t), 21.0 (d), 16.4 (d), 14.6 (d), 9.9 (t), 0.01 (q, 3C) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{21}H_{30}O_5NaSi$ 413.1755, found 413.1754.

(2-(3,4,5-Trimethoxy-2-(oct-1-yn-1-yl)benzyl)cyclopropyl)-methyl Acetate (8′). Following the procedure used in the preparation of **8**, the Sonogashira coupling of **7** (5.0 g, 11.9 mmol) with 1-octyne (3.93 g, 35.7 mmol) gave **8′** (4.30 g, 90%) as a yellow oil: R_f 0.3 (3:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.64 (s, 1H), 4.27 (dd, J = 11.7, 6.8 Hz, 1H), 4.04 (dd, J = 11.7, 7.8 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.83 (dd, J = 15.2, 6.4 Hz, 1H), 2.71 (dd, J = 15.2, 7.6 Hz, 1H), 2.48 (t, J = 7.0 Hz, 2H), 2.03 (s, 3H), 1.63 (quin, J = 7.3 Hz, 2H), 1.49 (dt, J = 14.7, 7.2 Hz, 2H), 1.27−1.35 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H), 0.85 (dt, J = 8.6, 4.8 Hz, 1H), 0.30 (q, J = 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2 (s), 154.6 (s), 152.8 (s), 140.0 (s), 129.2 (s), 113.7 (s), 107.5 (d), 97.2 (s), 74.8 (s), 65.3 (t), 61.0 (q), 61.0 (q), 56.0 (q), 32.8 (t), 31.4 (s), 28.9 (t), 28.6 (t), 22.6 (t), 21.0 (q), 19.8 (t), 16.3 (q), 14.6 (d), 14.0 (d), 9.9 (s) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{24}H_{34}O_5Na$ 425.2298, found 425.2300.

2-(2-Ethynyl-3,4,5-trimethoxybenzyl)cyclopropyl)methanol (9). A suspension of compound **8** (2.0 g, 5.1 mmol) and K_2CO_3 (2.1 g, 15.4 mmol) in methanol (30 mL) was stirred at rt for 6 h. The reaction mixture was filtered, and the precipitate was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **9** (1.31 g, 91%) as a yellow syrup: R_f 0.2 (2:3 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.73 (s, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (dd, J = 11.2, 5.6 Hz, 1H), 3.63 (dd, J = 11.3, 5.9 Hz, 1H), 3.41 (s, 1H), 2.85 (d, J = 6.9 Hz, 2H), 1.23−1.33 (m, 2H), 0.83 (dt, J = 8.4, 4.8 Hz, 1H), 0.24 (q, J = 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5 (s), 154.1 (s), 141.4 (s), 140.1 (s), 108.6 (s), 107.4 (d), 83.8 (d), 78.4 (s), 63.1 (t), 61.3 (q), 61.1 (q), 56.0 (q), 32.5 (t), 18.6 (d), 16.3 (d), 9.2 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{16}H_{20}O_4Na$ 299.1254, found 299.1252.

(2-(3,4,5-Trimethoxy-2-(oct-1-yn-1-yl)benzyl)cyclopropyl)-methanol (9′). Hydrolysis of acetate **8′** (5.0 g, 12.4 mmol) with K_2CO_3 (5.15 g, 37.3 mmol) in MeOH (50 mL) as described for **8** gave **9′** (4.14 g, 92%) as a yellow oil: R_f 0.3 (2:3 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.70 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (dd, J = 11.6, 6.3 Hz, 1H), 3.62 (dd, J = 11.6, 8.8 Hz, 1H), 2.81 (dq, J = 8.4, 6.9 Hz, 2H), 2.49 (t, J = 6.7 Hz, 2H), 1.39−1.73 (m, 3H), 1.15−1.39 (m, 7H), 0.91 (t, J = 6.7 Hz, 4H), 0.82 (dq, J = 8.5, 4.8 Hz, 1H), 0.22 (q, J = 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.7 (s), 153.0 (s), 140.3 (s), 140.2 (s), 107.3 (d, 2C), 97.2 (s), 74.7 (s), 63.1 (t), 61.1 (q, 2C), 56.0 (q), 32.6 (t), 31.4 (t), 28.9 (t), 28.6 (t), 22.6 (q), 19.8 (t), 18.6 (d), 16.3 (d), 14.1 (d), 9.2 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{22}H_{32}O_4Na$ 383.2193, found 383.2188.

