

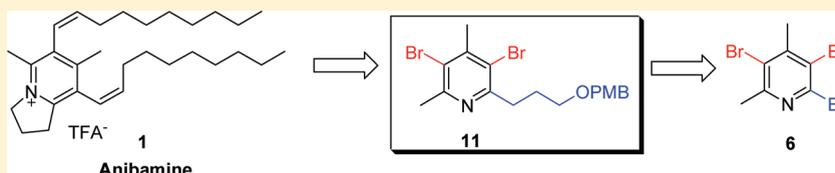
# Regio- and Stereoselective Syntheses of the Natural Product CCR5 Antagonist Anibamine and its Three Olefin Isomers

Feng Zhang, Saheem Zaidi, Kendra M. Haney, Glen E. Kellogg, and Yan Zhang\*

Department of Medicinal Chemistry, Virginia Commonwealth University, 800 East Leigh Street, Richmond, Virginia 23298, United States

Supporting Information

## ABSTRACT:



The syntheses of the natural product anibamine and its three olefin isomers have been achieved concisely and efficiently via highly regio- and stereoselective reactions. The crucial steps included a regioselective palladium-catalyzed alkylation by Sonogashira coupling and a stereoselective Suzuki coupling. Further conformation analyses and *in vitro* calcium mobilization studies were carried out to characterize the compounds' biological properties.

## INTRODUCTION

Anibamine, a pyridine quaternary alkaloid isolated from *Aniba panurensis*,<sup>1,2</sup> has been identified as a chemokine receptor CCR5 antagonist with an  $IC_{50}$  of  $1 \mu M$  in inhibiting the binding of  $^{125}I$ -gp120 to the CCR5 receptor. Anibamine has a novel structural skeleton compared with other small molecule CCR5 antagonists identified through high-throughput screenings, such as Vicriviroc,<sup>3</sup> Maraviroc,<sup>4</sup> and TAK-779<sup>5</sup> (Figure 1), all of which have been studied in anti-HIV therapeutics development.<sup>6</sup> Recent studies<sup>7</sup> also demonstrate that anibamine inhibits prostate cancer cell proliferation, adhesion, and invasion at micromolar to submicromolar levels. Preliminary *in vivo* studies further indicate that anibamine also inhibits prostate tumor growth in mice. Correspondingly, it has been found that the chemokine CCL5 and its receptor CCR5 may play important roles in cancer progression<sup>8</sup> and TAK-779 blocked CCL5-induced invasion and proliferation of prostate cancer cells.<sup>9</sup> Therefore, anibamine may serve as a new lead for the development of CCR5 antagonists with potential applications in both AIDS and cancer therapies.

The first total synthesis of anibamine has been recently reported by our group.<sup>10</sup> In this approach, the two ten-carbon side chains were introduced via the Wittig reagent of 1-bromononane and the 3,5-dialdehyde pyridine intermediate. Four isomers were obtained as a mixture from this reaction and were used in the next few steps without separation. At the last step, anibamine was isolated by preparative HPLC with 8% overall yield (10 steps). This synthetic route suffered from tedious separations in the last few steps and relatively low yield due to the limited stereoselectivity of the Wittig reaction. At that time, the difficulties in obtaining the other isomers of anibamine

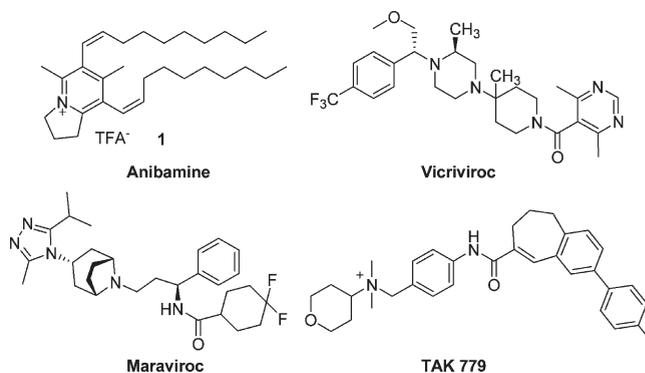


Figure 1. Anibamine and some known CCR5 antagonists.

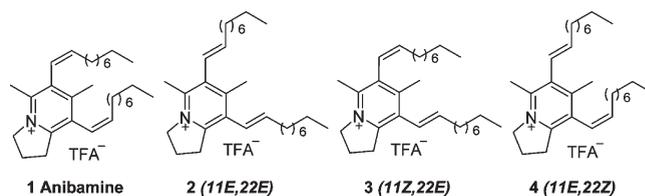


Figure 2. Anibamine and its three isomers.

(2, 3 and 4, Figure 2) prevented us from studying the effects of the double bond configuration and resulting conformation on

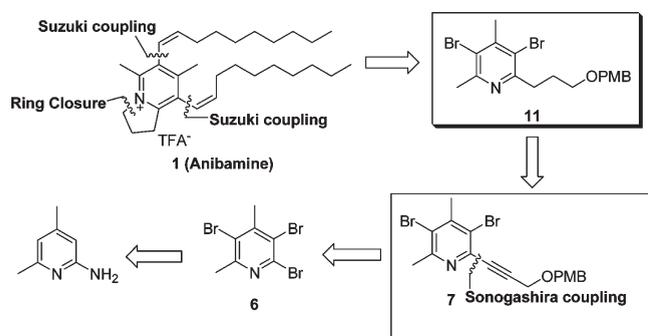
Received: July 7, 2011

Published: August 29, 2011

the biological activities of the molecules. Here we report new, highly regio- and stereoselective syntheses of anibamine and its three olefin isomers in a concise and efficient manner.

The retrosynthetic analysis of anibamine is depicted in Scheme 1. In this route, the two double bonds will be introduced stereoselectively by adopting different Suzuki coupling conditions while a regio-selective Sonogashira coupling will be applied to introduce the side chain at the 2-position and form the five-member ring system.

Scheme 1. Retrosynthetic Analysis of Anibamine

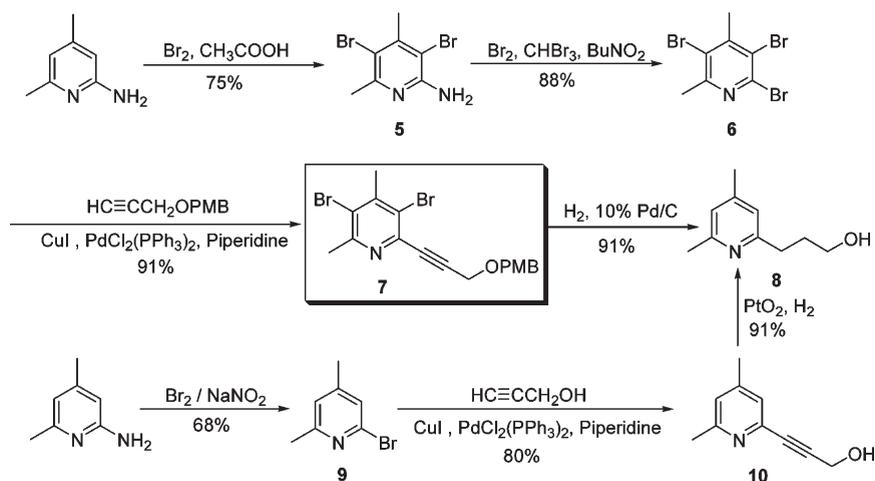


## RESULTS AND DISCUSSION

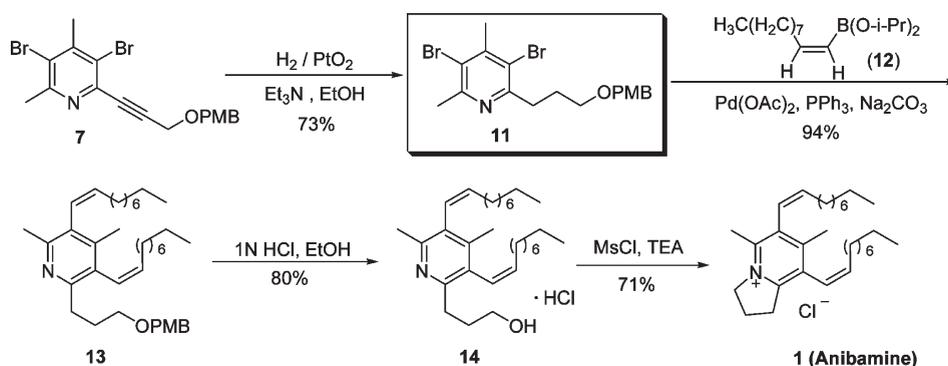
The synthesis was initiated (Scheme 2) from commercially available 2-amino-4,6-dimethylpyridine that was brominated in glacial acetic acid to give the desired 3,5-dibromo-4,6-dimethyl-2-aminopyridine (5) in 75% yield.<sup>11</sup> Diazotization of 5 under routine condition with Br<sub>2</sub>/NaNO<sub>2</sub> in 48% HBr as solvent did not yield the desired product 6 due to the poor solubility of the starting material. Cosolvents such as DMSO<sup>12</sup> or 1,4-dioxane<sup>13</sup> were added with limited success. However, a modified Sandmeyer reaction<sup>14</sup> by treating 5 with tert-butyl nitrite/CuBr<sub>2</sub> in CHBr<sub>3</sub> as the solvent obtained the desired product 6 in a reasonable yield. The reaction was further improved to a yield of 88% by replacing CuBr<sub>2</sub> with Br<sub>2</sub>.

