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Synthesis of structurally diverse benzosuberene analogues and their biological evaluation as anti-cancer agents

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Abstract

Diversely functionalized, fused aryl-alkyl ring systems hold a prominent position as well-established molecular frameworks for a variety of anti-cancer agents. The benzosuberene (6,7 fused, also referred to as dihydro-5*H*-benzo[7]annulene and benzocycloheptene) ring system has emerged as a valuable molecular core component for the development of inhibitors of tubulin assembly, which function as antiproliferative anti-cancer agents and, in certain cases, as vascular disrupting agents (VDAs). Both a phenolic-based analogue (known as **KGP18**, compound **39**) and its corresponding amine-based congener (referred to as **KGP156**, compound **45**), which demonstrate strong inhibition of tubulin assembly (low micromolar range) and potent cytotoxicity (picomolar range for **KGP18** and nanomolar range for **KGP156**) are noteworthy examples of such benzosuberene-based compounds. In order to extend the structure-activity relationship (SAR) knowledge base related to benzosuberene anti-cancer agents, a series of eleven analogues (including **KGP18**) were prepared in which the methoxylation pattern on the pendant aryl ring as well as functional group incorporation on the fused aryl ring were varied. The synthetic approach to these compounds featured a sequential Wittig olefination, reduction, Eaton's reagent-mediated cyclization strategy to achieve the core benzosuberone intermediate, and represented a higher-yielding synthesis of **KGP18** (which we prepared previously through a ring-expansion strategy). Incorporation of a fluorine or chlorine atom at the 1-position of the fused aryl ring or replacement of one of the methoxy groups with hydrogen (on the pendant aryl ring of **KGP18**) led to benzosuberene analogues that were both strongly inhibitory against tubulin assembly (IC_{50} approximately 1.0 M) and strongly cytotoxic against selected human cancer cell lines (for example, GI_{50} = 5.47 nM against NCI-H460 cells with fluorobenzosuberene analogue **37**). A water-soluble phosphate prodrug salt of **KGP18** (referred to as **KGP265**, compound **44**) and a

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Supplementary Data.
Characterization data (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HPLC, and HRMS) for final compounds, HMBC and HSQC data for compound **38**, X-ray crystallography for compounds **38** and **39**, mechanistic speculation regarding regioselective demethylation reactions for compounds **16** and **18**, information regarding the synthesis of compound **2**, an alternative synthetic route to compound **39**, and cLogP data for compounds **39**, **44**, **45**, and **48** can be found, in the online version, at .

water-soluble serinamide salt (compound **48**) of **KGP156** were also synthesized and evaluated in this study.

Keywords

inhibitors of tubulin assembly; benzosuberene-based anti-cancer agents; vascular disrupting agents (VDAs); combretastatin analogues

1. Introduction

The discovery and development of small-molecule, anti-cancer agents that demonstrate pronounced cytotoxicity against human cancer cell lines remains an important goal in the search for new cancer treatment agents and related therapeutic strategies. An established approach involves the selective targeting of tumor vasculature and more specifically the tubulinmicrotubule protein system. Research efforts in this area have led to a class of therapeutics known as vascular targeting agents (VTAs)[1,2] that is further sub-divided into angiogenic inhibiting agents (AIAs),[3,4,5] which interfere with tumor neovascularization and vascular disrupting agents (VDAs),[3,4,6-9] including both small-molecules and biologics, which selectively damage existing tumor vasculature. Tubulin-binding VDAs function through the inhibition of tubulin polymerization within endothelial cells lining tumor microvessels. A subsequent series of cell signaling events leads to morphological transformations (flat to round) of these endothelial cells and results in microvessel occlusion and vascular shutdown, which ultimately starves the tumor of necessary nutrients and oxygen.[3,6,10,11] While still an active area of research inquiry, there is evidence indicating that activated endothelial cells (such as those lining the vasculature supplying tumors) are affected by VDAs to a greater extent than quiescent endothelial cells found in vasculature feeding normal tissue.[12-14] A significant focal point centers on small-molecule VDAs that bind to the colchicine site[15,16] on the -tubulin heterodimer. It is important to note that AIAs and VDAs function biologically through mechanistically distinct pathways.[9,17]

A progressive research agenda in our laboratory, focused on the design and synthesis of inhibitors of tubulin assembly, led to the establishment of functionalized benzosuberene analogues as promising compounds for further evaluation as anti-cancer agents.[18-20] This exploration was guided, in part, by the molecular structures of colchicine and certain members of the combretastatin family of natural products along with our previously discovered dihydronaphthalene-based analogues[18,21,22] (Fig. 1).

Specifically, combretastatin A-4 (CA4)[24,25] and combretastatin A-1 (CA1)[26] are among the most potent colchicine site tubulin-binding agents and they were each further developed into their corresponding phosphate prodrug salts to improve aqueous solubility.[31-33] Efforts to mimic the combretastatin molecular-framework and optimize a wide-variety of biological parameters, resulted in a cadre of structural modifications.[34,35] A very limited sub-set of these molecules that were inspired by the combretastatins include benzophenone,[36,37] dihydronaphthalene,[18,21-23,38,39] indole,[40-43] and benzosuberene[18,19,20,44] analogues in which a single sp^2 hybridized carbon atom bridges the two aromatic rings and maintains the pseudo *cis*-orientation[45] that is important for enhanced biological activity. Two such benzosuberene-based compounds, referred to as **KGP18** (phenol-based)[18,20,46] and **KGP156** (amine-based),[19] have emerged as potential pre-clinical candidates (Fig. 1). In addition to their robust *in vitro* cytotoxicity against human cancer cell lines (picomolar for **KGP18** and nanomolar for **KGP156**), preliminary studies have shown that these benzosuberene analogues function as vascular disrupting agents (VDAs).[19,20,47] Our original synthetic route to these benzosuberene analogues included a ring expansion,

reduction, selective oxidation sequence that while reliable, was somewhat limiting due to low reaction yields.[18] A revised synthetic methodology that relies on an efficient ring-closing cyclization step was utilized in our synthesis[19] of the amine analogue, **KGP156**, and a recent publication by Maderna and co-workers[44] describes an efficient ring closing metathesis (RCM) step to assemble the benzosuberene molecular core followed by a Suzuki coupling reaction. In order to advance the known structure activity relationship (SAR) data, a collection of eleven benzosuberene analogues, selected primarily to explore functional group modification at the C-1 position, were prepared by chemical synthesis and evaluated for their cytotoxicity against selected human cancer cell lines, and for their ability to inhibit tubulin assembly.

2. Results and Discussions

2.1 Chemistry

A series of eleven functionalized benzosuberene-based analogues were prepared by chemical synthesis. The synthetic strategy relied on an intramolecular Friedel-Crafts annulation with Eaton's reagent[48,49] to install the benzosuberone ring system (Scheme 1). The prerequisite carboxylic acid derivatives were prepared through a sequential Wittig olefination followed by catalytic hydrogenation sequence, which, overall, is nearly identical to the synthetic methodology described by Negoro et al.[50] This synthetic strategy to prepare benzosuberone derivatives has proved to be highly proficient within our laboratory.[19,46,51] Protecting group strategies were included when necessary. Additional modifications of benzosuberones **16** and **18** were achieved through selective demethylation with ionic liquid $[TMAH][Al_2Cl_7]$[52] resulting in phenolic benzosuberones **21**-**22** which were subsequently converted to their corresponding silyl ethers **23**-**24** with TBSCl (Scheme 2). Confirmation of the regioselective demethylation to form benzosuberone intermediate **22** was provided by X-ray crystallographic analysis of the final compound **KGP18** (compound **39**) that resulted from further synthetic manipulation of intermediate **22** (see Supplementary Data). Similarly, the regioselective demethylation to form intermediate **21** was confirmed by HSQC and HMBC analysis, along with X-ray crystallography, of final compound **38** (see Supplementary Data). The functionalized pendant aryl ring was incorporated, in each case, through the addition of an appropriately functionalized aryllithium intermediate (prepared *in situ* from the corresponding aryl bromide) to the requisite benzosuberone derivative to generate the corresponding tertiary alcohol that underwent elimination to form the benzosuberene core structure (Scheme 3). This overall synthetic sequence proved to be quite robust and is complementary to other known synthetic routes toward benzosuberene ring systems[18,44,53,54] (including Friedel-Crafts cyclization[55]). An alternative synthetic strategy for the preparation of **KGP18** (compound **39**) that utilized an intramolecular acid chloride mediated cyclization strategy was also successful (see Supplementary Data for details).

The preparation of benzosuberene analogues **42**-**44** required further synthetic manipulation. Analogue **42** was achieved through desilylation with TBAF and analogue **43** was obtained by removal of the tosyl protecting group upon treatment with NaOH (Scheme 4). In order to facilitate a variety of planned *in vivo* studies, the hydrophobic benzosuberene analogue **39** (**KGP18**) was converted to its corresponding water-soluble, disodium phosphate prodrug salt **44** (**KGP265**) through phosphorylation with $POCl_3$ followed by treatment with NaOH. This phosphate prodrug strategy has proved to be highly effective for both combretastatin A-4P (CA4P)[33] and combretastatin A-1P (CA1P).[31]

Previously described hydrophobic aniline analogue **45** (**KGP156**)[19] was converted to its corresponding water-soluble, serinamide salt **48** through initial amide bond formation between benzosuberene **45** and acetyl-Fmoc protected serinamide to form serinamide **46** and subsequent treatment with NaOH to yield serinamide benzosuberene analogue **47** (Scheme

5). Treatment of serinamide **47** with HCl led to the corresponding hydrochloride serinamide salt **48**. This chemistry is reminiscent of the synthetic strategy employed by Ohsumi and co-workers[56] for the preparation of water-soluble amino acid (and related) prodrug salts of 3-amino-combretastatin (serinamide analogue referred to as AVE8062)[57,58] along with our later studies of 2-amino-combretastatin[10,29] and 2,3-diamino-combretastatin[30] serinamide salts.

2.2 Biological Evaluation

The batch of **KGP18** (prepared using the synthetic strategy described herein) along with ten new analogues (structures depicted in Fig. 2) incorporating functional group modifications were evaluated (Table 1) for their ability to inhibit tubulin assembly (cell free assay) and for their cytotoxicity against three human cancer cell lines (SK-OV-3, ovarian; NCI-H460, lung; and DU-145, prostate). As anticipated, the potent cytotoxicity (GI_{50} < 100 pM) observed for **KGP18** (compound **39**, bearing a 1-hydroxy group) in this study mirrors (within error-limits inherent to the assay) our previously reported data for **KGP18** (prepared by a separate synthetic methodology).[18] Replacement of the 1-hydroxy moiety with a fluorine atom resulted in a benzosuberene analogue **37** that was both strongly inhibitory against tubulin assembly (IC_{50} = 0.89 M) and potently cytotoxic (GI_{50} = 5.47 nM against NCI-H460 cells, for example). The chlorine atom congener **36** was equally active as an inhibitor of tubulin assembly and only slightly less cytotoxic. Fluorine atom substitution has been a productive strategy in certain structurally related combretastatin analogues.[59-60] An analogue of **KGP18** that replaced the pendant trimethoxyaryl ring with a dimethoxyaryl ring (compound **42**) was also active against tubulin assembly and as a cytotoxic agent (GI_{50} = 33.4 nM against SK-OV-3 cells). Other structural modifications (compounds **35**, **38**, **41**, and **43**) around the pendant aryl ring resulted in benzosuberene analogues that were inactive (IC_{50} > 40 M) as inhibitors of tubulin assembly and decidedly less cytotoxic (against these three cell lines) thus underscoring the limited structural variation that is tolerated in these molecules. Data for both combretastatin A-4 (CA4)[61] and our previously reported[19] 6-aminobenzosuberene analogue (**KGP156**, compound **45**) are included in Table 1 for comparative reference. The water-soluble phosphate prodrug salt of **KGP18**, referred to as **KGP265** (compound **44**) was inactive (IC_{50} > 40 M) against tubulin as anticipated in this cell-free assay (which is devoid of enzymes necessary to cleave the inactive prodrug to its active parent compound (**KGP18**)), however it was active in terms of cytotoxicity (GI_{50} = 9.51 nM against DU-145 cells, for example). It is well-established that human cancer cell lines have one or more phosphatase enzyme at their cell surface,[62] thus it was expected that the prodrug would be very effectively cleaved to yield the parent compound under these conditions. A water-soluble serinamide prodrug salt **48** of **KGP156** (compound **45**) proved to be inactive against tubulin assembly (as anticipated in this type of cell free assay) and also surprisingly inactive in terms of cytotoxicity. It is possible that either the level of requisite aminopeptidase enzymes secreted from these cells is not sufficient to cleave the prodrug construct, or that this particular benzosuberene prodrug (compound **48**) itself is not a good substrate for the enzyme, since other (structurally non-related) serinamide prodrug salts do show cytotoxicity in this type of assay[63] and some have been evaluated in the presence of exogenous peptidase enzymes to demonstrate enzyme-mediated hydrolysis with release of the parent amino-drug.[56,64] Further study is necessary in this regard. It is well documented throughout the literature[27,61] that the most active small-molecule inhibitors of tubulin assembly are typically in the low micromolar range (in terms of IC_{50}) while the same compounds demonstrate *in vitro* cytotoxicity with GI_{50} values in the nanomolar to sub-nanomolar range. This activity difference (cell-free tubulin assay versus cell-based *in vitro* cytotoxicity assay) can be attributed to several possible factors including stoichiometry (inhibitor to tubulin heterodimer ratio) differences between the cell-free assay and what takes place in cells, the cell-based release (during microtubule disassembly) of molecular

components (factors) that increase cytotoxicity through signal transduction pathways, and the practical lower limit inherent to this type of inhibition of tubulin assembly assay.[65]

3. Conclusion

In summary, we have prepared eleven new benzosuberene-based analogues through an extension of our previously reported synthetic methodology[19,20] directed towards these ring-fused systems. The most active compounds (in terms of inhibition of tubulin assembly and cytotoxicity against selected human cancer cell lines) feature fluorine atom (compound **37**) or chlorine atom (compound **36**) incorporation at position-1 of the fused aryl ring along with a dimethoxyaryl ring modification (compound **42**) of the trimethoxyaryl ring bearing-phenolic analogue **KGP18** (compound **39**). Thus the known SAR for benzosuberene derivatives of this type has been extended. The two water-soluble prodrug salts (**44** and **48**) should prove useful for future *in vivo* studies.

