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Total Synthesis of Anmindenol A and Its Application to the Design, Synthesis, and Biological Evaluation of Derivatives Thereof

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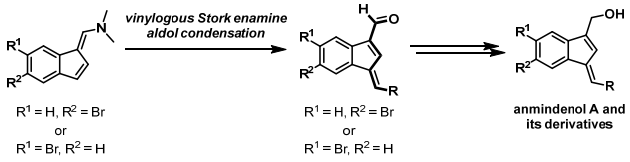


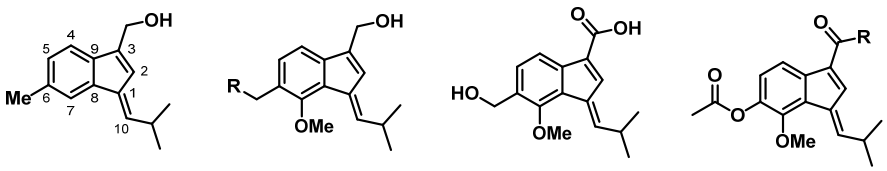
ABSTRACT

The first total synthesis of anmindenol A is described in four steps. A notable feature of the synthetic route includes the efficient construction of the 3,10-dialkylsubstituted benzofulvene core via a stereoselective vinylogous Stork enamine aldol condensation. The strategy provided a blueprint for the practical preparation of derivatives with modifications in the C-10 alkyl substituents. The novel derivatives inhibited nitric oxide production in stimulated RAW 264.7 macrophage cells.

INTRODUCTION

Benzofulvenes and related indenes are known as the key privileged structures of biologically active compounds[1] and are useful subunits in the field of materials science.[2] These semiaromatic structures with a polarized exocyclic olefin are rarely encountered in naturally occurring sesquiterpenoids.[3] Recently, a new class of benzofulvene sesquiterpenoids, which includes anmindenol A (**1**),[3a] nicotianasesterpenes A (**2**), B (**3**),[3b] and compounds **4**-**6**,[3c] was isolated from natural sources (Figure. 1).

Figure 1. Naturally occurring benzofulvene sesquiterpenoids.



anmindenol A (**1**) R = H : nicotianasesterpene A (**2**) R = OH : nicotianasesterpene B (**3**) **4** R = OH : **5** R = OMe : **6**

Despite their structural similarity, these natural benzofulvene sesquiterpenoids showed diverse biological activities, such as anti-inflammatory, antiviral, and anticancer.[3] Anmindenol A (**1**) was first identified from a marine-derived bacterium *Streptomyces sp.* in 2014.[3a] This target natural product consists of a unique indene skeleton, which is decorated by a synthetically formidable (*E*)-trisubstituted *exo*-olefin. Anmindenol A effectively inhibits inducible nitric oxide synthase (iNOS) without displaying any significant cytotoxicity.[3a] The structural uniqueness and biological properties of the benzofulvene sesquiterpenoid prompted us to attempt substantial synthetic effort toward total synthesis of **1** and its derivatization.

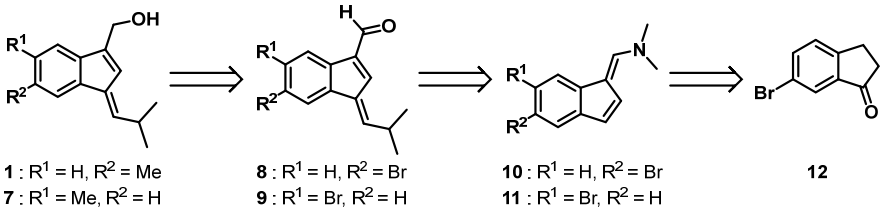
From a synthetic point of view, the major challenges for anmindenol A (**1**) are the stereoselective generation of the (*E*)-trisubstituted olefin at C-1/10 and the incorporation of the hydroxymethyl group at C-3. Several synthetic methods of structurally unique 3,10-disubstituted benzofulvenes have been reported: (a) condensation of 3-substituted indenes;[1,4] (b) acid-catalyzed cycloisomerization of 1,1,4-triphenylbutenyne;[5] (c) transition metal-catalyzed cycloisomerization of aromatic enynes;[6] and (d) Wolff rearrangement-induced cascade reaction of 1-diazonaphthalen-2(1*H*)-ones.[7] Although these reactions are highly relevant and valuable, almost all of them are probably inapplicable to the synthesis of **1** owing to harsh conditions, starting material incompatibility and poor synthetic efficiency and stereoselectivity. Recently, Lash *et al.* reported highly remarkable vinylogous-type Claisen-Schmidt condensation of indene-derived enamine, which successfully provides 10-aryl-3-formylbenzofulvenes under Lewis acid condition.[2a,8] Considering the reactive nucleophilicity of the enamine precursor and the mild conditions, the condensation would be feasible to form the uniquely challenging 3,10-dialkylbenzofulvenes by replacing aromatic aldehyde to aliphatic aldehyde even if the latter is enolizable. Accordingly, we sought to further expand the work of Lash *et al.* by exploiting vinylogous Stork enamine aldol condensation (VSEAC), thereby efficiently constructing the whole carbon framework of **1**. Herein, we describe our efforts toward total synthesis

of anmindenol A (**1**) through a stereoselective VSEAC, its application to the synthesis of a novel series of rationally designed 3,10-dialkylbenzofulvene derivatives, and biological evaluation of the synthesized compounds.

RESULTS AND DISCUSSION

Our retrosynthetic route for anmindenol A (**1**) and its regioisomer **7** is outlined in Scheme 1. The synthetic plan intended to utilize vinylogous Stork enamine aldol condensations of the enamine precursors **10** and **11** to construct the highly functionalized (*E*,*Z*)-*δ*-*i*Pr-*α*,*β*,*γ*,*δ*-unsaturated aldehydes **8** and **9**. The final benzofulvenes **1** and **7** could be readily obtained by Luche reduction[9] of the corresponding aldehydes **8** and **9** followed by Negishi cross-coupling with dimethylzinc.[10] Both enamine **10** and **11** were expected to be conveniently prepared as regioisomers from commercially available indanone **12**.

Scheme 1. Retrosynthesis of anmindenol A (**1**) and its regioisomer **7**.



