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PAPER

Neuronal growth promoting sesquiterpene–neolignans; syntheses and biological studies

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The use of small molecules that can promote neuronal growth represents a promising approach to regenerative science. Along these lines we have developed separate short or modular syntheses of the natural products caryolanemagnolol and clovanemagnolol, small molecules previously shown to promote neuronal growth and induce choline acetyltransferase activity. The postulated biosynthetic pathways, potentially leading to the assembly of these molecules in nature, have guided the laboratory syntheses, allowing the preparation of both natural products in as few as two steps. With synthetic access to the compounds as single enantiomers we have examined clovanemagnolol's ability to promote the growth of embryonic hippocampal and cortical neurons. Clovanemagnolol has been shown to be a potent neurotrophic agent, promoting neuronal growth at concentrations of 10 nM.

The lack of regeneration in the central nervous system (CNS) has been attributed to two factors; the inhibitory extrinsic environment formed after injury and the absence of intrinsic growth signals. In the 1980's Aguayo and coworkers showed that some axons, unable to regrow in their native CNS environment, have the ability to grow and extend into transplanted peripheral nervous system (PNS) nerve graphs.[1] This finding led to 30 years of research to uncover the basis of the growth inhibitory environment of the CNS.[2] Unfortunately, efforts to promote regeneration through the removal of these inhibitory signals have produced only limited results. However, regeneration in the CNS is possible, passing through the inhibitory glial environment, if appropriate signaling pathways are first activated. This was discovered in dorsal root ganglion (DRG) neurons, which have projections into both the PNS and CNS. If the peripheral branches of DRG neurons are cleaved, providing a "conditioned lesion", followed by severing the CNS branch, regeneration can occur in the CNS portion through a series of transcriptional events that enhance the intrinsic growth potential.[3] The identification of these and other growth promoting pathways, particularly ones that can be controlled by small molecules, could provide significant advancements to regenerative medicine. The recent development of a variety of hydrogels and other systems for continuous delivery, if coupled with a validated small molecule, would provide a unique and promising platform for therapeutic development.[4]

The majority of approaches toward inducing CNS regeneration focus on the use of gene therapy, growth factors, and stem cells. The pharmacologically appealing strategy of using small molecules, however, has received considerably less attention.[5] This follows from a poor understanding of how small molecules, traditionally used as inhibitors, can result in a gain of biological function. In an effort to identify small molecules with neurotrophic activity the sesquiterpene–neolignan caryolanemagnolol was isolated from the bark of *Magnolia obovata* in yields ranging from 0.0035% to 0.00022% (Fig. 1).[6] The highly lipophilic molecule was identified with seven other structurally related compounds in a screen for compounds with neurotrophic activity. Treatment of primary neuronal cell cultures with caryolanemagnolol leads to increased neurite outgrowth relative to controls, with pronounced growth at 0.1 μM, the lowest concentration reported.[6a] Treatment of cultured neurons at the same concentration resulted in choline acetyltransferase (ChAT) activity being increased by 163% relative to control cultures.[6a] Similarly, an isomeric natural product

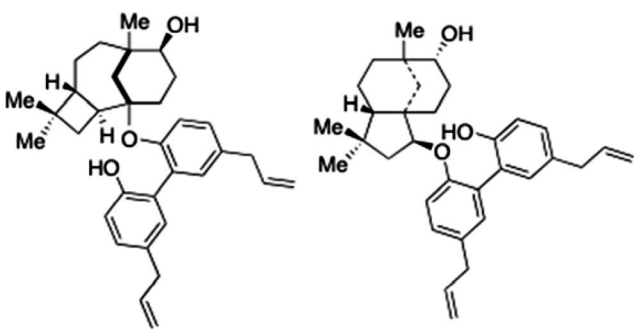

Fig. 1 Caryolanemagnolol and clovanemagnolol.

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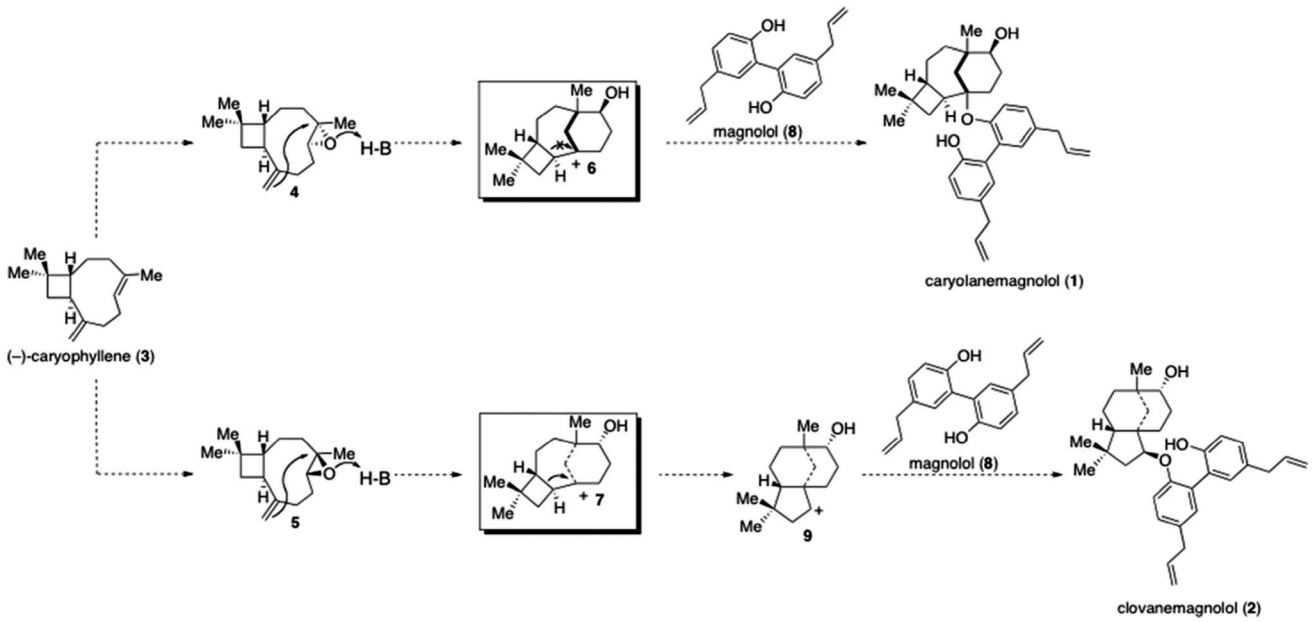


Fig. 2 The proposed biosynthesis of clovanemagnolol.

clovanemagnolol was shown to have related activity, promoting neurite growth at 0.1 μM and ChAT induction at 1 μM.[6a]

To examine the initially reported growth promoting activities of caryolanemagnolol and clovanemagnolol and to prepare biologically optimized analogs we have developed two syntheses for each of the natural products, allowing either the large scale synthesis or the preparation of analogs.[7] The proposed biosyntheses have provided insight into the development of short, flexible laboratory syntheses of both compounds commencing from the readily accessible starting material, (–)-caryophyllene, a plant-derived commodity chemical used in the flavor and fragrance industry.

The proposed biosynthetic pathway is initiated by the oxidation of (–)-caryophyllene, providing diastereomeric epoxides, α-caryophyllene oxide (**4**) or β-caryophyllene oxide (**5**) (Fig. 2). Brønsted activation of the epoxides **4** or **5** leads to an intramolecular attack of the exocyclic alkene, generating diastereomeric tricyclic intermediates **6** and **7** bearing bridgehead carbocations. In the caryolanemagnolol sequence the cation **6** is trapped by magnolol (**8**), directly forming the natural product. In the clovanemagnolol sequence the cation **7** has correctly aligned orbitals to enable a ring expansion of the adjacent cyclobutane ring, thus releasing ring strain, forming the cationic tricycle **9**. This secondary cation is subsequently trapped by magnolol (**8**), forming clovanemagnolol (**2**). In their work elucidating the structure of caryophyllene, Barton and coworkers were the first to describe these rearrangements as well as the generation of clovane and caryolane based structures from the parent caryophyllene compounds.[8]

In the laboratory setting, the syntheses of caryolanemagnolol and clovanemagnolol were initiated with diastereoselective epoxidation reactions. The system proved to have a relatively strong preference for the formation of the β-epoxide **5** as epoxidation of (–)-caryophyllene with *m*CPBA generated epoxides **4** and **5** in a 1 : 5 ratio, favoring the β-epoxide **5** (Fig. 3). Attempts to change the diastereoselectivity of the epoxidation reaction using halohydrin formation followed by base had failed, instead generating allylic halides through an ene-type process. This unexpected reaction is likely due to the lack of an appropriate pathway for the attack of water, opening the bromonium intermediate, from the inside of the nine-membered ring. Of the reagents examined, the Shi catalyst **10** proved successful in overriding the inherent bias of the system, providing epoxide **4** as the major product in a 2.2 : 1 ratio of α to β.[9]

