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Efficient synthesis of CCR5 antagonist, 2,3-dihydro-1-benzothiepine derivatives by improved intramolecular Claisen type reaction using dialkylcarbonate

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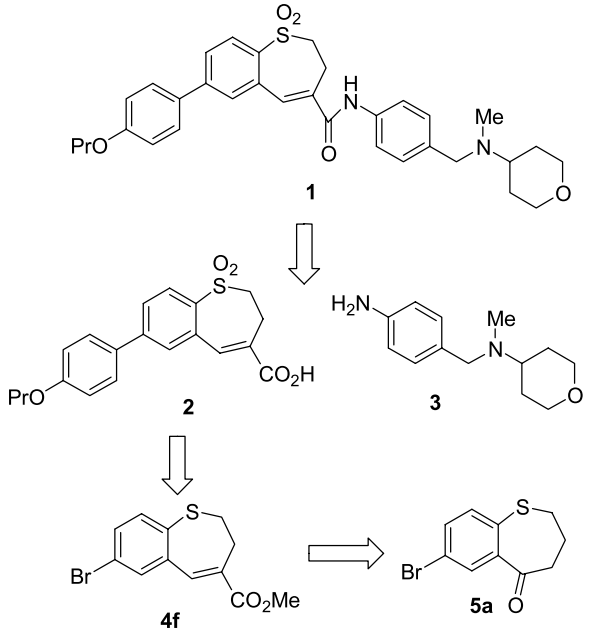
Abstract—The efficient synthesis of 2,3-dihydro-1-benzothiepine derivatives **4** has been developed. The intramolecular Claisen type reaction of the new products, 4-(*o*-formylphenylthio)butyrate **9**, with alcoholate in dialkylcarbonate as a solvent afforded **4** in good yields. According to this new procedure, we have accomplished the practical preparation of CCR5 antagonist **1** as a candidate for oral HIV-1 therapy.

1. Introduction

Recently, various small-molecular nonpeptide compounds have been reported as CC chemokine receptor 5 (CCR5) antagonist, because CCR5 was found to be a coreceptor for the entry of macrophage-tropic human immunodeficiency virus type 1 (HIV-1) into host cells.[1,2] Shiraishi et al. previously reported that TAK-779 as a CCR5 antagonist appeared to be a candidate for the therapy of HIV-1 infected individuals.[3] Furthermore, *N*-[4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxamide **1** showed CCR5 antagonistic activity when orally administered.[4] Hence, an efficient preparation of **1** on a large scale was required to support pharmacological and toxicological evaluations. In the early report,[4] the oxidation of 2,3-dihydro-1-benzothiepine **4f** with H_2O_2 followed by arylation and hydrolysis gave the acid **2**, which was amidated with the aniline **3** to provide the desired **1** (Scheme 1). For the preparation of 2,3-dihydro-1-benzothiepine **4**, there have been some syntheses based on the same generation (Scheme 2).[4,5] Compound **4** was led from β-oxo-ester **6** prepared from the ketone **5**. These methods via **6**, however, had some drawbacks, for example, the production of over-reduced compound **8** in the reduction of **7**, and the requirement of several processes to **4** from **5**. There were similar problems in the preparation of **4f** via β-oxo-ester. There has been no report of synthesis of **4** based on an other generation to the best of our knowledge. On the other hand, 2,3-dihydro-1-benzoxepine and 2,3-dihydro-1-benzazepine could be synthesized from the analogues of **9** with alcoholate according to the Claisen type reaction.[4,5a,6] The



Scheme 1.

Keywords: 2,3-Dihydro-1-benzothiepine; Claisen type condensation; Dialkylcarbonate; CCR5 antagonist.
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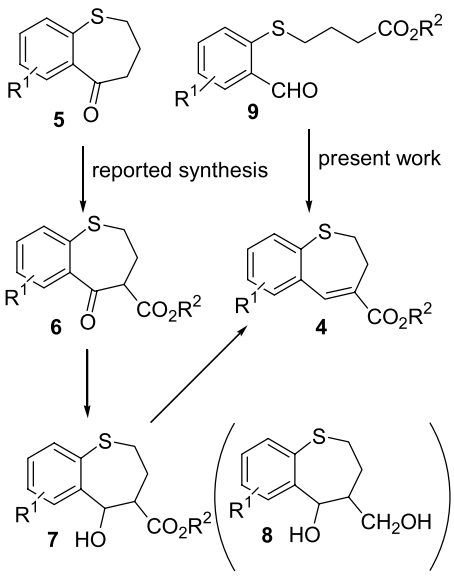


Scheme 2.

preparation of **4** from **9** attracted our interest regarding large-scale preparations because of its simple and wasteless protocol, even though the yields based on this generation were not sufficiently high. In this paper, we announce the facile and efficient synthesis of **4**, and the application for **1**.

