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One-Pot Synthesis of Esters of Cyclopropane Carboxylic Acids via Tandem Vicarious Nucleophilic Substitution−Michael Addition Process

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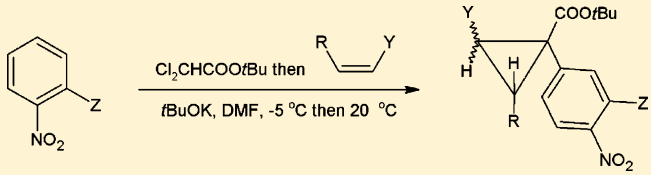
Supporting Information

ABSTRACT: α-Chlorocarbanions generated via base-induced vicarious nucleophilic substitution reaction of alkyl dichloroacetates with nitroarenes react with Michael acceptors to give esters of cyclopropane carboxylic acids substituted with *p*-nitroaromatic rings.



INTRODUCTION

A cyclopropane ring is present in many biologically active compounds and pharmaceuticals.[1] Substituted cyclopropanes are valuable intermediates in the synthesis of larger carbo- and heterocyclic rings via three-membered ring opening, followed by cycloaddition.[2] Because of that, synthesis of substituted cyclopropanes is of substantial interest and is the subject of many publications.[3] In general, there are two major ways of construction of cyclopropane rings: addition of carbenes and carbenoids to C=C double bonds and intramolecular 1,3-substitution in carbanions containing nucleofugal groups in γ-positions. The second pathway includes generation of γ-halocarbanions via addition of α-halocarbanions to Michael acceptors, deprotonation of γ-haloalkyl sulfones, esters and nitriles of γ-haloalkanoic acids, alkylation of methylenic carbanions with 1,2-dihaloalkanes, and reactions of Michael acceptors with ylides. Because of their instability, the reactions of α-halocarbanions with Michael acceptors are usually carried out via deprotonation of α-haloalkenoic nitriles, esters, sulfones, etc., in the presence of the Michael acceptors.

In this paper, we wish to report the synthesis of substituted cyclopropanes in reaction of Michael acceptors with α-chlorocarbanions generated via vicarious nucleophilic substitution (VNS) of hydrogen in nitroarenes.

VNS is a general reaction between α-halocarbanions and nitroarenes that proceeds via addition of the carbanions to the electron-deficient nitroaromatic rings in positions occupied by hydrogen to form σ^H adducts. Further base-induced β-elimination of hydrogen halide results in formation of nitrobenzylic carbanions of the products. Protonation of these carbanions gives products of replacement of the ring hydrogen with the carbanion moiety (Scheme 1).[4]

Besides of protonation to give products of VNS, these nitrobenzylic carbanions can be directly introduced into further reactions with electrophilic reagents: alkylation,[5] Wittig−Horner reaction,[6] nitroarylation,[7] etc.

VNS reaction of α,α-dichlorocarbanions such as those generated by deprotonation of alkyl dichloroacetates[8a] or dichloromethyl phenyl sulfone[8b] with nitroarenes gives nitrobenzylic α-chlorocarbanions that, upon protonation, produces typical VNS products.[8] It was already reported that such nitrobenzylic α-chlorocarbanions, products of VNS reaction between nitroarenes and carbanions of dichloromethyl oxazoline, can enter the Darzens condensation with aromatic aldehydes to give oxiranes.[9]

We have, therefore, expected that nitrobenzylic α-chlorocarbanions produced in the VNS reaction between alkyl dichloroacetates and nitroarenes should be able to add to electron-deficient alkenes—Michael acceptors giving as the ultimate products—esters of cyclopropane carboxylic acids substituted with nitroaromatic rings.

RESULTS AND DISCUSSION

In the preliminary experiments, we have attempted reactions of *t*-butyl α-chloro-α-(4-nitrophenyl)acetate, isolated product of VNS between nitrobenzene **1** and *t*-butyl dichloroacetate with acrylonitrile and ethyl acrylate under liquid−solid PTC conditions—in the presence of solid K_2CO_3 in DMF and tetrabutyl ammonium hydrogen sulfate catalyst.[10] The reaction proceeded smoothly to give substituted cyclopropanes in high yields as mixtures of stereoisomers. These results prompted us to perform a one-pot process: formation of the nitrobenzylic α-halocarbanions in the VNS reaction of *t*-butyl dichloroacetate with nitroarenes, followed by addition of the Michael acceptors to the reaction mixtures. The reaction of nitrobenzene with the bulky carbanion of *t*-butyl dichloroacetate carried out in the presence of *t*-BuOK in DMF at −5 °C is a fast process, completed within 5 min, and proceeds selectively at the *para* position. After addition of acrylonitrile or ethyl acrylate to the

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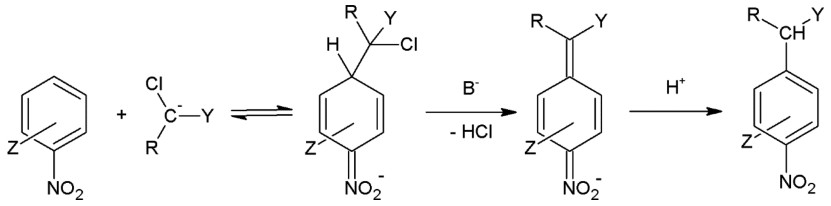
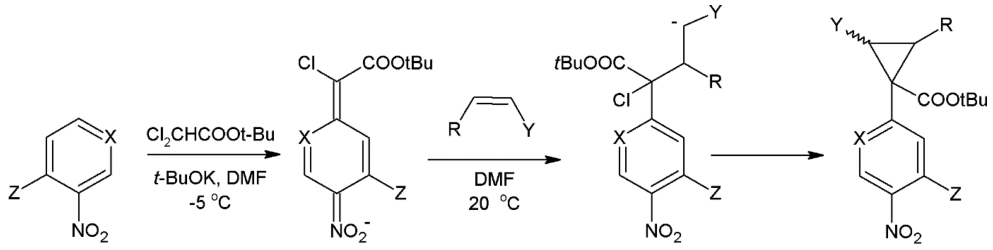
Scheme 1. Vicarious Nucleophilic Substitution in Nitroarenes with α-Chlorocarbanions[4]



Scheme 2. One-Pot Synthesis of Substituted Cyclopropanes via VNS–Michael Addition



X = CH, Z = H, **1**; F, **2**; Cl; **3**; Br, **4**; OMe, **5**

X = N, Z = OEt, **6**

R, Y = H, CN **1a-6a**
H, COOEt **1b-6b**
COOEt, COOEt **1c-6c**

Table 1. Results of the One-Pot Reaction of Nitroarenes with Carbanions of *tert*-Butyl Dichloroacetate and Michael Acceptors (Scheme 2)

	X	Z	Y	R	reaction time [min]	no.	total yield [%][a]	ratio of stereoisomers[b]
1	CH	H	CN	H	60	**1a**	70	1.3:1
2			COOEt	H	180	**1b**	81	6.7:1
3			COOEt	COOEt	360	**1c**	66	1
4	CH	F	CN	H	90	**2a**	59	1.2:1
5			COOEt	H	180	**2b**	56	1
6			COOEt	COOEt	480	**2c**	39	1
7	CH	Cl	CN	H	90	**3a**	82	1.1:1
8			COOEt	H	180	**3b**	63	1
9			COOEt	COOEt	360	**3c**	68	1
10	CH	Br	CN	H	90	**4a**	82	1.3:1
11			COOEt	H	180	**4b**	84	7.6:1
12			COOEt	COOEt	360	**4c**	85	1
13	CH	OMe	CN	H	30	**5a**	71	1:1
14			COOEt	H	60	**5b**	78	8.5:1
15			COOEt	COOEt	120	**5c**	70	1
16	N	OEt	CN	H	60	**6a**	85	1.9:1
17			COOEt	H	180	**6b**	72	1
18			COOEt	COOEt	480	**6c**	54	1

[a]Isolated yield under standard conditions. [b]Calculated on the basis of ^{1}H NMR spectra and/or mass of isolated products

reaction mixtures, the reaction was continued at room temperature for 2–3 h to give mixtures of stereoisomeric substituted cyclopropanes similar to those obtained under the solid–liquid PTC conditions. According to the identical standard procedure, reactions of *t*-butyl dichloroacetate and acrylonitrile, ethyl acrylate and diethyl maleate with 2-fluoro-, 2-chloro-, 2-bromo-, and 2-methoxynitrobenzenes **2**, **3**, **4** and **5** were carried out. In all of these cases, expected substituted cyclopropanes were obtained in good yields as single stereoisomers or mixtures of stereoisomers (Scheme 2, Table 1).

