Palladium(II)-Catalyzed Synthesis of α-Alkylidene-γ-butyrolactams from *N*-Allylic 2-Alkynamides. Total Synthesis of (±)-Isocynodine and (±)-Isocynometrine

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An efficient method for preparing α-alkylidene-γ-butyrolactams via the Pd(II)-catalyzed cyclization of acyclic *N*-allylic 2-alkynamides via halopalladation, intramolecular olefin insertion, and β-heteroatom elimination was developed. The reaction is less influenced by the leaving group and the concentration of the halide ions in comparison with the cyclization of acyclic alkynoates. The total syntheses of (±)-isocynodine and (±)-isocynometrine were realized using this method.

Introduction

γ-Butyrolactam structures are widely spread in medicinal chemistry.[1] In particular, α-alkylidene-γ-butyrolactams show important biological activities, such as cytotoxicity,[2] antitumor,[3] and antiinflamation activities but with lower toxicity[4] as compared with the corresponding lactones. Therefore, the development of new methods for the stereoselective synthesis of this kind of molecules appears to be highly desirable. Generally, α-alkylidene-γ-butyrolactams are synthesized by α-alkylidenation of preformed lactams[5] or from functionalized acyclic precursors.[6]

Transition metal-catalyzed cyclization reactions have received much attention owing to the template effect of the transition metal.[7] Recently, we have developed the facile intramolecular enyne cyclization of allylic alkynoates to build polysubstituted α-alkylidene-γ-butyrolactones via a palladium(II) catalyst.[8] However, their use in lactam synthesis was limitedly exploited.[9] In this paper, we wish to report our recent results on the palladium(II)-catalyzed synthesis of α-alkylidene-γ-butyrolactams from *N*-allylic-2-alkynamides and the total synthesis of (±)-isocynodine and (±)-isocynometrine using this methodology.

Results and Discussion

Cyclization of Acyclic *N*-Allylic-2-Alkynamides. In our previous work, α-alkylidene-γ-butyrolactones have been successfully synthesized from 4′-substituted allylic alkynoates catalyzed by Pd(II) species.[10a] In this method, the reaction was initiated by the halopalladation of the triple bond first, followed by intramolecular carbon−carbon double bond insertion, and the Pd(II) species is regenerated via β-heteroatom elimination to make the catalytic cycle possible. *N*-Allylic alkylamides (**1a**, **2a**, and **3a**) with different substitutents (Br, OAc, and OH) were tried using the reaction conditions similar to those reported for the cyclization of allylic alkynoates.[10] To our surprise, the variation of leaving groups has less influence on the β-heteroatom elimination as compared with the cyclization of allylic alkynoates[10b] (Table 1). Moreover, the rate of cyclization, the yield, and the stereoselectivity of the exocyclic double bond were less influenced by the concentration of the halide ions[11] (Table 2).

On the basis of the reaction conditions studied, *N*-(4′-acetoxybut-2′-enyl)alk-2-ynamides **2** were treated with 10 mol % of $Pd(OAc)_2$ and 6 equiv of lithium halide in HOAc. The results are shown in Table 3. Variation of the substituents on the nitrogen atom influenced the cyclization greatly on the rate of the reaction (Table 3, entries 1, 6, and 7). *N*-Benzyl-substituted amides are the most reactive. In all cases, the reaction gives high *Z*-selectivity of the exocyclic double bond. The *Z*-selectivity decreased with the increased bulkiness of R (Table 3, entries 1−4), which is similar to our previous results on the cyclization of allylic alkynoates.[10]

Taking into account of the fact that two types of conformation are possible for an amide,[12] a mechanism slightly different from our previous publication[10] was proposed (Scheme 1).

Compound **2** first coordinates with Pd(II), and the subsequent stereoselective halopalladation of carbon−carbon triple bond in the presense of LiX may afford the

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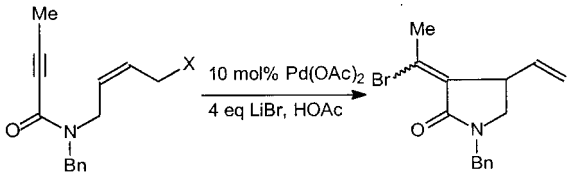
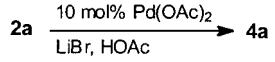
Table 1. Palladium(II)-Catalyzed Cyclization of *N*-Allylic Alkynamides with Different Leaving Groups[a]



entry	X	substrate	time (h)	yield[b] (%)	ratio[c] (*Z*/*E*)
1	Br	**1a**	4	89.5	95:5
2	OAc	**2a**	4	93.1	94:6
3	OH	**3a**	5	90.5	94:6

[a] A mixture of substrate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), LiBr (2 mmol), and HOAc (2 mL) was stirred at room temperature, and the reaction was monitored by TLC. [b] Isolated yield; the products were confirmed by ^{1}H NMR, IR, MS, and elemental analysis. [c] Ratio determined by ^{1}H NMR spectra of the isolated products.

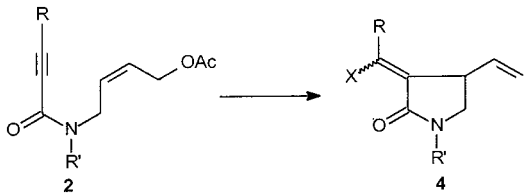
Table 2. Pd(II)-Catalyzed Cyclization of 2a with Different Concentration of Bromide Ions[a]



entry	LiBr (equiv)	time (h)	yield[b] (%)	ratio[c] (*Z*/*E*)
1	1	4	92	89:11
2	2	4	91	92:8
3	4	4	93	94:6
4	6	4	93	96:4
5	8	4	93	97:3

[a] A mixture of **2a** (137 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and HOAc (2 mL) was stirred at room temperature, and the reaction was monitored by TLC. [b] Isolated yield. [c] The *Z*/*E* ratios were determined by ^{1}H NMR spectra.

