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Synthetic Methods

Direct Synthesis of Benzofuro[2,3-*b*]pyrroles through a Radical Addition/[3,3]-Sigmatropic Rearrangement/Cyclization/Lactamization Cascade

Masafumi Ueda, Yuta Ito, Yuki Ichii, Maiko Kakiuchi, Hiroko Shono, and Okiko Miyata*[a]

Abstract: A straightforward synthetic method for the construction of benzofuro[2,3-*b*]pyrrol-2-ones by a novel domino reaction through a radical addition/[3,3]-sigmatropic rearrangement/cyclization/lactamization cascade has been developed. The domino reaction of *O*-phenyl-conjugated oxime ether with an alkyl radical allows the construction of two heterocycles with three stereogenic centers as a result of the formation of two C–C bonds, a C–O bond, and a C–N bond in a single operation, leading to pyrrolidine-fused dihydrobenzofurans, which are not easily accessible by existing synthetic methods. Furthermore, asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-one derivatives through a diastereoselective radical addition reaction to a chiral oxime ether was also developed.

Introduction

Indoline-fused dihydrobenzofurans are a core component of biologically active natural products such as the antitumor compound diazonamide A (Figure 1).[1] Accordingly, there is considerable interest from the synthetic community to access these molecules and evaluate their biological activities.[2,3] For purposes of further biological studies and investigation of structure–activity relationships aimed at designing new drugs, the pharmacophoric structural elements of diazonamide A and related structures need to be identified. For this purpose, establishing a conventional method for the synthesis of simplified analogues is highly desirable. Recently, Vincent[4] and Bisai[5] independently reported the stepwise synthesis of tetracyclic dihydrobenzofuro[2,3-*b*]indoles **1**.[6] The methods relied on the oxidative cyclization of 3-(2-hydroxyphenyl)indolines prepared by Freidel–Crafts reaction of indoles or oxindoles with phenol, and are similar to typical synthetic protocols for tricyclic tetrahydrofuro[2,3-*b*]indoles **2**.[7] Tetrahydrobenzofuro[2,3-*b*]pyrroles **3** are unique skeletons, but efficient routes for their synthesis are relatively unknown. Current approaches to their synthesis involve radical annulation of *N*-chlorosulfonamide with benzofuran,[8] cycloaddition of dichloroketene with sulfilimine,[9] cyclization of nitrone,[10] and skeletal rearrangement of benzoxazine[11] and chromen-2-one.[12] However, these strategies are limited by the requirement for functionalized starting materials, making it more difficult to achieve diversified structures. Development of straightforward, flexible, and general synthetic methods of this structural moiety from a relatively simple substrate is therefore highly desirable.

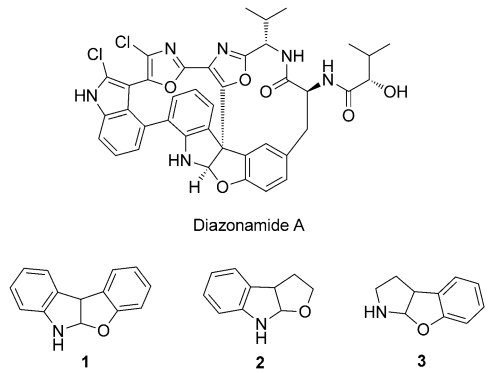

Figure 1. Pyrrolidine-fused dihydrobenzofurans and tetrahydrofuran.

For the synthesis of the benzofuro[2,3-*b*]pyrrole skeleton, we decided to employ a [3,3]-sigmatropic rearrangement of *O*-aryl-*N*-vinyl hydroxylamine, which is a potential approach to benzofurans from an *O*-aryl oxime ether developed by Sheradsky in 1966 and closely parallels the Fischer indole synthesis.[13] Although the Sheradsky reaction has considerable value for its operational simplicity, a significant drawback of the method is that strongly acidic conditions at high temperature are generally required for the isomerization of oxime ether **4** to enamine **A** and [3,3]-sigmatropic rearrangement (Scheme 1 a).[14] Because of the acidic conditions, elimination of the ammonium group usually occurs to give the aromatized benzofuran **5**. For purposes of synthesizing 2-aminobenzofuran and from the perspective of atom economy, the loss of the amino group is a serious disadvantage.[15] To address this problem, we reasoned that the generation of a highly reactive enamine under

[a] *Dr. M. Ueda, Y. Ito, Y. Ichii, M. Kakiuchi, H. Shono, Prof. Dr. O. Miyata*
Kobe Pharmaceutical University
Motoyamakita, Higashinada, Kobe 658-8558 (Japan)
Fax: (+81)78-441-7554
E-mail: miyata@kobepharma-u.ac.jp

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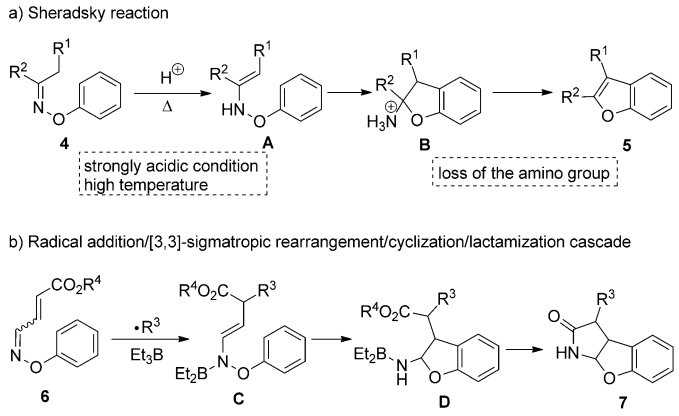


Scheme 1. Strategies for benzofuran synthesis.