2. Results and discussion

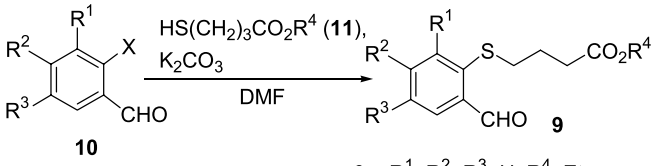
2.1. Development of new preparation of 2,3-dihydro-1-benzothiepines

We synthesized **9**, having various substituted groups, to develop a new synthetic procedure for **4**. The synthesis of new products **9a–e** was accomplished by thioalkylation of *o*-halogenobenzaldehyde **10** with 4-mercaptobutyrate **11**[7] and K_2CO_3 in DMF overnight at room temperature (Table 1), although there has been no report about the synthesis of **9**. Most thioalkylations of **10** gave **9** in good to excellent yields, while **10d** having an electron-donating group at the *p*-position of the halogen gave lower yields (entry 5).

To optimize the reaction conditions, the intramolecular cyclization of **9a** for producing **4a** was examined (Table 2). First, the conditions for synthesizing benzoxepines[5] were applied to the cyclization of **9a**. The treatment of **9a** was conducted with NaOEt in EtOH to give many products. After the workup, the chromatographic purification provided the desired **4a** in 27% yield and the hydrolyzed **12** in 18% yield (entry 1). The combinations of NaOEt and 1,2-dimethoxyethane (DME) or NaH and THF decreased the hydrolysis to increase the yields of **4a** (entries 2 and 3). However, these reactions could neither depress the production of impurities of which the structures were unknown, nor increase the total yields of cyclization (**4a**+**12**). It was thought that the value of pK_a at the α carbon of ester was insufficient for cyclization of **9a**, resulting in the production of impurities.[8] To decrease the value of pK_a, the reaction of **9a** was performed with the combination of NaOEt and diethylcarbonate as a solvent, which was converted to the malonate derivatives.[9] Surprisingly, this treatment made a breakthrough in the yield of cyclization, giving **4a** in 71% yield without detection of the malonate derivative and **12** (entry 4). For this reaction, 1.2 equiv of diethylcarbonate affected the cyclization to increase the yield of **4a** (entry 6 vs 1). Moreover, the same reaction of **9a** with NaOEt using ethyl formate as a solvent, expected to produce a similar effect, gave a slightly higher yield of **4a** than that using DME as a solvent (entry 2 vs 5).[10]

For research into the scope and limitation of the intramolecular Claisen type reaction, a variety of **9** reactions were next performed under the conditions of alcoholate/dialkylcarbonate (Table 3). The use of dimethylcarbonate

Table 1. Thioalkylation of *o*-halogenobenzaldehydes[a]

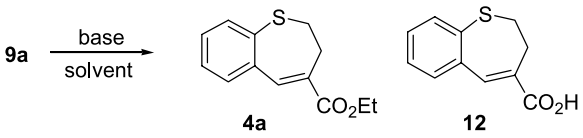


9a: R^1=R^2=R^3=H, R^4=Et
9b: R^1=R^2=R^3=H, R^4=Me
9c: R^1=R^2=H, R^3=Br, R^4=Et
9d: R^1=Cl, R^2=R^3=H, R^4=Et
9e: R^1=H, R^2=R^3=OMe, R^4=Et

Entry	Substrates		Yield (%)[b]
	10	**11**	
1	**10a** (R^1=R^2=R^3=H, X=F)	**11a** (R^4=Et)	**9a**: 67
2	**10a**	**11b** (R^4=Me)	**9b**: 95
3	**10b** (R^1=R^2=H, R^3=Br, X=F)	**11a**	**9c**: 78
4	**10c** (R^1=Cl, R^2=R^3=H, X=Cl)	**11a**	**9d**: 70
5	**10d** (R^1=R^2=H, R^3=OMe, X=Br)	**11a**	**9e**: 27

[a] *General procedure.* To a suspension of **10** (1.0 g, 1.0 equiv), K_2CO_3 (2.0 equiv) and DMF (3 v/w) was added **11** (2 equiv), and the whole suspension was stirred overnight at room temperature.
[b] Isolated yield.

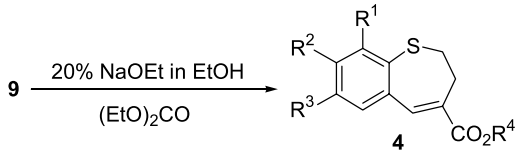
Table 2. Optimization of reaction conditions[a]



Entry	Solvent	Base	Conditions	Isolated yield (%)		
				9a	**4a**	**12**
1	EtOH	20% NaOEt in EtOH	rt, 3 h, then refluxed, 1 h	ND	27	18
2	DME	20% NaOEt in EtOH	rt, 45 min	ND	37	6
3	THF	NaH	rt, 1 h, then refluxed, 0.5 h	ND	44	6
4	$(EtO)_2CO$	20% NaOEt in EtOH	rt, 2 h	ND	71	ND
5	HCO_2Et	20% NaOEt in EtOH	rt, 4 h	26	58	ND
6	EtOH, $(EtO)_2CO$ (1.2 eqiv)	20% NaOEt in EtOH	rt, 3 h, then refluxed, 1 h	ND	53	4

[a] The mixture of **9a** (1.0 g, 1.0 equiv), base (1.2 equiv) and solvent (20 v/w) was reacted.