The reaction with *o*-fluoronitrobenzene **2** carried out under the standard conditions gave somewhat lower yields of the cyclopropanes **2a**, **2b** and **2c**. It appears that this is due to very facile nucleophilic substitution of fluorine located *ortho* to the nitro group; hence, during the reaction, particularly in the second part when the reaction mixtures are kept at room temperatures for a longer time, the side process of S_NAr could proceed.

VNS with *t*-butyl dichloroacetate proceeds also in heteroaromatic compounds that contain nitro groups: nitropyridines, nitrothiophene,[8a,c] and nitroimidazole;[8d] hence, we have attempted to synthesize cyclopropanes substituted with nitropyridine moiety. Indeed, the reaction of 2-ethoxy-5-nitropyridine **6** with *t*-butyl dichloroacetate, followed by the reaction of the produced α-chlorocarbanion with acrylonitrile, ethyl acrylate, and diethyl maleate carried out under standard conditions, gave the expected cyclopropanes containing nitropyridyl substituent.

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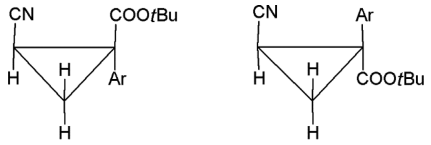
From the results presented in Table 1, it can be seen that reactions of α-halocarbanions generated via VNS of nitroarenes with *t*-butyl dichloroacetate with acrylonitrile to produce cyclopropanes **1a−6a** are not stereoselective. Isomers *cis* and *trans* are formed in almost equal quantities. On the other hand, the reaction with ethyl acrylates is highly stereoselective. The ratio of stereoisomers of products **1b−6b** is around 8:1 or only one isomer is formed, whereas the reaction with diethyl maleate proceeds stereoselectively, giving single stereoisomers **1c−6c**.

The ratio of the stereoisomers can reflect the stereochemistry of the intramolecular 1,3-substitution in the γ-chlorocarbanion−the Michael adducts or can be affected by epimerization of the C−H acidic chiral center of the products in the strongly basic reaction media. When separated major stereoisomer **2a′** was exposed to a solution of *t*-BuOK in DMF, rapid epimerization was observed. We can, therefore, suppose that the ratio of stereoisomers is controlled thermodynamically.

The structure of the products was established on the basis of high-resolution ^{1}H NMR spectra. Since analysis of values of the chemical shifts and coupling constants was insufficient for determination of the mutual location of the functional groups CN and COO*t*Bu in **1a−6a**, and COOEt and COO*t*Bu in **1b−6b**, this question was solved using NOE. Thus, irradiation of selected protons of the cyclopropane rings affected protons of the aromatic rings; thus, the mutual location of the functional groups could be unambiguously established. On this basis, the major isomer **3a′** was assigned *cis* geometry (CN and COO*t*Bu are on the one side of the cyclopropane ring), whereas **3a″** is a *trans* isomer. Spectra of other isomeric products major isomers **1a′−6a′** and minor isomers **1a″−6a″** are very similar to those of **3a′** and **3a″**; hence, we consider that **1a′−6a′** have *cis* and **1a″−6a″** and **1a″−6a″** have *trans* geometry (Scheme 3).

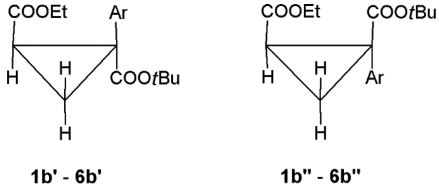
Scheme 3. Stereostructures of the Products 1a−6a Determined by ^{1}H NOESY Analysis



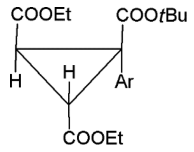
Similar analysis of the coupling constants and NOE effects for **4b′** and **4b″** revealed that the major isomer **4b′** has *trans* geometry; hence, all major or single isomers **1b′−6b′** have *trans* and minor **1b″**, **4b″**, **5b″** have *cis* geometry (Scheme 4).

Products of the reaction of diethyl maleate **1c−6c** are formed as single stereoisomers. On the basis of coupling constants of the cyclopropane ring protons in the ^{1}H NMR spectra that, for all products, were in the range of 6.1−6.5 Hz, we consider that, in all **1c−6c**, the ethoxycarbonyl groups are mutually *trans* located (Scheme 5).

Scheme 4. Stereostructures of the Products 1b−6a Determined by ^{1}H NOESY Analysis



Scheme 5. Stereostructures of the Products 1c−6c Determined by ^{1}H NOESY Analysis



A detailed discussion of the ^{1}H NMR and NOE effects, that is the basis of structural assignment, is presented in the Supporting Information.

In order to expand the scope of this cyclopropane synthesis and show its general character, we have attempted the reaction of the α-chloronitrobenzylic carbanions generated via VNS reaction with a cyclic Michael acceptor cyclopent-2-en-1-one. The reaction of *o*-bromonitrobenzene **4** and *o*-nitroanisole **5** with *t*-butyl dichloroacetate, followed by addition of cyclopent-2-en-1-one carried out under the standard conditions, gave expected substituted cyclopentanonecyclopropanes in high yields (Scheme 6).

The reported earlier reaction of cyclopent-2-en-1-one with the carbanion of methyl dichloroacetate proceeded with high diastereoselectivity.[11] The reaction of this Michael acceptor with α-chloronitrobenzylic carbanions generated via VNS was also diastereoselective.

Geometry of the products **4d** and **5d** was determined on the basis of ^{1}H NMR spectra using NOE effects. Irradiation of the cyclopropane rings protons δ 2.25 ppm and δ 2.26 ppm results in weak, but still measurable, NOE on the aromatic protons. On this basis, **4d** and **5d** was assigned *cis* geometry.

The bulky tertiary carbanion of *t*-butyl dichloroacetate reacts with nitroarenes selectively at position *para*; thus, the *p*-nitroaryl substituted cyclopropanes were obtained with high yield in the reaction with nitroarenes that contain substituents in position *ortho* to the nitro group. Attempts to perform VNS with this bulky carbanion in *p*-chloronitrobenzene, that can proceed only *ortho* to the nitro group, gave negative results. On the other hand, the somewhat less bulky carbanion of ethyl dichloroacetate reacts with *p*-chloronitrobenzene **7**, giving VNS product in position *ortho* to the nitro group in good yield.[8a] We have, therefore, attempted to synthesize *o*-nitroaryl substituted cyclopropane in the reaction of this product with acrylonitrile. The reaction was carried out under typical liquid−solid PTC conditions: K_2CO_3 in DMF and $Bu_4N^+HSO_4^-$ catalyst. Unfortunately, the expected cyclopropane **7a** was formed with low yield (8%), and the second product formed also in low yield (13%) was the *N*-oxide of substituted quinoline **7aa** (Scheme 7). It indicates that further reaction of the γ-chloro-α-cyano carbanion generated in the Michael addition of the VNS product to acrylonitrile proceeds along two pathways, intramolecular substitution to form the cyclopropane and rapid addition to the nitrogen atom of the vicinal nitro group, followed by elimination of OH^- and HCl.

