JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

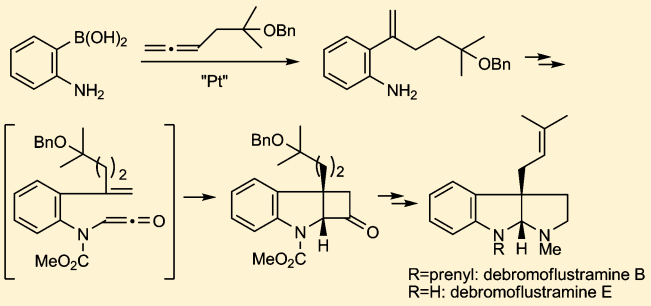
Total Synthesis of Debromoflustramines B and E Based on the Intramolecular Carbamoylketene−Alkene [2 + 2] Cycloaddition

Tsukasa Ozawa, Makoto Kanematsu, Hiromasa Yokoe, Masahiro Yoshida, and Kozo Shishido*

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

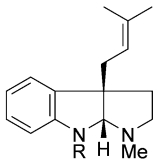
Supporting Information

ABSTRACT: Total synthesis of debromoflustramines B and E has been accomplished by using a platinum-catalyzed addition reaction of *o*-aminophenylboronic acid with the allene and an intramolecular carbamoylketene−alkene [2 + 2] cycloaddition for the construction of the basic carbon framework of the target alkaloids as the key steps.



INTRODUCTION

Debromoflustramines B (**1**) and E (**2**), members of the pyrrolidinoindoline alkaloid family, have been isolated from the marine bryozoan *Flustra foliacea*[1] and from Australian myobatrachid frogs *Pseudophryne*,[2] respectively. These alkaloids possess a characteristic prenylated hexahydropyrrolo[2,3-*b*]-indole backbone and are known to exhibit selective butyrylcholinesterase inhibitory[3] and antibacterial activity against vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus*.[4] Due to their intriguing structures and promising biological profiles, these compounds have attracted much attention in the synthetic community as targets for total synthesis. To date, a number of syntheses of the racemic[5] and optically active forms[6] have been reported.



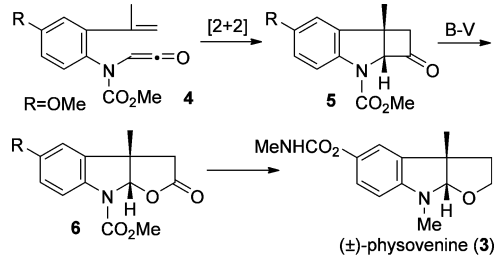
R=prenyl: debromoflustramine B (**1**)
R=H: debromoflustramine E (**2**)

Figure 1. Debromoflustramines.

During the course of our synthetic studies directed toward the Calabar bean alkaloids, we reported the synthesis of (±)-physovenine (**3**), employing an efficient intramolecular carbamoylketene−alkene [2 + 2] cycloaddition reaction (**4**→**5**) followed by Baeyer−Villiger (B−V) oxidation (**5**→**6**) as the key steps.[7] (Scheme 1)

Furthermore, we have recently developed a regiocontrolled addition of the arylboronic acids **8** to the allenes **7** using a palladium or platinum catalyst. The selectivity of the reaction can be controlled by the choice of the metal species and base.

Scheme 1. Synthesis of Physovenine via the Intramolecular Carbamoylketene−Alkene [2 + 2] Cycloaddition

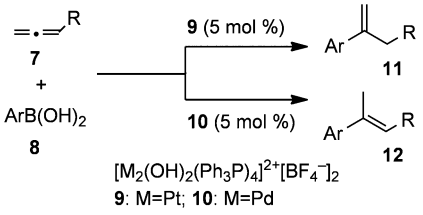


Whereas the endo-olefinic products **12** are formed when the hydroxopalladium complex **10** is used in the reaction, the exo-olefinic products **11** predominated when the hydroxoplatinum complex **9** was employed[8] (Scheme 2).

RESULTS AND DISCUSSION

As an application of the combined methodologies of the originally developed [2 + 2] cycloaddition and the platinum-catalyzed exo-selective alkenylation to the synthesis of

Scheme 2. Regiocontrolled Addition of Arylboronic Acids to Allenes Using Pt and Pd Catalyst

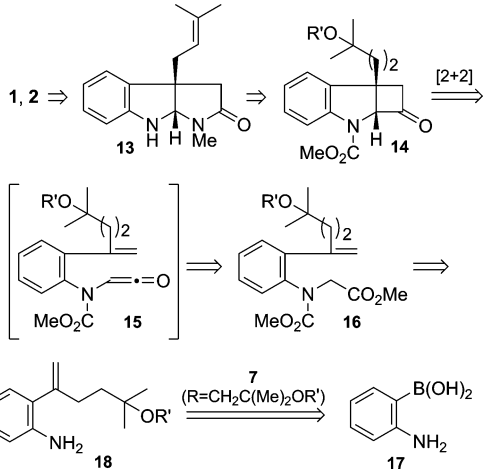


Received: August 24, 2012
Published: September 26, 2012

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240−9249

pyrrolidinoindoline alkaloids, we report here the total synthesis of (±)-debromoflustramines B (**1**) and E (**2**). Our retrosynthetic analysis of the debromoflustramines is shown in Scheme 3. We envisaged reducing the lactam and N-

Scheme 3. Retrosynthetic Analysis

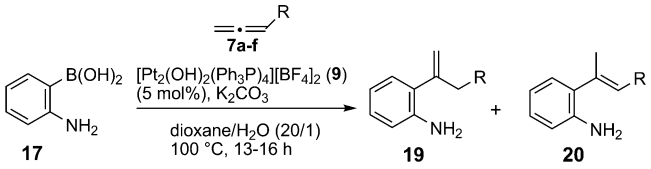


prenylation in the last stage of the synthesis. By means of a Beckmann-type ring expansion, the γ-lactam **13** could be derived from the cyclobutanone **14**, the [2 + 2] cycloadduct of the alkenyl carbamoylketene **15**, which would be generated from a ketene precursor **16**. Compound **16** can be derived from the aniline derivative **18**, which would be prepared through a platinum-catalyzed coupling reaction of *o*-aminophenylboronic acid **17**[9] and the corresponding allene **7** (R = $CH_2C(Me)_2OR'$).[10] (Scheme 3)

Because the addition of *o*-aminoarylboronic acid **17** with allenes had never been attempted before, we initially examined the reaction of **17** with a variety of allenes **7a–f**, which were prepared as has been described in ref 8. The results are shown in Table 1. Treatment of **17** with the allenes **7a–f** in the presence of platinum catalyst **9**[11] and K_2CO_3 as the base[12] resulted in the predominant formation of the exo-olefinic adducts **19** rather than the endo-adducts **20** in a ratio of 3:1 to >20:1 in good yield. It was revealed that allenes with bulky substituents near the reaction center (i.e., the central carbon of the allenes) showed higher selectivity for the expected *exo*-olefin formation (entries 3–6). Particularly, in the case of the allene **7e**, the exclusive formation of **19e** could be realized (entry 5). The amino alkene **19c**, the required adduct for the synthesis of the debromoflustramines, was obtained as a mixture of isomers in a ratio of 9:1, which can be separated by HPLC, in 90% yield (entry 3). The *E*-geometry of the undesired endo-adduct **20c** was confirmed by an NOE between the olefinic methyl and the allylic methylene proton. It should be noted that the coupling reaction proceeds cleanly without protection of the amino group (Table 1).

To verify the generality and substrate scope of the intramolecular [2 + 2] cycloaddition, we examined the reaction using these amino alkenes. Treatment of a mixture of adducts **19a–f**/**20a–d,f** with methyl chloroformate and potassium carbonate followed by methyl bromoacetate and sodium hydride provided **21a–f**/**22a–d,f**. After alkaline hydrolysis, the resulting carboxylic acids were treated with oxalyl chloride in refluxing benzene. Triethylamine was then added to the mixture in one pot[7] to give a readily separable mixture of the

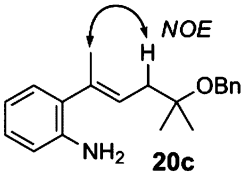
Table 1. Platinum-Catalyzed Coupling of 17 with 7a–f



entry	7a-f	yield % [a]	19:20 [b]
1	**a**: R=$(CH_2)_2OBn$	92	3:1
2	**b**: R=$(CH_2)_3OBn$	93	4:1
3	**c**: R=$CH_2C(Me)_2OBn$	90	9:1
4	**d**: R=$CH_2C(Me)_2OH$	62	9:1
5	**e**: R=$C(Me)_2CH_2OBn$	64	>20:1
6	**f**: R=$CH_2C(Me)_2CH_2OBn$	67	12:1

[a] Isolated yield as a mixture of **19** and **20**

[b] Determined by ^1H NMR after purification



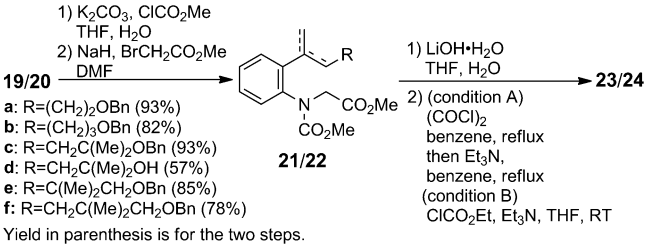
cycloadducts **23** and **24** as shown in Table 2. The stereochemistry of the *endo*-olefin derived cycloadduct **24c** was established by observation of a diagnostic NOE between the methyl and the methylene protons shown in entry 3. The cycloaddition of the substrate **21d**/**22d** with an unprotected hydroxyl group resulted in **23d** and an inseparable mixture of the olefinic isomers **25** and **26** (entry 4). To improve the yield of **23d**, treatment of a mixture of the carboxylic acids with ethyl chloroformate and triethylamine in THF at room temperature produced cleanly a separable mixture of **23d** and the cyclized product **24d** in 60% and 2% yield, respectively (entry 5). Thus, we were able to develop an alternative and mild procedure (condition B) for the generation of the carbamoylketene[13] (Table 2).

With the requisite tricycle **23c** in hand, we advanced to the key ring expansion. The cyclobutanone was converted to the oxime **27**, the configuration of which, determined by ^1H NMR using a shift reagent $Eu(dpm)_3$,[14] proved to be *Z*.[15] On exposure of **27** to the conditions of the Beckmann rearrangement ($SOCl_2$, benzene, RT, 11 h),[16] the desired tricyclic lactam **28** was not obtained at all but the ring-opened hemiaminal **29**, which was characterized as the methyl aminal **30**, was produced in 73% yield for the three steps (Scheme 4).