Table 3. The intramolecular Claisen type reaction[a]



Entry	Substrate	Time (h)	Isolated yield (%)
1[b]	**9b**	15	**4b** ($R^1=R^2=R^3=H$, $R^4=Me$): 71
2	**9c**	2	**4c** ($R^1=R^2=H$, $R^3=Br$, $R^4=Et$): 32
3	**9d**	7	**4d** ($R^1=Cl$, $R^2=R^3=H$, $R^4=Et$): 46
4	**9e**	6	**4e** ($R^1=H$, $R^2=R^3=OMe$, $R^4=Et$): 70

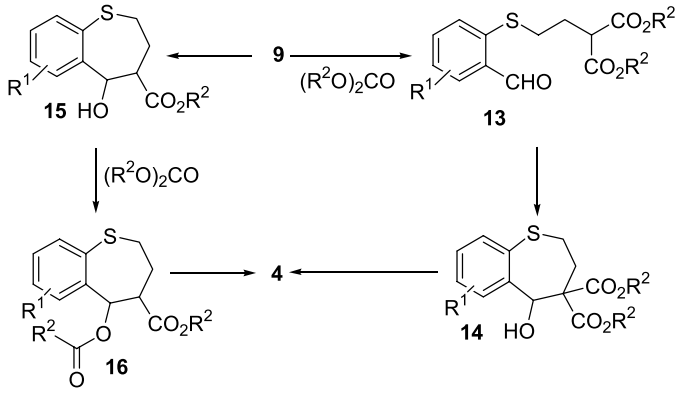
[a] To a solution of **9** (1.0 g) and diethyl carbonate (20 v/w) was added 20% NaOEt in EtOH (1.2 equiv), and the whole mixture was stirred at room temperature.
[b] 28% NaOMe in MeOH (1.2 equiv) and $(MeO)_2CO$ (20 mL) were used.

instead of diethylcarbonate as a solvent also affected the intramolecular condensation of **9b** to give **4b** in 71% yield (entry 1). The yields of **4** were decreased by the electron-withdrawing groups at the *o*- or *p*-position of thiobutyrate, while the treatment of **9e** having an electron donor group at the *p*-position of the sulfur atom afforded **4e** in 70% yield (entries 2, 3 and 4).

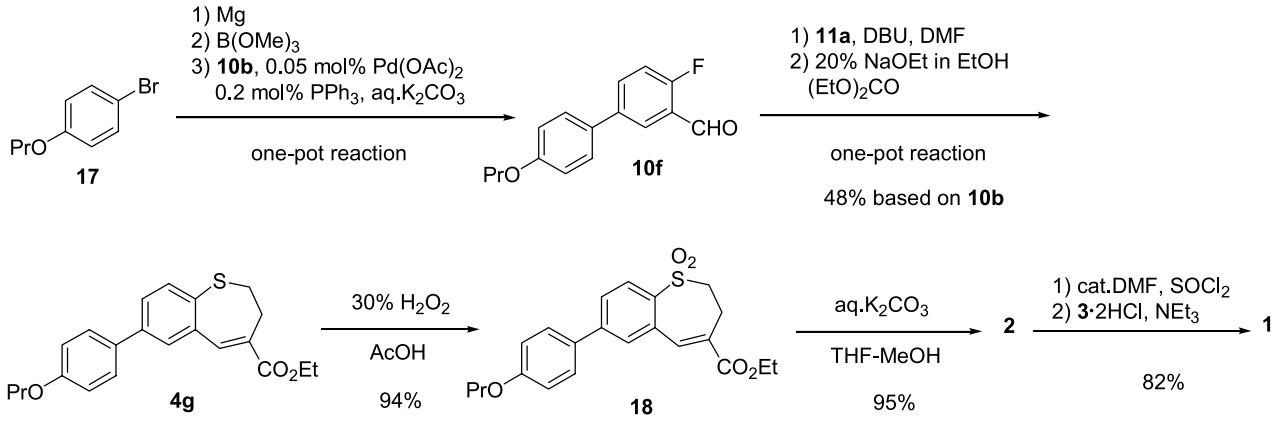
The reaction mechanism to **4** from **9** was not clear, although the addition of dialkylcarbonate was required for improvement in these reactions. We deduced that the treatment of **9** with alcoholate and dialkylcarbonate converted it to the malonate derivative **13**, which smoothly afforded the cyclization to give **4**. However, the role of dialkylcarbonate in the intramolecular cyclization also might be thought to the acceleration of dehydration of **16** (Scheme 3).

