JOC The Journal of Organic Chemistry

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Divergent Synthesis of α,γ-Disubstituted γ-Butyrolactones through Diastereoselective Bromolactonization with Alkali Metal Bromide: Asymmetric Total Synthesis of (+)-Dubiusamine C

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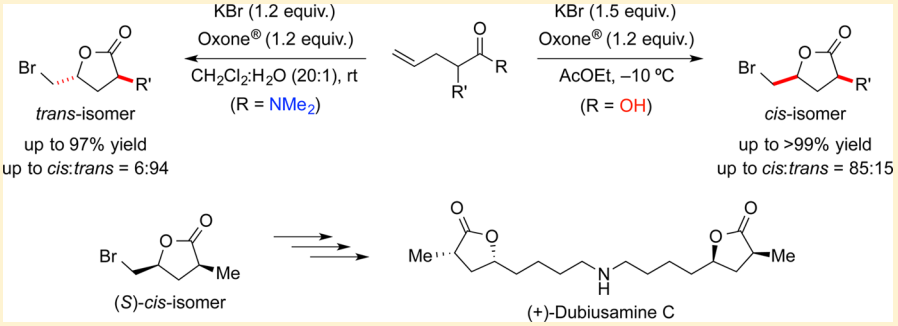
Supporting Information



ABSTRACT: A divergent synthesis of α-substituted bromomethyl γ-lactones was developed, which involves the diastereoselective bromolactonization of α-substituted 4-pentenoic acids and 4-pentenamides via umpolung of bromide by use of alkali metal bromide and Oxone (potassium peroxymonosulfate mixture, $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) to obtain mainly *cis*-products from α-substituted 4-pentenoic acids and *trans*-products from α-substituted 4-pentenamides, and it was found that the bromonium species generated from KBr and Oxone had higher activity than *N*-bromosuccinimide. Furthermore, the asymmetric total synthesis of (+)-dubiusamine C, which was isolated as a minor diastereomer from *Pandanus dubius*, was accomplished for the first time through the *cis*-selective bromolactonization of (*S*)-α-methyl-4-pentenoic acid in nine linear steps and 36% overall yield.

INTRODUCTION

α,γ-Disubstituted γ-butyrolactones are very important building blocks of natural products and biologically active products,[1] and the halolactonization of alkenyl carboxylic acid derivatives is a powerful tool for construction of the substituted lactone framework.[2] However, the use of an organic bromo reagent, such as *N*-bromosuccinimide (NBS), for the bromolactonization results in low reactivity. To overcome this drawback, organocatalysts that increase the electrophilicity of bromonium ion[3] and chiral catalysts[4] have been developed for this reaction. On the other hand, little work has been done on the diastereoselective halolactonization of α-substituted alkenyl carbonyl compounds. In 1984, Yoshida and co-workers[5] reported the 1,3-*trans*-selective halolactonization of α-alkyl-*N*,*N*-dimethyl-4-pentenamide with *N*-halosuccinimide (NXS) as the halogen reagent. Since then, the 1,3-*trans*-selective halolactonization of chiral α-alkyl-1-oxo-4-pentenyl carbonyl compounds bearing a chiral 2-oxazolidinone framework, derived from the method of Evans et al.,[6] has been extensively utilized for the asymmetric synthesis of biological products.[7] We have developed various oxidative transformations via umpolung of bromide from alkali metal bromide instead of organic bromo reagents,[8] and our approach has shown that alkali metal halides, one of the most abundant natural resources on earth, are stable in air, easy to handle, neutral, and nontoxic. Meanwhile, the oxidation of bromide (Br^-) into bromonium ion (Br^+) is a very important tool for the biosynthesis of halogenated natural products.[9] In particular, the bromonium ion species generated from bromide with Oxone (potassium peroxymonosulfate mixture, $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) is anticipated to exhibit higher electrophilicity than organic bromo reagents due to the stability of the counteranion. We report here the divergent synthesis of α-substituted bromolactones through diastereoselective bromolactonization that uses the highly electrophilic bromonium ion species generated from oxidation of alkali metal bromide upon treatment with Oxone (Figure 1) and the asymmetric total synthesis of (+)-dubiusamine C.

RESULTS AND DISCUSSION

First, we screened for solvent and temperature for the diastereoselective bromolactonization of α-methyl-4-pentenoic acid (**1a**) and *N*,*N*-dimethyl-α-methyl-4-pentenamide (**2a**) by use of the KBr/Oxone system (Table 1).

Received: July 1, 2015
Published: August 27, 2015

DOI: 10.1021/acs.joc.5b01497
J. Org. Chem. 2015, 80, 9132–9140

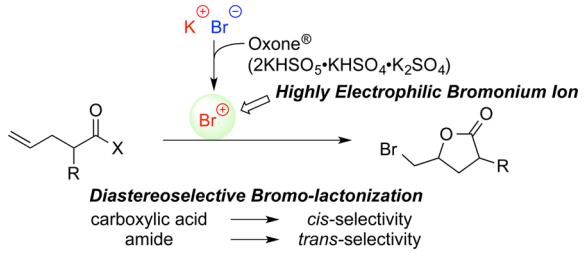
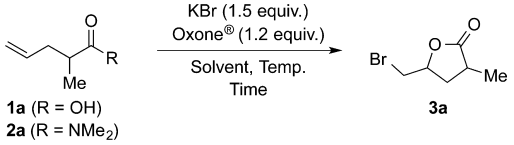


Figure 1. Divergent synthesis involving diastereoselective bromolactonization with alkali metal bromide.

Table 1. Screening for Diastereoselective Bromolactonization of 1a and 2a by Use of Alkali Metal Bromide



entry	substrate	solvent	temp (°C)	time (h)	yield[a] (%)	dr[b] (*cis*/*trans*)
1	**1a**	$MeNO_2$	rt	18	99	67/33
2	**1a**	AcOEt	rt	12	99	72/28
3	**1a**	$MeNO_2$	−10	12	99	72/28
4	**1a**	AcOEt	−10	12	98	77/23
5	**1a**	dioxane	−10	12	99	71/29
6	**1a**	MeCN	−10	12	93	73/27
7	**1a**	acetone	−10	12	88	75/25
8[c]	**2a**	MeCN	rt	5	86	12/88
9[c]	**2a**	CH_2Cl_2	rt	5	78	11/89
10[c]	**2a**	CH_2Cl_2/H_2O (9/1)	rt	5	92	15/85
11[c]	**2a**	CH_2Cl_2/H_2O (20/1)	rt	5	91	10/90
12[c]	**2a**	$MeCN/H_2O$ (20/1)	rt	5	87	12/88
13[c]	**2a**	dioxane/H_2O (20/1)	rt	5	84	15/85
14[c]	**2a**	AcOEt/H_2O (20/1)	rt	5	72	17/83

[a]Number indicates an isolated yield. [b]Diastereomeric ratio of **3a** was determined by ^{1}H NMR analysis. [c]KBr (1.2 equiv) was used.

Treatment of **1a** with KBr (1.5 equiv) and Oxone (1.2 equiv) in $MeNO_2$ at room temperature provided α-methyl-γ-butyrolactone (**3a**) in 99% yield with *cis*-selectivity (*cis*/*trans* = 67/33) (entry 1). The use of AcOEt as solvent gave improved *cis*-selectivity compared to the reaction run in $MeNO_2$, and decreasing the reaction temperature further increased the *cis*-selectivity for the bromolactonization of **1a** (entries 1−4). Other solvents, such as 1,4-dioxane, MeCN, and acetone, were much less effective than AcOEt in the present reaction (entries 5−7). When **2a** was used as the substrate with KBr/Oxone in MeCN at room temperature, the desired product *trans*-**3a** was obtained in 86% yield as the major isomer (*cis*/*trans* = 12/88) (entry 8). The addition of H_2O improved the yield of **3a**, whereas CH_2Cl_2 alone was not suitable for transformation of **2a** into *trans*-**3a** (entries 9 and 10). Decreasing the amount of H_2O in CH_2Cl_2 as the solvent mixture slightly increased the diastereoselectivity of *trans*-**3a** in the present reaction (entry 11). The use of MeCN, 1,4-dioxane, and AcOEt gave similar reactivities and *trans*-selectivities to the use of CH_2Cl_2 (entries 12−14).

To evaluate the activity of the KBr/Oxone system in bromolactonization, we investigated the bromolactonization of **2a** with NBS under previously published conditions,[5] and we found that 3 days of reaction was required to obtain desired product **3a** in 53% yield (*cis*/*trans* = 10/90), together with recovered **2a** in 20% yield.[10] The high performance of the KBr/Oxone system is due to the high electrophilicity of the bromonium ion species, a conjugate acid of hypobromate (H_2OBr^+) formed by the protonation[11] of hypobromate (HOBr) that is generated via the oxidation of KBr with Oxone to stabilize H_2O as a weak conjugate base (H_3O^+; pK_a = −1.7 vs succinimide; pK_a = 9.6[12] in H_2O) (Figure 2).