Unsuccessful attempts at the Beckmann rearrangement led us to seek an efficient, regioselective ring expansion from **23c** to the lactam. After numerous attempts, we found that rearrangement through a nitrone[14,17] could be applied to the conversion; thus, treatment of **23c** with *N*-methylhydroxylamine hydrochloride, $NaHCO_3$, and 3 Å molecular sieves in ethanol at 50 °C provided the nitrone **31**, which, without purification, was immediately reacted with *p*-TsCl and 4-pyrrolidinopyridine in refluxing chloroform to give the requisite γ-lactam **32** in 75% yield for the two steps. As a result, we were able to overcome a key hurdle and in so doing demonstrated that the procedure

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240–9249

Table 2. [2 + 2] Cycloaddition

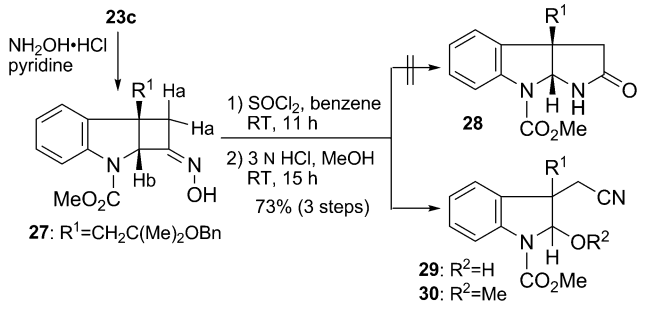


Yield in parenthesis is for the two steps.

entry	21/22	condition	cycloadduct(s) (yield %[a] for two steps, ratio)
1	a	A	**23a** (61%); **24a** (7%) (*dr*=1:0.6)
2	b	A	**23b** (68%); **24b** (7%)
3	c	A	**23c** (85%); **24c** (9%)
4	d	A	**23d** (10%); **25** (22%, 1:0.8); **26**
5	d	B	**23d** (60%); **24d** (2%)[b]
6	21e	A	**23e** (72%)
7	f	A	n.d.[c]; **23f** (70%)

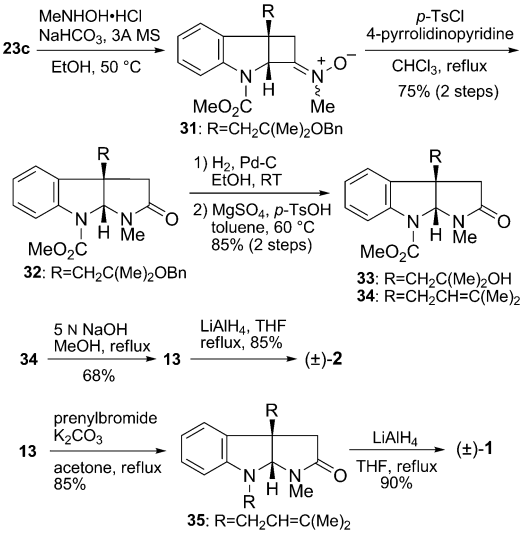
[a]Isolated yield. [b]Single product. [c]Not detected.

Scheme 4. Attempted Beckmann Rearrangement



could be successfully applied to install the hexahydropyrrolo-[2,3-*b*]indole backbone. Debenzylation followed by selective dehydration by treatment of the resulting **33** with *p*-TsOH in the presence of magnesium sulfate[18] provided the angular-prenylated tricycle **34** in good yield (85% for the two steps). After removal of the carbomethoxy group via alkaline hydrolysis, reduction of the lactam carbonyl of **13** with lithium aluminum hydride (LAH) in refluxing THF produced debromoflustramine E (**2**). On the other hand, prenylation of **13** gave **35**, which was reduced with LAH to give debromoflustramine B (**1**) uneventfully. The spectroscopic properties of the synthetic **1** and **2** were completely identical with those for the debromoflustramines B and E[5b] (Scheme 5).

Scheme 5. Total Synthesis of Debromoflustramines B and E



■ CONCLUSION

In summary, the total synthesis of debromoflustramines B (**1**) and E (**2**) has been accomplished in 18% (12 steps) and 20% (11 steps) overall yield, respectively, from *o*-aminophenylboronic acid. The unique features of this work include the combined use of the two originally developed reactions, that is, the platinum-catalyzed addition reaction of *o*-aminophenylboronic acid with allenes and the intramolecular [2 + 2] cycloaddition, for the construction of the basic carbon framework of the target alkaloids. We were also able to demonstrate the wide generality of the intramolecular carbamoylketene−alkene [2 + 2] cycloaddition, which could be applied not only to the synthesis of a variety of alkaloids but also to the assembly of nitrogen-containing heterocyclic compounds. In addition, it was revealed that the nitrone rearrangement could be successfully applied to the regioselective ring expansion of the indoline-fused cyclobutanone to give the γ-lactam for the installation of the hexahydropyrrolo-[2,3-*b*]indole backbone. Although there have been many synthetic reports on the flustramine families, the synthetic route developed here is quite unique and efficient and could also be applied to the synthesis of other alkaloids with more complex molecular structures.

■ EXPERIMENTAL SECTION

General Procedure. All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240−9249

otherwise indicated. Materials were obtained from commercial suppliers and used without further purification expect when otherwise noted. Solvents were dried and distilled according to standard protocols. NMR spectra were recorded on a 400 MHz instrument. ^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) or in C_6D_6 solution and referenced to C_6D_5H (7.16 ppm). ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm), in C_6D_6 solution and referenced to C_6D_5H (128.06 ppm), or in DMSO-d_6 and referenced to DMSO (39.3 ppm). Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. IR spectra were measured on FT/IR spectrometer. Type of mass analyzer was time of flight mass spectrometry (TOF-mass). Column chromatography was performed on silica gel using the indicated solvent. Thin layer chromatography was performed on precoated plates, and compounds were visualized with UV light and *p*-anisaldehyde stains. All melting points were reported as uncorrected.

General Procedure for Platinum-Catalyzed Coupling Reaction of *o*-Aminophenylboronic Acid (17) and the Corresponding Allenes. To a stirred solution of corresponding allenes (1.0 equiv) in dioxane−H_2O (20:1, 0.25 M) were added K_2CO_3 (5.0 equiv), boronic acid **17** (1.5 equiv), and $[Pt_2(OH)_2(PPh_3)_4][BF_4]_2$ (5 mol %). After being stirred at 100 °C for 13−16 h, the mixture was filtered through a pad of silica gel and evaporated in vacuo. The residue was purified by silica gel column chromatography.

*2-[5-(Benzyloxy)pent-1-en-2-yl]aniline and (E)-2-[5-(Benzyloxy)-pent-2-en-2-yl]aniline (**19a** and **20a**).* These compounds were prepared from allene **7a** (120 mg, 0.68 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave **19a** and **20a** as a colorless oil (175 mg, 92%, 3:1 mixture of **19a** and **20a**; the ratio was determined by ^{1}H NMR). For analysis, the mixture of **19a** and **20a** was partially separated by HPLC (Mightysil, 3% *i*-PrOH-hexane, 3.8 mL/min).

19a: R_f (hexane:AcOEt = 4:1) 0.59; IR (neat) 3467, 3366, 2856, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (5 H, m), 7.05 (1 H, t, J = 7.6 Hz), 6.97 (1 H, d, J = 7.6 Hz), 6.71 (1 H, t, J = 7.6 Hz), 6.67 (1 H, d, J = 7.6 Hz), 5.28 (1 H, s), 5.06 (1 H, s), 4.47 (2 H, s), 3.75 (2 H, br), 3.48 (2 H, t, J = 7.6 Hz), 2.48 (2 H, t, J = 7.6 Hz), 1.74 (2 H, quint, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (C), 143.2 (C), 138.5 (C), 128.6 (C), 128.4 (CH), 128.3 (2CH), 127.9 (CH), 127.7 (2CH), 127.5 (CH), 118.0 (CH), 115.4 (CH), 114.7 (CH_2), 72.9 (CH_2), 69.7 (CH_2), 33.8 (CH_2), 28.0 (CH_2); HRMS (ESI) calcd for $C_{18}H_{22}NO$ $[M + H]^+$: 268.1701, found 268.1699.

20a: R_f (hexane:AcOEt = 4:1) 0.59; IR (neat) 3464, 3367, 2856, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.27 (5 H, m), 7.02 (1 H, t, J = 7.6 Hz), 6.97 (1 H, d, J = 7.6 Hz), 6.71 (1 H, t, J = 7.6 Hz), 6.67 (1 H, d, J = 7.6 Hz), 5.50 (1 H, t, J = 6.8 Hz), 4.58 (2 H, s), 3.73 (2 H, br), 3.59 (2 H, t, J = 6.8 Hz), 2.52 (2 H, q, J = 6.8 Hz), 1.96 (3, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (C), 138.5 (C), 135.5 (C), 131.3 (C), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.6 (2CH), 127.5 (2CH), 126.7 (CH), 118.2 (CH), 115.4 (CH), 73.0 (CH_2), 69.9 (CH_2), 29.1 (CH_2), 17.5 (CH_3); HRMS (ESI) calcd for $C_{18}H_{22}NO$ $[M + H]^+$: 268.1699, found 268.1699.

*2-[6-(Benzyloxy)hex-1-en-2-yl]aniline and (E)-2-[6-(Benzyloxy)-hex-2-en-2-yl]aniline (**19b** and **20b**).* These compounds were prepared from allene **7b** (50.0 mg, 0.26 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave **19b** and **20b** as a colorless oil (68.0 mg, 93%, 4:1 mixture of **19b** and **20b**). For analysis, the mixture of **19b** and **20b** was partially separated by HPLC (Mightysil, 3% *i*-PrOH-hexane, 3.8 mL/min).

19b: R_f (hexane:AcOEt = 4:1) 0.66; IR (neat) 3467, 3369, 2936, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.23 (5 H, m), 7.05 (1 H, t, J = 7.6 Hz), 6.96 (1 H, d, J = 7.6 Hz), 6.70 (1 H, t, J = 7.6 Hz), 6.67 (1 H, d, J = 7.6 Hz), 5.26 (1 H, s), 5.05 (1 H, s), 4.47 (2 H, s), 3.75 (2 H, br), 3.45 (2 H, t, J = 8.0 Hz), 2.38 (2 H, t, J = 8.0 Hz), 1.65 (2 H, quint, J = 8.0 Hz), 1.50 (2 H, quint, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (C), 143.2 (C), 138.7 (C), 128.6 (C), 128.5 (2CH), 128.3 (2CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 118.0 (CH), 115.4 (CH), 114.5 (CH_2), 72.8 (CH_2), 70.2 (CH_2), 37.1 (CH_2), 29.4 (CH_2), 24.6 (CH_2); HRMS (ESI) calcd for $C_{19}H_{24}NO$ $[M + H]^+$: 282.1858, found 282.1855.

20b: R_f (hexane:AcOEt = 4:1) 0.66; IR (neat) 3460, 3366, 2926, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (5 H, m), 7.03 (1 H, t, J = 8.0 Hz), 6.95 (1 H, d, J = 8.0 Hz), 6.71 (1 H, t, J = 8.0 Hz), 6.66 (1 H, d, J = 8.0 Hz), 5.48 (1 H, t, J = 6.8 Hz), 4.52 (2 H, s), 3.69 (2 H, br), 3.53 (2 H, t, J = 6.8 Hz), 2.29 (2 H, q, J = 6.8 Hz), 1.94 (3 H, s), 1.77 (2 H, quint, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 138.6 (C), 134.1 (C), 131.5 (C), 129.9 (CH), 128.7 (CH), 128.4 (CH), 128.0 (2CH), 127.5 (2CH), 127.5 (CH), 118.2 (CH), 115.4 (CH), 73.0 (CH_2), 69.9 (CH_2), 29.7 (CH_2), 25.1 (CH_2), 17.3 (CH_3); HRMS (ESI) calcd for $C_{19}H_{24}NO$ $[M + H]^+$: 282.1858, found 282.1860.

*2-[5-(Benzyloxy)-5-methylhex-1-en-2-yl]aniline and (E)-2-[5-(Benzyloxy)-5-methylhex-2-en-2-yl]aniline (**19c** and **20c**).* These compounds were prepared from allene **7c** (1.00 g, 4.9 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave **19c** and **20c** as a colorless oil (1.30 g, 90%, 9:1 mixture of **19c** and **20c**). For analysis, the mixture of **19c** and **20c** were partially separated by HPLC (Mightysil, 3% *i*-PrOH-hexane, 3.8 mL/min).

19c: R_f (hexane:AcOEt = 9:1) 0.53; IR (neat) 3468, 3374, 3028, 2972, 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (5 H, m), 7.06 (1 H, t, J = 8.0 Hz), 6.98 (1 H, d, J = 8.0 Hz), 6.72 (1 H, t, J = 8.0 Hz), 6.69 (1 H, d, J = 8.0 Hz), 5.29 (1 H, s), 5.05 (1 H, s), 4.34 (2 H, s), 3.79 (2 H, br), 2.49 (2 H, dt, J = 3.8 and 16.8 Hz), 1.69 (2 H, dt, J = 3.8 and 16.8 Hz), 1.24 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (C), 143.2 (C), 139.7 (C), 128.5 (C), 128.5 (CH), 128.2 (2CH), 127.8 (CH), 127.3 (2CH), 127.1 (CH), 118.0 (CH), 115.4 (CH), 114.1 (CH_2), 74.8 (C), 63.5 (CH_2), 38.5 (CH_2), 31.7 (CH_2), 25.7 ($2CH_3$); HRMS (ESI) calcd for $C_{20}H_{26}NO$ $[M + H]^+$: 296.2014, found 296.2014.