1 : R^1 = H, R^2 = Me
7 : R^1 = Me, R^2 = H

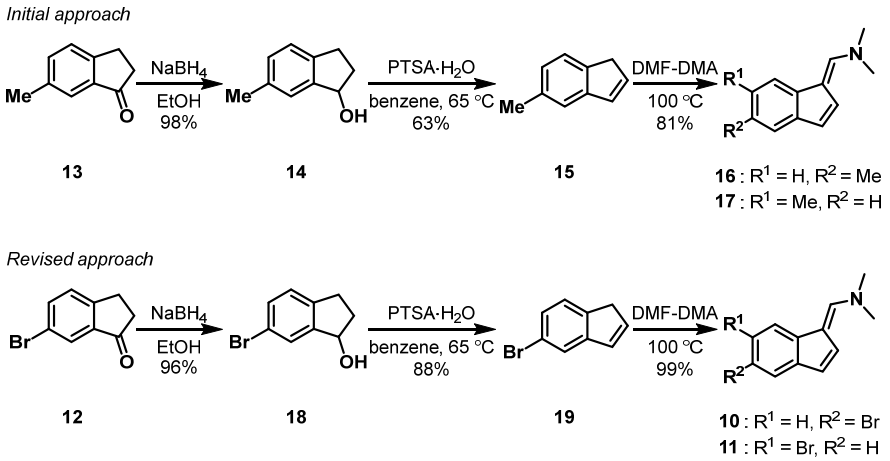
8 : R^1 = H, R^2 = Br
9 : R^1 = Br, R^2 = H

10 : R^1 = H, R^2 = Br
11 : R^1 = Br, R^2 = H

12

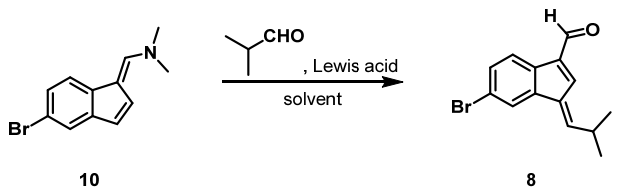
In order to prepare enamine precursors for VSEAC, we initially commenced the synthesis using indanone **13**, which had a methyl group inserted at the C-6 (Scheme 2). Exposure of **13** to $NaBH_4$ and the dehydration of the resulting alcohol **14** with *p*-toluenesulfonic acid afforded indene **15**.[11] Subsequent solvent-free condensation of **15** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) smoothly provided the enamine precursors **16** and **17** in a ratio of almost 1:1 in 81% combined yield.[12] Unfortunately, these regioisomers were inseparable by column chromatography. Thus, we circumvented the unexpected problem by employing 6-bromo-1-indanone (**12**) as a starting material, which was strategically advantageous not only to form stable enamines[13] but also to introduce a missing methyl group to the final benzofulvenes at the late stage. The same three-step sequence of **12** enabled to furnish the separable enamines **10** and **11** in a high yield (1.15:1 ratio by ^{1}H NMR analysis).

Scheme 2. Preparation of enamine precursors **10** and **11**.



With the stable enamine **10** in hand, we have investigated to determine the optimal reaction conditions for VSEAC (Table 1). Gratifyingly, an initial attempt with isobutyraldehyde stereoselectively resulted in the desired aldehyde **8** in a 7:1 *E*/*Z* ratio in a moderate yield under the relevant conditions (Table 1, entry 1).[8a] Encouraged by this result, further evaluation of different parameters, such as reagent, temperatures, concentration, and solvent, was performed to improve the stereoselectivity and productivity. Previous studies by Lash *et al.* showed that $TiCl_4$ as a Lewis acid is also applicable to vinylogous-type Claisen-Schmidt condensation.[2a] However, the use of $TiCl_4$ gave very low yield of the desired product **8** with the lower stereoselectivity (Table 1, entry 2). Although higher temperature (reflux) accelerated the reaction rate, no significant changes were observed (Table 1, entry 3). In addition, cooling the reaction temperature to −20 °C decreased the yield and stereoselectivity (Table 1, entry 4). Subsequently, we manipulated the reaction by increasing the enamine concentration by 10 times to allow eco-friendly scale-up synthesis,[14] however, the yield and stereoselectivity of aldehyde **8** were slightly diminished (Table 1, entry 5). Notably, switching the reaction solvent to THF led to greatly improved yield with the consistent stereoselectivity (Table 1, entry 6). Taken together, we concluded that the optimal reaction conditions are those in entry 6.

Table 1. Optimization of VSEAC of enamine **10** with isobutyraldehyde.

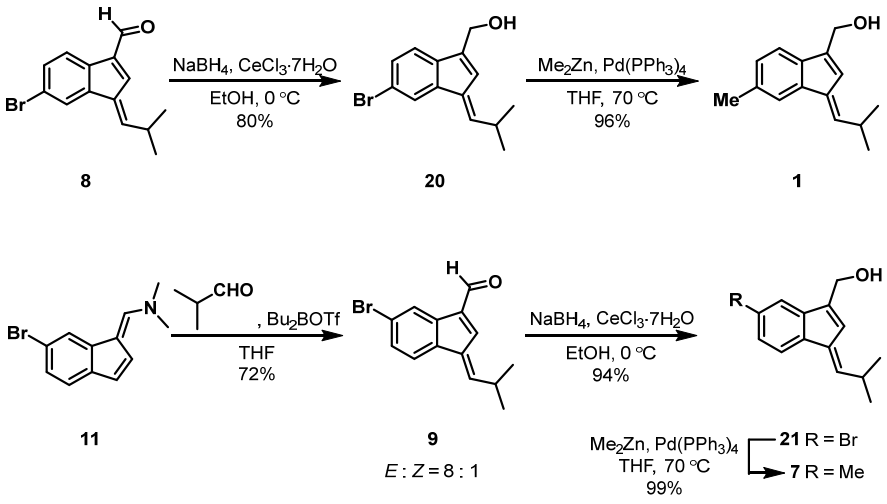


entry	Lewis acid	solvent	conc.(N)[a]	temp.	time	yield[b] (*E*/*Z* ratio)[c]
1	Bu_2BOTf	DCM	0.005	rt	4 h	65% (7 : 1)
2	$TiCl_4$	DCM	0.005	rt	14 h	7% (4.5 : 1)
3	Bu_2BOTf	DCM	0.005	reflux	3 h	62% (6 : 1)
4	Bu_2BOTf	DCM	0.005	-20 °C	24 h	16% (4.5 : 1)
5	Bu_2BOTf	DCM	0.05	rt	4 h	44% (5.5 : 1)
6	Bu_2BOTf	THF	0.05	rt	3 h	77% (7 : 1)

[a]Concentration of the enamine **10**. [b]Isolated yield. [c]The *E*/*Z* ratio of product was determined by ^{1}H NMR.

Having successfully constructed the benzofulvene sesquiterpenoid skeleton, we then explored the total synthesis of anmindenol A (**1**) and its regioisomer **7** (Scheme 3). *α*,*β*,*γ*,*δ*-Unsaturated aldehyde **8** was carefully reduced with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ under the cooled condition, providing alcohol **20** in 80% yield.[9] Subsequent Negishi cross-coupling of 6-bromobenzofulvene **20** with Me_2Zn in the presence of $Pd(PPh_3)_4$ finally rendered anmindenol A (**1**) in high yield.[10] The structure of **1** was confirmed through comparison of its spectra (^{1}H NMR and $^{13}C\{^1H\}$ NMR) with those reported in the literature.[3a] Next, synthesis of **7** commenced from the enamine **11**, which was previously prepared in Scheme 2. The precursor **11** was successfully converted into benzofulvene aldehyde **9** in an 8:1 *E*/*Z* ratio in 71% yield under the established procedure. Finally, Luche reduction of **9**, followed by Negishi cross-coupling produced the regioisomer **7** in an excellent yield.