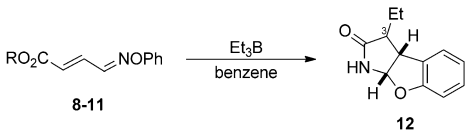
neutral and mild conditions would provide a dihydrobenzofuran bearing an aminal moiety. We focused our attention on *N*-aryloxy-*N*-boryl enamine **C** as a reactive intermediate, which is generated by triethylborane-mediated radical addition to a conjugated oxime ether (Scheme 1 b).[16]

We envisaged that the regioselective intermolecular alkyl radical addition to the conjugated oxime ether **6** bearing an ester gave *N*-boryl enamine **C**, which would spontaneously undergo [3,3]-sigmatropic rearrangement and cyclization to generate 2-borylaminodihydrobenzofuran **D**. Because **D** has a highly nucleophilic amine moiety, undesired elimination is inhibited and thus lactamization would proceed effectively to produce tetrahydrobenzofuro[2,3-*b*]pyrrol-2-one **7**. The domino-type sequential reaction involving radical, concerted, and ionic reactions represents a novel cascade reaction.[17] Domino reactions are transformations that allow for complex molecules to be constructed from a simple substrate in one operation in a straightforward, efficient, and elegant way without isolation of intermediates.[18] Consequently, the development of a new type of domino reaction is of great importance to the field of synthetic chemistry. Herein, we report the direct synthesis of benzofuro[2,3-*b*]pyrrol-2-ones from a conjugated oxime ether by a domino reaction through the generation of *N*-borylenamine as a reactive intermediate.

Results and Discussion

We initiated our investigation with the *O*-phenyl-conjugated oxime ether **8** containing an ethoxycarbonyl group (Table 1). Treatment of **8** with triethylborane as an ethyl radical source in benzene at room temperature did not afford the desired product and a complex mixture was obtained probably because of unsuitable conditions for rearrangement and lactamization (entry 1). In the presence of trimethylaluminum, the reaction did afford the desired *cis*-fused tricyclic compound **12**, benzofuro[2,3-*b*]pyrrol-2-one, as a 1:1 mixture of diastereomers at the C3-position, which were easily separated by preparative TLC (entry 2). The reaction temperature played a significant role in this process, thus, improvement of chemical yield was observed in benzene at reflux (entries 3 and 4). Examination of

Table 1. Optimization studies for the formation of benzofuro[2,3-*b*]pyrrol-2-one **12**.[a]



8-11 → 12

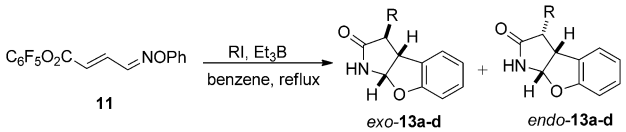
	Substrate	Additive[b]	*T*	Yield [%]
1	**8** (R = Et)	–	RT	n.d.[d]
2	**8** (R = Et)	Me_3Al	RT	50
3	**8** (R = Et)	Me_3Al	reflux	64
4[c]	**8** (R = Et)	Me_3Al	reflux	49
5	**9** (R = Ph)	Me_3Al	reflux	73
6	**10** ($R = C_6Cl_5$)	Me_3Al	reflux	67
7	**11** ($R = C_6F_5$)	Me_3Al	reflux	88
8	**11** ($R = C_6F_5$)	Me_3Al	RT	75
9	**11** ($R = C_6F_5$)	–	reflux	81
10	**11** ($R = C_6F_5$)	–	RT	95

[a] Reaction conditions: **8**–**11** (0.2 mmol) and Et_3B (1.0 mmol) for 1–2 h. Ratio of stereoisomer: *endo*/*exo* = 1:1. [b] With 2.4 equiv of Me_3Al. [c] Toluene was used as a solvent. [d] n.d. = not detected.

the effect of the ester moiety on the reaction revealed that the yield was improved by changing from an ethyl ester to phenyl esters (**9** and **10**, entries 5 and 6). Furthermore, the pentafluorophenyl ester **11** was found to be the most effective substrate and gave **12** in 88% yield (entry 7). It is worth noting that the domino reaction of **11** proceeded even in the absence of trimethylaluminum at room temperature to furnish the benzofuro[2,3-*b*]pyrrol-2-one **12** in high yield (entry 10). The pentafluorophenoxy group enhanced not only the lactamization reaction but also the reactivity toward the nucleophilic ethyl radical. To the best of our knowledge, this reaction represents the first reported example of [3,3]-sigmatropic rearrangement of an *N*-aryloxy-*N*-borylenamine generated through a radical process.

To investigate the molecular diversity of this transformation, we next examined the reaction in the presence of a range of alkyl iodides as carbon radical precursors (Table 2). When **11** was treated with ethyl iodoacetate and triethylborane in reflux-

Table 2. Domino reaction with various alkyl iodides.[a]



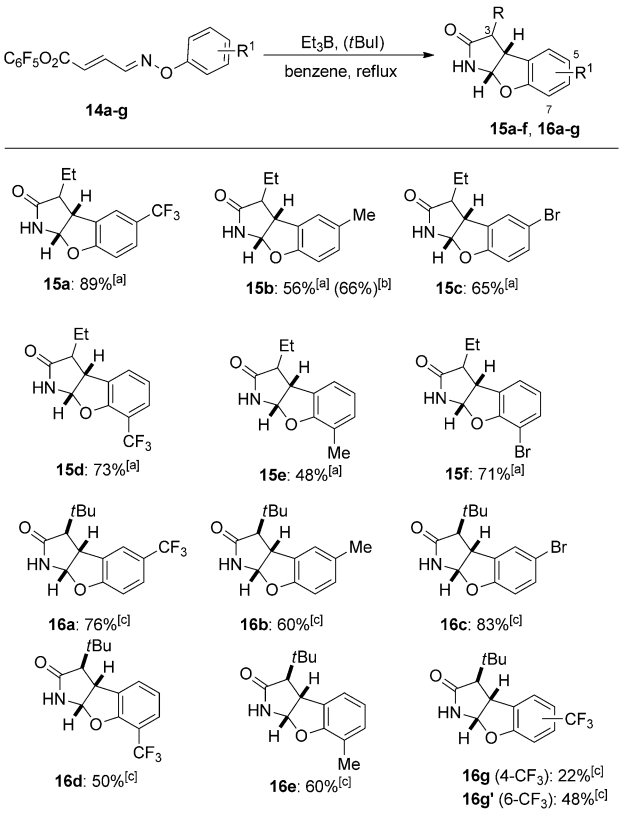
11 → *exo*-**13a-d** + *endo*-**13a-d**

	RI	Product	Yield [%]	Selectivity (*exo*:*endo*)
1	EtO_2CCH_2I	**13a**	67	1:1
2	*i*PrI	**13b**	81	2:1
3	*c*-C_5H_9I	**13c**	62	2:1
4	*t*BuI	**13d**	66	>10:1
5[b]	*t*BuI	**13d**	98	>10:1

[a] Reaction conditions: **11** (0.2 mmol), RI (12 mmol) and Et_3B (1.0 mmol) for 1 h. [b] With 3.5 equiv of $Na_2S_2O_3$.

ing benzene,[19] the expected domino reaction proceeded to give **13a**, which has an ester functionality (entry 1). Interestingly, employment of secondary alkyl radicals, such as isopropyl and cycloalkyl, increased the stereoselectivity of the reaction (entries 2 and 3). It should be noted that the reaction with the *tert*-butyl radical proceeded stereoselectively to afford *exo*-**13d** as a sole stereoisomer, albeit in relatively low yield because of the instability of the product **13d** under the reaction conditions (entry 4). Indeed, treatment of the isolated **13d** with *t*BuI and Et_3B in benzene at reflux led to decomposition by I_2 generated from *t*BuI. Therefore, the reaction was carried out in the presence of sodium thiosulfate as an iodine scavenger[20] and as expected, an excellent chemical yield and stereoselectivity was observed (entry 5).