20c: R_f (hexane:AcOEt = 9:1) 0.53; IR (neat) 3466, 3371, 3028, 2972, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (5 H, m), 7.04 (1 H, t, J = 7.6 Hz), 6.98 (1 H, d, J = 7.6 Hz), 6.72 (1 H, t, J = 7.6 Hz), 6.66 (1 H, d, J = 7.6 Hz), 5.63 (1 H, t, J = 7.6 Hz), 4.40 (2 H, s), 3.70 (2 H, br), 2.48 (2 H, d, J = 7.6 Hz), 1.97 (3 H, s), 1.33 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (C), 139.7 (C), 135.4 (C), 131.5 (C), 128.6 (CH), 128.3 (CH), 127.5 (2CH), 127.3 (CH), 127.1 (2CH), 126.2 (CH), 118.1 (CH), 115.4 (CH), 75.8 (C), 63.9 (CH_2), 39.6 (CH_2), 25.6 ($2CH_3$), 17.6 (CH_3); HRMS (ESI) calcd for $C_{20}H_{26}NO$ $[M + H]^+$: 296.2014, found 296.2010.

*5-(2-Aminophenyl)-2-methylhex-5-en-2-ol and (E)-5-(2-Aminophenyl)-2-methylhex-4-en-2-ol (**19d** and **20d**).* These compounds were prepared from allene **7d** (19.0 mg, 0.16 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 7:3) gave **19d** and **20d** as a colorless oil (20.4 mg, 62%, 9:1 mixture of **19d** and **20d**). For analysis, the mixture of **19d** and **20d** was partially separated by HPLC (Mightysil, 3% *i*-PrOH-hexane, 3.8 mL/min).

19d: R_f (hexane:AcOEt = 7:3) 0.20; IR (neat) 3367, 2970, 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1 H, t, J = 7.6 Hz), 7.00 (1 H, d, J = 7.6 Hz), 6.73 (1 H, t, J = 7.6 Hz), 6.70 (1 H, d, J = 7.6 Hz), 5.31 (1 H, s), 5.07 (1 H, s), 3.79 (2 H, br), 2.47 (2 H, t, J = 8.4 Hz), 1.60 (2 H, t, J = 8.4 Hz), 1.54 (1 H, br), 1.21 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9 (C), 143.0 (C), 128.5 (C), 128.4 (CH), 127.8 (CH), 118.0 (CH), 115.4 (CH), 114.2 (CH_2), 70.5 (C), 41.8 (CH_2), 32.0 (CH_2), 29.1 ($2CH_3$); HRMS (ESI) calcd for $C_{13}H_{20}NO$ $[M + H]^+$: 206.1545, found 206.1549.

20d: R_f (hexane:AcOEt = 7:3) 0.20; IR (neat) 3372, 2970, 1615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1 H, t, J = 7.2 Hz), 6.98 (1 H, d, J = 7.2 Hz), 6.72 (1 H, t, J = 7.2 Hz), 6.69 (1 H, d, J = 7.2 Hz), 5.59 (1 H, t, J = 7.6 Hz), 3.75 (2 H, br), 2.39 (2 H, t, J = 7.6 Hz), 1.97 (3 H, s), 1.43 (1 H, br), 1.29 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 136.8 (C), 131.5 (C), 128.7 (CH), 127.7 (CH), 125.9 (CH), 118.3 (CH), 115.5 (CH), 71.5 (C), 42.4 (CH_2), 29.4 ($2CH_3$), 17.6 (CH_3); HRMS (ESI) calcd for $C_{13}H_{20}NO$ $[M + H]^+$: 206.1545, found 206.1555.

*2-[5-(Benzyloxy)-4,4-dimethylpent-1-en-2-yl]aniline (**19e**).* This compound was prepared from allene **7e** (30.0 mg, 0.14 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave **19e** as a colorless oil (26.5 mg, 64%); R_f (hexane:AcOEt =

dx.doi.org/10.1021/jo301817w | *J. Org. Chem.* 2012, 77, 9240−9249

4:1) 0.57; IR (neat) 3477, 3383, 2956, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (5 H, m), 7.03 (1 H, t, J = 8.2 Hz), 7.01 (1 H, d, J = 8.2 Hz), 6.68 (1 H, t, J = 8.2 Hz), 6.65 (1 H, d, J = 8.2 Hz), 5.27 (1 H, s), 5.17 (1 H, s), 4.27 (2H, s), 3.82 (2 H, br), 3.02 (2 H, s), 2.52 (2 H, s), 0.85 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (C), 142.7 (C), 139.0 (C), 129.4 (C), 128.8 (CH), 128.2 (2CH), 127.6 (CH), 127.4 (2CH), 127.2 (CH), 118.3 (CH_2), 118.0 (CH), 115.6 (CH), 78.5 (CH_2), 72.8 (CH_2), 46.2 (CH_2), 35.8 (C), 25.2 ($2CH_3$); HRMS (ESI) calcd for $C_{20}H_{26}NO$ $[M + H]^+$: 296.2014 found 296.2014.

*2-[6-(Benzyloxy)-5,5-dimethylhex-1-en-2-yl]aniline and (E)-2-[6-(Benzyloxy)-5,5-dimethylhex-2-en-2-yl]aniline (**19f** and **20f**).* These compounds were prepared from allene **7f** (34.0 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave **19f** and **20f** as a colorless oil (31.2 mg, 67%, 12:1 mixture of **19f** and **20f**); R_f (hexane:AcOEt = 4:1) 0.61; IR (neat) 3471, 3374, 2953, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (5 H, m), 7.05 (1 H, t, J = 7.6 Hz), 6.97 (1 H, d, J = 7.6 Hz), 6.71 (1 H, t, J = 7.6 Hz), 6.69 (1 H, d, J = 7.6 Hz), 5.28 (0.08 H, t, J = 8.0 Hz), 5.26 (1 H, s), 5.04 (1 H, s), 4.51 (0.16 H, s), 4.48 (2 H, s), 3,76 (2 H, br), 3.19 (0.17 H, s), 3.13 (2 H, s), 2.30 (2 H, dt, J = 8.0 and 8.4 Hz), 2.19 (0.17 H, d, J = 8.0 Hz), 1.93 (0.25 H, s), 1.45 (2 H, dt, J = 8.0 and 8.4 Hz), 0.97 (0.5 H, s), 0.89 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 148.5 (C), 143.1 (C), 139.0 (C), 129.0 (C), 128.4 (2CH), 128.2 (CH), 127.7 (2CH), 127.3 (CH), 127.2 (CH), 118.0 (CH), 115.4 (CH), 113.9 (CH_2), 79.0 (CH_2), 73.2 (CH_2), 37.5 (CH_2), 34.4 (C), 31.8 (CH_2), 24.6 ($2CH_3$); HRMS (ESI) calcd for $C_{21}H_{27}NONa$ $[M + Na]^+$: 332.1990 found 332.1986.

General Procedure for Preparation of Esters 21 and 22. To a stirred solution of the aminoalkenes (1.0 equiv) in THF−H_2O (3:1, 0.3 M) were added K_2CO_3 (10 equiv) and methyl chloloformate (1.5 equiv). After being stirred at RT for 3 h, H_2O was added and extracted with Et_2O. The organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give an inseparable mixture of the carbamates. The ratio of the mixture was determined by ^1H NMR. To a suspention of NaH (1.5 equiv) in DMF (0.2 M) was added the carbamate (1.0 equiv) in DMF at 0 °C. After being stirred at 0 °C for 30 min, methyl bromoacetate (1.5 equiv) was added at 0 °C and the mixture was stirred at RT. After completion of the reaction, H_2O was added at 0 °C and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography.

*Methyl 2-[{2-((5-Benzyloxy)pent-1-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate and (E)-Methyl 2-[{2-(5-(Benzyloxy)pent-2-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21a** and **22a**).* The mixture of carbamates was prepared from aminoalkene (**19a**/**20a**) (45.0 mg, 0.16 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave the corresponding carbamates as a colorless oil (49.6 mg, 95%, an inseparable 3:1 mixture of methyl 2-[5-(benzyloxy)pent-1-en-2-yl]phenylcarbamate and (*E*)-methyl 2-[5-(benzyloxy)pent-2-en-2-yl]-phenylcarbamate); R_f (hexane:AcOEt = 4:1) 0.61; IR (neat) 3412, 1740, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, d, J = 8.0 Hz), 7.52−7.22 (6 H, m), 7.11 (1 H, br), 7.05 (1 H, t, J = 8.0 Hz), 6.99 (1 H, d, J = 8.0 Hz), 5.46 (0.33 H, t, J = 6.4 Hz), 5.35 (1 H, s), 5.02 (1 H, s), 4.57 (0.62 H, s), 4.48 (2 H, s), 3,74 (3 H, s), 3.68 (1 H, s), 3.58 (0.65 H, t, J = 6.8 Hz), 3.47 (2 H, t, J = 8.0 Hz), 2.52 (0.65 H, q, J = 6.8 Hz), 2.00 (2 H, t, J = 8.0 Hz), 1.95 (0.6 H, s), 1.72 (2 H, quint, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (C), 146.6 (C), 138.4 (C), 134.6 (C), 132.1 (C), 128.4 (2CH), 128.1 (CH), 127.9 (CH), 127.6 (2CH), 127.5 (CH), 122.8 (CH), 119.3 (CH), 116.2 (CH_2), 72.9 (CH_2), 69.8 (CH_2), 69.4 (CH_2 isomer), 52.1 (CH_3), 34.8 (CH_2), 29.1 (CH_2 isomer), 27.8 (CH_2), 18.2 (CH_3 isomer); HRMS (ESI) calcd for $C_{20}H_{23}NO_3Na$ $[M + Na]^+$: 348.1576, found 348.1572. The mixture of the carbamates (50.0 mg, 0.15 mmol) was converted to an inseparable 3:1 mixture of **21a** and **22a** (58.0 mg, 98%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 4:1); R_f (hexane:AcOEt = 4:1) 0.48; IR (neat) 2952, 1756, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.43 (1 H, m), 7.35−7.27 (7 H, m), 7.18−7.16 (1 H, m), 5.42 (0.33 H, t, J = 6.4 Hz), 5.19 (1 H, s), 4.95 (1 H, s), 4.65 (1 H, d, J = 17.6 Hz), 4.54 (0.66 H, s), 4.46 (2 H, s), 3,73 (3 H, s), 3.72 (1 H, d, J = 17.6 Hz), 3.65 (1 H, s), 3.62 (3 H, s), 3.54 (0.66 H, t, J = 6.4 Hz), 3.44 (2 H, t, J = 6.4 Hz), 2.41 (2 H, m), 1.91 (0.66 H, s), 1.69 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C), 156.3 (C), 155.9 (C isomer), 147.9 (C), 140.6 (C), 138.6 (C), 138.5 (C), 135.5 (C isomer), 129.9 (CH), 129.7 (CH), 128.3 (CH), 127.9 (2CH), 127.8 (2CH), 127.6 (CH), 127.5 (CH), 115.3 (CH_2), 115.2 (CH isomer), 73.0 (CH_2 isomer), 72.9 (CH_2), 69.5 (CH_2), 53.0 (CH_3), 52.5 (CH_3 isomer), 52.0 (CH_3), 52.0 (CH_3 isomer), 51.7 (CH_2), 33.0 (CH_2), 29.1 (CH_2 isomer), 28.2 (CH_2), 17.0 (CH_3 isomer); HRMS (ESI) calcd for $C_{23}H_{28}NO_5$ $[M + H]^+$: 398.1967, found 398.1967.