2.2. Large-scale preparation of 1 as a candidate for orally administered HIV-1 therapy

According to the new procedure for 2,3-dihydro-1-benzothiepines, we tried to develop a large-scale preparation of the desired **1** (Scheme 4). The biarylaldehyde **10f** was selected as an intermediate, because the intramolecular condensation of **9c** as a substrate afforded a lower yield, as mentioned. Although there were many syntheses of biaryl compounds, the preparation of **10f** was attempted using the convenient procedure of the Suzuki–Miyaura reaction in one-pot for large-scale preparation.[11,12] The treatment of **17** was conducted with magnesium in THF under the refluxing condition, followed by cooling to −10 °C and boronation with trimethoxyborane, which was reacted with **10b**, aqueous K_2CO_3, and a catalytic amount of $Pd(PPh_3)_4$ under the refluxing condition to give **10f** in excellent yield. The coupling reaction also proceeded smoothly when 0.05 mol% of $Pd(OAc)_2$ and 0.2 mol% of PPh_3 instead of $Pd(PPh_3)_4$ were employed. As a result, all reactions from the Grignard reaction of **17** to the cross-coupling reaction were performed in one-pot to give **10f** almost quantitatively. After workup followed by extraction and concentration, **10f** was used without further purification. The thioalkylation of crude **10f** with **11a** using K_2CO_3 in DMF as a base, followed



Scheme 3.



Scheme 4.

by cyclization with the combination of NaOEt in EtOH solution and diethyl carbonate at room temperature provided 1-benzothiepine **4g** in one-pot. However, it was difficult to adopt these conditions for a large-scale preparation, because the reaction time was unstable in the thioalkylation when the reaction was scaled up to multi-decade grams. It was thought that the thioalkylation of **10f** with **11a** proceeded heterogenously. The use of DBU instead of K_2CO_3 afforded a stable reaction time, because the salt was dissolved in DMF. The reactions to **4g** in two steps afforded 48% yield using only the crystallization procedure.

The preparation of **2** from **4g** was conducted using two methods. The hydrolysis of **4g** with 2 N NaOH gave carboxylic acid, which was oxidated with H_2O_2 in AcOH. However, the oxidation was not completed, giving **2** containing the sulfoxide. The oxidation from the sulfide **4g** to the sulfone **18** was accomplished in 94% yield by the reaction of 30% hydrogen peroxide in acetic acid. The sulfone **18** was hydrolyzed with aqueous K_2CO_3 solution in a mixture of THF and MeOH under the refluxing condition to give **2** in 95% yield. The hydrolysis using NaOH as a base provided some by-products, and the hydrolysis of **18** also was not completed under the acidic conditions.

Finally, the acid-chloride generated from **2** was amidated with the amine **3**·2HCl (**3** dihydrochloride)[13] to give **1**. The reaction in *N*,*N*-dimethylacetamide (DMAc) proceeded smoothly, although the acid **2** was left in **1** when DMF or 1-methyl-2-pyrrolidone was used. After the reaction was completed, the addition of water to the reaction mixture caused crystallization to give the high-quality target product **1** in 82% yield.

3. Conclusion

We have developed a facile and novel synthetic preparation of 2,3-dihydro-1-benzothiepine derivatives **4**. The new compound, alkyl 4-(*o*-formylphenylthio)butyrate **9**, was prepared from *o*-halogenobenzaldehyde **10** and mercapto-butylate **11**. The improved intramolecular Claisen type reaction of **9** with alcoholate in dialkylcarbonate as a solvent provided **4** in good yields.

Furthermore, the practical preparation of **1** as a candidate for orally administered HIV-1 therapy was accomplished by employing the new method, and did not require any chromatographic purification. This synthetic route was consisted of five steps in 35% yield, as compared with the previous nine steps.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. ^{1}H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet and m, mutiplet), coupling constants spectra (Hz) and integration. ^{13}C NMR spectra recorded in ppm (δ) relative to the central line for $CDCl_3$ at 77 ppm and DMSO-d_6 at 39.7 ppm. The column chromatography was performed on BW820 (Fuji Silysia Chemical Ltd) Elemental and HRMS analyses were performed at Takeda Analytical Research Laboratories, Ltd.

4.1.1. General procedure for the preparation of 9. Compound **11** (2 equiv) was added to a suspension of **10** (1.0 g) and K_2CO_3 (2 equiv) in DMF (3 v/w), and stirred overnight at room temperature. The reaction mixture was diluted in AcOEt, and washed successively with water, 0.5 N HCl, and brine. The organic layer was dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica-gel with *n*-hexane–AcOEt.