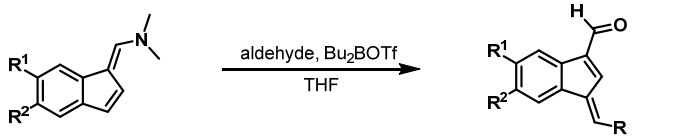
Scheme 3. Total syntheses of anmindenol A (**1**) and its regioisomer **7**.



Our synthetic efforts of the benzofulvene sesquiterpenoids **1** and **7** simultaneously led us into such a journey of discovering novel analogs with potent biological activities. A molecular modeling study revealed that the hydroxy group of anmindenol A tends to form a hydrogen bond with a crucial residue of iNOS (Supporting Information).[15] Therefore, our derivatization was focused on the modification of the isopropyl group at C-10 to decipher the effect of alkyl substituents on iNOS inhibition.

Initially, we explored the substrate scope of the VSEAC between enamines **10** and **11** and several alkyl aldehydes (Table 2). Fortunately, all condensations proceeded smoothly and resulted in good to moderate yields. In the case of one- or two-carbon truncated aldehydes, the *E*/*Z* ratios were slightly decreased to approximately 4:1, compared with those in the synthetic results of **8** and **9** (Table 2, entries 1-4). In particular, the condensation with pivalaldehyde, which was decorated with an additional one-carbon, gave the desired *E*-isomer only (Table 2, entries 5 and 6). These results indicated that the stereoselectivity of our VSEAC was presumably affected by the steric property of alkyl aldehydes.

Table 2. VSEAC of enamine substrates **10** and **11** with alkyl aldehydes.



10 : R^1 = H, R^2 = Br
or
11 : R^1 = Br, R^2 = H

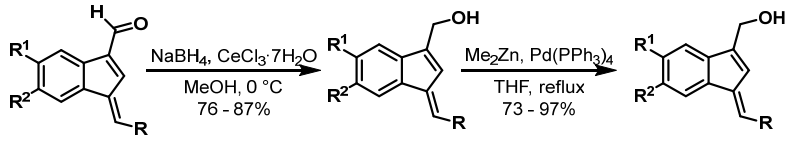
22-27
22 : R^1 = H, R^2 = Br, R = Me
23 : R^1 = Br, R^2 = H, R = Me
24 : R^1 = H, R^2 = Br, R = Et
25 : R^1 = Br, R^2 = H, R = Et
26 : R^1 = H, R^2 = Br, R = *t*-Bu
27 : R^1 = Br, R^2 = H, R = *t*-Bu

entry	enamine	aldehyde	product	yield[a] (*E*/*Z* ratio)[b]
1	**10**	acetaldehyde	**22**	57% (4.5 : 1)
2	**11**	acetaldehyde	**23**	68% (4 : 1)
3	**10**	propionaldehyde	**24**	42% (4.5 : 1)
4	**11**	propionaldehyde	**25**	35% (4 : 1)
5	**10**	pivalaldehyde	**26**	39% (*E*-isomer only)
6	**11**	pivalaldehyde	**27**	57% (*E*-isomer only)

[a]Isolated yield. [b]The *E*/*Z* ratio of product was determined by ^{1}H NMR.

With the carefully purified *E* stereoisomers **22**-**27** in hand, we then executed syntheses of novel derivatives of natural benzofulvene anmindenol A for the construction of a structurally unexplored chemical library. As depicted in Scheme 4, reductions of aldehydes **22**-**27** under Luche condition and Negishi cross-couplings of the resultant alcohols **28**-**33** with Me_2Zn successfully afforded the final analogs **34**-**39** in high yields.

Scheme 4. Syntheses of anmindenol A analogs **34**-**39**.



22 : R^1 = H, R^2 = Br, R = Me
23 : R^1 = Br, R^2 = H, R = Me
24 : R^1 = H, R^2 = Br, R = Et
25 : R^1 = Br, R^2 = H, R = Et
26 : R^1 = H, R^2 = Br, R = *t*-Bu
27 : R^1 = Br, R^2 = H, R = *t*-Bu

28 : R^1 = H, R^2 = Br, R = Me
29 : R^1 = Br, R^2 = H, R = Me
30 : R^1 = H, R^2 = Br, R = Et
31 : R^1 = Br, R^2 = H, R = Et
32 : R^1 = H, R^2 = Br, R = *t*-Bu
33 : R^1 = Br, R^2 = H, R = *t*-Bu

34 : R^1 = H, R^2 = Me, R = Me
35 : R^1 = Me, R^2 = H, R = Me
36 : R^1 = H, R^2 = Me, R = Et
37 : R^1 = Me, R^2 = H, R = Et
38 : R^1 = H, R^2 = Me, R = *t*-Bu
39 : R^1 = Me, R^2 = H, R = *t*-Bu

In order to assess the iNOS inhibitory activities of newly synthesized anmindenol A and its analogs, all compounds including structurally closely related intermediates **20** and **21** were tested against lipopolysaccharide (LPS)-activated macrophage RAW264.7 cells in a dose-dependent manner.[16] The results of the biological evaluation are shown in Table 3. Anmindenol A (**1**) as a positive control inhibited nitric oxide production with an IC_{50} value of 33.6 μM nearly equal to the previously reported value.[3a] In general, most of the novel derivatives exhibited slightly improved activities (IC_{50} = 17.3−35.5 μM) compared to that of **1**, which presumably indicated that the benzofulvene moiety played a crucial role in the iNOS inhibitory activity of the compounds. Interestingly, one-carbon-truncated analog **36** showed approximately 2-fold higher potency to the natural product **1**. Moreover, among the regioisomers, one-carbon-truncated analog **37** also displayed the highest activity against NO release.

Table 3. Inhibitory effects of the synthesized compounds on NO production.

comp.	IC_{50} (μM)	comp.	IC_{50} (μM)
1	33.6	**7**	22.7
20	18.4	**21**	33.0
34	28.3	**35**	23.3

36	17.3	**37**	21.5
38	21.2	**39**	35.5

CONCLUSION

In conclusion, we have accomplished the first total synthesis of rare benzofulvene sesquiterpenoid anmindenol A (**1**) (27% overall yield) in only four steps from the known indene **19**. The key feature of our synthesis includes the stereoselective construction of the 3,10-dialkylsubstituted benzofulvene backbone utilizing a vinylogous Stork enamine aldol condensation. The developed synthetic strategy was applied to synthesize unexplored derivatives of **1**, which were rationally designed by using computational docking analysis. The synthesized 3,10-dialkylbenzofulvenes were evaluated for their iNOS inhibitory activities in stimulated RAW 264.7 macrophage cells. The findings in this work suggested that benzofulvene-based compounds may have a chance to be developed as a potential anti-inflammatory or anti-senescence agents. Employing this practical synthetic route, our further studies toward syntheses of other natural benzofulvenes and evaluation of their biological activities are currently underway.