In a single reaction we were able to convert epoxides **4** and **5** to caryolanemagnolol and clovanemagnolol, respectively, using diphenyl phosphate and magnolol (**8**) in dichloromethane at 23 °C (Fig. 4). Significant optimization of the acid component was necessary as a number of other Brønsted and Lewis acids failed to induce the desired reaction. Acid mediated rearrangement of epoxide **4** with diphenyl phosphate and trapping with magnolol led to the formation of caryolanemagnolol (**1**) in 15% yield. The major by-product in this reaction was competitive trapping of the cation with diphenyl phosphate. Analogously, the rearrangement of epoxide **5** in the presence of diphenyl phosphate generated clovanemagnolol in 10% yield. Elimination proceeding the trapping of the cation proved to be the major competitive pathway, generating clovene as the major by-product. While low yielding we have found these single-step transformations starting from the corresponding epoxides have proven to scale well providing the natural products on the multigram scale. In addition, the reaction can be run on the diastereomeric mixture of epoxides, generating both natural products.

In addition to the single step reactions, multi-step syntheses to both molecules were developed to access analogs. In an optimized procedure the rearrangement of α-epoxide **4** was achieved using an *in situ* aluminum phenoxide reagent generated through the combination of 4-bromophenol and trimethylaluminum in a 3 : 1 ratio in dichloromethane at 0 °C.[10] This reagent, when combined with **4**, provided the carbocyclic core of caryolanemagnolol in a single operation, yielding bromide **11** in 69% yield (Scheme 1). In

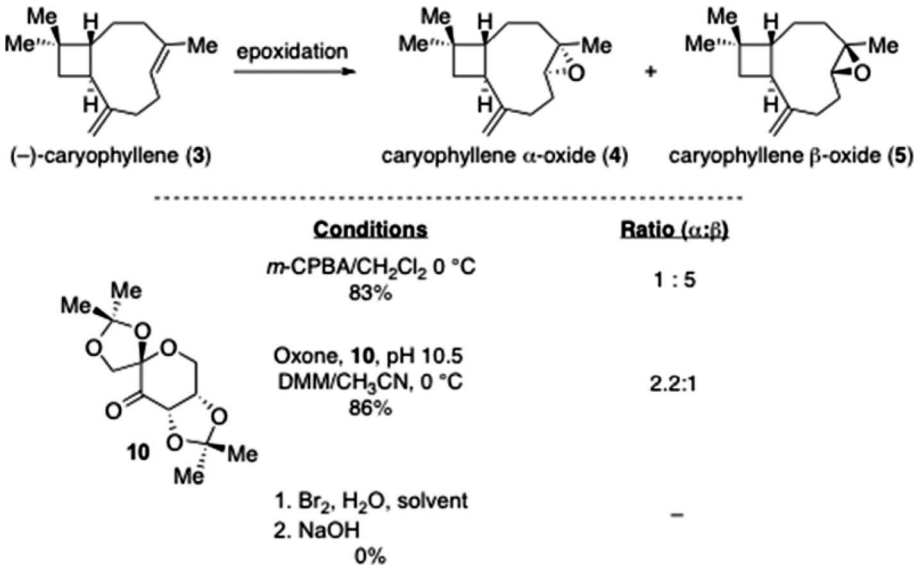


Fig. 3 The diastereoselective epoxidation of (–)-caryophyllene **3**.

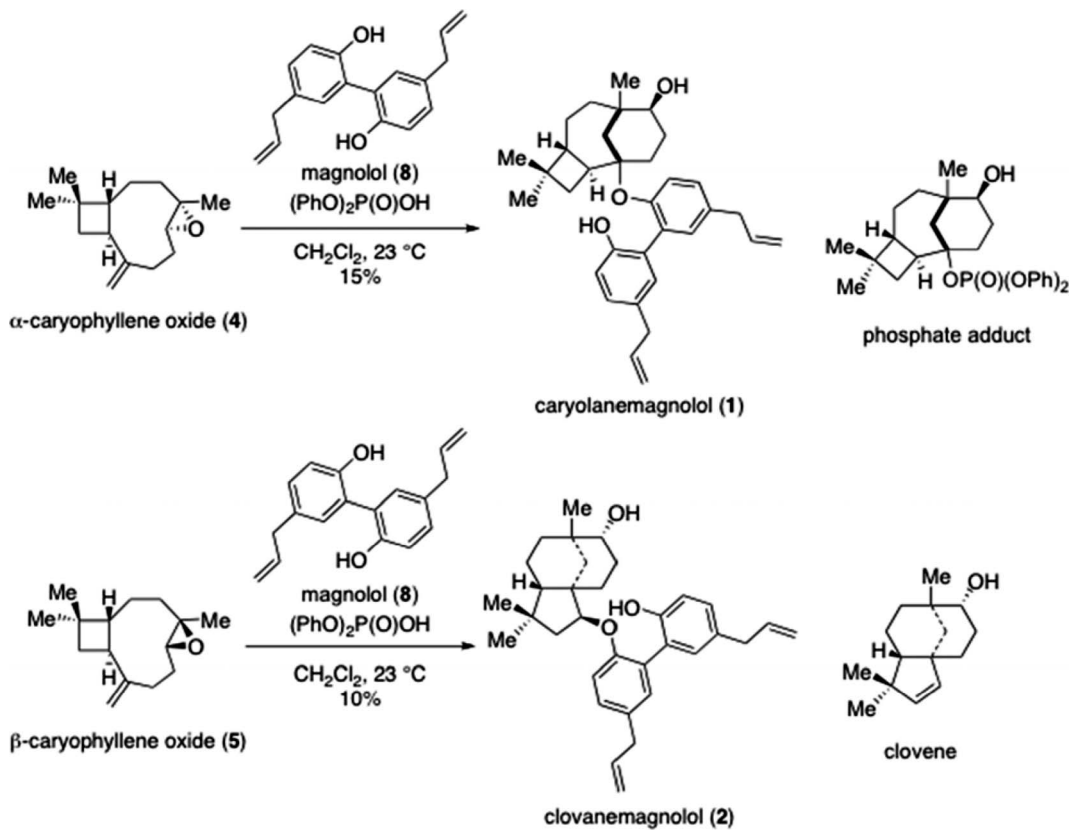
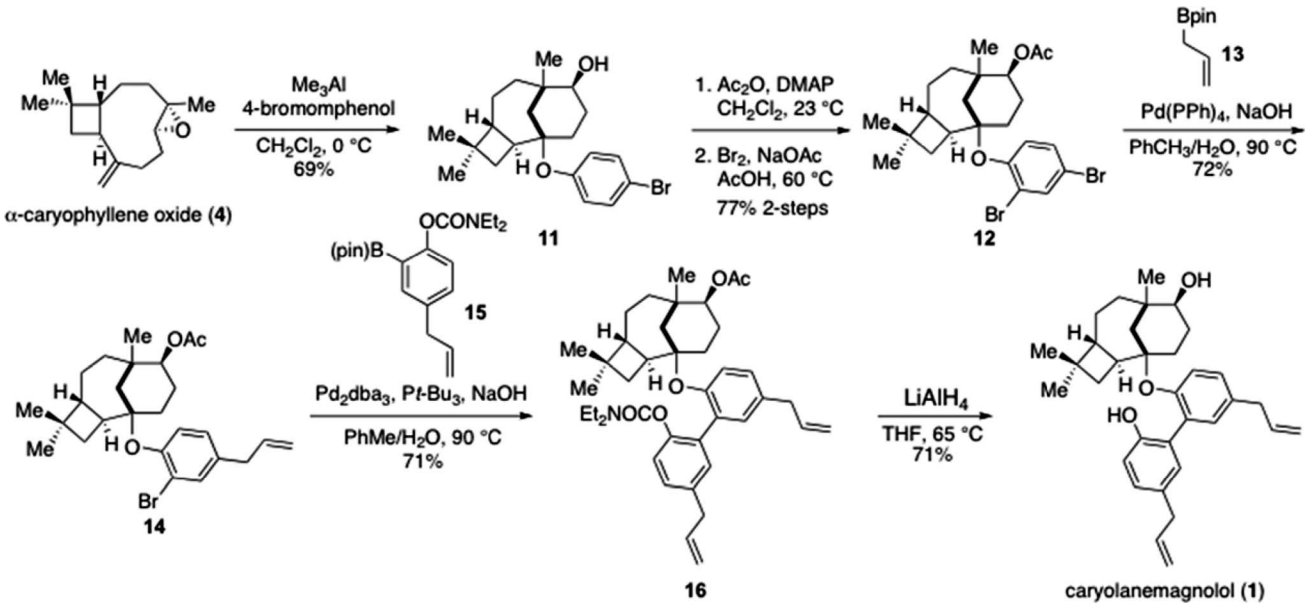


