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Diastereodivergent Synthesis of Bromoiminolactones: Electrochemical and Chemical Bromoiminolactonization of α-Allylmalonamides

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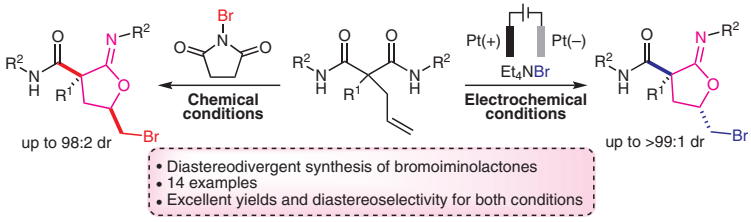

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Abstract A diastereodivergent synthesis of N-substituted iminolactones by bromoiminolactonization of α-substituted α-allylmalonamides is reported. Whereas bromocyclization under conventional chemical conditions provided *cis*-bromoiminolactones, electrochemical conditions exhibited complementary diastereoselectivity to afford the *trans*-products. A variety of substituents on the nitrogen atoms and an α-position of the malonamide were tolerated under both sets of conditions to afford the corresponding iminolactones in excellent yields and high diastereoselectivities.

Key words diastereodivergent synthesis, electrochemical synthesis, N-bromosuccinimide, iminolactones, malonamides, bromoiminolactonization

Lactone skeletons are widely found in natural products and biologically active molecules, and they are also valuable building blocks in organic synthesis.[1,2] Halolactonization of unsaturated bonds is a fundamental and effective strategy for the construction of halogenated lactones.[3] To date, a number of enantio- and diastereoselective halolactonizations have been developed with transition-metal catalysts or organocatalysts.[4] Halocyclization of olefinic amides (haloiminolactonization) is also a useful approach for the synthesis of halolactones. The resulting iminolactones are easily transformed into the corresponding lactones. Olefinic amides sometimes gave better yields and stereoselectivities than those obtained from olefinic acids.[5] Although the reported diastereoselective halo(imino)cyclization reactions provide the desired products with high degrees of selectivity, modifications of the substrate structure are commonly required to obtain products with the opposite relative configuration.[6,7] Considering the stereodiversity of naturally occurring lactones, a diastereodivergent synthesis of iminolactones from common substrates would be highly valuable.

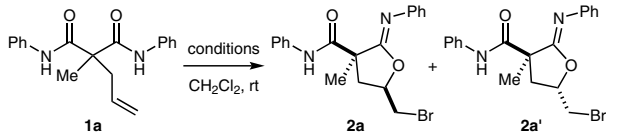
Electrochemical transformations are considered to be environmentally friendly, and they have attracted much attention in the field of synthetic organic chemistry.[8,9] Olefinic carboxylic acids have been widely used in the well-known Kolbe electrolysis, affording carbocycles as well as heterocycles.[10] Recently, Moeller and co-workers have developed electrochemical lactonizations of carboxylic acids or amides bearing an electron-rich alkene moiety through generation of olefinic radical cations followed by intramolecular coupling with a nucleophilic site.[11] Nonactivated olefins also participate in electrochemical cyclizations with a halogen cation (Cl^+, Br^+, or I^+) or a selenium cation as a mediator or reactant to afford various heterocycles, including cyclic carbonates,[12] oxazolines,[13] ethers,[14] and amines.[15] Although these electrochemical cyclizations proceeded diastereoselectively, the selectivity was dominated by the stereochemistry of the substrate. To the best our knowledge, electrochemical approaches to the synthesis of brominated iminolactones have not been disclosed, although they would be synthetically valuable in terms of reactivity and further derivatization.

In this paper, we report a diastereodivergent synthesis of bromo-functionalized iminolactones from easily accessible allylmalonamides under chemical and electrochemical conditions. Chemically and electrochemically generated bromo cations promoted the bromocyclization of allylmalonamides to give *cis*- and *trans*-isomers, respectively, from the same substrate in excellent yields with high diastereoselectivities.