EXPERIMENTAL SECTION

General Experimental Procedure

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under argon atmosphere. All solvents used for routine isolation of products and chromatography were reagent grade. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Varian Unity 400, AVANCE NEO 500 and Unity-Inova 500 as solutions in the indicated solvents. Chemical shifts were expressed in parts per million (ppm, δ) downfield from tetramethylsilane and were referenced to the deuterated solvent. ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz). Infrared (IR) spectra were obtained by an FT/IR spectrometer and are reported as absorption wavenumbers (cm^{-1}). High resolution mass spectra were obtained with an Agilent 6530 Accurate-Mass Q-TOF and a JEOL JMS-AX 505WA instrument.

*6-Methyl-2,3-dihydro-1H-inden-1-ol (**14**).*[17] To a solution of 6-methyl-1-indanone (526 mg, 3.60 mmol) in EtOH (12.0 mL) was added $NaBH_4$ (136 mg, 3.60 mmol) at ambient temperature. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl and then concentrated in vacuo. The residue was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) to

afford 522 mg (98%) of alcohol **14** as white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (s, 1H), 7.15 (d, 1H, J = 7.7 Hz), 7.09 (d, 1H, J = 7.7 Hz), 5.20 (q, 1H, J = 6.2 Hz), 3.02 (m, 1H), 2.78 (m, 1H), 2.48 (m, 1H), 2.37 (s, 3H), 1.94 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 145.2, 140.4, 136.5, 129.3, 124.8, 124.7, 76.5, 36.2, 29.5, 21.4.

*5-Methyl-1H-indene (**15**).*[11] To a solution of alcohol **14** (502 mg, 3.38 mmol) in benzene (14.0 mL) was added PTSA·H_2O (64.4 mg, 0.338 mmol) at ambient temperature. After being stirred for 3 h at 65 ℃, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane) to afford 279 mg (63%) of **15** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, 1H, J = 7.6 Hz), 7.23 (s, 1H), 7.02 (d, 1H, J = 7.5 Hz), 6.84 (m, 1H), 6.54 (m, 1H), 3.36 (s, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 145.2, 140.8, 135.9, 134.6, 132.1, 125.5, 123.5, 121.8, 38.8, 21.6.

*(E)-N,N-Dimethyl-1-(5-methyl-1H-inden-1-ylidene)methanamine (**16**) and (E)-N,N-dimethyl-1-(6-methyl-1H-inden-1-ylidene)methanamine (**17**).* To an indene **15** (81.0 mg, 0.622 mmol) was added DMF-DMA (83.0 μL, 0.622 mmol) at ambient temperature. After being stirred for 17 h at 100 ℃, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 5, TEA 2%) to afford 93.6 mg (81% yield as a 1 : 1 regioisomeric enamine mixture) of **16** as brown solid: FT-IR (thin film, neat) ν_{max} 3001, 2913, 2859, 1705, 1625, 1489, 1451, 1439, 1408, 1384, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (mixture of regioisomer **17**) 7.51 (d, 1H, J = 7.9 Hz), 7.43 (s, 1H), 7.39 (m, 2H), 7.37 (s, 1H), 7.31 (s, 1H), 7.05 (d, 1H, J = 5.1 Hz), 7.01 (d, 1H, J = 5.4 Hz), 7.00 (m, 1H), 6.98 (m, 1H), 6.81 (m, 2H), 3.25 (s, 6H), 3.24 (s, 6H), 2.48 (s, 3H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (mixture of regioisomer **17**) 140.3, 140.2, 138.5, 138.4, 135.8, 135.7, 131.8, 131.4, 123.7, 123.3, 123.0, 122.1, 121.7, 121.7, 120.7, 120.0, 116.5, 115.7, 109.8, 109.7, 43.5, 22.0, 21.7; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}N$ 186.1277; Found 186.1277.

*6-Bromo-2,3-dihydro-1H-inden-1-ol (**18**).*[11] To a solution of indanone **12** (5.00 g, 23.7 mmol) in EtOH (250 mL) was added $NaBH_4$ (806 mg, 21.3 mmol) at ambient temperature. After being stirred for 12 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl and then concentrated in vacuo. The residue was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) to afford 4.86 g (96%) of **18** as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 1H), 7.36 (dd, 1H, J = 8.0, 1.7 Hz), 7.11 (d, 1H, J = 8.0 Hz), 5.21 (q, 1H, J = 6.4 Hz), 2.98 (m, 1H), 2.75 (m, 1H), 2.49 (m, 1H), 1.94 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 147.4, 142.3, 131.4, 127.6, 126.6, 120.4, 76.2, 36.3, 29.5.

*5-Bromo-1H-indene (**19**).*[11] To a solution of alcohol **18** (4.47 g, 21.0 mmol) in benzene (150 mL) was added PTSA·H_2O (399 mg, 2.10 mmol) at ambient temperature. After being stirred for 14 h at 65 ℃, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane) to afford 3.58 g (88%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.32 (m, 2H), 6.82 (m, 1H), 6.60 (m, 1H), 3.36 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 147.1, 142.5, 136.1, 131.4, 127.4, 125.1, 124.2, 120.4, 38.9.

*(E)-1-(5-Bromo-1H-inden-1-ylidene)-N,N-dimethylmethanamine (**10**) and (E)-1-(6-Bromo-1H-inden-1-ylidene)-N,N-dimethylmethanamine (**11**).* To an indene **19** (330 mg, 1.69 mmol) was added DMF-DMA (226 μL, 1.69 mmol) at ambient temperature. After being stirred for 12 h at 100 ℃, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 3) to afford 417 mg (99%) of **10** and **11** as a 1.15 : 1 mixture.

Compound **10**: Brown solid; FT-IR (thin film, neat) ν_{max} 2917, 1623, 1587, 1447, 1383, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1H, J = 1.7 Hz), 7.44 (d, 1H, J = 8.2 Hz), 7.41 (s, 1H), 7.20 (dd, 1H, J = 8.3, 1.8 Hz), 7.07 (d, 1H, J = 5.2 Hz), 6.75 (d, 1H, J = 5.2 Hz), 3.29 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 141.6, 139.5, 136.5, 124.4, 124.0, 123.0, 120.4, 117.3, 115.7, 109.0, 43.7; HRMS (FAB+) *m*/*z*: $[M]^+$ Calcd for $C_{12}H_{12}BrN$ 249.0153; Found 249.0151.

Compound **11**: Brown solid; FT-IR (thin film, neat) ν_{max} 2919, 1628, 1450, 1421, 1410, 1384, 1337 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (m, 1H), 7.38 (s, 1H), 7.32 (d, 1H, J = 8.1 Hz), 7.20 (dd, 1H, J = 8.1, 1.7 Hz), 7.04 (d, 1H, J = 5.2 Hz), 6.77 (d, 1H, J = 5.1 Hz), 3.28 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 141.7, 139.8, 136.4, 124.8, 123.3, 121.6, 120.7, 119.0, 115.9, 108.8, 43.5; HRMS (FAB+) *m*/*z*: $[M]^+$ Calcd for $C_{12}H_{12}BrN$ 249.0153; Found 249.0146.