*Methyl 2-[(2-{6-(Benzyloxy)hex-1-en-2-yl}phenyl)(methoxycarbonyl)amino)acetate and (E)-Methyl 2-[{2-(6-(Benzyloxy)hex-2-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21b** and **22b**).* The mixture of carbamates was prepared from aminoalkene (**19b**/**20b**) (20.0 mg, 0.71 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave the corresponding carbamates as a colorless oil (35.0 mg, 90%, an inseparable 4:1 mixture of methyl 2-[6-(benzyloxy)hex-1-en-2-yl]-phenylcarbamate and (*E*)-methyl 2-[6-(benzyloxy)hex-2-en-2-yl]-phenylcarbamate); R_f (hexane:AcOEt = 4:1) 0.68; IR (neat) 3412, 2939, 2857, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (1 H, d, J = 7.6 Hz), 7.35−7.27 (6 H, m), 7.05 (1 H, t, J = 7.6 Hz), 7.01 (1 H, d, J = 7.6 Hz), 6.96 (1 H, br, J = 8.0 Hz), 5.44 (0.25 H, t, J = 8.0 Hz), 5.34 (1 H, s), 5.02 (1 H, s), 4.53 (0.43 H, s), 4.48 (2 H, s), 3,75 (3 H, s), 3.54 (0.52 H, t, J = 6.4 Hz), 3.45 (2 H, t, J = 8.0 Hz), 2.35 (2 H, t, J = 8.0 Hz), 1.94 (0.5 H, s), 1.64 (2 H, quint, J = 8.0 Hz), 1.49 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (C), 150.7 (C isomer), 146.9 (C), 138.6 (C), 134.4 (C), 132.2 (C isomer), 128.4 (C), 128.3 (CH), 128.1 (2CH), 127.9 (2CH), 127.6 (CH), 127.5 (CH), 122.8 (CH), 119.2 (CH), 116.1 (CH_2), 73.0 (CH_2 isomer), 72.9 (CH_2), 70.0 (CH_2 isomer), 69.9 (CH_2), 69.7 (CH_2 isomer), 52.2 (CH_3), 37.7 (CH_2), 29.4 (CH_2), 25.2 (CH_2 isomer), 24.4 (CH_2), 17.9 (CH_3 isomer); HRMS (ESI) calcd for $C_{21}H_{26}NO_3$ $[M + H]^+$: 340.1913, found 340.1902. The mixture of the carbamates (95.0 mg, 0.27 mmol) was converted to an inseparable 4:1 mixture of **21b** and **22b** (103 mg, 91%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 4:1); R_f (hexane:AcOEt = 4:1) 0.41; IR (neat) 2951, 2858, 1756, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.43 (1 H, m), 7.35−7.26 (7 H, m), 7.19−7.17 (1 H, m), 5.37 (0.25 H, t, J = 6.4 Hz), 5.17 (1 H, s), 4.94 (1 H, s), 4.64 (1 H, d, J = 17.6 Hz), 4.52 (0.45 H, s), 4.47 (2 H, s), 3,73 (1 H, d, J = 17.6 Hz), 3.72 (3 H, s), 3.64 (3 H, s), 3.52 (0.25 H, t, J = 6.4 Hz), 3.43 (2 H, t, J = 7.6 Hz), 2.30 (2 H, t, J = 7.6 Hz), 1.87 (0.67 H, s), 1.59 (2 H, quint, J = 7.6 Hz), 1.45 (2 H, quint, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C), 156.4 (C), 148.2 (C), 140.8 (C), 138.6 (C), 130.0 (C), 129.7 (2CH), 128.4 (CH isomer), 128.3 (CH), 127.9 (2CH), 127.8 (2CH), 127.7 (CH isomer), 127.6 (CH), 127.5 (CH), 115.2 (CH_2), 114.9 (CH isomer), 73.0 (CH_2 isomer), 72.9 (CH_2), 70.2 (CH_2 isomer), 70.1 (CH_2), 53.1 (CH_3), 52.1 (CH_3), 51.7 (CH_2), 36.2 (CH_2), 29.4 (CH_2), 24.7 (CH_2), 22.6 (CH_2 isomer), 21.0 (CH_2 isomer), 16.7 (CH_3 isomer); HRMS (ESI) calcd for $C_{24}H_{30}NO_5$ $[M + H]^+$: 412.2124, found 412.2113.

*Methyl 2-[{2-(5-Benzyloxy-5-methylhex-1-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate and (E)-Methyl 2-[{2-(5-Benzyloxy-5-methylhex-2-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21c** and **22c**).* The mixture of carbamates was prepared from aminoalkene (**19c**/**20c**) (300 mg, 1.0 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave the corresponding carbamates as a colorless oil (347 mg, 98%, an inseparable 9:1 mixture of methyl 2-[5-(benzyloxy)-5-methylhex-1-en-2-yl]-phenylcarbamate and (*E*)-methyl 2-[5-(benzyloxy)-5-methylhex-2-en-2-yl]phenylcarbamate); R_f (hexane:AcOEt = 9:1) 0.54; IR (neat) 3412, 3064, 2972, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (1 H, br), 7.52−7.22 (6 H, m), 7.08 (1 H, d, J = 7.8 Hz), 7.02 (1 H, t, J = 7.8 Hz), 7.00 (1 H, br), 5.62 (0.11 H, t, J = 8.0 Hz), 5.37 (1 H, s), 5.01 (1 H, s), 4.59 (0.22 H, s), 4.32 (2 H, s), 3,73 (3 H, s), 3.67 (0.34 H, s), 2.46 (2 H, dt, J = 4.4 and 8.4 Hz), 1.95 (0.33 H, s), 1.65 (2H, dt, J =

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240−9249

4.4 and 8.4 Hz), 1.34 (0.67 H, s), 1.24 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 153.9 (C), 147.2 (C), 139.6 (C), 134.5 (C), 132.1 (C), 128.2 (2CH), 128.0 (CH), 127.9 (CH), 127.2 (2CH), 127.1 (CH), 122.8 (CH), 119.2 (CH), 115.8 (CH_2), 74.7 (C), 63.6 (CH_2), 52.2 (CH_3), 38.3 (CH_2), 32.3 (CH_2), 25.6 ($2CH_3$); HRMS (ESI) calcd for $C_{22}H_{27}NO_3Na$ $[M + Na]^+$: 376.1889, found 376.1889. The mixture of the carbamates (390 mg, 1.1 mmol) was converted to an inseparable 9:1 mixture of **21c** and **22c** (494 mg, 95%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 7:3); R_f (hexane:AcOEt = 7:3) 0.54; IR (neat) 2970, 1757, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.44 (1 H, m), 7.32−7.26 (7 H, m), 7.20−7.18 (1 H, m), 5.43 (0.11 H, t, J = 7.6 Hz), 5.56 (0.1 H, t, J = 6.4 Hz), 5.20 (1 H, s), 4.92 (1 H, s), 4.62 (1 H, d, J = 7.6 Hz), 4.47 (0.2 H, s), 4.36 (2 H, d, J = 6.4 Hz), 3.79 (1 H, d, J = 6.4 Hz), 3,72 (3 H, s), 3.54 (3 H, s), 2.41 (2 H, m), 1.89 (0.33 H, s), 1.64 (2H, m), 1.30 (0.67 H, s), 1.21 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 169.9 (C), 156.4 (C), 148.6 (C), 140.9 (C), 139.7 (C), 138.7 (C), 129.8 (CH), 129.7 (CH), 128.2 (2CH), 127.9 (2CH), 127.8 (CH), 127.2 (CH), 127.0 (CH), 114.7 (CH_2), 74.8 (C), 63.6 (CH_2), 53.0 (CH_3), 52.0 (CH_2), 51.8 (CH_3), 39.3 (CH_2), 30.9 (CH_2), 25.5 (CH_3), 25.4 (CH_3); HRMS (ESI) calcd for $C_{25}H_{31}NO_5Na$ $[M + Na]^+$: 448.2100, found 448.2095.

*Methyl 2-[{2-(5-Hydroxy-5-methylhex-1-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate and (E)-Methyl 2-[{2-(5-Hydroxy-5-methylhex-2-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21d** and **22d**).* The mixture of carbamates was prepared from aminoalkene (**19d**/**20d**) (30.0 mg, 0.14 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 7:3) gave the corresponding carbamates as a colorless oil (37.3 mg, quant., an inseparable 9:1 mixture of methyl 2-(5-hydroxy-5-methylhex-1-en-2-yl)phenylcarbamate and (*E*)-methyl 2-(5-hydroxy-5-methylhex-2-en-2-yl)phenylcarbamate); R_f (hexane:AcOEt = 7:3) 0.20; IR (neat) 3412, 2968, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1 H, d, J = 7.6 Hz), 7.26 (1 H, t, J = 7.6 Hz), 7.11 (1 H, br), 7.08 (1 H, d, J = 7.6 Hz), 7.03 (1 H, t, J = 7.6 Hz), 5.56 (0.11, t, J = 7.2 Hz), 5.38 (1 H, s), 5.02 (1 H, s), 3.80 (3 H, s), 2.45 (2 H, t, J = 8.0 Hz), 2.39 (0.09, d, J = 7.6 Hz), 1.95 (0.30, s), 1.56 (2 H, t, J = 8.0 Hz), 1.35 (1 H, br), 1.30 (0.65, s), 1.20 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 154.1 (C), 147.1 (C), 134.5 (C), 132.3 (C), 128.1 (CH), 128.0 (CH), 122.9 (CH), 119.5 (CH), 115.9 (CH_2), 70.7 (C), 52.2 (CH_3), 41.4 (CH_2), 32.7 (CH_2), 29.3 ($2CH_3$); HRMS (ESI) calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$: 264.1600, found 264.1595. The mixture of the carbamates (45.0 mg, 0.17 mmol) was converted to an inseparable 9:1 mixture of **21d** and **22d** (34.0 mg, 57%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 1:1); R_f (hexane:AcOEt = 1:1) 0.57; IR (neat) 3487, 2964, 1755, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.44 (1 H, m), 7.33−7.23 (2 H, m), 7.20−7.18 (1 H, m), 5.51 (0.11 H, t, J = 8.0 Hz), 5.21 (1 H, s), 4.95 (1 H, s), 4.66 (1 H, d, J = 17.6 Hz), 3.74 (1 H, d, J = 17.6 Hz), 3,73 (3 H, s), 3.67 (3 H, s), 2.45 (1 H, br), 2.38 (2 H, t, J = 8.4 Hz), 1.96 (0.21 H, s), 1.54 (2 H, t, J = 8.4 Hz), 1.46 (0.21 H, t, J = 8.0 Hz), 1.27 (0.6 H, s), 1.12 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 169.9 (C), 156.4 (C), 148.6 (C), 140.1 (C), 138.6 (C), 130.0 (CH), 129.7 (CH), 128.0 (CH), 127.8 (CH), 114.9 (CH_2), 70.5 (C), 53.1 (CH_3), 52.0 (CH_2), 51.8 (CH_3), 42.2 (CH_2), 31.2 (CH_2), 29.3 (CH_3), 29.1 (CH_3); HRMS (ESI) calcd for $C_{18}H_{26}NO_5$ $[M + H]^+$: 336.1811, found 336.1804.