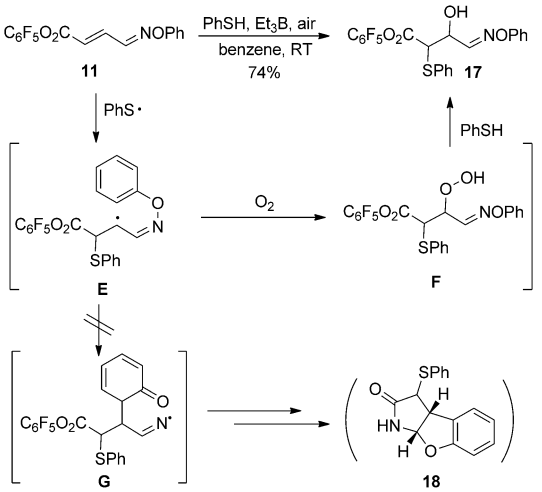
We then proceeded to investigate the substituent effect on the phenyl group, first with respect to the domino reaction initiated by ethyl radical addition (Scheme 2). The substrate bearing a trifluoromethyl group at the *para*-position afforded 5-trifluoromethylbenzofuropyrrole **15a** in 89% yield. A slightly lower yield was observed for product **15b** with a methyl group as an electron-donating substituent. Interestingly, running the reaction in the presence of Me_3Al improved the chemical yield (**15b**). Notably, a bromo group was tolerated



Scheme 2. Substituent effect. [a] Reaction conditions: **14a–f** (0.2 mmol), Et_3B (1.0 mmol) and benzene at reflux for 1 h. Ratio of stereoisomer: 1:1. [b] In the presence of Me_3Al (0.48 mmol). [c] Reaction conditions: **14a–e, g** (0.2 mmol), *t*BuI (12 mmol), $Na_2S_2O_3$ (0.7 mmol), Et_3B (1.0 mmol) and benzene at reflux for 0.5 h. Ratio of stereoisomer: $>10:1$.

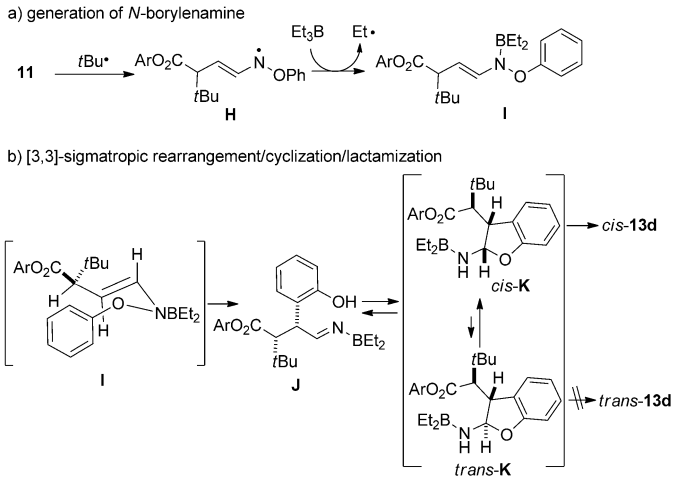
under these radical reaction conditions, thereby facilitating further transformation (**15c**). Although steric hindrance induced to the substrate by substituents at the *ortho*-position slightly affected the reaction, 7-substituted benzofuro[2,3-*b*]pyrrol-2-ones **15d–f** were obtained in moderate to good yields. To investigate the role of the substrate in the stereoselective synthesis of benzofuro[2,3-*b*]pyrrol-2-ones, a *tert*-butyl radical was employed for the domino reaction. As expected, 3-*tert*-butylbenzofuro[2,3-*b*]pyrrol-2-ones **16a–e** were obtained with excellent stereoselectivities, whereas the substrate bearing the trifluoromethyl group at the *meta*-position was converted to **16g** and **16g′** as regioisomers.

To gain an understanding of the rearrangement process, we investigated the reaction of the conjugated oxime ether **11** with a thiyl radical (Scheme 3). When **11** was treated with thiophenol and triethylborane under an air atmosphere, β-hydroxysulfide **17** was formed as the sole product instead of the expected benzofuro[2,3-*b*]pyrrol-2-one **18**. The hydroxysulfenylation proceeded via generation of the α-imino radical **E**, trapping with molecular oxygen, and reduction.[21] The result indicated that the α-imino radical **E** could not participate in the rearrangement process for the benzofuran synthesis, thus the [3.3]-sigmatropic rearrangement proceeded via *N*-borylenamine.

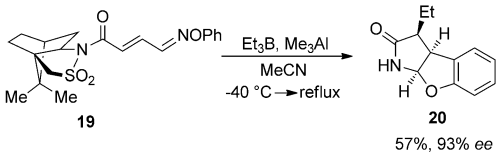


Scheme 3. Reaction of **11** with thiyl radical.

A possible reaction pathway that could account for the formation of **13d** is illustrated in Scheme 4. It involves the regioselective addition of a *tert*-butyl radical, generated from an ethyl radical and *t*BuI by means of an iodine-atom transfer, to a C–C double bond, generating an aminyl radical **H**, which is trapped by Et_3B to form *N*-borylenamine **I** (Scheme 4a). The *N*-boryl-*N*-phenoxyenamine **I** undergoes [3,3]-sigmatropic rearrangement via a six-membered transition state that minimizes the steric repulsion between the *tert*-butyl group and the phenyl group to eventually lead to the stereoselective formation of *syn*-α-arylimine **J** (Scheme 4b). Since the subsequent cyclization of **J** would be reversible, equilibrium exists between



Scheme 4. Reaction pathway.