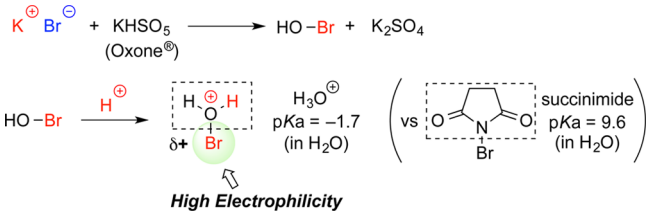
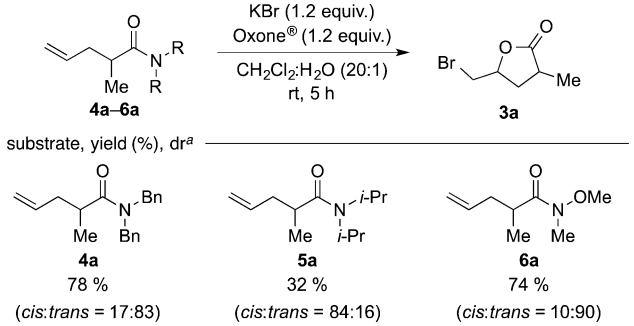


Figure 2. Effect of electrophilicity on bromonium ion species by conjugate base.

Then, to investigate the effect of substituent on the amide groups, various amides (**4a**−**6a**) were used as substrates under optimum conditions for *trans*-selective bromolactonization. However, those reactions were much less reactive and diastereoselective than the reaction of **2a** (Scheme 1). From these results, the presence of water and the *N*-substituent on the amide group have an important role for bromolactonization of 4-pentenamide (**2**). Therefore, we suggest that this reaction depends largely on the reactivity of hydrolysis of iminium cation intermediate formed by bromocyclization.

Scheme 1. Effect of Substituent on Amide Group for *trans*-Selective Bromolactonization



[a]Diastereomeric ratio of **3a** was determined by ^{1}H NMR analysis.

To explore the substrate scope for divergent synthesis of α-substituted bromolactones through diastereoselective bromolactonization by use of the KBr/Oxone system, various α-substituted 4-pentenoic acids (**1**) and 4-pentenamides (**2**) were examined under optimum conditions (Scheme 2).

For the bromolactonization of **1** (condition A), substrates bearing *i*-Pr (**1b**), *n*-octyl (**1c**), cyclopentyl (**1d**), cyclohexyl (**1e**), cyclooctyl (**1f**), benzyl (**1g**), 4-bromobenzyl (**1h**), and phenethyl (**1i**) groups at the α-position gave desired products (**3b**−**3i**) in high yields (92−99%) with *cis*-selectivity (*cis*/*trans* = 72/28 to 85/15). The use of 4-pentenoic acids bearing functional groups such as propargyl (**1j**), sulfonamide (**1k**), and

DOI: 10.1021/acs.joc.5b01497
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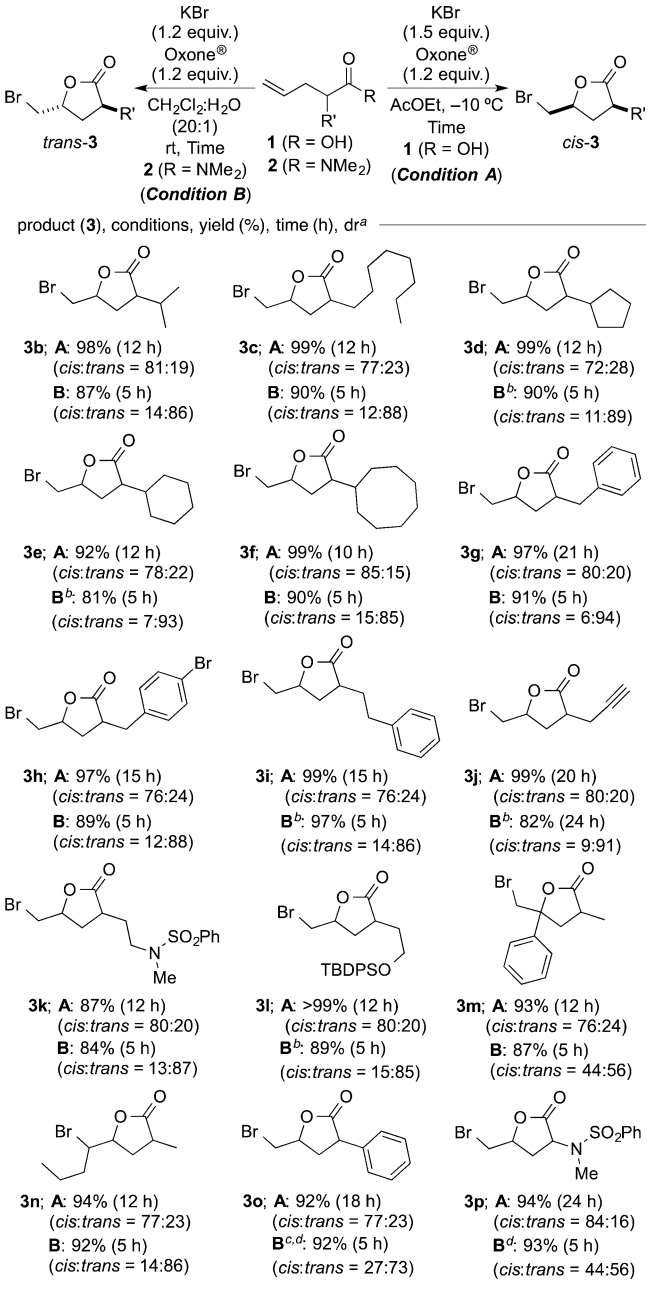
Scheme 2. Divergent Synthesis of α-Substituted Bromolactones via Diastereoselective Bromolactonization in a KBr/Oxone System

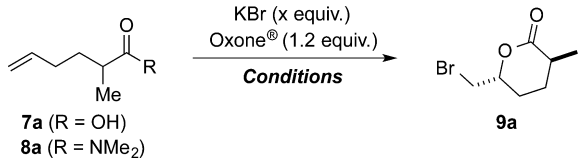


[a]Diastereomeric ratio of **3** was determined by ^{1}H NMR analysis. [b]TsOH·H_2O (10 mol %) was added. [c]The reaction was carried out in MeCN/H_2O (20/1). [d]TsOH·H_2O (1.2 equiv) was added.

silyl ether (**1l**), alkenoic acids with disubstituted olefin (**1m** and **1n**), and 4-pentenoic acids with an acidic proton at α-position (**1o** and **1p**) gave also corresponding *cis*-products (**3j**−**3p**) in high yields (87% to >99%). On the other hand, the bromolactonization of **2** proceeded with high diastereoselectivity (*cis*/*trans* = 29/71 to 6/94) to obtain the *trans*-products (**3**) in high yields (81−97%) in many cases. Two notable exceptions are the lowered diastereoselectivity found with **3m** and **3p** (*cis*/*trans* = 44/56).

When α-methyl-5-hexenoic acid (**7a**) and *N*,*N*-dimethyl-5-hexenamide (**8a**) were used for the six-membered ring in bromolactonization via the KBr/Oxone system, α-methyl-δ-bromomethyl-δ-valerolactone (**9a**) was obtained as mainly a *trans*-isomer in each case (Table 2).

Table 2. Synthesis of α-Substituted Bromomethyl-δ-valerolactone by Diastereoselective Bromolactonization via the KBr/Oxone System



substrate	KBr (equiv)	conditions	yield of **9a** (%)	dr[a] (*cis*/*trans*)
7a	1.5	TsOH (20 mol %), $MeNO_2$/ toluene (3/1), 0 °C, 8 h	86	30/70
8a	1.2	CH_2Cl_2/H_2O (20/1), −10 °C, 5 h	82	35/65

[a]Diastereomeric ratio of **9a** was determined by ^{1}H NMR analysis.