Table 3. Cyclization of *N*-(4′-Acetoxybut-2′-enyl)alk-2-ynamides[a]



entry	R	R′	substrate	X	time (h)	product[b]	yield[c] (%) (*Z*/*E*)
1	Me	Bn	**2a**	Br	4	**4a**	94 (96:4)
2	*n*-Pr	Bn	**2b**	Br	4	**4b**	98 (88:12)
3	C_7H_{15}	Bz	**2c**	Br	9	**4c**	88 (85:15)
4	Ph	Bn	**2d**	Br	6	**4d**	95 (60:40)[d]
5	H	Bn	**2e**	Br	1	**4e**	89 (100:0)[e]
6	H	Bn	**2e**	Cl	1	**4e′**	61 (100:0)[e]
7	Ph	Me	**2f**	Br	24	**4f**	92 (55:45)[d]
8	Me	Me	**2g**	Br	14	**4g**	96 (92:8)[e]
9	Me	H	**2h**	Br	18	**4h**	78 (92:8)[e]
10	Ph	H	**2i**	Br	30	**4i**	79 (53:47)[d]
11	H	H	**2j**	Br/Cl		—[f]	

[a] A mixture of **1** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), and LiX (3 mmol) in HOAc (2 mL) was stirred at room temperature; the reaction was monitored by TLC. [b] The products were identified by ^{1}H NMR, IR, MS, and elemental analysis or HRMS. [c] Isolated yield. [d] Determined by ^{1}H NMR spectra. [e] Isolated ratio. [f] Disordered reaction.

vinylpalladium intermediate **A** and **B**. The intramolecular insertion of the carbon−carbon double bond into the carbon−palladium bond in **A** yields the cyclic intermediate **C**, which in turn gives product **4** via β-acetoxy elimination and regenerates the Pd(II) species. As there exists a cis−trans isomer of amides **A** and **B**,[12] the insertion of a carbon−carbon double bond will be impossible with the intermediate **B**. In the literature,[13] it was reported that the equilibrium distribution of two types of conformation of alkynamides in solution depends mainly upon the steric repulsion between the groups on the carbonyl carbon atom and the nitrogen atom. Thus, compounds **2** with bulkier benzyl group on nitrogen atom have a stronger preference of **A** over **B**, which should be responsible for the sharp difference of the cyclization rate of substrates **2** with different substituents on the nitrogen atom.

Stereochemistry of Palladium-Catalyzed Cyclization of *N*-(1′-Substituted-4′-acetoxybut-2′-enyl)alk-2-ynamides. Based on the cyclization reaction of **2**, we further studied the relative stereochemistry of the β,γ-substituents in the cyclization products when 1′-substitutent was introduced. The results are outlined in Table 4.

Similar to the cyclization of allylic substituted alkunoates,[11] the cyclization of substituted alkynamides (Table 4, entries 1, 3, and 4, R= alkyl group) predominantly afforded β,γ-cis products, which became the only product in the case of N-unblocked amides (Table 4, entries 3 and 4, R′ = H), while the cyclization of unsubstituted propynamide (Table 4, entry 2, R = H) showed low diastereoselectivity.

Synthesis of (±)-Isocynometrine (7) and (±)-Isocynodine (13). The cyclization products **4** are polyfunctional γ-lactams that can undergo further transformation for the synthesis of natural products. Isocynometrine is an imidazole alkaloid isolated from *Cynometra* species. It has been used in Africa as a traditional folk medicine with antitussive and analgesic activities.[14] The structure of isocynometrine was determined by Riche et al. as **7**,[15] and Khuong-Huu et al. reported its synthesis from 1-methyl-5-methoxycarbonylimidazole.[16] Comparing the structure of isocynometrine with our cyclization product **4f,** we envisioned that **4f** can be used as the key precursor to achieve the synthesis of isocynometrine (Scheme 2).

We first tried the hydrolysis of vinylic bromide in **4f** to **8**. In our previous work toward the synthesis of (±)-A factor, the vinylic bromide in the γ-lactone was hydrolyzed by first reacting with Et_2NH to form the enamine followed by the acid hydrolysis of the latter to form the enol or the ketone.[17,18] In the case of the hydrolysis of **4f** using the same reaction conditions, the reaction did not take place. Then we tried the hydrolysis of the vinylic bromide in different kinds of lactones and lactams (Table 5) and found that the electron density of the nitrogen atom in the lactams greatly influenced the reactivity of the vinylic bromide. Only the vinylic bromide in lactams

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Scheme 1

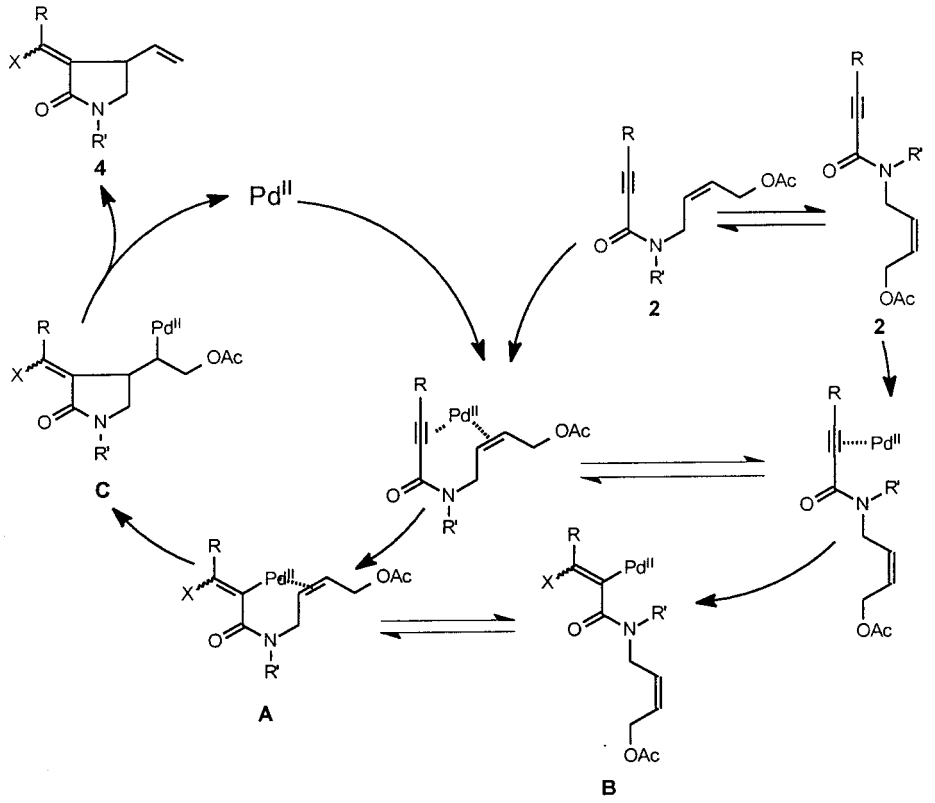
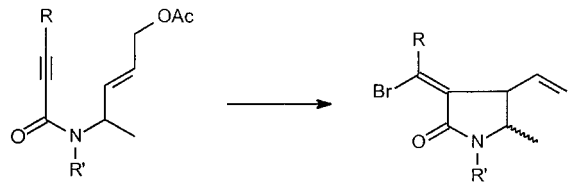