Fig. 4 Single step syntheses of caryolanemagnolol and clovanemagnolol following from the proposed biosynthetic pathway.

addition to NMR, the structure of bromide **11** was confirmed by X-ray diffraction of the 3,5-dinitrobenzoyl derivative (Fig. 5). Due to the inability of 2,4-dibromophenol or any *ortho*-substituted phenols to participate in the reaction the bromination of **11** was required. Preliminary attempts at bromination were competitive with oxidation of the secondary alcohol, forming the corresponding ketone of **11**, therefore, protection of the secondary alcohol was required. An acetate was appended under standard conditions followed by the installation of a second bromide using bromine and sodium acetate at elevated temperature (60 °C) in acetic acid, generating dibromide **12** in 77% yield over the two steps (Scheme 1). With the bromine atoms installed, Suzuki reactions were used to sequentially form the allyl appendage and the biaryl bond.[11] In the majority of allylation reactions examined, Suzuki cross-coupling led to rapid bisallylation of **14**. However, using pinacol allylboronate **13**, tetrakis(triphenylphosphine)palladium



Scheme 1 The multistep synthesis of caryolanemagnolol (**1**).

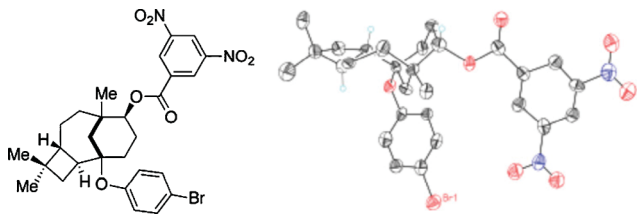
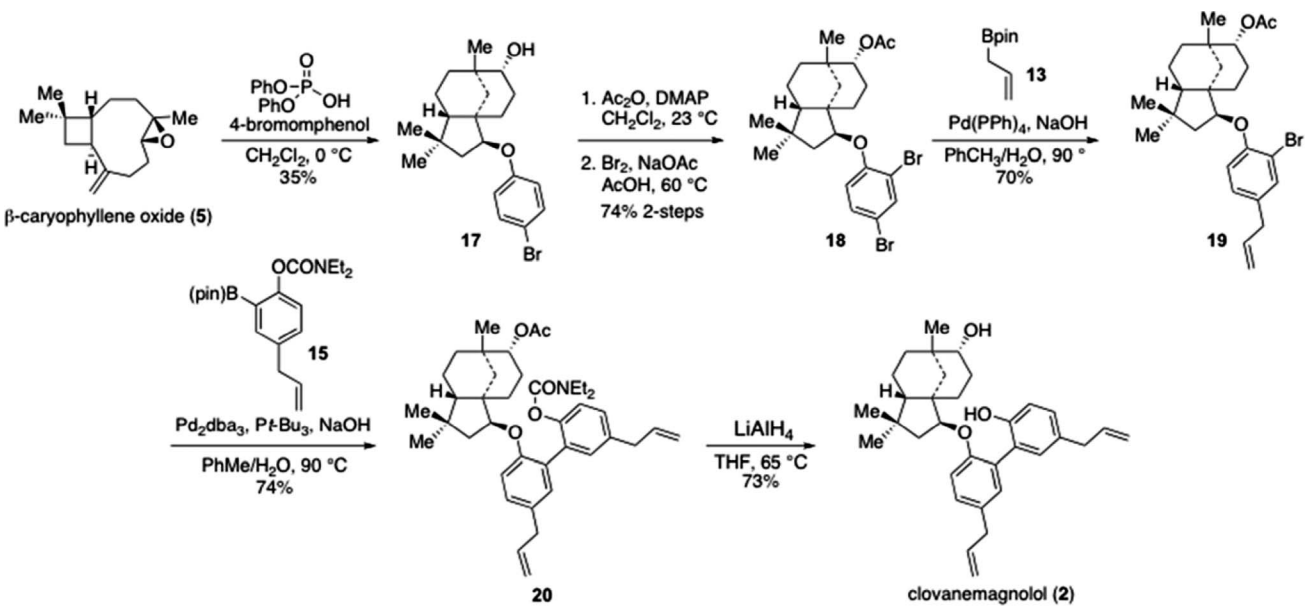


Fig. 5 The X-ray crystal structure of the 3,5-dinitrobenzoyl derivative of bromide **11**.

catalysis, and close monitoring of the reaction by TLC compound **14** could be isolated in 72% yield. Selective cross-coupling of the *para*-bromide over the *ortho* can be attributed to both steric and electronic factors. A second Suzuki reaction between monobromide **14** and pinacol ester **15** using conditions developed by Fu and coworkers formed the hindered biaryl bond, generating **16** in 71% yield (Scheme 1).[12] The removal of the acetate and carbamoyl groups was simultaneously achieved with lithium aluminum hydride in THF heated to reflux, providing caryolanemagnolol (**1**) in 71% yield. While the synthetic material matched the spectra for isolated caryolanemagnolol, we found that the original isolation report incorrectly stated the chemical shifts for caryolanemagnolol.[6a,7]

The synthesis of clovanemagnolol was achieved over six-steps using similar transformations to those used for the synthesis of caryolanemagnolol (Scheme 2). Unfortunately, the aluminum phenoxide reagent used in the first step of the caryolanemagnolol



Scheme 2 The multistep synthesis of clovanemagnolol (**2**).

Table 1 Neurite outgrowth of embryonic hippocampal neurons after treatment with magnolol and clovanemagnolol

Treatment	Average Neurite Length per Neuron (μm)	Percent Change from Control
Control	176.6 ± 27.0	—
DMSO	168.7 ± 21.5	–4.5
Mag (0.01 μM)	265.1 ± 67.6	**50.1**
Mag (0.1 μM)	218.8 ± 40.7	23.9
Mag (1.0 μM)	54.7 ± 17.3	–69.0*
CM (0.01 μM)	287.6 ± 82.8	**62.8**
CM (0.1 μM)	223.4 ± 49.9	26.5
CM (1.0 μM)	28.5 ± 10.9	–83.9

Table 2 Neurite outgrowth of embryonic cortical neurons after treatment with magnolol and clovanemagnolol

Treatment	Average Neurite Length per Neuron (μm)	Percent Change from Control
Control	352.7 ± 54.4	—
DMSO	347.2 ± 82.8	–1.6
Mag. (0.01 μM)	424.1 ± 24.2	20.2
Mag. (0.1 μM)	548.8 ± 124.0	**55.6**
Mag. (1.0 μM)	57.8 ± 27.4	–74.6*
CM (0.01 μM)	508.5 ± 87.0	**44.2**
CM (0.1 μM)	432.9 ± 64.5	22.7
CM (1.0 μM)	68.2 ± 22.2	–80.7*

sequence failed to convert epoxide **5** to the carbocyclic clovane core. Therefore, starting from the recrystallized caryophyllene β-oxide (**5**) the rearrangement was achieved using diphenyl phosphate and 4-bromophenol, providing the clovane core structure **17** in 35% yield with clovene as a major by-product. Conversion of bromide **17** to clovanemagnolol was achieved in 28% yield over the five steps using the same set of transformations as the caryolanemagnolol approach. The spectral data of isolated and synthetic clovanemagnolol fully matched.

With access to clovanemagnolol we have been able to test and quantify the small molecule's effects on different neuronal types. In preliminary studies we found that while clovanemagnolol consistently promoted outgrowth, caryolanemagnolol appeared to induce neuronal pruning in embryonic hippocampal neurons. This effect will be reported in due course. We therefore studied the small molecule-mediated outgrowth using clovanemagnolol.[13] For comparison, we measured the effects of clovanemagnolol *versus* the effects to the related and more extensively studied compound magnolol (**8**).[14] In both hippocampal and cortical neurons we found clovanemagnolol to be more effective at promoting neuronal growth (Fig. 6 and 7.). Interestingly, both compounds demonstrated biphasic dose profiles.