*Methyl 2-[{2-(5-(Benzyloxy)-4,4-dimethylpent-1-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21e**).* The carbamate was prepared from aminoalkene (**19e**) (110 mg, 0.37 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave the corresponding carbamate as a colorless oil (127 mg, 95% of methyl 2-[5-(benzyloxy)-4,4-dimethylpent-1-en-2-yl]phenylcarbamate); R_f (hexane:AcOEt = 4:1) 0.57; IR (neat) 3414, 2955, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, d, J = 7.6 Hz), 7.35−7.25 (4 H, m), 7.24−7.21 (2 H, m), 7.14 (1 H, d, J = 7.6 Hz), 7.00 (1 H, t, J = 7.6 Hz), 5.35 (1 H, s), 5.12 (1 H, s), 4.29 (2 H, s), 3.79 (3 H, s), 3.00 (2 H, s), 2.51 (2 H, s), 0.82 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (C), 144.6 (C), 138.7 (C), 134.2 (C), 128.3 (C), 128.1 (2CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.2 (2CH), 124.1 (CH), 122.8 (CH), 119.8 (CH_2), 78.6 (CH_2), 72.9 (CH_2), 52.2 (CH_3), 47.3 (CH_2), 35.9 (C), 25.4 ($2CH_3$); HRMS (ESI) calcd for $C_{22}H_{28}NO_3$ $[M + H]^+$: 354.2069, found 354.2065. The carbamate (95.0 mg, 0.26 mmol) was converted to **21e** (120 mg, 89%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 4:1); R_f (hexane:AcOEt = 4:1) 0.47; IR (neat) 2953, 1757, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1 H, d, J = 7.6 Hz), 7.31−7.29 (4 H, m), 7.27−7.20 (4 H, m), 5,17 (1 H, s), 5.07 (1 H, s), 4.60 (1 H, d, J = 16.8 Hz), 4.30 (1 H, d, J = 12.0 Hz), 4.21 (1 H, d, J = 12.0 Hz), 3.72 (1 H, d, J = 16.8 Hz), 3.70 (3 H, s), 3.60 (3 H, s), 3.04 (1 H, d, J = 12.0 Hz), 2.97 (1 H, d, J = 12.0 Hz), 2.40 (1 H, d, J = 13.6 Hz), 2.28 (1 H, d, J = 13.6 Hz), 0.80 (3 H, s), 0.79 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 156.3 (C), 146.8 (C), 142.0 (C), 138.8 (C), 138.6 (C), 130.5 (CH), 129.5 (CH), 128.1 (2CH), 127.7 (CH), 127.6 (CH), 127.4 (2CH), 127.2 (CH), 119.9 (CH_2), 78.8 (CH_2), 72.9 (CH_2), 52.9 (CH_3), 51.9 (CH_3), 51.3 (CH_2), 44.3 (CH_2), 35.8 (C), 25.6 (CH_3), 24.6 (CH_3); HRMS (ESI) calcd for $C_{25}H_{32}NO_5$ $[M + H]^+$: 426.2280, found 426.2280.

*Methyl 2-[{2-(6-(Benzyloxy)-5,5-dimethylhex-1-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate and (E)-Methyl 2-[{2-(6-(Benzyloxy)-5,5-dimethylhex-2-en-2-yl)phenyl}(methoxycarbonyl)amino]acetate (**21f** and **22f**).* The mixture of carbamates was prepared from aminoalkenes (**19f**/**20f**) (33.0 mg, 0.10 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 9:1) gave the corresponding carbamates as a colorless oil (35.0 mg, 90%, an inseparable 12:1 mixture of methyl 2-[6-(benzyloxy)-5,5-dimethylhex-1-en-2-yl]phenylcarbamate and (*E*)-methyl 2-[6-(benzyloxy)-5,5-dimethylhex-2-en-2-yl]phenylcarbamate); R_f (hexane:AcOEt = 4:1) 0.61; IR (neat) 3413, 2953, 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1 H, d, J = 8.0 Hz), 7.34−7.24 (6 H, m), 7.05 (1 H, t, J = 8.0 Hz), 7.02 (1 H, d, J = 8.0 Hz), 6.97 (1 H, br), 5.48 (0.07 H, t, J = 6.4 Hz), 5.34 (1 H, s), 5.00 (1 H, s), 4.52 (0.16 H, s), 4.47 (2 H, s), 3.74 (3 H, s), 3.19 (0.16 H, s), 3.10 (2 H, s), 2.25 (2 H, dt, J = 4.0 and 8.0 Hz), 2.21 (0.2 H, d, J = 8.0 Hz), 1.91 (0.25 H, s), 1.41 (2 H, dt, J = 4.0 and 8.0 Hz), 0.98 (0.5 H, s), 0.83 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 154.0 (C), 147.7 (C), 138.9 (C), 134.4 (C), 128.3 (C), 127.9 (2CH), 127.8 (3CH), 127.3 (2CH), 122.8 (CH), 119.1 (CH), 115.5 (CH_2), 78.9 (CH_2), 73.2 (CH_2), 52.2 (CH_3), 37.3 (C), 34.4 (CH_2), 32.5 (CH_2), 24.6 ($2CH_3$); HRMS (ESI) calcd for $C_{23}H_{30}NO_3$ $[M + H]^+$: 368.2226, found 368.2220. The mixture of the carbamates (85.0 mg, 0.23 mmol) was converted to an inseparable 12:1 mixture of **21f** and **22f** (88.0 mg, 87%) as a colorless oil, after purification by silica gel column chromatography (hexane:AcOEt = 4:1); R_f (hexane:AcOEt = 4:1) 0.30; IR (neat) 2953, 1757, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.43 (1 H, m), 7.33−7.27 (7 H, m), 7.18−7.16 (1 H, m), 5.42 (0.08 H, t, J = 6.8 Hz), 5.17 (1 H, s), 4.90 (1 H, s), 4.65 (1 H, d, J = 18 Hz), 4.51 (0.16 H, s), 4.48 (2 H, s), 3.75 (1 H, d, J = 18 Hz), 3.72 (3 H, s), 3.62 (3 H, s), 3.18 (0.16 H, s), 3.10 (2 H, s), 2.24 (2 H, m), 1.86 (0.2 H, s), 1.37 (2 H, m), 0.96 (0.5 H, s), 0.87 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer only) δ 169.9 (C), 156.4 (C), 148.9 (C), 140.9 (C), 138.9 (C), 138.8 (C), 129.9 (CH), 129.7 (CH), 128.2 (2CH), 127.8 (CH), 127.7 (CH), 127.3 (3CH), 114.6 (CH_2), 79.1 (CH_2), 73.2 (CH_2), 53.1 (CH_3), 52.0 (CH_3), 51.7 (CH_2), 37.8 (CH_2), 34.4 (C), 30.9 (CH_2), 24.8 (CH_3), 24.4 (CH_3); HRMS (ESI) calcd for $C_{26}H_{34}NO_5$ $[M + H]^+$: 440.2437, found 440.2426.

General Procedure for [2 + 2] Cycloaddition: Condition A. To a stirred solution of corresponding esters (1.0 equiv) in THF−H_2O (3:1, 0.2 M) was added LiOH·H_2O (2.0 equiv). After being stirred at RT for 3 h, the mixture was evaporated in vacuo and the residue was washed with Et_2O. The water layers were treated with 1 N HCl (pH 1−2) and then extracted with Et_2O. The organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was used in the next steps without further purification. To a stirred solution of carboxylic acid (1.0 equiv) in dry benzene (0.2 M) was dropwised oxalyl chrolide (5.0 equiv) at 0 °C. After being stirred at RT for 1 h and then refluxed for 30 min, the mixture was evaporated in vacuo. The residue was diluted with dry benzene (0.2 M), and Et_3N (3.0 equiv) was added and then refluxed for 1.5 h. H_2O was added and extracted with benzene. The organic layers were dried over $MgSO_4$,

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240−9249

filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography.

*Methyl 7b-[3-(Benzyloxy)propyl]-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate and Methyl 1-[2-(Benzyloxy)ethyl]-7b-methyl-2-oxo-2,2a-dihydro-1H-cyclobuta[b]-indole-3(7bH)-carboxylate (**23a** and **24a**).* These compounds were prepared from the mixture of ester (**21a**/**22a**) (48.0 mg, 0.12 mmol). **23a** and **24a** could be separated by silica gel column chromatography (hexane:AcOEt = 9:1).

23a: Yield (26.5 mg, 61%); colorless oil. R_f (hexane:AcOEt = 4:1) 0.45; IR (neat) 2952, 2856, 1790, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1 H, br), 7.37−7.22 (6 H, m), 7.23 (1 H, d, J = 7.2 Hz), 7.07 (1 H, t, J = 7.2 Hz), 5.24 (1 H, br), 4.48 (2 H, s), 3.84 (3 H, s), 3.44 (2 H, t, J = 6.2 Hz), 3.40 (1 H, d, J = 18.4 Hz), 3.16 (1 H, dd, J = 2.4 and 18.4 Hz), 2.23 (1 H, dt, J = 4.8 and 12.8 Hz), 2.12 (1 H, dt, J = 4.8 and 12.8 Hz), 1.62−1.45 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.2 (C), 152.8 (C), 143.3 (C), 138.4 (C), 134.1 (C), 128.9 (2CH), 128.4 (2CH), 127.6 (2CH), 124.1 (CH), 123.9 (CH), 115.7 (CH), 79.2 (CH), 73.1 (CH_2), 69.7 (CH_2), 60.6 (CH_2), 52.9 (CH_3), 43.9 (C), 33.9 (CH_2), 26.2 (CH_2); HRMS (ESI) calcd for $C_{22}H_{23}NO_4Na$ $[M + Na]^+$: 388.1525, found 388.1521.

24a: Yield (2.80 mg, 7%; dr = 1:0.6); colorless oil. R_f (hexane:AcOEt = 4:1) 0.50; IR (neat) 2863, 1784, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1.6 H, br), 7.36−7.28 (10 H, m), 7.16 (0.6 H, d, J = 7.2 Hz), 7.11 (1.0 H, d, J = 7.2 Hz), 7.04−6.99 (1.6 H, m), 5.18 (0.6 H, br), 4.99 (1.0 H, br), 4.51 (1.2 H, s), 4.48 (2.0 H, s), 3.85 (4.8 H, s), 3.64−3.49 (3.8 H, m), 3.38 (1.0 H, t, J = 7.6 Hz), 2.02 (2.0 H, q, J = 7.6 Hz), 1.71 (1.9 H, s), 1.56 (3.0 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 206.3 (C), 205.0 (C isomer), 152.9 (C), 138.3 (2C), 138.2 (C), 137.9 (CH isomer), 128.9 (CH isomer), 128.4 (2CH), 127.8 (2CH), 127.7 (CH), 123.7 (CH), 123.4 (CH), 123.1 (CH), 116.2 (CH isomer), 115.5 (CH), 81.2 (CH), 79.2 (CH), 73.2 (CH_2), 68.4 (CH_2 isomer), 68.0 (CH_2), 52.8 (CH_3), 45.2 (C isomer), 42.8 (C), 26.4 (CH_2), 25.9 (CH_2 isomer), 25.2 (CH_3 isomer), 17.2 (CH_3); HRMS (ESI) calcd for $C_{22}H_{23}NO_4Na$ $[M + Na]^+$: 388.1525, found 388.1534.

*Methyl 7b-[4-(Benzyloxy)butyl]-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate and Methyl 1-[3-(Benzyloxy)propyl]-7b-methyl-2-oxo-2,2a-dihydro-1H-cyclobuta[b]-indole-3(7bH)-carboxylate (**23b** and **24b**).* These compounds were prepared from the mixture of ester (**21b**/**22b**) (40.0 mg, 0.097 mmol). **23b** and **24b** could be separated by silica gel column chromatography (hexane:AcOEt = 9:1).