Table 4. Palladium(II)-Catalyzed Cyclization of *N*-(1′-Methyl-4′-acetoxybut-2′-enyl)alkynamides 5[a]



entry	R	R′	substrate	time (h)	product	yield %[b] (cis/trans)[c]
1	Me	Bn	**5a**	4	**6a**	89 (86:14)
2	H	Bn	**5c**	1	**6c**	87 (46:54)
3	Me	H	**5f**	16	**6f**	70 (>98:2)
4	*n*-Pr	H	**5i**	18	**6i**	72 (>98:2)

[a] Reaction conditions: substrate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), LiBr (3 mmol), and HOAc (2 mL) at room temperature. [b] Isolated yield. [c] The stereochemistry was determined by NOESY spectra, and the ratio was determined by ^{1}H NMR spectra.

with electron-deficient substituent on the nitrogen atom can be easily hydrolyzed.

For the hydrolysis of **4f**, **14b**, and **14d**, we still met difficulties probably due to the presence of the phenyl group (Table 5, entries 2, 4, and 5). Recently, Buchwald and Hartwig independently reported the nucleophilic substitution of aromatic halides with amines.[19] It occurs to us that it is possible to convert the vinylic bromide to the enamine using the similar method. Fortunately, compound **8** could be obtained by a palladium-catalyzed amination of the vinylic bromide **4f** with piperidine followed by hydrolysis of the enamine formed. Further reduction of **8** with $NaBH_4$ gave a pair of diastereisomers **9** and **10** in a 5:1 ratio, which could be separated by column chromatography. The major product **9** has the same relative stereochemistry with isocynometrine,[16] as confirmed by comparing the ^{1}H NMR and IR spectra and by X-ray diffraction. Protection the hydroxy group of **9** with benzoyl group and then ozonolysis of the double bond at −78 °C produced the corresponding aldehyde **12**. The aldehyde **12** was treated successively in three steps without purification to construct the imidazole ring to obtain (±)-isocynodine (**13**) according to the literature[20] and then deprotected to give the target molecule (±)-isocynometrine (**7**).

In summary, we developed an efficient method for preparing γ-butyrolactams via the Pd(II)-catalyzed cyclization of acyclic *N*-allylic 2-alkynamides. Referring to the reaction rate and the stereoselectivity of the exocyclic double bond, the reaction is less influenced by the leaving group and the concentration of the halide ions in comparison with the cyclization of acyclic allylic alkynoates. Furthermore, the total syntheses of (±)-isocynodine and (±)-isocynometrine were realized using the cyclized product as the key intermediate.

Experimental Section

Materials. The catalysts $Pd_2(dba)_3{\cdot}CHCl_3$[21] and $Pd(OAc)_2$[22] were prepared by literature methods. LiBr and LiCl were dried at 120 °C under reduced pressure for 4 h before use.

Cyclization of *N*-(4′-Acetoxybut-2′-enyl)alk-2-ynamides (2): Typical Procedure. To a solution of $Pd(OAc)_2$ (11 mg,

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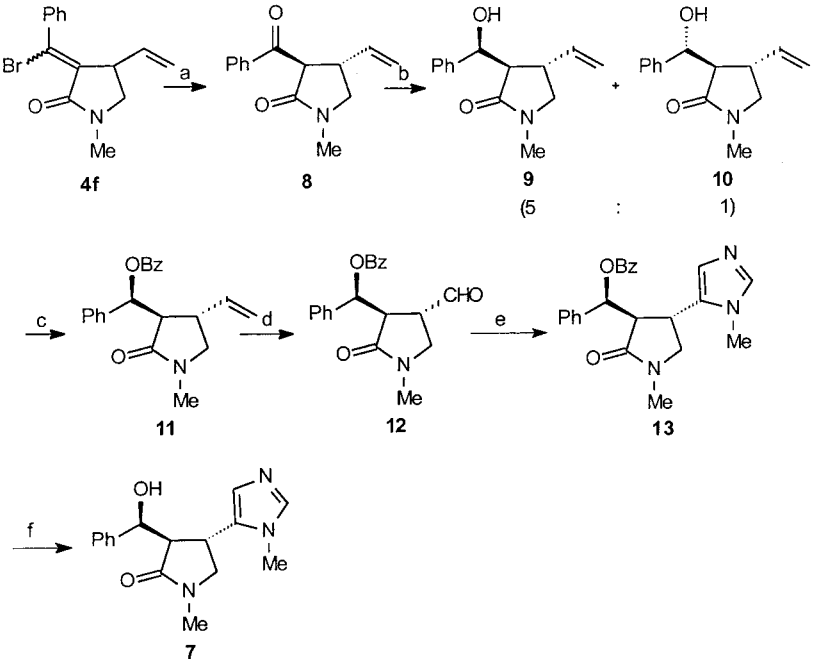
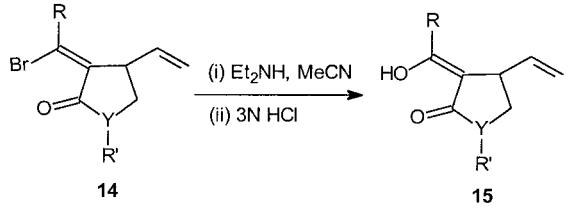
Scheme 2[a]



[a] Reaction conditions: (a) (i) $Pd_2(dba)_3$·$CHCl_3$ (4 mol %), dppf (8 mol %), piperidine (1.2 equiv), *t*-BuOK (1 equiv), THF, 55 °C, (ii) 3 N HCl; (b) $NaBH_4$, MeOH, −40 °C; (c) BzCl, DMAP, pyridine; (d) (i) O_3, MeOH−CH_2Cl_2, −78 °C, (ii) Me_2S, −78 to 0 °C; (e) (i) $TsCH_2NC$, *t*-BuOK, THF, −10 °C, (ii) $POCl_3$, Et_3N, THF, (iii) $MeNH_2$, MeOH; (f) NaOH−MeOH.