Effects of clovanemagnolol and magnolol on hippocampal neurons *in vitro* is concentration dependent

Dissociated embryonic hippocampal neurons were cultured *in vitro* in the presence of control, DMSO, or varying amounts of magnolol or clovanemagnolol (Fig. 6). After 2 days *in vitro*, we found that treatment with either magnolol (0.01 μM; $p < 0.02$) or clovanemagnolol (0.01 μM; $p < 0.03$) was able to significantly enhance the neurite outgrowth of neurons compared to control cultures. At 0.1 μM concentration, the addition of either molecule resulted in a modest enhancement in neurite outgrowth. At micromolar concentrations, treatment with either compound resulted in a significant decrease in the average neurite outgrowth (69.45 and 84.08% reduction for magnolol and clovanemagnolol, respectively). Therefore, we found that both magnolol and clovanemagnolol have neurite outgrowth enhancing properties in embryonic hippocampal neurons in a concentration dependent manner (Table 1).[12]

Effects of clovanemagnolol and magnolol on cortical neurons *in vitro* is concentration dependent

Dissociated embryonic cortical neurons were treated with either magnolol or clovanemagnolol (Fig. 7). At lower concentrations clovanemagnolol's effects on growth were shown to be greater than magnolol. After 2 days *in vitro* we found that treatment with magnolol resulted in enhanced neurite outgrowth at both 0.01 and 0.1 μM concentrations, although only treatment at 0.1 μM reached statistical significance ($p < 0.03$). Treatment with clovanemagnolol resulted in a significant increase in neurite outgrowth at 0.01 μM ($p < 0.01$), whereas treatment at 0.1 μM resulted in a slight increase in average neurite length ($p > 0.05$) (Table 2). At higher concentration (1 μM), the addition of both compounds resulted in significant reduction for both magnolol and clovanemagnolol treated cells ($p < 0.001$) compared to neurons in the control culture. Therefore, similar to hippocampal neurons, we found that treatment with either magnolol or clovanemagnolol has neurite outgrowth enhancing properties for embryonic cortical neurons, and this effect is concentration dependent.

Cell culture and isolation of primary cells

Primary neuronal cells were obtained from E16–E18 mouse embryos. Pregnant mice were sacrificed using isoflurane asphyxiation and embryos were collected in 1x Hank's buffered salt solution (HBSS) with gentamycin. After removing the meninges, cortical tissue or hippocampi were dissected away from the surrounding tissue. Samples were treated with 0.25% Trypsin/EDTA (Sigma–Aldrich) for 20 min and were mechanically dissociated using fire polished Pasteur pipettes. Cells were plated on 12 mm round glass coverslips coated with Poly-D-Lysine (20 μg ml^{-1}) at a density of 30 000 cells per coverslip in a DMEM/F12 media supplemented with N2 in the absence of serum. All cultures were grown at standard condition with 37 °C in 5% CO_2. Cells were fed every 3 days by replacing half of the media with fresh medium.

Immunostaining

After 2–4 days in culture, cells were fixed with 2% paraformaldehyde at room temperature for 20 min, and incubated in blocking buffer (3% normal goat serum + 0.3% Triton X-100 in PBS) for 1 h at room temperature. Primary antibody staining against betaIII tubulin (1 : 1000, Abcam) was used to visualize neurons. Samples were incubated with primary antibody in blocking buffer overnight at 4 °C. Samples were washed with PBS and incubated with goat anti-mouse IgG conjugated to AlexaFluor 488 (Invitrogen). Samples were counter stained with DAPI (1 : 1000, Sigma–Aldrich) to visualize all nuclei, and mounted onto glass slides using Fluoromount G (SouthernBiotech, Birmingham,

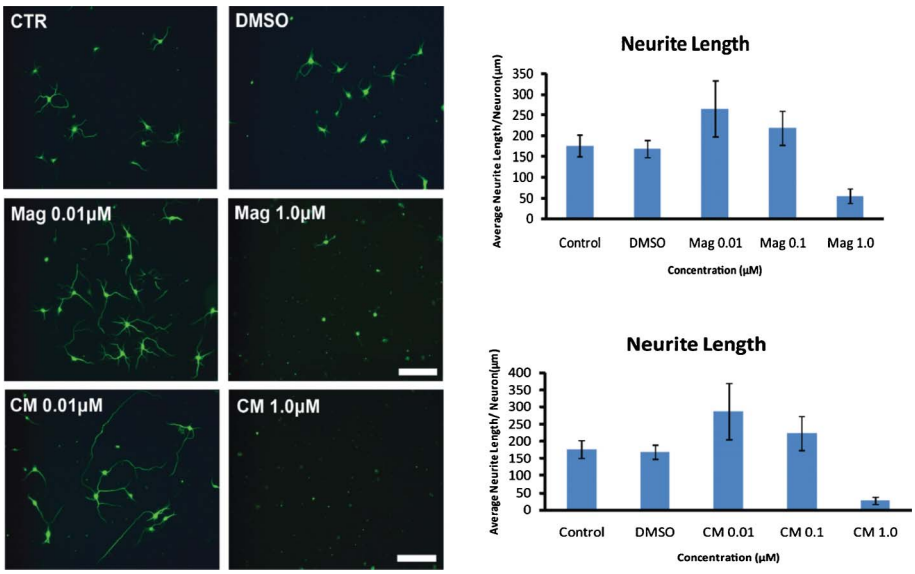


Fig. 6 Embryonic hippocampal neurons showed enhanced neurite outgrowth after treatment with magnolol (Mag) and clovanemagnolol (CM). Dissociated E18 mouse hippocampal neurons were cultured in control (CTR, medium only), DMSO (medium + DMSO), magnolol (0.01–1.0 μM), or clovanemagnolol (0.01–1.0 μM). After 2 days *in vitro*, 0.01 μM concentration magnolol can significantly increase the neurite length (48%, $p < 0.02$). Treatment with clovanemagnolol also resulted in significant increase in neurite outgrowth at 0.01 μM (63%, $p < 0.03$). However, treatment with higher concentration of either compound resulted in fewer numbers of neurons, bearing significantly shorter neurites for both.[12]

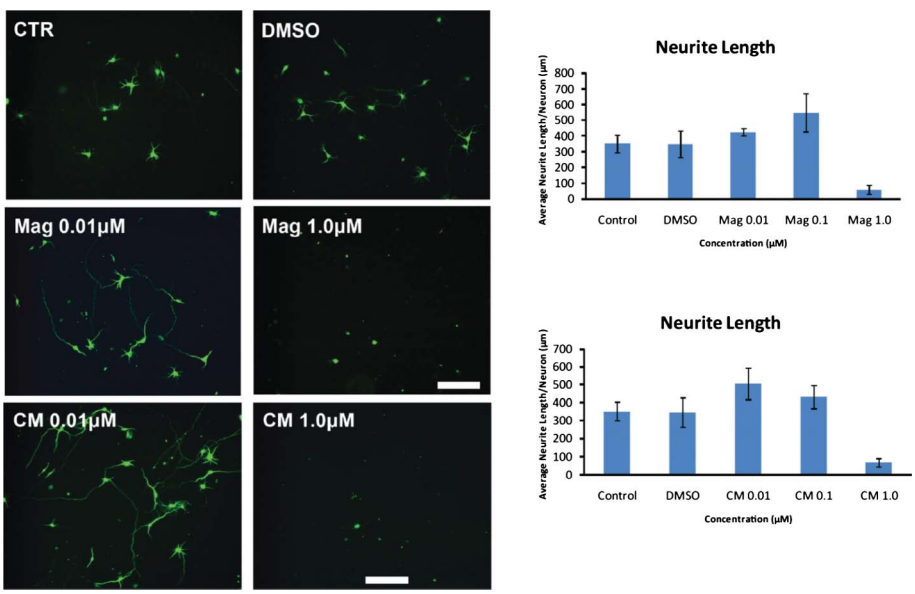


Fig. 7 Embryonic cortical neurons showed enhanced neurite outgrowth after treatment with magnolol (Mag) and clovanemagnolol (CM). Dissociated E18 mouse hippocampal neurons were cultured in control (CTR, medium only), DMSO (medium + DMSO), magnolol (0.01–1.0 μM), or clovanemagnolol (0.01–1.0 μM). After 2 days *in vitro*, 0.1 μM concentration magnolol can significantly increase the neurite length (56%, $p < 0.03$). Treatment with clovanemagnolol also resulted in significant increase in neurite outgrowth at 0.01 μM (44%, $p < 0.01$). However, treatment with higher concentration of either compound resulted in fewer numbers of neurons, bearing significantly shorter neurites.[12]

Alabama). Three to five random areas (covering 30% of the total surface area of the 12 mm glass coverslip) were recorded using an Olympus IX70 (Olympus America, Melville, NY) inverted microscope and the images were captured with an Optronics MagnaFire (Goleta, CA) digital color camera. Acquired images were analyzed using ImageJ, and composite figures were produced using Adobe Photoshop CS4.