4. Experimental Section

4.1 Chemistry

4.1.1 Materials and instrumentation—Methylene chloride (CH_2Cl_2), acetonitrile, methanol (MeOH), ethanol (EtOH), dimethylformamide (DMF), and tetrahydrofuran (THF) were used in their anhydrous form as obtained from the chemical suppliers. Reactions were performed under an inert atmosphere using nitrogen gas unless specified. Thin-layer chromatography (TLC) plates (pre-coated glass plates with silica gel 60 F_{254}, 0.25 mm thickness) were used to monitor reactions. Reactions carried out under microwave irradiation were performed with a Biotage Initiator Microwave Synthesizer. Purification of intermediates and products was carried out with a Biotage Isolera 1 or 4 flash purification system using silica gel (200-400 mesh, 60 Å) or RP-18 prepacked columns. Intermediates and products synthesized were characterized on the basis of their ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), ^{31}P NMR (202 MHz), and ^{19}F NMR (470 MHz) spectroscopic data. All the chemical shifts are expressed in ppm (δ), coupling constants (J) are presented in Hz, and peak patterns are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), pentet (p), septet (sept), and multiplet (m). Mass spectrometry was carried out under positive ESI (electrospray ionization) using a Thermo scientific LTQ Orbitrap Discovery instrument. Purity of the final compounds was further analyzed at 25 °C using a Agilent 1200 HPLC system with a diode-array detector (= 190-400 nm), a Zorbax XDB-C18 HPLC column (4.6 mm × 150 mm, 5 μm), and a Zorbax reliance cartridge guard-column; eluents, solvent A: H_2O, solvent B: acetonitrile; gradient, 90%A / 10%B to 0%A / 100%B over 0 to 40 min; flow rate 1.0 mL/min; injection volume 20 μL; monitored at wavelengths of 254, 280 and 300 nm. Column volume is represented by CV.

Experimental Procedures for Final Compound 38

4.1.2. (Z)/(E)- 5-(2′,3′,4′-Trimethoxyphenyl)pent-4-enoic acid (6).[20]—To a well-stirred solution of (3-carboxypropyl)triphenylphosphonium bromide (24.06 g, 56.05 mmol) in THF (400 mL) was added K-O*t*Bu (12.30 g, 109.6 mmol). The reaction mixture was then cooled to 0 °C and stirred for 15 min. A solution of aldehyde **1** (9.84 g, 50.2 mmol) in THF (25 mL) was added dropwise and the reaction mixture was stirred and allowed to reach room temperature. The reaction mixture was diluted with H_2O (50 mL) and extracted with Et_2O (2 × 200 mL). The aqueous phase was acidified with 2 M HCl until the product precipitated making the solution cloudy and then becoming clear again. The acidified aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. Purification by flash chromatography using a prepacked 160 g silica column [solvent A: EtOAc; solvent B:

hexanes; gradient: 20%A / 80%B (1 CV), 20%A / 80%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] afforded the mixture of *E*/*Z*-isomers **6** (9.48 g, 35.6 mmol, 64%) as a pale yellow liquid. **^{1}H NMR** (Mixture of *E* and *Z*) ($CDCl_3$, 500 MHz): δ 7.11 (1H, d, *J* = 8.7 Hz, H-6′), 6.94 (1H, d, *J* = 8.6 Hz, H-6′), 6.65 (1H, d, *J* = 8.7 Hz, H-5′), 6.65 (1H, d, *J* = 8.6 Hz, H-5′), 6.64 (1H, d, *J* = 16.1 Hz, H-5), 6.52 (1H, dt, *J* = 11.5, 2 Hz, H-5), 6.11 (1H, m, H-4), 5.63 (1H, dt, *J* = 11.5, 7 Hz, H-4), 3.88-3.83 (3 × 3H, s, OCH_3-2′, -3′, -4′), 3.88-3.83 (3 × 3H, s, OCH_3-2′, -3′, -4′), 2.59 (2H, m, CH_2-2/3), 2.56-2.54 (4H, m, CH_2-2, -3), 2.47 (2H, m, CH_2-3/2). **^{13}C NMR** ($CDCl3_3$, 125 MHz) δ 178.9, 178.7, 152.9, 152.8, 151.7, 151.1, 142.3, 142.2, 129.5, 127.5, 125.4, 125.2, 124.4, 124.2, 123.9, 120.7, 107.7, 106.9, 61.1, 61.0, 60.95, 60.89, 56.0, 55.9, 34.0, 33.9, 28.3, 23.9.

4.1.3. 5-(2′,3′,4′-Trimethoxyphenyl)pentanoic acid (11).[20,66]—To a solution of **6** (9.15 g, 34.4 mmol) in MeOH (200 mL) was added 10% Pd-C. The flask was evacuated under vacuum and H_2 gas was introduced via balloon. The reaction was stirred for 24 h and checked for completion by filtering a small amount of the reaction mixture through Celite®, evaporating the solvent, and recording the ^{1}H NMR. On completion, the reaction mixture was filtered through Celite®, concentrated under reduced pressure, and the resulting pale yellow liquid was subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording **11** (8.76 g, 32.6 mmol, 95%) as a pale yellow liquid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.81 (1H, d, *J* = 8.5 Hz, H-6′), 6.60 (1H, d, *J* = 8.5 Hz, H-5'), 3.87 (3H, s, OCH_3-2′), 3.86 (3H, s, OCH_3-3′), 3.84 (6H, s, OCH_3-4′), 2.57 (2H, t, *J* = 7.5 Hz, H-5), 2.39 (2H, t, *J* = 7.3 Hz, H-2), 1.68 (2H, m, H-3), 1.61 (2H, m, H-4). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 179.9 (C=O, C-1), 152.0 (C, C-4′), 151.8 (C, C-2′), 142.3 (C, C-3′), 128.0 (C, C-1′), 123.7 (CH, C-6′), 107.2 (CH, C-5′), 60.9 (CH_3, OCH_3-2′), 60.7 (CH_3, OCH_3-3′), 56.0 (CH_3, OCH_3-4′), 33.9 (CH_2, C-2), 30.2 (CH_2, C-4), 29.3 (CH_2, C-5), 24.5 (CH_2, C-3).

4.1.4. 1,2,3-Trimethoxy-benzocycloheptan-5-one (16).[18,20,66]—Pentanoic acid **11** (2.68 g, 10 mmol) was dissolved in Eaton's reagent [40.2 mL, P_2O_5 (7.7 wt%) in methanesulfonic acid] and the reaction mixture was stirred for 12 h. The reaction mixture was poured over ice and the ice was allowed to melt. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extract was washed with saturated $NaHCO_3$ (2 × 200 mL). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure, subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording **16** (2.34 g, 9.34 mmol, 93%) as a pale yellow liquid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.13 (1H, s, H-4), 3.93 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-3), 3.84 (3H, s, OCH_3-1), 2.94 (2H, dd, *J* = 6.9, 5.2 Hz, H-9), 2.72 (2H, m, H-6), 1.83 (2H, m, H-8), 1.81 (2H, m, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 205.0 (C=O, C-5), 151.6 (C, C-3), 151.0 (C, C-1), 145.9 (C, C-2), 134.4 (C, C-10/11), 128.9 (C, C-10/11), 107.5 (CH, C-4), 61.4 (CH_3, OCH_3-1), 60.8 (CH_3, OCH_3-2), 56.0 (CH_3, OCH_3-3), 40.8 (CH_2, C-6), 25.0 (CH_2, C-8), 23.0 (CH_2, C-9), 20.9 (CH_2, C-7).

4.1.5. *[TMAH][Al$_2$Cl$_7$].*[52]—To a suspension of $AlCl_3$ (26.71 g, 101.4 mmol) in 200 mL CH_2Cl_2 cooled to 0 °C, trimethylammonium chloride [TMAH] (9.55 g, 50.7 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The transparent yellow solution of ionic liquid was used as such for the deprotection of methyl ethers of benzosuberones.

4.1.6. 2-Hydroxy-1,3-dimethoxy-benzocycloheptan-5-one (21).[20]—To a solution of **16** (5.30 g, 21.2 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C, [TMAH][Al_2Cl_7] (36.00 mL, 23.32 mmol, 1.93 M in CH_2Cl_2) was added dropwise. The reaction was monitored by TLC and upon completion, ice cold water was added to the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated, and subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm]; to afford phenol **21** (0.58 g, 2.45 mmol, 12%). NMR characterization took place after the TBS protection (see compound 23).

4.1.7. 2-[(tert-Butyldimethylsilyl)oxy]-1,3-dimethoxy-benzocycloheptan-5-one (23).[20]—To a solution of phenol **21** (0.58 g, 2.45 mmol) and DIPEA (2.00 mL, 11.5 mmol) in DMF (5 mL) at 0 °C was added TBSCl (0.82 g, 5.44 mmol) in portions. The reaction mixture was stirred for 6 h, diluted with H_2O (5 mL), and extracted with Et_2O (2 × 20 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 3%A / 97%B (1 CV), 3%A / 97%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford ketone **23** (0.82 g, 2.34 mmol, 94%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.03 (1H, s, H-4), 3.72 (3H, s, OCH_3-1/3), 3.65 (3H, s, OCH_3-1/3), 2.85 (2H, m, H-9), 2.61 (2H, m, H-6), 1.71 (4H, m, H-7, -8), 0.93 (9H, (CH_3)$_3$), , 0.07 (6H, Si(CH_3)$_2$. **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 204.8 (C, C-9), 149.9 (C, C-3), 149.3 (C, C-1), 142.6 (C, C-2), 131.9 (C, C-10/11), 129.4 (C, C-10/11), 40.8 (CH, C-8), 107.2 (CH, C-4), 60.8 (CH_3, OCH_3-2/3), 55.3 (CH_3, OCH_3-2/3), 25.7 (CH_3, (CH_3)$_3$), 25.1 (CH_2, C-8), , 23.1 (CH_2, C-9), 21.0 (CH_2, C-7), 18.7 (C, (C(CH$_3$)$_3$), -4.6 (CH_3, Si(CH_3)$_2$)

4.1.8. 2-[(tert-Butyldimethylsilyl)oxy]-1,3-dimethoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocycloheptan-5-ol (30).[20]—To a solution of 3,4,5-trimethoxyphenyl bromide (1.04 g, 4.21 mmol) in THF (50 mL) at −78 °C, *n*-BuLi (1.70 mL, 2.5 M) was added and the reaction mixture was stirred for 30 min. Ketone **23** (0.73 g, 2.08 mmol) in 5 mL THF was added using an addition funnel over a period of 15 min. The reaction mixture was stirred for 12 h and was allowed to warm to room temperature. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (2 × 25 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 15%A / 85%B (1 CV), 15%A / 85%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] resulting in alcohol **30** (0.80 g, 1.54 mmol, 74%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.92 (1H, s), 6.28 (2H, s), 3.70-3.48 (15H, m), 2.97 (1H, m), 2.48 (1H, m), 2.41 (1H, m), 1.98 (2H, m), 1.77 (2H, m), 1.58 (1H, m), 0.87 (9H, s), 0.00 (6H, s).

4.1.9. 1,3-Dimethoxy-2-hydroxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene (38).[20]—A solution of **30** (0.77 g, 10.6 mmol) in AcOH (20 mL) and H_2O (20 mL) was heated to reflux at 110 °C for 24 h. The reaction mixture was cooled and the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording benzosuberene **38** (0.49 g, 5.48 mmol, 52%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.50 (2H, s, H-2′, H-6′), 6.38 (1H, s, H-4), 6.37 (1H, t, *J* = 12.0 Hz, H-6), 5.62 (1H, s, O*H*-2), 3.92 (3H, s, OCH_3-1), 3.88 (3H, s, OCH_3-4′), 3.81 (6H, s, OCH_3-3′, -5′), 3.75 (3H,

s, OC*H*$_3$-1), 2.66 (2H, t, *J* = 7.0 Hz, H-9), 2.15 (2H, p, *J* = 7.1 Hz, H-8), 1.97 (2H, q, *J* = 7.2 Hz, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.1 (C, C-3′, C-5′), 145.4 (C, C-3), 144.6 (C, C-1), 143.0 (C, C-5), 138.2 (C, C-1′), 137.7 (C, C-2), 137.5 (C, C-4′), 131.7 (C, C-10), 128.4 (C, C-11), 127.8 (CH, C-4), 108.3 (CH, C-6), 105.3 (CH, C-2′, C-6′), 61.5 (CH_3, O*C*H_3-1), 61.1 (CH_3, O*C*H_3-4′), 56.5 (CH_3, O*C*H_3-3′, -5′), 56.3 (CH_3, O*C*H_3-3), 35.3 (CH_2, C-8), 25.8 (CH_2, C-7), 23.9 (CH_2, C-9). **Analysis:** Calculated for $C_{23}H_{26}O_6$, C 68.38, H 6.78, O 24.84. Found: C 68.22, H 6.85. **HRMS**: *m*/*z*: observed 409.1629 $[M + Na]^+$, calculated for $C_{22}H_{26}O_6Na^+$, 409.1622. **HPLC:** 14.68 min.