Table 5. Hydrolysis of Vinyl Bromides in γ-Lactones and γ-Lactams



	substrate					yield (%)
entry	Y	R	R′		time (d)	**15**
1	O	H		**(14a)**[10]	1	78
2	O	Ph		**(14b)**[10]		no reaction
3	N	Me	BOC	**(14c)**	3	59
4	N	Ph	BOC	**(14d)**		no reaction
5	N	Ph	Me	**(4f)**		no reaction
6	N	Me	Me	**(4g)**		no reaction

0.05 mmol) and LiX (3 mmol) in HOAc (2 mL) was added **2** (0.5 mmol). The reaction was carried out at room temperature. After the reaction was complete as monitored by TLC, CH_2Cl_2 (50 mL) was added. The mixture was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by chromatography (silica gel, petroleum ether/ethyl acetate) to give cyclization product **4**.

***N*-Benzyl-α-bromoethylidene-β-vinyl-γ-butyrolactam (4a).** *Z*-isomer: oil; IR (neat) *ν* 2918, 1689, 1651, 1424, 701 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.32−7.23 (m, 5H), 5.72−5.63 (m, 1H), 5.10−5.03 (m, 2H), 4.61 (d, *J* = 14.6 Hz, 1H), 4.43 (d, *J* = 14.6 Hz, 1H), 3.61−3.56 (m, 1H), 3.43 (dd, *J* = 9.7, 7.9 Hz, 1H), 2.92 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.40 (d, *J* = 0.7 Hz, 3H); MS (*m*/*e*) 307 [M^+, (^{81}Br)], 305 [M^+, (^{79}Br)], 226, 91 (100), 79, 77. Anal. Calcd for C_{15} H_{16}NOBr: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.65; H, 5.38; N, 4.39. *E*-Isomer: oil; IR (neat) *ν* 2961, 1689, 1651, 1439, 701 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.23−7.20 (m, 5H), 5.76−5.65 (m, 1H), 5.13−5.07 (m, 2H), 4.56 (d, *J* = 14.7 Hz, 1H), 4.41 (d, *J* = 14.7 Hz, 1H), 3.61−3.56 (m, 1H), 3.45 (dd, J_1=9.7 Hz, J_2=7.7 Hz, 1H), 2.98 (dd, J_1=9.7 Hz, J_2=1.2 Hz, 1H), 2.94 (d, *J* = 1.2 Hz, 3H); MS (*m*/*e*) 307 [M^+, (^{81}Br)], 305 [M^+, (^{79}Br)], 227, 226, 107, 91 (100.00). Anal. Calcd for C_{15} H_{16}NOBr: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.56; H, 5.35; N, 4.61.

***N*-Benzyl-α-bromobutylidene-β-vinyl-γ-butyrolactam (4b).** *Z*-Isomer: oil; IR (neat) *ν* 2963, 1690, 1639, 1423, 1153, 701 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.24−7.16 (m, 5H), 5.63−5.57 (m, 1H), 5.03−4.97 (m, 2H), 4.57 (d, *J* = 14.6 Hz, 1H), 4.32 (d, *J* = 14.6 Hz, 1H), 3.55−3.50 (m, 1H), 3.33 (dd, *J* = 9.7, 7.8 Hz, 1H), 2.83 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.44 (t, *J* = 7.8 Hz, 2H), 1.67−1.53 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); MS (*m*/*e*) 335 [M^+, (^{81}Br)], 333 [M^+, (^{79}Br)], 334, 332, 255, 254, 135, 91. Anal. Calcd for $C_{17}H_{20}$NOBr: C, 61.09; H, 6.03; N, 4.19. Found: C, 61.32; H, 6.19; N, 4.38. *E*-Isomer: oil; IR (neat) *ν* 2962, 1687, 1645, 1424, 1275, 701 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.26−7.14 (m, 5H), 5.64−5.59 (m, 1H), 5.06−5.00 (m, 2H), 4.48 (d, *J* = 14.7 Hz, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.55−3.51 (m, 1H), 3.37 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.37−3.30 (m, 1H), 3.21−3.11 (m, 1H), 2.90 (dd, *J* = 9.8, 1.3 Hz, 1H), 1.61 (tq, *J* = 7.3, 7.3 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); MS (*m*/*e*) 335 [M^+, (^{81}Br)], 333 [M^+, (^{79}Br)], 255, 254, 92, 91; HRMS calcd for $C_{17}H_{20}$NOBr 333.0728, found 333.0725.

***N*-Benzyl-α-bromooctylidene-β-vinyl-γ-butyrolactam (4c):** *Z*-Isomer: oil; IR (neat) *ν* 2928, 1691, 1638, 1423, 1276, 701 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.35−7.23 (m, 5H), 5.70−5.64 (m, 1H), 5.10−5.04 (m, 2H), 4.64 (d, *J* = 14.6 Hz, 1H), 4.39 (d, *J* = 14.6 Hz, 1H), 3.59 (m, 1H), 3.41 (dd, *J* = 9.8, 7.8 Hz, 1H), 2.90 (dd, *J* = 9.8, 1.7 Hz, 1H), 2.56−2.50 (m, 2H), 1.63−0.87 (m, 13H); MS (*m*/*e*) 391 [M^+, (^{81}Br)], 389 [M^+, (^{79}Br)], 311, 310, 92, 91. Anal. Calcd for $C_{21}H_{28}$NOBr: C, 64.61; H, 7.23; N, 3.59. Found: C, 64.92; H, 7.28; N, 3.33. *E*-Isomer: oil; IR (neat) *ν* 2928, 1689, 1646, 1424, 1276, 700 cm^{-1};^1H NMR ($CDCl_3$) *δ* 7.33−7.21 (m, 5H), 5.77−5.66 (m, 1H), 5.14−5.07 (m, 2H), 4.55 (d, *J* = 14.7 Hz, 1H), 4.43 (d, *J* = 14.7 Hz, 1H), 3.59 (m, 1H), 3.44 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.40 (m, 1H), 3.26 (m, 1H), 2.98 (dd, *J* = 9.8, 1.3 Hz, 1H), 1.55−0.86 (m, 13H); MS (*m*/*e*) 392 [M^+ + 1, (^{81}Br)], 390 [M^+ + 1, (^{79}Br)], 311, 310, 93, 91.