2-Ethynyl-1-((2-ethynylcyclopropyl)methyl)-3,4,5-trimethoxybenzene (2). To a solution of compound **9** (2.50 g, 9.1 mmol) in CH_2Cl_2 (30 mL) was added Dess−Martin periodinane (5.76 g, 13.6 mmol), and the reaction mixture was stirred at rt for 6 h. The reaction mixture was filtered through Celite, and the precipitate was washed with CH_2Cl_2 (30 mL). The combined organic layer was washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resultant crude aldehyde product was dissolved in dry methanol (30 mL), Ohira−Bestmann reagent (2.61 g, 13.6 mmol) and K_2CO_3 (3.75 g, 27.1 mmol) were added, and the mixture was stirred at rt for 8 h. After completion of the reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2 (100 mL) and filtered through Celite. The filtrate was washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30 → 60% EtOAc in petroleum ether) to obtain **2** (1.87 g, 76%) as a yellow syrup: R_f 0.7 (1:4 v/v EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.81 (s, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.42 (s, 1H), 2.94 (qd, J = 8.3, 6.3 Hz, 2H), 1.95 (d, J = 2.1 Hz, 1H), 1.34−1.53 (m, 2H), 1.03 (td, J = 8.4, 4.7 Hz, 1H), 0.64 (q, J = 5.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4 (s), 154.0 (s), 140.8 (s), 140.2 (s), 108.7

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(s), 108.4 (d), 85.2 (s), 83.6 (d), 78.4 (s), 66.6 (d), 61.2 (q), 61.0 (q), 55.9 (q), 34.1 (t), 18.9 (d), 14.4 (t), 5.7 (d) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{17}H_{18}O_3Na$ 293.1154, found 293.1146.

1-((2-Ethynylcyclopropyl)methyl)-3,4,5-trimethoxy-2-(oct-1-yn-1-yl)benzene (2′). Following the procedures described for **2**, the reaction of alcohol **9′** (1.6 g, 4.44 mmol) with Dess−Martin periodinane (2.82 g, 6.6 mmol), Ohira−Bestmann reagent (1.28 g, 6.6 mmol), and K_2CO_3 (1.84 g, 13.3 mmol) gave alkyne **2′** (1.15 g, 73%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 2.95 (dd, J = 14.4, 6.6 Hz, 1H), 2.86 (dd, J = 14.5, 7.2 Hz, 1H), 2.49 (t, J = 7.0 Hz, 2H), 1.93 (d, J = 2.0 Hz, 1H), 1.57−1.69 (m, 2H), 1.42−1.54 (m, 4H), 1.28−1.38 (m, 3H), 1.00 (td, J = 8.4, 4.6 Hz, 1H), 0.90 (t, J = 6.7 Hz, 4H), 0.62 (q, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (s), 152.8 (s), 140.2 (s), 139.7 (s), 110.7 (s), 108.2 (d), 97.0 (s), 85.2 (s), 74.7 (s), 66.4 (d), 61.0 (q), 55.9 (q), 34.2 (t), 31.4 (t), 28.8 (t), 28.6 (t), 22.6 (s), 22.4 (t), 19.8 (t), 18.9 (q), 14.3 (t), 14.0 (d), 5.6 (d) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{23}H_{30}O_3Na$ 377.2087, found 377.2083.

[2 + 2 + 2]-Cyclotrimerization Reaction of 2 and 2′ with Various Alkynes. *Procedure A.* A solution of diyne **2**/**2′** (1.0 equiv) and alkyne (3 equiv) in 1,4-dioxane (3 mL) was degassed with dry argon for 20 min, and then catalyst $Co(CO)_2Cp$ (20 mol %) and PPh_3 (20 mol %, not required when methyl propiolate and dimethyl acetylenedicarboxylate are employed as the alkyne partners) were introduced. The reaction mixture was heated at 150 °C for 15 h and then allowed to cool to rt. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the corresponding cyclotrimerization product.

Procedure B. A solution of diyne **2** (1.0 equiv) and PPh_3 (20 mol %) in toluene (3 mL) in a sealed tube was degassed with dry argon for 20 min, and then $Co(CO)_2Cp$ (20 mol %) was introduced. The reaction mixture was cooled to −78 °C, and acetylene gas was bubbled for 10 min. The sealed tube was capped and irradiated under light (200 W bulb) for 15 h, allowed to cool to 0 °C, and opened carefully. The reaction mixture was concentrated under reduced pressure, and resulting crude was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the corresponding cyclotrimerization products.