Analysis of neurite outgrowth

To determine the average neurite length, samples were imaged at 3–5 random areas (covering over 30% of the glass coverslip). Using the ImageJ Plug-in "Neurite Tracer" program automated quantification of neurite growth was determined as previously described.[15]

Conclusion

The previous data for clovanemagnolol in primary neuronal cultures had reported the growth effects at 100 nM.[6] In this study we have shown that clovanemagnolol, in primary neuronal culture, demonstrates a biphasic dose response an shows activity at the lower concentration than previously reported, 10 nM. This effect was seen in both hippocampal and cortical neurons. Magnolol showed a similar effect in cortical but not hippocampal neurons. These interesting biological effects warrant further study to determine the mechanism of action. This biphasic activity leads us to hypothesize that clovanemagnolol is functioning by inducing the dimerization of cell surface receptors similar to proteinaceous growth factors. These studies will be reported in due course.

Experimental

General

All reactions were performed in flame dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or canula. Where necessary (so noted), solutions were deoxygentated by alternative freeze (liquid N_2)/evacuation/thaw cycles (≥three iterations). Organic solutions were concentrated by rotary evaporation at ~20 Torr. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or exposure to an acidic solution of *p*-anisaldehyde or ceric ammonium molybdate solution followed by heating on a hot plate. Dichloromethane, tetrahydrofuran, toluene, and benzene were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). All commercial reagents were used directly, without further purification unless otherwise notes. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Varian Gemini (400 MHz) or Varian (300 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane and referenced relative to residual protium in NMR solvents ($CHCl_3$: δ 7.26 ppm, C_6D_5H: δ 7.15 ppm: D_2HCOD: δ 3.31 ppm). Chemical shifts for carbon are reported in ppm downfield of tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ δ 77.0, C_6D_6 δ 128.0, D_3COD: δ 44.9). Infrared spectra (IR) were recorded on a Nicolet 380 FTIR using thin film (neat). Optical rotations were measured on an ATAGO AP-300 automatic polarimeter with a path length of 100 mm. Melting points were measured on a MEL-TEMP device without correction. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 at the UT Mass Spectrometry Facility.

Epoxides 4 & 5

To a solution of (β)-caryophyllene (2.27 g (90% purity), 10 mmol, 1 equiv.) in acetonitrile (50 mL) and dimethoxymethane (100 mL) was added a buffer solution (100 mL, 0.05 M $Na_2B_4O_7$·10 H_2O in 4 × 10^{-4} M Na_2(EDTA)), *n*-Bu_4HSO_4 (140 mg, 0.4 mmol, 0.04 equiv.), L-Shi catalyst **10** (2.58 g, 10 mmol, 1 equiv.), and cooled to 0 °C. Addition of Oxone® (8.5 g, 13.8 mmol, 1.38 equiv.) in buffer aqueous solution (65 mL, 4 × 10^{-4} M Na_2EDTA aqueous solution) and K_2CO_3 aqueous solution (9.3 g, 67.3 mmol, 6.73 equiv. in water (65 mL) in separate syringes over 1.5 h using a syringe pump. After complete addition, the reaction mixture was extracted with hexane (100 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by silica gel chromatography (hexane/EtOAc = 95 : 5 as eluent) to give a light yellow oil, 1.64 g, yield 74%. TLC R_f 0.24, Hex/EA = 95 : 5. ^{1}H NMR showed a 2.2 : 1 diastereomeric ratio of epoxides **4** and **5**, respectively, with epoxide **4** as the major isomer. NMR data matches that reported.[16]

To a solution of (β)-carophyllene (5.6 g (90% purity), 24.7 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) under argon at 0 °C was added *m*-CPBA (4.51 g, 25.9 mmol, 1.05 equiv.) in CH_2Cl_2 (30 mL) over 30 min *via* syringe pump, the reaction mixture became heterogeneous after 15 min. After stirring for an additional hour at 0 °C the mixture was filtered through cotton. The filtrate was concentrated, diluted with hexane (40 mL), and washed with 1 N NaOH (30 mL × 2). The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95 : 5 as eluent) provided a colorless oil (4.5 g, 83%). TLC R_f 0.24, Hex/EA = 95 : 5. ^{1}H NMR showed a 1 : 5 diastereomeric ratio of epoxides **4** and **5**, respectively. NMR data matches that reported.[16]

Caryolanemagnolol (1)

To a solution of (β)-caryophyllene α-oxide **4** (40 mg, 2.2 : 1 ratio of α-oxide **4** to β-oxide **5**, 0.125 mmol of **4**, 1 equiv. of **4**) and magnolol (**8**) (49.3 mg, 0.185 mmol, 1.5 equiv.) in dichloromethane (2 mL) at 23 °C was added a solution of diphenylphosphate (15.4 mg, 0.062 mmol, 0.5 equiv.) in dichloromethane (1 mL) over 3 min. Then the orange solution was stirred at 38 °C for 2.5 h the solvent was removed and the residue was diluted with hexane (50 mL). The hexane solution was washed with phosphate buffer (pH 7.4, 2 × 10 mL) and 1 N NaOH (3 × 10 mL (to recover the magnolol)). The organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solution was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc = 85 : 15 as eluent) to yield a mixture of caryolanemagnolol **1** and clovanemagnolol **2**. The mixture was purified by a second round of silica gel chromatography (100% dichloromethane as eluent) to provide pure caryolanemagnolol **1** as a colorless oil (9.1 mg, 15% yield). TLC R_f 0.25, hexane/EtOAc = 80 : 20; $[\alpha]_D^{26}$ = 61.6, (*c* 2.1, $CHCl_3$); ^{1}HNMR (400 MHz, C_6D_6): δ 0.60 (s, 3H), 0.80 (dt, *J* = 4.2, 14.7 Hz, 1H), 0.88 (s, 3H), 1.08 (s, 3H), 1.12–1.41 (m, 6H), 1.44–1.59 (m, 2H), 1.64–1.82 (m, 2H), 1.91–2.03 (m, 2H), 2.16 (ddd, *J* = 1.9, 10.2, 20.1 Hz, 1H), 2.90 (t, *J* = 3.0 Hz, 1H), 3.16 (d, *J* = 6.8 Hz, 2H), 3.24 (d, *J* = 6.6 Hz, 2H), 4.94–5.04 (m, 4H), 5.82 (ddt, *J* = 6.8, 10.1, 16.8 Hz, 1H), 5.94 (ddt, *J* = 6.6, 10.2, 20.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.97 (dd, *J* = 2.2, 8.3 Hz, 1H), 7.03 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 20.2, 20.5, 26.3, 28.4, 29.2, 30.0, 34.6, 35.3, 36.1, 38.7, 39.2, 39.41, 39.44, 39.5, 43.8, 71.0, 84.1, 115.0, 118.4, 123.7, 128.2, 128.7, 129.4, 131.3, 132.0, 133.5, 135.6, 137.2, 138.1, 149.4, 153.0; FTIR: 3361, 1638, 1491, 1209, 1045, 938, 822 cm^{-1}. MS (ESI): M+Na^+ 509. HRMS (ESI+), calculated for $C_{33}H_{41}O_3$ (M–(H^-)) 485.3060, found 485.3061.

Note: reported optical rotations $[\alpha]_D^{23.5} = 11.2$, synthetic material $[\alpha]_D^{26} = 61.6$, see ref. 6.