***N*-Benzyl-α-bromobenzylidene-β-vinyl-γ-butyrolactam (4d):** oil; IR (neat) *ν* 2918, 1690, 1639, 1422, 700 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.44−7.22 (m, 10H), 5.82−5.77 (m, 0.4H, *E*), 5.57−5.45 (m, 0.6H, *Z*), 5.29−5.18 (m, 1H), 4.82−4.28 (m, 3H), 3.81−3.76 (m, 0.4H), 3.57−3.50 (m, 1H), 3.40 (dd, *J* = 9.5, 7.5 Hz, 0.6H), 3.06 (d, *J* = 9.9 Hz, 0.4H), 2.90 (dd, *J* =

9.8, 0.8 Hz, 0.6H); MS (*m/e*) 368 [$M^+ + 1$, (^{81}Br)], 366 [$M^+ + 1$, (^{79}Br)], 288, 169, 141, 115, 91 (100). Anal. Calcd for $C_{20}H_{18}NOBr$: C, 65.23; H, 4.93, N, 3.80. Found: C, 65.26; H, 4.97; N, 3.79.

***N*-Benzyl-α-(*Z*)-bromomethylene-*β*-vinyl-*γ*-butyrolactam (4e):** oil; IR (neat) *ν* 3061, 1692, 1636, 1424, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.36−7.25 (m, 5H), 6.47 (d, *J* = 2.3 Hz, 1H), 5.72−5.60 (m, 1H), 5.19−5.12 (m, 2H), 4.60 (d, *J* = 14.6 Hz, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.52−3.45 (m, 1H), 3.40 (dd, *J* = 9.5, 8.5 Hz, 1H), 3.01 (dd, *J* = 9.5, 5.3 Hz, 1H); MS (*m/e*) 293 [M^+, (^{81}Br)], 291 [M^+, (^{79}Br)], 212, 93, 92, 91(100), 65; HRMS calcd for $C_{14}H_{14}NOBr$ 291.0258, found 291.0278.

***N*-Benzyl-α-(*Z*)-chloromethylene-*β*-vinyl-*γ*-butyrolactam (4e′):** oil; IR (neat) *ν* 3063, 2925, 1693, 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.34−7.25 (m, 5H), 6.28 (d, *J* = 2.4 Hz, 1H), 5.69−5.60 (m, 1H), 5.19−5.12 (m, 2H), 4.59 (d, *J* = 14.7 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.57−3.49 (m, 1H), 3.42 (dd, *J* = 9.6, 8.6 Hz, 1H), 2.95 (dd, *J* = 9.6, 5.5 Hz, 1H); MS (*m/e*) 249 [M^+, (^{81}Br)], 247 [M^+, (100), (^{79}Br)], 249, 248, 212, 92, 91; HRMS calcd for $C_{14}H_{14}NOCl$ 247.0764, found 247.0746.

***N*-Methyl-α-bromobenzylidene-*β*-vinyl-*γ*-butyrolactam (4f):** oil; IR (neat) *ν* 2961, 1688, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.43−7.29 (m, 5H), 5.94−5.85 (m, 0.45H, *E*), 5.64−5.55 (m, 0.55H, *Z*), 5.33 (d, *J* = 17.0 Hz, 0.45H, *E*), 5.27 (d, *J* = 10.1 Hz, 0.45 H, *E*), 4.86 (d, *J* = 10.1 Hz, 0.55H, *Z*), 4.65 (d, *J* = 17.0 Hz, 0.55H, *Z*), 3.83−3.00 (m, 3H), 2.99 (s, 1.65H), 2.86 (s, 1.35H); MS (*m/e*) 293 [M^+, (^{81}Br)], 291 [M^+, (^{79}Br)], 212, 155, 141 (100), 115. Anal. Calcd for C_{14} $H_{14}NOBr$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.63; H, 4.66; N, 4.59.

***N*-Methyl-α-bromoethylidene-*β*-vinyl-*γ*-butyrolactam (4g).** *Z*-Isomer: mp 61−62 °C; IR (Nujol) 2926, 1680, 1647, 1398, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 5.78−5.67 (m, 1H), 5.12−5.05 (m, 2H), 3.61−3.50 (m, 2H), 3.02−2.98 (m, 1H), 2.89 (s, 3H), 2.37(s, 3H); MS (*m/e*) 232 [$M^+ + 1$, (^{81}Br)], 230 [$M^+ + 1$, (^{79}Br)], 150 (100), 107, 79, 77, 42. Anal. Calcd for $C_9H_{12}NOBr$: C, 46.98; H, 5.26; N, 6.09. Found: C, 47.19; H, 5.41; N, 5.92. *E*-Isomer: oil; IR (neat) *ν* 2928, 1680, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 5.81−5.69(m, 1H), 5.18−5.13 (m, 2H), 3.64−3.54 (m, 2H), 3.08 (d, *J* = 8.5 Hz, 1H), 2.96 (s, 3H), 2.95 (s, 3H); MS (*m/e*) 232 [$M^+ + 1$, (^{81}Br)], 230 [$M^+ + 1$, (^{79}Br)], 150 (100), 107, 79, 77, 42; HRMS calcd for $C_9H_{12}NOBr$ 229.0102, found 229.0117.