Experimental Procedures for Final Compounds 39 and 44

4.1.10. (Z)/(E)- 5-(2′,3′-Dimethoxyphenyl)pent-4-enoic acid (8).[20]—To a well-stirred solution of (3-carboxypropyl)triphenylphosphonium bromide (21.65 g, 50.43 mmol) in THF (500 mL) was added K-O*t*Bu (11.3 g, 101 mmol). The reaction mixture was then cooled to 0 °C and stirred for 15 min. A solution of aldehyde **3** (8.42 g, 50.7 mmol) in THF (60 mL) was added dropwise and the reaction mixture was allowed to reach room temperature. The reaction mixture was diluted with H_2O (50 mL) and extracted with Et_2O (2 × 200 mL). The aqueous phase was acidified with 2 M HCl until the product precipitated making the solution cloudy and then becoming clear again. This acidified aqueous phase was extracted with EtOAc (3 × 100 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure and subjected to flash chromatography using a prepacked 160 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 20%A / 80%B (1 CV), 20%A / 80%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording a mixture of *E*/*Z*-isomers **8** (6.98 g, 29.5 mmol, 58%) as a pale yellow oil. **^{1}H NMR** (*E*/*Z*-isomers) ($CDCl_3$, 500 MHz): δ 7.03-6.99 (3H, m), 6.85-6.74 (3H, m), 6.76 (1H, d, *J* = 15.9 Hz), 6.59 (1H, dt, *J* = 11.5, 1.5 Hz), 6.22 (1H, dt, *J* = 15.9, 6.0 Hz), 5.70 (1H, dt, *J* = 11.5, 7.5 Hz), 3.86 (3H, s), 3.85 (3H, s), 3.78 (3H, s), 3.76 (3H, s), 2.60-2.53 (6H, m), 2.46 (2H, m). **^{13}C NMR** (*E*/*Z*-isomers) ($CDCl_3$, 125 MHz): δ 179.14, 179.12, 153.0, 152.8, 146.9, 146.3, 131.5, 131.4, 130.7, 129.5, 125.7, 125.4, 124.0, 123.6, 121.9, 118.0, 111.3, 111.0, 60.8, 60.6, 55.8, 55.8, 34.0, 33.8, 28.3, 24.0.

4.1.11. *5-(2′,3′-Dimethoxyphenyl)pentanoic acid (13).*[20,67]—To a solution of **8** (6.78 g, 28.7 mmol) in MeOH (100 mL) was added 10% Pd-C (0.70 g). The flask was evacuated under vacuum and H_2 gas was introduced via balloon and the reaction mixture was stirred for 24 h. The reaction was monitored by filtering a small amount of the reaction mixture through Celite®, evaporating the solvent, and recording the ^{1}H NMR spectrum. Upon completion, the reaction mixture was filtered through Celite®, concentrated under reduced pressure and subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording compound **13** (6.71 g, 28.2 mmol, 98%) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.97 (1H, t, *J* = 8.6 Hz, H-5′), 6.76 (2H, d, *J* = 8.6 Hz, H-4′, -6′), 3.85 (3H, s, OC*H*$_3$-3′), 3.81 (3H, s, OC*H*$_3$-2′), 2.65 (2H, t, *J* = 7.0 Hz, H-2), 2.38 (2H t, *J* = 7.0, H-5), 1.67 (4H, m, H-3, -4). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 180.0 (C, C-1), 152.7 (C, C-3′), 147.1 (C, C-2′), 135.9 (C, C-1′), 123.8 (CH, C-5′), 121.9 (CH, C-6′), 110.2 (CH, C-4′), 60.6 (CH_3, O*C*H_3-2′), 55.7 (CH_3, O*C*H_3-3′), 34.0 (CH_2, C-5), 30.1 (CH_2, C-4), 29.3 (CH_2, C-2), 24.5 (CH_2, C-3). **HRMS:** *m*/*z*: observed 261.1100 $[M+Na]^+$, calculated for $C_{13}H_{18}O_4Na^+$, 261.1097. **HPLC:** 10.67 min.

4.1.12. *1,2-Dimethoxy-benzocycloheptan-5-one (18).*[20,68]—Pentanoic acid **13** (6.76 g, 28.4 mmol) was dissolved in Eaton's reagent [75 mL, P_2O_5 (7.7 wt%) in methanesulfonic acid] and stirred for 12 h. The reaction mixture was poured over ice and the ice was allowed

to melt. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the organic extract was washed with saturated $NaHCO_3$ (2 × 200 mL). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure and subjected to flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording compound **18** (5.39 g, 24.5 mmol, 86%) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.54 (1H, d, *J* = 8.5 Hz, H-4), 6.84 (1H, d, *J* = 8.5 Hz, H-3), 3.91 (3H, s, OC*H*$_3$-1), 3.80 (3H, s, OC*H*$_3$-2), 3.01 (2H, m, H-9), 2.70 (2H, m, H-6), 1.85 (2H, m, H-7), 1.81 (2H, m, H-8). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 205.0 (C=O, C-5), 156.1 (C, C-1), 145.9 (C, C-2), 135.7 (CH, C-10/11), 132.8 (C, C-10/11), 125.5 (CH, C-4), 109.7 (CH, C-3), 61.1 (CH_3, O*C*H$_3$-1/2), 55.8 (CH_3, O*C*H$_3$-1/2), 40.6 (CH_2, C-6), 24.9 (CH_2, C-7), 23.3 (CH_2, C-9), 20.9 (CH_2, C-8). **Analysis**: Calculated for $C_{13}H_{16}O_3$: C 70.89, H 7.32, O 21.79. Found: C 70.94, H 7.26. **HPLC**: 10.55 min.

4.1.13. 1-Hydroxy-2-methoxy-benzocycloheptan-5-one (22).[20,37,69]—To a solution of methyl aryl ether **18** (2.22 g, 10.1 mmol) in CH_2Cl_2 (5 mL) was added [TMAH][Al_2Cl_7] (13.00 mL, 1.93 M in CH_2Cl_2) and the reaction mixture was subjected to microwave irradiation at 80 °C for 1h. After the reaction was complete, water was added. The reaction mixture was stirred vigorously for 2 min and the organic layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording phenol **22** (1.59 g, 7.70 mmol, 77%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.34 (1H, d, *J* = 8.6 Hz, H-4), 6.79 (1H, d, *J* = 8.6 Hz, H-3), 5.79 (1H, s, O*H*), 3.94 (3H, s, OC*H*$_3$-2), 3.02 (2H, m, H-9), 2.71 (2H, t, *J* = 12.0 Hz, H-6), 1.85 (2H, m, H-8), 1.80 (2H, m, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 205.0 (C, C-5), 149.2 (C, C-2), 142.4 (C, C-1), 133.3 (C, C-10/11), 127.7 (C, C-10/11), 120.8 (CH, C-4), 107.9 (CH, C-3), 56.1 (CH_3, O*C*H$_3$-2), 40.8 (CH_2, C-6), 24.5 (CH_2, C-8), 23.1 (CH_2, C-9), 21.3 (CH_2, C-7). **Analysis:** Calculated for $C_{12}H_{14}O_3$: C 69.88, H 6.84. Found: C 69.93, H 6.86. **HPLC:** 7.08 min.

4.1.14. 1-[(tert-Butyldimethylsilyl)oxy]-2-methoxy-benzocycloheptan-5-one (24).[20]—To a solution of phenol **22** (6.36 g, 30.8 mmol) and DIPEA (5.75 g, 44.5 mmol) in DMF (25 mL) at 0 °C was added TBSCl (7.01 g, 46.5 mmol) in portions. The reaction mixture was stirred for 6 h and diluted with H_2O (50 mL). The reaction mixture was extracted with Et_2O (2 × 100 mL) and the organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 0%A / 100%B (1 CV), 0%A / 100%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording aldehyde **24** (9.80 g, 30.6 mmol, 99%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.38 (1H, d, *J* = 8.6 Hz, H-4), 6.78 (1H, d, *J* = 8.6 Hz, H-3), 3.84 (3H, s, OC*H*$_3$-2), 3.01 (2H, dd, *J* = 7.5, 5 Hz, H-9), 2.70 (2H, t, *J* = 12.0 Hz, H-6), 1.82 (2H, m, H-7), 1.80 (2H, m, H-8), 1.02 (9H, (*C*H$_3$)$_3$), 0.19 (6H, Si(*C*H$_3$)$_2$). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 205.3 (C, C-5), 153.2 (C, C-2), 141.8 (C, C-1), 133.10 (C, C-10/11), 133.08 (C, C-10/11), 122.3 (CH, C-4), 108.8 (CH, C-3), 54.8 (CH_3, O*C*H$_3$-2), 40.7 (CH_2, C-6), 26.1 (CH_3, (*C*H$_3$)$_3$), 24.7 (CH_2,C-7), 24.0 (CH_2,C-9), 21.2 (CH_2,C-8), 18.9 (C, (*C*(CH$_3$)$_3$), -3.90 (CH_3, Si(*C*H$_3$)$_2$). **Analysis**: Calculated for $C_{18}H_{28}O_3Si$: C 67.46, H 8.81. Found: C 67.70, H 8.82. **HPLC**: 20.96 min.

4.1.15. 1-[(tert-Butyldimethylsilyl)oxy]-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocycloheptan-5-ol (31).[20]—To a solution 3,4,5-trimethoxyphenyl bromide (16.8 g, 68.0 mmol) in THF (400 mL) at -78 °C was added *n*-BuLi (27.2 mL, 2.5 M in hexanes) and the reaction mixture was stirred for 30 min. Benzosuberone **24** (9.80 g, 30.6 mmol) in 25 mL THF was added using an addition funnel over a period of 15 min. The reaction mixture was allowed to warm to room temperature over 12 h. Upon completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (2 × 100 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 15%A / 85%B (10 CV), 15%A / 85%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording alcohol **31** (11.6 g, 17.4 mmol, 57%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.16 (1H, d, J = 8.7 Hz), 6.70 (1H, d, J = 8.7 Hz), 6.50 (2H, s), 3.84 (3H, s), 3.80 (3H, s), 3.75 (6H, s), 3.37 – 3.23 (1H, m), 2.62 – 2.49 (1H, m), 2.30 – 2.22 (1H, m), 2.18 – 2.05 (1H, m), 1.99 – 1.85 (1H, m), 1.83 – 1.65 (2H, m), 1.47 – 1.34 (1H, m), 0.99 (9H, s), 0.17 (3H, s), 0.15 (3H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 152.4, 148.6, 145.2, 141.5, 136.5, 135.1, 130.0, 121.3, 109.4, 104.0, 75.5, 60.8, 56.1, 54.7, 41.0, 26.2, 24.8, 19.2, 19.0, -3.6, -3.8.

4.1.16. 1-Hydroxy-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene (39).[18,20,44]—A solution of **31** (11.6 g, 10.6 mmol) in AcOH (150 mL) and H_2O (100 mL) was heated to reflux at 110 °C for 12 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and subjected to flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 15%A / 85%B (10 CV), 15%A / 85%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording benzosuberene **39** (6.20 g, 17.4 mmol, 57%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.71 (1H, d, *J* = 8.6 Hz, H-3), 6.57 (1H, d, *J* = 8.6 Hz, H-4), 6.50 (2H, s, H-2′, H-6′), 6.33 (1H, t, *J* = 7.0 Hz, H-6), 5.74 (1H, s, OH), 3.91 (3H, s, OC*H*$_3$-2), 3.86 (3H, s, OC*H*$_3$-4), 3.80 (6H, s, OC*H*$_3$-3′, -5′), 2.76 (2H, t, *J* = 7.0 Hz, H-9), 2.14 (2H, p, *J* = 7.0 Hz, H-8), 1.96 (2H, q, *J* = 7.0 Hz, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.0 (C, C-3′, C-5′), 145.2 (C, C-2), 142.9 (C, C-1), 142.5 (C, C-5), 138.6 (C, C-1′), 137.4 (C, C-4′), 134.4 (C, C-10/11), 127.9 (C, C-10/11), 127.3 (CH, C-6), 121.0 (CH, C-4), 107.8 (CH, C-3), 105.4 (CH, C-2′, C-6′), 61.1 (CH_3, O*C*H$_3$-4′), 56.3 (CH_3, O*C*H$_3$-3′, -5′), 56.1 (CH_3, O*C*H$_3$-2), 33.7 (CH_2, C-8), 25.8 (CH_2, C-7), 23.7 (CH_2, C-9). **Analysis**: Calculated for $C_{21}H_{24}O_5$: C 70.77, H 6.79, O 22.45. Found: C 71.05, H 6.77. **HRMS:** *m/z:* observed 379.1565 $[M+Na]^+$, calculated for $C_{21}H_{24}O_5Na^+$, 379.1516. **HPLC:** 15.59 min.