Formation of the quinoline *N*-oxide resembles the reaction of *o*-nitrobenzyl phenyl sulfones with dimethyl maleate and fumarate giving quinoline *N*-oxides in good yield.[12]

Not all mixtures of **1a−6a** were separated to give individual stereoisomers. **2a** and **6a** were separated, so the individual major and minor isomers **2a′** and **2a″**, **6a′** and **6a″** were

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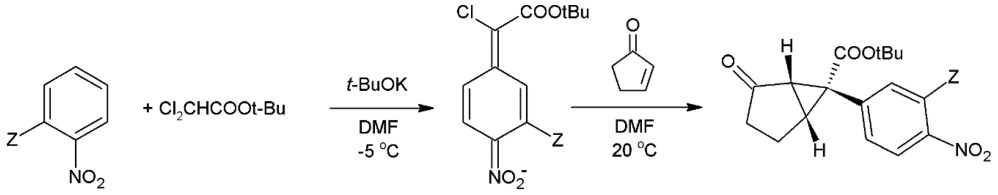
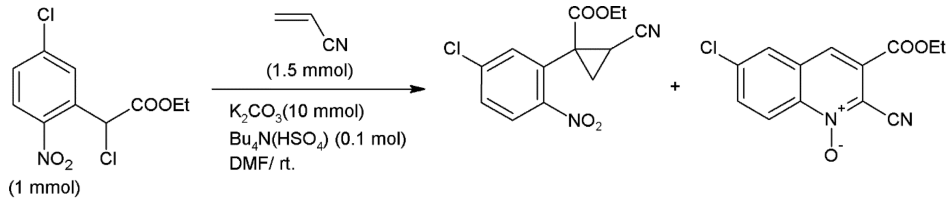
Scheme 6. One-Pot Synthesis of Bicyclic Cyclopropanes via VNS–Michael Addition



Z = Br, **4**; OMe, **5**

Z = Br, **4d** (76%, reaction time = 60 min), OMe, **5d** (70%, reaction time = 30 min)

Scheme 7. Reaction of Ethyl Chloro(2-nitro-5-chlorophenyl)acetate with Acrylonitrile Carried Out under PTC Conditions



7

7a (8%)

7aa (13%)

obtained. From the mixture of **3a**, the individual major stereoisomer **3a′** was isolated. The individual products were subjected to spectral and elemental analyses. In the remaining cases, the mixtures were analyzed. From the ^{1}H NMR spectra of the mixtures, it was possible to subtract spectra of individual major or minor isomers. Products **2b**, **3b**, and **6b** were formed as single stereoisomers, and the samples of major isomers of **1b′**, **4b′**, and **5b′** were separated from the product mixtures. Thus, all individual major isomers of **1b–6b** were obtained and analyzed. The minor isomers **1b″**, **4b″**, and **5b″** were not isolated. From the spectra of the residual mixtures, after isolation of the major isomers, it was possible to subtract spectra of the minor isomers. All spectral data, scans of NMR spectra of all compounds, and ^{1}H NMR signals of cyclopropane ring protons in tabular form are given in the experimental section in the Supporting Information.

CONCLUSION

We have shown that *p*-nitrobenzylic *α*-chlorocarbanions readily produced in the VNS reaction of *t*-butyl dichloroacetate with nitroarenes add to a variety of Michael acceptors to generate *γ*-chlorocarbanions that enter intramolecular substitution, giving esters of cyclopropane carboxylic acids containing *p*-nitroaryl substituents.

This simple generation of the active intermediates opens a versatile way of synthesis of a variety of substituted cyclopropanes and expands the applications of S_NArH reaction in organic synthesis.[14]

EXPERIMENTAL SECTION

General Information. The ^{1}H and ^{13}C NMR spectra were recorded at a temperature of 298 K in $CDCl_3$ solutions (in some cases, C_6D_6 was also used) with a 500 MHz apparatus (500 and 125 MHz, for ^{1}H and ^{13}C, respectively). To assign the structures under consideration, the following 1D and 2D experiments were employed: ^{1}H selective NOESY 2D: COSY and ^{1}H–^{13}C gradient selected HSQC. The ^{1}H and ^{13}C NMR chemical shifts are given relative to the TMS signal at 0.0 ppm. The concentration of solutions used for measurements was about 15–30 mg of compounds in 0.6 mL of solvent. Mass spectra were recorded using an electron spray ionization (ESI) technique. Melting point temperatures were determinated with a heating rate of 5 °C/min and were uncorrected. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). Thin-layer chromatography was performed on precoated silica gel plates and visualized under a UV lamp. For column chromatography, hexane/ethyl acetate mixtures were used as the eluents. Solid cyclopropanes were recrystallized from hexane/Et_2O. All solvents were distilled before use. Dry DMF was obtained by distillation from CaH_2. *tert*-Butyl dichloroacetate, ethyl chloro(2-nitro-5-chlorophenyl)acetate, and *t*-butyl chloro(4-nitrophenyl)acetate were prepared according to a literature procedure adequately.[8a,c] All other chemicals were commercial and used as received.

General Procedure for Synthesis of Substituted Cyclopropanes. To a suspension of potassium *t*-butoxide (243 mg, 2.1 mmol) in dry DMF (3 mL) cooled to −5 °C under argon, a solution of a nitroarene (1.0 mmol) and *tert*-butyl dichloroacetate (206 mg, 1.1 mmol) in DMF (1 mL) was added at once. The mixture was stirred at −5 °C for 5 min, and DMF (5 mL) and a solution of a Michael acceptor (1.5 mmol) in DMF (2 mL) were added. The cooling bath was removed, and the mixture was stirred at room temperature until VNS product was consumed (TLC control). The reaction mixture was poured in water (20 mL), and the product was extracted with dichloromethane (3 × 15 mL). The combined extract was washed with water (3 × 20 mL) and dried, and the solvent was evaporated. The products were purified by column chromatography on silica gel, hexane–ethyl acetate eluent. Evaporation of the solvent gave final products as single or a mixture of stereoisomers. Ratio of stereoisomers was determined by ^{1}H NMR using integration of diagnostic signals of methylene protons.

1a. Yield 203 mg, 70%, ratio of stereoisomers = 1.3:1, not separated, solidified upon standing. From ^{1}H NMR spectra of the mixture, signals of both isomers were assigned.

1a′. ^{1}H NMR (500 Hz, $CDCl_3$) *δ* (ppm) 1.47 (s, 9H, *t*Bu), 1.71 (dd, *J* = 9.4 Hz, *J* = 5.4 Hz, 1H, CH_2), 2.06–2.08 (m, 1H, CHCN), 2.30 (dd, 1H, *J* = 6.3 Hz, *J* = 5.4 Hz, CH_2), 7.53 (d, *J* = 8.7 Hz, 2H, ArH), 8.21 (d, *J* = 8.7 Hz, 2H, ArH).

1a″. ^{1}H NMR (500 Hz, $CDCl_3$) *δ* (ppm) 1.37 (s, 9H, *t*Bu), 1.82–1.84 (m, 1H, CH_2), 2.04–2.06 (m, 1H, CH_2), 2.53 (dd, *J* = 9.4 Hz, *J* = 6.4 Hz, 1H, CHCN), 7.56 (d, *J* = 8.7 Hz, 2H, ArH), 8.26 (d, *J* = 8.7 Hz, 2H, ArH).

*Analysis of the Mixtures of Isomers **1a′** and **1a″***. ^{13}C NMR (125 Hz, $CDCl_3$) *δ* 12.7, 13.0, 19.5, 20.4, 27.7, 27.8, 35.8, 36.8, 83.8, 84.3, 117.1, 117.4, 123.7, 123.7, 130.9, 131.7, 140.9, 143.5, 147.7, 166.6, 168.2; Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.46; H, 5.70; N, 9.70; MS (ESI, MeOH): 311 $[M + Na]^+$, 599 $[2M + Na]^+$.