α-Bromoethylidene-*β*-vinyl-*γ*-butyrolactam (4h). *Z*-Isomer: mp 102−103 °C; IR (Nujol) *ν* 3183, 1694, 1637, 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.10−6.90 (br, 1H), 5.86−5.75 (m, 1H), 5.16−5.10 (m, 2H), 3.72 (m, 1H), 3.61 (m, 1H), 3.13 (d, *J* = 9.3 Hz, 1H), 2.43 (s, 3H); MS (*m/e*) 218 [$M^+ + 1$, (^{81}Br)], 216 ($M^+ + 1$, (^{79}Br)], 188, 136 (100), 107, 79, 77. Anal. Calcd for C_8 $H_{10}NOBr$: C, 44.47; H, 4.66; N, 6.48. Found: C, 44.10; H, 4.52; N, 6.33. *E*-Isomer: oil; IR (neat) *ν* 3101, 1686, 1642, 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 6.50−6.30 (br, 1H), 5.87−5.76 (m, 1H), 5.22−5.15 (m, 2H), 3.76 (m, 1H), 3.62 (m, 1H), 3.40 (d, *J* = 9.5 Hz, 1H), 2.95 (s, 3H); MS (*m/e*) 217 [M^+, (^{81}Br)], 215 [(M^+, (^{79}-Br)], 188, 186, 137, 136(100), 79, 77; HRMS calcd for C_8 H_{10}-NOBr 214.9940, found 214.9948.

α-Bromobenzylidene-*β*-vinyl-*γ*-butyrolactam (4i): oil; IR (neat) *ν* 3191, 1691, 1630, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.70 (br, 0.53H), 7.20 (br, 0.47H), 7.43−7.24 (m, 5H), 5.96−5.85 (m, 0.47H, *E*), 5.69−5.58 (m, 0.53H, *Z*), 5.30 (d, *J* = 17.0 Hz, 0.47H, *E*), 5.25 (d, *J* = 10.1 Hz, 0.47H, *E*), 4.86 (d, *J* = 17.0 Hz, 0.53H, *Z*), 4.66 (d, *J* = 10.1 Hz, 0.53H, *Z*), 3.88 (m, 0.47H, *E*), 3.68 (dd, *J* = 9.8, 7.3 Hz, 0.47H, *E*), 3.60 (m, 0.53H, *Z*), 3.51 (dd, *J* = 9.6, 7.5 Hz, 0.53H, *Z*), 3.21 (d, *J* = 9.8 Hz, 0.47H, *E*), 3.05 (d, *J* = 9.1 Hz, 0.53H, *Z*); MS (*m/e*) 279 (M^+, (^{81}Br)], 277(M^+, (^{79}Br)], 169, 155, 153, 141 (100), 115. Anal. Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04. Found: C, 56.09; H, 4.09; N, 4.79.

Cyclization of *N*-(1′-Methyl-4′-acetoxybut-2′-enyl)alk-2-ynamides 5. The procedure is the same as that for cyclization of **2**.

***cis*- and *trans*-*N*-benzyl-α-(*Z*)-(bromoethylidene)-*β*-vinyl-*γ*-methyl-*γ*-butyrolactam (6a):** oil; IR (Nujol) *ν* 2978, 1690, 1650, 1404, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.33−7.23 (m, 5H), 5.64−5.55 (m, 1H), 5.21−5.07 (m, 2.14H), 4.97 (d, *J* = 15.0 Hz, 0.86H), 4.14 (d, *J* = 15.0 Hz, 0.86H, cis), 3.96 (d, *J* = 15.0 Hz, 0.14H, trans), 3.65−3.50 (m, 1.72H), 3.16−3.13 (m, 0.28H), 2.39 (s, 3H), 1.17 (d, *J* = 6.3 Hz, 0.42H, trans), 1.08 (d, *J* = 6.3 Hz, 2.58H, cis); MS (*m/e*) 320 [$M^+ + 1$, 81Br)], 318 [$M^+ + 1$, (^{79}Br)], 241, 240, 91 (100), 107, 79. Anal. Calcd for $C_{16}H_{18}NO_2Br$: C, 60.01; H, 5.67; N, 4.37. Found: C, 59.99; H, 5.70; N, 4.30.

***cis*- and *trans*-*N*-benzyl-α-(*Z*)-(bromomethylidene)-*β*-vinyl -*γ*-methyl-*γ*-butyrolactam (6c):** oil; IR (neat) *ν* 2972, 1693, 1413, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.27−7.18(m, 5H), 6.37 (d, *J* = 2.4 Hz, 0.54H, trans), 6.32 (d, *J* = 2.6 Hz, 0.46H, cis), 5.72−5.53 (m, 1H), 5.23−5.08 (m, 2H), 5.05 (d, *J* = 14.9 Hz, 0.46H), 4.93 (d, *J* = 14.9 Hz, 0.54H), 3.91 (d, *J* = 14.9 Hz, 0.54H), 3.91 (d, *J* = 14.9 Hz, 0.46H), 3.51 (dq, *J* = 6.6, 6.4 Hz, 0.46H), 3.39 (m, 0.46H), 3.13 (dq, *J* = 6.1, 6.1 Hz, 0.54H), 2.89 (m, 0.54H), 1.12 (d, *J* = 6.2 Hz, 1.62H), 1.00 (d, *J* = 6.2 Hz, 1.38H); MS (*m/e*) 307 [M^+, (^{81}Br)], 305 [M^+, (^{79}Br)], 227, 226, 91 (100), 65. Anal. Calcd for $C_{15}H_{16}NO_2Br$: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.76; H, 5.39; N, 4.58.

***cis*-α-(*Z*)-(Bromoethylidene)-*β*-vinyl -*γ*-methyl-*γ*-butyrolactam (6f):** mp 122−123 °C; IR (Nujol) *ν* 3187, 2978, 1692, 1641, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 6.41(br, 1H), 5.73−5.61 (m, 1H), 5.21−5.12 (m, 2H), 3.84 (dq, *J* = 6.7, 6.7 Hz, 1H), 3.61 (m, 1H), 2.38 (s, 3H), 1.08 (d, *J* = 6.5 Hz, 3H); MS *m/e*: 232 [$M^+ + 1$, (^{81}Br)], 230 [$M^+ + 1$, (^{79}Br)], 150 (100), 107, 79, 78, 77. Anal. Calcd for $C_9H_{12}NOBr$: C, 46.98; H, 5.26; N, 6.09. Found: C, 47.01; H, 5.28; N, 6.05.