4.1.17. Disodium 2-Methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene-1-phosphate (44).[20]—To a solution of **39** (0.32 g, 0.83 mmol) in CH_2Cl_2 was added $POCl_3$ (0.3 mL, 3.3 mmol) and pyridine (0.25 mL, 3.01 mmol) and the reaction mixture was stirred for 8 h. NaOH (5 mL, 2M) was added dropwise to the reaction mixture and the reaction was stirred for 5 min. The reaction mixture was extracted with CH_2Cl_2 (2 × 25 mL) and concentrated under reduced pressure. NaOH (5 mL, 2 M) was added to the viscous liquid obtained and the solution was stirred at 60 °C for 15 min. The aqueous phase was concentrated under reduced pressure and subjected to flash chromatography using a prepacked 25 g RP-18 silica column [solvent A: water; solvent B: CH_3CN; gradient: 100%A / 0%B (1 CV), 100%A / 0%B → 60%A / 40%B (10 CV), 0%A / 100%B (3 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording **44** (0.245 g, 0.478 mmol, 58%) as white solid. **^{1}H NMR** (D_2O, 500 MHz) δ 6.85 (1H, d, J = 8.5 Hz), 6.70 (3H, d, J = 8.5 Hz), 6.66 (2H, s), 6.46 (1H, t, J = 7.3 Hz), 3.84 (3H, s), 3.80 (6H, s), 3.77 (3H, s), 2.85 (2H, t, *J* = 10 Hz), 2.16 (2H, m), 1.92 (2H, q, J = 7.2 Hz). **^{13}C NMR** (D_2O, 125 MHz): δ

152.1 (C, C-3′, C-5′), 151.0 (C, C-2), 141.8 (C, C-5), 140.5 (C, C-1), 139.4 (C, C-1′), 136.5 (C, C-10/11), 135.9 (C, C-4′), 133.4 (C, C-10/11), 128.7 (CH, C-6), 124.1 (CH, C-4), 109.4 (CH, C-3), 105.5 (CH, C-2′, C-6′), 60.9 (CH_3, OCH_3-4′), 55.9 (CH_3, OCH_3-3′, -5′), 55.5 (CH_3, OCH_3-2), 33.3 (CH_2, C-8), 25.1 (CH_2, C-7), 24.6 (CH_2, C-9). **^{31}P NMR** (D_2O, 202 MHz): δ 2.95. **HRMS**: *m/z:* observed 481.0999 $[M+H]^+$, calculated for $C_{21}H_{24}O_8Na_2P^+$, 481.0999. **HPLC:** 3.66 min.

Experimental Procedures for Final Compound 43

4.1.18. (Z)/(E)-5-(3′,4′-Dimethoxy-2′-(tosyloxy)phenyl)pent-4-enoic acid (7).[20]— To a well-stirred solution of (3-carboxypropyl)triphenylphosphonium bromide (3.82 g, 8.90 mmol) in THF (200 mL) at −50 °C was added *n*-BuLi (5.4 mL, 2.5 M in hexanes). The reaction mixture was allowed to warm to room temperature and stirred for 15 min and then cooled to −78 °C. Aldehyde **2** (2.01 g, 5.97 mmol) dissolved in THF (15 mL) was added dropwise and the reaction mixture was allowed to reach room temperature. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3 × 200 mL). The organic extract was washed with brine, dried with $MgSO_4$, concentrated under reduced pressure, and subjected to flash chromatography [silica gel, 40% EtOAc, 60% Hexanes] to obtain a mixture of *E/Z*-isomers **7** (1.03 g, 2.53 mmol, 42%) as an off-white solid. **^{1}H NMR** (Mixture of *E* and *Z*) ($CDCl_3$, 500 MHz): δ 7.89 (2H, d, *J* = 8.2 Hz, H-2″, -6″), 7.87 (2H, d, *J* = 8.2 Hz, H-2″, -6″), 7.35 (2H, d, *J* = 8.2 Hz, H-3″, -5″), 7.32 (2H, d, *J* = 8.2 Hz, H-3″, -5″), 7.16 (1H, d, *J* = 8.8 Hz, H-5′/6′), 6.96 (1H, d, *J* = 8.6 Hz, H-5′/6′), 6.81 (1H, d, *J* = 8.6 Hz, H-5′/6′), 6.79 (1H, d, *J* = 8.8 Hz, H-5′/6′), 6.35 (1H, d, *J* = 16.0 Hz, H-5), 6.35 (1H, d, *J* = 11.0 Hz, H-5), 6.04 (1H, dt, *J* = 15.8, 6.3 Hz, H-4), 5.55 (1H, dt, *J* = 11.5, 6.9 Hz, H-4), 3.88-3.83 (2 × 3H, s, OC*H*$_3$-3′, -4′), 3.88-3.83 (2 × 3H, s, OC*H*$_3$-3′, -4′), 2.59 (2H, m, H-2/3), 2.56-2.54 (4H, m, H-2, -3), 2.47 (2H, m, H-2/3), 2.46 (6H, s, CH_3-4″). **^{13}C NMR** δ 178.1, 178.0, 152.74, 152.72, 144.9, 144.8, 142.5, 141.6, 141.0, 134.6, 134.58, 131.1, 129.5, 129.4, 128.9, 128.34, 128.30, 125.3, 125.0, 124.7, 124.4, 124.2, 120.3, 111.1, 110.46, 110.42, 60.71, 60.70, 56.2, 56.1, 33.6, 33.3, 27.9, 23.8, 21.7, 21.68. **HRMS**: *m/z*: observed 429.0977 $[M+Na]^+$, calculated for $C_{20}H_{22}O_7NaS^+$, 429.0978. **HPLC**: 13.53 min.

4.1.19. 5-(3′,4′-Dimethoxy-2′-(tosyloxy)phenyl)pentanoic acid (12).[20]— To a solution of pentanoic acid **7** (1.25 g, 20.2 mmol) in MeOH (40 mL) and EtOH (15 mL) was added 10% Pd-C (400 mg). The flask was evacuated and H_2 gas was introduced via balloons. The reaction mixture was stirred for 12 h and was checked for completion by filtering a small amount of the reaction mixture through Celite®, concentrating under reduced pressure, and recording the ^{1}H NMR spectrum. Upon completion, the reaction mixture was filtered through Celite® and concentrated under reduced pressure to obtain **12** (0.94 g, 2.3 mmol, 75%) as an off-white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.93 (2H, d, *J* = 8.2 Hz, H-2″, -6″), 7.35 (2H, d, *J* = 8.2 Hz, H-3″, -5″), 6.89 (1H, d, *J* = 8.6 Hz, H-6′), 6.77 (1H, d, *J* = 8.6 Hz, H-5′), 3.82 (3H, s, OC*H*$_3$-4′), 3.51 (3H, s, OC*H*$_3$-3′), 2.58 (2H, m, H-5), 2.46 (3H, s, C*H*$_3$-4″), 2.34 (2H, m, H-2), 1.61 (4H, m, H-3,-4). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 179.0 (C, C-1), 151.8 (C, C-4′), 144.7 (C, C-4″), 142.3 (C, C-2′), 142.1 (C, C-3′), 134.9 (C, C-1″), 129.5 (CH, C-3″,-5″), 129.0 (C, C-1′), 128.1 (C, C-2″,-6″), 123.9 (CH, C-6′), 110.8 (CH, C-5′), 60.5 (CH_3, OCH_3-3′), 56.1 (CH_3, OCH_3-4′), 33.7 (CH_2, C-2), 29.6 (CH_2, C-5), 29.5 (CH_2, C-4), 24.4 (CH_2, C-3), 21.7 (CH_3, *C*H_3-4″).

4.1.20. 1-Tosyloxy-2,3-dimethoxy-benzocycloheptan-5-one (17).[20]— Pentanoic acid **12** (0.90 g, 2.2 mmol) was dissolved in Eaton's reagent [14 mL, P_2O_5 (7.7 wt%) in methanesulfonic acid] and the solution was stirred for 12 h. The reaction mixture was poured over ice and the ice was allowed to melt. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and $NaHCO_3$ powder was added in small amounts until neutralized. The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under

reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 25%A / 75%B (1 CV), 25%A / 75%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording **17,** (0.70 g, 1.8 mmol, 81%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.93 (2H, d, *J* = 8.0 Hz, H-2′, -6′), 7.37 (2H, d, *J* = 8.0 Hz, H-3′, -5′), 7.29 (1H, s, H-4), 3.87 (3H, s, OC*H*$_3$-2), 3.58 (3H, s, OCH_3-3), 2.95 (2H, dd, *J* = 6.9, 4.9 Hz, H-9), 2.73 (3H, m, H-6), 2.48 (3H, s, C*H*$_3$-4″), 1.84 (2H, m, H-8), 1.81 (2H, m, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 204.0 (C, C-5), 151.3 (C, C-3), 145.4 (C, C-2), 145.0 (C, C-4′), 141.2 (C, C-1), 134.32 (C, C-10/11), 134.28 (CH, C-1′), 129.9 (C, C-10/11), 129.5 (CH, C-3′,-5′), 128.2 (CH, C-2′,-6′), 110.9 (CH, C-4), 60.5 (CH_3, O*C*H$_3$-3), 56.0 (CH_3, O*C*H$_3$-2), 40.7 (CH_2, C-6), 24.7 (CH_2, C-8), 24.5 (CH_2, C-9), 21.7 (CH_3, *C*H$_3$-4′), 20.8 (CH_2, C-7).

4.1.21. 1-Tosyloxy-2,3-dimethoxy-5-(3′,4′,5′-trimethoxyphenyl-benzocycloheptan-5-ol(26).[20]—To a solution of 3,4,5-triemethoxyphenyl bromide (0.85 g, 3.4 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (1.4 mL, 2.5 M in hexanes) and the reaction mixture was stirred for 30 min. Benzosuberone **17** (0.67 g, 1.7 mmol) in THF (15 mL) was added using an addition funnel over a period of 15 min. The reaction mixture was allowed to reach room temperature over 12 h. Upon completion, the reaction mixture was extracted with Et_2O (150 mL) and EtOAc (15 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 25%A / 75%B (1 CV), 25%A / 75%B → 80%A / 20%B (10 CV), 80%A / 20%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] afforded alcohol **26** (0.61 g, 1.1 mmol, 64%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.91 (2H, d, *J* = 8.3 Hz, H-2″, -6″), 7.37 (1H, s, H-4), 7.35 (2H, d, *J* = 8.3 Hz, H-3″, -5″), 6.46 (2H, s, H-2′, H-6′), 3.844 (3H, s, OC*H*$_3$-4′), 3.840 (3H, s, OC*H*$_3$-3), 3.78 (6H, s, OC*H*$_3$-3′, -5′), 3.54 (3H, s, OC*H*$_3$-2), 3.12 (1H, m, H-9), 2.62 (1H, m, H-6), 2.46 (3H, s, C*H*$_3$-4″), 2.23 (1H, m, H-9), 2.13 (1H, m, H-6), 1.88 (1H, s, H-7/8), 1.72 (3H, m, H-7/8). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.2 (C, C-3′, C-5′), 150.5 (C, C-3), 144.7 (C, C-4″), 141.7 (C, C-1), 141.4 (C, C-10/11), 140.7 (C, C-2), 139.9 (C, C-1′), 137.5 (CH, C-4′), 134.7 (C, C-1″), 129.4 (C, C-3″, C-5″), 128.4 (C, C-10/11), 128.1 (C, C-2″, C-6″), 110.2 (CH, C-4), 104.2 (CH, C-2′, C-6′), 80.2 (C, C-5), 60.8 (CH_3, O*C*H$_3$-4′), 60.5 (CH_3, O*C*H$_3$-2), 56.2 (CH_3, O*C*H$_3$-3′, -5′), 56.0 (CH_3, O*C*H$_3$-3), 41.1 (CH_2, C-6), 26.7 (CH_2, C-7/8), 26.6 (CH_2, C-9), 26.3 (CH_2, C-7/8), 21.7 (CH_3, *C*H$_3$-4″).

4.1.22. 1-Tosyloxy-2,3-dimethoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene (34).[20]—Alcohol **26** (0.54 g, 0.97 mmol) was dissolved in AcOH (20 mL) and H_2O (30 mL) and was heated to reflux at 180 °C for 12 h. The reaction mixture was cooled, concentrated under reduced pressure, subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 15%A / 85%B (1 CV), 15%A / 85%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording benzosuberene **34** (0.41 g, 0.75 mmol, 78%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.99 (2H, d, *J* = 8.3 Hz, H-2″, -6″), 7.37 (2H, d, *J* = 8.3 Hz, H-3″, -5″), 6.54 (1H, s, H-4), 6.48 (2H, s, H-2′, H-6′), 6.44 (1H, t, *J* = 7.4 Hz, H-6), 3.87 (3H, s, OC*H*$_3$-4′), 3.82 (6H, s, OC*H*$_3$-3′, -5′), 3.69 (3H, s, OC*H*$_3$-3), 3.54 (3H, s, OC*H*$_3$-2), 2.71 (2H, t, *J* = 6.5 Hz, H-9), 2.48 (3H, s, C*H*$_3$-4″), 2.21 (2H, p, *J* = 7.0 Hz, H-8), 1.99 (2H, q, *J* = 7.1 Hz, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.0 (C, C-3′, C-5′), 151.0 (C, C-3), 144.7 (C, C-4″), 141.9 (C, C-5), 141.6 (C, C-1), 140.8 (C, C-2), 137.6 (C, C-1′), 137.5 (C, C-4′), 136.1 (C, C-10/11), 134.8 (C, C-1″), 129.6 (C, C-10/11), 129.5 (CH, C-3″, C-5″), 129.4 (CH, C-6), 128.2 (CH, C-2″, C-6″), 112.0 (CH, C-4), 105.2 (CH,

C-2′, C-6′), 60.94 (CH_3, O*C*H_3-4′), 60.93 (CH_3, O*C*H_3-2), 60.5 (CH_3, O*C*H_3-3′, -5′), 56.2 (CH_3, O*C*H_3-3) 34.6 (CH_2, C-8), 25.5 (CH_2, C-7), 25.1 (CH_2, C-9), 21.7 (CH_3, *C*H_3-4″).