Regarding the diastereoselectivity of the bromolactonization, Kurth and co-workers[13] reported the calculation of some transition states for electrophilic cyclization. On the basis of their results, the difference in diastereoselectivity for bromolactonization is suggested through the plausible transition states shown in Figure 3. In the *trans*-selective reaction of

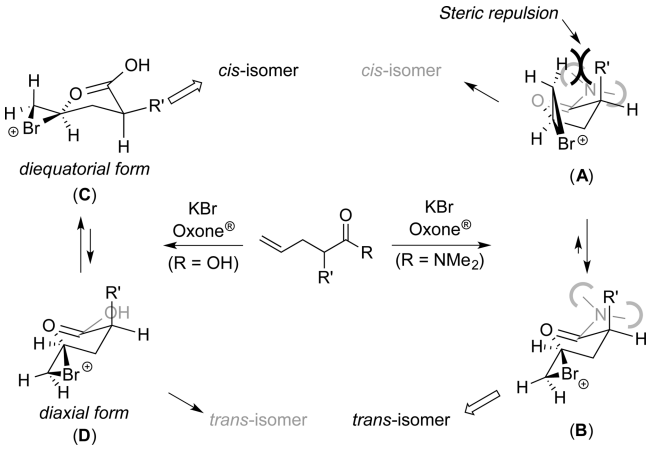


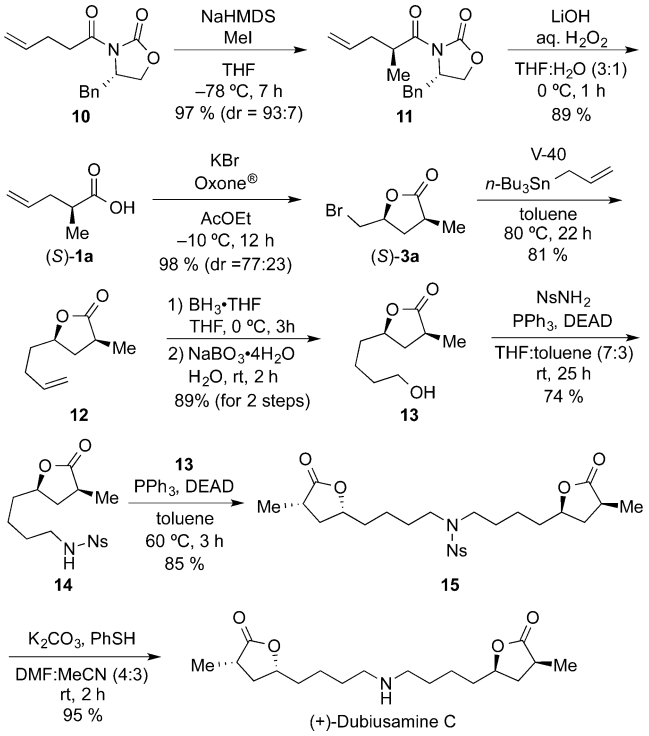
Figure 3. Plausible transition states for diastereoselective bromolactonization.

amides (**2**), the substituent at α-position takes the axial form due to the steric hindrance of the dimethylamino moiety, and therefore axial olefin (**B**) prevails over equatorial olefin (**A**) to avoid interaction between the substituents. By contrast, the *cis*-selective reaction of carboxylic acid (**1**) favors diequatorial form (**C**) over diaxial form (**D**), where there is not so much energy difference between the two transition states (**C** is more stable by 0.307 kcal/mol than **D**, when R′ = Me[13]) to induce lower selectivity than the *trans*-selective reaction.

To demonstrate the present reaction, we attempted to perform the asymmetric total synthesis of (+)-dubiusamine C (Scheme 3). Dubiusamine C was isolated as a minor diastereomer of dubiusamine A (diastereomeric ratio dr = 4/1) from the crude base of *Pandanus dubius*, and its racemic total synthesis was reported by Takayama and co-workers.[14]

DOI: 10.1021/acs.joc.5b01497
J. Org. Chem. 2015, 80, 9132−9140

Scheme 3. Asymmetric Total Synthesis of (+)-Dubiusamine C



However, its asymmetric total synthesis has never been accomplished. Asymmetric alkylation, according to Evans et al.,[6] of **10** with sodium bis(trimethylsilyl)amide (NaHMDS) and MeI in THF at −78 °C afforded alkylated product **11** in 97% yield (dr = 93/7), and (*S*)-**1a** was obtained by cleavage of the chiral auxiliary from **11** with LiOH and aqueous H_2O_2.[15] As the key step, *cis*-selective bromolactonization of (*S*)-**1a** by use of the KBr/Oxone system provided mainly chiral *cis*-bromolactone (*S*)-**3a** in 98% yield with 77/23 diastereomeric ratio, which could be separated by column chromatography. Alkyl−allyl coupling reaction[16] of (*S*)-**3a** with allyltributyltin in the presence of V-40 [1,1′-azobis(cyclohexane-1-carbonitrile)] as the radical initiator provided allylated compound **12** in 81% yield. This was followed by hydroboration with BH_3·THF complex and oxidation with $NaBO_3·4H_2O$[17] to obtain alcohol **13** in 89% yield in two steps. After the Mitsunobu reaction[18] of **13** with $NsNH_2$, PPh_3, and diethyl azodicarboxylate (DEAD) in a mixture of THF and toluene (7/3) at room temperature, resultant amide **14** was subjected to the second Mitsunobu reaction with **13**, PPh_3, and DEAD in toluene at 60 °C to give symmetrical amide **15** in 85% yield. Cleavage of the nosyl group[18] with PhSH and K_2CO_3 in a mixture of DMF and MeCN (4/3) provided (+)-dubiusamine C in 95% yield. Spectral data of the synthesized product were in good agreement with those reported previously,[14] and the optical rotation was $[\alpha]_D^{18}$ +28.8 (*c* 1.07, $CHCl_3$).

In conclusion, we developed a divergent synthesis of α-substituted bromolactones through the diastereoselective bromolactonization of α-substituted 4-pentenoic acids and 4-pentenamides via oxidative umpolung of bromide ion by use of alkali metal bromide with Oxone. Furthermore, the asymmetric total synthesis of (+)-dubiusamine C was accomplished for the first time through *cis*-selective bromolactonization of (*S*)-α-methyl-4-pentenoic acid in nine linear steps and 36% overall yield.:

EXPERIMENTAL SECTION

General Procedure. ^1H NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts are reported as follows: chemical shift in parts per million (ppm) from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (hertz), integration, and assignment. ^{13}C NMR spectra were measured on a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were performed by Orbitrap mass spectrometers. Characteristic peaks in the Infrared (IR) spectra are recorded in wavenumbers (cm^{-1}) by use of attenuated total reflectance (ATR). Melting points are reported as uncorrected. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (60F-254). The products were purified by column chromatography on silica gel 60 (63−200 mesh). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid.

Condition A for Bromolactonization of α-Substituted Alkenylcarboxylic Acids by Use of a KBr/Oxone System (Table 1, entry 4, and Scheme 2). To a solution of **1a** (28.5 mg, 0.25 mmol) and KBr (44.6 mg, 0.375 mmol) in AcOEt (1.0 mL) was added Oxone (184.4 mg, 0.30 mmol) at −10 °C. After the mixture was stirred at −10 °C for 12 h, saturated Na_2SO_3 aqueous solution (10 mL) was added and the product was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 3/1) to give desired product **3a** (47.3 mg, 98% yield, *cis*/*trans* = 77/23).

Condition B for Bromolactonization of α-Substituted Alkenylamides by Use of a KBr/Oxone System (Table 1, entry 11, and Scheme 2). To a solution of **2a** (35.3 mg, 0.25 mmol) and KBr (35.7 mg, 0.30 mmol) in a mixture of CH_2Cl_2 (1.0 mL) and H_2O (50.0 μL) was added Oxone (184.4 mg, 0.30 mmol) at room temperature. After the mixture was stirred at room temperature for 5 h, saturated $NaHCO_3$ aqueous solution (5 mL) was added, and the reaction mixture was stirred for 2 h. The product was extracted with AcOEt (10 mL × 3), and then the combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 3/1) to give desired product **3a** (44.1 mg, 91% yield, *cis*/*trans* = 10/90).

*5-(Bromomethyl)-3-methyldihydrofuran-2(3H)-one (**3a**).* Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7.1 Hz, 3H), 1.65−1.78 (m, 1H), 2.64 (ddd, *J* = 12.8, 9.1, 6.1 Hz, 1H), 2.69−2.83 (m, 1H), 3.51 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.59 (dd, *J* = 11.0, 4.8 Hz, 1H), 4.52−4.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 33.3, 35.5, 35.6, 75.9, 178.4. IR (neat) 2973, 1766, 1454, 1344, 1154, 1014 cm^{-1}; $[\alpha]_D^{23}$ = −16.3 (*c* 1.5, $CHCl_3$, (*S*)); MS (atmospheric pressure chemical ionization, APCI) calcd for $C_6H_{10}BrO_2$ $[M + H]^+$ 192.9859, found 192.9861.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7.6 Hz, 3H), 2.10 (dt, *J* = 13.8, 8.5 Hz, 1H), 2.41 (ddd, *J* = 13.8, 9.7, 4.0 Hz, 1H), 2.77−2.90 (m, 1H), 3.50 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.55 (dd, *J* = 11.0, 4.5 Hz, 1H), 4.71−4.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 33.8 (2C), 33.9, 75.7, 179.1; IR (neat) 2973, 1766, 1455, 1343, 1158, 1012 cm^{-1}; MS (APCI) calcd for $C_6H_{10}BrO_2$ $[M + H]^+$ 192.9859, found 192.9868.