For the initial screening, we examined the bromoiminolactonization of the α-allylmalonamide **1a** under chemical and electrochemical conditions (Table 1). The electrochemical reaction was performed in a beaker-type undivided cell under a constant-current condition (20 mA). When **1a** was treated with *N*-bromosuccinimide (NBS) in CH_2Cl_2, bromoiminolactone **2a** was obtained in a high yield with high

diastereoselectivity (Table 1, entry 1). The combination of NBS and $Cu(OTf)_2$ provided **2a**/**2a′** in an identical yield with high selectivity toward **2a** (entry 2).[16] Whereas the electrochemical bromocyclization with Et_4NBr as a supporting electrolyte in CH_2Cl_2 gave only trace amounts of products, the use of a copper catalyst and Et_4NBr afforded **2a′** in 78% yield with a diastereomeric ratio of 9:91 (entries 3 and 4).[17] As both diastereomers were obtained as crystalline solids, their relative configurations were unambiguously determined by X-ray crystal-structure analysis.[18] The chemical conditions predominantly gave the diastereomer with the *cis*-configuration between the amide group and the bromomethyl group, whereas the electrochemical conditions provided the *trans*-isomer predominantly (see Supporting Information for details).

Table 1 Initial Screening of the Bromoiminolactonization of **1a**

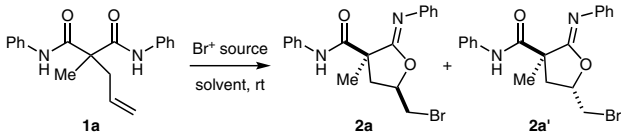


Entry	Conditions	Yield[a] (%) of **2**	dr[b] (**2a**/**2a′**)
1[c]	NBS (2.0 equiv)	97	89:11
2[c]	NBS (2.0 equiv), $Cu(OTf)_2$ (10 mol%)	97	84:16
3[d]	Pt(+)/Pt(−), Et_4NBr (2.0 equiv)	trace	n.d.[e]
4[d]	Pt(+)/Pt(−), Et_4NBr (2.0 equiv), $Cu(OTf)_2$ (10 mol%)	76	9:91

[a] Combined isolated yield of both diastereomers.
[b] Ratio of isolated yields of the two diastereomers
[c] Reaction conditions: **1a** (0.5 mmol), NBS (1.0 mmol, 2.0 equiv), $Cu(OTf)_2$ (0–10 mol%), CH_2Cl_2 (6.0 mL), rt.
[d] Reaction conditions: **1a** (0.5 mmol), Et_4NBr (1.0 mmol, 2.0 equiv), $Cu(OTf)_2$ (0-10 mol%), CH_2Cl_2 (6.0 mL), beaker-type undivided cell, Pt plate electrode (1.0 × 2.0 cm^2), 20 mA, 4 F/mol, rt.
[e] n.d. = not determined.

Encouraged by these results, we began an optimization of both the chemical and electrochemical conditions for the diastereodivergent synthesis of **2a** and **2a′**. First, the effects of the bromo cation source and the solvent on the bromoiminolactonization under chemical conditions were investigated (Table 2). Both molecular bromine and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave **2a**/**2a′** in excellent yields, but with lower diastereoselectivities toward **2a** (entries 2 and 3). Halving the amount of NBS resulted in a decreased yield of **2a**/**2a′** despite a prolonged reaction time (entry 4). This reaction proceeded in various solvents to afford **2a**/**2a′**, but the diastereoselectivity depended on the polarity of the solvent. Whereas polar solvents such as DMSO or MeOH provided **2a**/**2a′** with almost no selectivity, less-polar solvents exhibited better diastereoselectivity toward **2a** (entries 5–9). The highest yield and diastereoselectivity were obtained in toluene, affording **2a** in 99% yield with a diastereomeric ratio of 94:6 (entry 5). On the basis of these results, we selected NBS and toluene as the optimal bromo cation source and solvent, respectively.