4.1.23. 1-Hydroxy-2,3-dimethoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene (43).[20]—A solution of sulfonate ester **34** (0.250 g, 0.462 mmol) dissolved in NaOH (1 mL, 2 M) and methanol (4 mL) in a 5 mL microwave safe sealed vial was subjected to microwaved irradiation at 100 °C for 1h. Upon completion, the reaction mixture was neutralized (1 mL, 2 M HCl), concentrated under reduced pressure, and subjected to flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 0%A / 100%B (1 CV), 0%A / 100% B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording phenol **43** (0.15 g, 0.388 mmol, 84%) as an off-white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.50 (2H, s, H-2′, H-6′), 6.39 (1H, t, *J* = 7.4 Hz, H-6), 6.18 (1H, s, H-4), 5.94 (1H, s, O*H*-1), 3.95 (3H, s, OC*H*$_3$-2), 3.86 (3H, s, OC*H*$_3$-4′), 3.81 (6H, s, OC*H*$_3$-3′, -5′), 3.70 (3H, s, OC*H*$_3$-3), 2.67 (2H, t, *J* = 6.9 Hz, H-9), 2.13 (2H, p, *J* = 6.9 Hz, H-8), 1.96 (2H, q, *J* = 7.1 Hz, H-7). **^{13}C NMR** (CDCl3, 125 MHz): δ 153.0 (C, C-3′, C-5′), 149.8 (C, C-3), 146.3 (C, C-1), 142.8 (C, C-5), 138.1(C, C-1′), 137.5 (C, C-4′), 136.3 (C, C-10/11), 134.3 (C, C-2), 128.5 (CH, C-6), 121.4 (C, C-10/11), 105.3 (CH, C-2′, C-6′), 105.1 (CH, C-4), 61.08 (CH_3, O*C*H_3-2), 61.06 (CH_3, O*C*H_3-4′), 56.3 (CH_3, O*C*H_3-3′, -5′), 56.1 (CH_3, O*C*H_3-3), 34.3 (CH_2, C-8), 25.8 (CH_2, C-7), 23.4 (CH_2, C-9). **HRMS**: *m/z*: observed 387.1807 $[M+H]^+$, calculated for $C_{22}H_{27}O^+_6$, 387.1802. **HPLC**: 15.16 min.

Experimental Procedures for Final Compound 37

4.1.24. (E)/(Z) 5-(2′-Fluoro-3′-methoxyphenyl)pent-4-enoic acid (10).[20]—To a well stirred solution of (3-carboxypropyl)triphenylphosphonium bromide (17.2 g, 40.1 mmol) in THF (250mL) was added K-O*t*Bu (8.96 g, 79.9 mmol). The reaction mixture was then cooled to 0 °C and stirred for 15 min. A solution of 2-fluoro-3-methoxybenzaldehyde (3.08 g, 20.0 mmol) in THF (25mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with Et_2O (2 × 250 mL) and the aqueous phase was acidified with 2 M HCl until the product precipitated making the solution cloud and then becoming clear again. The acidified aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, affording a mixture of the *E/Z* isomers **10** (4.14 g, 18.5 mmol, crude yield 92%) as a colorless liquid. The crude product was used in the next step without purification.

4.1.25. 5-(1′-Fluoro-2′-methoxyphenyl)pentanoic acid (15).[20]—To a solution of pentanoic acid **10** (1.25 g, 20.2 mmol) in EtOH (15 mL) was added 10% Pd-C (400 mg). The flask was evacuated and H_2 gas was introduced via balloon. The reaction mixture was stirred for 12 h and checked for completion by filtering a small amount of the reaction mixture through Celite®, concentrating under reduced pressure and recording the ^{1}H NMR spectrum. Upon completion, the reaction mixture was filtered through Celite® and concentrated under reduced pressure to obtain **15** (0.94 g, 2.3 mmol, 75%), as an off-white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.99 (1H, t, *J* = 8.2 Hz, H-4′), 6.82 (1H, t, *J* = 8.2 Hz, H-3′), 6.76 (1H, t, *J* = 8.6 Hz, H-5′), 3.88 (3H, s, OCH_3-2′), 2.68 (2H, t, *J* = 6 Hz, H-5), 2.39 (2H, t, *J* = 7 Hz, H-2), 1.69 (4H, m, H-3,-4).**^{13}C NMR** ($CDCl_3$,125 MHz): δ 179.8 (C, C-1), 150.8 (C*F*, d, *J* = 243.7 Hz, C-1′), 147.7 (C, d, *J* = 11.2 Hz, C-2′), 129.7 (CH, d, *J* = 13.5 Hz, C-6′), 123.5 (CH, d, *J* = 4.6 Hz, C-5′/3′), 121.9 (CH, d, *J* = 4.0 Hz, C-5′/3′), 110.9 (C, d, *J* = 1.7 Hz, C-4′), 56.2 (CH_3, O*C*H_3-2′), 33.8 (CH_2, C-2), 29.4 (CH C-3/4), 28.5 (CH_2, C-5), 24.2 (CH_2, C-4/3). **^{19}F NMR** ($CDCl_3$, 470 MHz): δ -141.9 (m). **Analysis**: Calculated for $C_{12}H_{15}FO_3$, C 63.70, H 6.68. Found: C 63.77, H 6.70.

4.1.26. *1-Fluoro-2-methoxy-benzocycloheptan-5-one (20).*[20]—Pentanoic acid **15** (0.90 g, 2.2 mmol) was dissolved in Eaton's reagent [14 mL, P_2O_5 (7.7 wt%) in methanesulfonic acid] and the solution was stirred for 12 h. The reaction mixture was poured over ice and the ice was allowed to melt. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and $NaHCO_3$ powder was added in small amounts until neutralized. The organic extract washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 25%A / 75%B (1 CV), 25%A / 75%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording **20** (0.70 g, 1.8 mmol, 81%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.57 (1H, dd, *J* = 8.7, 1.7 Hz, H-4), 6.88 (1H, t, *J* = 8.3, Hz, H-3), 3.93 (3H, s, OC*H*$_3$-2), 3.00 (2H, m, H-9), 2.72 (2H, m, H-6), 1.87 (2H, m, H-8), 1.82 (2H, m, H-7). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6 (C, d, *J* = 2.4 Hz, C-5), 150.9 (C, d, *J* = 12.4 Hz, C-2), 149.2 (C*F*, d, *J* = 243.3 Hz, C-1), 132.4 (CH, d, *J* = 1.3 Hz, C-4), 129.6 (C, d, *J* = 13.8 Hz, C-10/11), 125.0 (C, d, *J* = 4.2 Hz, C-10/11), 110.2 (CH, d, *J* = 2.1 Hz, C-3), 56.2 (CH_3, O*C*H$_3$-2) , 40.6 (CH_2, C-6) , 24.4 (CH_2, C-8) , 22.4 (CH_2, d, *J* = 5.8 Hz, C-9), 20.9 (CH_2, C-7) . **^{19}F NMR** ($CDCl_3$, 470 MHz): δ -140.8 (m). **Analysis**: Calculated for $C_{12}H_{13}FO_2$, C 69.22, H 6.29. Found: C 69.00, H 6.30. **HRMS**: *m/z*: observed 209.0974 [M +H]$^+$, calculated for $C_{12}H_{14}O_2F^+$, 209.0972. **HPLC**: 12.57 min.

4.1.27. 1-Fluoro-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocycloheptan-5-ol (29).[20]—To a solution of 3,4,5-trimethoxyphenyl bromide (0.85 g, 3.4 mmol) in THF (100 mL) at -78 °C was added *n*-BuLi (1.4 mL, 2.5 M in hexanes) and the reaction mixture was stirred for 30 min. Benzosuberone **20** (0.67 g, 1.7 mmol) in THF (15 mL) was added using an addition funnel over a period of 15 min. The reaction mixture was allowed to reach room temperature over 12 h. Upon completion, the reaction mixture extracted with Et_2O (150 mL) and EtOAc (15 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 25%A / 75%B (1 CV), 25%A / 75%B → 80%A / 20%B (10 CV), 80%A / 20%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording alcohol **29** (0.61 g, 1.1 mmol, 64%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.27 (1H, d, *J* = 8.8 Hz, H-4), 6.79 (1H, t, *J* = 8.7 Hz, H-3), 6.48 (2H, s, H-2′, H-6′), 3.90 (3H, s, OC*H*$_3$-2), 3.85 (3H, s, OC*H*$_3$-4′), 3.76 (6H, s, OC*H*$_3$-3′, -5′), 3.16 (1H, m, H-9), 2.37 (1H, m, H-9), 2.57 (1H, m, H-8), 2.11 (1H, m, H-8), 1.94 (1H, s, H-6), 1.77 (2H, m, H-6, -7), 1.49 (1H, m, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.1 (C, C-3′, C-5′), 149.6 (C*F*, d, *J* = 240.7 Hz, C-1), 146.7 (C, d, *J* = 13.4 Hz, C-2), 141.1 (C, C-1′), 138.8 (C, C-4′), 137.4 (CH, C-4), 129.1 (C, d, *J* = 12.7 Hz, C-10/11), 122.1 (C, d, *J* = 4.1 Hz, C-10/11), 109.4 (C, d, *J* = 2.36 Hz C-3), 104.2 (CH, C-2′, C-6′), 79.8 (C, d, *J* = 1.9 Hz, C-5), 60.8 (CH_3, O*C*H$_3$-4′), 56.1 (CH_3, O*C*H$_3$-3′, -5′), 56.0 (CH_3, O*C*H$_3$-2), 41.2 (CH, C-6), 26.6 (CH_2, *C*H$_2$-8/7), 26.2 (CH_2, *C*H$_2$-7/8), 24.2 (CH_2, d, *J* = 7.8 Hz, *C*H$_2$-9). **^{19}F NMR** ($CDCl_3$, 470 MHz): δ -139.9 (m). **Analysis**: Calculated for $C_{21}H_{25}FO_5$, C 67.01, H 6.69. Found: C 67.11, H 6.66.

4.1.28. 1-Fluoro-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocyclohept-5-ene (37).[20]—A solution of alcohol **29** (1.27 g, 0.97 mmol) in AcOH (20 mL) and H_2O (30 mL) was heated to reflux at 150 °C for 12 h. The reaction mixture was cooled, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording benzosuberene **37** (1.07 g, 0.75 mmol, 78%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.81-6.77 (2H, m, H-3, H-4), 6.47 (2H, s, H-2′, H-6′), 6.36 (1H, t, *J* = 7.4 Hz, H-6), 3.91 (3H, s, OC*H*$_3$-2), 3.86 (3H, s, OC*H*$_3$-4′), 3.80 (6H, s,

OCH_3-3′, -5′), 2.74 (2H, td, *J* = 2.2, 7.0 Hz, H-9), 2.16 (2H, p, *J* = 7.1 Hz, H-8), 1.97 (2H, q, *J* = 7.2 Hz, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.0 (C, C-3′, C-5′), 149.6 (C, d, *J* = 242.1 Hz, C-1), 146.4 (C, d, *J* = 12.1 Hz, C-2), 142.2 (C, d, *J* = 2.0 Hz, C-5), 138.1 (C, C-1′), 137.6 (C, C-4′), 134.0 (C, d, *J* = 3.30 Hz, C-10/11), 129.6 (C, d, *J* = 13.83 Hz, C-10/11), 127.8 (CH, C-6), 124.9 (CH, d, *J* = 3.90 Hz, C-3), 110.1 (CH, d, *J* = 2.00 Hz, C-4), 105.3 (CH, C-2′, C-6′), 60.9 (CH_3, O*C*H_3-4′), 56.3 (CH_3, O*C*H_3-3′, -5′,-2), 33.8 (CH_2, C-8), 25.7 (CH_2, C-7), 23.3 (CH_2, d, *J* = 4.37 Hz, C-9). **^{19}F NMR** ($CDCl_3$, 470 MHz): δ -142.4 (m). **HRMS**: *m/z*: observed 381.1474 $[M + Na]^+$, calculated for $C_{21}H_{23}O_4FNa^+$, 381.1473. **HPLC**: 18.20 min.

Experimental Procedures for Final Compound 36

4.1.29. (E)/(Z) 5-(2′-Chloro-3′-methoxyphenyl)pent-4-enoic acid (9).[20]—To a well stirred solution of (3-carboxypropyl)triphenylphosphonium bromide (13.1g, 30.5 mmol) in THF (250 mL) was added K-O*t*Bu (6.99, 62.3 mmol). The reaction mixture was then cooled to 0° C and stirred for 15 min. A solution of 2-fluoro-3-methoxybenzaldehyde **5** (3.44 g, 20.2 mmol) in THF (25 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. H_2O (50 mL) was added and the reaction mixture was extracted with Et_2O (2 × 250 mL). The aqueous phase was acidified with 2 M HCl until the product precipitated making the solution cloudy, and then becoming clear again. The acidified aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure affording a crude mixture of the *E/Z* isomers **9** (4.80 g, 19.9 mmol, crude yield 98%) as a colorless liquid. The crude product was used in the next step without further purification.