4.1.2. Ethyl 4-(2-formylphenylthio)butyrate (9a), from 10a and 11a. A pale yellow oil; yield: 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H), 1.95–2.07 (m, 2H), 2.49 (t, J=7.2 Hz, 2H), 3.02 (t, J=7.1 Hz, 2H), 4.13 (q, J=7.1 Hz, 2H), 7.27–7.34 (m, 1H), 7.45–7.53 (m, 2H), 7.83–7.86 (m, 1H), 10.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.9, 32.4, 33.0, 60.5, 125.5, 128.3, 132.1, 134.0, 134.2, 141.3, 172.7, 191.4; IR (neat) 1731, 1695,

1196 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_3S$ ($[M]^+$) 252.0820; Found 252.0820.

4.1.3. Methyl 4-(2-formylphenylthio)butyrate (9b), from 10a and 11b. A pale yellow oil; yield: 95%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96–2.06 (m, 2H), 2.50 (t, $J=7.2$ Hz, 2H), 3.01 (t, $J=7.1$ Hz, 2H), 3.68 (s, 3H), 7.27–7.34 (m, 1H), 7.46–7.55 (m, 2H), 7.81–7.84 (m, 1H), 10.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 32.3, 32.7, 51.6, 125.5, 128.2, 132.1, 134.0, 134.1, 141.3, 173.1, 191.3; IR (neat) 1735, 1693, 1197 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}O_3S$ ($[M]^+$) 238.0664; Found 238.0664.

4.1.4. Ethyl 4-(4-bromo-2-formylphenylthio)butyrate (9c), from 10b and 11a. A pale yellow solid; yield: 78%; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J=7.1$ Hz, 3H), 1.95–2.05 (m, 2H), 2.48 (t, $J=7.1$ Hz, 2H), 3.00 (t, $J=7.2$ Hz, 2H), 4.13 (q, $J=7.1$ Hz, 2H), 7.35 (d, $J=8.5$ Hz, 1H), 7.60–7.64 (m, 1H), 7.94 (d, $J=2.3$ Hz, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.9, 32.7, 32.9, 60.6, 119.6, 130.4, 134.1, 135.5, 136.7, 140.3, 172.6, 189.8; IR (KBr) 1732, 1678, 1458, 1178 cm^{-1}; mp 48–49 °C; HRMS (FAB) calcd for $C_{13}H_{16}O_3BrS$ ($[MH]^+$) 331.0004; Found 331.0004. Anal. Calcd for $C_{13}H_{15}O_3SBr$: C, 47.14; H, 4.56; S, 9.68; Br, 24.12. Found: C, 47.19; H, 4.48; S, 9.58; Br, 24.23.

4.1.5. Ethyl 4-(2-chloro-6-formylphenylthio)butyrate (9d), from 10c and 11a. A pale yellow oil; yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, $J=7.2$ Hz, 3H), 1.84–1.94 (m, 2H), 2.43 (t, $J=7.2$ Hz, 2H), 2.95 (t, $J=7.2$ Hz, 2H), 4.11 (q, $J=7.2$ Hz, 2H), 7.42 (dd, $J=7.9$, 7.2 Hz, 1H), 7.71 (d, $J=7.9$ Hz, 1H,), 7.84 (d, $J=7.7$ Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 24.7, 32.8, 36.0, 60.5, 126.9, 129.8, 135.0, 136.8, 140.2, 141.2, 172.5, 192.0; IR (neat) 1739, 1685, 1037 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{16}O_3ClS$ ($[MH]^+$) 287.0509; Found 287.0509.

4.1.6. Ethyl 4-(3,4-dimethoxy-6-formylphenylthio)butyrate (9e), from 10d and 11a. A pale yellow solid; yield: 27%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, $J=7.1$ Hz, 3H), 1.80–2.07 (m, 2H), 2.43 (t, $J=7.1$ Hz, 2H), 2.92 (t, $J=7.4$ Hz, 2H), 3.93 (s, 3H), 3.99 (s, 3H), 4.12 (q, $J=7.1$ Hz, 2H), 7.02 (s, 1H),7.41 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 23.9, 32.2, 35.1, 55.5, 55.8, 60.0, 110.0, 114.4, 129.2, 133.3, 148.3, 153.3, 172.1, 189.7; IR (nujol) 1718, 1671, 1272 cm^{-1}; mp 87–88 °C; HRMS (FAB) calcd for $C_{15}H_{20}O_5S$ ($[M]^+$) 312.1031; Found 312.1031. Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26; O, 25.61. Found: C, 57.50; H, 6.47; S, 10.37.