Table 2 Diastereoselective Bromoiminolactonization under Chemical Conditions[a]



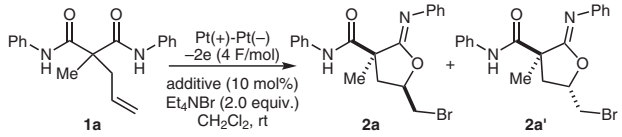
Entry	Br^+ source (equiv)	Solvent	Time (min)	Yield[b] (%) of **2**	dr[c] (**2a**/**2a′**)
1	NBS (2.0)	CH_2Cl_2	10	97	89:11
2	Br_2 (2.0)	CH_2Cl_2	10	99	75:25
3	DBDMH (1.0)	CH_2Cl_2	10	99	85:15
4	NBS (1.0)	CH_2Cl_2	60	64	89:11
5	NBS (2.0)	toluene	30	99	94:6
6	NBS (2.0)	THF	10	96	82:18
7	NBS (2.0)	MeCN	30	99	57:43
8	NBS (2.0)	DMSO	30	93	48:52
9	NBS (2.0)	MeOH	10	95	45:55

[a] Reaction conditions: **1a** (0.5 mmol), Br^+ source (1.0 mmol, 2.0 equiv), solvent (6.0 mL), rt.
[b] Combined isolated yield of both diastereomers.
[c] Ratio of isolated yields of the two diastereomers.

Next, we examined the effects of some metal catalysts and ligands on the electrochemical bromoiminolactonization of **1a** (Table 3). Although $Mg(OTf)_2$ did not promote the cyclization of **1a**, $Zn(OTf)_2$ led to an increase in both the yield and diastereoselectivity toward **2a′** compared with $Cu(OTf)_2$ (entries 1–3). The use of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA) with $Zn(OTf)_2$ afforded **2a**/**2a′** in 94% yield with a diastereomeric ratio of 6:94, whereas the use of 2,2′-bipyridine gave **2a′** almost exclusively in 87% yield (entries 4 and 5). $ZnCl_2$ was ineffective in this reaction, affording **2a**/**2a′** in a low yield (entry 6). $Zn(OAc)_2$ promoted the cyclization of **1a** with high efficiency, but a lower diastereoselectivity was observed (entry 7). Thus, the combination of $Zn(OTf)_2$ and 2,2′-bipyridine was therefore selected as optimal for the electrochemical bromoiminolactonization.

With the optimized conditions for both the chemical and electrochemical bromoiminolactonization in hand, we evaluated the scope of the reaction toward the α-allylmalonamide (Table 4). With respect to the substituent on the α-position of malonamide, alkyl groups (**1b** and **1c**) were well tolerated in the reaction under chemical and electrochemical conditions, affording the corresponding iminolactones in high yields and high diastereoselectivities (Table 4, entries 1–4). Whereas the α-phenyl-substituted

Table 3 Diastereoselective Bromoiminolactonization under Electrochemical Conditions[a]

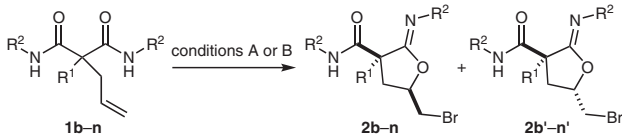


Entry	Additive(s) (10 mol%)	Yield[b] (%) of **2**	dr[c] (**2a**/**2a′**)
1	$Cu(OTf)_2$	76	9:91
2	$Mg(OTf)_2$	trace	n.d.[d]
3	$Zn(OTf)_2$	89	8:92
4	$Zn(OTf)_2$ + TMEDA	93	6:94
5	$Zn(OTf)_2$ + 2,2′-bipyridine	87	0.1:99.9
6	$ZnCl_2$ + 2,2′-bipyridine	20	n.d.
7	$Zn(OAc)_2$ + 2,2′-bipyridine	99	10:90

[a] Reaction conditions: **1a** (0.5 mmol), Et_4NBr (1.0 mmol, 2.0 equiv), additive(s) (10 mol%), CH_2Cl_2 (6.0 mL), beaker-type undivided cell, Pt plate electrode (1.0 × 2.0 cm^2), 20 mA, 4 F/mol, rt.
[b] Combined isolated yield of both diastereomers.
[c] Ratio of isolated yields of the two diastereomers.
[d] n.d. = not determined.