Scheme 5. Asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-one.

cis- and *trans*-**K**. The irreversible lactamization pushes the equilibrium toward the formation of the sterically favored *cis*-fused tricyclic compound **13 d**.[22]

Finally, we demonstrated the asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-ones involving traceless cleavage of a chiral auxiliary (Scheme 5). The auxiliary of choice was Oppolzer's camphorsultam, because it had shown excellent stereoselectivity in our previous work on radical reactions.[16,23,24] Triethylborane was added to the solution of chiral conjugated oxime ether **19** and trimethylaluminum in acetonitrile at −40 °C and then the reaction mixture was warmed to reflux. In contrast to the reaction with pentafluorophenyl ester **11**, the *endo*-isomer **20** was predominately obtained in 57% yield with 93% *ee*, which confirmed the [3,3]-sigmatropic rearrangement would proceed thereby avoiding the steric interaction of the camphorsultam moiety with the phenyl group in a six-membered transition state.[25] Although the removal of a chiral auxiliary is generally tedious in a diastereoselective reaction, use of the domino reaction allows release of the chiral auxiliary.

Conclusion

We have established a straightforward synthetic method for the construction of benzofuro[2,3-*b*]pyrrol-2-ones by a novel domino reaction through a radical addition/[3,3]-sigmatropic rearrangement/cyclization/lactamization cascade. This domino reaction employs readily accessible starting material and allows the construction of two heterocycles with three stereogenic centers as a result of the formation of two C–C bonds, a C–O bond, and a C–N bond in a single operation, leading to pyrrolidine-fused dihydrobenzofurans which are not easily accessible from existing synthetic methods. Furthermore, asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-ones by means of a diastereoselective radical addition reaction to a chiral oxime ether was also developed. Clarification of the reaction mechanism, extension of this methodology to other heterocycles, and further study of the asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-ones are currently underway in our laboratory.

Experimental Section

General

NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) or 500 MHz/125 MHz (^{1}H NMR/^{13}C NMR) using Varian Gemini-300 (300 MHz), Varian MERCURY plus 300 (300 MHz), or Varian NMR system AS 500 (500 MHz) spectrometers. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants, and integration. IR spectra were obtained on a PerkinElmer SpectrumOne A spectrometer. High-resolution mass spectra were obtained by ESI methods on Thermo Fisher Scientific Exactive instrument. Melting points (uncorrected) were determined on a BÜCHI M-565 apparatus. Optical rotation was measured with a JASCO DIP-370 digital polarimeter. Preparative TLC separations (PTLC) were carried out on precoated silica gel plates (E. Merck 60F254). Medium-pressure column chromatography was performed using Lobar größe B (E. Merck 310–25, Lichroprep Si60). HPLC was performed on a Hitachi L-7100 liquid chromatograph coupled with a Hitachi L-7400 spectrophotometeric detector. *tert*-Butyl iodide was purified by column chromatography on Al_2O_3 prior to use. Unless otherwise stated, all the reagents and solvents were used as received from the manufacturer.

General procedure for domino reaction of conjugated oxime ether with ethyl radical

Et_3B (1.0 M in hexane, 1.0 mmol) was added to a solution of **11** (0.2 mmol) in benzene (5 mL) under an N_2 atmosphere at reflux. After being stirred for 1 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by PTLC (hexane/AcOEt = 1:2) to afford the corresponding benzofuro[2,3-*b*]pyrrol-2-one **12** and **15 a**–**f**.

Data for *exo*-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-12): White solid; m.p. 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.14 (m, 3H), 6.93 (dd, J = 8.0, 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.10 (d, J = 7.5 Hz, 1H), 3.83 (dd, J = 7.5, 3.0 Hz, 1H), 2.55–2.50 (m, 1H), 2.05–1.91 (m, 1H), 1.74–1.59 (m, 1H), 1.14 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7, 157.6, 129.2, 128.5, 124.6, 121.7, 110.4, 90.7, 50.0, 47.3, 25.4, 11.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{14}O_2N$ $[M+H]^+$: 204.1019; found: 204.1021.

Data for *endo*-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-12): White solid; m.p. 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.17 (m, 3H), 6.91 (dd, J = 8.0, 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.10 (d, J = 7.0 Hz, 1H), 4.26 (dd, J = 9.0, 7.0 Hz, 1H), 2.72 (td, J = 9.0, 5.0 Hz, 1H), 1.91–1.77 (m, 1H), 1.73–1.58 (m, 1H), 1.12 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.0, 158.3, 129.3, 126.5, 124.4, 121.1, 110.5, 90.0, 45.4,

45.2, 20.1, 12.8 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1713 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{14}O_2N$ $[M+H]^+$: 204.1019; found: 204.1013.

Data for *exo*-3-ethyl-5-trifluoromethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15a): White solid; m.p. 157–158 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.75$ (br s, 1H), 7.45 (d, $J=8.5$ Hz, 1H), 7.39 (s, 1H), 6.86 (d, $J=8.5$ Hz, 1H), 6.20 (d, $J=7.5$ Hz, 1H), 3.86 (dd, $J=7.5$, 3.0 Hz, 1H), 2.57–2.51 (m, 1H), 2.06–1.93 (m, 1H), 1.76–1.61 (m, 1H), 1.15 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=179.1$, 160.4 (d, $J=1.0$ Hz), 129.5, 127.1 (q, $J=4.0$ Hz), 124.2 (q, $J=270.0$ Hz), 124.1 (q, $J=32.0$ Hz), 122.0 (q, $J=4.0$ Hz), 110.5, 92.0, 50.0, 46.6, 25.2, 11.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=330$, 1719 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{13}O_2NF_3$ $[M+H]^+$: 272.0893; found: 272.0888.

Data for *endo*-3-ethyl-5-trifluoromethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15a): White solid; m.p. 192–193 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.49$ (d, $J=8.5$ Hz, 1H), 7.46 (s, 1H), 7.10 (br s, 1H), 6.89 (d, $J=8.5$ Hz, 1H), 6.20 (d, $J=7.0$ Hz, 1H), 4.30 (dd, $J=9.0$, 7.0 Hz, 1H), 2.75 (td, $J=9.0$, 5.5 Hz, 1H), 1.88–1.74 (m, 1H), 1.69–1.54 (m, 1H), 1.12 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.6$, 161.1, 127.3 (q, $J=4.0$ Hz), 125.5, 124.2 (q, $J=270.0$ Hz), 123.7 (q, $J=32.0$ Hz), 123.7 (q, $J=3.5$ Hz), 110.6, 91.0, 45.0, 44.9, 20.4, 12.6 ppm; IR ($CHCl_3$): $<$Gñ$=$ 3431, 1720 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{13}O_2NF_3$ $[M+H]^+$: 272.0893; found: 272.0889.