***cis*-α-(*Z*)-(Bromobutylidene)-*β*-vinyl-*γ*-methyl-*γ*-butyrolactam (6i):** mp 93−95 °C; IR (Nujol) *ν* 3178, 2958, 1697, 1629, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 6.36(br, 1H), 5.76−5.65 (m, 1H), 5.22−5.12 (m, 2H), 3.82 (dq, *J* = 6.5, 6.5 Hz, 1H), 3.64 (m, 1H), 2.53−2.48 (m, 2H), 1.73−1.59 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); MS (*m/e*) 261 [M^+, (81Br)], 259 [M^+, (^{79}Br)], 258, 178 (100), 135, 105, 91, 79. Anal. Calcd for $C_{11}H_{16}NOBr$: C, 51.18; H, 6.25; N, 5.43. Found: C, 51.54; H, 6.25; N, 5.23.

***N*-Methyl-*trans*-(α-benzoyl-*β*-vinyl)-*γ*-butyrolactam (8).** To a Schlenk tube was added successively **4f** (292 mg, 1 mmol), $Pd_2(dba)_3$·$CHCl_3$ (41 mg, 0.04 mmol), dppf (44 mg, 0.08 mmol), and piperidine (0.15 mL, 1.2 mmol) in dried THF (8 mL) under Ar. The mixture was stirred at room temperature for 10 min, and then KOBu^t (169 mg, 1.5 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h and cooled to room temperature, 3 N HCl (5 mL) was added, and the mixture was stirred for an additional 3 h at room temperature. CH_2Cl_2 (50 mL) was added, and the solution was washed with saturated brine, dried ($MgSO_4$), and purified by chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) to give **8** (125 mg, yield 54.6%): oil; IR (neat) *ν* 2929, 1698, 1677, 1260, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 8.05 (d, *J* = 7.3 Hz, 2H), 7.57−7.42 (m, 3H), 5.86−5.77 (m, 1H), 5.14−5.04 (m, 2H), 4.25 (d, *J* = 6.2 Hz, 1H), 3.70−3.58 (m, 2H), 3.19 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.84 (s, 3H); MS (*m/e*) 230 ($M^+ + 1$), 124, 105 (100), 83, 42; HRMS calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1099. The relative stereochemistry of α- and *β*-substituents was assigned as trans after determination of the relative configuration of **9** by X-ray diffraction analysis.

***N*-Methyl-*trans*-[α-(1-hydroxybenzyl)-*β*-vinyl]-*γ*-butyrolactam (9) + (10).** A solution of **8** (51 mg, 0.22 mmol) in MeOH (2 mL) was cooled to −40 °C, and then $NaBH_4$ (12 mg, 0.33 mmol) was added. The mixture was stirred. After the reaction was complete as monitored by TLC, a drop of HOAc was added to quench the reaction and the mixture was allowed to raise to room temperature. MeOH was evaporated, and CH_2-Cl_2 (20 mL) was then added. The solution was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) to give **9** (35 mg) and **10** (7 mg). Total yield: 83.2%.

9: mp 98−100 °C; IR (KBr) *ν* 3378, 2926, 1662, 1505, 1430, 1401, 1259, 770, 707 cm^{-1}, ^{1}H NMR ($CDCl_3$) *δ* 7.30−7.09 (m, 5H), 5.43 (br, 1H), 5.14−5.02 (m, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 4.52 (dt, *J* = 10.2, 0.9 Hz, 1H), 4.44 (dt, *J* = 17.0, 1.0 Hz, 1H), 3.27 (dd, *J* = 9.8, 8.6 Hz, 1H), 3.02 (dd, *J* = 9.8, 7.9 Hz, 1H), 2.81 (s, 3H), 2.62−2.45 (m, 2H); MS (*m/e*) 231(M^+), 125 (100), 124, 110, 98, 77. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41;

N, 6.06. Found: C, 72.50; H, 7.47; N, 5.95. The relative stereochemistry of α and β-substituents was determined by X-ray crystallography.

10: mp 130−131 °C; IR (KBr) ν 3377, 3061, 1687, 1506, 1442, 1404, 1265, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.26 (m, 5H), 5.56−5.44 (m, 1H), 5.14 (dd, J = 6.6, 3.6 Hz, 1H), 4.88−4.79 (m, 2H), 4.11 (d, J = 6.6 Hz, 1H), 3.18 (dd, J = 9.5, 8.6 Hz, 1H), 2.96 (dd, J = 9.5, 7.2 Hz, 1H), 2.83 (s, 3H), 2.86−2.81 (m, 2H); MS (*m*/*e*) 232 (M^+ + 1), 231(M^+), 214, 125 (100), 124, 110, 98, 77. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.76; H, 7.45; N, 6.07.

***N*-Methyl-*O*-benzoyl-*trans*-[α-(1-hydroxybenzyl)-β-vinyl]-γ-butyrolactam (11).** To a solution of **9** (100 mg, 0.4 mmol) and a catalytic amount of DMAP in pyridine (2 mL) was added dropwise under cooling benzoyl chloride (0.55 mL, 0.52 mmol). After being stirred at room temperature for 10 h, the mixture was poured into water and extracted with CH_2Cl_2 (10 mL × 4). The organic layer was washed successively with $CuSO_4$ solution and brine, dried (Na_2SO_4), and concentrated. The residue was further purified by chromatography (silica gel, petroleum ether/ethyl acetate = 2:1) to give a colorless solid (**11**) (110 mg, yield 80%): mp 95−97 °C; IR (KBr) ν 3035, 1723, 1693, 1268, 1111, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12−8.09 (m, 2H), 7.62−7.51 (m, 1H), 7.48−7.43 (m, 4H), 7.33−7.27 (m, 3H), 6.60 (d, J = 3.8 Hz, 1H), 5.91−5.80 (m, 1H), 5.17 (dd, J = 17.1, 0.5 Hz, 1H), 5.13 (dd, J = 10.2, 0.5 Hz, 1H), 3.09−2.95 (m, 4H), 2.75 (s, 3H); MS (*m*/*e*) 335 (M^+), 230, 105 (100), 86, 84, 77, 49. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.19; H, 6.31; N, 4.19. Found: C, 75.01; H, 5.93; N, 4.22.