Clovanemagnolol (2)

To a solution of recrystallized β-caryophyllene β-oxide **5** (60 mg, 0.259 mmol, 1 equiv.) and magnolol (**8**) (103 mg, 0.388 mmol, 1.5 equiv.) in dichloromethane (2 mL) was added a solution of diphenylphosphate (32.4 mg, 0.129 mmol, 0.5 equiv.) in dichloromethane (1 mL) over 3 min. The orange solution was stirred at 38 °C for 2.5 h then the solvent was removed. The residue was diluted with hexane (50 mL) and washed with phosphate buffer (pH 7.4, 2 × 10 mL) and 1 N NaOH (3 × 10 mL (to recover the magnolol)). The organic layer was washed with brine (10 mL) and dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 85 : 15 as eluent) to yield clovanemagnolol (**2**) as a colorless oil (12 mg, 10% yield). TLC R_f 0.22, hexane/EtOAc = 80 : 20; $[\alpha]_D^{26} = 96.0$, (*c* 1.5, $CHCl_3$); ^{1}HNMR (400 MHz, C_6D_6): δ 0.64 (s, 3H), 0.70 (d, J = 12.8 Hz, 1H), 0.83 (s, 3H), 0.83 (m, 1H), 0.92 (s, 3H), 0.98–1.18 (m, 4H), 1.26 (dd, J = 5.5, 11.4 Hz, 1H), 1.35 (m, 1H), 1.50–171 (m, 4H), 1.79 (dt, J = 3.7, 13.3 Hz, 1H), 3.04 (s, 1H), 3.18 (d, J = 6.8 Hz, 2H), 3.23 (d, J = 6.6 Hz, 2H), 4.10 (dd, J = 5.7, 8.5 Hz, 1H), 4.96–5.01 (m, 3H), 5.03 (dd, J = 1.7, 3.4 Hz, 1H), 5.81–5.98 (m, 2H), 6.58 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 2.3, 8.2 Hz, 1H), 7.04 (dd, J = 2.3, 8.4 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 20.6, 25.1, 26.5, 26.7, 28.3, 30.9, 32.8, 34.4, 35.4, 37.4, 39.3, 39.4, 44.2, 45.0, 49.9, 74.3, 89.4, 115.0, 115.4, 115.9, 117.4, 127.1, 128.9, 129.2, 129.4, 131.2, 131.8, 132.5, 133.8, 137.4, 138.0, 152.8, 154.2; FTIR: 3394, 1638,1232, 822 cm^{-1}; HRMS (CI+), calculated for $C_{33}H_{42}O_3$ 486.3131, found 486.3134.

Note: reported optical rotations $[\alpha]_D^{25} = 21.0$, synthetic material $[\alpha]_D^{26} = 96.0$, see ref. 6.

Bromide 11

To a solution of *p*-bromophenol (1.93 g, 11.2 mmol, 1.5 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of $AlMe_3$ in hexane (1 M, 3.72 mL, 3.72 mmol, 0.5 equiv.) over 5 min, followed by stirring at 0 °C for 30 min, warmed to 23 °C, and stirred for 1 h. Then the solution was concentrated and *p*-bromophenol (1.93 g, 11.2 mmol, 1.5 equiv.) in CH_2Cl_2 (30 mL) was added at 0 °C dropwise. After stirring for 10 min a solution of caryophyllene oxide (1.64 g (2.2 : 1 ratio of epoxides), 5.1 mmol of **4**, 1 equiv. of **4**) in CH_2Cl_2 (20 mL) was added over 30 min. The mixture was stirred at 0 °C for an additional 2 h then the solvent was removed and the residue was suspended with hexane (200 mL). The organic layer was washed with 2 N HCl (50 mL), 1 N NaOH (50 mL), and brine (30 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated to provide a viscous residue. The residue was purified by silica gel chromatography (hexane/EtOAc = 9 : 1 as eluent) to give bromide **11** as a clear oil (1.37 g, yield 69% from **4**). TLC R_f 0.24, hexane/EtOAc = 85 : 15. $[\alpha]_D^{26} = 90.3°$, (*c* 1.5, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.00 (s, 3H), 1.14–1.21 (m, 1H), 1.37–1.87 (m, 10H), 1.96–2.06 (m, 2H), 2.34 (ddd, J = 2.1, 3.4, 18.2 Hz, 1H), 3.49 (dd, J = 3.0, 4.6 Hz, 1H), 6.73 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.1, 26.4, 28.3, 30.3, 30.5, 34.7, 36.0, 37.5, 39.2, 40.3, 41.9, 44.8, 71.6, 80.7, 114.0, 123.2, 131.5, 154.7; FTIR: 3394, 1638, 1493, 1232 cm^{-1}; HRMS (ESI+) calculated for $C_{21}H_{29}BrO_2Na$ 415.1249, found 415.1243.

Dibromide 12

To a solution of bromide **11** (1.23 g, 3.13 mmol, 1 equiv.), triethylamine (0.87 mL, 6.25 mmol, 2 equiv.), and 4-dimethylaminopyridine (0.382 g, 3.13 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) at 0 °C was added acetic anhydride (0.443 mL, 4.69 mmol, 1.5 equiv.). The solution was stirred at 23 °C for 20 min then the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2 N HCl (30 mL), 1 N NaOH (20 mL), and brine (10 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 95 : 5 as eluent) to yield the acetate of **11** as a colorless oil (1.14 g, 84%). TLC R_f 0.28, hexane/EtOAc = 95 : 5; ^{1}HNMR (400 MHz, $CDCl_3$): δ 0.87 (s, 3H), 0.99 (s, 3H), 1.01 (s, 3H), 1.20–1.28 (m, 1H), 1.39–2.06 (m, 9H), 1.91–2.06 (m, 3H), 2.01 (s, 3H), 2.36 (ddd, J = 1.3, 10.2, 11.7 Hz, 1H), 4.71 (t, J = 3.7 Hz, 1H), 6.73 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.1, 21.2, 25.7, 26.6, 30.3, 34.7, 35.9, 37.8, 38.3, 40.2, 43.1, 44.9, 73.6, 80.4, 113.8, 122.7, 131.6, 154.7, 170.6. FTIR: 1734, 1486, 1245 cm^{-1}; HRMS (ESI+), calculated for $C_{23}H_{31}BrO_3Na$ 457.1349, found 457.1349.

To a reaction flask containing the acetate of **11** (0.832 g, 1.91 mmol, 1 equiv.) and sodium acetate (0.314 g, 3.82 mmol, 2 equiv.) in acetic acid (10 mL) was added bromine (0.404 mL, 7.64 mmol, 4 equiv.) dissolved in acetic acid (5 mL) in a single portion. The reaction was heated to 60 °C for 4 h. The reaction was diluted with hexane (100 mL) and washed with water (100 mL × 3), 1 N NaOH (20 mL × 3), and then brine (30 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95 : 5) provided dibromide **12** as a colorless oil (0.902 g, 92%). TLC R_f 0.28, hexane/EtOAc = 95 : 5; ^{1}HNMR (400 MHz, $CDCl_3$): δ 0.89 (s, 3H), 1.01 (s, 3H), 1.02 (s, 3H), 1.23–1.29 (m, 1H), 1.39–2.01 (m, 11H), 2.03 (s, 3H), 2.13 (m, 1H), 2.29–2.43 (m, 1H), 4.71 (t, J = 3.2 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 7.24 (dd, J = 2.4, 8.8 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.0, 21.2, 25.7, 26.7, 30.3, 30.9, 34.8, 35.8, 37.7, 38.4, 40.3, 42.4, 44.7, 73.6, 83.0, 114.0, 117.9, 122.5, 130.2, 135.4, 152.1, 170.6. FTIR: 1738, 1467, 1040, 1017 cm^{-1}; HRMS (ESI+), calculated for $C_{23}H_{30}Br_2O_3Na$ 535.0455, found 535.0454.

Acetate 14

To a mixture of dibromide **12** (640 mg, 1.24 mmol, 1 equiv.), $Pd(PPh_3)_4$ (288 mg, 0.249 mmol, 0.2 equiv.), and NaOH (0.995 g, 24.9 mmol, 20 equiv.) was added toluene (18 mL), water (9 mL), and pinacol allylboronate **13** (4.0 mL, 16.0 mmol, 13 equiv.) followed by vigorous stirring (1200 rpm) at 90 °C for 55 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic extracts were combined with silica gel (1 g) and the sample was concentrated to dryness. The sample was purified by silica gel chromatography (hexane/EtOAc = 95 : 5 as eluent) to provide **14** as a colorless oil (430 mg, 72%). TLC R_f 0.30, hexane/EtOAc = 95 : 5; ^{1}HNMR

(400 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.01 (s, 3H), 1.02 (s, 3H), 1.21–1.27 (m, 1H), 1.39–1.65 (m, 4H), 1.73 (dd, J = 8.0, 9.6 Hz, 1H), 1.88–1.91 (m, 5H), 1.95–2.00 (m, 1H), 2.02 (s, 3H), 2.16 (m, 1H), 2.37 (ddd, J = 1.7, 3.6, 18.2 Hz, 1H), 3.28 (d, J = 6.7 Hz, 2H), 4.70 (t, J = 3.0 Hz, 1H), 5.03–5.06 (m, 1H), 5.08–5.09 (m, 1H), 5.86–5.96 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 2.2, 8.4 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.0, 21.2, 25.7, 26.7, 30.3, 30.8, 34.8, 35.8, 37.5, 38.4, 39.0, 40.3, 42.4, 44.6, 73.8, 82.2, 116.1, 117.1, 121.7, 127.4, 133.1, 134.8, 136.9, 150.9, 170.6; FTIR: 1737, 1486, 1247 cm^{-1}; HRMS (ESI+), calculated for $C_{26}H_{35}BrO_3Na$ 497.1665, found 497.1662.