Data for *exo*-3-ethyl-1,3,3a,8a-tetrahydro-5-methyl-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15b): White solid; m.p. 161–163 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=6.98$–6.95 (m, 3H), 6.69 (d, $J=8.5$ Hz, 1H), 6.08 (d, $J=7.5$ Hz, 1H), 3.79 (dd, $J=7.5$, 3.0 Hz, 1H), 2.54–2.49 (m, 1H), 2.29 (s, 3H), 2.02–1.90 (m, 1H), 1.73–1.58 (m, 1H), 1.14 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 178.9, 155.5, 131.1, 129.6, 128.5, 125.0, 109.9, 90.9, 50.1, 47.3, 25.3, 20.8, 11.5 ppm; IR ($CHCl_3$): $\tilde{\nu}=3430$, 1713 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1171.

Data for *endo*-3-ethyl-1,3,3a,8a-tetrahydro-5-methyl-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15b): White solid; m.p. 171–172 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.01$–6.97 (m, 3H), 6.70 (d, $J=8.0$ Hz, 1H), 6.07 (d, $J=7.0$ Hz, 1H), 4.21 (dd, $J=9.0$, 7.0 Hz, 1H), 2.69 (td, $J=9.0$, 5.0 Hz, 1H), 2.29 (s, 3H), 1.90–1.76 (m, 1H), 1.74–1.59 (m, 1H), 1.13 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.9$, 156.2, 130.4, 129.7, 126.9, 124.4, 110.0, 90.0, 45.4, 45.3, 20.9, 20.1, 12.8 ppm; IR ($CHCl_3$):$\tilde{\nu}=3432$, 1714 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1171.

Data for *exo*-5-bromo-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15c): White solid; m.p. 157–158 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.28$ (d, $J=8.5$ Hz, 1H), 7.26 (s, 1H), 6.70 (d, $J=8.5$ Hz, 1H), 6.42 (br s, 1H), 6.12 (d, $J=7.5$ Hz, 1H), 3.84 (dd, $J=7.5$, 3.0 Hz, 1H), 2.53–2.48 (m, 1H), 2.04–1.90 (m, 1H), 1.73–1.57 (m, 1H), 1.14 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.5$, 156.9, 132.1, 131.0, 127.6, 113.4, 112.0, 91.4, 49.9, 47.1, 25.3, 11.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1717 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{13}O_2N^{79}Br$ $[M+H]^+$: 282.0124; found: 282.0119.

Data for *endo*-5-bromo-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15c): White solid; m.p. 197–198 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.32$–7.29 (m, 2H), 6.96 (br s, 1H), 6.71 (dd, $J=9.0$ Hz, 1H), 6.12 (d, $J=7.5$ Hz, 1H), 4.25 (dd, $J=9.0$, 7.5 Hz, 1H), 2.71 (td, $J=9.0$, 5.0 Hz, 1H), 1.90–1.56 (m, 2H), 1.12 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.4$, 157.6, 132.3, 129.3, 126.9, 113.0, 112.1, 90.5, 45.3, 45.1, 20.3, 12.8 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1718 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{13}O_2N^{79}Br$ $[M+H]^+$: 282.0124; found: 282.0120.

Data for *exo*-3-ethyl-7-trifluoromethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15d): White solid; m.p. 186–187 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.42$ (d, $J=8.0$ Hz, 1H), 7.33 (d, $J=7.5$ Hz, 1H), 7.01 (dd, $J=8.0$, 7.5 Hz, 1H), 6.65 (br s, 1H), 6.25 (dd, $J=7.5$, 1.5 Hz, 1H), 3.87 (dd, $J=7.5$, 3.0 Hz, 1H), 2.52 (m, 1H), 2.07–1.93 (m, 1H), 1.76–1.63 (m, 1H), 1.15 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.4$, 155.0 (d, $J=2.5$ Hz), 130.8, 128.2, 126.1 (q, $J=4.5$ Hz), 123.1 (q, $J=270.5$ Hz), 121.5, 113.6 (q, $J=33.0$ Hz), 92.2, 50.0, 46.6, 25.3, 11.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=3427$, 1718 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{13}O_2NF_3$ $[M+H]^+$: 272.0893; found: 272.0884.

Data for *endo*-3-ethyl-7-trifluoromethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15d): White powder; m.p. 203–204 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.45$ (d, $J=8.0$ Hz, 1H), 7.40 (d, $J=7.5$ Hz, 1H), 7.01 (dd, $J=8.0$, 7.5 Hz, 1H), 6.48 (br s, 1H), 6.25 (d, $J=7.0$ Hz, 1H), 4.31 (dd, $J=9.0$, 7.0 Hz, 1H), 2.75 (td, $J=9.0$, 5.0 Hz, 1H), 1.87–1.76 (m, 1H), 1.69–1.54 (m, 1H), 1.13 ppm (t, $J=7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.1$, 155.6, 130.1, 126.8, 126.3 (q, $J=4.5$ Hz), 123.1 (q, $J=270.0$ Hz), 121.0, 113.8 (q, $J=33.0$ Hz), 91.2, 45.0, 44.7, 20.3, 12.7 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1717 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{13}O_2NF_3$ $[M+H]^+$: 272.0893; found: 272.0888.

Data for *exo*-3-ethyl-1,3,3a,8a-tetrahydro-7-methyl-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15e): White powder; m.p. 170–172 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.01$–6.98 (m, 2H), 6.87 (br s, 1H), 6.84 (dd, $J=8.0$, 7.0 Hz, 1H), 6.10 (d, $J=7.0$ Hz, 1H), 3.84 (dd, $J=7.0$, 3.0 Hz, 1H), 2.54–2.49 (m, 1H), 2.20 (s, 3H), 2.05–1.91 (m, 1H), 1.73–1.58 (m, 1H), 1.14 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.9$, 156.1, 130.3, 127.8, 121.8, 121.6, 120.6, 90.4, 50.2, 47.6, 25.3, 15.2, 11.5 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1170.