malonamide **1d** was transformed into **2d** in excellent yield with high diastereoselectivity under chemical conditions, the diastereoselectivity toward **2d′** slightly decreased under electrochemical conditions (entries 5 and 6). Substrates bearing benzyl groups with electron-neutral (**1e**), electron-donating (**1f–h**), or electron-withdrawing (**1i**) substituents were successfully employed under both conditions, affording the *cis*- and *trans*-diastereomers under chemical and electrochemical conditions, respectively (entries 7–16). The effects of substituents on the nitrogen atom of the amide moiety were also examined. Under both sets of conditions, the *p*-methoxyaniline-derived malonamide **1j** was successfully transformed into the corresponding iminolactones **2j**/**2j′** in excellent yields with over 95:5 selectivity toward the major diastereomer (entries 17 and 18). Iminolactones bearing a *p*-chlorophenyl group (**2k**/**2k′**) were also obtained with high efficiency (entries 19 and 20). Bromoiminolactonization of **1l** under chemical conditions was performed in a mixed solvent because of the low solubility of **1l** in toluene, and **2l** was obtained in high yield with excellent diastereoselectivity (entry 21). However, the yield and diastereoselectivity toward **2l′** under electrochemical conditions decreased slightly (entry 22). **2m**, containing a sterically hindered cyclohexyl group was obtained in good yield with high diastereoselectivity under chemical conditions, but a lower selectivity was observed under electrochemical conditions (entries 23 and 24). Under the appropriate reaction conditions, **2n** and **2n′** containing a linear alkyl group, were successfully obtained in high yields and high diastereoselectivities (entries 25 and 26).[19]

Table 4 Substrate Scope of the Bromoiminolactonization under Chemical or Electrochemical Conditions[a]

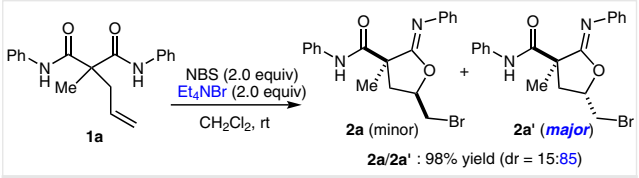


Entry	**1**	R^1	R^2	Conditions	Yield[b] (%) of **2**	dr[c] (**2a**/**2a′**)
1	**1b**	Et	Ph	A	98	95:5
2				B	73	0.1:99.9
3	**1c**	Bu	Ph	A	99	95:5
4				B	90	6:94
5	**1d**	Ph	Ph	A	98	93:7
6				B	82	12:88
7	**1e**	Bn	Ph	A	98	96:4
8				B	86	2:98
9	**1f**	2-methylbenzyl	Ph	A	93	98:2
10				B	79	6:94
11	**1g**	3-methylbenzyl	Ph	A	96	98:2
12				B	84	6:94
13	**1h**	3-methoxybenzyl	Ph	A	97	98:2
14				B	81	4:96
15	**1i**	3-chlorobenzyl	Ph	A	97	98:2
16				B	90	6:94
17	**1j**	Me	4-$MeOC_6H_4$	A	97	95:5
18				B	97	1:99
19	**1k**	Me	4-ClC_6H_4	A	90	92:8
20				B	78	5:95
21[d]	**1l**	Me	Bn	A	88	91:9
22[e]				B	77	12:88
23	**1m**	Me	Cy	A	71	93:7
24[f]				B	68	21:79
25	**1n**	Me	$(CH_2)_7Me$	A	89	94:6
26				B	73	8:92

[a] Conditions A: **1a** (0.5 mmol), NBS (1.0 mmol, 2.0 equiv), toluene (6.0 mL), rt.; Conditions B: **1a** (0.5 mmol) , Et_4NBr (1.0 mmol, 2.0 equiv), $Zn(OTf)_2$ (10 mol%), 2,2′-bipyridine (10 mol%), CH_2Cl_2 (6.0 mL), beaker-type undivided cell, Pt plate electrode (1.0 × 2.0 cm^2), 20 mA, 4 F/mol, rt.
[b] Combined isolated yield of both diastereomers.
[c] Ratio of the isolated yields of the two diastereomers.
[d] Toluene–CH_2Cl_2 (5.9:0.1).
[e] 3 F/mol.
[f] 2.7 F/mol.