General procedure for the preparation of **4**. 20% NaOEt (1.2 equiv) in EtOH (or 28% NaOMe in MeOH) was added to a solution of **9** (1.0 g) and diethyl carbonate (20 v/w) (or dimethyl carbonate), and stirred at room temperature. After cooling to 0 °C, the reaction mixture was neutralized with 1 N HCl. The resulting solution was extracted with AcOEt, and the organic layer was washed with water, dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica-gel with *n*-hexane–AcOEt.

4.1.7. Ethyl 2,3-dihydro-1-benzothiepin-4-carboxylate (4a). A yellow oil; yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.96–3.00 (m, 2H), 3.16–3.21 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.18–7.27 (m, 2H), 7.36–7.48 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 32.8, 35.3, 61.1, 127.0, 128.5, 132.2, 133.4, 134.4, 136.8, 138.8, 139.4, 168.1; IR (neat) 1703, 1267, 1240 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}O_2S$ ($[M]^+$) 234.0715; Found 234.0715.

4.1.8. Methyl 2,3-dihydro-1-benzothiepin-4-carboxylate (4b). A white solid; yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.96–3.00 (m, 2H), 3.16–3.21 (m, 2H), 3.83 (s, 3H), 7.18–7.27 (m, 2H), 7.36–7.48 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 35.2, 52.2, 127.0, 128.6, 132.2, 133.0, 134.5, 136.7, 138.8, 139.7, 168.5; IR (KBr) 1706, 1631, 1428 cm^{-1}; mp 52–54.3 °C; HRMS (FAB) calcd for $C_{12}H_{12}O_2S$ ($[M]^+$) 220.0558; Found 220.0558. Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.57; H, 5.43; F, 14.32.

4.1.9. Ethyl 7-bromo-2,3-dihydro-1-benzothiepin-4-carboxylate (4c). A yellow solid; yield: 32%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.95–2.99 (m, 2H), 3.15–3.20 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.26–7.34 (m, 2H), 7.51–7.52 (m, 1H), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 33.1, 35.8, 61.7, 121.1, 131.6, 134.1, 135.3, 136.9, 138.2, 138.3, 139.2, 168.0; IR (KBr) 1704, 1629, 1465 cm^{-1}; mp 82–83 °C; HRMS (FAB) calcd for $C_{13}H_{13}O_2SBr$ ($[M]^+$) 311.9820; Found 311.9820. Anal. Calcd for $C_{13}H_{13}O_2SBr$: C, 49.85; H, 4.18; S, 10.24; Br, 25.51. Found: C, 50.13; H, 4.12; S, 10.11; Br, 25.55.

4.1.10. Ethyl 9-chloro-2,3-dihydro-1-benzothiepin-4-carboxylate (4d). A yellow oil; yield: 46%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.99–3.03 (m, 2H), 3.15–3.20 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.12–7.27 (m, 1H), 7.26–7.36 (m, 2H), 7.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 33.2, 34.3, 61.2, 126.9, 129.3, 133.5, 134.1, 135.6, 137.9, 138.6, 138.9, 167.8; IR (neat) 1712, 1631 cm^{-1}. HRMS (FAB) calcd for $C_{13}H_{13}O_2ClS$ ($[M]^+$) 268.0325; Found 268.0325.

4.1.11. Ethyl 7,8-dimethoxy-2,3-dihydro-1-benzothiepin-4-carboxylate (4e). A yellow oil; yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.95–2.98 (m, 2H), 3.16–3.21 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 4.28 (q, $J=7.1$ Hz, 2H), 6.86 (s, 1H), 6.96 (s, 1H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 32.8, 35.7, 55.9, 60.9, 114.7, 116.6, 129.4, 130.9, 131.8, 139.2, 147.8, 148.8, 168.1; IR (neat) 1700, 1594, 1502 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{18}O_4S$ ($[M]^+$) 294.0926; Found 294.0926.

4.1.12. Ethyl 7-(4-propoxyphenyl)-2,3-dihydro-1-benzothiepin-4-carboxylate (4g). Under an argon atmosphere, a solution of **17** (37.1 g, 172.4 mmol) and THF (90 mL) was added dropwise to a suspension of magnesium (4.3 g, 177.3 mmol) and THF (270 mL) under a refluxing condition, and the whole was stirred for 1.5 h under the same conditions. After cooling to −11 °C, a solution of trimethoxyborane (17.9 g, 172.4 mmol) and THF (90 mL) was added dropwise to the reaction mixture and stirred for 1 h at −10 °C. After warming to room temperature,