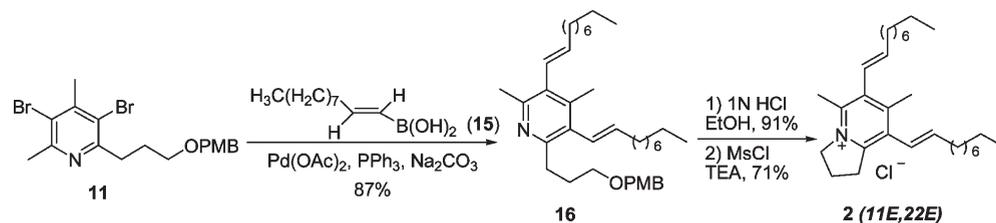
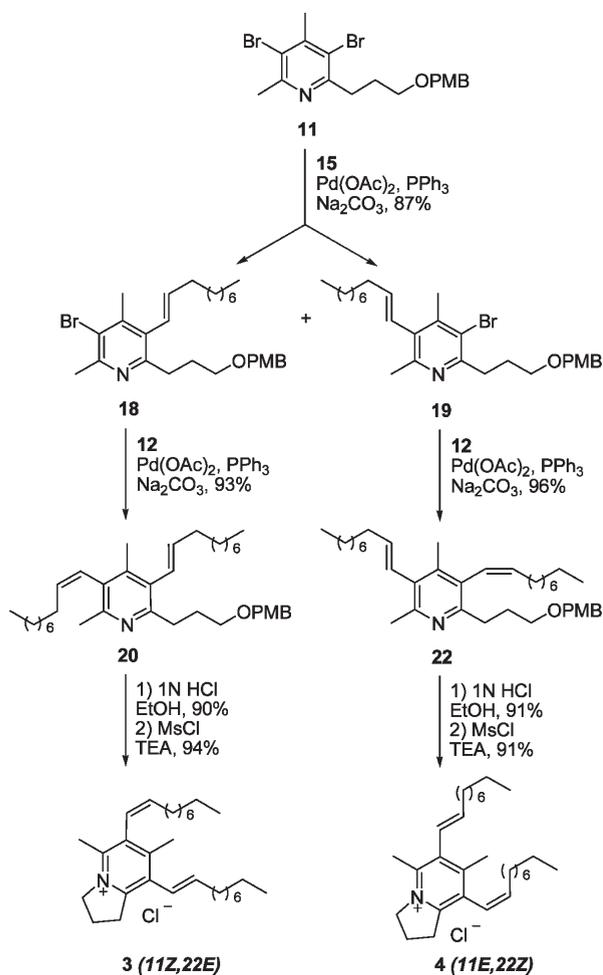
The regioselective synthesis of the key intermediate 2-alkynyl-3,5-dibromo-4,6-dimethylpyridine (7) was achieved by reacting 6 with terminal acetylenes under palladium-catalyzed Sonogashira conditions<sup>15</sup> with 91% yield (Scheme 2). To ascertain the regiochemistry of the coupling product 7, it was hydrogenated over palladium/carbon to give 8. Simultaneously, 8 was prepared by another method starting with 2-amino-4,6-dimethylpyridine. The corresponding 2-bromopyridine (9) was obtained in a reasonable yield by diazotization in a bromine and 48% hydrobromic acid mixture.<sup>16</sup> Further treatment of 9 with propargyl

Scheme 2. Preparation of Intermediate 7



Scheme 3. Synthesis of Anibamine



Scheme 4. Synthesis of (11*E*, 22*E*)-AnibamineScheme 5. Synthesis of (11*Z*, 22*E*)-Anibamine and (11*E*, 22*Z*)-Anibamine

alcohol under palladium-catalyzed Sonogashira conditions gave the alkynylated pyridine **10** in 80% yield. Catalytic hydrogenation of the triple bond<sup>15a</sup> afforded the pyridylpropanol, whose NMR spectra were unequivocally consistent with the product **8**. Thus, the regio-selective synthesis of **7** via a Sonogashira coupling condition was confirmed.

Next, the alkynyl bond of **7** was chemo-selectively reduced while minimizing the possible reductive debromination product.<sup>15a</sup> The hydrogenation of **7** over platinum oxide in ethanol was stopped after 2 equivalents of hydrogen were consumed yielding the key intermediate 3,5-dibromo-2-substituted-4,6-dimethylpyridine (**11**) in 73% yield (Scheme 3).

To stereoselectively introduce the two aliphatic side chains onto positions 3 and 5 of intermediate **11**, excess organoborane reagent was used under Suzuki coupling conditions. Recent development<sup>17</sup> on the utilization of alkyl- and alkenylboronic acids and esters suggested a convenient method for the preparation of diisopropyl (*Z*)-1-decenylboronate (**12**). Under standard Suzuki reaction conditions,<sup>18</sup> 1.0 equiv of **11** and 4.0 equiv of **12** were coupled in the presence of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub> in a mixture of solvents (toluene/EtOH/water = 2:1:1) at refluxing temperature for 6 h. Compound **13** was obtained stereoselectively in an excellent yield. The crude <sup>1</sup>H NMR and <sup>13</sup>C NMR of the reaction showed no observable stereoisomers.

Subsequently, the PMB group of **13** was removed under acidic conditions to give compound **14** in 80% yield. The ring closure was achieved by treating **14** with methanesulfonylchloride and triethylamine at room temperature to give the natural product anibamine (**1**) in 71% yield (Scheme 3). The spectral properties of the synthesized target compound **1** were identical to those of the natural product.<sup>1</sup>

The (11*E*, 22*E*) isomer of anibamine (**2**) was prepared in a similar fashion to anibamine. (*E*)-dec-1-enylboronic acid (**15**) was readily obtained by the hydroboration of 1-decyne with BHBBr<sub>2</sub> · SME<sub>2</sub>, followed by hydrolysis.<sup>19</sup> Under the same Suzuki cross-coupling reaction conditions, 1.0 equiv of **11** and 4.0 equiv of **15** were reacted to give the intermediate **16** stereoselectively in an excellent yield. Then, by following the same procedure described for **1**, the (11*E*, 22*E*) isomer **2** was obtained in 64% yield via two steps from compound **16** (Scheme 4).

Both electronic and steric considerations suggest that the regioselective introduction of the two side chains of isomers **3** and **4** would be challenging due to the similar reactivity of the two bromo-substitutions at the 3- and 5-positions of intermediate **11** toward coupling reactions. The electronic effects arising from substitutions on the pyridinyl ring system are similar and the steric hindrance effects of the bulky 2-position OPMB group would be diminished due to the relatively long aliphatic chain connection to the parent ring. Unsurprisingly, Suzuki coupling of **11** with an equivalent of **15** with varied temperatures and solvent systems gave products **18** and **19** in roughly similar amounts. The successful chromatographic separation of the two isomers, however, allowed the preparation of **3** and **4** in reasonably good yields (Scheme 5).