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1b. Yield 271 mg, 81%, ratio of stereoisomers = 6.7:1. Major isomer **1b′** isolated by double recrystallization.

1b′. White solid, mp = 81.5−82.5 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 2981, 1734, 1717, 1601, 1515, 1474, 1455, 1392, 1382, 1372, 1366, 1340, 1294, 1280, 1258, 1203, 1159, 1105, 1028, 985, 854, 843, 803, 752, 699, 533; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.04 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.37 (s, 9H, *t*Bu), 1.91 (dd, J = 8.5 Hz, J = 4.5 Hz, 1H, CH_2), 1.98, (dd, J = 6.4 Hz, J = 4.5 Hz, 1H, CH_2), 2.72 (dd, J = 8.5 Hz, J = 6.5 Hz, 1H, $\underline{CH}$-COOEt), 3.88−3.95 (m, 2H, CH_3-$\underline{CH_2}$), 7.42 (d, J = 8.7 Hz, 2H, ArH), 8.16 (2H, d, J = 8.7 Hz, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 19.1, 27.8, 29.20, 37.4, 61.1, 82.6, 123.0, 131.5, 143.0, 147.2, 168.8, 169.7; Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.98; H, 6.34; N, 4.05; MS (ESI, MeOH): 358 [M + Na]$^+$, 693 [2M + Na]$^+$.

1b″. NMR spectra were subtracted from the spectra of the mixtures. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.38 (s, 9H, *t*Bu), 1.49 (dd, J = 8.5 Hz, J = 5.1 Hz, 1H, CH_2), 2.15−2.18 (m, 1H, CH_2), 2.23, (dd, J = 8.5 Hz, J = 6.6 Hz, 1H, $\underline{CH}$-COOEt), 4.20−4.25 (m, 2H, CH_3-$\underline{CH_2}$), 7.58 (d, J = 8.8 Hz, 2H, ArH), 8.18 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.3, 18.7, 27.7, 28.5, 39.0, 61.3, 82.3, 123.6, 130.0, 142.8, 146.1, 167.4, 169.6.

1c. Yield 271 mg, 66%, pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2980, 1723, 1605, 1521, 1446, 1393, 1369, 1346, 1269, 1257, 1208, 1146, 1113, 1095, 1080, 1035, 1014, 904, 853, 847, 789, 749, 737, 695, 668, 654; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.09 (t, J = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 1.31−1.34 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 3.00 (d, J = 6.2 Hz,1H, $\underline{CH}$-COOEt), 3.22 (d, J = 6.2 Hz, 1H, $\underline{CH}$-COOEt), 3.95−3.99 (m, 2H, CH_3-$\underline{CH_2}$), 4.22−4.26 (m, 2H, CH_3-$\underline{CH_2}$), 7.49−7.51 (m, 2H, ArH), 8.16−8.18 (m, 2H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.2, 27.6, 31.8, 32.0, 44.9, 61.5, 61.7, 83.1, 123.6, 130.4, 141.9, 147.6, 165.9, 167.5, 167.7; Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.18; N, 3.44. Found: C, 58.87; H, 6.01; N, 3.36; MS (ESI, MeOH): 430 [M + Na]$^+$, 837 [2M + Na]$^+$.

2a. Yield 182 mg, 59%, ratio of stereoisomers = 1.2:1, separated by column chromatography.

2a′. White solid, mp = 120.5−122.5 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 3118, 2988, 2243, 1722, 1610, 1602, 1526, 1489, 1457, 1434, 1418, 1393, 1370, 1345, 1313, 1258, 1220, 1203, 1155, 1109, 1084, 954, 938, 888, 864, 843, 830, 792, 750, 736, 693, 672, 626, 552, 455; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, *t*Bu), 1.72 (dd, J = 9.5 Hz, J = 5.5 Hz, 1H, CH_2), 2.06 (dd, J = 9.5 Hz, J = 6.5 Hz, 1H, CH−CN), 2.31 (dd, J = 6.5, J = 5.5, 1H, CH_2), 7.29−7.32 (m, 2H, ArH), 8.04−8.07 (m, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 12.9, 19.6, 27.8, 36.2 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 84.7, 116.7, 120.1 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 126.0 (d, $^3J_{C\text{-}F}$ = 4.0 Hz), 126.3 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 136.9 (d, $^3J_{C\text{-}F}$ = 6.9 Hz), 144.9 (d, $^2J_{C\text{-}F}$ = 8.1 Hz), 155.1 (d, $^1J_{C\text{-}F}$ = 265.5 Hz), 166.1; Anal. Calcd for $C_{15}H_{15}FN_2O_4$: C, 58.82; H, 4.92; F, 6.20; N, 9.15; Found: 58.80; H, 4.91; F, 6.23; N, 9.09; MS (ESI, MeOH): 329 [M + Na]$^+$, 635 [2M + Na]$^+$.

2a″. White solid, mp = 112.5−114.5 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 3057, 2982, 2248, 1721, 1612, 1599, 1530, 1494, 1429, 1415, 1371, 1356, 1337, 1307, 1286, 1226, 1158, 1106, 1085, 939, 889, 839, 775, 750, 734, 727, 702, 636, 560, 462; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.38 (s, 9H, *t*Bu), 1.81 (dd, J = 6.3 Hz, J = 5.1 Hz, 1H, CH_2), 2.06 (dd, J = 9.4 Hz, J = 5.1 Hz, 1H, CH_2), 2.53 (dd, J = 9.4, J = 6.3, 1H, CH-CN), 7.26−7.33 (m, 2H, ArH), 8.09−8.12 (m, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 13.2, 20.4, 27.7, 35.5 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 84.2, 117.1, 120.8 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 126.3 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 126.8 (d, $^3J_{C\text{-}F}$ = 5.0 Hz), 137.1 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 142.4 (d, $^2J_{C\text{-}F}$ = 8.8 Hz), 155.2 (d, $^1J_{C\text{-}F}$ = 263.8 Hz), 167.6; Anal. Calcd for $C_{15}H_{15}FN_2O_4$: C, 58.82; H, 4.92; F, 6.20; N, 9.15. Found: C, 58.62; H, 4.94; F, 6.13; N, 9.09; MS (ESI, MeOH): 329 [M + Na]$^+$, 635 [2M + Na]$^+$.

2b′. Yield 197 mg, 56%, white solid, mp = 76−77 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 2980, 2940, 1734, 1721, 1612, 1602, 1520, 1491, 1455, 1384, 1372, 1366, 1342, 1281, 1252, 1229, 1281, 1196, 1157, 1109, 1083, 1030, 991, 949, 842, 831, 761, 753, 693, 673, 593, 560; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.10 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.38 (s, 9H, *t*Bu), 1.91 (dd, J = 8.5 Hz, J = 4.6 Hz, 1H, CH_2), 1.94 (dd, J = 6.5 Hz, J = 4.6 Hz, 1H, CH_2), 2.71 (dd, J = 8.5 Hz, J = 6.5 Hz, 1H, $\underline{CH}$-COOEt), 3.99−3.94 (m, 2H, CH_3-$\underline{CH_2}$), 7.26−7.17 (m, 2H, ArH), 8.01−7.98 (m, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 19.2, 27.8, 29.3, 37.1 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 61.3, 83.0, 120.6 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 125.5 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 126.8 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 136.3 (d, $^3J_{C\text{-}F}$ = 6.2 Hz), 144.7 (d, $^2J_{C\text{-}F}$ = 8.8 Hz), 155.0 (d, $^1J_{C\text{-}F}$ = 262.5 Hz), 168.7, 169.1; Anal. Calcd for $C_{17}H_{20}FNO_6$: C, 57.79; H, 5.71; F, 5.38; N, 3.96. Found: C, 57.80; H, 5.74; F, 5.39; N, 3.92. MS (ESI, MeOH): 376 [M + Na]$^+$, 729 [2M + Na]$^+$.