*(E)-6-Bromo-1-(2-methylpropylidene)-1H-indene-3-carbaldehyde (**8**).* To a solution of isobutyraldehyde (24.9 μL, 0.273 mmol) in THF (4.10 mL) was added Bu_2BOTF (273 μL of a 1.0 M solution in CH_2Cl_2) at ambient temperature. To a reaction mixture was immediately added a solution of enamine **10** (68.3 mg, 0.273 mmol) in THF (1.36 mL) via cannula. After being stirred for 3 h, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 7) to afford 58.5 mg (77% yield, E : Z = 7 : 1) of aldehyde **8** as yellow solid: FT-IR (thin film, neat) ν_{max} 2966, 2921, 2852, 2352, 2307, 1718, 1679, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.12 (s, 1H), 7.94 (d, 1H, J = 8.1 Hz), 7.75 (d, 1H, J = 1.7 Hz), 7.54 (s, 1H), 7.44 (dd, 1H, J = 8.1, 1.7 Hz), 6.84 (d, 1H, J = 10.3 Hz), 3.15 (m, 1H), 1.23 (d, 6H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 188.9, 149.5, 140.7, 138.8, 136.4, 130.5, 124.1, 124.0, 122.8, 122.7, 120.7, 30.8, 23.1; HRMS (FAB+) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{14}BrO$ 277.0228; Found 277.0223.

*(E)-(6-Bromo-1-(2-methylpropylidene)-1H-inden-3-yl)methanol (**20**).* To a solution of aldehyde **8** (49.9 mg, 0.180 mmol) in EtOH (3.00 mL) was added a solution of $CeCl_3 \cdot 7H_2O$ (101 mg, 0.271 mmol), $NaBH_4$ (7.49 mg, 0.198 mmol) in EtOH (2.00 mL) dropwise at 0 ℃. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with 1N HCl and then concentrated in vacuo. The residue was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 3) to afford 40.2 mg (80%) of alcohol **20** as yellow solid: FT-IR (thin film, neat) ν_{max} 3361, 2960, 2927, 2868, 1712, 1647, 1595, 1448, 1416, 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, 1H, J = 1.8, 0.5 Hz), 7.35 (dd, 1H, J = 8.0, 1.8 Hz), 7.17 (d, 1H, J = 7.9 Hz), 6.74 (m, 1H), 6.42 (dd, 1H, J = 10.0, 0.7 Hz), 4.73 (s, 2H), 3.02 (m, 1H), 1.96 (s, 1H), 1.16 (d, 6H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz) δ 145.5, 141.4, 141.2, 141.0, 137.8, 130.4, 123.2, 122.4, 121.5, 120.1, 59.5, 30.8, 23.4; HRMS (FAB+) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}BrO$ 278.0306; Found 278.0299.

*Anmindenol A (**1**).* To a solution of alcohol **20** (4.60 mg, 16.5μmol) in THF (300 μL) was added a solution of $Pd(PPh_3)_4$ (3.0 mg, 2.60 μmol) in THF (200 μL) and Me_2Zn (41.3 μL of a 1.2 M solution in toluene) at ambient temperature. After being refluxed for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 4) to afford 3.4 mg (96%) of anmindenol A (**1**) as a yellow oil: FT-IR (thin film, neat) ν_{max} 3370, 2960, 2924, 2867, 1708, 1648, 1607, 1464, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (m, 1H), 7.21 (d, 1H, J = 7.6 Hz), 7.06 (ddd, 1H, J = 7.6, 1.5, 0.7 Hz), 6.70 (d, 1H, J = 1.0 Hz), 6.40 (dd, 1H, J = 9.9, 0.6 Hz), 4.76 (dd, 2H, J = 5.8, 0.9 Hz), 3.04 (m, 1H), 2.40 (s, 3H), 1.16 (d, 6H, J = 6.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.3, 138.7, 138.5, 138.1, 137.1, 135.2, 127.7, 120.5, 120.0, 118.8, 60.1, 29.7, 23.4, 21.8; HRMS (FAB+) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{18}O$ 214.1358; Found 214.1352.

*(E)-5-Bromo-1-(2-methylpropylidene)-1H-indene-3-carbaldehyde (**9**).* To a solution of isobutyraldehyde (22.2 μL, 0.243 mmol) in THF (3.65 mL) was added Bu_2BOTF (243 μL of a 1.0 M solution in CH_2Cl_2) at ambient temperature. To a reaction mixture was immediately added a solution of enamine **11** (60.9 mg, 0.243 mmol) in THF (1.21 mL) via cannula. After being stirred for 3 h, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 7) to afford 48.9 mg (72% yield, E : Z = 8 : 1) of aldehyde **9** as yellow solid: FT-IR (thin film, neat) ν_{max} 2963, 2928, 2868, 2809, 2713, 1714, 1677, 1638, 1597, 1570, 1538, 1445, 1421, 1391, 1364, 1306 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.12 (s, 1H), 8.25 (d, 1H, J = 1.7 Hz), 7.58 (s, 1H), 7.48 (d, 1H, J = 8.1 Hz), 7.42 (dd, 1H, J = 8.1, 1.8 Hz), 6.84 (d, 1H, J = 10.3 Hz), 3.16 (m, 1H), 1.23 (d, 6H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 188.8, 149.3, 140.4, 139.6, 139.3, 136.6, 135.6, 129.4, 125.9, 121.8, 120.6, 30.8, 23.2; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{14}BrO$ 277.0223; Found 277.0226.

*(E)-(5-Bromo-1-(2-methylpropylidene)-1H-inden-3-yl)methanol (**21**).* To a solution of aldehyde **9** (98.2 mg, 0.354 mmol) in EtOH (6.00 mL) was added a solution of $CeCl_3 \cdot 7H_2O$ (186 mg, 0.499 mmol), $NaBH_4$ (16.0 mg, 0.423 mmol) in EtOH (8.00 mL) dropwise at 0 ℃. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with 1N HCl and then concentrated in vacuo. The residue was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 6 to 1 : 4) to afford 92.7 mg (94%) of alcohol **21** as yellow solid: FT-IR (thin film, neat) ν_{max} 3348, 2960, 2927, 2868, 1712, 1648, 1596, 1558, 1446, 1416, 1385, 1362, 1323 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, 1H, J = 1.7 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.32 (dd, 1H, J = 8.0, 1.7 Hz), 6.78 (m, 1H) 6.42 (dd, 1H, J = 10.0, 0.3 Hz), 4.72 (d, 2H, J = 1.8 Hz), 3.02 (m, 1H), 1.96 (s, 1H), 1.16 (d, 6H, 6.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.4, 142.8, 140.5, 136.4, 136.3, 128.0, 122.6, 122.4, 120.8, 120.4, 59.7, 29.9, 23.3; HRMS (FAB+) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}BrO$ 278.0306; Found 278.0300.