To predict the influence of the double bond configuration of **1–4** with respect to interaction with the receptor CCR5, *in silico* conformation analyses were conducted. As shown in Figure 3, the conformations of the core portions of all four isomers were similar with varied, but somewhat kinked, side chain orientations. Overall, however, their molecular shapes were quite similar and almost overlapped. To validate such results from the conformation analyses as to if the binding affinity of these isomers to the

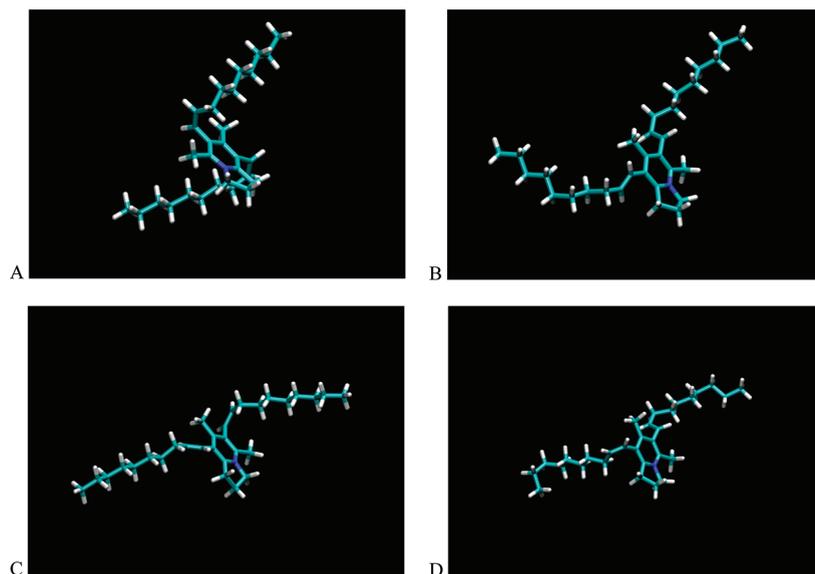


Figure 3. Conformation analyses of compound 1 (A), 2 (B), 3 (C), and 4 (D).

Table 1. Calcium Mobilization Inhibition Assay Results of All the Four Isomers<sup>a</sup>

compound	1	2	3	4
IC <sub>50</sub>	5.43	6.53	9.23	10.09
SEM	0.91	1.79	0.59	3.87

<sup>a</sup> Values shown were from at least three separate experiments performed in triplicate. The IC<sub>50</sub> values were calculated using Prism.

receptor CCR5 would be influenced, further biological assay is deemed to be conducted.

To experimentally characterize the influence of the double bond configuration of compounds 1–4 on their affinity to the receptor, the calcium mobilization assay<sup>20</sup> was adopted by using CCR5MOLT-4 cell lines. The IC<sub>50</sub> values of the calcium reflux inhibitory effect for all four isomers are summarized in Table 1. First, the comparable IC<sub>50</sub> of anibamine (1) to its inhibitory binding affinity of RANTES at the receptor (1.0 μM) validated the calcium mobilization assay protocol. Second, not surprisingly, all four isomers showed similar inhibitory effect on calcium reflux, which indicates that their binding affinity, as well as possibly their binding mode to the receptor, is comparable. This supports the conformation analyses results: the double bond configuration does not significantly influence the overall conformation of the whole molecule because of the two long aliphatic chains.

## CONCLUSION

In conclusion, the regio- and stereoselective total synthesis of anibamine has been achieved in 7 steps with an overall yield of 23%, which is a 3-fold improvement over previous results. Its three isomers were also obtained in similar yields. The methodology described above for the preparation of intermediate 7 and 11 will allow more convenient synthesis of a variety of anibamine derivatives for our further biological evaluations and structure–activity relationship studies. Conformational analyses of 1–4 are supported by the calcium mobilization screens, which together, suggest that the configuration of the double bond may

not critical for binding to the receptor. These results shed light on a possible conserved binding mode of these ligands to the receptor and will facilitate our next step molecular design to identify novel anibamine derivatives as the chemokine receptor CCR5 antagonists and potential anti-HIV and anticancer agents.

## EXPERIMENTAL SECTION

**General Information and Methods.** All reagents were used directly as obtained commercially unless otherwise noted. Melting points were determined on a melting point apparatus and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were taken on a 400 MHz spectrometer and tetramethylsilane was used as an internal standard. Infrared spectra were obtained on a FT-IR spectrometer. LC-MS was performed on a QTOF-2 instrument using ESI ion source. High-Resolution mass spectral analyses were performed on a QTOF-2 instrument using ESI ion source operated in positive ion mode. Column chromatography was performed on silica gel (grade 60 mesh). Preparative thin-layer chromatography (TLC) was performed on silica gel GF plates (1000 μm, 20 × 20 cm).

**3,5-Dibromo-4,6-dimethylpyridin-2-amine (5).** A solution of 2-amino-4,6-dimethylpyridine (2.44 g, 20 mmol) in 15 mL of glacial acetic acid under nitrogen was treated with a solution of 7.36 g (46 mmol) Br<sub>2</sub> in 5 mL of glacial acetic acid over 15 min. The solution became a solid mass and was allowed to stand at r.t. for 1 h. After cooling in an ice bath, the material was made alkaline with 20% cold NaOH solution. Then the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL), the combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (Hexane/EtOAc, 2:1–1:1) to afford the product (4.21 g, 75%) as a yellow solid. Mp 136–137 °C. (lit.<sup>11</sup> Mp 136–136.5 °C). IR (KBr, cm<sup>-1</sup>) ν<sub>max</sub>: 3459, 3283, 3124, 1628, 1428, 659. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.86 (br, 2H), 2.53 (s, 3H), 2.49 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.9, 153.6, 147.0, 111.5, 103.9, 25.2, 24.3.

**2,3,5-Tribromo-4,6-dimethylpyridine (6).** To a solution of 5 (556 mg, 2 mmol) and Br<sub>2</sub> (384 mg, 2.4 mmol) in bromoform (6 mL), was added dropwise BuNO<sub>2</sub> (618 mg, 6 mmol) at r.t. The solution was stirred at r.t. for 2 h. Then the solution was stopped by addition of saturated Na<sub>2</sub>CO<sub>3</sub> solution, followed by extraction with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous

$\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (Hexane/EtOAc, 40:1) to afford the product (600 mg, 88%) as a pale-yellow solid. Mp 124–125 °C. (lit.<sup>16</sup> Mp 124–125 °C). IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 1535, 1373, 1241, 1045, 847.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.68 (s, 3H), 2.63 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  156.6, 149.6, 141.6, 123.3, 123.0, 26.1, 25.4.

**2-(3-(4-Methoxybenzyloxy)prop-1-ynyl)-3,5-dibromo-4,6-dimethylpyridine (7).** To a solution of *p*-methoxybenzylalcohol (3.32 g, 24 mmol) in anhydrous  $\text{Et}_2\text{O}$  (24 mL) was added NaH (60%) (100 mg, 2.4 mmol) at r.t. under  $\text{N}_2$ . After stirring for 30 min, the mixture was cooled to 0 °C and trichloroacetonitrile (3.46 g, 24 mmol) was added. The resulting mixture was allowed to warm up slowly to room temperature and stirred for 4 h. After concentrated to remove  $\text{Et}_2\text{O}$ , the residue was dissolved in hexane (28 mL) and MeOH (0.12 mL). The suspension was filtered through Celite. The filtrate was concentrated to give a yellow oil (6.68 g). The crude intermediate was dissolved in anhydrous dichloromethane (25 mL). Propargyl alcohol (896 mg, 16 mmol) was added to the reaction and the solution was cooled to 0 °C and treated with a catalytic amount of 10-camphorsulfonic acid. The reaction was allowed to warm up slowly to r.t. and stirred overnight under  $\text{N}_2$  protection. The solution was filtered, washed with saturated aqueous  $\text{NaHCO}_3$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude product was purified on silica gel (Hexane/EtOAc, 8:1) to afford 1-methoxy-4-((prop-2-ynyloxy)methyl)benzene (2.42 g, 86%) as a pale-yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 2H), 6.88 (m, 2H), 4.54 (s, 2H), 4.13 (d,  $J = 2.4$  Hz, 2H), 3.79 (s, 3H), 2.45 (t,  $J = 2.4$  Hz, 1H). (lit.<sup>10</sup>)

A solution of **6** (682 mg, 2.0 mmol), 1-methoxy-4-((prop-2-ynyloxy)methyl)benzene (422 mg, 2.4 mmol), CuI (19 mg, 0.1 mmol) and piperidine (510 mg, 6.0 mmol) in 15 mL THF was purged by the passage of nitrogen through the solution, and 140 mg (0.2 mmol) of  $\text{PdCl}_2(\text{PPh}_3)_2$  was added all at once. The reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EtOAc, washed with water, saturated brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (Hexane/EtOAc, 8:1) to afford the product (797 mg, 91%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2921, 2850, 1736, 1512, 1359, 1245, 1043, 818.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (m, 2H), 6.89 (m, 2H), 4.67 (s, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 2.65 (s, 3H), 2.64 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 156.6, 147.4, 140.8, 129.9, 129.9, 129.4, 123.8, 123.1, 113.9, 113.9, 90.3, 84.7, 71.3, 57.3, 55.3, 25.8, 24.8. HRMS  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{Br}_2\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 437.9704, found 437.9691.