Data for *endo*-3-ethyl-1,3,3a,8a-tetrahydro-7-methyl-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15e): White solid; m.p. 193–194 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.05$ (d, $J=7.5$ Hz, 1H), 7.02 (d, $J=8.0$ Hz, 1H), 6.82 (dd, $J=8.0$, 7.5 Hz, 1H), 6.74 (br s, 1H), 6.10 (d, $J=7.0$ Hz, 1H), 4.27 (dd, $J=9.0$, 7.0 Hz, 1H), 2.70 (td, $J=9.0$, 5.0 Hz, 1H), 2.19 (s, 3H), 1.90–1.58 (m, 2H), 1.12 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.7$, 156.7, 130.5, 123.8, 123.6, 121.0, 120.7, 89.5, 45.6, 45.4, 20.1, 15.2, 12.9 ppm; IR ($CHCl_3$): $\tilde{\nu}=$ 3431, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1178.

Data for *exo*-7-bromo-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-15f): White solid; m.p. 170–172 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.34$ (d, $J=8.0$ Hz, 1H), 7.09 (d, $J=7.5$ Hz, 1H), 7.00 (br s, 1H), 6.82 (dd, $J=8.0$, 7.5 Hz, 1H), 6.20 (d, $J=7.5$ Hz, 1H), 3.92 (dd, $J=7.5$, 2.5 Hz, 1H), 2.54–2.49 (m, 1H), 2.05–1.91 (m, 1H), 1.74–1.59 (m, 1H), 1.14 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.9$, 155.6, 132.7, 130.4, 124.0, 123.5, 103.8, 91.5, 50.4, 48.5, 25.7, 11.9 ppm; IR ($CHCl_3$): $\tilde{\nu}=3431$, 1716 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{13}O_2N^{79}Br$ $[M+H]^+$: 282.0124; found: 282.0119.

Data for *endo*-7-bromo-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-15f): White powder; m.p. 187–188 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.37$ (d, $J=8.0$ Hz, 1H), 7.16 (d, $J=8.0$ Hz, 1H), 6.82 (t, $J=8.0$ Hz, 1H), 6.45 (br s, 1H), 6.21 (d, $J=7.0$ Hz, 1H), 4.37 (dd, $J=9.0$, 7.0 Hz, 1H), 2.73 (td, $J=9.0$, 5.5 Hz, 1H), 1.89–1.75 (m, 1H), 1.70–1.55 (m, 1H), 1.12 ppm (t, $J=7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.1$, 155.7, 132.5, 125.9, 125.4, 122.5, 103.6, 90.2, 46.2, 45.1, 20.2, 12.8 ppm; IR ($CHCl_3$): $\tilde{\nu}=$ 3431, 1718 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{12}H_{13}O_2N^{79}Br$ $[M+H]^+$: 282.0124; found: 282.0120.

General procedure for domino reaction of conjugated oxime ether with RI

RI (12.0 mmol) and Et_3B (1.0 M in hexane, 1.0 mmol) were added to a solution of **11** (0.2 mmol) in benzene (5 mL) under an N_2 atmosphere at reflux. After being stirred for 1 h, the reaction mixture was diluted with H_2O extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by PTLC (hexane/AcOEt = 1:2) to afford the corresponding benzofuro[2,3-*b*]pyrrol-2-one **13a–c**.

Data for *exo*-1,2,3a,8a-tetrahydro-2-oxo-3*H*-benzofuro[2,3-*b*]pyrrole-3-acetic acid ethyl ester (*exo*-13a): Colorless crystals; m.p. 151–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 7.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.10 (br s, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.15 (d, J = 7.0 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 3.96 (dd, J = 7.0, 3.0 Hz, 1H), 3.00–2.90 (m, 2H), 2.76–2.66 (m, 1H), 1.31 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 171.4, 157.6, 129.4, 128.1, 125.0, 121.8, 110.3, 90.8, 61.1, 47.6, 45.0, 36.0, 14.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1725 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{14}H_{16}O_4N$ $[M+H]^+$: 262.1074; found: 262.1081.

Data for *endo*-1,2,3a,8a-tetrahydro-2-oxo-3*H*-benzofuro[2,3-*b*]pyrrole-3-acetic acid ethyl ester (*endo*-13a): Colorless crystals; m.p. 151–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.79 (br s, 1H), 6.17 (d, J = 7.0 Hz, 1H), 4.43 (dd, J = 9.5, 7.0 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.34 (ddd, J = 10.5, 9.5, 3.5 Hz, 1H), 2.92 (dd, J = 18.0, 3.5 Hz, 1H), 2.48 (dd, J = 18.0, 10.5 Hz, 1H), 1.29 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.9, 172.2, 158.3, 129.5, 126.1, 123.9, 121.1, 110.5, 90.3, 61.0, 44.9, 40.3, 32.3, 14.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1721 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{14}H_{16}O_4N$ $[M+H]^+$: 262.1074; found: 262.1069.

Data for *exo*-1,3,3a,8a-tetrahydro-3-(1-methylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-13b): White solid; m.p. 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (dd, J = 8.0, 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.00 (br s, 1H), 6.93 (dd, J = 8.0, 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.06 (d, J = 7.5 Hz, 1H), 3.87 (dd, J = 7.5, 3.0 Hz, 1H), 2.56 (dd, J = 4.0, 3.0 Hz, 1H), 2.39–2.28 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 0.97 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 157.6, 129.1, 128.8, 124.5, 121.7, 110.4, 90.9, 55.1, 43.6, 29.1, 20.7, 17.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1167.

Data for *endo*-1,3,3a,8a-tetrahydro-3-(1-methylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*endo*-13b): White solid; m.p. 194–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 8.0, 7.5 Hz, 1H), 6.92 (dd, J = 8.0, 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.34 (br s, 1H), 6.07 (dd, J = 7.5, 1.5 Hz, 1H), 4.25 (dd, J = 10.0, 7.5 Hz, 1H), 2.66 (dd, J = 10.0, 5.0 Hz, 1H), 2.11–2.05 (m, 1H), 1.22 (d, J = 6.5 Hz, 3H), 0.71 ppm (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 158.9, 129.4, 126.4, 124.8, 121.1, 110.1, 89.9, 48.2, 45.5, 27.0, 23.2, 17.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1713 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$: 218.1176; found: 218.1168.