*5-(Bromomethyl)-3-isopropyldihydrofuran-2(3H)-one (**3b**).* Condition A, 54.2 mg, 98%; condition B, 48.0 mg, 87%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.72−1.91 (m, 1H), 2.16−2.30 (m, 1H), 2.39 (ddd, *J* = 13.0, 9.3, 6.2 Hz, 1H), 2.65 (ddd, *J* = 12.4, 9.3, 5.2 Hz, 1H), 3.49 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.60 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.50−4.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

DOI: 10.1021/acs.joc.5b01497
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δ 18.2, 20.5, 27.6, 29.1, 33.4, 46.8, 75.7, 176.9; IR (neat) 2961, 1766, 1467, 1335, 1152, 1011 cm^{-1}; MS (APCI) calcd for $C_8H_{14}BrO_2$ $[M + H]^+$ 221.0172, found 221.0167.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 2.13−2.30 (m, 3H), 2.70 (ddd, J = 10.3, 7.8, 5.1 Hz, 1H), 3.49 (dd, J = 11.0, 6.3 Hz, 1H), 3.54 (dd, J = 11.0, 4.3 Hz, 1H), 4.64−4.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 20.3, 27.9, 28.9, 34.5, 45.2, 76.1, 177.7; IR (neat) 2962, 1766, 1469, 1334, 1155, 1010 cm^{-1}; MS (APCI) calcd for $C_8H_{14}BrO_2$ $[M + H]^+$ 221.0172, found 221.0167.

*5-(Bromomethyl)-3-octyldihydrofuran-2(3H)-one (**3c**).* Condition A, 72.4 mg, 99%; condition B, 65.5 mg, 90%.

Cis isomer: white solid, mp 37.0−37.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.16−1.53 (m, 13H), 1.65−1.78(m, 1H), 1.86−1.98 (m, 1H), 2.53−2.72 (m, 2H), 3.49 (dd, J = 10.8, 6.6 Hz, 1H), 3.59 (dd, J = 10.8, 4.7 Hz, 1H), 4.51−4.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 27.3, 29.2, 29.29, 29.34, 30.3, 31.8, 33.4, 33.6, 40.7, 76.1, 177.9; IR (neat) 2917, 1756, 1465, 1365, 1164, 1013 cm^{-1}; MS (APCI) calcd for $C_{13}H_{24}BrO_2$ $[M + H]^+$ 291.0954, found 291.0948.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.17−1.54 (m, 13H), 1.78−1.92 (m, 1H), 2.13 (dt, J = 13.5, 8.2 Hz, 1H), 2.33 (ddd, J = 13.5, 9.7, 4.6 Hz, 1H), 2.66−2.80 (m, 1H), 3.49 (dd, J = 11.0, 6.4 Hz, 1H), 3.54 (dd, J = 11.0, 4.4 Hz, 1H), 4.68−4.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 27.1, 29.1, 29.2, 29.3, 31.1, 31.8, 31.9, 34.1, 39.0, 76.0, 178.5; IR (neat) 2923, 1769, 1468, 1338, 1151, 1018 cm^{-1}; MS (APCI) calcd for $C_{13}H_{24}BrO_2$ $[M + H]^+$ 291.0954, found 291.0945.

*5-(Bromomethyl)-3-cyclopentyldihydrofuran-2(3H)-one (**3d**).* Condition A, 61.5 mg, 99%; condition B, 55.4 mg, 90%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21−1.38 (m, 2H), 1.50−1.72 (m, 4H), 1.72−1.88 (m, 2H), 1.99−2.10 (m, 1H), 2.12−2.26 (m, 1H), 2.50 (ddd, J = 12.8, 8.9, 6.0 Hz, 1H), 2.71 (ddd, J = 11.9, 8.9, 7.3 Hz, 1H), 3.49 (dd, J = 10.9, 6.5 Hz, 1H), 3.59 (dd, J = 10.9, 4.7 Hz, 1H), 4.50−4.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.3, 29.7, 30.6, 31.8, 33.4, 40.2, 44.8, 75.8, 177.1; IR (neat) 2950, 1769, 1451, 1337, 1153, 1018 cm^{-1}; MS (APCI) calcd for $C_{10}H_{16}BrO_2$ $[M + H]^+$ 247.0328, found 247.0322.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21−1.42 (m, 2H), 1.51−1.74 (m, 4H), 1.74−1.84 (m, 1H), 1.89−2.00 (m, 1H), 2.10−2.33 (m, 3H), 2.73 (dt, J = 9.6, 7.7 Hz, 1H), 3.48 (dd, J = 11.0, 6.5 Hz, 1H), 3.54 (dd, J = 11.0, 4.4 Hz, 1H), 4.66−4.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.2, 29.9, 30.3, 30.6, 34.3, 41.0, 43.1, 75.9, 177.8; IR (neat) 2952, 1769, 1468, 1356, 1158, 1020 cm^{-1}; MS (APCI) calcd for $C_{10}H_{16}BrO_2$ $[M + H]^+$ 247.0328, found 247.0322.

*5-(Bromomethyl)-3-cyclohexyldihydrofuran-2(3H)-one (**3e**).* Condition A, 67.1 mg, 92%; condition B, 52.9 mg, 81%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00−1.21 (m, 3H), 1.22−1.38 (m, 2H), 1.52−1.93 (m, 7H), 2.39 (ddd, J = 13.0, 9.4, 6.2 Hz, 1H), 2.63 (ddd, J = 12.4, 9.3, 5.0 Hz, 1H), 3.48 (dd, J = 10.8, 6.6 Hz, 1H), 3.59 (dd, J = 10.8, 4.6 Hz, 1H), 4.48−4.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.1, 26.2, 28.5, 29.7, 31.2, 33.4, 37.5, 46.1, 75.8, 176.9; IR (neat) 2924, 1768, 1448, 1339, 1164, 1021 cm^{-1}; MS (APCI) calcd for $C_{11}H_{18}BrO_2$ $[M + H]^+$ 261.0485, found 261.0479.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01−1.21 (m, 3H), 1.21−1.37 (m, 2H), 1.54−1.64 (m, 1H), 1.64−1.72 (m, 1H), 1.72−1.88 (m, 4H), 2.17 (ddd, J = 13.9, 10.6, 5.5 Hz, 1H), 2.27 (ddd, J = 13.9, 8.2, 7.3 Hz, 1H), 2.68 (ddd, J = 10.6, 7.3, 5.0 Hz, 1H), 3.48 (dd, J = 11.0, 6.4 Hz, 1H), 3.53 (dd, J = 11.0, 4.5 Hz, 1H), 4.62−4.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (2C), 26.1, 28.6 (2C), 30.8, 34.4, 38.8, 44.9, 76.3, 177.8; IR (neat) 2924, 1764, 1449, 1340, 1156, 1018 cm^{-1}; MS (APCI) calcd for $C_{11}H_{18}BrO_2$ $[M + H]^+$ 261.0485, found 261.0478.

*5-(Bromomethyl)-3-cyclooctyldihydrofuran-2(3H)-one (**3f**).* Condition A, 71.9 mg, 99%; condition B, 65.1 mg, 90%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31−1.78 (m, 14H), 1.85 (dt, J = 12.6, 10.1 Hz, 1H), 2.13−2.25 (m, 1H), 2.41 (ddd, J = 12.6, 9.2, 6.2 Hz, 1H), 2.71 (ddd, J = 12.6, 9.2, 4.4 Hz, 1H), 3.50 (dd, J = 11.0, 6.4 Hz, 1H), 3.60 (dd, J = 11.0, 4.7 Hz, 1H), 4.47−4.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.8, 26.4 (2C), 26.7, 29.46, 29.51, 32.5, 33.4, 36.4, 48.2, 75.8, 177.1; IR (neat) 2917, 1770, 1446, 1337, 1160, 1022 cm^{-1}; MS (APCI) calcd for $C_{13}H_{22}BrO_2$ $[M + H]^+$ 289.0798, found 289.0791.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32−1.80 (m, 14H), 2.10−2.30 (m, 3H), 2.76 (ddd, J = 10.3, 8.7, 4.6 Hz, 1H), 3.49 (dd, J = 10.9, 6.0 Hz, 1H), 3.52 (dd, J = 10.9, 4.4 Hz, 1H), 4.65−4.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 25.9, 26.39 (2C), 26.43, 28.1, 29.4, 32.3, 34.6, 37.7, 46.4, 76.0, 178.0; IR (neat) 2918, 1768, 1446, 1340, 1155, 1022 cm^{-1}; MS (APCI) calcd for $C_{13}H_{22}BrO_2$ $[M + H]^+$ 289.0798, found 289.0789.