**3-(4,6-Dimethylpyridin-2-yl)propan-1-ol (8).** Hydrogenation was conducted on a mixture of compound **7** (131 mg, 0.3 mmol), Pd/C (13 mg, 10%) in 16 mL MeOH/EtOAc (1:1) under 60 psi.  $\text{H}_2$  overnight. The reaction mixture was filtered and concentrated. The residue was purified on silica gel (DCM/MeOH, 10:1) to afford the product (45 mg, 91%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3262, 2922, 2864, 1610, 1451, 1058, 843.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.83 (s, 2H), 4.55 (br s, 1H), 3.73 (t,  $J = 5.6$  Hz, 2H), 2.92 (t,  $J = 6.4$  Hz, 2H), 2.48 (s, 3H), 2.28 (s, 3H), 1.92–1.98 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.2, 156.9, 148.5, 121.8, 121.2, 62.6, 35.6, 31.3, 23.7, 20.9. HRMS  $m/z$  calcd for  $\text{C}_{10}\text{H}_{16}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  = 166.1232, found 166.1219.

**2-Bromo-4,6-dimethylpyridine (9).** To a solution of 2-amino-4,6-dimethylpyridine (610 mg, 5 mmol) in 2.5 mL HBr (48%), was added  $\text{Br}_2$  (2.21 g, 13.8 mmol) at –10 °C, keeping the temperature below 0 °C.  $\text{NaNO}_2$  (0.86 g, 12.5 mmol) was added with the reaction temperature being kept below 0 °C. After a further 30 min, NaOH (2 g in 2 mL water) was added, keeping the temperature below 10 °C and then more NaOH was added to make the solution strongly alkaline. Extracted with EtOAc (3  $\times$  50 mL) and the combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 6:1) to afford the product (626 mg, 68%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2922, 1597, 1540, 1274, 1191,

1127, 825.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (s, 1H), 6.92 (s, 1H), 2.48 (s, 3H), 2.28 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4, 150.2, 141.4, 125.6, 123.3, 24.0, 20.6. (lit.<sup>16</sup>)

**3-(4,6-Dimethylpyridin-2-yl)prop-2-yn-1-ol (10).** A solution of **9** (370 mg, 2 mmol), prop-2-yn-1-ol (168 mg, 3 mmol), CuI (19 mg, 0.1 mmol) and piperidine (510 mg, 6 mmol) in 10 mL THF was purged by the passage of nitrogen through the solution, and 140 mg (0.2 mmol) of  $\text{PdCl}_2(\text{PPh}_3)_2$  was added all at once. The reaction mixture was stirred at room temperature for 3 h. Then the mixture was diluted with EtOAc, washed with water, saturated brine and dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (EtOAc) to afford the product (257 mg, 80%) as a white solid. Mp 93–94 °C. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3195, 2916, 1604, 1025, 850.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (s, 1H), 6.94 (s, 1H), 4.52 (br s, 2H), 2.79 (br s, 1H), 2.50 (s, 3H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.6, 147.8, 141.7, 125.2, 124.0, 87.1, 84.9, 51.3, 24.2, 20.7. HRMS  $m/z$  calcd for  $\text{C}_{10}\text{H}_{12}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  = 162.0919, found 162.0909.

**3-(4,6-Dimethylpyridin-2-yl)propan-1-ol (8).** A solution of **10** (200 mg, 1.24 mmol) in 10 mL of ethanol and 0.2 mL of triethylamine was hydrogenated over 20 mg (0.09 mmol) of  $\text{PtO}_2$  overnight. The reaction mixture was filtered and concentrated. The residue was purified on silica gel (DCM/MeOH, 10:1) to afford the product (187 mg, 91%) as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.81 (s, 2H), 5.05 (br s, 1H), 3.71 (t,  $J = 5.7$  Hz, 2H), 2.90 (t,  $J = 6.5$  Hz, 2H), 2.47 (s, 3H), 2.27 (s, 3H), 1.91–1.98 (m, 2H). The NMR spectra were unequivocally consistent with the product **8**.

**2-(3-(4-Methoxybenzyloxy)propyl)-3,5-dibromo-4,6-dimethylpyridine (11).** A solution of **7** (746 mg, 1.71 mmol) in 10 mL of ethanol and 0.2 mL of triethylamine was hydrogenated over 16 mg (0.07 mmol) of  $\text{PtO}_2$  for 1 h. The reaction mixture was filtered and concentrated. The residue was purified on silica gel (Hexane/EtOAc, 8:1) to afford the product (547 mg, 73%) as pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2930, 2851, 1612, 1511, 1360, 1244, 1098, 1036, 818.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (m, 2H), 6.86 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.54 (t,  $J = 6.5$  Hz, 2H), 2.97–3.01 (m, 2H), 2.61 (s, 3H), 2.60 (s, 3H), 2.00–2.07 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 157.7, 155.1, 146.6, 130.8, 129.2, 129.2, 121.4, 121.0, 113.7, 113.7, 72.4, 69.5, 55.3, 34.7, 28.3, 25.6, 24.8. HRMS  $m/z$  calcd for  $\text{C}_{18}\text{H}_{22}\text{Br}_2\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 442.0017, found 442.0003.

**Diisopropyl (Z)-1-Decenylboronate (12).** To a solution of 1-decyne (1.38 g, 10 mmol) in acetone (50 mL) was added NBS (3.56 g, 20 mmol) and  $\text{AgNO}_3$  (170 mg, 1 mmol) at r.t. with protection from light. After 4 h, the solvent was carefully removed under reduced pressure, diluted with hexane and filtered. The filtrate was concentrated and purified on silica gel (Hexane) to afford 1-bromo-1-decyne (1.84 g, 85%) as a colorless oil.

To a solution of 1-bromo-1-decyne (1.84 g, 8.49 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) in a 100 mL round-bottom flask surrounded by a water bath under argon, was slowly added a solution of  $\text{BHBBr}_2 \cdot \text{Me}_2\text{S}$  (1 M in  $\text{CH}_2\text{Cl}_2$ , 8.49 mL). After stirring of the reaction mixture overnight, pentane (8.49 mL) was added and the water bath was replaced with an ice–water bath. Isopropyl alcohol (33.96 mmol) was slowly introduced to the flask and stirring is continued for an additional 15 min. Then the mixture was concentrated to remove off  $\text{CH}_2\text{Cl}_2$ , the pentane layer was separated, the alcohol layer was extracted with pentane. The combined pentane extracts were concentrated to get diisopropyl (Z)-(1-bromo-1-decenyl)boronate.

To an ice-cooled solution of diisopropyl (Z)-(1-bromo-1-decenyl)boronate in THF (10 mL) in a 100 mL round-bottom flask was added, with stirring, a solution of KIPBH (1 M in THF, 8.49 mL) dropwise. The cold bath was then removed, and the stirring was continued at r.t. for 1 h. Then the mixture was filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 4:1) to afford diisopropyl (Z)-1-decenyl boronate (1.31 g, 58%) as a colorless oil. The product was used for next

step without further purification. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2923, 2854, 1621, 1418, 1337, 1246, 733.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{Cl}_3$ )  $\delta$  6.61 (dt,  $J = 7.5, 13.6$  Hz, 1H), 5.42 (dt,  $J = 1.3, 13.6$  Hz, 1H), 2.55 (m, 2H), 1.16–1.43 (m, 26H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{Cl}_3$ ):  $\delta$  158.9, 151.1, 65.6, 60.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.29, 29.27, 25.4, 24.6, 22.6, 14.1.