4.1.30. 5-(1′-Chloro-2′-methoxyphenyl)pentanoic acid (14).[20]—To pentanoic acid **9** (4.87 g, 20.2 mmol) in EtOH (50 mL) was added 10% Pd-C (729 mg). The flask was evacuated and H_2 gas was introduced via balloons. The reaction was monitored for completion by filtering a small amount of the reaction mixture through Celite®, concentrating under reduced pressure, and recording the ^{1}H NMR spectrum. Upon completion, the reaction mixture was filtered through Celite® and concentrated under reduced pressure to obtain **14** (2.55 g, 2.3 mmol, 75%) as an off-white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.14 (1H, t, *J* = 8.2, 7.7 Hz, H-4′), 6.84 (1H, d, *J* = 7.7 Hz, H-5′), 6.79 (1H, d, *J* = 8.2 Hz, H-3′), 3.89 (3H, s, OCH_3-2′), 2.77 (2H, m, H-5), 2.40 (2H, t, *J* = 7.5 Hz, H-2), 1.70 (4H, m, H-3, -4). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 179.3 (C, C-1), 155.2 (C, C-2′), 141.3 (C, C-6′), 126.8 (CH, C-4′), 122.2 (C, C-1′), 122.16 (CH, C-5′), 109.6 (C, C-3′), 56.2 (CH_3, O*C*H_3-2′), 33.8 (CH_2, C-2), 33.3 (CH_2, C-5), 29.0 (CH_2, C-3/4), 24.4 (CH_2, C-4/3). **Analysis**: Calculated for $C_{12}H_{15}ClO_3$: C 59.39, H 6.23. Found: C 59.57, H 6.23. **HRMS**: *m/z*: observed 265.0603 $[M+Na]^+$, calculated for $C_{12}H_{15}O_3ClNa^+$, 265.0602. **HPLC**: 11.99 min.

4.1.31. *1-Chloro-2-methoxy-benzocycloheptan-5-one (19).[20]*—Pentanoic acid **14** (2.50 g, 10.3 mmol) was dissolved in Eaton's reagent (55 mL) and the solution was stirred for 12 h. The reaction mixture was poured over ice and the ice was allowed to melt. The aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL) and $NaHCO_3$ powder was added in small amounts until neutralized. The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording **19** (2.23 g, 9.93 mmol, 96%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.61 (1H, d, *J* = 8.7 Hz, H-4), 6.86 (1H, d, *J* = 8.7, Hz, H-3), 3.95 (3H, s, OCH_3-2), 3.14 (2H, m, H-9), 2.69 (2H, m, H-6), 1.86 (2H, m, H-8), 1.78 (2H, m, H-7). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 204.7

(C, C-5), 157.9 (C, C-2), 140.3 (C, C-1), 133.3 (C, C-10/11), 128.1 (C, C-10/11), 122.0 (C, C-4), 109.3 (C, C-3), 56.4 (CH_3, O*C*H_3-2), 40.5 (CH_2, C-6), 27.8 (CH_2, C-8), 23.8 (CH_2, C-9), 20.7 (CH_2, C-7). **HRMS**: *m/z:* observed 225.0680 $[M+H]^+$, calculated for $C_{12}H_{14}O_2Cl^+$, 225.0677. **HPLC**: 13.86 min.

4.1.32. 1-Chloro-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocycloheptan-5-ol (28).[20]—To a solution of 3,4,5-trimethoxyphenyl bromide (3.60 g, 14.6 mmol) in THF (250 mL) at -78 °C was added *n*-BuLi (6.0 mL, 2.5 M in hexanes) and the reaction was stirred for 30 min. Benzosuberone **19** (1.87 g, 8.32 mmol) in THF (15 mL) was added using an addition funnel over a period of 15 min. The reaction mixture was allowed to warm to room temperature over 12 h. Upon completion, H_2O (100 mL) was added and the reaction mixture was extracted with EtOAc (2 × 200 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording alcohol **28** (2.41 g, 6.13 mmol, 74%) as an off-white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.50 (1H, d, *J* = 8.8 Hz, H-4), 6.80 (1H, d, *J* = 8.8 Hz, H-3), 6.49 (2H, s, H-2′, H-6′), 3.92 (3H, s, OC*H*$_3$-2), 3.84 (3H, s, OC*H*$_3$-4′), 3.76 (6H, s, OC*H*$_3$-3′, -5′), 3.41 (1H, m, H-9), 2.58 (1H, m, H-6), 2.51 (1H, m, H-9), 2.12 (1H, m, H-6), 1.88 (2H, m, H-7), 1.76 (1H, m, H-8), 1.47 (1H, m, H-8). **^{13}C NMR** (CDCl3, 125 MHz): δ 154.1 (C, C-2), 153.1 (C, C-3′, C-5′), 141.3 (C, C-1′), 140.1 (C, C-10/11), 138.9 (CH, C-10/11), 137.5 (CH, C-4′), 125.9 (CH, C-4), 122.4 (C, C-1), 108.6 (CH, C-3), 104.1 (CH, C-2′, C-6′), 79.9 (C, C-5), 60.8 (CH_3, O*C*H_3-4′), 56.2 (CH_3, O*C*H_3-3′, -5′), 56.1 (CH_3, O*C*H_3-2), 41.1 (CH, C-6), 29.5 (CH_2, C-9), 25.9 (CH_2, C-7), 25.8 (CH_2, C-8). **Analysis**: Calculated for $C_{21}H_{25}ClO_5$: C 64.20, H 6.41. Found: C 64.41, H 6.45.

4.1.33. 1-Chloro-2-methoxy-5-(3′,4′,5′-trimethoxyphenyl)-benzocycloheptan-5-ene (36).[20]—A solution of alcohol **28** (2.37 g, 6.03 mmol) in AcOH (50 mL) and H_2O (50 mL) was heated to reflux at 110 °C for 12 h. The reaction mixture was cooled, concentrated under reduced pressure, and subjected to flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording benzosuberene **36** (2.18 g, 5.81 mmol, 97%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.92 (1H, d, H-4), 6.78 (1H, d, H-3), 6.48 (2H, s, H-2′, H-6′), 6.37 (1H, t, *J* = 7.4 Hz, H-6), 3.92 (3H, s, OC*H*$_3$-2), 3.86 (3H, s, OC*H*$_3$-4′), 3.80 (6H, s, OC*H*$_3$-3′, -5′), 2.90 (2H, t, *J* = 7.0 Hz, H-9), 2.17 (2H, p, *J* = 7.0 Hz, H-8), 1.92 (2H, q, *J* = 7.2 Hz, H-7). **^{13}C NMR** (CDCl3, 125 MHz): δ 154.0 (C, C-2), 153.1 (C, C-3′, C-5′), 142.7 (C, C-5), 141.2 (C, C-10/11), 138.0 (C, C-1′), 137.4 (CH, C-4′), 134.2 (CH, C-10/11), 128.3 (C, C-4), 127.8 (CH, C-6), 121.5 (C, C-1), 109.1 (C, C-3), 105.2 (CH, C-2′, C-6′), 61.1 (CH_3, O*C*H_3-4′), 56.31 (CH_3, O*C*H_3-2), 56.28 (CH_3, O*C*H_3-3′, -5′), 33.8 (CH_2, C-8), 28.7 (CH_2, C-9), 25.6 (CH_2, C-7). **Analysis**: Calculated for $C_{21}H_{23}ClO_4$: C 67.29, H 6.18. Found: C, 67.40, H, 6.21. **HRMS**: *m/z*: observed 397.1180 $[M + Na]^+$, calculated for $C_{21}H_{23}O_4ClNa^+$, 397.1177. **HPLC**: 19.26 min.

Experimental Procedures for Final Compound 35

4.1.34. 1,2-Dimethoxy-5-(3,4-dimethoxyphenyl)-benzocycloheptan-5-ol (27).— To a solution of 3,4-dimethoxyphenylbromide (0.455 g, 2.09 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (0.85 mL, 2.5 M in hexanes) and the reaction mixture was stirred for 1 h. Ketone **18** (0.453 g, 2.06 mmol) in THF (5 mL) was slowly added and the reaction mixture was allowed to warm to room temperature over 12 h. Upon completion, H_2O (5 mL) was added and the reaction mixture was extracted with EtOAc (4 × 15 mL). The organic

extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude tertiary alcohol **27** (0.442 g, 1.23 mmol, crude yield 60%) was obtained as a clear oil. The crude product was used without further purification.

4.1.35. 1,2-Dimethoxy-5-(3,4-dimethoxyphenyl)-benzocyclohept-5-ene (35).— Tertiary alcohol **27** (0.442 g, 1.23 mmol) dissolved in EtOH (5 mL) and EtOAc (10 mL) was added 2 M HCl (5 mL) and the reaction mixture was stirred for 12 h. The reaction was extracted with EtOAc (4 × 20 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica gel column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B → 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm]. Benzosuberene analogue **35** (0.302 g, 0.888 mmol, 72%) was obtained as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.81 (3H, m), 6.77 (1H, *J* = 8.6 Hz), 6.75 (1 H, d, *J* = 8.6 Hz), 6.60 (1H, t, *J* = 7.3 Hz), 3.88 (3H, s), 3.866 (3H, s), 3.865 (3H, s), 3.84 (3H, s), 2.75 (2H, t, *J* = 6.9 Hz), 2.16 (2H, p, *J* = 7.1 Hz), 1.96 (2H, q, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 151.5, 148.7, 148.4, 146.2, 142.6, 136.0, 135.7, 134.2, 126.3, 125.3, 120.6, 111.3, 110.8, 109.3, 61.3, 56.04, 56.02, 55.7, 34.7, 25.7, 24.2. **HRMS**: *m/z:* observed 363.1568 $[M+Na]^+$, calculated for $C_{21}H_{24}O_4Na^+$, 363.1567. **HPLC**: 17.63 min.

Experimental Procedures for Final Compound 42

4.1.36 1-((tert-Butyldimethylsilyl)oxy)-2-methoxy-5-(3,4-dimethoxyphenyl)-benzocycloheptan-5-ol (32).—To a solution of 3,4-dimethoxyphenylbromide (0.257 g, 1.51 mmol) in THF (11 mL) at -78 °C was added *n*-BuLi (0.52 mL, 2.5 M in hexanes) and the reaction mixture stirred for 1 h. Ketone **24** (0.312 g, 0.972 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to room temperature over 12 h. Upon completion, H_2O (3 mL) was added and the reaction mixture was extracted using EtOAc (4 × 15 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B → 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (12 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm]. Tertiary alcohol **32** (0.344 g, 0.750 mmol, 77%) was obtained as a clear oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.21 (1H, d, *J* = 8.8 Hz), 6.85 (1H, d, *J* = 2.0 Hz), 6.75 (1H, d, *J* = 8.3 Hz), 6.71 (2H, m), 3.85 (3H, s), 3.80 (3H, s), 3.79 (3H, s), 3.32 (1H, dd, *J* = 13.7, 6.8 Hz), 2.60 (1H, ddd, *J* = 14.2, 6.1, 2.9 Hz), 2.12 (3H, m), 1.89 (1H, m), 1.71 (2H, m), 1.35 (1H, m), 0.99 (9 H, s), 0.18 (3 H, s), 0.14 (3 H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 149.3, 148.9, 148.3, 142.0, 139.0, 138.4, 132.8, 119.7, 119.4, 110.8, 110.5, 108.0, 79.8, 56.0, 55.9, 54.8, 41.3, 27.2, 26.7, 26.2, 25.6, 19.0, -3.8, -4.0.

4.1.37. 1-((tert-Butyldimethylsilyl)oxy)-2-methoxy-5-(3,4-Dimethoxyphenyl)-benzocyclohept-5-ene (40).—Tertiary alcohol **32** (0.236 g, 0.515 mmol) was dissolved in AcOH (5 mL) and the reaction mixture was stirred for 12 h. The reaction mixture was concentrated under reduced pressure and subjected to flash chromatography using a pre-packed 25 g silica gel column [solvent A: EtOAc; solvent B: hexanes; gradient: 0%A / 100%B → 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (12 CV), 20%A / 80%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm]. Benzosuberene analogue **40** (0.156 g, 0.355 mmol, 69%) was obtained as a clear oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.81 (3H, m), 6.69 (1H, d, *J* = 8.4 Hz), 6.61 (1H, d, *J* = 8.6 Hz), 6.30 (1H, t, *J* = 7.3 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.81 (3H, s), 2.78 (2H, t, *J* = 7.0 Hz), 2.11 (2H, q, *J* = 7.0 Hz), 1.95 (2H, p, *J* = 7.2 Hz), 1.05 (9 H, s), 0.24 (6 H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 148.7, 148.6, 148.3, 142.8, 141.6, 136.0, 134.2, 133.4, 126.0, 122.3, 120.5, 111.4, 110.8, 108.4, 56.01, 55.96, 54.8, 34.1, 26.3, 25.7, 24.3, 19.1, -3.7.