2c. Yield 165 mg, 39%, pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2981, 1724, 1613, 1601, 1528, 1491, 1447, 1418, 1394, 1369, 1346, 1275, 1257, 1197, 1143, 1097, 1035, 976, 895, 861, 835, 787, 751, 730, 688, 668, 655; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.32−1.36 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 2.97 (d, J = 6.2 Hz, 1H, $\underline{CH}$-COOEt), 3.21 (d, J = 6.2 Hz, 1H, $\underline{CH}$-COOEt), 4.02 (q, J = 7.2 Hz, 2H, CH_3-$\underline{CH_2}$), 4.24 (q, J = 7.1, 2H, CH_3-$\underline{CH_2}$), 7.25−7.29 (m, 2H, ArH), 8.01−8.04 (m, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.2, 27.6, 31.9, 32.2, 44.5 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 61.7, 61.9, 83.6, 119.6 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 125.6 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 126.1 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 136.8 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 143.5 (d, $^2J_{C\text{-}F}$ = 8.8 Hz), 155.2 (d, $^1J_{C\text{-}F}$ = 263.8 Hz), 165.5, 167.4, 167.4; Anal. Calcd for $C_{20}H_{24}FNO_8$: C, 56.47; H, 5.69; F, 4.47; N, 3.29. Found: C, 56.47; H, 5.77; F, 4.42; N, 3.30; MS (ESI, MeOH): 448 [M + Na]$^+$, 873 [2M + Na]$^+$.

3a. Yield 265 mg, 82%, ratio of stereoisomers = 1.1:1. Major isomer **3a′** isolated by column chromatography.

3a′. White solid, mp = 118−120 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 3103, 2988, 2247, 1719, 1593, 1580, 1524, 1475, 1436, 1371, 1364, 1354, 1320, 1287, 1255, 1214, 1155, 1141, 1102, 1051, 930, 919, 864, 848, 837, 815, 805, 769, 741, 700, 663, 623, 566, 482; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, *t*Bu), 1.71 (dd, J = 9.4 Hz, J = 5.3 Hz, 1H, CH_2), 2.04 (dd, J = 9.4 Hz, J = 6.8 Hz, 1H, CH-CN), 2.29−2.31 (m, 1H, CH_2), 7.41 (dd, J = 8.3 Hz, J = 1.2 Hz, 1H, ArH), 7.53 (d, J = 1.2 Hz, 1H, ArH), 7.87 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 12.8, 19.4, 27.8, 36.1, 84.7, 116.8, 125.7, 127.3, 129.2, 133.3, 142.4, 147.4, 166.2; Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; Cl, 10.98; N, 8.68; Found: C, 55.75; H, 4.71; Cl, 10.82; N, 8.51; MS (ESI, MeOH): 345 [M + Na]$^+$.

3a″. NMR spectra were subtracted from the spectra of the mixtures. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.38 (s, 9H, *t*Bu), 1.82 (dd, J = 6.4 Hz, J = 5.2 Hz, 1H, CH_2), 2.06 (dd, J = 9.4 Hz, J = 5.2 Hz, 1H, CH_2), 2.53 (dd, J = 9.4, J = 6.4, 1H, CH-CN), 7.44 (dd, J = 8.4 Hz, J = 1.8 Hz 1H, ArH), 7.56 (d, J = 1.8 Hz, 1H, ArH), 7.93 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 13.1, 20.3, 27.7, 35.3, 84.2, 117.1, 125.8, 127.3, 130.0, 134.0, 139.9, 147.5, 167.7.

3b′. Yield 235 mg, 63%, pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2979, 1716, 1595, 1582, 1527, 1478, 1457, 1393, 1381, 1368,1346, 1274, 1253, 1200, 1151, 1093, 1049, 1033, 986, 920, 861, 839, 802, 749, 738, 699, 668, 654; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.09 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.39 (s, 9H, *t*Bu), 1.91 (dd, J = 8.5 Hz, J = 4.6 Hz, 1H, CH_2), 1.95 (dd, J = 6.5 Hz, J = 4.6 Hz, 1H, CH_2), 2.70 (dd, J = 8.5 Hz, J = 6.5 Hz, 1H, $\underline{CH}$-COOEt), 4.00−3.94 (m, 2H, CH_3-$\underline{CH_2}$), 7.28 (dd, J = 7.5 Hz, J = 1.8, 1H, ArH), 7.44 (d, J = 1.8 Hz, 1H, ArH), 7.84 (d, J = 8.4 Hz,1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 19.0, 27.8, 29.2, 36.9, 61.2, 82.9, 125.2, 126.7, 129.8, 134.0, 142.0, 146.7, 168.6, 169.2; Anal. Calcd for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; Cl, 9.59; N, 3.79, Found: C, 55.11; H, 5.35; Cl, 9.73; N, 3.83; MS (ESI, MeOH): 392 [M + Na]$^+$, 761 [2M + Na]$^+$.

3c. Yield 301 mg, 68%, pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2981, 1723, 1595, 1581, 1530, 1446, 1393, 1369, 1338, 1272, 1254, 1209, 1146, 1094, 1035, 864, 839, 803, 787, 749, 668; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.13 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.32−1.36 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 2.97 (d, J = 6.2 Hz, 1H, $\underline{CH}$-COOEt), 3.21 (d, J = 6.2 Hz, 1H, $\underline{CH}$-COOEt), 4.00−4,05 (m, 2H, CH_3-$\underline{CH_2}$), 4.24 (q, J = 7.1 Hz, 2H, CH_3-$\underline{CH_2}$), 7.37 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, ArH), 7.51 (d, J = 1.8 Hz, 1H, ArH), 7.84 (d, J = 8.4 Hz 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.2, 27.6, 31.8, 32.1, 44.3, 61.7, 61.8, 83.5, 125.7, 127.2, 128.7, 132.9, 140.9, 147.2, 165.6, 167.4, 167.5; Anal. Calcd for $C_{20}H_{24}ClNO_8$: C, 54.36; H, 5.47; Cl, 8.02; N, 3.17. Found: C, 54.10; H, 5.52; Cl, 8.05; N, 3.12; MS (ESI, MeOH): 464 [M + Na]$^+$, 905 [2M + Na]$^+$.

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4a. Yield 302 mg, 82%, ratio of stereoisomers = 1.3:1, not separated, solidified upon standing.

From ^{1}H NMR spectra of the mixture, signals of both isomers were assigned:

4a′. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, *t*Bu), 1.71 (dd, J = 9.4 Hz, J = 5.4 Hz, 1H, CH_2), 2.03 (dd, J = 9.4 Hz, J = 6.7 Hz, 1H, CH-CN), 2.29 (1H, dd, J = 6.7 Hz, J = 5.4 Hz, CH_2), 7.45 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H, ArH), 7.72 (d, J = 1.7 Hz, 1H, ArH), 7.83 (d, J = 8.4 Hz, 1H, Ar-H).

4a″. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.38 (s, 9H, *t*Bu), 1.80−1.83 (m, 1H, CH_2), 2.06 (dd, J = 9.4 Hz, J = 5.1 Hz, 1H, CH_2) 2.51 (dd, J = 9.4, J = 6.4, 1H, CH-CN), 7.48 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H, ArH), 7.75 (d, J = 1.7 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 1H, ArH).