**2-(3-(4-Methoxybenzyloxy)propyl)-3,5-di((Z)-dec-1-enyl)-4,6-dimethylpyridine (13).** Pd(OAc) $_2$  (9 mg, 0.04 mmol), PPh $_3$  (32 mg, 0.12 mmol), and **11** (149 mg, 0.34 mmol) were stirred in toluene (1.36 mL) and aq Na $_2$ CO $_3$  (0.68 mL, 2M), under a nitrogen atmosphere for 0.5 h. To this solution was added a solution of **12** (361 mg, 1.35 mmol) in ethanol (0.68 mL). The solution was refluxed 6 h, then diluted with EtOAc, filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 10:1) to afford the product (178 mg, 94%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3000, 2923, 2852, 1613, 1512, 1246, 1099, 1038, 732.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (m, 2H), 6.86 (m, 2H), 6.28 (d,  $J = 11.8$  Hz, 1H), 6.24 (d,  $J = 11.8$  Hz, 1H), 5.74–5.81 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50 (t,  $J = 6.7$  Hz, 2H), 2.75 (br s, 2H), 2.39 (s, 3H), 2.04 (s, 3H), 1.92–2.00 (m, 2H), 1.74–1.81 (m, 4H), 1.19–1.34 (m, 24H), 0.86 (t,  $J = 6.8$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 156.4, 153.3, 134.7, 134.4, 131.0, 129.3, 129.2, 129.1, 129.1, 128.8, 125.9, 125.4, 113.9, 113.7, 72.3, 70.1, 55.3, 32.6, 31.9, 29.4, 29.4, 29.4, 29.4, 29.3, 29.2, 29.2, 28.9, 28.8, 28.7, 23.1, 22.7, 17.5, 14.1, 14.1. HRMS  $m/z$  calcd for C $_{38}$ H $_{60}$ NO $_2$  [M + H] $^+$  = 562.4624, found 562.4621.

**3-(3,5-Di((Z)-dec-1-enyl)-4,6-dimethylpyridin-2-yl)propan-1-ol (14).** To a solution of **13** (178 mg, 0.32 mmol) in 7 mL of EtOH was added 1N HCl (3.5 mL). Then the mixture was refluxed for 3 h. After cooled down, the mixture was concentrated to remove EtOH. The water layer was extracted with CH $_2$ Cl $_2$  (3  $\times$  30 mL) and the combined organic layers were washed with brine, dried over anhydrous Na $_2$ SO $_4$ , filtered and concentrated. The residue was purified on silica gel (DCM/MeOH, 20:1) to give 121 mg of pale-yellow oil in 80% yield as the hydrochloride salt. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3235, 2954, 2923, 2853, 1613, 1512, 1245, 1094, 1038, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (d,  $J = 11.5$  Hz, 1H), 6.23 (d,  $J = 11.5$  Hz, 1H), 5.76–5.84 (m, 2H), 3.71 (t,  $J = 5.5$  Hz, 2H), 2.92 (br s, 2H), 2.38 (s, 3H), 2.06 (s, 3H), 1.89–1.94 (m, 2H), 1.73–1.80 (m, 4H), 1.19–1.32 (m, 24H), 0.86 (t,  $J = 6.8$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  155.6, 152.7, 144.5, 135.0, 134.9, 129.6, 129.2, 125.3, 125.2, 63.2, 33.7, 31.7, 31.7, 30.2, 29.4, 29.4, 29.4, 29.3, 29.2, 28.9, 28.9, 28.78, 28.76, 22.6, 22.6, 17.6, 14.1, 14.1. HRMS  $m/z$  calcd for C $_{30}$ H $_{52}$ NO [M + H] $^+$  = 442.4049, found 442.4035.

**Anibamine (1).** Methanesulfonyl chloride (53 mg, 0.46 mmol) was added to an ice-cooled solution of **14** (110 mg, 0.23 mmol) and triethylamine (70 mg, 0.69 mmol) in 6 mL CH $_2$ Cl $_2$ . The resulting mixture was allowed to warm to r.t. over 1 h. The mixture was diluted with CH $_2$ Cl $_2$  and washed with 1N HCl twice, dried over Na $_2$ SO $_4$ , filtered and concentrated. The residue was purified on silica gel (DCM/MeOH, 10:1) to afford the product (75 mg, 71%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3382, 2955, 2923, 2853, 1605, 1466, 728.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{Cl}_3$ )  $\delta$  6.23 (d,  $J = 11.2$  Hz, 2H), 6.06 (dt,  $J = 7.3$  and 11.3 Hz, 1H), 6.03 (dt,  $J = 7.4$  and 11.3 Hz, 1H), 5.38 (br, 1H), 5.09 (br, 1H), 3.37 (m, 2H), 2.83 (s, 3H), 2.62 (m, 2H), 2.28 (s, 3H), 1.79–1.84 (m, 4H), 1.22–1.39 (m, 24H), 0.86 (t,  $J = 6.8$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{Cl}_3$ ):  $\delta$  154.6, 154.3, 148.8, 138.9, 138.8, 135.2, 131.3, 122.0, 121.0, 58.9, 32.6, 31.8, 31.8, 29.43, 29.40, 29.40, 29.33, 29.28, 29.2, 29.2, 29.2, 28.8, 28.6, 22.6, 20.9, 18.8, 18.7, 14.1, 14.1. MS (ESI)  $m/z$  424.6 (M $^+$ ). (lit. $^{10}$ ) HRMS  $m/z$  calcd for C $_{30}$ H $_{50}$ N [M] $^+$  = 424.3943, found 424.3926.

**(E)-Dec-1-enylboronic acid (15).** A solution of 1-decyne (690 mg, 5 mmol) in anhydrous CH $_2$ Cl $_2$  was cooled to 0  $^\circ\text{C}$ , BHB $_2$ ·Me $_2$ S (1 M in CH $_2$ Cl $_2$ , 5 mL) was slowly added. After 4 h at r.t., the solution was carefully transferred into a cooled solution of 10% aqueous NaOH (10 mL) and the mixture was stirred at 0  $^\circ\text{C}$  for 15 min. Saturated aqueous

NH $_4$ Cl (17 mL) was added, and a voluminous white precipitate formed, CH $_2$ Cl $_2$  was removed under reduced pressure. The (*E*)-decene-boronic acid was filtered and washed extensively with ice–water, afford (*E*)-dec-1-enylboronic acid (784 mg, 85%) as a white solid. The product was directly used for next step without any further purification. Mp 52–53  $^\circ\text{C}$ . IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3443, 3322, 2921, 2848, 1634, 1346, 1151, 991.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  6.52 (dt,  $J = 6.6, 17.6$  Hz, 1H), 5.55 (dt,  $J = 1.4, 17.6$  Hz, 1H), 4.79 (s, 2H), 2.14 (m, 2H), 1.22–1.43 (m, 12H), 0.90 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  154.0, 152.3, 37.0, 33.0, 30.6, 30.4, 30.3, 29.7, 23.7, 14.4.

**2-(3-(4-Methoxybenzyloxy)propyl)-3,5-di((E)-dec-1-enyl)-4,6-dimethylpyridine (16).** Pd(OAc) $_2$  (6 mg, 0.03 mmol), PPh $_3$  (19 mg, 0.07 mmol), and **11** (88 mg, 0.2 mmol) were stirred in toluene (0.8 mL) and aqueous Na $_2$ CO $_3$  (0.4 mL, 2M), under a nitrogen atmosphere for 0.5 h. To this solution was added a solution of **15** (147 mg, 0.8 mmol) in ethanol (0.4 mL). The solution was refluxed for 6 h, then diluted with EtOAc, filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 10:1) to afford the product (97 mg, 87%) as a pale yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2954, 2922, 2852, 1613, 1512, 1246, 1098, 1038, 971.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (m, 2H), 6.86 (m, 2H), 6.29 (d,  $J = 15.9$  Hz, 1H), 6.26 (d,  $J = 16.0$  Hz, 1H), 5.56–5.67 (m, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.50 (t,  $J = 6.6$  Hz, 2H), 2.79–2.84 (m, 2H), 2.45 (s, 3H), 2.18–2.26 (m, 4H), 2.18 (s, 3H), 1.93–2.00 (m, 2H), 1.42–1.50 (m, 4H), 1.28–1.38 (m, 20H), 0.88 (t,  $J = 6.5$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 156.0, 152.9, 143.1, 137.0, 137.0, 131.0, 130.7, 130.6, 129.1, 129.1, 126.2, 125.8, 113.7, 113.7, 72.3, 70.0, 55.3, 33.4, 33.3, 32.6, 31.9, 29.6, 29.49, 29.47, 29.4, 29.4, 29.31, 29.31, 29.30, 29.30, 29.2, 23.7, 22.7, 22.7, 18.1, 14.1, 14.1. HRMS  $m/z$  calcd for C $_{38}$ H $_{60}$ NO $_2$  [M + H] $^+$  = 562.4624, found 562.4589.