Data for *exo*-3-cyclopentyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro-[2,3-*b*]pyrrol-2-one (*exo*-13c): White solid; m.p. 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.12 (m, 3H), 6.92 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.08 (d, J = 7.5 Hz, 1H), 3.85 (dd, J = 7.5, 2.5 Hz, 1H), 2.63 (dd, J = 6.5, 2.5 Hz, 1H), 2.37–2.24 (m, 1H), 2.03–1.43 (m, 7H), 1.34–1.22 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4, 157.6, 129.2, 128.6, 124.6, 121.7, 110.4, 90.8, 52.2, 45.8, 41.9, 30.5, 29.3, 25.2, 25.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1713 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{15}H_{18}O_2N$ $[M+H]^+$: 244.1332; found: 244.1328.

Data for *endo*-3-cyclopentyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro-[2,3-*b*]pyrrol-2-one (*endo*-13c): White solid; m.p. 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 8.0, 7.5 Hz, 1H), 6.91 (dd, J = 8.0, 7.5 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.55 (br s, 1H), 6.06 (d, J = 7.5 Hz, 1H), 4.22 (dd, J = 9.0, 7.5 Hz, 1H), 2.81 (dd, J = 9.0, 7.0 Hz, 1H), 2.20–2.09 (m, 1H), 1.99–1.89 (m, 1H), 1.83–1.22 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 158.7, 129.4, 126.5, 125.1, 121.1, 110.3, 89.7, 47.2, 46.2, 38.1, 32.7, 29.1, 25.7, 24.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 1713 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{15}H_{18}O_2N$ $[M+H]^+$: 244.1332; found: 244.1329.

General procedure for domino reaction of conjugated oxime ether with *t*BuI

*t*BuI (12.0 mmol) and Et_3B (1.0 M in hexane, 1.0 mmol) were added to a solution of **11** (0.2 mmol) and $Na_2S_2O_3$ (0.7 mmol) in benzene (5 mL) under an N_2 atmosphere at reflux. After being stirred for 30 min, the reaction mixture was diluted with 10% $Na_2S_2O_3$ solution and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by PTLC (hexane/AcOEt = 1:2) to afford the corresponding benzofuro[2,3-*b*]pyrrol-2-one **13d** and **16a–g**.

Data for *exo*-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-13d): White solid; m.p. 181–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (dd, J = 8.0, 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.94 (dd, J = 8.0, 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.52 (br s, 1H), 6.03 (d, J = 7.0 Hz, 1H), 3.97 (dd, J = 7.0, 2.5 Hz, 1H), 2.36 (d, J = 2.5 Hz, 1H), 1.15 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 157.5, 129.2, 128.9, 124.6, 121.8, 110.4, 90.3, 58.9, 45.3, 33.4, 27.6 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{14}H_{18}O_2N$ $[M+H]^+$: 232.1332; found: 232.1324.

Data for *exo*-5-trifluoromethyl-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16a): White solid; m.p. 224–225 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 6.88 (br s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.12 (d, J = 7.0 Hz, 1H), 3.99 (dd, J = 7.0, 2.5 Hz, 1H), 2.36 (d, J = 2.5 Hz, 1H), 1.16 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 160.3, 129.9, 127.1 (q, J = 4.0 Hz), 124.3 (q, J = 32.5 Hz), 124.2 (q, J = 270.0 Hz), 122.0 (q, J = 4.0 Hz), 110.5, 91.4, 58.7, 44.7, 33.5, 27.5 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 1712 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{15}H_{17}O_2NF_3$ $[M+H]^+$: 300.1206; found: 300.1206.

Data for *exo*-1,3,3a,8a-tetrahydro-5-methyl-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16b): White solid; m.p. 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H), 6.86 (br s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.00 (d, J = 7.0 Hz, 1H), 3.91 (dd, J = 7.0, 2.5 Hz, 1H), 2.35 (d, J = 2.5 Hz, 1H), 2.29 (s, 3H), 1.15 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 155.3, 131.1, 129.5, 128.8, 125.0, 109.9, 90.5, 58.9, 45.2, 33.4, 27.6 (3C), 20.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 1705 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{15}H_{20}O_2N$ $[M+H]^+$: 246.1489; found: 246.1492.

Data for *exo*-5-bromo-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16c): White solid; m.p. 215–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (dd, J = 8.5, 2.0 Hz, 1H), 7.21 (s, 1H), 7.12 (br s, 1H), 6.67 (d, J = 8.5 Hz, 1H), 6.04 (d, J = 7.5 Hz, 1H), 3.93 (dd, J = 7.5, 2.5 Hz, 1H), 2.33 (d, J = 2.5 Hz, 1H), 1.14 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 156.8, 132.0, 131.4, 127.5, 113.4, 112.0, 91.1, 58.7, 45.0, 33.4, 27.5 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 1710 cm^{-1}; ESI-HRMS: *m/z* calcd for $C_{14}H_{17}O_2N^{79}Br$ $[M+H]^+$: 310.0437; found: 310.0444.

Data for *exo*-7-trifluoromethyl-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16d): White solid; m.p. 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J =

8.0 Hz, 1H), 7.30 (d, J=7.5 Hz, 1H), 7.01 (dd, J=8.0, 7.5 Hz, 1H), 6.66 (br s, 1H), 6.17 (d, J=7.0 Hz, 1H), 3.99 (dd, J=7.0, 3.0 Hz, 1H), 2.35 (d, J=3.0 Hz, 1H), 1.16 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=176.7, 154.8, 131.2, 128.2, 126.0 (q, J=4.5 Hz), 123.1 (q, J=270.0 Hz), 121.5, 113.6 (q, J=33.0 Hz), 91.7, 58.7, 44.5, 33.5, 27.5 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$=3427, 1710 cm^{-1}; ESI-HRMS: m/z calcd for $C_{15}H_{17}O_2NF_3$ $[M+H]^+$: 300.1206; found: 300.1204.

Data for *exo*-1,3,3a,8a-tetrahydro-7-methyl-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16e): White solid; m.p. 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99–6.94 (m, 3H), 6.83 (t, J=7.5 Hz, 1H), 6.01 (d, J=7.0 Hz, 1H), 3.94 (dd, J=7.0, 2.5 Hz, 1H), 2.34 (d, J=2.5 Hz, 1H), 2.19 (s, 3H), 1.14 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.6, 155.9, 130.2, 128.1, 121.8, 121.6, 120.5, 90.1, 59.0, 45.4, 33.3, 27.6 (3C), 15.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$=3431, 1705 cm^{-1}; ESI-HRMS: m/z calcd for $C_{15}H_{20}O_2N$ $[M+H]^+$: 246.1489; found: 246.1490.