23b: Yield (26.0 mg, 68%); colorless oil. R_f (hexane:AcOEt = 7:3) 0.57; IR (neat) 2937, 2858, 1791, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, br), 7.33−7.21 (6 H, m), 7.21 (1 H, d, J = 7.2 Hz), 7.07 (1 H, t, J = 7.2 Hz), 5.22 (1 H, br), 4.46 (2 H, s), 3.85 (3 H, s), 3.42 (2 H, t, J = 6.2 Hz), 3.37 (1 H, d, J = 18.4 Hz), 3.13 (1 H, d, J = 18.4 Hz), 2.12 (1 H, dt, J = 4.8 and 12.4 Hz), 1.98 (1 H, dt, J = 4.8 and 12.4 Hz), 1.62 (2 H, quint, J = 6.2 Hz), 1.42 (1 H, m), 1.25 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.1 (C), 152.7 (C), 143.2 (C), 138.4 (C), 134.2 (C), 128.7 (CH), 128.2 (CH), 127.5 (2CH), 127.4 (2CH), 123.9 (CH), 123.7 (CH), 115.5 (CH), 79.0 (CH), 72.8 (CH_2), 69.6 (CH_2), 60.3 (CH_2), 52.8 (CH_3), 44.0 (C), 36.8 (CH_2), 29.6 (CH_2), 22.4 (CH_2); HRMS (ESI) calcd for $C_{23}H_{25}NO_4Na$ $[M + Na]^+$: 402.1681, found 402.1684.

24b: Yield (2.50 mg, 7%); colorless oil. R_f (hexane:AcOEt = 7:3) 0.64; IR (neat) 2926, 1784, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (1 H, br), 7.34−7.26 (6 H, m), 7.17 (1 H, d, J = 7.6 Hz), 7.05 (1 H, t, J = 7.6 Hz), 5.01 (1 H, br), 4.49 (2 H, s), 3.86 (3 H, s), 3.49 (2 H, m), 3.20 (1 H, s), 1.81−1.72 (4 H, m), 1.58 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 205.6 (C), 138.6 (2C), 138.0 (C), 128.5 (C), 128.4 (2CH), 127.6 (2CH), 127.5 (2CH), 123.8 (CH), 122.9 (CH), 115.6 (CH), 81.1 (CH_2), 73.0 (CH_2), 70.9 (CH), 69.6 (CH), 52.9 (CH_3), 43.0 (C), 28.0 (CH_2), 23.4 (CH_2), 17.2 (CH_3); HRMS (ESI) calcd for $C_{23}H_{26}NO_4$ $[M + H]^+$: 380.1862, found 380.1862.

*Methyl 7b-[3-(Benzyloxy)-3-methylbutyl]-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)carboxylate and Methyl 1-[2-(Benzyloxy)2-methylpropyl]-7b-methyl-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**23c** and **24c**).* These compounds were prepared from the mixture of ester (**21c**/**22c**) (1.20 g, 2.8 mmol). **23c** and **24c** could be separated by silica gel column chromatography (hexane:AcOEt = 9:1).

23c: Yield (985 mg, 85%); colorless oil. R_f (hexane:AcOEt = 7:3) 0.60; IR (neat) 2972, 1792, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1 H, br), 7.51−7.28 (6 H, m), 7.20 (1 H, d, J = 7.2 Hz), 7.06 (1 H, t, J = 7.2 Hz), 5.17 (1 H, s), 4.35 (2 H, dd, J = 1.2 and 15.4 Hz), 3.86 (3 H, s), 3.38 (1 H, d, J = 18.0 Hz), 3.16 (1 H, dd, J = 2.8 and 18.0 Hz), 2.28 (1 H, dt, J = 3.4 and 12.8 Hz), 2.10 (1 H, dt, J = 3.4 and 12.8 Hz), 1.51 (1 H, dt, J = 4.0 and 12.8 Hz), 1.32 (1 H, dt, J = 4.0 and 12.8 Hz), 1.24 (3 H, s), 1.22 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.1 (C), 152.8 (C), 143.3 (C), 139.7 (C), 134.3 (C), 128.8 (2CH), 128.2 (2CH), 127.1 (2CH), 127.0 (CH), 123.9 (CH), 115.6 (CH), 79.0 (CH), 74.5 (C), 63.7 (CH_2), 60.8 (CH_2), 52.9 (CH_3), 43.8 (C), 36.6 (CH_2), 31.3 (CH_2), 25.6 (CH_3), 25.4 (CH_3); HRMS (ESI) calcd for $C_{24}H_{27}NO_4Na$ $[M + Na]^+$: 416.1838, found 416.1839.

24c: Yield (106 mg, 9%); colorless oil. R_f (hexane:AcOEt = 7:3) 0.64; IR (neat) 2956, 1785, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (1 H, br), 7.36−7.21 (2 H, m), 7.24−7.20 (4 H, m), 6.97−6.92 (2 H, m), 4.88 (1 H, br), 4.35 (2 H, dd, J = 10.8 and 13.2 Hz), 3.85 (3 H, s), 3.59 (1 H, m), 1.97 (2 H, d, J = 6.4 Hz), 1.52 (3 H, s), 1.29 (3 H, s), 1.22 (3 H, s); ^{13}C NMR (100 MHz, DMSO-d_6, 60 °C) δ 205.4 (C), 152.2 (C), 141.2 (C), 139.2 (C), 138.1 (C), 127.7 (2CH), 127.0 (3CH), 126.7 (CH), 123.2 (CH), 123.1 (CH), 114.4 (CH), 80.5 (CH), 73.6 (C), 66.9 (CH_3), 62.9 (CH_2), 52.5 (CH), 42.1 (C), 35.9 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 16.9 (CH_3); HRMS (ESI) calcd for $C_{24}H_{27}NO_4Na$ $[M + Na]^+$: 416.1838, found 416.1836.

*Methyl 7b-(3-Hydroxy-3-methylbutyl)-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate, (2a,7b)-Methyl 7b-(3-methylbut-2-enyl)-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate and (2a,7b)-Methyl 7b-(3-Methylbut-3-enyl)-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**23d**, **25**, and **26**).* These compounds were prepared from the mixture of ester (**21d**/**22d**) (20 mg, 0.09 mmol). **23d** and **25**/**26** could be separated by silica gel column chromatography (hexane:AcOEt = 7:3).

23d: Yield (3.00 mg, 10%); colorless oil. R_f (hexane:AcOEt = 7:3) 0.50; IR (neat) 3502, 2968, 1791, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, br), 7.29−7.23 (2 H, m), 7.08 (1 H, t, J = 7.2 Hz), 5.21 (1 H, br), 3.86 (3 H, s), 3.40 (1 H, d, J = 19.6 Hz), 3.18 (1 H, dd, J = 2.8 and 19.6 Hz), 2.26 (1 H, dt, J = 4.0 and 13.0 Hz), 2.10 (1 H, dt, J = 4.0 and 13.0 Hz), 1.46 (1 H, dt, J = 4.0 and 13.0 Hz), 1.25 (1 H, dt, J = 4.0 and 13.0 Hz), 1.05 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.1 (C), 152.8 (C), 143.3 (C), 134.2 (C), 128.9 (CH), 124.0 (CH), 123.9 (CH), 115.7 (CH), 79.1 (CH), 70.3 (C), 60.7 (CH_2), 53.0 (CH_3), 43.9 (C), 39.3 (CH_2), 31.7 (CH_2), 29.6 (CH_3), 29.3 (CH_3); HRMS (ESI) calcd for $C_{17}H_{22}NO_4$ $[M + H]^+$: 304.1549, found 304.1548.

25/**26**: Yield (6.10 mg, 22%, 1:0.8 mixture; ^1H NMR); colorless oil; R_f (hexane:AcOEt = 7:3) 0.75; IR (neat) 2956, 1792, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1.8 H, br), 7.37−7.10 (1.8 H, m), 7.09−7.04 (2.8 H, m), 5.38 (0.8 H, br), 5.24 (1 H, br), 5.16 (2 H, t, J = 6.8 Hz), 4.71 (0.8 H, s), 4.63 (0.8 H, s), 3.86 (5.4 H, s), 3.43 (2.0 H, t, J = 16.0 Hz), 3.13 (1.6 H, dd, J = 18.0 and 36.4 Hz), 2.70 (2.0 H, ddd, J = 6.4, 16.0, and 32.0 Hz), 2.28 (0.8 H, m), 2.13 (0.8 H, m), 1.96 (0.8 H, m), 1.84 (0.8 H, m), 1.72 (2.4 H, s), 1.70 (3 H, s), 1.67 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.3 (C), 203.2 (C), 144.4 (C), 136.3 (C), 128.9 (C), 128.8 (C), 128.3 (CH), 124.1 (CH), 123.9 (CH), 123.8 (CH), 118.5 (CH), 115.7 (CH_2), 115.6 (CH), 110.6 (CH), 79.1 (CH), 78.9 (CH), 60.7 (CH_2), 59.1 (CH_2), 52.9 (CH_3), 44.1 (C), 35.2 (CH_2), 35.0 (CH_2), 33.8 (CH_2), 25.8 (CH_3), 22.4 (CH_3), 18.0 (CH_3); HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na$ $[M + Na]^+$: 308.1263, found 308.1256.

*Methyl 7b-[3-(Benzyloxy)-2,2-dimethylpropyl]-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**23e**).* This compound was prepared from the ester (**21e**) (56.0 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 4:1) gave **23e** as a colorless oil (43.0 mg, 72%); R_f (hexane:AcOEt = 4:1) 0.62; IR (neat) 2956, 1792, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, d, J = 7.4 Hz), 7.38−7.23 (7 H, m), 7.03 (1 H, t, J = 7.4 Hz), 5.46 (1 H, br), 4.38 (1 H, d, J = 12.0 Hz), 4.32 (1 H, d, J = 12.0 Hz), 3.85 (3 H, s), 3.37 (1 H, d, J = 17.8 Hz), 3.16 (1 H, dd, J =

2.4 and 17.8 Hz), 2.92 (1 H, d, J = 9.4 Hz), 2.78 (1 H, d, J = 9.4 Hz), 2.42 (1 H, d, J = 14.8 Hz), 2.14 (1 H, d, J = 14.8 Hz), 0.79 (3 H, s), 0.69 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 204.7 (C), 152.8 (C), 143.0 (C), 138.6 (C), 134.7 (C), 128.7 (CH), 128.3 (2CH), 127.5 (CH), 127.4 (2CH), 125.1 (CH), 123.6 (CH), 115.9 (CH), 78.6 (CH), 73.0 (CH_2), 64.7 (CH_2), 52.9 (CH_3), 45.2 (CH_2), 43.4 (C), 36.2 (C), 26.4 (CH_2), 26.1 ($2CH_3$); HRMS (ESI) calcd for $C_{24}H_{27}NO_4Na$ $[M + Na]^+$: 416.1838, found 416.1843.

*Methyl 7b-[4-(Benzyloxy)-3,3-dimethylbutyl]-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**23f**).* This compound was prepared from the mixture of ester (**21f**/**22f**) (51.0 mg, 0.11 mmol). Purification by silica gel column chromatography (hexane:AcOEt = 4:1) gave **23f** as a colorless oil (31.6 mg, 70%); R_f (hexane:AcOEt = 4:1) 0.50; IR (neat) 2971, 1792, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, br), 7.35−7.27 (6 H, m), 7.18 (1 H, d, J = 7.2 Hz), 7.05 (1 H, t, J = 7.2 Hz), 5.16 (1 H, br), 4.50 (1 H, d, J = 12.0 Hz), 4.45 (1 H, d, J = 12.0 Hz), 3.83 (3 H, s), 3.33 (1 H, d, J = 16.8 Hz), 3.12 (1 H, dd, J = 2.4 and 16.8 Hz), 3.09 (2 H, s), 2.04 (1 H, dt, J = 4.0 and 13.2 Hz), 1.86 (1 H, dt, J = 4.0 and 13.2 Hz), 1.33 (1 H, dt, J = 4.0 and 13.2 Hz), 1.09 (1 H, dt, J = 4.0 and 13.2 Hz), 0.88 (3 H, s), 0.87 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 203.3 (C), 152.8 (C), 143.2 (C), 138.8 (C), 134.5 (C), 128.7 (2CH), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 123.9 (CH), 115.5 (CH), 79.0 (CH), 78.6 (CH_2), 73.3 (CH_2), 60.4 (CH_2), 52.9 (CH_3), 44.0 (C), 34.6 (C), 34.2 (CH_2), 31.3 (CH_2), 24.8 (CH_3), 24.6 (CH_3); HRMS (ESI) calcd for $C_{25}H_{29}NO_4Na$ $[M + Na]^+$: 430.1994, found 430.1995.