**3-(4,6-Dimethyl-3,5-di((E)-prop-1-enyl)pyridin-2-yl)propan-1-ol (17).** The same procedure described for **14** was used and the residue was purified to give 75 mg pale-yellow oil in 91% yield as the hydrochloride salt. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3242, 2922, 2852, 1552, 1454, 1245, 1059, 970.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.27 (d,  $J = 16.1$  Hz, 1H), 6.24 (d,  $J = 16.1$  Hz, 1H), 5.56–5.68 (m, 2H), 3.70 (t,  $J = 5.4$  Hz, 2H), 2.96–2.99 (m, 2H), 2.44 (s, 3H), 2.20–2.26 (m, 4H), 2.19 (s, 3H), 1.88–1.94 (m, 2H), 1.44–1.51 (m, 4H), 1.24–1.38 (m, 20H), 0.89 (t,  $J = 6.6$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  155.2, 152.3, 144.0, 137.49, 137.46, 131.0, 131.0, 125.7, 125.6, 62.8, 33.6, 33.4, 33.3, 31.9, 31.9, 30.6, 29.4, 29.4, 29.3, 29.3, 29.23, 29.23, 29.21, 23.1, 22.7, 22.7, 18.1, 14.1, 14.1. HRMS  $m/z$  calcd for C $_{30}$ H $_{52}$ NO [M + H] $^+$  = 442.4049, found 442.4019.

**(11E,22E) Isomer of Anibamine (2).** The same procedure described for **1** was used and the product was obtained as a pale-yellow oil, yield: 51 mg (71%). IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3384, 2955, 2923, 2853, 1602, 1466, 976.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{Cl}_3$ )  $\delta$  6.26 (d,  $J = 16.2$  Hz, 1H), 6.23 (d,  $J = 16.2$  Hz, 1H), 5.98 (dt,  $J = 6.8$  and 16.2 Hz, 1H), 5.82 (dt,  $J = 6.8$  and 16.2 Hz, 1H), 5.18 (t,  $J = 7.6$  Hz, 2H), 3.52 (t,  $J = 7.8$  Hz, 2H), 2.85 (s, 3H), 2.53–2.61 (m, 2H), 2.37 (s, 3H), 2.24–2.31 (m, 4H), 1.45–1.50 (m, 4H), 1.24–1.32 (m, 20H), 0.89 (t,  $J = 6.6$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{Cl}_3$ ):  $\delta$  153.3, 153.1, 148.1, 142.1, 141.9, 136.7, 132.2, 122.4, 121.9, 58.8, 33.4, 33.23, 33.16, 31.9, 31.9, 29.38, 29.37, 29.27, 29.27, 29.25, 29.20, 28.84, 28.80, 22.7, 22.7, 21.2, 19.2, 19.0, 14.1, 14.1. MS (ESI)  $m/z$  424.2 (M $^+$ ). (lit. $^{10}$ ) HRMS  $m/z$ : calcd for C $_{30}$ H $_{50}$ N [M] $^+$  = 424.3943, found 424.3930.

**2-(3-(4-Methoxybenzyloxy)propyl)-5-bromo-3-((E)-dec-1-enyl)-4,6-dimethylpyridine (18)** and **2-(3-(4-Methoxybenzyloxy)propyl)-3-bromo-5-((E)-dec-1-enyl)-4,6-dimethylpyridine (19).** Pd(OAc) $_2$  (11 mg, 0.05 mmol), PPh $_3$  (37 mg, 0.14 mmol), and **11** (348 mg, 0.79 mmol) were stirred in toluene (1.6 mL) and aqueous Na $_2$ CO $_3$  (0.79 mL, 2M), under a nitrogen atmosphere for 0.5 h. To this solution was added a solution of (*E*)-dec-1-enylboronic acid (174 mg, 0.95 mmol) in ethanol (0.79 mL). The solution was then refluxed for 5 h,

diluted with EtOAc, filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 8:1) to afford a mixture (345 mg, 87%) as a pale-yellow oil.  $^1\text{H}$  NMR indicated 1:1 (3*E*/5*E*) ratio. The isomers were separated on preparative TLC plates with Hexane/EtOAc (4:1, v/v) as eluent after twice development give **18** as the top band a pale-yellow oil (68 mg) and **19** as the lower band a pale-yellow oil (70 mg).

**Compound 18.** IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2953, 2923, 2852, 1512, 1246, 1100, 1038, 974, 820.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (m, 2H), 6.86 (m, 2H), 6.28 (d,  $J = 16.1$  Hz, 1H), 5.61 (dt,  $J = 6.9$  and 16.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.48 (t,  $J = 6.6$  Hz, 2H), 2.77–2.81 (m, 2H), 2.62 (s, 3H), 2.36 (s, 3H), 2.18–2.24 (m, 2H), 1.92–1.99 (m, 2H), 1.42–1.50 (m, 2H), 1.24–1.36 (m, 10H), 0.89 (t,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 156.8, 154.2, 144.9, 138.2, 132.1, 130.8, 129.1, 129.1, 125.3, 122.2, 113.7, 113.7, 72.4, 69.8, 55.2, 33.2, 32.3, 31.9, 29.5, 29.32, 29.30, 29.2, 29.2, 25.9, 22.7, 21.3, 14.1. HRMS  $m/z$  calcd for  $\text{C}_{28}\text{H}_{41}\text{BrNO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 502.2321, found 502.2302.

**Compound 19.** IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2954, 2924, 2853, 1512, 1248, 1101, 1037, 974, 820.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (m, 2H), 6.87 (m, 2H), 6.26 (d,  $J = 16.1$  Hz, 1H), 5.64 (dt,  $J = 6.9$  and 16.1 Hz, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.55 (t,  $J = 6.6$  Hz, 2H), 2.98–3.02 (m, 2H), 2.41 (s, 3H), 2.37 (s, 3H), 2.22–2.27 (m, 2H), 2.01–2.08 (m, 2H), 1.44–1.52 (m, 2H), 1.24–1.38 (m, 10H), 0.89 (t,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 156.7, 153.7, 144.8, 138.1, 132.3, 130.9, 129.2, 129.2, 125.8, 122.0, 113.7, 113.7, 72.4, 69.7, 55.3, 35.0, 32.2, 31.9, 29.4, 29.3, 29.2, 29.2, 28.6, 23.4, 22.7, 21.3, 14.1. HRMS  $m/z$  calcd for  $\text{C}_{28}\text{H}_{41}\text{BrNO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 502.2321, found 502.2295.

**2-(3-(4-Methoxybenzyloxy)propyl)-3-((*E*)-dec-1-enyl)-5-((*Z*)-dec-1-enyl)-4,6-dimethylpyridine (20).** Pd(OAc) $_2$  (4 mg, 0.02 mmol), PPh $_3$  (13 mg, 0.05 mmol), and **18** (65 mg, 0.13 mmol) were stirred in toluene (0.38 mL) and aqueous Na $_2$ CO $_3$  (0.19 mL, 2M), under a nitrogen atmosphere for 0.5 h. To this solution was added a solution of diisopropyl (*Z*)-1-decenylboronate (104 mg, 0.39 mmol) in ethanol (0.19 mL). The solution was refluxed 4 h, then diluted with EtOAc, filtered and concentrated, the residue was purified on silica gel (Hexane/EtOAc, 8:1) to afford the product (68 mg, 93%) as a pale-yellow oil. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2954, 2922, 2852, 1512, 1456, 1246, 1100, 1038, 971, 721.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (m, 2H), 6.86 (m, 2H), 6.30 (d,  $J = 16.1$  Hz, 1H), 6.22 (d,  $J = 11.2$  Hz, 1H), 5.77 (dt,  $J = 7.2$  and 11.2 Hz, 1H), 5.62 (dt,  $J = 6.9$  and 16.1 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.51 (t,  $J = 6.7$  Hz, 2H), 2.83 (t,  $J = 7.8$  Hz, 2H), 2.37 (s, 3H), 2.20–2.24 (m, 2H), 2.11 (s, 3H), 1.95–2.02 (m, 2H), 1.76–1.82 (m, 2H), 1.43–1.50 (m, 2H), 1.20–1.31 (m, 22H), 0.88 (t,  $J = 6.7$  Hz, 3H), 0.86 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 156.4, 152.9, 143.3, 137.0, 134.4, 130.9, 130.2, 129.4, 129.1, 129.1, 125.9, 125.7, 113.7, 113.7, 72.3, 70.0, 55.2, 33.4, 32.6, 31.9, 31.8, 30.9, 29.6, 29.5, 29.4, 29.34, 29.30, 29.26, 29.2, 28.9, 28.7, 23.2, 22.7, 22.6, 17.7, 14.11, 14.09. HRMS  $m/z$  calcd for  $\text{C}_{38}\text{H}_{60}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 562.4624, found 562.4598.