*3-Benzyl-5-(bromomethyl)dihydrofuran-2(3H)-one (**3g**).* Condition A, 65.0 mg, 97%; condition B, 61.4 mg, 91%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (ddd, J = 13.0, 11.4, 9.6 Hz, 1H), 2.42 (ddd, J = 13.0, 9.2, 6.4 Hz, 1H), 2.80 (dd, J = 14.0, 9.2 Hz, 1H), 2.99 (dtd, J = 11.4, 9.2, 4.4 Hz, 1H), 3.28 (dd, J = 14.0, 4.4 Hz, 1H), 3.34 (dd, J = 11.0, 6.5 Hz, 1H), 3.48 (dd, J = 11.0, 4.7 Hz, 1H), 4.49−4.58 (m, 1H), 7.17−7.22 (m, 2H), 7.22−7.28 (m, 1H), 7.28−7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 33.1, 36.1, 42.5, 76.2, 126.8, 128.75 (2C), 128.83 (2C), 138.1, 177.0; IR (neat) 2925, 1769, 1453, 1336, 1159, 1013 cm^{-1}; MS (APCI) calcd for $C_{12}H_{14}BrO_2$ $[M + H]^+$ 269.0172, found 269.0166.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13−2.26 (m, 2H), 2.83 (dd, J = 14.0, 9.1 Hz, 1H), 3.03−3.14 (m, 1H), 3.19 (dd, J = 14.0, 4.6 Hz, 1H), 3.44 (dd, J = 11.0, 6.0 Hz, 1H), 3.47 (dd, J = 11.0, 4.6 Hz, 1H), 4.47−4.57 (m, 1H), 7.17−7.23 (m, 2H), 7.23−7.29 (m, 1H), 7.29−7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 34.0, 36.6, 40.8, 76.0, 126.9, 128.8 (2C), 128.9 (2C), 137.7, 177.8; IR (neat) 2927, 1770, 1454, 1338, 1150, 1015 cm^{-1}; MS (atmospheric pressure photoionization, APPI) calcd for $C_{12}H_{14}BrO_2$ $[M + H]^+$ 269.0172 found 269.0164.

*3-(4-Bromobenzyl)-5-(bromomethyl)dihydrofuran-2(3H)-one (**3h**).* Condition A, 84.1 mg, 97%; condition B, 77.5 mg, 89%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (ddd, J = 13.0, 11.9, 9.8 Hz, 1H), 2.42 (ddd, J = 13.0, 9.0, 6.2 Hz, 1H), 2.77 (dd, J = 14.2, 9.3 Hz, 1H), 2.91−3.02 (m, 1H), 3.21 (dd, J = 14.2, 4.3 Hz, 1H), 3.40 (dd, J = 11.0, 6.4 Hz, 1H), 3.51 (dd, J = 11.0, 4.6 Hz, 1H), 4.50−4.60 (m, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 33.1, 35.3, 42.3, 76.1, 120.7, 130.6 (2C), 131.8 (2C), 137.0, 176.6; IR (neat) 2926, 1769, 1487, 1335, 1158, 1011 cm^{-1}; MS (APCI) calcd for $C_{12}H_{13}Br_2O_2$ $[M + H]^+$ 346.9277, found 346.9293.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09−2.28 (m, 2H), 2.81 (dd, J = 13.8, 8.6 Hz, 1H), 3.02−3.17 (m, 2H), 3.46 (dd, J = 11.0, 5.7 Hz, 1H), 3.49 (dd, J = 11.1, 4.6 Hz, 1H), 4.51−4.60 (m, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 34.2, 36.1, 40.6, 76.1, 121.0, 130.8 (2C), 132.0 (2C), 136.8, 177.6; IR (neat) 2928, 1770, 1487, 1338, 1150, 1011 cm^{-1}; MS (APPI) calcd for $C_{12}H_{13}Br_2O_2$ $[M + H]^+$ 346.9277, found 346.9264.

*5-(Bromomethyl)-3-phenethyldihydrofuran-2(3H)-one (**3i**).* Condition A, 70.4 mg, 99%; condition B, 68.4 mg, 97%.

Cis isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68−1.86 (m, 2H), 2.22−2.34 (m, 1H), 2.50−2.75 (m, 3H), 2.75−2.86 (m, 1H), 3.49 (dd, J = 11.0, 6.4 Hz, 1H), 3.58 (dd, J = 11.0, 4.6 Hz, 1H), 4.48−4.59 (m, 1H), 7.16−7.25 (m, 3H), 7.26−7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 33.1, 33.4, 33.6, 39.7, 76.0, 126.3, 128.4 (2C), 128.5 (2C), 140.5, 177.6; IR (neat) 2919, 1763, 1455, 1372, 1161, 1019 cm^{-1}; MS (APCI) calcd for $C_{13}H_{16}BrO_2$ $[M + H]^+$ 283.0328, found 283.0324.

Trans isomer: white solid, mp 53.5−54.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73−1.86 (m, 1H), 2.08−2.27 (m, 2H), 2.34 (ddd, J = 13.9, 9.8, 4.3 Hz, 1H), 2.66−2.84 (m, 3H), 3.47 (dd, J = 11.0, 6.3 Hz, 1H), 3.52 (dd, J = 11.0, 4.4 Hz, 1H), 4.70−4.78 (m, 1H), 7.16−7.24 (m, 3H), 7.27−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0. 32.9, 33.2, 34.0, 38.2, 76.0, 126.3, 128.4 (2C), 128.6 (2C), 140.5, 178.2; IR (neat) 2950, 1764, 1455, 1373, 1153, 1018 cm^{-1}; MS (APCI) calcd for $C_{13}H_{16}BrO_2$ $[M + H]^+$ 283.0328, found 283.0320.

DOI: 10.1021/acs.joc.5b01497
J. Org. Chem. 2015, 80, 9132−9140

*5-(Bromomethyl)-3-(prop-2-yn-1-yl)dihydrofuran-2(3H)-one (**3j**).* Condition A, 53.5 mg, 99%; condition B, 44.7 mg, 82%.

Cis isomer: white solid, mp 51.5−52.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.08 (m, 1H), 2.04 (t, J = 2.7 Hz, 1H), 2.56 (ddd, J = 17.4, 7.8, 2.7 Hz, 1H), 2.61−2.72 (m, 2H), 2.91 (dddd, J = 12.0, 9.2, 7.8, 4.5 Hz, 1H), 3.51 (dd, J = 10.8, 6.5 Hz, 1H), 3.62 (dd, J = 10.8, 4.8 Hz, 1H), 4.59−4.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.5, 33.0, 39.9, 71.0, 76.2, 79.9, 175.8; IR (neat) 3263, 2921, 1771, 1421, 1353, 1152, 1009 cm^{-1}; MS (APCI) calcd for $C_8H_{10}BrO_2$ [M + H]$^+$ 216.9859, found 216.9857.

Trans isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (t, J = 2.6 Hz, 1H), 2.38−2.52 (m, 2H), 2.56−2.70 (m, 2H), 2.96−3.07 (m, 1H), 3.55 (d, J = 5.0 Hz, 2H), 4.79−4.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 30.6, 34.4, 38.3, 71.0, 76.1, 79.7, 176.7; IR (neat) 3289, 2924, 1770, 1424, 1358, 1156, 1015 cm^{-1}; MS (APCI) calcd for $C_8H_{10}BrO_2$ [M + H]$^+$ 216.9859, found 216.9856.

*N-[2-(5-(Bromomethyl)-2-oxotetrahydrofuran-3-yl)ethyl]-N-methylbenzenesulfonamide (**3k**).* Condition A, 81.6 mg, 87%; condition B, 80.4 mg, 85%.

Cis isomer: white solid, mp 102.5−103.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.73 (m, 1H), 1.73−1.85 (m, 1H), 2.15−2.28 (m, 1H), 2.74 (s, 3H), 2.82 (ddd, J = 12.6, 9.2, 6.0 Hz, 1H), 2.87−2.96 (m, 1H), 2.99 (dt, J = 13.5, 5.5 Hz, 1H), 3.27 (ddd, J = 13.5, 9.2, 5.5 Hz, 1H), 3.59 (d, J = 5.0 Hz, 2H), 4.60−4.69 (m, 1H), 7.51−7.59 (m, 2H), 7.59−7.66 (m, 1H), 7.75−7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 33.2, 33.5, 34.6, 38.0, 47.8, 76.3, 127.2 (2C), 129.2 (2C), 132.8, 136.7, 177.6; IR (neat) 2934, 1769, 1446, 1334, 1156, 1018 cm^{-1}; MS (APCI) calcd for $C_{14}H_{19}BrNO_4S$ [M + H]$^+$ 376.0213, found 376.0204.