Data for *exo*-4-(trifluoromethyl)-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16g): White solid; m.p. 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31 (dd, J=8.0, 7.5 Hz, 1H), 7.23 (d, J=7.5 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 6.66 (br s, 1H), 6.09 (d, J=6.5 Hz, 1H), 4.18 (d, J=6.5 Hz, 1H), 2.71 (s, 1H), 1.13 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=176.8, 158.6, 129.8, 127.8 (q, J=32.5 Hz), 125.7, 123.6 (q, J=271.0 Hz), 119.3 (q, J=5.0 Hz), 114.6, 90.9, 56.9, 46.4, 33.7, 27.7 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$=3431, 1710 cm^{-1}; ESI-HRMS: m/z calcd for$C_{15}H_{17}O_2NF_3$ $[M+H]^+$: 300.1206; found: 300.1199.

Data for *exo*-6-(trifluoromethyl)-1,3,3a,8a-tetrahydro-3-(1,1-dimethylethyl)-2*H*-benzofuro[2,3-*b*]pyrrol-2-one (*exo*-16g′): White solid; m.p. 172–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.21 (m, 2H), 7.08 (br s, 1H), 7.03 (s, 1H), 6.11 (d, J=7.0 Hz, 1H), 3.99 (dd, J=7.0, 3.0 Hz, 1H), 2.35 (d, J=3.0 Hz, 1H), 1.16 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.1, 157.9, 133.1 (d, J=1.0 Hz), 131.7 (q, J=32.0 Hz), 124.9, 123.8 (q, J=271.0 Hz), 118.8 (q, J=4.0 Hz), 107.6 (q, J=4.0 Hz), 91.2, 58.7, 44.9, 33.5, 27.5 ppm (3C); IR ($CHCl_3$): $\tilde{\nu}$=3431, 1710 cm^{-1}; ESI-HRMS: m/z calcd for $C_{15}H_{17}O_2NF_3$ $[M+H]^+$: 300.1206; found: 300.1200.

3-Hydroxy-4-(phenoxyimino)-2-(phenylthio)butanoic acid 2,3,4,5,6-pentafluorophenyl ester (17)

Thiophenol (77 mg, 0.7 mmol) and Et_3B (1.0 M in hexane, 0.1 mL, 0.1 mmol) were added to a solution of **11** (71 mg, 0.2 mmol) in benzene (5 mL) under an air atmosphere at room temperature. After being stirred for 18 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt=10:1) afforded **17** (72 mg, 74%) as a 1:2:5:10 mixture of stereoisomers. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.00 (d, J=5.0 Hz, 10/18H), 8.00 (d, J=4.0 Hz, 5/18H), 7.63–7.58 (m, 2H), 7.38–7.25 (m, 5H), 7.17–7.01 (m, 3H + 3/18H), 4.94–4.85 (m, 1H), 4.49 (d, J=3.5 Hz, 1/18H), 4.36 (d, J=7.0 Hz, 2/18H), 4.27 (d, J=7.0 Hz, 5/18H), 4.18 (d, J=8.0 Hz, 10/18H), 3.28 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.6, 158.8, 150.9, 150.7, 134.1, 134.0, 131.2, 130.9, 129.6, 129.5, 129.4 (2C), 129.3, 122.9, 122.8, 114.8, 114.5, 69.4, 68.5, 55.4, 54.3 ppm; IR (neat): $\tilde{\nu}$=3446, 1780 cm^{-1}; ESI-HRMS: m/z calcd for $C_{22}H_{15}O_4NF_5S$ $[M+H]^+$: 484.0636; found: 484.0638.

Asymmetric synthesis of benzofuro[2,3-*b*]pyrrol-2-one 20

Et_3B (1.0 M in hexane, 0.4 mL, 0.4 mmol) was added to a solution of **19** (78 mg, 0.2 mmol) in MeCN (5 mL) under an N_2 atmosphere at −40 °C. After being stirred for 1 h, Me_3Al (1.1 M in hexane, 0.65 mL, 0.72 mmol) was added dropwise and the resulting solution was warmed up to reflux. After being stirred for 2 h, the reaction mixture was diluted with Rochelle salt aqueous solution (1.0 M, 15 mL) and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by PTLC (hexane/AcOEt=1:2) to afford benzofuro-[2,3-*b*]pyrrol-2-one **20** (23 mg, 57%).

Data for (3*S*,3a*S*,8a*R*)-3-ethyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro-[2,3-*b*]pyrrol-2-one (20): $[\alpha]_D^{25}=-114.0$ (c=1.00 in $CHCl_3$, 93% *ee*); the enantiomeric purity was determined by HPLC analysis (Daicel CHIRALCEL OD-H, hexane/*i*PrOH=80:20, flow rate=1.0 mL min^{-1}, λ=254 nm, retention times: 9.77 min [minor] and 12.86 min [major]).

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Keywords: domino reaction · heterocycles · radical reactions · rearrangement · synthetic methods

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[25] The absolute configurations at the newly formed stereocenters were deduced by our previous results and NMR studies (see reference [17a]).

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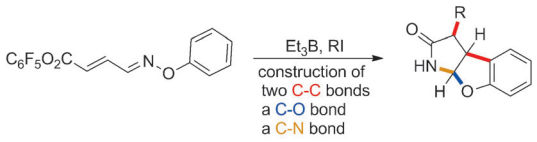
FULL PAPER



Straightforward, efficient, and elegant: Synthesis of benzofuro[2,3-*b*]pyrrol-2-ones from a conjugated oxime ether by a novel domino reaction through a radical addition/[3,3]-sigmatropic rearrangement/cyclization/lactamization cascade was developed. This domino reaction employing readily accessible starting material allows the construction of two heterocycles and three stereogenic centers as a result of the formation of two C–C bonds, a C–O bond and a C–N bond in a single operation.

Synthetic Methods

*M. Ueda, Y. Ito, Y. Ichii, M. Kakiuchi, H. Shono, O. Miyata**

■■ – ■■

Direct Synthesis of Benzofuro[2,3-*b*]pyrroles through a Radical Addition/[3,3]-Sigmatropic Rearrangement/Cyclization/Lactamization Cascade