*(±)-Methyl 8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]-cycloprop[e][7]annulene-2-carboxylate (**1a**).* Cycloaddition of diyne **2** (100 mg) with methyl propiolate following procedure A gave compound **1a** (103 mg, 79%, exclusive regioisomer) as a white solid: mp 104−105 °C; R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.91 (dd, J = 8.2, 1.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 6.61 (s, 1H), 3.93 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.69 (s, 3H), 2.90 (dd, J = 13.4, 4.9 Hz, 1H), 1.86−2.03 (m, 2H), 1.27 (t, J = 3.7 Hz, 1H), 0.97−1.07 (m, 1H), 0.51 (q, J = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (s), 152.3 (s), 145.0 (s), 141.1 (s), 137.6 (s), 135.4 (s), 134.6 (s), 133.3 (d), 132.8 (d),127.8 (d), 127.6 (d), 124.5 (s), 106.8 (d), 61.1 (q), 61.1 (q), 56.1 (q), 52.0 (q), 36.5 (t), 22.4 (d), 16.5 (d), 11.7 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{21}H_{22}O_5Na$ 377.1359, found 377.1357.

*(±)-Methyl 1-Hexyl-8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cycloprop[e][7]annulene-2-carboxylate (**1′a**).* Cycloaddition of diyne **2′** (60 mg) with methyl propiolate following procedure A gave compound **1′a** (56 mg, 76%, 3:1, inseperable regioisomeric mixture) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major regiooisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.62 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.42 (s, 3H), 3.09 (ddd, J = 13.4, 10.1, 5.2 Hz, 1H), 2.82 (dd, J = 13.1, 4.9 Hz, 1H), 2.49−2.61 (m, 2H), 1.82−1.98 (m, 2H), 1.37−1.48 (m, 1H), 1.19−1.35 (m, 2H), 0.89−1.12 (m, 6H), 0.71−0.79 (m, 3H), 0.50 (q, J = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (s), 152.2 (s), 152.1 (s), 143.8 (s), 143.3 (s), 140.5 (s), 138.4 (s), 135.8 (s), 131.2 (d), 129.8 (s), 129.0 (d), 122.9 (s), 106.3 (d), 61.2 (q), 60.9 (q), 52.0 (q), 51.9 (q), 35.8 (t), 31.3 (t), 31.1 (t), 30.5 (t), 29.1 (t), 23.2 (q), 22.4 (t), 16.7 (d), 14.0 (d), 12.9 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{27}H_{34}O_5Na$ 461.2298, found 461.2292.

*(±)-8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]-cycloprop[e][7]annulene (**1b**).* Cycloaddition of diyne **2** (130 mg) with acetylene gas following procedure B gave compound **1b** (97 mg, 68%) as a colorless liquid: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 5.5, 2.8 Hz, 1H), 7.41 (dd, J = 6.3, 2.8 Hz, 1H), 7.21−7.29 (m, 2H), 6.61 (s, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 3.62 (s, 3H), 2.87 (dd, J = 13.3, 5.0 Hz, 1H), 2.03 (t, J = 11.3 Hz, 1H), 1.91 (td, J = 8.5, 5.0 Hz, 1H), 1.45−1.57 (m, 1H), 0.97 (td, J = 8.2, 4.5 Hz, 1H), 0.51 (q, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3 (s), 151.9 (s), 141.1 (s), 139.6 (s), 137.9 (s), 135.1 (s), 132.5 (d), 131.6 (d), 127.0 (d), 125.6 (d), 125.4 (s), 106.8 (d), 61.1 (q), 60.9 (q), 56.0 (q), 36.6 (t), 22.4 (d), 16.3 (d), 11.6 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{19}H_{20}O_3Na$ 319.1305, found 319.1302.