Trans isomer: white solid, mp 82.5−83.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66−1.79 (m, 1H), 2.08−2.19 (m, 1H), 2.21 (dt, J = 13.5, 8.8 Hz, 1H), 2.54 (ddd, J = 13.5, 9.8, 3.4 Hz, 1H), 2.75 (s, 3H), 2.89−3.01 (m, 1H), 3.08 (dt, J = 13.9, 6.2 Hz, 1H), 3.21 (ddd, J = 13.9, 7.9, 6.2 Hz, 1H), 3.54 (d, J = 5.2 Hz, 2H), 4.77−4.85 (m, 1H), 7.51−7.58 (m, 2H), 7.59−7.65 (m, 1H), 7.76−7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 31.5, 34.0, 35.0, 36.2, 47.8, 76.2, 127.3 (2C), 129.2 (2C), 132.8, 136.9, 178.2; IR (neat) 2929, 1768, 1446, 1334, 1156, 1022 cm^{-1}; MS (APCI) calcd for $C_{14}H_{19}BrNO_4S$ [M + H]$^+$ 376.0213, found 376.0202.

*5-(Bromomethyl)-3-{2-[(tert-butyldiphenylsilyl)oxy]ethyl}-dihydrofuran-2(3H)-one (**3l**).* Condition A, 114.8 mg, 99%; condition B, 102.8 mg, 89%.

Cis isomer: white solid, mp 110.0−110.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.57−1.75 (m, 2H), 2.18−2.30 (m, 1H), 2.47 (ddd, J = 12.8, 9.2, 6.2 Hz, 1H), 2.88 (dtd, J = 12.1, 9.4, 4.1 Hz, 1H), 3.44 (dd, J = 10.8, 6.4 Hz, 1H), 3.55 (dd, J = 10.8, 4.6 Hz, 1H), 3.70 (ddd, J = 10.5, 7.8, 4.6 Hz, 1H), 3.85 (dt, J = 10.5, 5.7 Hz, 1H), 4.48−4.58 (m, 1H), 7.35−7.47 (m, 6H), 7.62−7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.8 (3C), 33.1, 33.3, 33.9, 38.0, 61.4, 76.2, 127.7 (4C), 129.8 (2C), 133.3, 133.4, 135.5 (4C), 177.9; IR (neat) 2930, 1777, 1471, 1362, 1164, 1107, 1020 cm^{-1}; MS (APCI) calcd for $C_{23}H_{30}BrO_3Si$ [M + H]$^+$ 461.1142, found 461.1133.

Trans isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.60−1.72 (m, 1H), 2.06−2.22 (m, 2H), 2.28 (ddd, J = 13.6, 9.6, 3.9 Hz, 1H), 2.97 (qd, J = 9.6, 4.6 Hz, 1H), 3.47 (dd, J = 10.8, 6.0 Hz, 1H), 3.51 (dd, J = 10.8, 4.4 Hz, 1H), 3.70 (ddd, J = 10.8, 7.6, 4.8 Hz, 1H), 3.82 (dt, J = 10.8, 5.7 Hz, 1H), 4.66−4.75 (m, 1H), 7.36−7.48 (m, 6H), 7.62−7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.9 (3C), 31.9, 33.7, 34.1, 36.3, 61.4, 76.1, 127.9 (4C), 129.9 (2C), 133.4 (2C), 135.6 (4C), 178.8; IR (neat) 2930, 1775, 1471, 1361, 1158, 1110, 1023 cm^{-1}; MS (APCI) calcd for $C_{23}H_{30}BrO_3Si$ [M + H]$^+$ 461.1142, found 461.1131.

*5-(Bromomethyl)-3-methyl-5-phenyldihydrofuran-2(3H)-one (**3m**).* Condition A, 62.8 mg, 93%; condition B, 58.7 mg, 87%.

Cis isomer: white solid, mp 101.5−102.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.1 Hz, 3H), 2.46 (t, J = 12.1 Hz, 1H), 2.52−2.65 (m, 1H), 2.78 (dd, J = 12.1, 8.5 Hz, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.76 (d, J = 11.4 Hz, 1H), 7.32−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 34.7, 40.2, 40.4, 84.0, 125.1 (2C), 128.7, 128.8 (2C), 139.8, 177.9; IR (neat) 2971, 1769, 1450, 1316, 1195, 1026 cm^{-1}; MS (APCI) calcd for $C_{12}H_{14}BrO_2$ [M + H]$^+$ 269.0172, found 269.0167.

Trans isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 7.1 Hz, 3H), 2.16−2.30 (m, 1H), 3.05−3.20 (m, 2H), 3.66 (d, J = 11.4 Hz, 1H), 3.71 (d, J = 11.4 Hz, 1H), 7.32−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 35.7, 40.7, 41.1, 84.4, 124.8 (2C), 128.5, 128.7 (2C), 141.8, 178.5; IR (neat) 2973, 1767, 1450, 1313, 1191, 1026 cm^{-1}; MS (APCI) calcd for $C_{12}H_{14}BrO_2$ [M + H]$^+$ 269.0172, found 269.0170.

*5-(1-Bromobutyl)-3-methyldihydrofuran-2(3H)-one (**3n**).* Condition A, 55.4 mg, 94%; condition B, 54.1 mg, 92%.

Cis isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 1.38−1.53 (m, 1H), 1.60−1.83 (m, 3H), 2.01 (dddd, J = 14.6, 9.7, 6.2, 3.2 Hz, 1H), 2.63−2.78 (m, 2H), 3.99 (ddd, J = 9.8, 8.0, 3.2 Hz, 1H), 4.38 (ddd, J = 10.0, 8.0, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 15.0, 20.2, 35.5, 35.9, 36.9, 57.1, 79.2, 178.7; IR (neat) 2961, 1772, 1455, 1343, 1167, 1013 cm^{-1}; MS (APCI) calcd for $C_9H_{16}BrO_2$ [M + H]$^+$ 235.0328, found 235.0325.

Trans isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.31 (d, J = 7.6 Hz, 3H), 1.37−1.53 (m, 1H), 1.58−1.74 (m, 1H), 1.74−1.84 (m, 1H), 1.88−2.00 (m, 1H), 2.08 (dt, J = 13.7, 8.0 Hz, 1H), 2.48 (ddd, J = 13.7, 9.8, 5.0 Hz, 1H), 2.74−2.87 (m, 1H), 4.05 (ddd, J = 10.3, 7.2, 3.4 Hz, 1H), 4.54 (ddd, J = 8.0, 7.2, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 16.4, 20.3, 33.5, 34.1, 36.6, 57.2, 79.3, 179.3; IR (neat) 2961, 1773, 1455, 1345, 1171, 1009 cm^{-1}; MS (APPI) calcd for $C_9H_{16}BrO_2$ [M + H]$^+$ 235.0328, found 235.0324.

*5-(Bromomethyl)-3-phenyldihydrofuran-2(3H)-one (**3o**).* Condition A, 58.4 mg, 92%; condition B, 58.6 mg, 92%.

Cis isomer: white solid, mp 70.0−70.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22−2.36 (m, 1H), 2.88 (ddd, J = 13.1, 9.4, 6.0 Hz, 1H), 3.59 (dd, J = 11.0, 6.3 Hz, 1H), 3.66 (dd, J = 11.0, 4.6 Hz, 1H), 3.94 (dd, J = 12.6, 9.4 Hz, 1H), 4.66−4.75 (m, 1H), 7.28−7.35 (m, 3H), 7.35−7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 36.3, 46.9, 75.7, 127.8, 128.1 (2C), 128.9 (2C), 136.0, 175.7; IR (neat) 2951, 1767, 1450, 1352, 1146, 1015 cm^{-1}; MS (APPI) calcd for $C_{11}H_{11}BrO_2$ [M]$^+$ 253.9937, found 253.9936.

Trans isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (dt, J = 13.9, 7.8 Hz, 1H), 2.67 (ddd, J = 13.9, 10.1, 5.3 Hz, 1H), 3.57−3.63 (m, 2H), 4.03 (dd, J = 10.1, 7.8 Hz, 1H), 4.83−4.92 (m, 1H), 7.24−7.34 (m, 3H), 7.34−7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 34.8, 45.4, 76.1, 127.5 (2C), 127.7, 129.0 (2C), 136.8, 176.3; IR (neat) 2958, 1768, 1452, 1334, 1149, 1011 cm^{-1}; MS (APCI) calcd for $C_{11}H_{12}BrO_2$ [M + H]$^+$ 255.0015, found 255.0019.