*Analysis of the Mixtures of Isomers **4a′** and **4a″***. ^{13}C NMR (125 Hz, $CDCl_3$) δ 12.8, 13.1, 19.4, 20.3, 27.7, 27.8, 35.2, 36.0, 84.1, 84.7, 114.6, 114.6, 116.8, 117.1, 125.6, 125.7, 129.92, 130.7, 136.5, 137.2, 139.8, 142.3, 149.3, 166.2, 167.7; Anal. Calcd for $C_{15}H_{15}BrN_2O_4$: C, 49.06; H, 4.12; Br, 21.76; N, 7.63. Found: C, 49.26; H, 4.08; Br, 21.99; N, 7.43; MS (ESI, MeOH): 389 $[M + Na]^+$.

4b. Yield 350 mg, 84%, ratio of stereoisomers = 7.6:1. Major isomer **4b′** isolated by column chromatography; the residue was a 1.1:1 mixture of isomers.

4b′. Pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2979, 1716, 1594, 1578, 1528, 1476, 1457, 1394, 1380, 1368, 1354, 1199, 1149, 1093, 1038, 985, 917, 858, 839, 799, 749, 735, 698, 668, 652; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.08 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.38 (s, 9H,*t*Bu), 1.90 (dd, J = 8.5 Hz, J = 4.6 Hz, 1H, CH_2), 1.96 (dd, J = 6.4 Hz, J = 4.6 Hz, 1H, CH_2), 2.69 (dd, J = 8.5 Hz, J = 6.4 Hz, 1H, $\underline{CH}$-COOEt), 3.91- 4.00 (m, 2H, CH_3-$\underline{CH_2}$), 7.33 (dd, J = 8.4 Hz, J = 1.8, 1H, ArH), 7.63 (1H, d, J = 1.7 Hz, ArH), 7.81 (1H, d, J = 8.4 Hz, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.1, 19.0, 27.8, 29.2, 36.8, 61.26, 82.9, 114.0, 125.2, 130.5, 137.2, 141.9, 148.5, 168.6, 169.2; Anal. Calcd for $C_{17}H_{20}BrNO_6$: C, 49.29; H, 4.87; Br, 19.29; N, 3.38; Found: C, 49.11; H, 4.83; Br, 19.23; N, 3.45; MS (ESI, MeOH): 436 $[M + Na]^+$, $[2M + Na]^+$.

4b″. NMR spectra were subtracted from the spectra of the mixtures. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.39 (s, 9H, *t*Bu), 1.48 (dd, J = 8.6 Hz, J = 5.1 Hz, 1H, CH_2), 2.16−2.13 (m, 1H, CH_2), 2.20 (dd, J = 8.5 Hz, J = 6.7 Hz, 1H, $\underline{CH}$-COOEt, 4.18−4.25 (m, 2H, CH_3-$\underline{CH_2}$), 7.50 (dd, J = 8.4 Hz, J = 1.8, 1H, ArH), 7.78 (d, J = 1.7 Hz, 1H, ArH), 7.80 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.2, 18.5, 27.8, 28.6, 38.4, 61.4, 82.6, 114.5, 125.6, 129.0, 135.7, 144.9, 148.9, 167.0, 169.3.

4c. Yield 416 mg, 85%, yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2981, 1723, 1592, 1577, 1531, 1457, 1393, 1368, 1337, 1271, 1255, 1209, 1145, 1094, 1037, 859, 840, 783, 748, 700, 668; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.32−1.36 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 2.97 (d, J = 6.3 Hz, 1H, $\underline{CH}$-COOEt), 3.20 (d, J = 6.3 Hz, 1H, $\underline{CH}$-COOEt), 4.00−4,05 (m, 2H, CH_3-$\underline{CH_2}$), 4.24 (q, J = 7.1, 2H, CH_3-$\underline{CH_2}$), 7.41 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, ArH), 7.69 (d, J = 1.8 Hz, 1H, ArH), 7.45 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.1, 14.2, 27.6, 31.8, 32.0, 44.2, 61.7, 61.8, 83.5, 114.5, 125.6, 129.4, 136.0, 140.8, 149.1, 165.6, 167.3, 167.5; Anal. Calcd for $C_{20}H_{24}BrNO_8$: C, 49.40; H, 4.97; Br, 16.43; N, 2.88; Found: C, 49.18; H, 5.09; Br, 16.34; N, 2.84; MS (ESI, MeOH): 508 $[M + Na]^+$, 995 $[2M + Na]^+$.

4d. Yield 299 mg, 76%, white solid, mp = 112−115 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 3097, 2972, 1723, 1594, 1576, 1543, 1369, 1323, 1290, 1249, 1161, 1145, 1073, 949, 897, 861, 852, 839, 808, 733, 658, 614, 572, 500, 474; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 0.89−0.97 (m, 1H), 1.35 (s, 9H), 1.93−2.03 (m, 2H), 2.36−2.44 (m, 1H), 2.80−2.87 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H); ^{1}H NMR (500 Hz, C_6D_6) δ (ppm) 0.37−0.33 (m, 1H, CH_2(C═O)), 1.09−1.04 (m, 10H, 9H from *t*Bu and 1H from CH_2), 1.39−1.33 (m, 2H, 1H from CH_2 and 1H from CH_2(C═O)), 2.25 (t, J = 5.7, 1H, CH), 2.66 (d, J = 6.1 Hz, 2H, CH(C═O)), 6.70 (d, J = 6.0 Hz, 1H, Ar), 7.00 (d, J = 6.4 Hz, 1H, ArH), 7.36 (s, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 20.6, 27.8, 34,8, 35.0, 39.2, 41.6, 83.2, 114.6, 125.8, 130.4, 137.1, 139.8, 149.0, 168.2, 211.5; ^{13}C NMR (125 Hz, C_6D_6) δ 20.3, 27.5, 34.5, 35.0, 39.0, 41.5, 82.2, 125.62, 125.65, 130.5, 137.0, 139.7, 149.5, 168.2, 209.5; Anal. Calcd for $C_{17}H_{18}BrNO_5$: C, 51.53; H, 4.58; N, 3.53; Br, 20.17; Found: C, 51.69; H, 4.52; N, 3.53; Br, 20.08; MS (ESI, MeOH): 345 $[M + Na]^+$.

5a. Yield 226 mg, 71%, ratio of stereoisomers = 1:1, not separated. From ^{1}H NMR spectra of the mixture, signals of both isomers were assigned.

5a′. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.47 (s, 9H, *t*Bu), 1.70 (dd, J = 9.4 Hz, J = 5.3 Hz, 1H, CH_2), 2.02−2.04 (m, 1H, CHCN), 2.29 (dd, 1H, J = 6.6 Hz, J = 5.3 Hz CH_2), 3.99 (s, 3H, OCH_3), 7.04 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz ArH), 7.10 (d, 1H, J = 1.6 Hz, ArH), 7.87 (d, 1H, J = 8.4 Hz, ArH).

5a″. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.38 (s, 9H, *t*Bu), 1.79 (dd, J = 6.4 Hz, J = 5.1 Hz, 1H, CH_2), 2.04−2.05 (m, 1H, CH_2), 2.50 (dd, J = 9.4, J = 6.4, 1H, CH-CN), 3.97 (s, 3H, OCH_3), 6.99 (dd, J = 8.3 Hz, J = 1.6 Hz, 1H, ArH), 7.08 (d, J = 1.5 Hz, 1H, ArH), 7.80 (d, J = 8.3 Hz, 1H, ArH).

*Analysis of the Mixtures of Isomers **5a′** and **5a″***. ^{13}C NMR (125 Hz, $CDCl_3$) δ 12.7, 12.9, 19.5, 20.6, 27.8, 27.9, 36.1, 36.9, 56.7, 83.8, 84.3, 115.3, 116.0, 117.2, 117.5, 121.5, 122.5, 125.9, 126.0, 139.3, 139.4, 140.6, 143.1, 152.8, 152.9, 166.6, 168.1; Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80; Found: C, 60.50; H, 5.56; N, 8.75; MS (ESI, MeOH): 341 $[M + Na]^+$, 659 $[2M + Na]^+$.