*Regioisomer of anmindenol A (**7**).* To a solution of alcohol **21** (31.0 mg, 0.111 mmol) in THF (3.00 mL) was added a solution of $Pd(PPh_3)_4$ (19.0 mg, 16.4 μmol) in THF (2.00 mL) and Me_2Zn (278 μL of a 1.2 M solution in toluene) at ambient temperature. After being refluxed for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 4)

to afford 23.6 mg (99%) of **7** as a yellow oil: FT-IR (thin film, neat) ν_{max} 3370, 2961, 2867, 1708, 1648, 1610, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, 1H, J = 7.6 Hz), 7.15 (m, 1H), 7.03 (d, 1H, J = 7.6 Hz), 6.74 (m, 1H), 6.36 (d, 1H, J = 9.8 Hz), 4.76 (dd, 2H, J = 5.8, 1.0 Hz), 3.04 (m, 1H), 2.39 (s, 3H), 1.16 (d, 6H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.1, 141.2, 138.5, 136.9, 136.9, 135.2, 126.2, 121.6, 119.9, 118.9, 60.1, 29.8, 23.5, 21.8; HRMS (FAB+) m/z: $[M]^+$ Calcd for $C_{15}H_{18}O$ 214.1358; Found 214.1346.

*(E)-6-Bromo-1-ethylidene-1H-indene-3-carbaldehyde (**22**).* To a solution of the acetaldehyde (35.4 μL, 0.631 mmol) in THF (9.46 mL) was added Bu_2BOTF (631 μL of a 1.0 M solution in CH_2Cl_2) at ambient temperature. To a reaction mixture was immediately added a solution of enamine **10** (158 mg, 0.631 mmol) in THF (3.16 mL) via cannula. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 10) to afford 80.4 mg (57% yield, E : Z = 4.5 : 1) of **22** as yellow solid: FT-IR (thin film, neat) ν_{max} 3402, 3063, 2965, 2927, 2817, 2718, 1714, 1678, 1641, 1597, 1559, 1538, 1452, 1416, 1389 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.12 (s, 1H), 7.94 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 1.7 Hz), 7.53 (s, 1H), 7.43 (dd, 1H, J = 8.1, 1.8 Hz), 7.06 (q, 1H, J = 7.5 Hz), 2.31 (d, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 188.9, 140.7, 139.6, 138.6, 138.3, 138.0, 136.4, 130.6, 124.0, 122.6, 120.8, 17.0; HRMS (ESI-) m/z: $[M - H]^+$ Calcd for $C_{12}H_8BrO$ 246.9764; Found 246.9766.

*(E)-5-Bromo-1-ethylidene-1H-indene-3-carbaldehyde (**23**).* Enamine **11** (114 mg, 0.456 mmol) was reacted under the condition described above for **22**. The crude product was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 7) to afford 76.6 mg (68% yield, E : Z = 4 : 1) of **23** as yellow solid: FT-IR (thin film, neat) ν_{max} 3401, 3061, 2963, 2929, 2872, 2825, 2718, 1881, 1716, 1679, 1641, 1596, 1568, 1541, 1450, 1419, 1379, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.11 (s, 1H), 8.24 (d, 1H, J = 0.9 Hz), 7.57 (s, 1H), 7.44 (d, 1H, J = 8.1 Hz), 7.40 (dd, 1H, J = 8.1, 1.3 Hz), 7.08 (q, 1H, J = 7.5 Hz), 2.31 (d, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 188.8, 140.3, 139.8, 139.2, 139.2, 137.8, 135.4, 129.4, 125.9, 121.7, 120.5, 17.0; HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{12}H_{10}BrO$ 248.9910; Found 248.9913.

*(E)-6-Bromo-1-propylidene-1H-indene-3-carbaldehyde (**24**).* To a solution of the propionaldehyde (45.7 μL, 0.636 mmol) in THF (9.50 mL) was added Bu_2BOTF (636 μL of a 1.0 M solution in CH_2Cl_2) at ambient temperature. To a reaction mixture was immediately added a solution of enamine **10** (159 mg, 0.636 mmol) in THF (3.20 mL) via cannula. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 7) to afford 69.9 mg (42% yield, E : Z = 4.5 : 1) of **24** as yellow solid: FT-IR (thin film, neat) ν_{max} 2967, 2932, 2873, 2814, 2716, 1715, 1678, 1638, 1595, 1538, 1450, 1415, 1391 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.12 (s, 1H), 7.94 (d, 1H, J = 8.2 Hz), 7.74 (d, 1H, J = 1.6 Hz), 7.53 (s, 1H), 7.44 (dd, 1H, J = 8.2, 1.7 Hz), 7.01 (t, 1H, J = 8.1 Hz), 2.69 (quintet, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 189.0, 144.6, 140.7, 138.7, 138.6, 138.1, 136.4, 130.6, 124.0, 122.7, 120.8, 24.6, 14.1; HRMS (ESI-) m/z: $[M - H]^+$ Calcd for $C_{13}H_{10}BrO$ 260.9921; Found 260.9927.

*(E)-5-Bromo-1-propylidene-1H-indene-3-carbaldehyde (**25**).* Enamine **11** (103 mg, 0.412 mmol) was reacted under the condition described above for **24**. The crude product was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) to afford

38.2 mg (35% yield, *E* : *Z* = 4 : 1) of **25** as yellow solid: FT-IR (thin film, neat) ν_{max} 3062, 2964, 2930, 2873, 2716, 1716, 1678, 1636, 1596, 1564, 1541, 1447, 1421, 1383, 1306 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.12 (s, 1H), 8.25 (d, 1H, *J* = 1.4 Hz), 7.57 (s, 1H), 7.47 (d, 1H, *J* = 8.1 Hz), 7.41 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.02 (t, 1H, *J* = 8.1 Hz), 2.70 (quintet, 2H, *J* = 7.7 Hz), 1.25 (t, 1H, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 188.8, 144.3, 140.4, 139.4, 139.3, 138.3, 135.5, 129.5, 125.9, 121.8, 120.6, 24.7, 14.1; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{12}BrO$ 263.0066; Found 263.0051.

*(E)-6-Bromo-1-(2,2-dimethylpropylidene)-1H-indene-3-carbaldehyde (**26**).* To a solution of the pivalaldehyde (31.0 μL, 0.281 mmol) in THF (4.22 mL) was added Bu_2BOTF (281 μL of a 1.0 M solution in CH_2Cl_2) at ambient temperature. To a reaction mixture was immediately added a solution of enamine **10** (70.3 mg, 0.281 mmol) in THF (1.40 mL) via cannula. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc / *n*-hexane = 1 : 7) to afford 32.0 mg (39%) of **26** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.13 (s, 1H), 7.95 (d, 1H, *J* = 8.1), 7.74 (s, 1H), 7.72 (s, 1H), 7.44 (d, 1H, *J* = 8.1 Hz), 7.06 (s, 1H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 190.4, 155.7, 140.7, 140.3, 140.0, 134.7, 134.1, 129.9, 123.1, 123.0, 119.8, 36.5, 30.6; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{16}BrO$ 291.0379; Found 291.0383.

*(E)-5-Bromo-1-(2,2-dimethylpropylidene)-1H-indene-3-carbaldehyde (**27**).* Enamine **11** (107 mg, 0.428 mmol) was reacted under the condition described above for **26**. The crude product was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 8) to afford 71.1 mg (57%) of **27** as yellow solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.12 (s, 1H), 8.25 (s, 1H), 7.77 (s, 1H), 7.47 (d, 1H, *J* = 8.1 Hz), 7.41 (d, 1H, *J* = 8.1 Hz), 7.07 (s, 1H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 190.2, 154.9, 141.3, 139.6, 137.6, 137.1, 134.3, 128.7, 124.1, 121.5, 120.2, 36.3, 30.6; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{16}BrO$ 291.0379; Found 291.0391.