*N-[5-(Bromomethyl)-2-oxotetrahydrofuran-3-yl]-N-methylbenzenesulfonamide (**3p**).* Condition A, 82.1 mg, 94%; condition B, 81.1 mg, 93%.

Cis isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16−2.28 (m, 1H), 2.61 (ddd, J = 13.0, 9.3, 6.0 Hz, 1H), 2.80 (s, 3H), 3.58 (dd, J = 11.4, 4.1 Hz, 1H), 3.63 (dd, J = 11.4, 5.3 Hz, 1H), 4.56−4.67 (m, 1H), 5.14 (dd, J = 12.1, 9.3 Hz, 1H), 7.50−7.58 (m, 2H), 7.58−7.65 (m, 1H), 7.86−7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 30.3, 33.3, 57.5, 74.2, 127.4 (2C), 129.1 (2C), 133.1, 138.4, 171.0; IR (neat) 2944, 1782, 1446, 1335, 1153, 980 cm^{-1}; MS (APCI) calcd for $C_{12}H_{15}BrNO_4S$ [M + H]$^+$ 347.9900, found 347.9902.

Trans isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39−2.59 (m, 2H), 2.75 (s, 3H), 3.53 (dd, J = 11.4, 3.9 Hz, 1H), 3.59 (dd, J = 11.4, 5.2 Hz, 1H), 4.81−4.90 (m, 1H), 5.13 (t, J = 10.3 Hz, 1H), 7.50−7.57 (m, 2H), 7.57−7.65 (m, 1H), 7.86−7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 30.9, 34.4, 56.3, 75.2, 127.6 (2C), 129.1 (2C), 133.2, 138.4, 171.9; IR (neat) 2961, 1779, 1446, 1335, 1156, 980 cm^{-1}; MS (APCI) calcd for $C_{12}H_{15}BrNO_4S$ [M + H]$^+$ 347.9900, found 347.9892.

*6-(Bromomethyl)-3-methyltetrahydro-2H-pyran-2-one (**9a**).* Condition A, 44.5 mg, 86%; condition B, 42.6 mg, 82%.

Cis isomer: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3H), 1.53−1.67 (m, 1H), 1.73−1.88 (m, 1H), 2.07−2.20 (m, 2H), 2.55−2.68 (m, 1H), 3.44 (dd, J = 11.0, 6.3 Hz, 1H), 3.54 (dd, J = 11.0, 5.0 Hz, 1H), 4.47−4.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

DOI: 10.1021/acs.joc.5b01497
J. Org. Chem. 2015, 80, 9132−9140

δ 16.2, 25.0, 25.1, 33.0, 33.3, 76.7, 174.8; IR (neat) 2935, 1737, 1460, 1374, 1160, 1015 cm^{-1}; MS (APCI) calcd for $C_7H_{12}BrO_2$ $[M + H]^+$ 207.0015, found 207.0015.

Trans isomer: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 7.1 Hz, 3H), 1.54−1.70 (m, 1H), 1.73−1.87 (m, 1H), 2.02−2.20 (m, 2H), 2.42−2.55 (m, 1H), 3.50 (dd, J = 11.0, 6.0 Hz, 1H), 3.53 (dd, J = 11.0, 4.6 Hz, 1H), 4.46−4.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 27.5, 27.7, 34.4, 36.0, 79.3, 173.3; IR (neat) 2936, 1728, 1459, 1379, 1163, 1013 cm^{-1}; MS (APCI) calcd for $C_7H_{12}BrO_2$ $[M + H]^+$ 207.0015, found 207.0014.

Asymmetric Total Synthesis of (+)-Dubiusamine C. *(S)-4-Benzyl-3-(pent-4-enoyl)oxazolidin-2-one (**10**).* To a solution of 4-pentenoic acid (1.00 g, 10.0 mmol) and Et_3N (1.52 mL, 11.0 mmol) in THF (25.0 mL) was added pivaloyl chloride (1.52 mL, 10.5 mmol) dropwise over 5 min at −78 °C, and the mixture was stirred at 0 °C for 1 h. To obtain (*S*)-4-benzyl-2-oxazolidione lithium salt, *n*-BuLi (1.6 M in *n*-hexane, 6.56 mL, 10.5 mmol) was added to a solution of (*S*)-4-benzyl-2-oxazolidione (1.86 g, 10.5 mmol) in THF (25.0 mL) dropwise over 5 min at −78 °C and the mixture was stirred for 30 min. This was added to the first solution dropwise over 5 min at −78 °C, and the resulting mixture was stirred at −78 °C for 15 min and then allowed to warm to 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (30 mL) and extracted with AcOEt (30 mL × 3). The combined extracts were washed with saturated $NaHCO_3$ aqueous solution (30 mL) and brine (30 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 3/1) to give desired product **10** (2.46 g, 95% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41−2.52 (m, 2H), 2.76 (dd, J = 13.8, 9.8 Hz, 1H), 3.02 (dt, J = 17.7, 7.6 Hz, 1H), 3.11 (dd, J = 17.7, 7.6 Hz, 1H), 3.30 (dd, J = 13.8, 3.3 Hz, 1H), 4.14−4.24 (m, 2H), 4.63−4.72 (m, 1H), 5.00−5.16 (m, 2H), 5.89 (ddt, J = 17.4, 10.3, 6.8 Hz, 1H), 7.18−7.24 (m, 2H), 7.25−7.31 (m, 1H), 7.31−7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 34.8, 37.9, 55.1, 66.2, 115.7, 127.3, 129.0 (2C), 129.4 (2C), 135.2, 136.7, 153.5, 172.5; IR (neat) 2974, 1775, 1698, 1384, 1351, 1209 cm^{-1}; $[\alpha]_D^{19}$ = +56.3 (*c* 1.3, $CHCl_3$, (*S*)).

*(S)-4-Benzyl-3-[(S)-2-methylpent-4-enoyl]oxazolidin-2-one (**11**).* To a solution of **10** (129.7 mg, 0.50 mmol) in THF (2.5 mL) was added NaHMDS (1.1 M in THF, 682 μL, 0.75 mmol) dropwise over 5 min at −78 °C. After the mixture was stirred at −78 °C for 1 h, MeI (125 μL, 2.0 mmol) was added dropwise over 5 min at −78 °C and the mixture was stirred at −78 °C for 7 h. Saturated NH_4Cl aqueous solution (20 mL) was added to the reaction mixture, and the product was extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 5/1) to give desired product **11** (131.9 mg, 97% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 2.13−2.26 (m, 1H), 2.42−2.54 (m, 1H), 2.77 (dd, J = 13.6, 9.7 Hz, 1H), 3.27 (dd, J = 13.6, 3.3 Hz, 1H), 3.83 (sextet, J = 7.1 Hz, 1H), 4.13−4.24 (m, 2H), 4.62−4.71 (m, 1H), 5.00−5.12 (m, 2H), 5.78 (ddt, J = 17.4, 10.3, 7.2 Hz, 1H), 7.19−7.24 (m, 2H), 7.25−7.30 (m, 1H), 7.30−7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 37.4, 37.5, 37.9, 55.3, 66.0, 117.0, 127.3, 128.9 (2C), 129.4 (2C), 135.2, 135.5, 153.0, 176.4; IR (neat) 2978, 1774, 1695, 1383, 1349, 1208 cm^{-1}; $[\alpha]_D^{19}$ = +79.5 (*c* 1.0, $CHCl_3$, (*S*)).

*(S)-2-Methylpent-4-enoic acid ((S)-**1a**).* To a solution of **11** (273.3 mg, 1.0 mmol) in a mixture of THF (7.5 mL) and H_2O (2.5 mL) was added a solution of 30% aqueous H_2O_2 (511.0 μL, 5.0 mmol) and LiOH (47.9 mg, 2.0 mmol) in H_2O (2.0 mL) dropwise over 5 min at 0 °C. After the mixture was stirred at 0 °C for 1 h, THF was removed under reduced pressure. The aqueous layer was adjusted to pH 2 with 1 N HCl aqueous solution and then extracted with AcOEt (20 mL × 3). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent hexane/ether = 1/1) to give desired product (*S*)-**1a** (101.5 mg, 89% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 7.1 Hz, 3H), 2.15−2.27 (m, 1H), 2.39−2.50 (m, 1H), 2.56 (sextet, J = 7.1 Hz, 1H), 5.02−5.14 (m, 2H), 5.70−5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 37.4, 39.1, 117.2, 135.1, 182.4; IR (neat) 2979, 1703, 1463, 1286, 1244, 916 cm^{-1}; $[\alpha]_D^{20}$ = +10.6 (*c* 1.0, $CHCl_3$, (*S*)).