Carbamate 16

To a flask containing acetate **14** (330 mg, 0.694 mmol, 1 equiv.), borate ester **15** (997 mg, 2.78 mmol, 4 equiv.), and NaOH (333 mg, 8.33 mmol, 12 equiv.) followed by addition of toluene (7 mL) and water (5 mL, sparged with argon for 5 min). A solution of $Pd_2(dba)_3$ (39.9 mg, 0.069 mmol, 0.1 equiv.) and ^{t}Bu$_3$P (51 µL, 0.208 mmol, 0.3 equiv.) in toluene (3 mL) was then added. The mixture was immediately placed in a 90 °C oil bath and stirred at 1200 rpm for 30 min (color transition of red to yellow to brown to dark brown). After cooling the mixture was diluted with EtOAc (50 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 90 : 10 as eluent) provided **16** as colorless oil (308 mg, 71%). TLC R_f 0.42, hexane/EtOAc = 80 : 20; ^{1}HNMR (300 MHz, C_6D_6): δ 0.72 (s, 3H), 0.77 (t, J = 7.2 Hz, 3H), 0.82–0.87 (m, 3H), 0.91 (s, 3H), 0.99 (s, 3H), 1.03–1.60 (m, 10H), 1.66 (s, 3H), 1.68–1.82 (m, 2H), 1.88 (t, J = 9.7 Hz, 1H), 2.09 (dd, J = 8.8, 20.8 Hz, 1H), 2.90–3.12 (m, 4H), 3.21 (t, J = 8.0 Hz, 4H), 4.23 (bs, 1H), 4.91–5.03 (m, 4H), 5.82–5.96 (m, 2H), 6.87 (d, J = 8.3 Hz, 1H), 6.97 (dd, J = 1.9, 8.5 Hz, 2H), 7.20 (d, J = 1.9 Hz, 2H), 7.32 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 13.4, 14.0, 20.6, 20.9, 24.8, 25.9, 26.7, 30.3, 30.7, 34.6, 35.8, 36.7, 38.3, 39.7, 39.9, 40.3, 41.5, 41.9, 42.0, 44.2, 73.5, 80.8, 115.5, 115.7, 122.5, 123.3, 131.9, 132.4, 132.8, 133.1, 133.3, 135.8, 136.7, 137.6, 137.7, 137.8, 148.1, 151.7, 153.8, 169.5. FTIR: 1737, 1486, 1247 cm^{-1}; HRMS (CI+), calculated for $C_{40}H_{53}NO_5$ 627.3924, found 627.3921.

Caryolanemagnolol (1)

To the solution of carbamate **16** (80 mg, 0.127 mmol, 1 equiv.) in tetrahydrofuran (2 mL) was added $LiAlH_4$ solution in tetrahydrofuran (1 M, 2.55 mL, 2.55 mmol, 20 equiv.) dropwise at 23 °C. The mixture was heated to reflux for 2 h and then cooled to 23 °C and **cautiously** quenched with water (5 mL). The mixture was diluted with diethyl ether (10 mL) and 2 N HCl (5 mL). The organic layer was collected and washed with brine (20 mL). The organic phase was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc = 85 : 15) to provide caryolanemagnolol (**1**) as a colorless pasty oil (44 mg, 71%).

Bromide 17

To a solution of β-caryophyllene β-oxide (recrystallized from benzene)[3] (5 g, 21.6 mmol, 1 equiv.) and *p*-bromophenol (11.9 g, 64.7 mmol, 3 equiv.) in CH_2Cl_2 (80 ml) at 0 °C was added a solution of diphenylphosphate (2.70 g, 10.8 mmol, 0.5 equiv.) in CH_2Cl_2 (20 mL) over 30 min. The gray solution was stirred at 0 °C for 4 h and then the solvent was removed under vacuum. The residue was diluted with hexane (300 mL) and washed with 1 N NaOH (50 mL × 3). The organic layer was washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 90 : 10 as eluent) to provide bromide **17** as a white solid (3.1 g, 35% yield). TLC R_f: 0.34 hexane/EtOAc = 85 : 15; Mp 114–116 °C; $[\alpha]_d^{26}$ = 93.1°, (c 1.7, $CHCl_3$); ^{1}HNMR (400 MHz, CDCl3): δ 0.94 (s, 3H), 0.95 (s, 3H), 0.96–1.04 (m, 2H), 1.06 (s, 3H), 1.09–1.21 (m, 1H), 1.32–1.43 (m, 3H), 1.48–1.68 (m, 6H), 1.79 (dt, J = 4.7, 13.6 Hz, 1H), 1.85 (dd, J = 5.4, 12.7 Hz, 1H), 1.98–2.07 (m, 1H), 3.34 (bs, 1H), 4.19 (dd, J = 5.4, 7.9 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 20.9, 25.7, 26.6, 27.2, 28.3, 31.6, 33.1, 34.7, 36.0, 38.3, 43.8, 45.3, 50.0, 74.9, 86.5, 112.3, 117.5, 132.1, 158.1; FTIR: 3416, 1486, 1243 cm^{-1}; HRMS (ESI+), calculated for $C_{21}H_{28}BrO$ (M–H_2O) 375.1323, found 375.1318.

Dibromide 18

To a solution of bromide **17** (2.6 g, 6.38 mmol, 1 equiv.) and 4-dimethylaminoyridine (0.78 g, 6.38 mmo, 1 equiv.) in CH_2Cl_2 (40 mL) at 0 °C was added triethylamine (1.78 mL, 12.8 mmol, 2 equiv.). Subsequently, acetic anhydride (1.21 mL, 12.8 mmol, 2 equiv.) was added dropwise over 10 min. The solution was stirred at 0 °C for 1 h then diluted with CH_2Cl_2 (100 mL) washed with 1 N NaOH (30 mL), 2 N HCl (30 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 95 : 5) to provide the acetate of **17** as a colorless oil (2.50 g yield 87%). TLC R_f 0.32, hexane/EtOAc = 95 : 5; ^{1}HNMR (400 MHz, CDCl3): δ 0.85 (s, 3H), 0.94 (s, 3H), 1.05 (s, 3H), 1.09 (d, J = 12.6 Hz, 1H), 1.21–1.28 (m, 1H), 1.33–1.74 (m, 9H), 1.85 (d, J = 5.4, 12.8 Hz, 1H), 1.93–1.99 (m, 1H), 2.02 (s, 3H), 4.20 (dd, J = 1.9, 7.4 Hz, 1H), 4.57 (b, 1H), 6.77 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 20.8, 21.3, 24.1, 25.8, 27.8, 28.1, 31.7, 32.8, 33.6, 36.9, 38.5, 43.7, 45.3, 50.0, 86.5, 112.4, 117.6, 132.1, 157.9, 170.8; FTIR: 1733, 1486 cm^{-1}; HRMS (ESI+), calculated for $C_{23}H_{31}BrO_3Na$ 457.1356, found 457.1349.

To a solution of the acetate of **17** (2.00 g, 4.45 mmol, 1 equiv.) and sodium acetate (0.73 g, 8.9 mmol, 2 equiv.) in acetic acid (30 mL) was added a solution of bromine (0.918 mL, 17.8 mmol, 4 equiv.) in acetic acid (10 mL) over 1 min. The flask was stirred at 60 °C for 4 h. The mixture was diluted with hexane (200 mL) and washed with water (3 × 100 mL), 1 N NaOH (3 × 100 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95 : 5 as eluent) gave dibromide **18** as a colorless oil (2.01 g, 85%). TLC R_f 0.32, hexane/EtOAc = 95 : 5; ^{1}HNMR (400 MHz, CDCl3): δ 0.87 (s, 3H), 0.96 (s, 3H), 1.08 (s, 3H), 1.10 (d, J = 13.2 Hz, 1H), 1.24–1.31 (m, 1H), 1.35–1.48 (m, 1H), 1.53–1.85 (m, 7H), 1.88 (dd, J = 5.3, 13.0 Hz, 1H), 1.96–2.01 (m, 1H), 2.03 (s, 3H), 4.21 (dd, J = 0.9, 6.5 Hz, 1H), 4.58 (bs, 1H), 6.73 (d, J = 8.9 Hz, 1H), 7.32 (dd, J = 2.4, 8.8 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3): δ 20.8, 21.3,

24.3, 25.9, 27.9, 28.1, 31.8, 32.8, 33.6, 36.8, 39.0, 43.7, 45.9, 49.9, 87.9, 112.3, 114.0, 115.4, 130.9, 135.5, 154.4, 170.8; FTIR: 1735, 1246, 1042 cm^{-1}; HRMS (ESI+), calculated for $C_{23}H_{30}Br_2O_3Na$ 535.0455, found 535.0454.