5b. Yield 284 mg, 78%, ratio of stereoisomers = 8.8:1. Major isomer **5b′** isolated by column chromatography; the residue was a 1.1:1 mixture of isomers.

5b′. Pale yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2979, 1716, 1607, 1591, 1519, 1492, 1458, 1406, 1381, 1368, 1348, 1303, 1277, 1244, 1197, 1146, 1108, 1085, 1024, 992, 936, 856, 840, 799, 755, 727, 720, 704, 675, 668, 650; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.05 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.38 (s, 9H, *t*Bu), 1.88 (dd, J = 8.5 Hz, J = 4.6 Hz, 1H, CH_2), 1.96 (dd, J = 6.4 Hz, J = 4.6 Hz, 1H, CH_2), 2.70 (dd, J = 8.4 Hz, J = 6.4 Hz, 1H, $\underline{CH}$-COOEt), 3.91−3.96 (m, 5H), 6.92 (dd, J = 8.4 Hz, J = 1.6, 1H, ArH), 6.97 (d, J = 1.6 Hz, 1H, ArH), 7.80 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 19.1, 27.8, 29.2, 37.6, 56.5, 61.1, 82.6, 115.9, 122.6, 125.4, 138.6, 142.7, 152.7, 168.8, 169.6; Anal. Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83; Found: C, 58.96; H, 6.14; N, 4.04; MS (ESI, MeOH): 388 $[M + Na]^+$, 753 $[2M + Na]^+$.

5b″. NMR spectra were subtracted from the spectra of the mixtures. ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.39 (s, 9H, *t*Bu), 1.48 (dd, J = 8.6 Hz, J = 5.1 Hz, 1H, CH_2), 2.12 (dd, J = 6.5 Hz, J = 5.1 Hz, 1H, CH_2), 2.21 (dd, J = 8.6 Hz, J = 6.5 Hz, 1H, $\underline{CH}$-COOEt), 3.97 (s, 3H, CH_3O), 4.18−4.25 (m, 2H, CH_3-$\underline{CH_2}$), 7.05 (dd, J = 8.4 Hz, J = 1.8, 1H, ArH), 7.15 (d, J = 1.8 Hz, 1H, ArH), 7.79 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.2, 18.7, 27.8, 30.9, 39.6, 56.6, 61.2, 82.2, 114.4, 120.7, 125.8, 138.9, 145.6, 152.9, 167.4, 169,8.

5c. Yield 308 mg, 70%, yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2980, 1724,1607, 1590, 1522, 1495, 1463, 1407,1393, 1368, 1244, 1204, 1185, 1144, 1097, 1029, 908, 876, 859, 834, 785, 755, 728, 668; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.10 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.32−1.36 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 3.00 (d, J = 6.1 Hz, 1H, $\underline{CH}$-COOEt), 3.20 (d, J = 6.1 Hz, 1H, $\underline{CH}$-COOEt), 3.95−4,02 (m, 5H), 4.24 (q, J = 7.1, 2H, CH_3-$\underline{CH_2}$), 7.00−7.02 (m, 2H, ArH), 7.81 (d, J = 8.3 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.2, 27.6, 31.7, 31.9, 45.4, 56.7, 61.5, 61.7, 83.1, 114.5, 121.3, 125.8, 139.2, 141.5, 152.9, 165.9, 167.4, 167.9; Anal. Calcd for $C_{21}H_{27}NO_9$: C, 57.66; H, 6.22; N, 3.20; Found: C, 57.68; H, 5.99; N, 3.08; MS (ESI, MeOH): 460 $[M + Na]^+$, 897 $[2M + Na]^+$.

5d. Yield 242 mg, 70%, white solid, mp = 146−148 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 2977, 2941, 1719, 1607, 1591, 1514, 1491, 1464, 1406, 1370, 1352, 1302, 1290, 1267, 1254, 1237, 1162, 1146, 1095, 1076, 1056, 1028, 944, 904, 885, 856, 841, 835, 779, 759, 708, 641, 562, 481, 457; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 0.90−0.98 (m, 1H), 1.35 (s, 9H), 1.94−2.00 (m, 2H), 2.33−2.41 (m, 1H), 2.78−2.87 (m, 2H), 3.93 (s, 3H), 6.98 (bs, 2H), 7.85 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 20.9, 27.8, 35,0, 35.2, 40.2, 41.6, 56.7, 82.8, 115.8, 122.6, 125.9, 138.9, 140.5, 153.0, 168.6, 212.4, Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.17; H, 6.12; N, 4.09; MS (ESI, MeOH): 370 $[M + Na]^+$.

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6a. Yield 283 mg, 85%, ratio of stereoisomers = 1.9:1, separated by column chromatography.

6a′. Pale yellow oil, FT-IR (film, ν_{max}/cm^{-1}) 2981, 2244, 1721, 1597, 1562, 1520, 1471, 1392, 1368, 1351, 1277, 1248, 1155, 1125, 1077, 1025, 975, 950, 907, 864, 839, 786, 767, 729, 701; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.42 (s, 9H, *t*Bu), 1.54 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$), 1.98 (dd, J = 9.4 Hz, J = 5.0 Hz, 1H, CH_2), 2.34 (dd, J = 6.7 Hz, J = 5.0 Hz, 1H, CH_2), 2.56 (dd, J = 9.4 Hz, J = 6.7 Hz, 1H, CH-CN), 4.31 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 7.23 (s, 1H, ArH), 8.95 (s, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.2, 27.9, 37.4, 66.0, 83.9, 111.4, 117.2, 136.1, 146.3, 158.3, 158.4, 167.7; Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.50; H, 5.69; N, 12.73; MS (ESI, MeOH): 356 $[M + Na]^+$.

6a″. White solid, mp = 120−122 °C; FT-IR (KBr, ν_{max}/cm^{-1}) 2984, 2249, 1712, 1603, 1562, 1523, 1488, 1472, 1455, 1394, 1365,1352, 1320, 1295, 1248, 1208, 1157, 1126, 1109, 1087, 1069, 1029, 972, 937, 869, 841, 771, 765, 730, 571, 505, 468, 440; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.52−1.56 (m, 12H, 3H from $\underline{CH_3}CH_2$ and 9H from *t*Bu), 1.94 (dd, J = 9.0 Hz, J = 5.0 Hz, 1H, CH_2), 2.27 (dd, J = 7.0 Hz, J = 5.0 Hz, 1H, CH_2), 2.76 (dd, J = 9.0 Hz, J = 7.0 Hz, 1H, CH-CN), 4.30 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 7.56 (s, 1H, ArH), 8.81 (s, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.2, 14.7, 22.5, 28.0, 36.6, 65.9, 84.4, 109.6, 117.4, 135.5, 146.2, 158.4, 159.9, 166.4; Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.62; H, 5.72; N, 12.50; MS (ESI, MeOH): 356 $[M + Na]^+$.

6b′. Yield 275 mg, 72%, yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2980, 1717, 1596, 1561, 1520, 1471, 1392, 1367, 1352, 1279, 1256, 1246, 1200, 1155, 1126, 1085, 1027, 997, 961, 908, 857, 840, 803, 752, 727, 668; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.11 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 1.38 (s, 9H, *t*Bu), 1.50 (t, J = 7.0 Hz, 3H, $\underline{CH_3}$-CH_2), 1.89 (dd, J = 8.5 Hz, J = 4.5 1H, Hz, CH_2), 2.09 (dd, J = 6.6 Hz, J = 4.5 Hz, 1H, CH_2), 2.76 (dd, J = 8.5 Hz, J = 6.6 Hz, 1H, $\underline{CH}$-COOEt), 4.20−4.29 (m, 2H, CH_3-$\underline{CH_2}$), 6.98 (s, 1H, ArH), 8.90 (s, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.0, 14.1, 19.8, 27.8, 29.0, 39.6, 61.2, 65.8, 82.8, 111.0, 135.5, 146.0, 158.3, 161.2, 169.1, 169.3; Anal. Calcd for $C_{18}H_{24}N_2O_7$: C, 56.83; H, 6.36; N, 7.36. Found: C, 56.72; H, 6.45; N, 7.20; MS (ESI, MeOH): 403 $[M + Na]^+$, 783 $[2M + Na]^+$.