General procedure for preparation of alcohols 28-33: To a solution of the starting aldehyde in EtOH was added a solution of $CeCl_3 \cdot 7H_2O$ (1.0 equiv), $NaBH_4$ (1.0 equiv) in EtOH dropwise at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with 1N HCl and then concentrated in vacuo. The residue was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel.

*(E)-(6-Bromo-1-ethylidene-1H-inden-3-yl)methanol (**28**).* Aldehyde **22** (90.7 mg, 0.364 mmol) afforded 76.2 mg (83%) of **28** as yellow solid via the above general procedure. Compound **28** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) : FT-IR (thin film, neat) ν_{max} 3361, 2912, 2866, 1708, 1650, 1596, 1447, 1416, 1373, 1317 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, 1H, *J* = 1.1 Hz), 7.36 (dd, 1H, *J* = 8.0, 1.3 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 6.78 (s, 1H), 6.66 (q, 1H, *J* = 7.3 Hz), 4.75 (d, 2H, *J* = 2.4 Hz), 2.18 (d, 3H, *J* = 7.3 Hz), 1.65 (t, 1H, *J* = 5.3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.8, 139.7, 139.5, 139.4, 129.6, 128.7, 122.4, 121.4, 120.5, 119.6, 59.9, 16.1; HRMS (ESI-) *m*/*z*: $[M - H]^+$ Calcd for $C_{12}H_{10}BrO$ 248.9920; Found 248.9924.

*(E)-(5-Bromo-1-ethylidene-1H-inden-3-yl)methanol (**29**).* Aldehyde **23** (212 mg, 0.851 mmol) afforded 186 mg (87%) of **29** as yellow solid via the above general procedure. Compound **29** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) : FT-IR (thin film, neat) ν_{max} 3315, 3070, 2913, 2863, 1871, 1711, 1650, 1596, 1558, 1445, 1417, 1368, 1315 cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz) δ 7.48 (s, 1H), 7.42 (d, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.0 Hz), 6.82 (s, 1H), 6.67 (q, 1H, J = 7.3 Hz), 4.75 (s, 2H), 2.17 (d, 3H, J = 7.3 Hz), 1.62 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.4, 142.8, 139.4, 136.2, 128.5, 128.1, 122.5, 122.3, 120.8, 120.3, 59.8, 16.1.

*(E)-(6-Bromo-1-propylidene-1H-inden-3-yl)methanol (**30**).* Aldehyde **24** (52.4 mg, 0.199 mmol) afforded 40.0 mg (76%) of **30** as yellow solid via the above general procedure. Compound **30** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) : FT-IR (thin film, neat) ν_{max} 3350, 2966, 2931, 2871, 1707, 1648, 1596, 1557, 1449, 1415, 1376, 1341, 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, J = 1.8 Hz), 7.37 (dd, 1H, J = 8.0, 1.7 Hz), 7.20 (d, 1H, J = 8.0 Hz), 6.76 (m, 1H), 6.60 (t, 1H, J = 7.9 Hz), 4.76 (d, 2H, J = 4.0 Hz), 2.57 (quintet, 2H, J = 7.6 Hz), 1.62 (t, 1H, J = 5.9 Hz), 1.18 (t, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.9, 139.8, 139.6, 138.0, 135.6, 129.7, 122.6, 121.6, 120.5, 119.6, 59.9, 23.8, 14.4; HRMS (ESI-) *m/z*: $[M - H]^+$ Calcd for $C_{13}H_{12}BrO$ 263.0077; Found 263.0076.

*(E)-(5-Bromo-1-propylidene-1H-inden-3-yl)methanol (**31**).* Aldehyde **25** (50.7 mg, 0.193 mmol) afforded 42.0 mg (82%) of **31** as yellow solid via the above general procedure. Compound **31** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3347, 3327, 2966, 2931, 2872, 1711, 1648, 1596, 1559, 1446, 1416, 1378, 1324 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, 1H, J = 1.5 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.34 (dd, 1H, J = 8.0, 1.6 Hz), 6.80 (s, 1H), 6.61 (t, 1H, J = 7.9 Hz), 4.75 (d, 2H, J = 4.2 Hz), 2.57 (quintet, 2H, J = 7.6 Hz), 1.61 (t, 1H, J = 5.1 Hz), 1.18 (t, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 143.4, 142.8, 137.9, 136.3, 135.4, 128.1, 122.5, 122.5, 120.8, 120.4, 59.8, 23.8, 14.4.

*(E)-(6-Bromo-1-(2,2-dimethylpropylidene)-1H-inden-3-yl)methanol (**32**).* Aldehyde **26** (18.1 mg, 0.062 mmol) afforded 15.6 mg (86%) of **32** as yellow solid via the above general procedure. Compound **32** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3305, 2957, 2929, 2903, 2866, 1636, 1587, 1556, 1451, 1415, 1396, 1363, 1346, 1317 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, J = 1.7 Hz), 7.36 (dd, 1H, J = 8.0, 1.7 Hz), 7.19 (d, 1H, J = 8.0 Hz), 6.93(m, 1H), 6.66 (s, 1H), 4.75 (s, 1H), 1.73 (s, 1H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.4, 144.2, 141.1, 138.3, 135.1, 129.6, 122.3, 122.3, 120.3, 119.6, 59.9, 35.4, 31.4.

*(E)-(5-Bromo-1-(2,2-dimethylpropylidene)-1H-inden-3-yl)methanol (**33**).* Aldehyde **27** (32.5 mg, 0.111 mmol) afforded 26.4 mg (81%) of **33** as yellow solid via the above general procedure. Compound **33** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) : FT-IR (thin film, neat) ν_{max} 3304, 2957, 2930, 2903, 2865, 1864, 1713, 1636, 1594, 1558, 1447, 1417, 1362, 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, 1H, J = 1.7 Hz), 7.43 (d, 1H, J = 8.1 Hz), 7.33 (dd, 1H, J = 8.1, 1.7 Hz), 6.97 (m, 1H), 6.67 (s, 1H), 4.74 (s, 2H), 1.71 (s, 1H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.0, 144.0, 141.4, 137.8, 135.1, 128.0, 123.2, 122.3, 120.7, 120.1, 59.8, 35.4, 31.5.

General procedure for preparation of 34-39: To a solution of the starting alcohol in THF was added a solution of $Pd(PPh_3)_4$ (0.3 equiv) in THF and Me_2Zn (3.0 equiv) at ambient temperature. After being refluxed for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel.