Acetate 19

To a flask charged with substrate **18** (0.488 g, 0.948 mmol, 1 equiv.), NaOH (0.758 g, 17.0 mmol, 18 equiv.), and tetrakis(triphenylphosphine)palladium (0.219 g, 0.190 mmol, 0.2 equiv.) under argon was added toluene (10 mL), water (5 mL, sparged with argon for 5 min), and allyl pinacol borate **13** (3.05 mL, 15.17 mmol, 16 equiv.). The biphasic mixture was stirred at 1200 rpm at 90 °C for 50 min whereupon TLC (hexane/EtOAc = 97 : 3) showed full conversion. The mixture was cooled to 23 °C and extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 97 : 3 as eluent) to provide acetate **19** as a colorless oil (0.316 g, yield 70%). TLC R_f 0.33, hexane/EtOAc = 95 : 5; ^{1}HNMR (400 MHz, CDCl3): δ 0.87 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 1.10 (d, J = 7.2 Hz, 1H), 1.25–1.48 (m, 4H), 1.53–1.78 (m, 5H), 1.88 (dd, J = 5.3, 12.9 Hz, 2H), 1.96–2.01 (m, 1H), 2.03 (s, 3H), 3.29 (d, J = 6.7 Hz, 2H), 4.22 (dd, J = 5.4, 7.0 Hz, 1H), 4.58 (b, 1H), 5.04–5.07 (m, 1H), 5.07–5.09 (m, 1H), 5.86–5.96 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 2.2, 8.3 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3): δ 20.8, 21.3, 24.2, 25.8, 27.9, 28.1, 31.8, 32.8, 33.6, 36.8, 38.8, 38.9, 43.9, 45.7, 49.9, 87.7, 113.0, 114.4, 116.0, 128.2, 133.2, 133.3, 137.1, 153.5, 170.9; FTIR: 1735, 1248 cm^{-1}; HRMS (ESI+), calculated for $C_{26}H_{35}BrO_3Na$ 497.1665, found 497.1662.

Carbamate 20

To a flask charged with acetate **19** (200 mg, 0.421 mmol, 1 equiv.), the pinacol ester **15** (604 mg, 1.683 mmol, 4 equiv.), and NaOH (202 mg, 5.05 mmol, 12 equiv.) under argon was added toluene (6 mL), water (4 mL, sparged with argon for 5 min) and a solution of $Pd(dba)_2$ (24.2 mg, 0.042 mmol, 0.1 equiv.), and $^tBu_3P$ (31 µL, 0.126 mmol, 0.3 equiv.) solution in toluene (2 mL, stirring for 10 min before addition). The mixture was immediately placed in a 90 °C oil bath and stirred at 1200 rpm for 30 min (red to yellow to brown to dark brown color sequence) then the reaction was diluted with EtOAc (30 mL) and water (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (hexane/EtOAc = 90 : 10 as eluent) provided carbamate **20** as a colorless pasty oil (196 mg, 74%). TLC R_f 0.40, hexane/EtOAc = 80 : 20; ^{1}HNMR (400 MHz, C_6D_6): δ 0.70 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 0.71–0.90 (m, 8H), 0.95–1.24 (m, 5H), 1.44 (d, J = 12.7 Hz, 1H), 1.50–1.70 (m, 5H), 1.80 (s, 3H), 2.91 (d, J = 5.4 Hz, 2H), 3.00 (d, J = 5.6 Hz, 2H), 3.18 (t, J = 7.5 Hz, 4 H), 4.01 (dd, J = 5.8, 15.6 Hz, 1H), 4.68 (b, 1H), 4.93–5.02 (m, 4H), 5.80–6.00 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 2.3, 8.3 Hz, 1H), 7.01 (dd, J = 2.3, 8.3 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H, Ar-H), 7.20 (d, J = 2.3 Hz, 1H, Ar-H), 7.31 (d, J = 8.3 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, C_6D_6): δ 13.1, 13.7, 18.1, 20.6, 24.2, 25.5, 27.8, 28.0, 31.4, 32.7, 33.3, 36.6, 38.2, 39.4, 39.6, 41.3, 41.7, 43.7, 45.4, 49.7, 76.3, 87.2, 115.0, 115.1, 115.4, 122.9, 129.1, 131.7, 131.8, 132.1, 135.7, 137.4, 137.8, 148.0, 153.5, 154.7, 169.4; FTIR: 1720, 1246, cm^{-1}; HRMS (CI+), calculated for $C_{40}H_{54}O_5N$ 628.4002, found 628.3986.

Clovanemagnolol (2)

To a solution of carbamate **20** (100 mg, 0.159 mmol, 1 equiv.) in tetrahydrofuran (4 mL) was added $LiAlH_4$ solution in tetrahydrofuran (1 M, 3.19 mL, 3.19 mmol, 20 equiv.) dropwise at 23 °C. The mixture was heated to reflux for 2 h and then cooled to 23 °C and the excess $LiAlH_4$ was **carefully** quenched with water (10 mL). The mixture was diluted with Et_2O (40 mL) and 2 N HCl (20 mL). The organic layer was collected and washed with brine (10 mL). The concentrated organic phase was purified by silica gel chromatography with hexane/EtOAc = 85 : 15 to provide the clovanemagnolol **2** as a colorless oil (57 mg, 73%).

Pinacol ester 15

To a solution of 4-allylphenol (2.0 g, 14.9 mmol, 1 equiv.) and 4-dimethylamino pyridine (3.64 g, 29.8 mmol, 2 equiv.) in CH_2Cl_2 (40 mL) was added a solution of diethyl chlorocarbamate (3.77 ml, 29.8 mmol, 2 equiv.) in CH_2Cl_2 (20 mL) at 0 °C. The solution was stirred at 0 °C for 2 h, 23 °C for 4 h, then diluted with CH_2Cl_2 (200 mL), washed with 1 N NaOH (100 mL), 2 N HCl (100 mL), and brine (50 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by silica gel chromatography (hexane/EtOAc = 85 : 15 as eluent) provided the carbamate as a yellow oil (2.7 g, 78% yield). TLC R_f 0.45, hexane/EtOAc = 80 : 20.

To THF (40 mL) under argon at −78 °C was added *s*-BuLi (1.21 M, 12.75 mL, 15.4 mmol, 1.2 equiv.) followed by TMEDA (2.33 mL, 15.4 mmol, 1.2 equiv.) providing a light yellow solution. After 30 min, a solution of the carbamate prepared above (3.0 g, 12.9 mmol) in THF (10 mL) was added over 10 min. The yellow solution was stirred for 2 h at −78 °C then trimethyl borate (2.87 mL, 25.7 mmol, 2 equiv.) was added followed by warming to 23 °C over 1 h (color fade upon addition of trimethyl borate). A solution of 0.1 N HCl (100 mL) was added and the aqueous phase was extracted with ether (20 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The oily residue was dissolved in methanol (40 mL) and pinacol (4.56 g, 38.6 mmol, 3 equiv.) was added as a solid. The solution was stirred at 23 °C for 1 h and the mixture was concentrated. The viscous residue was dissolved in EtOAc (30 mL) and washed with water (20 mL × 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (hexane/EtOAc = 90 : 10 as eluent) yielded the pinacol ester **15** as a colorless oil (3.8 g, 82% yield). TLC R_f 0.37, hexane/EtOAc = 80 : 20; ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.19 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.30 (s, 12H), 3.37 (q, J = 7.2 Hz, 2H), 3.37 (d, J = 8.0 Hz, 2H), 3.50 (q, J = 7.2 Hz, 2H), 5.03–5.09 (m, 2H), 5.95 (ddt, J = 6.7, 10.1, 16.8 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H, 7.24 (d, J = 2.3, 8.3 Hz, 1H), 7.57 (d, J = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 14.1, 24.9, 39.5, 41.6, 41.9, 83.4, 115.7, 122.2, 132.3, 136.2, 136.3, 137.5, 154.5, 154.9; FTIR: 1720, 1510 cm^{-1}; HRMS (CI+), calculated for $C_{20}H_{31}O_4NB$ 360.2348, found 360.2346.

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