**3-(3-((*E*)-Dec-1-enyl)-5-((*Z*)-dec-1-enyl)-4,6-dimethylpyridin-2-yl)propan-1-ol (21).** The same procedure described for **14** was used and the residue was purified to give 50 mg of pale-yellow oil in 90% yield as the hydrochloride salt. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3267, 2954, 2922, 2853, 1553, 1455, 1246, 1041, 970, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.28 (d,  $J = 16.1$  Hz, 1H), 6.21 (d,  $J = 11.2$  Hz, 1H), 5.79 (dt,  $J = 7.2$  and 11.2 Hz, 1H), 5.62 (dt,  $J = 6.8$  and 16.1 Hz, 1H), 3.71 (t,  $J = 5.3$  Hz, 2H), 3.00 (t,  $J = 6.0$  Hz, 2H), 2.37 (s, 3H), 2.21–2.27 (m, 2H), 2.13 (s, 3H), 1.92–1.96 (m, 2H), 1.75–1.80 (m, 2H), 1.45–1.50 (m, 2H), 1.20–1.33 (m, 22H), 0.89 (t,  $J = 6.4$  Hz, 3H), 0.86 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  155.5, 152.3, 144.3, 137.4, 134.9, 130.6, 129.7, 125.5, 125.4, 62.9, 33.6, 33.3, 31.9, 31.8, 30.6, 29.44, 29.38, 29.31, 29.28, 29.25, 29.23, 29.21, 29.21, 28.9, 28.7, 22.7, 22.6, 17.8, 14.10, 14.09. HRMS  $m/z$  calcd for  $\text{C}_{30}\text{H}_{52}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  = 442.4049, found 442.4024.

**(11*Z*,22*E*) Isomer of Anibamine (3).** The same procedure described for **1** was used. The product was obtained as a yellow oil, yield: 44 mg (94%). IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3386, 2955, 2923, 2853, 1604, 1466, 1340, 978, 723.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.27 (d,  $J = 16.2$  Hz, 1H), 6.21 (d,  $J = 11.4$  Hz, 1H), 6.05 (dt,  $J = 7.3$  and 11.4 Hz, 1H), 6.02 (dt,  $J = 6.9$  and 16.2 Hz, 1H), 5.28 (br, 1H), 4.99 (br, 1H), 3.54 (m, 2H), 2.76 (s, 3H), 2.54–2.63 (m, 2H), 2.33 (s, 3H), 2.25–2.31 (m, 2H), 1.77–1.83 (m, 2H), 1.46–1.53 (m, 2H), 1.22–1.35 (m, 22H), 0.89 (t,  $J = 6.7$  Hz, 3H), 0.86 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.8, 153.4, 148.0, 142.0, 138.8, 135.2, 132.2, 122.1, 121.8, 58.6, 33.5, 33.2, 31.9, 31.8, 29.4, 29.4, 29.25, 29.25, 29.22, 29.17, 29.10, 28.8, 28.6, 22.7, 22.6, 21.2, 18.7, 18.6, 14.11, 14.09. MS (ESI)  $m/z$  424.3 ( $\text{M}^+$ ). HRMS  $m/z$  calcd for  $\text{C}_{30}\text{H}_{50}\text{N}$  [ $\text{M}^+$ ] = 424.3943, found 424.3932.

**2-(3-(4-Methoxybenzyloxy)propyl)-5-((*E*)-dec-1-enyl)-3-((*Z*)-dec-1-enyl)-4,6-dimethylpyridine (22).** The same procedure described for **20** was used. The product was obtained as a pale-yellow oil, yield: 70 mg (96%). IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2954, 2922, 2852, 1612, 1512, 1455, 1246, 1100, 1038, 971, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (m, 2H), 6.86 (m, 2H), 6.27 (d,  $J = 16.1$  Hz, 1H), 6.26 (d,  $J = 11.2$  Hz, 1H), 5.77 (dt,  $J = 7.2$  and 11.2 Hz, 1H), 5.65 (dt,  $J = 6.9$  and 16.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.49 (t,  $J = 6.7$  Hz, 2H), 2.74 (br s, 2H), 2.47 (s, 3H), 2.21–2.26 (m, 2H), 2.12 (s, 3H), 1.91–1.98 (m, 2H), 1.75–1.81 (m, 2H), 1.45–1.52 (m, 2H), 1.19–1.39 (m, 22H), 0.89 (t,  $J = 6.6$  Hz, 3H), 0.86 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 155.9, 153.3, 143.1, 136.9, 134.6, 131.0, 130.4, 129.1, 129.1, 129.1, 126.2, 125.5, 113.7, 113.7, 72.2, 70.1, 55.3, 33.4, 32.6, 31.88, 31.85, 29.45, 29.41, 29.35, 29.34, 29.30, 29.2, 29.2, 29.1, 28.9, 28.76, 23.75, 22.7, 22.6, 17.7, 14.09, 14.08. HRMS  $m/z$  calcd for  $\text{C}_{38}\text{H}_{60}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  = 562.4624, found 562.4588.

**3-(5-((*E*)-Dec-1-enyl)-3-((*Z*)-dec-1-enyl)-4,6-dimethylpyridin-2-yl)propan-1-ol (23).** The same procedure described for **14** was used and the residue was purified to give 53 mg of pale-yellow oil in 91% yield as the hydrochloride salt. IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3374, 2954, 2923, 2853, 1643, 1455, 1300, 1062, 973, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.22 (m, 2H), 5.94 (dt,  $J = 7.3$  and 11.2 Hz, 1H), 5.76 (dt,  $J = 6.9$  and 16.2 Hz, 1H), 3.72 (t,  $J = 5.5$  Hz, 2H), 3.06 (t,  $J = 6.6$  Hz, 2H), 2.65 (s, 3H), 2.24–2.30 (m, 2H), 2.24 (s, 3H), 1.88–1.94 (m, 2H), 1.74–1.80 (m, 2H), 1.46–1.53 (m, 2H), 1.21–1.35 (m, 22H), 0.89 (t,  $J = 6.7$  Hz, 3H), 0.87 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.6, 151.8, 146.3, 138.4, 135.8, 131.6, 130.2, 124.8, 124.4, 62.5, 33.4, 32.4, 31.85, 31.81, 30.5, 29.40, 29.36, 29.29, 29.27, 29.18, 29.17, 29.17, 29.17, 28.83, 28.80, 22.64, 22.61, 18.0, 14.06, 14.05. HRMS  $m/z$  calcd for  $\text{C}_{30}\text{H}_{52}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  = 442.4049, found 442.4019.

**(11*E*,22*Z*) Isomer of Anibamine (4).** The same procedure described for **1** was used. The product was obtained as a yellow oil, yield: 46 mg (91%). IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3388, 2955, 2922, 2853, 1604, 1466, 978, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.23 (d,  $J = 16.2$  Hz, 1H), 6.20 (d,  $J = 11.3$  Hz, 1H), 6.05 (dt,  $J = 7.3$  and 11.3 Hz, 1H), 6.02 (dt,  $J = 6.9$  and 16.2 Hz, 1H), 5.26 (t,  $J = 7.3$  Hz, 2H), 3.34 (t,  $J = 7.6$  Hz, 2H), 2.92 (s, 3H), 2.54–2.62 (m, 2H), 2.31 (s, 3H), 2.26–2.31 (m, 2H), 1.79–1.84 (m, 2H), 1.47–1.54 (m, 2H), 1.22–1.38 (m, 22H), 0.89 (t,  $J = 6.6$  Hz, 3H), 0.87 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 153.6, 148.8, 142.2, 138.9, 136.6, 131.2, 122.2, 121.0, 59.0, 33.2, 32.6, 31.84, 31.81, 29.4, 29.4, 29.4, 29.3, 29.23, 29.20, 29.16, 28.75, 28.74, 22.64, 22.61, 20.9, 19.2, 18.9, 14.09, 14.06. MS (ESI)  $m/z$  424.3 ( $\text{M}^+$ ). HRMS  $m/z$  calcd for  $\text{C}_{30}\text{H}_{50}\text{N}$  [ $\text{M}^+$ ] = 424.3943, found 424.3924.