4.1.38. 1-Hydroxy-2-methoxy-5-(3,4-dimethoxyphenyl)-benzocyclohept-5-ene (42).—To a solution of TBS-protected analogue **40** (0.156 g, 0.355 mmol) dissolved in THF (5 mL) was added TBAF (0.45 mL, 1 M in THF). The reaction mixture was stirred for 12 h at room temperature, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica gel column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B →7%A / 93%B (1 CV), 7%A / 93%B → 44%A / 56%B (10 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm]. Phenol analogue **42** (0.100 g, 0.305 mmol, 86%) was obtained as a light brown solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.81 (3H, m), 6.70 (1H, d, *J* = 8.3 Hz), 6.56 (1H, d, *J* = 8.3 Hz), 6.30 (1H, t, *J* = 7.5 Hz), 5.73 (1H, s), 3.91 (3H, s), 3.88 (3H, s), 3.83 (3H, s), 2.76 (2H, t, *J* = 7.0 Hz), 2.14 (2H, p, *J* = 7.0 Hz), 1.96 (2H, q, *J* = 7.2 Hz). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.6, 148.3, 145.1, 142.5, 142.4, 135.8, 134.7, 127.9, 126.4, 120.8, 120.6, 111.3, 110.8, 107.7, 56.1, 55.9, 55.0, 33.8, 25.8, 23.6. **HRMS**: *m/z*: observed 349.1411 $[M+Na]^+$, calculated for $C_{20}H_{22}O_4Na^+$, 349.1410. **HPLC**: 15.58 min.

Experimental Procedures for Final Compound 41

4.1.39. 1-Hydroxy-5-(3,4,5-trimethoxyphenyl)-benzocyclohept-5-ene (33).[20]—To a solution of 3,4,5-trimethoxyphenylbromide (0.910 g, 3.68 mmol) in THF (40 mL) at -78 °C was added *n*-BuLi (1.5 mL, 2.5 M in hexanes) and the reaction mixture was stirred for 1 h. Commercially available benzocycloheptan-5-one **25** (0.536 g, 3.34 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to room temperature over 12 h. Upon completion, H_2O (5 mL) was added and the reaction mixture was extracted using EtOAc (4 × 15 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B → 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (12.5 CV), 60%A / 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm]. Tertiary alcohol **33** (0.320 g, 0.794 mmol, 11%) was obtained as a clear oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.57 (1H, dd, *J* = 9.0, 1.7 Hz), 7.22 (2H, pd, *J* = 7.3, 1.82 Hz), 7.12 (1H, dd, *J* = 6.6, 1.2 Hz), 6.48 (2H, s), 3.84 (3H, s), 3.74 (6H, s), 2.74 (1H, dd, *J* = 14.4, 6.8 Hz), 2.63 (1H, m), 2.57 (1H, s), 2.21 (1H, m), 2.14 (1H, m), 1.95 (1H, m) 1.78 (2H, m), 1.54 (1H, m). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.0, 145.2, 141.3, 141.1, 137.3, 130.5, 127.6, 127.2, 126.2, 104.4, 80.1, 60.8, 56.1, 41.1, 36.3, 27.3, 26.1.

4.1.40. 5-(3,4,5-trimethoxyphenyl)-benzocyclohept-5-ene (41).[20]—Tertiary alcohol **33** (0.123 g, 0.375 mmol) was dissolved in AcOH (5 mL) and stirred for 12 h. H_2O (40 mL) was added and the reaction mixture was extracted with EtOAc (3 × 15 mL). The organic extract was washed with H_2O (3 × 20 mL), washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica gel column [solvent A: EtOAc; solvent B: hexanes; gradient: 0%A / 100%B → 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (11.5 CV), 20%A / 80%B (2.5 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm]. Benzosuberene analogue **41** (0.082 g, 0.264 mmol, 70%) was obtained as a clear oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.28 (1H, dd, *J* = 7.3, 1.7 Hz), 7.21 (2H, m), 7.05 (1H, dd, *J* = 7.1, 2.0 Hz), 6.49 (2H, s), 6.42 (1H, t, *J* = 7.3 Hz), 3.87 (3H, s), 3.80 (6H, s), 2.67 (2H, t, *J* = 7.1 Hz), 2.19 (2H, p, *J* = 7.1 Hz), 1.97 (2H, q, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 153.0, 143.1, 142.3, 140.1, 138.3, 137.5, 129.5, 128.7, 128.2, 127.3, 125.9, 105.4, 61.0, 56.3, 35.4, 32.6, 25.5. **HRMS**: *m/z*: observed 311.1646 $[M+H]^+$, calculated for $C_{20}H_{23}O^{+}{}_3$, 311.1642. **HPLC**: 18.84 min.

Experimental Procedures for Final Compounds 47 and 48

4.1.41. 1-(O-acetyl-N-Fmoc-L-ser)amido-5-(3′,4′,5′-trimethoxyphenyl)-2-methoxy-benzocyclohept-5-ene(46)—To a well-stirred solution of amino-benzosuberene **45** (0.355 g, 1.00 mmol) in CH_2Cl_2 (25 mL) Fmoc-(Ac)-L-serine (0.553 g, 1.50 mmol), T3P (0.75 mL, 2.50 mmol), and Et_3N (0.21 mL, 1.50 mmol) were added, and the reaction mixture was allowed to stir for 12 h at room temperature. H_2O (100 mL) was added and the reaction mixture was extracted with EtOAc. The organic extract was washed with brine, dried with Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography (35% EtOAc/hexanes) to give the desired Fmoc-L-serinamide acetate **46** (0.393 g, 0.56 mmol, 56%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.74 (2H, d, *J* = 7.0 Hz, Ar*H*), 7.65 (1H, s, N*H*), 7.57 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.38 (2H, dd, *J* = 7.5, 7.0 Hz, Ar*H*), 7.27 (2H, dd, *J* = 7.5, 7.0 Hz, Ar*H*), 6.97 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.73 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.49 (2H, s, Ar*H*), 6.36 (1H, t, *J* = 7.5 Hz, C=C*H*), 5.94 (1H, d, *J* = 6.5 Hz, N*H*), 4.82 (1H, bs, C*H*), 4.49 (3H, m, CH_2), 4.23 (1H, t, *J* = 6.5 Hz, C*H*), 3.86 (3H, s, OCH_3), 3.79 (6H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.59 (2H, t, *J* = 7.5 Hz, CH_2), 2.14 (2H, m, CH_2), 2.10 (3H, s, CH_3), 1.95 (2H, m, CH_2). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.8, 168.4, 156.2, 153.2, 152.9, 143.6, 143.5, 142.4, 141.2, 140.7, 138.3, 137.3, 133.4, 129.4, 127.8, 127.1, 125.0, 122.1, 120.0, 108.3, 105.3, 67.2, 64.5, 60.9, 56.6, 55.1, 54.2, 47.1, 33.8, 27.0, 25.6, 20.7. **HRMS**: *m/z*: observed 729.2794 $[M+Na]^+$, calculated for $C_{41}H_{42}N_2O_9Na^+$, 729.2783.

4.1.42. 1-(L-ser)amido-5-(3′,4′,5′-trimethoxyphenyl)-2-methoxy-benzocyclohept-5-ene (47)—To a solution of Fmoc-L-serinamide acetate in CH_2Cl_2:MeOH (3 mL/3 mL) was added **46** (0.393 g, 0.56 mmol) and 2 M NaOH (0.63 mL, 1.26 mmol). After stirring for 13 h at the reaction mixture concentrated under reduced pressure and water (10 mL) was added. The reaction mixture was extracted with EtOAc (15 mL × 3) and washed with brine, dried with Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography (5% MeOH / 95% CH_2Cl_2) to give the desired serinamide **47** (0.19 g, 0.42 mmol, 75%) as a white solid. **^{1}H NMR** ($CDCl_3$,500 MHz): δ 8.73 (1H, s, N*H*), 6.97 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.78 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.49 (2H, s, Ar*H*), 6.36 (1H, t, *J* = 7.5 Hz, C=C*H*), 4.04 (1H, dd, *J* = 11, 4.5 Hz, CH_2), 3.86 (3H, s, OCH_3), 3.84 (6H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.80 (1H, dd, *J* = 11, 4.5 Hz, CH_2), 3.71 (1H, t, *J* = 4.5 Hz, C*H*), 2.62 (2H, t, *J* = 6.5 Hz, CH_2), 2.16 (2H, m, CH_2), 1.98 (2H, q, *J* = 7.0 Hz, CH_2). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 173.5, 153.1, 152.8, 142.5, 140.6, 138.3, 133.5, 129.1, 127.6, 122.5, 109.9, 108.4, 105.3, 65.9, 60.9, 56.3, 56.1, 55.8, 34.0, 27.0, 25.5. **HRMS**: *m/z:* observed 443.2190 $[M+H]^+$, calculated for $C_{24}H_{31}N_2O_6^+$, 443.2177. **HPLC**: 8.23 min.

4.1.43. 1-(L-ser)amido-5-(3′,4′,5′-trimethoxyphenyl)-2-methoxy-benzocyclohept-5-ene hydrochloride (48)—To a solution of Serinamide **47** (0.10 g, 0.23 mmol) in CH_3OH/CH_2Cl_2 (3 mL/3 mL) was added 4 M HCl-dioxane (0.28 mL, 1.13 mmol). After stirring for 3 h, the reaction mixture was concentrated under reduced pressure and upon recrystallization in EtOAc/CH_3OH gave the desired serinamide salt **48** (0.074 g, 0.15 mmol, 67%) as a white solid. **^{1}H NMR** (CD_3OD, 500 MHz): δ 6.96 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.92 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.53 (2H, s, Ar*H*), 6.39 (1H, t, *J* = 7.5 Hz, C=C*H*), 4.26 (1H, dd, *J* = 7.5, 4.5 Hz, C*H*), 4.19 (1H, dd, *J* = 11.5, 4.0 Hz, CH_2), 3.99 (1H, dd, *J* = 11.5, 7.5 Hz, CH_2), 3.82 (3H, s, OCH_3), 3.76 (6H, s, OCH_3), 3.75 (3H, s, OC*H*), 2.62 (2H, m, CH_2), 2.16 (2H, m, CH_2), 1.92 (2H, m, CH_2). **^{13}C NMR** (CD_3OD, 125 MHz): δ 166.9, 153.9, 152.8, 142.5, 140.7, 138.4, 137.1, 133.3, 129.3, 126.9, 121.7, 108.5, 105.1, 60.7, 59.7, 55.18, 55.16, 54.8, 33.5, 26.2, 24.9. **HRMS**: *m/z:* observed 443.2214 $[M-Cl]^+$, calculated for $C_{24}H_{31}N_2O_6^+$, 443.2177. **HPLC:** 8.32 min.

4.2 Biological Evaluation

4.2.1. Inhibition of Tubulin Assembly—In brief, 160 uL of tubulin (1.25 mg/mL in 1M glutamate) and 8 uL of desired inhibitor concentration dissolved in either water or DMSO were mixed in a microfuge vial and incubated at 37 °C for 15 minutes. Microfuge vials were then placed on ice for 15 minutes. 32 uL of GTP (2.5 mM) was added to vials and contents of vials (200 uL) were placed in their appropriate cells. Cells were placed in the cell holder of the UV/Vis spectrophotometer and allowed to cool at 0 °C for 8 minutes. UV/Vis settings were as follows: absorption: 350 nm, length of experiment: 3800 s, measurement intervals: 30 s. Each experiment was initiated and UV/Vis spectrophotometer took readings for 100 seconds at 0 °C. At 100 s, the temperature was switched to 38 °C for 120 seconds, followed by a temperature change to 31 °C until 2600 total seconds had passed since initiation of the experiment. At 2600 seconds, the cells were cooled to 0 °C throughout the remainder of the experiment which ended once 3800 seconds had passed. Tubulin was purified from calf brain. For details regarding effects on tubulin assembly, see references 70 and 71.