General Procedure for [2 + 2] Cycloaddition: Condition B. *Methyl 7b-(3-Hydroxy-3-methylbutyl)-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate and Methyl 8b-Hydroxy-2,2,3b-trimethyl-3,3a,8a,8b-tetrahydro-2H-furo[3′,2′:3,4]cyclobuta-[1,2-b]indole-8(3bH)-carboxylate (**23d** and **24d**).* To a stirred solution of ester (**21d**/**22d**) (22.0 mg, 0.065 mmol) in THF−H_2O (0.9−0.3 mL) was added LiOH·H_2O (5.40 mg, 0.13 mmol). After being stirred at RT for 3 h, the mixture was evaporated in vacuo and the residue was washed with Et_2O. The water layers were treated with 1 N HCl (pH 1−2) and then extracted with Et_2O. The organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was used in the next steps without further purification. To a stirred solution of carboxylic acid (crude, 0.065 mmol) in THF (0.5 mL) were added Et_3N (0.02 mL, 0.14 mmol) and ethyl chlololformate (0.01 mL, 0.078 mmol). After being stirred at RT for 3 h, the reaction mixture was filtrated through a pad of Celite and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 4:1) to afford **23d** and **24d** (**23d**: 11.8 mg, 60%, **24d**: 0.50 mg, 2%) as a colarless oil.

24d: R_f (hexane:AcOEt = 7:3) 0.54; IR (neat) 3424, 2966, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, br), 7.20 (1 H, t, J = 6.4 Hz), 7.05 (1 H, d, J = 6.4 Hz), 6.99 (1 H, t, J = 6.4 Hz), 4.23 (1 H, s), 3.86 (3 H, s), 2.80 (2 H, dd, J = 4.8 and 9.2 Hz), 2.05 (2 H, ddd, J = 4.8, 13.6, and 23.0 Hz), 1.46 (3 H, s), 1.39 (3 H, s), 1.36 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 142.5 (C), 139.1 (2C), 128.0 (CH), 123.4 (CH), 122.4 (CH), 115.1 (CH), 105.4 (C), 86.1 (C), 71.3 (CH), 56.0 (CH), 52.9 (CH_3), 41.4 (C), 40.9 (CH_2), 30.0 (CH_3), 28.6 (CH_3), 19.7 (CH_3); HRMS (ESI) calcd for: $C_{17}H_{21}NO_4Na$ $[M + Na]^+$: 326.1368, found 326.1362.

*Methyl 7b-[3-(Benzyloxy)-3-methylbutyl]-2-(hydroxyimino)-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**27**).* To a stirred solution of cyclobutanone (**23c**) (10.0 mg, 0.024 mmol) in pyridine (0.5 mL) was added hydroxylamine hydrochloride (8.00 mg, 0.12 mmol). After being stirred at RT for 3 h, H_2O was added and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was used in the next step without further purification. [For analysis, **27** was purified by silica gel column chromatography (hexane:AcOEt = 7:3).]; R_f (hexane:AcOEt = 1:1) 0.60; IR (neat) 3281, 1711, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1 H, d, J = 7.6 Hz), 7.52−7.26 (6 H, m), 7.14 (1 H, d, J = 7.6 Hz), 7.04 (1 H, t, J = 7.6 Hz), 5.13 (1 H, br), 4.36 (1 H, d, J = 11.6 Hz), 4.32 (1 H, d, J = 11.6 Hz), 3.85 (3 H, s), 3.06 (2 H, s), 2.12 (1 H, dt, J = 4.0 and 13.2 Hz), 2.01 (1 H, dt, J = 4.0 and 13.2 Hz),1.61 (1 H, br), 1.49 (1 H, dt, J = 4.0 and 13.2 Hz), 1.29 (1 H, dt, J = 4.0 and 13.2 Hz), 1.26 (3 H, s), 1.21 (3 H, s); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 154.8 (C), 153.3 (C), 144.2 (C), 140.5 (C), 135.6 (C), 128.9 (2CH), 128.5 (2CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 123.6 (CH), 116.1 (CH), 74.4 (C), 68.3 (CH), 63.9 (CH_2), 52.5 (CH_3), 47.8 (C), 43.7 (CH_2), 36.0 (CH_2), 30.9 (CH_2), 25.6 (CH_3), 25.4 (CH_3); HRMS (ESI) calcd for $C_{24}H_{29}N_2O_4$ $[M + H]^+$: 409.2127, found 409.2130.

*Methyl 3-[3-(Benzyloxy)-3-methylbutyl]-3-(cyanomethyl)-2-methoxyindoline-1-carboxylate (**30**).* To a stirred solution of oxime (**27**) (crude, 0.024 mmol) in benzene (0.5 mL) was added $SOCl_2$ (0.025 mL, 0.073 mmol). After being stirred at RT for 12 h, H_2O was added and extracted with benzene. The organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was diluted with MeOH (0.5 mL), and 3 N HCl (one drop) was added. After being stirred at RT for 24h, the mixture was evaporated in vacuo. Water layer was extracted with AcOEt, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 7:3) to afford **30** (7.30 mg, 72%) as a colorless oil; R_f (hexane:AcOEt = 7:3) 0.75; IR (neat) 2970, 2250, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.67 (1 H, br), 7.30−7.26 (3 H, m), 7.23−7.18 (3 H, m), 7.09 (1 H, dd, J = 1.2 and 7.4 Hz), 7.03 (1 H, dt, J = 1.2 and 7.4 Hz), 5.32 (1 H, s), 4.20 (1 H, d, J = 11.2 Hz), 4.12 (1 H, d, J = 11.2 Hz), 3.90 (3 H, s), 3.61 (3 H, s), 2.83 (1 H, d, J = 16.8 Hz), 2.74 (1 H, d, J = 16.8 Hz), 1.88 (1 H, dt, J = 4.8 and 13.6 Hz), 1.81 (1 H, dt, J = 4.8 and 13.6 Hz), 1.46 (1 H, dt, J = 4.8 and 13.6 Hz), 1.35 (1 H, dt, J = 4.8 and 13.6 Hz), 1.17 (3 H, s), 1.16 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 154.0 (C), 140.2 (C), 139.5 (C), 133.7 (C), 128.9 (CH), 128.2 (2CH), 127.2 (2CH), 127.1 (CH), 123.6 (CH), 122.7 (CH), 118.1 (C), 116.5 (CH), 96.7 (CH), 74.4 (C), 63.6 (CH_2), 58.4 (CH_3), 52.9 (CH_3), 49.8 (C), 33.9 (CH_2), 32.1 (CH_2), 25.6 (CH_3), 25.5 (CH_3), 20.9 (CH_2); HRMS (ESI) calcd for $C_{25}H_{31}N_2O_4$ $[M + H]^+$: 423.2284, found 423.2286.

*Methyl 3a-[3-(Benzyloxy)-3-methylbuthyl]-1-methyl-2-oxo-1,2,3,3,a-tetrahydropyrrolo[2,3-b]indoline-8(8aH)-carboxylate (**32**).* To a stirred solution of cyclobutanone (**23c**) (450 mg, 1.1 mmol) and 3 Å molecular sieves in EtOH (23 mL) were added $NaHCO_3$ (554 mg, 6.6 mmol) and *N*-methylhydroxylamine hydrochloride (184 mg, 2.2 mmol). After the mixture was stirred at 50 °C for 15 h, AcOEt was added and the solution was washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was diluted with $CHCl_3$ (23 mL), and 4-pyrrolidinopyrridine (244 mg, 1.7 mmol) and *p*-toluenesulufonyl chloride (419 mg, 2.2 mmol) were added at 0 °C. After the mixture was refluxed for 3.5 h, H_2O was added and stirred at RT for 1.5 h. To the mixture was added CH_2Cl_2, and it was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 2:1) to afford **32** (348 mg, 75%) as a colorless oil; R_f (hexane:AcOEt = 3: 2) 0.25; IR (neat) 2970, 1703 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (1 H, br), 7.36 (1 H, d, J = 7.6 Hz), 7.32−7.20 (6 H, m), 7.10 (1 H, t, J = 7.6 Hz), 5.70 (1 H, s), 4.21 (2 H, s), 3.83 (3 H, s), 2.72 (3 H, s), 2.66 (2 H, s), 1.86−1.75 (2 H, m), 1.47 (1 H, dt, J = 5.2 and 12.2 Hz), 1.24 (1 H, dt, J = 5.2 and 12.2 Hz), 1.11 (6 H, s); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 170.9 (C), 153.9 (C), 140.7 (C), 140.3 (C), 137.0 (C), 129.0 (CH), 128.5 (2CH), 127.3 (2CH), 127.3 (CH), 124.3 (CH), 123.9 (CH), 117.1 (CH), 83.1 (CH), 74.3 (C), 63.8 (CH_2), 52.4 (CH_3), 48.9 (C), 42.1 (CH_2), 35.4 (CH_2), 33.4 (CH_2), 27.4 (CH_3), 25.4 (CH_3), 25.3 (CH_3); HRMS (ESI) calcd for $C_{25}H_{31}N_2O_4$ $[M + H]^+$: 423.2284, found 423.2283.

*Methyl 1-Methyl-3a-(3-methylbut-2-enyl)-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-b]indole-8-(8aH)-carboxylate (**34**).* A mixture of lactam **32** (100 mg, 0.23 mmol) and Pd−C (10.0 mg, 10% w/w) in EtOH (2 mL) was stirred at RT under H_2 for 5 h. The solution was filtered, and the filtrate was evaporated in vacuo. The residue was diluted with toluene, and $MgSO_4$ (17.0 mg, 0.14 mmol) and *p*-TsOH·H_2O (27.0 mg, 0.14 mmol) were added and then stirred at 60 °C for 24 h. After completion of the reaction, AcOEt was added and washed with sat. $NaHCO_3$ and brine. The organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 1:9) to

dx.doi.org/10.1021/jo301817w | J. Org. Chem. 2012, 77, 9240−9249

afford **34** (60.0 mg, 85%) as a colorless oil; R_f (AcOEt) 0.67; IR (neat) 2958, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.44 (1 H, br), 7.26 (1 H, t, J = 8.0 Hz), 7.17 (1 H, d, J = 8.0 Hz), 7.08 (1 H, t, J = 8.0 Hz), 5.65 (1 H, br), 5.00 (1 H, t, J = 8.0 Hz), 3.92 (3 H, s), 2.88 (3 H, s), 2.72 (2 H, d, J = 17.2 and 20.6 Hz), 2.35 (1 H, dd, J = 8.0 and 14.6 Hz), 2.43 (1 H, dd, J = 8.0 and 14.6 Hz), 1.68 (3 H, s), 1.53 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 172.3 (C), 139.8 (C), 136.9 (2C), 136.6 (C), 128.8 (CH), 124.3 (CH), 123.6 (CH), 117.8 (CH), 116.8 (CH), 82.5 (CH), 53.0 (CH_3), 49.5 (C), 40.9 (CH_2), 36.8 (CH_2), 27.5 (CH_3), 25.8 (CH_3), 18.0 (CH_3); HRMS (ESI) calcd for $C_{18}H_{22}N_2O_3Na$ $[M + Na]^+$: 337.1528, found 337.1525.