**Molecular Modeling Procedure.** The structures of anibamine and its three isomers were built using Sybyl 8.1 with, unless specified, default parameters, followed by energy minimization (Tripos forcefield, Gasteiger-Hückel charges) with default termination at 0.05 kcal mol $^{-1}$  Å $^{-1}$ . The energy minimized structures were then solvated in a water box (compound 1, periodic box size, 79,170.4 Å $^3$ , 42.76 Å each side, number of waters, 3474; compound 2, periodic box size, 119,018.2 Å $^3$ , 49.19 Å each side, number of waters, 5288; compound 3, periodic box size, 104,737.0 Å $^3$ ,

46.99 Å each side, number of waters, 4609; compound 4, periodic box size, 95,426.2 Å<sup>3</sup>, 45.33 Å each side, number of waters, 4156). The isomers in these water boxes were again energy minimized (Tripos forcefield, Gasteiger-Hückel charges, constant dielectric =80, termination 0.05 kcal mol<sup>-1</sup> Å<sup>-1</sup>). Dynamic simulations were run on the four isomers within their respective water boxes for 200 000 fs. Average structures from the last 10 000 fs of the dynamic simulation run were generated and again energy minimized as above. Structures thus obtained were in the corresponding figures.

**Calcium Assay Protocol.** MOLT-4/CCR5 cells were plated in black 96-well plates with transparent bottom (Greiner Bio-one) at 100 000 cells per well in 50:1 HBSS:HEPES assay buffer. They were incubated for 1 h at 37 °C and 5% CO<sub>2</sub> with control buffer or varying concentration of compound for a total volume of 130 μL per well. Cells were then incubated with 50 μL of Fluo-4 a.m. loading buffer (40 μL 2 μM Fluo-4 dye, 100 μL 2.5 mM probenacid, in 5 mL assay buffer) for an additional hour. Then 20 μL 200 nM RANTES solution in assay buffer or assay buffer alone were added to the wells right before changes in Ca<sup>2+</sup> concentration were monitored by RFU for 90 s using a microplate reader (FlexStation3, Molecular Devices). Peak values were obtained using SoftMaxPro software (Molecular Devices) and nonlinear regression curves were generated using Prism (GraphPad) to calculate IC<sub>50</sub> values.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Purity test results and copies of spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

yzhang2@vcu.edu

## ■ ACKNOWLEDGMENT

We are grateful for the funding support from US Army Prostate Cancer Research Program PC073739, and NIH/NIAID AI074461. The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, nor the US Army Prostate Cancer Research Program. We thank the NIH AIDS Research and Reference Reagent Program for providing the MOLT-4/CCR5 cell line.

## ■ REFERENCES

- (1) Jayasuriya, H.; Herath, K. B.; Ondeyka, J. G.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Springer, M. S.; Siciliano, S.; Malkowitz, L.; Sanchez, M.; Guan, Z. Q.; Tiwari, S.; Stevenson, D. W.; Borris, R. P.; Singh, S. B. *J. Nat. Prod.* **2004**, *67*, 1036–1038.
- (2) Klausmeyer, P.; Chmurny, G. N.; McCloud, T. G.; Tucker, K. D.; Shoemaker, R. H. *J. Nat. Prod.* **2004**, *67*, 1732–1735.
- (3) (a) Tagat, J. R.; McCombie, S. W.; Nazareno, D.; Labroli, M. A.; Xiao, Y.; Steensma, R. W.; Strizki, J. M.; Baroudy, B. M.; Cox, K.; Lachowicz, J.; Varty, G.; Watkins, R. *J. Med. Chem.* **2004**, *47*, 2405–2408. (b) Strizki, J. M.; Tremblay, C.; Xu, S.; Wojcik, L.; Wagner, N.; Gonsiorek, W.; Hipkin, R. W.; Chou, C. C.; Pugliese-Sivo, C.; Xiao, Y.; Tagat, J. R.; Cox, K.; Priestley, T.; Sorota, S.; Huang, W.; Hirsch, M.; Reyes, G. R.; Baroudy, B. M. *Antimicrob. Agents Chemother.* **2005**, *49*, 4911–4919.
- (4) Dorr, P.; Westby, M.; Dobbs, S.; Griffin, P.; Irvine, B.; Macartney, M.; Mori, J.; Rickett, G.; Smith-Burchnell, C.; Napier, C.; Webster, R.;

Armour, D.; Price, D.; Stammen, B.; Wood, A.; Perros, M. *Antimicrob. Agents Chemother.* **2005**, *49*, 4721–4732.

(5) Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *86*, 5698–5703. (b) Maeda, K.; Nakata, H.; Koh, Y.; Miyakawa, T.; Ogata, H.; Takaoka, Y.; Shibayama, S.; Sagawa, K.; Fukushima, D.; Moravek, J.; Koyanagi, Y.; Mitsuya, H. *J. Virol.* **2004**, *78*, 8654–8662.

(6) (a) Samson, M.; Libert, F.; Doranz, B. J.; Rucker, J.; Liesnard, C.; Farber, C.-M.; Saragosti, S.; Lapoumeroulie, C.; Cognaux, J.; Forceille, C.; Muyldermans, G.; Verhofstede, C.; Burtonboy, G.; Georges, M.; Imai, T.; Rana, S.; Yi, Y.; Smyth, R. J.; Collman, R. G.; Doms, R. W.; Vassart, G.; Parmentier, M. *Nature* **1996**, *382*, 722–725. (b) Littman, D. R. *Cell* **1998**, *93*, 677–680. (c) Howard, O. M.; Oppenheim, J. J.; Wang, J. M. *J. Clin. Immunol.* **1999**, *19*, 280–292. (d) Schwarz, M. K.; Wells, T. N. C. *Nat. Rev. Drug Discovery* **2002**, *1*, 347–357. (e) Lusso, P. *EMBO J.* **2006**, *25*, 447–456.

(7) Zhang, X.; Haney, K. M.; Richardson, A. C.; Wilson, E.; Gewirtz, D. A.; Ware, J. L.; Zehner, Z. E.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4627–4630.

(8) (a) Coussens, L. M.; Werb, Z. *Nature* **2002**, *420*, 860–867. (b) Nelson, W. G.; De Marzo, A. M.; Isaacs, W. B. *N. Engl. J. Med.* **2003**, *349*, 366–381. (c) Robinson, S. C.; Scott, K. A.; Wilson, J. L.; Thompson, R. G.; Proudfoot, A. E. L.; Balkwill, F. *Cancer Res.* **2003**, *63*, 8360–8365. (d) Koenig, J. E.; Senge, T.; Allhoff, E. P.; Koenig, W. *Prostate* **2004**, *58*, 121–129.

(9) Vaday, G. G.; Peehl, D. M.; Kadam, P. A.; Lawrence, D. M. *Prostate* **2006**, *66*, 124–134.

(10) Li, G.; Watson, K.; Buckheit, R. W.; Zhang, Y. *Org. Lett.* **2007**, *9*, 2043–2046.

(11) Mariella, R. P.; Belcher, E. P. *J. Am. Chem. Soc.* **1952**, *74*, 1916–1919.

(12) Woon, P. B.; Jung, M. K.; Young, S. K.; Cheol, H. Y.; Shin, J. K.; Seok, W. L. U.S. Patent, 0092718 A1, 2004.

(13) Pitterna, T.; Renold, P.; Hueter, O. F.; Maienfisch, P.; Zambach, W. W. O. Patent, 109539 A2, 2009.

(14) (a) Siméon, F. G.; Wendahl, M. T.; Pike, V. W. *J. Org. Chem.* **2009**, *74*, 2578–2580. (b) Bracher, F.; Daab, J. *Eur. J. Org. Chem.* **2002**, *14*, 2288–2291.

(15) (a) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386–390. (b) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109–6112.

(16) Potts, K. T.; Burton, H. R. *J. Org. Chem.* **1966**, *31*, 251–260.

(17) (a) Brown, H. C.; Imal, T. *Organometallics* **1984**, *3*, 1392–1395. (b) Brown, H. C.; Somayaji, V. *Synthesis* **1984**, 919–920. (c) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745–3748. (d) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Prasad, J. V. N. V. *J. Org. Chem.* **1988**, *53*, 239–246.

(18) (a) Yanagi, T.; Oh-e, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3892–3895. (b) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F.-J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285–4299.

(19) (a) Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287–8297. (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429.

(20) (a) Thoma, G.; Nuninger, F.; Schaefer, M.; Akyel, K. G.; Albert, R.; Beerli, C.; Bruns, C.; Francotte, E.; Luyten, M.; MacKenzie, D.; Oberer, L.; Streiff, M. B.; Wagner, T.; Walter, H.; Weckbecker, G.; Zerwer, H. G. *J. Med. Chem.* **2004**, *47*, 1939–55. (b) Kaighn, M. E.; Narayan, S.; Ohnuki, Y.; Lechner, J. F.; Jones, L. W. *Invest. Urol.* **1979**, *17*, 16–23. (c) Haney, K. M.; Zhang, F.; Arnatt, C. K.; Yuan, Y.; Li, G.; Ware, J. L.; Gewirtz, D. A.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5159–5163.