*(±)-Dimethyl 8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo-[a,c]cycloprop[e][7]annulene-2,3-dicarboxylate (**1c**).* Cycloaddition of diyne **2** (50 mg) with dimethyl acetylenedicarboxylate following procedure A gave compound **1c** (67 mg, 88%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.82 (s, 1H), 6.60 (s, 1H), 3.94 (s, 3H), 3.92 (s, 6H), 3.90 (s, 3H), 3.66 (s, 3H), 2.90 (dd, J = 13.7, 4.9 Hz, 1H), 1.89−1.98 (m, 2H), 1.53−1.59 (m, 1H), 1.03 (td, J = 7.9, 4.9 Hz, 1H), 0.54 (q, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (s), 168.1 (s), 152.8 (s), 152.3 (s), 143.3 (s), 141.2 (s), 138.4 (s), 137.6 (s), 133.3 (d), 132.8 (d), 130.2 (s), 128.8 (s), 123.6 (s), 107.0 (d), 61.2 (q), 61.1 (q), 56.0 (q), 52.6 (q), 52.5 (q), 36.5 (t), 22.5 (d), 16.3 (d), 11.5 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{23}H_{24}O_7Na$ 435.1414, found 435.1412.

*(±)-Dimethyl 1-Hexyl-8,9,10-trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]cycloprop[e][7]annulene-2,3-dicarboxylate (**1′c**).* Cycloaddition of diyne **2′** (50 mg) with dimethyl acetylenedicarboxylate following procedure A gave compound **1′c** (53 mg, 76%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.63 (s, 1H), 3.93 (s, 3H), 3.92 (s, 6H), 3.91 (s, 3H), 3.89 (s, 3H), 3.44 (s, 3H), 2.84 (dd, J = 13.4, 4.3 Hz, 1H), 2.64−2.76 (m, 1H), 2.30−2.43 (m, 1H), 1.84−1.94 (m, 1H), 1.40−1.51 (m, 1H), 1.12−1.21 (m, 1H), 0.99−1.10 (m, 2H), 0.84−0.99 (m, 4H), 0.74 (t, J = 7.0 Hz, 3H), 0.50 (q, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s), 166.3 (s), 152.7 (s), 151.8 (s), 141.1 (s), 140.8 (s, 2C), 140.3 (s), 138.2 (s), 133.6 (s), 132.1 (d), 126.4 (s), 122.1 (s), 106.5 (d), 61.3 (q), 61.2 (q), 56.0 (q), 52.4 (q, 2C), 35.7 (t), 31.6 (t), 30.9 (t), 30.3 (t), 29.1 (t), 23.1 (q), 22.3 (t), 16.3 (t), 13.9 (t), 12.8 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{29}H_{36}O_7Na$ 519.2353, found 519.2350.

*(±)-(8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]-cycloprop[e][7]annulene-2,3-diyl)bis(methylene) Diacetate (**1d**).* Cycloaddition of diyne **2** (80 mg) with but-2-yne-1,4-diyl diacetate following procedure A gave compound **1d** (84 mg, 64%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.45 (s, 1H), 6.60 (s, 1H), 5.21 (d, J = 4.0 Hz, 2H), 5.19 (d, J = 3.4 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.68 (s, 3H), 2.88 (dd, J = 13.4, 4.6 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.00 (dd, J = 13.3, 11.7 Hz, 1H), 1.89 (td, J = 8.5, 5.0 Hz, 1H), 1.51−1.55 (m, 1H), 0.98 (td, J = 8.2, 4.6 Hz, 1H), 0.50 (q, J = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (s), 170.7 (s), 152.2 (s), 141.1 (s), 140.3 (s), 137.8 (s), 135.7 (s), 134.2 (d), 133.3 (d), 132.8 (s), 132.5 (s), 131.7 (s), 124.4 (s), 106.9 (d), 63.9 (t), 63.9 (t), 61.1 (q), 61.0 (q), 56.0 (q), 36.6 (t), 22.3 (t), 21.0 (q), 21.0 (q), 16.1 (t), 11.5 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{25}H_{28}O_7Na$ 463.1727, found 463.1725.

*(±)-8,9,10-Trimethoxy-2,3-dipropyl-4b,5,5a,6-tetrahydrodibenzo-[a,c]cycloprop[e][7]annulene (**1e**).* Cycloaddition of diyne **2** (100 mg) with 4-octyne following procedure A gave compound **1e** (125 mg, 89%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 2H), 6.64 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.68 (s, 3H), 2.88 (dd, J = 13.3, 4.7 Hz, 1H), 2.62−2.70 (m, 3H), 2.57 (td, J = 14.0, 7.6 Hz, 1H), 2.08 (t, J = 12.4 Hz, 1H), 1.89 (td, J = 8.4, 5.2 Hz, 1H), 1.65−1.74 (m, 4H),