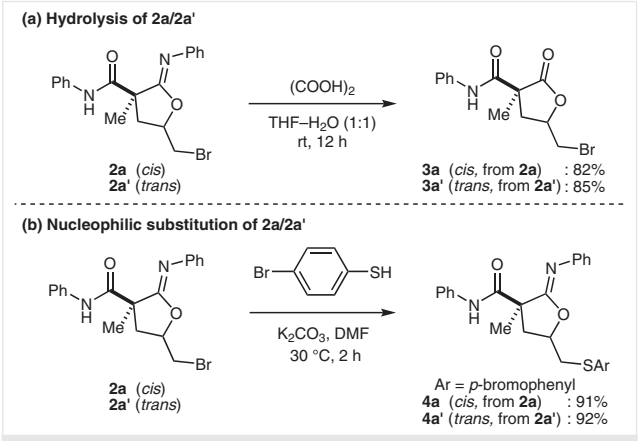
To gain insight into the origin of the diastereodivergency in these reactions, we examined the effect of Et_4NBr on the chemical bromoiminolactonization. Control experiments were performed according to the same procedure as used for the chemical bromocyclization, except that two

equivalents each of Et_4NBr and NBS were premixed in CH_2Cl_2 at room temperature before the addition of the substrate. As shown in Scheme 1, substrate **1a** was preferentially transformed into the *trans*-iminolactone **2a′** under the NBS/Et_4NBr conditions. However, the diastereoselectivities were lower than those observed under the electrochemical conditions. Although the actual role of $Zn(OTf)_2$ and 2,2′-bipyridine in the electrochemical bromoiminolactonization remains unclear, these results indicate that complexes of Et_4NBr with an electrochemically generated bromo cation might play a crucial role in the selectivity-determining step.[20,21]



Scheme 1 Diastereoselective synthesis of bromoiminolactones using NBS with Et_4NBr

Finally, the transformations of the products were examined to demonstrate the synthetic utility of the present reaction (Scheme 2). Iminolactones **2a** and **2a′** were easily transformed into the polysubstituted lactones **3a** and **3a′** in high yields by treatment with oxalic acid in THF–H_2O at room temperature [Scheme 2(a)].[22] Nucleophilic substitution of **2a** and **2a′** with 4-bromobenzenethiol afforded the corresponding iminolactones **4a** and **4a′** with a thioether moiety in excellent yields [Scheme 2(b)]



Scheme 2 Transformations of iminolactones **2a** and **2a′**

In conclusion, we have successfully developed a diastereodivergent synthesis of bromo-substituted iminolactones by chemical or electrochemical bromoiminolactonization of α-allylmalonamides.[23] A variety of malonamides with an alkyl or an aryl substituent on the nitrogen atom or at an α-position were tolerated in the reaction. Both diastereomers were accessible in excellent yields with excellent diastereoselectivities. Further investigations to gain mechanistic insight into the diastereoselectivity and to develop asymmetric variants of the present reactions are currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611791.

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(17) Applied currents of 10 or 30 mA led to a decrease in the yield of **2**; see Supporting Information for details.

(18) CCDC 1893915 and 1893916 contain the supplementary crystallographic data for compounds **2a** and **2a′**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures .

(19) The symmetrical bisallyl malonamide **1** (R^1 = Allyl; R^2 = Ph) gave a complex mixture under both chemical and electrochemical conditions.

(20) Although the combination of NBS and Et_4NBr can generate molecular bromine, molecular bromine itself provided **2a** as a major product (Table 2, entry 2). The use of $Cu(OTf)_2$ with molecular bromine did not affect the selectivity (99% yield of **2**; **2a**/**2a′** = 73:27).