palladium (II) acetate (11 mg, 0.049 mmol) and triphenylphosphine (52 mg, 0.197 mmol) were added to the resulting mixture, and stirred for 30 min at room temperature. Compound **10b** (20.0 g, 98.5 mmol), K_2CO_3 (71.5 g, 517.2 mmol) and distilled water (85 mL) were added to the resulting mixture, and the whole was refluxed for 4 h. After cooling to room temperature, 2 N HCl (450 mL) was added dropwise to the reaction mixture at 20–30 °C and separated. The aqueous solution was extracted with toluene (450 mL), and the combined organic solution was washed successively with 2 N HCl (300 mL), 2 N NaOH (300 mL×2), 2 N HCl (300 mL) and 20% NaCl solution (300 mL×2). Activated charcoal (1.0 g) was added to the organic solution, and the mixture was stirred for 20 min at room temperature. The charcoal was filtered off and washed with toluene (50 mL). The filtrate and washing were concentrated in vacuo to give crude 2-fluoro-5-(4-propoxyphenyl)benzaldehyde (**10f**, 30.5 g) as a brown oil. An analytically pure sample of **10f** was obtained by chromatography on silica-gel as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.77–1.90 (m, 2H), 3.96 (t, J=6.6 Hz, 2H), 6.95–6.98 (m, 2H), 7.18–7.25 (m, 1H), 7.46–7.50 (m, 2H), 7.74–7.78 (m, 1H), 8.00–8.04 (m, 1H), 10.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.6, 70.0, 115.0, 116.7, 117.0, 124.1, 126.3, 128, 131.1, 134.3, 137.8, 159.2, 162.1, 165.6, 187.2; IR (KBr) 2875, 1691, 1608, 1484, 1216 cm^{-1}; mp 42–43 °C; HRMS (FAB) calcd for $C_{16}H_{15}O_2F$ ($[M]^+$) 258.1056; Found 258.1056. Anal. Calcd for $C_{16}H_{15}O_2F$: C, 74.40; H, 5.85; F, 7.36. Found: C, 74.66; H, 5.67; F, 7.28.

DBU (34.4 mL, 229.9 mmol) was added dropwise to a solution of the above crude **10f** and **11a** (32.6 mL, 229.9 mmol) in DMF (59 mL) at 0–10 °C under an argon atmosphere, and the whole was stirred for 1 h at 20–30 °C. After diethyl carbonate (590 mL) was added the reaction mixture, 20% NaOEt in EtOH (156.0 g, 459.8 mmol) was added dropwise to the resulting mixture, and the whole was stirred for 3 h at 20–30 °C. After cooling to 5 °C, 2 N HCl (338 mL) was added dropwise to the reaction mixture, and separated. The aqueous solution was extracted with AcOEt (290 mL), and the combined organic layer was washed successively with water (300 mL), 5% $NaHCO_3$ solution (300 mL) and 5% NaCl solution (300 mL). Activated charcoal (3.5 g) and tri-*n*-butylphosphine (4 mL) were added to the organic solution, and the mixture was stirred for 20 min. The charcoal was filtered off, and washed with AcOEt (60 mL). After the filtrate and washing was concentrated in vacuo, the resulting residue was dissolved in diisopropyl ether (60 mL) under a refluxing condition. After cooling to room temperature, stirring for 1.5 h at room temperature and stirring for 2 h at 0 °C, the resulting crystals were collected by filtration, washed with cold diisopropyl ether (60 mL) and dried in vacuo to give **4g** (20.3 g, yield, 48% based on **10b**) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.36 (t, J=7.1 Hz, 3H), 1.77–1.90 (m, 2H), 3.00 (t, J=5.3 Hz, 2H), 3.22 (t, J=5.6 Hz, 2H), 3.96 (t, J=6.6 Hz, 2H), 4.29 (q, J=7.1 Hz, 2H), 6.94–7.00 (m, 2H), 7.36–7.57 (m, 5H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.4, 22.6, 32.7, 35.6, 61.1, 69.6, 114.9, 126.7, 127.9, 132.0, 132.5, 132.7, 133.6, 136.7, 137.2, 139.6, 139.7, 159.1, 168.1; IR (KBr) 2927, 1704, 1240, 819 cm^{-1}; mp 87–88 °C; HRMS (FAB) calcd for $C_{22}H_{24}O_3S$ ($[M]^+$) 368.1446; Found 368.1446. Anal. Calcd for $C_{22}H_{24}O_3S$: C, 71.71; H, 6.56; S, 8.70. Found: C, 71.72; H, 6.77; S, 8.64.