*(E)-(1-Ethylidene-6-methyl-1H-inden-3-yl)methanol (**34**).* Alcohol **28** (76.2 mg, 0.303 mmol) afforded 41.2 mg (73%) of **34** as yellow solid via the above general procedure. Compound **34** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) : FT-IR (thin film, neat) ν_{max} 3303, 3007, 2973, 2915, 2856, 1651, 1610, 1590, 1564, 1439, 1370, 1321 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 7.21 (d, 1H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.5 Hz), 6.72 (s, 1H), 6.63 (q, 1H, J = 7.3 Hz), 4.76 (d, 2H, J = 3.9 Hz), 2.40 (s, 3H), 2.16 (d, 3H, J = 7.3 Hz), 1.57 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.3, 140.3, 138.4, 137.9, 135.2, 127.7, 126.4, 120.2, 119.9, 118.8, 60.1, 21.8, 15.9; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{15}O$ 187.1117; Found 187.1111.

*(E)-(1-Ethylidene-5-methyl-1H-inden-3-yl)methanol (**35**).* Alcohol **29** (186.2 mg, 0.741 mmol) afforded 118 mg (85%) of **35** as yellow solid via the above general procedure. Compound **35** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 4) : FT-IR (thin film, neat) ν_{max} 3379, 3047, 2978, 2930, 2868, 1708, 1650, 1610, 1576, 1450, 1373, 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, 1H, J = 7.7 Hz), 7.16 (s, 1H), 7.03 (d, 1H, J = 7.6 Hz), 6.77 (s, 1H), 6.60 (q, 1H, J = 7.3 Hz), 4.76 (d, 2H, J = 2.8), 2.40 (s, 3H), 2.16 (d, 3H, J = 7.4 Hz), 1.59 (t, 1H, J = 5.3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 144.0, 141.1, 139.9, 136.7, 134.9, 126.2, 126.1, 121.2, 119.8, 118.7, 60.0, 21.7, 15.8; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{15}O$ 187.1117; Found 187.1112.

*(E)-(6-Methyl-1-propylidene-1H-inden-3-yl)methanol (**36**).* Alcohol **30** (65.5 mg, 0.247 mmol) afforded 43.2 mg (87%) of **36** as yellow solid via the above general procedure. Compound **36** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3322, 2966, 2931, 2873, 1706, 1648, 1608, 1456, 1377, 1324 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (s, 1H), 7.21 (d, 1H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.6 Hz), 6.70 (s, 1H), 6.57 (t, 1H, J = 7.8 Hz), 4.76 (s, 2H), 2.56 (quintet, 2H, J = 7.6 Hz), 2.40 (s, 3H), 1.58 (s, 1H), 1.17 (t, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 144.4, 138.7, 138.5, 138.0, 135.2, 133.4, 127.7, 120.4, 120.0, 118.8, 60.1, 23.6, 21.8, 14.5; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{17}O$ 201.1274; Found 201.1266.

*(E)-(5-Methyl-1-propylidene-1H-inden-3-yl)methanol (**37**).* Alcohol **31** (48.0 mg, 0.181 mmol) afforded 34.0 mg (94%) of **37** as a yellow oil via the above general procedure. Compound **37** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3342, 2966, 2930, 2872, 2732, 1709, 1648, 1611, 1570, 1458, 1378, 1326 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, 1H, J = 7.6 Hz), 7.16 (s, 1H), 7.03 (d, 1H, J = 7.6 Hz), 6.74 (s, 1H), 6.54 (t, 1H, J = 7.8 Hz), 4.76 (d, 2H, J = 5.0 Hz), 2.56 (quintet, 2H, J = 7.6 Hz), 2.40 (s, 3H), 1.58 (t, 1H, J = 5.6 Hz), 1.17 (t, 3H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 144.2, 141.2, 138.6, 136.9, 135.1, 133.3, 126.2, 121.5, 119.9, 118.9, 60.1, 23.6, 21.8, 14.6; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{17}O$ 201.1274; Found 201.1265.

*(E)-(1-(2,2-Dimethylpropylidene)-6-methyl-1H-inden-3-yl)methanol (**38**).* Alcohol **32** (10.3 mg, 0.035 mmol) afforded 7.3 mg (96%) of **38** as yellow solid via the above general procedure. Compound **38** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3313, 2956, 2926, 2864, 1715, 1634, 1561, 1461, 1394, 1376, 1363, 1345, 1322 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1H), 7.21 (d, 1H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.6 Hz), 6.87 (m, 1H), 6.64 (s, 1H), 4.76 (s, 2H), 2.41 (s, 3H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 145.0, 142.1, 139.5, 137.1, 135.9, 135.2, 127.6, 121.2, 119.7, 118.7, 60.2, 35.1, 31.6, 21.8; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{21}O$ 229.1587; Found 229.1583.

*(E)-(1-(2,2-Dimethylpropylidene)-5-methyl-1H-inden-3-yl)methanol (**39**).* Alcohol **33** (6.0 mg, 0.020 mmol) afforded 4.2 mg (97%) of **39** as a yellow oil via the above general procedure. Compound **39** was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) : FT-IR (thin film, neat) ν_{max} 3312, 2957, 2927, 2904, 2865, 1636, 1611, 1595, 1559, 1461, 1396, 1377, 1363, 1322 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, 1H, J = 7.7 Hz), 7.16 (m, 1H), 7.04 (m, 1H), 6.92 (d, 1H, J = 1.0 Hz), 6.62 (s, 1H), 4.77 (s, 2H), 2.40 (s, 3H), 1.65 (s, 1H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.8, 142.0, 139.8, 136.8, 136.6, 135.8, 126.2, 122.2, 119.7, 118.6, 60.1, 35.1, 31.6, 21.7; HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{21}O$ 229.1587; Found 229.1581.

Molecular Docking Simulations

The 3D ligand structure was prepared and minimized by MM2 using Chem 3D Pro 12.0 software. The structure of iNOS was downloaded from the RCSB protein data bank (PDB ID: 1M8D). Chain B and all non-standard residues of the protein were removed by using UCSF Chimera 1.11.[18] Resulting ligand and protein files were processed in accordance with the AutoDock protocol for docking simulations.[19] Molecular docking analysis were performed using AutoDock Tools 1.5.6. and AutoDock 4.2.6[20] and the visual investigation and hydrogen bonding analysis were accomplished using UCSF Chimera 1.11.

Nitric Oxide Detection

RAW 264.7 cells (American Type Culture Collection, Manassas, VA, USA) were plated at a density of 1.5×10^5 cells/cm^2 on 48 well plates. Cells were stabilized for 24 h in Dulbecco's Modified Eagle Medium with high glucose (Gibco BRL, Grand Island, NY, USA) containing 10% Fetal Bovine Serum (Gibco BRL) at 37 °C in a humidified incubator with 5% CO_2 followed by media replacement. Cells were treated with 1 μg/mL LPS (Invivogen, San Diego, California, USA) for 24 h in the presence or absence of chemical compounds in concentrations ranging from 6.25 to 100 μM (2-fold serial dilution). NO was measured from culture supernatant using a Griess reagent (Promega, Madison, Wisconsin, USA) according to the manufacturer's instruction. Absorbance at 535 nm was measured using a microplate reader (Bio-Tek, Winooski, VT, USA).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of the ^1H and $^{13}C\{^1H\}$ NMR spectra for all compounds, natural and synthetic compound comparison tables and computational docking analysis. (PDF)

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