4.2.2. SRB Assay[72]—We assessed inhibition of human cancer cell growth using the National Cancer Institute's standard sulforhodamine B assay, as previously described.[72] Briefly, cancer cell lines in a 5% fetal bovine serum/RPMI1640 medium, 1% gentamicin solution were plated in 96-well plates and incubated for 24 h. Serial dilutions of the compounds were then added. After 48 h, the plates were fixed with trichloroacetic acid, stained with sulforhodamine B, and read with an automated Biotek plate reader. A growth inhibition of 50% (GI_{50} or the drug concentration causing a 50% reduction in the net protein increase) was calculated from optical density data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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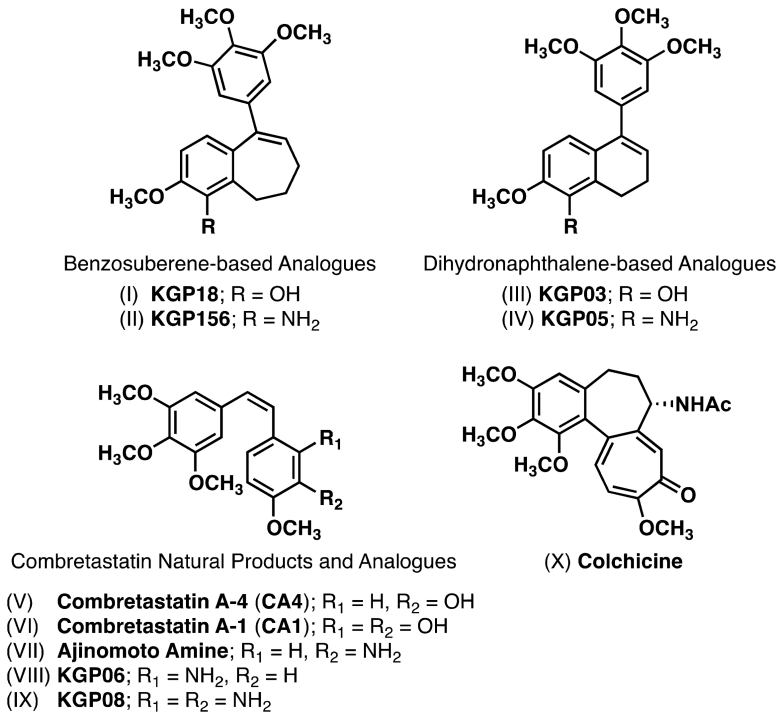
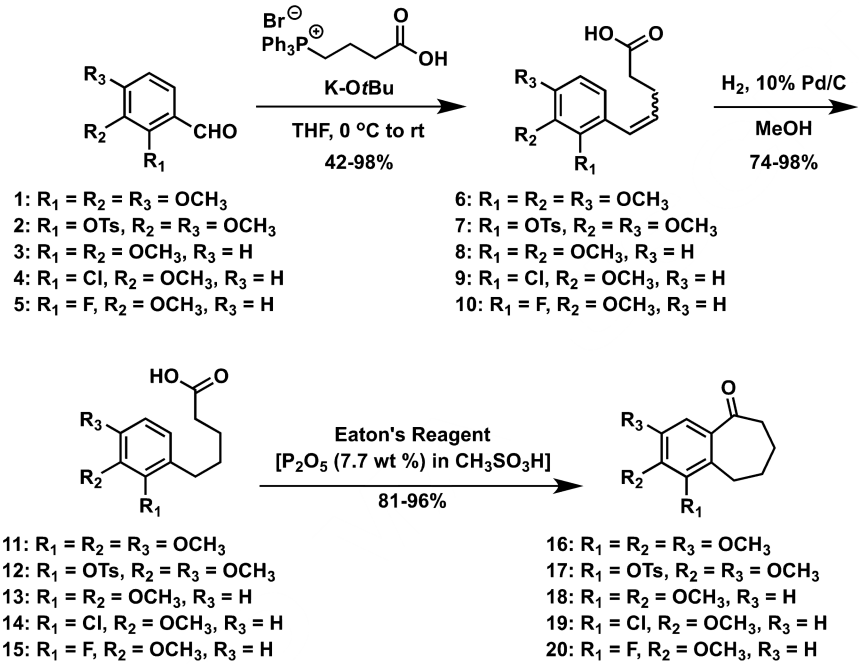


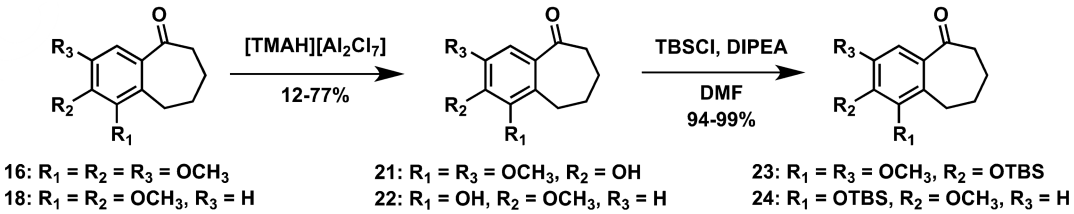
Figure 1.

Representative Small-Molecule Inhibitors of Tubulin Assembly That Bind to the Colchicine Site; Including: Benzosuberene Analogues (**KGP18**,[18]**KGP156**[19]), Dihydronaphthalene Analogues (**KGP03**,[18,21-23]**KGP05**[22,23]), and Combretastatin Analogues (**CA4**,[24,25]**CA1**,[26] Ajinomoto Amine,[27,28]**KGP06**,[10,29]**KGP08**[30]).



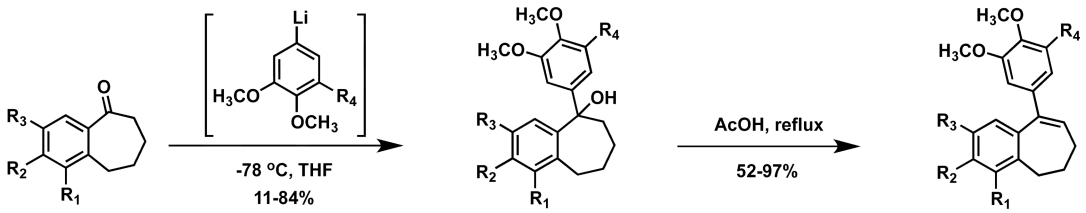
Scheme 1.

Synthetic route to benzosuberone intermediates **16-20**.



Scheme 2.

Synthetic modifications affording benzosuberone intermediates **23-24**.

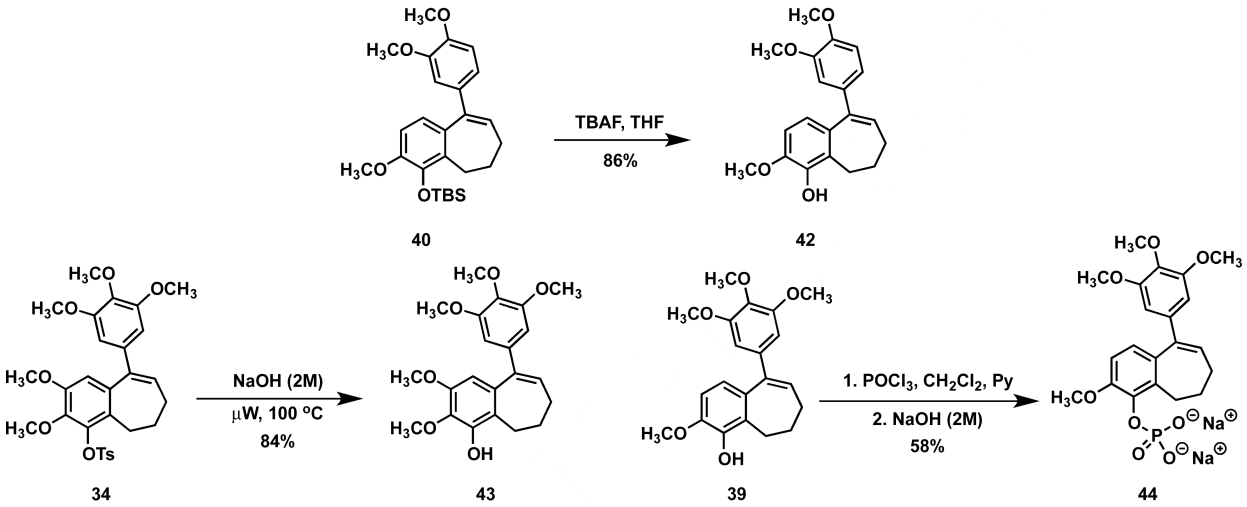


17: R_1 = OTs, R_2 = R_3 = OCH_3
18: R_1 = R_2 = OCH_3, R_3 = H
19: R_1 = Cl, R_2 = OCH_3, R_3 = H
20: R_1 = F, R_2 = OCH_3, R_3 = H
23: R_1 = R_3 = OCH_3, R_2 = OTBS
24: R_1 = OTBS, R_2 = OCH_3, R_3 = H
25: R_1 = R_2 = R_3 = H

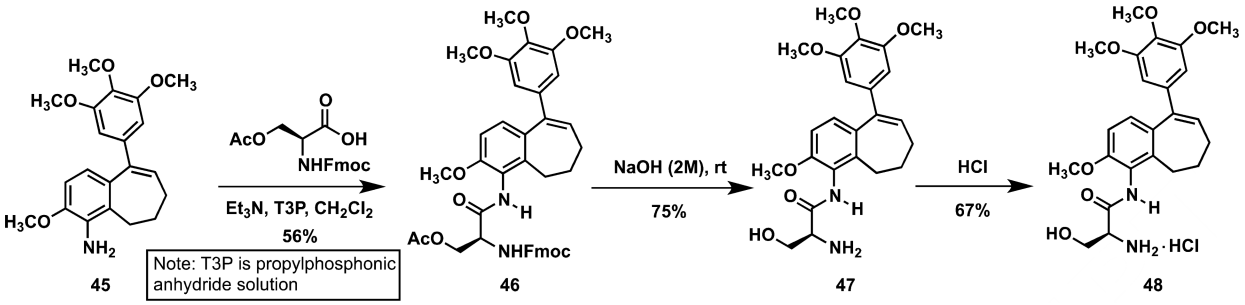
26: R_1 = OTs, R_2 = R_3 = OCH_3, R_4 = OCH_3
27: R_1 = R_2 = OCH_3, R_3 = H, R_4 = H
28: R_1 = Cl, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
29: R_1 = F, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
30: R_1 = R_3 = OCH_3, R_2 = OTBS, R_4 = OCH_3
31: R_1 = OTBS, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
32: R_1 = OTBS, R_2 = OCH_3, R_3 = H, R_4 = H
33: R_1 = R_2 = R_3 = H, R_4 = OCH_3

34: R_1 = OTs, R_2 = R_3 = OCH_3, R_4 = OCH_3
35: R_1 = R_2 = OCH_3, R_3 = H, R_4 = H
36: R_1 = Cl, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
37: R_1 = F, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
38: R_1 = R_3 = OCH_3, R_2 = OH, R_4 = OCH_3
39: R_1 = OH, R_2 = OCH_3, R_3 = H, R_4 = OCH_3
40: R_1 = OTBS, R_2 = OCH_3, R_3 = H, R_4 = H
41: R_1 = R_2 = R_3 = H, R_4 = OCH_3

Scheme 3.
Synthetic route to benzosuberene analogues **34-41**.



Scheme 4.
Synthetic route to benzosuberene analogues **42-44**.



Scheme 5.
Synthetic route to benzosuberene analogues **47-48**.

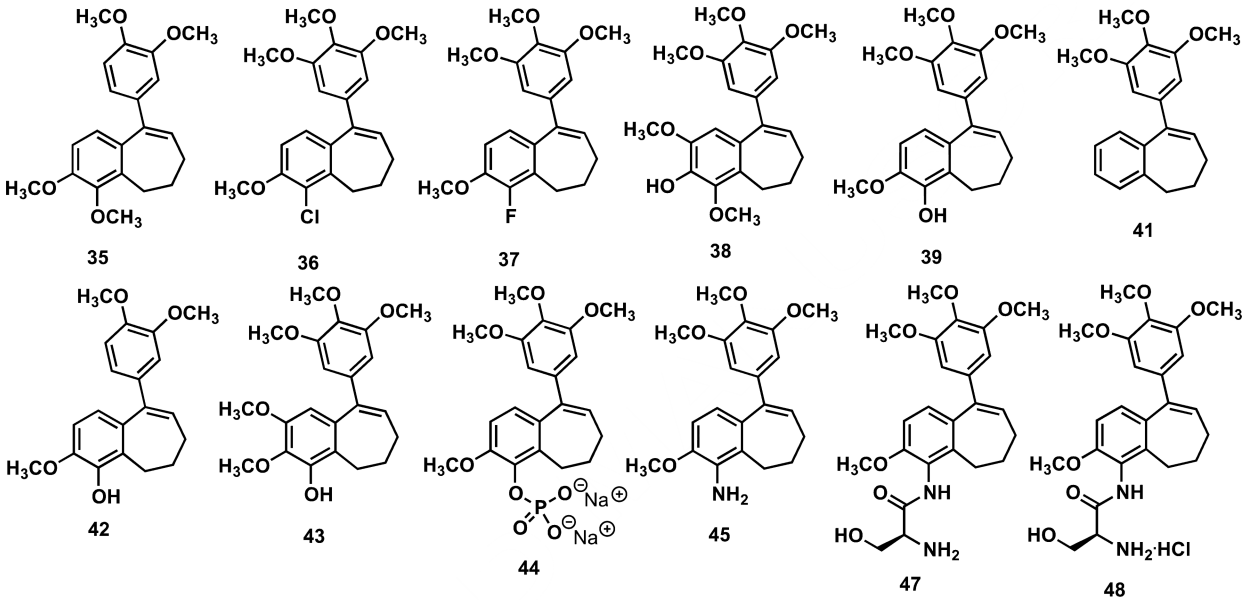


Figure 2.
Molecular Structures of Target Benzosuberene Analogues

Table 1

Inhibition of tubulin polymerization and cytotoxicity against human cancer cell lines SK-OV-3, NCI-H460, and DU-145.

Compound	Inhibition of tubulin polymerization IC_{50} (M)	GI_{50} (M) SRB assay[a]		
		SK-OV-3	NCI-H460	DU-145
CA4	1.0[b]	0.00455	0.00223[c]	0.00327[c]
CA4P	>40[b]	0.00119	0.00194[c]	0.00323[c]
35	>40	>89.5	>136.5	42.5
36	0.93	0.0444	0.0713	0.152
37	0.89	0.00751	0.00547	0.0189
38	>40	7.13	18.0	15.7
39	1.4[d]	0.0000543[e]	0.0000418[e]	0.0000249[e]
41	>40	19.1	32.5	22.0
42	0.74	0.0334	0.262	0.109
43	>40	18.1	25.9	38.4
44	>40	0.00772	0.00796	0.00951
45	1.2[f]	0.000102[g]	0.00280[g]	0.00223[g]
47	nd[h]	36.8	39.0	70.5
48	nd[h]	35.0	53.8	69.4

[a] Average of n ≥ 3 independent determinations.

[b] Data from ref. 61

[c] For additional data see ref. 61.

[d] Data from ref. 19.

[e] For additional data see ref. 18.

[f] Data from ref. 19.

[g] For additional data see ref. 19.

[h] nd = not determined in this study.