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1.42−1.54 (m, 1H), 1.07 (t, J = 7.3 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 0.96 (td, J = 8.1, 4.3 Hz, 1H), 0.51 (q, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (s), 151.5 (s), 141.0 (s), 139.2 (s), 138.0 (s), 137.6 (s), 136.7 (s), 132.9 (d), 132.2 (s), 132.1 (d), 125.6 (s), 106.8 (d), 61.1 (q), 60.9 (q), 56.0 (q), 36.7 (t), 34.6 (t), 34.4 (t), 24.4 (t), 24.2 (t), 22.0 (d), 16.0 (d), 14.3 (q), 14.2 (d), 11.6 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{25}H_{32}O_3Na$ 403.2244, found 403.2243.

*(±)-1-Hexyl-8,9,10-trimethoxy-2,3-dipropyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cycloprop[e][7]annulene (**1′e**).* Cycloaddition of diyne **2′** (100 mg) with 4-octyne following procedure A gave compound **1′e** (120 mg, 85%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.60 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.36 (s, 3H), 2.78 (dd, J = 13.0, 4.9 Hz, 1H), 2.51−2.67 (m, 6H), 2.02 (t, J = 12.1 Hz, 1H), 1.74−1.81 (m, 1H), 1.62−1.72 (m, 3H), 1.48−1.57 (m, 2H), 1.28−1.39 (m, 2H), 0.99−1.10 (m, 10H), 0.90−0.98 (m, 3H), 0.75 (t, J = 7.1 Hz, 3H), 0.45 (q, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (s), 151.5 (s), 140.8 (s), 140.3 (s), 139.8 (s), 138.8 (s), 136.7 (s), 136.4 (s), 132.1 (s), 130.5 (d), 124.4 (s), 106.1 (d), 61.2 (q), 60.8 (q), 56.0 (q), 35.9 (t), 35.4 (t), 31.2 (t), 31.1 (t, 2C), 30.1 (t), 29.3 (t), 24.9 (t), 24.5 (t), 22.9 (t), 22.4 (q), 16.2 (q), 14.7 (q), 14.4 (d), 14.0 (d), 12.8 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{31}H_{44}O_3Na$ 487.3183, found 487.3185.

*(±)-8,9,10-Trimethoxy-2,3-diphenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cycloprop[e][7]annulene (**1f**).* Cycloaddition of diyne **2** (50 mg) with 1,2-diphenylethyne following procedure A gave compound **1f** (71 mg, 86%) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether). Major atropisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.52 (s, 1H), 7.14−7.27 (m, 10H), 6.64 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.75 (s, 3H), 2.93 (dd, J = 13.4, 4.9 Hz, 1H), 2.17 (dd, J = 13.3, 11.4 Hz, 1H), 1.98 (td, J = 8.6, 4.7 Hz, 1H), 1.55−1.52 (m 1H), 1.00 (td, J = 8.2, 4.6 Hz, 1H), 0.60 (q, J = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (s), 152.0 (s), 141.5 (s), 141.4 (s), 141.1 (s), 139.0 (s), 138.9 (s), 138.0 (s), 137.8 (s), 134.7 (s), 134.3 (s), 133.9 (s), 129.9 (d, 2C), 129.9 (d, 2C), 127.8 (d, 2C), 127.7 (d, 2C), 126.3 (s), 126.2 (s), 124.9 (s), 106.9 (d), 61.1 (q), 61.1 (q), 56.0 (q), 36.7 (t), 22.2 (d), 16.2 (d), 11.7 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{31}H_{28}O_3Na$ 471.1931, found 471.1930.