4.1.13. Ethyl 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxylate (18). After **4g** (15.0 g, 40.7 mmol) was dissolved in acetic acid (135 mL) at 56 °C, 30% H_2O_2 (9.5 g, 83.5 mmol) in acetic acid (15 mL) was added dropwise to a solution at the same temperature and stirred for 3 h at 65–70 °C. Water (15 mL) and 5% Na_2SO_3 solution (60 mL) were added dropwise to the reaction mixture, and then the whole was cooled to room temperature and stirred for 2 h at the same temperature. The resulting crystals were collected by filtration, washed successively with acetic acid/water (3/2, 15 mL) and water (150 mL), and dried in vacuo to give **18** (15.4 g, yield, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.38 (t, J=7.2 Hz, 3H), 1.78–1.90 (m, 2H), 3.14 (t, J=6.3 Hz, 2H), 3.64 (t, J=7.1 Hz, 2H), 3.98 (t, J=6.6 Hz, 2H), 4.32 (q, J=7.2 Hz, 2H), 6.99–7.02 (m, 2H), 7.53–7.57 (m, 2H), 7.65–7.69 (m, 2H), 7.89 (s, 1H), 8.18 (d, J=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.3, 22.6, 25.0, 55.8, 61.7, 69.7, 115.2, 126.7, 127.9, 128.4, 130.5, 131.8, 132.6, 132.9, 137.9, 138.3, 146.1, 160.0, 166.6; IR (KBr) 2933, 1706, 1606, 1517, 1243 cm^{-1}; mp 139–140 °C; HRMS (FAB) calcd for $C_{22}H_{24}O_5S$ ($[M]^+$) 400.1344; Found 400.1344. Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.89; H, 6.04; S, 8.01. Found: C, 65.72; H, 5.87; S, 7.96.

4.1.14. 7-(4-Propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxylic acid (2). A solution of K_2CO_3 (342 g, 2.47 mol) and water (4.2 L) was added dropwise to a solution of **18** (495 g, 1.24 mol), THF (4.95 L) and MeOH (2.48 L), and the whole was refluxed for 6.5 h. Under the same condition, 3 N HCl (1.85 L) was added dropwise to the reaction mixture and the whole was cooled to room temperature. Under the same temperature, 6 N HCl (84 mL) was added dropwise to the resulting mixture and stirred for 1 h with ice-bathing. The resulting crystals were collected by filtration, washed with THF/MeOH/water (1/1/3, 2.97 L), and dried in vacuo to give **2** (443 g, yield, 96%) as a light white-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (t, J=7.4 Hz, 3H), 1.70–1.78 (m, 2H), 2.95 (t, J=6.2 Hz, 2H), 3.73 (t, J=6.4 Hz, 2H), 3.98 (t, J=6.5 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 7.75 (d, J=8.7 Hz, 2H), 7.86–7.88 (m, 2H), 8.02–8.05 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.6, 22.2, 25.4, 53.9, 69.3, 115.3, 126.4, 127.1, 128.6, 129.9, 132.1, 132.4, 134.0, 136.8, 138.8, 144.9, 160.0, 168.5; IR (KBr) 3500, 1673, 1608, 1519, 1294, 1251 cm^{-1}; mp 271–272 °C; HRMS (FAB) calcd for $C_{20}H_{20}O_5S$ ($[M]^+$) 372.1031; Found 372.1031. Anal. Calcd for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41; S, 8.61. Found: C, 64.40; H, 5.47; S, 8.55.

4.1.15. *N*-[4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxamide (1). Thionyl chloride (0.70 g, 5.91 mmol) was added dropwise to a suspension of **2** (2.0 g, 5.37 mmol) in *N*,*N*-dimethylacetoamide (10 mL) at room temperature, and the whole was stirred for 2 h at room temperature. The reaction mixture was added dropwise to a suspension of **3**·2HCl (1.9 g, 6.44 mmol) and NEt_3 (5.8 mL, 41.87 mmol) in

N,*N*-dimethylacetamide (10 mL) at 0–10 °C, and stirred for 1 h at room temperature. Water (20 mL) was added to the resulting mixture at room temperature and stirred for about 1 h at the same temperature. The resulting crystals were collected by filtration, washed with water (5 mL) and MeOH (5 mL), and dried in vacuo to give **1** (2.5 g, yield, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.64–1.88 (m, 6H), 2.20 (s, 3H), 2.60–2.67 (m, 1H), 3.13 (t, J=6.6 Hz, 2H), 3.33–3.41 (m, 2H), 3.56 (s, 2H), 3.69 (t, J=6.3 Hz, 2H), 3.95–4.07 (m, 4H), 6.98 (d, J=8.7 Hz, 2H), 7.29–7.34 (m, 3H, 7.48–7.61 (m, 6H), 8.08–8.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.6, 25.0, 29.2, 37.5, 57.3, 57.5, 59.6, 67.7, 69.7, 115.2, 120.3, 126.3, 128.1, 128.4, 129.4, 130.4, 130.6, 132.0, 133.2, 136.4, 136.5, 137.3, 139.3, 146.1, 160.1, 166.6; IR (KBr) 3485, 2948, 1654, 1635, 1606, 1519, 1315, 1292, 1130 cm^{-1}; mp 239.6–240.8 °C; HRMS (FAB) calcd for $C_{33}H_{39}N_2O_5S$ ($[MH]^+$) 575.2580; Found 575.2580. Anal. Calcd for $C_{33}H_{38}N_2O_5S$; C, 68.96; H, 6.66; N, 4.87; S, 5.58. Found: C, 68.79; H, 6.56; N, 4.95; S, 5.66.

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