***N*-Methyl-*O*-benzoyl-*trans*-[α-(1-hydroxybenzyl)-β-formyl]-γ-butyrolactam (12).** Ozone was bubbled into a solution of **9** (479 mg, 1.4 mmol) in MeOH (30 mL) and CH_2Cl_2 (15 mL) at −78 °C. After the reaction was complete as monitored by TLC, Ar was bubbled into the mixture for 5 min and then Me_2S (2.5 mL) was added. The mixture was stirred for an additional 2 h then allowed the temperature raising to room temperature, concentrated, and purified by chromatography on silica gel (petroleum ether/ethyl acetate =1:1) to give compound **12** (437 mg, yield: 91%): oil; IR (neat) ν 2928, 2885, 1725, 1687, 1269, 1110, 788, 773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (s, 1H), 8.11−8.09 (dd, J = 7.1, 1.6 Hz, 2H), 7.65−7.59 (m, 1H), 7.52−7.27 (m, 7H), 6.66 (d, J = 4.4 Hz, 1H), 3.57−3.48 (m, 2H), 3.30−3.23 (m, 1H), 2.82−2.71 (m, 1H), 2.74 (s, 3H); MS (*m*/*e*) 337 (M^+), 232 (100), 202, 186, 131, 105, 91, 77; HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1319.

Synthesis of (±)-Isocynodine (13). Compound **12** was treated according to the literature method to construct the imidazole ring.[20] A solution of tosylmethylisocyanide (104 mg, 0.5 mmol) in THF (10 mL) was added dropwise to a solution of *t*-BuOK (81 mg, 0.7 mmol) in THF (5 mL) at −30 °C. After the mixture was stirred for 10 min and cooled to −40 °C, a solution of **12** (181 mg, 0.5 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 30 min and poured into ice−water (20 mL). After being neutralized with HOAc, the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The crude product was purified by a short column of silica gel chromatography (petroleum ether/ethyl acetate = 1:1) to obtain an oil. To the solution of the crude oil in THF (10 mL) was added first Et_3N (0.38 mL) and then a solution of $POCl_3$ (0.05 mL, 0.59 mmol) in THF at −10 °C. After being stirred for 30 min, the mixture was poured into ice−water (20 mL), extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. To the solution of the crude product in MeOH (8 mL) was added dropwise a MeOH solution of $MeNH_2$ (1.67 M, 8 mL). After being stirred for 1 h, the mixture was concentrated and purified by chromatography (silica gel, CH_2Cl_2/ethanol = 98:2) to obtain a colorless solid **13** (98 mg, overall yield from **12**: 47%): mp 158−162 °C; IR (KBr) ν 1721, 1689, 1269, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94−7.91 (m, 2H), 7.59−7.54 (m, 1H), 7.46−7.30 (m, 8H), 6.98 (s, 1H), 6.60 (d, J = 3.7 Hz, 1H), 3.45 (s, 3H), 3.44−3.33 (m, 2H), 3.26−3.21 (m, 1H), 3.13 (dd, J = 9.6, 6.4 Hz, 1H), 2.82 (s, 3H); MS (*m*/*e*) 390 (M^+ + 1), 267, 211, 210 (100), 209, 195, 178, 105, 77.

Synthesis of (±)-Isocynometrine (7). To a solution of NaOH (21 mg, 0.53 mmol) in MeOH (4 mL) was added compound **13**, and the mixture was stirred for 0.5 h and concentrated. Water (2 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel, CH_2Cl_2/ethanol = 95:5) to yield colorless solid **7** (18 mg, yield: 82%) and recrystallized from acetone−hexane to yield colorless needles: mp 215−216 °C; IR (KBr) ν 1721, 1689, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27−7.21 (m, 5H), 7.10 (s, 1H), 6.69 (s, 1H), 4.85 (d, J = 8.3 Hz, 1H), 3.42 (t, J = 9.2 Hz, 1H), 3.22 (dd, J = 9.6, 6.4 Hz, 1H), 3.16−3.09 (m, 1H), 3.12 (s, 3H), 2.98 (t, J = 7.8 Hz, 1H), 2.90 (s, 3H); MS (*m*/*e*) 285 (M^+), 206, 179 (100), 136, 135, 109, 108, 107, 95. The ^1H NMR spectrum of compound **7** is identical to the ^1H NMR spectrum of original synthetic isocynometrine.[16] The X-ray crystallographic structure of **7** is identical to the structure of isocynometrine.[15]

Hydrolysis of Vinyl Bromides in γ-Lactones and γ-Lactams (14). Compounds **14** were hydrolyzed using the literature procedure.[17,18]

α-Formyl-β-vinyl-γ-butyrolactone (15a) from α-(*Z*)-bromomethylidine -β-vinyl-γ-butyrolactone (14a):[10] mp 89−90 °C; IR (Nujol) ν 2985−2750, 1723, 1677, 1415, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.15 (br, 0.53H), 9.85 (s, 0.47H), 6.96 (s, 0.53H), 5.82−5.71 (m, 1H), 5.31−5.16 (m, 2H), 4.59−4.46 (m, 1H), 4.10−4.03 (m, 1H), 3.81−3.60 (m, 1H), 3.49 (d, J = 9.5 Hz, 0.47H); MS 140 (M^+), 111, 81, 67, 54, 53 (100). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.16; H, 5.71.

***N*-(*tert*-Butyloxycarbonyl)-α-acetyl-β-vinyl-γ-butyrolactam (15c) from *N*-(*t*-Butyloxycarbonyl)-α-bromoethylidene-β-vinyl-γ-butyrolactam (14c):** oil; IR (neat) ν 3274, 2985, 1700, 1361 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (br, 1H), 5.77−5.71 (m, 1H), 5.16−5.06 (m, 2H), 3.62−3.49 (m, 2H), 3.34 (d, J = 8.0 Hz, 1H), 3.14−3.09 (m, 1H), 2.18 (s, 3H); MS (*m*/*e*) 154 (M^+ + 1, 100), 111, 110, 81, 69. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.25; H, 7.33; N, 9.30.

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Supporting Information Available: Synthetic procedure and analytical data of comounds **1a**, **3a**, **2a**−**j**, **5a**,**c**,**f**,**i**, and **14c**,**d**; ^1H NMR spectra of compounds **2a**−**2c**,**f**,**h**,**i**, **3a**, (*E*)-**4b**, (*E*)-**4c**, **4e**, **4e′**, **5c**, **7**, **8**, **12**, and **13**; X-ray diffraction analytical data of **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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