*1-Methyl-3a-(3-methylbut-2-enyl)-3,3a,8,8a-tetrahydropyrrolo-[2,3-b]indol-2(1H)-one (**13**).* A stirred solution of lactam **34** (50.0 mg, 0.15 mmol) in 5 N NaOH (2 mL) and MeOH (4 mL) was refluxed for 6 h. After the mixture was cooled to RT, sat. $NaHCO_3$ was added, extracted with AcOEt, and then washed with brine. The organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (AcOEt) to afford **13** (33.0 mg, 68%) as a colorless oil; R_f (AcOEt) 0.57; IR (neat) 3317, 2917, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (1 H, t, J = 8.0 Hz), 7.09 (1 H, d, J = 8.0 Hz), 6.83 (1 H, t, J = 8.0 Hz), 6.67 (1 H, d, J = 8.0 Hz), 5.01 (1 H, t, J = 8.0 Hz), 4.92 (1 H, s), 2.84 (3 H, s), 2.71 (2 H, s), 2.44 (1 H, dd, J = 8.0 and 15.0 Hz), 2.38 (1 H, dd, J = 8.0, 15.0 Hz), 1.70 (3 H, s), 1.57 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C), 147.4 (C), 135.8 (C), 134.9 (C), 128.5 (CH), 123.6 (CH), 120.2 (CH), 118.4 (CH), 110.7 (CH), 81.9 (CH), 51.1 (C), 41.6 (CH_2), 36.8 (CH_2), 26.7 (CH_3), 26.9 (CH_3), 18.1 (CH_3): HRMS (ESI) calcd for $C_{16}H_{20}N_2ONa$ $[M + Na]^+$: 279.1473, found 279.1478.

*1-Methyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole: Debromoflustramine E [(±)-**2**].* This material was prepared according to the literature method[5e] from lactam **13** (27.0 mg, 0.10 mmol). (±)-**2** was obtained as a colorless oil (21.0 mg, 85%); R_f (AcOEt:MeOH = 4:1) 0.15; IR (neat) 3288, 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (1 H, d, J = 7.6 Hz), 7.01 (1 H, t, J = 7.6 Hz), 6.71 (1 H, t, J = 7.6 Hz), 6.58 (1 H, d, J = 8.0 Hz), 5.06 (1 H, t, J = 7.6 Hz), 4.35 (1 H, s), 4.11 (1 H, br), 2.66−2.57 (2 H, m), 2.42 (2 H, s), 2.42 (3 H, s), 2.09 (1 H, dt, J = 5.2 and 12.0 Hz), 1.95 (1 H, dt, J = 5.2 and 12.0 Hz), 1.66 (3 H, s), 1.58 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (C), 135.5 (C), 133.9 (C), 127.5 (CH), 123.3 (CH), 120.3 (CH), 118.8 (CH), 109.1 (CH), 86.4 (CH), 57.8 (C), 52.4 (CH_2), 38.8 (CH_2), 38.0 (CH_2), 37.0 (CH_3), 25.9 (CH_3), 18.2 (CH_3); HRMS (ESI) calcd for $C_{16}H_{23}N_2$ $[M + H]^+$: 243.1861, found. 243.1859.

*1-Methyl-3a,8-bis(3-methylbut-2-enyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1H)-one (**35**).* To a stirred solution of lactam **13** (25.0 mg, 0.09 mmol) in acetone were added K_2CO_3 (40.0 mg, 0.29 mmol) and 4-bromo-2-methyl-2-butene (0.03 mL, 0.29 mmol). After the mixture was refluxed for 24 h, H_2O was added and the organic layer was evaporated in vacuo. The water layer was extracted with AcOEt, and the extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 1:1) to afford **35** (26.0 mg, 85%) as a colorless oil; R_f (hexane:AcOEt = 3: 7) 0.50; IR (neat) 2915, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (1 H, dt, J = 1.2 and 7.4 Hz), 7.02 (1 H, dd, J = 1.2 and 7.4 Hz), 6.75 (1 H, dt, J = 1.2 and 7.4 Hz), 6.52 (1 H, d, J = 7.4 Hz), 5.23 (1 H, t, J = 6.6 Hz), 4.99 (1 H, t, J = 7.2 Hz), 4.70 (1 H, s), 3.99 (1 H, dd, J = 7.2 and 15.8 Hz), 3.90 (1 H, dd, J = 7.2 and 15.8 Hz), 2.88 (3 H, s), 2.67 (2 H, s), 2.40 (1 H, dd, J = 8.0 and 15.0 Hz), 2.34 (1 H, dd, J = 8.0 and 15.0 Hz), 1.74 (6 H, s), 1.70 (3 H, s), 1.57 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C), 149.3 (C), 135.6 (C), 135.4 (C), 135.3 (C), 128.6 (CH), 123.2 (CH), 120.9 (CH), 119.0 (CH), 118.6 (CH), 109.0 (CH), 87.4 (CH), 49.9 (C), 47.1 (CH_2), 41.8 (CH_2), 37.6 (CH_2), 27.8 (CH_3), 26.0 (CH_3), 25.7 (CH_3), 18.1 (CH_3), 18.0 (CH_3); HRMS (ESI) calcd for $C_{21}H_{28}N_2ONa$ $[M + Na]^+$: 347.2099, found. 347.2100.

*1-Methyl-3a-8,bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a,hexahydropyrrolo[2,3-b]indole: Debromoflustramine B [(±)-**1**].* This material was prepared according to the literature method[5e] from lactam **35** (25.0 mg, 0.08 mmol). (±)-**1** was obtained as a colorless oil (23.0 mg, 90%); R_f (AcOEt) 0.30; IR (neat) 2927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (1 H, t, J = 8.0 Hz), 6.97 (1 H, d, J = 8.0 Hz), 6.65 (1 H, t, J = 8.0 Hz), 6.41 (1 H, d, J = 8.0 Hz), 5.17 (1 H, t, J = 6.0 Hz), 4.97 (1 H, t, J = 6.0 Hz) 4.26 (1 H, s), 3.92 (1 H, dd, J = 6.0 and 15.8 Hz), 3.80 (1 H, dd, J = 6.0 and 15.8 Hz), 2.69−2.64 (1 H, m), 2.59−2.58 (1 H, m), 2.48 (3 H, s), 2.42 (2 H, d, J = 7.2 Hz), 2.07−2.02 (1 H, m), 1.93−1.90 (1 H, m), 1.71 (3 H, s), 1.70 (3 H, s), 1.65 (3 H, s), 1.58 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (C), 135.7 (C), 134.0 (C), 133.4 (C), 127.5 (CH), 122.8 (CH), 121.5 (CH), 120.8 (CH), 117.4 (CH), 107.3 (CH), 91.5 (CH), 57.1 (C), 52.8 (CH_2), 46.8 (CH_2), 39.0 (CH_2), 38.5 (CH_2), 38.0 (CH_3), 25.9 (CH_3), 25.7 (CH_3), 18.1 (CH_3), 18.0 (CH_3); HRMS (ESI) calcd for $C_{21}H_{30}N_2Na$ $[M + Na]^+$: 333.2307, found. 333.2309.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for preparation of **17** and **7a−f**. ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shishido@ph.tokushima-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A Grant-in-Aid for JSPS Fellows (22-9957) to T.O. from the JSPS is gratefully acknowledged. This work was supported financially by a Grant-in-Aid for the Program for Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

■ REFERENCES

(1) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997−1000.

(2) Smith, B. P.; Tyler, M. J.; Kaneko, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **2002**, *65*, 439−447.

(3) Becerril, E. R.; Nathan, P. J.; Alvarez, V. M. P.; Rios, M. S. M. *J. Med. Chem.* **2008**, *51*, 5271−5284.

(4) (a) Hodgson, J. W.; Mitchell, M. O.; Thomas, M. L.; Waters, K. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2527−2528. (b) Dix, A. W.; Meseck, C. M.; Lowe, A. J.; Mitchell, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522−2524.

(5) For the racemic syntheses, see: (a) Mitchell, M. O.; Dorroh, P. *Tetrahedron Lett.* **1991**, *32*, 7641−7642. (b) Jensen, J.; Anthoni, U.; Christophersen, C.; Nielsen., P. H. *Acta Chem. Scand.* **1995**, *49*, 68−71. (c) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327−2330. (d) Rios, M. S. M.; Castillo, O. R. S.; Nathan, P. J. *J. Org. Chem.* **1999**, *64*, 1086−1087. (e) Rios, M. S. M.; Castillo, O. R. S.; Serrato, J. J. T.; Nathan, P. J. *J. Org. Chem.* **2001**, *66*, 1186−1192. (f) Rios, M. S. M.; Castillo, O. R. S.; Nathan, P. J. *Tetrahedron* **2002**, *58*, 1479−1484. (g) Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801−1803. (h) Rios, M. S. M.; Sanches, N. F. S.; Perez., Y. M.; Nathan, P. J. *Heterocycles* **2004**, *63*, 1131−1142. (i) Alvarad, P. L.; Caballero, E.; Avendano, C.; Menendez, J. C. *Org. Lett.* **2006**, *8*, 4303−4306. (j) Aburano, D.; Yoshida, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 6878−6884. (k) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2007**, *48*, 1805−1808. (l) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687−4695.

(6) For the asymmetric syntheses, see: (a) Bruncko., M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543−5549. (b) Cardoso, A. S.; Srinivasan, N.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2001**, *42*, 6663−6666. (c) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482−

5487. (d) Rios, M. S. M.; Becerri, E. R.; Nathan, P. J. *Tetrahedron: Asymmetry* **2005**, *16*, 2493−2499. (e) Cardoso, A. S. P.; Marques, M. M. B.; Srinivasan, N.; Prabhakar, S.; Lobo, A. M. *Tetrahedron* **2007**, *63*, 10211−10225. (f) Nakazaki, A.; Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 124−138. (g) Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959−5964. (h) Sanchis, P. R.; Savina, S. A.; Albericio, F.; Alvarez, M. *Chem. Eur. J.* **2011**, *17*, 1388−1408. (i) Trost, B. M.; Zhang, Y. *Chem. Eur. J.* **2011**, *17*, 2916−2922. (j) Zhou, Y.; Xi, Y.; Zhao, J.; Sheng, X.; Zhang, S.; Zhang, H. *Org. Lett.* **2012**, *14*, 3116−3119.

(7) Shishido, K.; Azuma, T.; Shibuya, M. *Tetrahedron Lett.* **1990**, *31*, 219−220.

(8) (a) Yoshida, M.; Matsuda, K.; Shoji, Y.; Gotou, T.; Ihara, M.; Shishido, K. *Org. Lett.* **2008**, *10*, 5183−5186. (b) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441−1443. (c) Yoshida, M.; Shoji, Y.; Shishido, K. *Tetrahedron* **2010**, *66*, 5053−5058. (d) Osaka, M.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Heterocycles* **2010**, *80*, 1003−1012.

(9) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597−7605.

(10) Searles, S.; Li, Y.; Nassim, B.; Lopes, M. T. R.; Tran, P. T.; Crabbe, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747−751.

(11) Bushnell, G. W.; Dixon, K. R.; Hunter, R. G.; McFarland, J. J. *Can. J. Chem.* **1972**, *50*, 3694−3699.

(12) Although we have used KOH as a base in the original paper,[8a] the reaction of **17** under the conditions using KOH provided aniline. After extensive screening of the bases, it was found that K_2CO_3 was the best choice.

(13) This protocol was also adapted to **21c**/**22c** and resulted in the formation of a separable mixture of **23c** and **24c** in 55% and 5% yield, respectively; cf., Bonnaud, B.; Mariet, N.; Vacher, B. *Eur. J. Org. Chem.* **2006**, 245−256.

(14) Jeffs, P. W.; Molina, G.; Cortesst, N. A.; Hauck, P. R.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3876−3881.

(15) The shift differences ($\Delta\delta$) of H_a and H_b induced by $Eu(dpm)_3$ were 0.090 and 0.180 Hz, respectively.

(16) Attempted Beckmann rearrangement under various conditions [e.g., TsCl (or MsCl), 4-DMAP, Et_3N in $CHCl_3$, etc.] resulted in the formation of the same fragmentation product **29**, which was characterized as **30**, in lower yields.

(17) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1971**, 945−946.

(18) Ehara, T.; Tanikawa, S.; Ono, M.; Akita, H. *Chem. Pharm. Bull.* **2007**, *55*, 1361−1364.