*(3S,5R)-5-(But-3-en-1-yl)-3-methyldihydrofuran-2(3H)-one (**12**).* To a solution of (*S*)-**3a** (193.0 mg, 1.0 mmol) and V-40 (48.9 mg, 0.2 mmol) in degassed toluene (3.1 mL) was added allyltributyltin (6.13 mL, 20.0 mmol) at room temperature. After the solution was stirred at 80 °C for 22 h, it was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (10% w/w anhydrous K_2CO_3−silica gel; eluent hexane/AcOEt = 6/1) to give desired product **12** (124.1 mg, 81% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.1 Hz, 3H), 1.52 (td, J = 12.5, 10.6 Hz, 1H), 1.65−1.76 (m, 1H), 1.79−1.92 (m, 1H), 2.12−2.32 (m, 2H), 2.50 (ddd, J = 12.5, 8.7, 5.5 Hz, 1H), 2.68 (ddd, J = 12.1, 8.7, 7.1 Hz, 1H), 4.36 (ddt, J = 10.6, 7.8, 5.5 Hz, 1H), 4.98−5.11 (m, 2H), 5.81 (ddt, J = 17.2, 10.3, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 29.5, 34.6, 35.8, 37.2, 77.8, 115.5, 137.1, 179.5; IR (neat) 2935, 1766, 1453, 1357, 1188, 1010, 913 cm^{-1}; $[\alpha]_D^{23}$ = +23.7 (*c* 1.2, $CHCl_3$, (*S*)); MS (electrospray ionization, ESI) calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1067, found 155.1061.

*(3S,5R)-5-(4-Hydroxybutyl)-3-methyldihydrofuran-2(3H)-one (**13**).* To a solution of **12** (38.6 mg, 0.25 mmol) in THF (1.0 mL) was added BH_3·THF (0.92 M in THF, 270 μL, 0.25 mmol) at 0 °C. After the mixture was stirred at 0 °C for 3 h, H_2O (1 mL) was added dropwise over 10 min at 0 °C. Then $NaBO_3$·$4H_2O$ (57.7 mg, 0.375 mmol) was added to this mixture at room temperature. After the reaction mixture was stirred at room temperature for 2 h, it was extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced puressure. The crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 1/3) to give desired product **13** (32.9 mg, 76% yield): white solid, mp 65.5−66.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.1 Hz, 3H), 1.36−1.71 (m, 7H), 1.72−1.83 (m, 1H), 2.50 (ddd, J = 12.8, 8.7, 5.5 Hz, 1H), 2.61−2.75 (m, 1H), 3.67 (t, J = 6.4 Hz, 2H), 4.35 (ddt, J = 10.8, 7.7, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.6, 32.2, 35.2, 35.9, 37.2, 62.4, 78.5, 179.6; IR (neat) 3385, 2947, 1747, 1361, 1190, 1047, 989 cm^{-1}; $[\alpha]_D^{23}$ = +20.0 (*c* 1.0, $CHCl_3$, (*S*)); MS (ESI) calcd for $C_9H_{17}O_3$ $[M + H]^+$ 173.1172, found 173.1170.

*N-{4-[(2R,4S)-4-Methyl-5-oxotetrahydrofuran-2-yl]butyl}-2-nitrobenzenesulfonamide (**14**).* To a solution of **13** (68.9 mg, 0.40 mmol), $NsNH_2$ (202.3 mg, 1.0 mmol), and Ph_3P (136.4 mg, 0.52 mmol) in a mixture of THF (5.6 mL) and toluene (2.4 mL) was added DEAD (2.2 M in toluene, 236 μL, 0.52 mmol) dropwise over 5 min at 0 °C. After the mixture was stirred at room temperature for 25 h, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 2/3) to give desired product **14** (106.0 mg, 74% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.1 Hz, 3H), 1.38−1.74 (m, 7H), 2.47 (ddd, J = 12.7, 8.7, 5.5 Hz, 1H), 2.58−2.73 (m, 1H), 3.04−3.18 (m, 2H), 4.29 (ddt, J = 10.8, 7.7, 5.5 Hz, 1H), 5.29 (t, J = 6.2 Hz, 1H), 7.70−7.80 (m, 2H), 7.84−7.92 (m,1H), 8.10−8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 22.4, 29.3, 34.8, 35.8, 37.2, 43.5, 78.2, 125.4, 131.0, 132.8, 133.5, 133.6, 148.0, 179.4; IR (neat) 3327, 2936, 1758, 1539, 1340, 1163, 1080 cm^{-1}; $[\alpha]_D^{19}$ = +6.5 (*c* 1.5, $CHCl_3$, (*S*)); MS (ESI) calcd for $C_{15}H_{21}N_2O_6S$ $[M + H]^+$ 357.1115, found 357.1104.

*N,N-Bis{4-[(2R,4S)-4-methyl-5-oxotetrahydrofuran-2-yl]butyl}-2-nitrobenzenesulfonamide (**15**).* To a solution of **14** (56.1 mg, 0.16 mmol), **13** (38.7 mg, 0.22 mmol), and Ph_3P (51.1 mg, 0.20 mmol) in toluene (0.94 mL) was added DEAD (2.2 M in toluene, 89 μL, 0.19 mmol) dropwise over 5 min at 0 °C. After the mixture was stirred at 60 °C for 3 h, it was filtreted through Celite and the organic layer was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent hexane/AcOEt = 1/1 to 2/5) to give desired product **15** (68.6 mg, 85% yield): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.1 Hz, 6H), 1.33−1.74 (m, 14H), 2.47 (ddd, J = 12.7, 8.7, 5.5 Hz, 2H), 2.59−2.73 (m, 2H), 3.21−

DOI: 10.1021/acs.joc.5b01497
J. Org. Chem. 2015, 80, 9132−9140

3.36 (m, 4H), 4.30 (ddt, J = 10.7, 7.4, 5.3 Hz, 2H), 7.58−7.66 (m, 1H), 7.66−7.74 (m, 2H), 7.97−8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9 (2C), 22.4 (2C), 27.8 (2C), 34.8 (2C), 35.7 (2C), 37.1 (2C), 47.1 (2C), 78.2 (2C), 124.0, 130.4, 131.6, 133.2, 133.5, 147.8, 179.4 (2C); IR (neat) 2936, 1760, 1543, 1345, 1160, 997 cm^{-1}; $[\alpha]_D^{19}$ = +22.5 (c 0.9, $CHCl_3$, (S)); MS (ESI) calcd for $C_{24}H_{35}N_2O_8S$ $[M + H]^+$ 511.2109, found 511.2098.

(+)-Dubiusamine C. To a solution of **15** (57.9 mg, 0.11 mmol) and K_2CO_3 (30.1 mg, 2.2 mmol) in a mixture of MeCN (159 μL) and DMF (119 μL) was added PhSH (14.5 μL, 0.14 mmol) at room temperature. After the mixture was stirred at room temperature for 2 h, it was filtered through Celite and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent $CHCl_3$/MeOH/Et_3N = 100/10/1) to give (+)-dubiusamine C (35.0 mg, 95% yield): white solid, mp 83.0−83.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.3 Hz, 6H), 1.30−1.58 (m, 11H), 1.58−1.69 (m, 2H), 1.69−1.81 (m, 2H), 2.49 (ddd, J = 12.8, 8.7, 5.5 Hz, 2H), 2.61 (t, J = 6.8 Hz, 4H), 2.60−2.74 (m, 2H), 4.34 (ddt, J = 10.6, 7.6, 5.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1 (2C), 23.2 (2C), 29.8 (2C), 35.4 (2C), 35.9 (2C), 37.3 (2C), 49.7 (2C), 78.5 (2C), 179.5 (2C); IR (neat) 3311, 2926, 1762, 1456, 1353, 1193, 987 cm^{-1}; $[\alpha]_D^{18}$ = +28.8 (c 1.1, $CHCl_3$, (S)); MS (ESI) calcd for $C_{18}H_{32}NO_4$ $[M + H]^+$ 326.2326, found 326.2312.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01497.

^{1}H and ^{13}C NMR spectra of compounds in the diastereoselective bromolactonization and asymmetric total synthesis of (+)-dubiusamine C (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support in the form of a Grant-in-Aid for Scientific Research (20550033) from the Ministry of Education, Culture, Sports, Science and Technology in Japan (K.M.) and the Naito Foundation in Japan (K.M.) is gratefully acknowledged.

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