*(±)-2-Ethyl-8,9,10-trimethoxy-3-phenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]cycloprop[e][7]annulene and (±)-3-Ethyl-8,9,10-trimethoxy-2-phenyl-4b,5,5a,6-tetrahydrodibenzo[a,c]-cycloprop[e][7]annulene (**1g**).* Cycloaddition of diyne **2**(100 mg) with 1-phenyl-1-butyne following procedure A gave compound **1g** (90 mg, 61%, inseperable regioisomeric mixture 3:4) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) najor regioisomer δ 7.32−7.51 (m, 6H), 6.65 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.72 (s, 3H), 2.93 (dd, J = 13.4, 4.9 Hz, 1H), 2.60−2.74 (m, 2H), 2.15 (dd, J = 11.3, 3.9 Hz, 1H), 1.90−2.03 (m, 1H), 1.49−1.62 (m, 1H), 1.20 (t, J = 7.6 Hz, 3H), 0.96 (dt, J = 8.0, 4.1 Hz, 2H), 0.59 (q, J = 4.9 Hz, 1H); minor regioisomer: δ 7.32−7.51 (m, 6H), 6.67 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.78 (s, 3H), 2.93 (dd, J = 13.4, 4.9 Hz, 1H), 2.60−2.74 (m, 2H), 2.15 (dd, J = 11.3, 3.9 Hz, 1H), 1.90−2.03 (m, 1H), 1.49−1.62 (m, 1H), 1.17 (t, J = 7.6 Hz, 3H), 0.96 (dt, J = 8.0, 4.1 Hz, 2H), 0.55 (q, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) major regioisomer δ 152.2 (s), 151.7 (s), 141.8 (s), 140.9 (s), 140.1 (s), 138.6 (s), 137.9 (s), 136.8 (s), 134.0 (s), 133.0 (d), 132.3 (d), 129.3 (d, 2C), 127.9 (d, 2C), 126.5 (d), 125.1 (s), 106.7 (d), 61.0 (q), 60.9 (q), 55.9 (q), 36.7 (t), 25.8 (t), 22.1 (q), 16.1 (d), 15.5 (d), 11.6 (t); minor regioisomer δ 152.2 (s), 151.8 (s), 141.9 (s), 140.9 (s), 140.2 (s), 139.0 (s), 138.0 (s), 136.8 (s), 134.0 (s), 132.2 (d), 131.7 (d), 129.3 (d, 2C), 127.9 (d, 2C), 126.6 (d), 125.2 (s), 106.7 (d), 61.0 (q), 60.9 (q), 55.9 (q), 36.7 (t), 25.8 (t), 22.1 (q), 15.9 (d), 15.8 (d), 11.6 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{27}H_{28}O_3Na$ 423.1931, found 423.1928.

*(±)-2,2′-(8,9,10-Trimethoxy-4b,5,5a,6-tetrahydrodibenzo[a,c]-cycloprop[e][7]annulene-2,3-diyl)bis(propan-2-ol) (**1h**).* Cycloaddition of diyne **2** (100 mg) with 2,5-dimethylhex-3-yne-2,5-diol following procedure A gave compound **1h** (112 mg, 73%, 1:1, inseperable mixture of atropisomeric mixture) as a yellow oil: R_f 0.5 (2:3 v/v EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.41 (s, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.61 (s, 1H), 6.61 (s, 1H), 3.92 (s, 6H), 3.91 (s, 6H), 3.64 (s, 3H), 3.63 (s, 3H), 2.87 (dd, J = 13.3, 4.4 Hz, 2H), 2.87 (dd, J = 13.3, 4.4 Hz, 2H), 2.00−2.11 (m, 2H), 1.81−1.92 (m, 2H), 1.78 (s, 3H), 1.74−1.77 (m, 1H), 1.67 (s, 3H), 1.56 (s, 6H), 1.51 (s, 9H), 1.48 (s, 6H), 0.89−1.02 (m, 2H), 0.52 (q, J = 4.6 Hz, 1H), 0.46 (q, J = 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2 (s), 152.2 (s), 151.9 (s), 151.8 (s), 145.1 (s), 144.1 (s), 143.8 (s), 142.9 (s), 141.0 (s), 138.9 (s), 138.0 (s), 137.9 (s), 137.2 (s), 134.2 (s), 132.6 (s), 132.0 (d), 131.6 (d), 125.4 (s), 124.9 (s), 124.4 (d), 123.7 (d), 106.9 (d), 106.8 (d), 86.7 (s), 84.1 (s), 84.0 (s), 75.0 (s), 74.6 (s), 65.0 (q), 61.1 (q), 60.9 (q, 2C), 56.0 (q, 2C), 36.7 (t), 36.5 (t), 34.2 (q), 33.8 (q), 33.7 (q), 31.4 (q), 31.0 (q), 30.9 (q), 30.8 (q), 30.5 (q), 22.4 (d), 21.8 (d), 16.3 (d), 16.0 (d), 11.7 (t), 11.5 (t) ppm; HRMS (m/z) [M + Na]$^+$ calcd for $C_{25}H_{32}O_5Na$ 435.2142, found 435.2138.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00020.

^{1}H/^{13}C NMR and HRMS spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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