(21) Braude and Waight have reported the formation of complexes between tetraalkylammonium salts and NBS, and the formation of a 1:1 complex between Et_4NBr and NBS has been reported by Finkelstein et al.; see: (a) Braude, E. A.; Waight, E. S. *Nature* **1949**, *164*, 241. (b) Braude, E. A.; Waight, E. S. *J. Chem. Soc.* **1952**, 1116. (c) Finkelstein, M.; Hart, S. A.; Moore, M.; Ross, S. D.; Eberson, L. *J. Org. Chem.* **1986**, *51*, 3548.

(22) Diethyl allyl(methyl)malonate afforded a diastereoisomeric mixture of the corresponding lactones in moderate yield with almost no diastereoselectivity under the chemical conditions.

(23) **Bromoiminolactonization of Compounds 1; General Procedure under Chemical Conditions**

NBS (178 mg, 2.0 equiv) was added to a solution of **1** (0.5 mmol) in toluene (6 mL), and the mixture was stirred at rt until all the starting material was consumed (TLC). The reaction was quenched with sat. aq $Na_2S_2O_3$, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, hexane–EtOAc] to afford **2** and **2′**.

Bromoiminolactonization of Compounds 1; General Procedure under Electrochemical Conditions

In a beaker-type undivided cell, substrate **1** (0.5 mmol), Et_4NBr (322 mg, 2.0 equiv), $Zn(OTf)_2$ (18.2 mg, 10 mol%), and 2,2′-bipyridine (7.8 mg, 10 mol%) were dissolved in CH_2Cl_2 (6 mL), and the mixture was stirred for 20 min. The reaction vessel was fitted with a Pt plate electrode (1.0 × 2.0 cm^2), and 4 F/mol of electricity was supplied under constant-current conditions (20 mA). The reaction was then quenched with sat. aq $Na_2S_2O_3$ and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, hexane–EtOAc] to afford **2** and **2′**.

(*cis*)-5-(Bromomethyl)-3-ethyl-*N*-phenyl-2-(phenylimino)tetrahydrofuran-3-carboxamide (2b) (Prepared under Chemical Conditions)

Colorless oil; yield: 187 mg (93%). IR (ATR): 692, 756, 1198, 1445, 1487, 1551, 1599, 1686, 3065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.66 (s, 1 H), 7.59 (dd, *J* = 8.5, 1.2 Hz, 2 H), 7.39–7.32 (m, 4 H), 7.26–7.24 (m, 2 H), 7.18–7.14 (m, 1 H), 7.13–7.09 (m, 1 H), 4.76–4.69 (m, 1 H), 3.50 (d, *J* = 5.4 Hz, 2 H), 2.79 (dd, *J* = 13.9, 8.0 Hz, 1 H), 2.48 (dd, *J* = 13.7, 6.8 Hz, 1 H), 2.19–2.05 (m, 2 H), 1.10 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 163.0, 144.5, 137.8, 128.9, 128.7, 124.8, 124.1, 123.2, 119.5, 78.1, 56.5, 35.0, 34.9, 33.7, 9.25. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{20}H_{21}{}^{81}BrN_2O_2$: 402.0766; found: 402.0763.

(*trans*)-5-(Bromomethyl)-3-ethyl-*N*-phenyl-2-(phenylimino)tetrahydrofuran-3-carboxamide (2b′) (Prepared under Electrochemical Conditions)

Colorless oil; yield: 146 mg (73%). IR (ATR): 692, 756, 1198, 1443, 1489, 1541, 1599, 1684, 3323 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.37–7.33 (m, 4 H), 7.23 (t, *J* = 9.0 Hz, 2 H), 7.16–7.10 (m, 2 H), 4.62–4.56 (m, 1 H), 3.66 (dd, *J* = 10.7, 4.8 Hz, 1 H), 3.57 (dd, *J* = 11.2, 3.9 Hz, 1 H), 3.34 (dd, *J* = 13.2, 6.3 Hz, 1 H), 2.32–2.22 (m, 1 H), 2.10–1.96 (m, 2 H), 1.05 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 163.6, 145.1, 137.7, 129.0, 128.7, 124.6, 124.3, 123.1, 119.3, 78.6, 58.3, 34.0, 33.6, 33.1, 9.5. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{20}H_{21}{}^{81}BrN_2O_2$: 402.0766; found: 402.0763.