6c. Yield 245 mg, 54%, yellow oil; FT-IR (film, ν_{max}/cm^{-1}) 2981, 1725, 1597, 1562, 1524, 1470, 1391, 1368, 1352, 1334, 1279, 1246, 1206, 1149, 1118, 1095, 1026, 986, 933, 859, 838, 766, 750, 726, 668; ^{1}H NMR (500 Hz, C_6D_6) δ (ppm) 0.75 (t, J = 7.0 Hz, 3H, $COOCH_2\underline{CH_3}$), 0.82 (t, J = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 0.96 (t, J = 7.0 Hz, 3H, $COOCH_2\underline{CH_3}$), 1.34 (s, 9H, *t*Bu), 3.07−3.20 (m, 2H, $O\underline{CH_2}CH_3$), 3.57 (d, J = 6.5 Hz, 1H, CH-COOEt), 3.69 (d, J = 6.5 Hz, 1H, CH-COOEt), 3.73 (dd, J = 14 Hz, J = 7.0 Hz, 2H, $COO\underline{CH_2}CH_3$), 3.94−4.01 (m, 2H, $COO\underline{CH_2}CH_3$), 6.91 (s, 1H, ArH), 8.74 (s, 1H, ArH); ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm)1.13 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.32 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.39 (s, 9H, *t*Bu), 1.51 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.26 (s, 2H, $\underline{CH}$COOEt), 2.00 (m, 2H, $CH_3\underline{CH_2}$), 4.25 (m, 4H, $\underline{CH_2}CH_3$), 7.04 (s, 1H, ArH), 8.88 (s, 1H, ArH); ^{13}C NMR (125 Hz, C_6D_6) δ 13.8, 13.8, 14.1, 27.7, 32,6, 33.1, 47.2, 61.4, 61.7, 65.3, 82.8, 110.0, 136.5, 146.2, 158.5, 160.0, 166.0, 167.6, 168.0; ^{13}C NMR (125 Hz, $CDCl_3$); δ 14.0, 14.1, 14.2, 27.7, 32,2, 32.3, 46.3, 61.6, 61.8, 66.0, 83.4, 109.7, 135.8, 146.2, 158.5, 159.80, 165.6, 167.6, 167.7; Anal. Calcd for $C_{21}H_{28}N_2O_9$: C, 55.75; H, 6.24; N, 6.19. Found: C, 55.60; H, 6.14; N, 5.99; MS (ESI, MeOH): 475 $[M + Na]^+$.

Reaction of Ethyl Chloro(2-nitro-5-chlorophenyl)acetate with Acrylonitrile under Solid−Liquid PTC Condition. To a suspension of anhydrous potassium carbonate (1382 mg, 10 mmol) in dry DMF (10 mL), solid $Bu_4N^+HSO_4^-$ (34 mg, 0.1 mmol) was added, at room temperature. The mixture was intensively stirred for 10 min, and a solution of ethyl chloro(2-nitro-5-chlorophenyl)acetate (1 mmol) and acrylonitrile (1.5 mmol) in 5 mL of DMF was added. The mixture was stirred at room temperature until aryl ester was consumed (TLC control). The reaction mixture was poured in water (20 mL), and the product was extracted with dichloromethane (3 × 15 mL). The combined extract was washed with water (3 × 20 mL) and dried, and the solvent was evaporated. The products were purified by column chromatography on silica gel, hexane−ethyl acetate eluent. Evaporation of the solvent gave final products as single or a mixture of stereoisomers.

7a. Yield 24 mg, 8%, white solid; mp = 129.5−131.5 °C; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.22 (t, J = 7.0 Hz, 3H, CH_3), 1.68 (bs, 1H, CH_2), 2.18−2.21 (m, 1H, CH_2), 2.42−2.44 (m, 1H, CH-CN), 4.24 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 7.45 (d, J = 1.5 Hz, 1H, ArH), 7.53 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H, ArH), 8.10 (d, J = 8.5 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 13.9, 14.9, 20.9, 34.5, 62.6, 116.5, 127.0, 129.9, 132.3, 133.5, 140.2, 147.5, 167.1; Anal. Calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.98; H, 3.76; Cl, 12.03; N, 9.51. Found: C, 52.86; H, 3.84; Cl, 12.07; N, 9.46; MS (ESI, MeOH): 317 $[M + Na]^+$, 611 $[2M + Na]^+$.

7aa. Yield 37 mg, 13%, pale yellow solid, mp = 157−160,5 °C; ^{1}H NMR (500 Hz, $CDCl_3$) δ (ppm) 1.48 (t, J = 7.1 Hz, 3H, CH_3), 4.50 (q, J = 7.1 Hz, 2H, CH_2), 7.77 (dd, J = 9.3 Hz, J = 1.8 Hz, 1H, ArH), 8.27 (s, 1H, ArH), 8.63 (d, J = 9.3 Hz, 1H, ArH), 9.20 (d, J = 1.7 Hz, 1H, ArH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.2, 62.6, 112.0, 120.7, 121.5, 121.7, 126.5, 127.9, 129.5, 132.4, 139.6, 141.2, 162.9; Anal. Calcd for $C_{13}H_9ClN_2O_3$: C, 56.43; H, 3.28; Cl, 12.81; N, 10.13. Found: C, 56.26; H, 3.13; Cl, 12.79; N, 9.98; MS (ESI, MeOH): 299 $[M + Na]^+$, 575 $[2M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR chemical shifts and coupling constants of cyclopropane ring protons in tabular form, assignment of the stereochemistry of the cyclopropanes, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all new compounds.The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00204.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Wessjohann, I. A.; Brandt, W.; Thiemann, I. *Chem. Rev.* **2003**, *103*, 1625. (b) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. (c) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (d) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (e) Chen, D.J-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.

(2) (a) Green, J. R.; Snieckus, V. *Synlett* **2014**, 2558 and the following papers. (b) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 803. (d) Campbell, M. J.; Johnson, J. S.; Parson, A. T.; Polhaus, P. W.; Sanders, S. S. *J. Org. Chem.* **2010**, *75*, 6317. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (f) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (g) Melnikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2001**, *21*, 293. (h) Mąkosza, M.; Barbasiewicz, M. *Helv. Chim. Acta* **2012**, *95*, 1871.

(3) (a) Billups, W. E.; Haley, M. M.; Lee, G.-A. *Chem. Rev.* **1989**, *89*, 1147. (b) de Mejere, A.; Kozhushkov, S.; Schill, H. *Chem. Rev.* **2006**, *106*, 4926. (c) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099. (d) Zwannenburg, B.; de Kimpe, N. In *Houben-Weyl Methods in Organic Chemistry*; de Mejere, A., Ed.; Thieme: Stuttgart, 1997; p 69. (e) Rabasso, N.; Fadel, A. *Tetrahedron Lett.* **2014**, *55*, 6068. (f) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270. (g) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (h) Cotugno, P.; Monopoli, A.; Ciminale, F.; Milella, A.; Nacci, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 13563. (i) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (j) Papageorgian, C. D.; Cubilo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641.

(4) (a) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631. (c) Mąkosza, M. *Synthesis* **2011**, 2341.

DOI: 10.1021/acs.joc.5b00204
J. Org. Chem. 2015, 80, 5436−5443

(5) Jackson, D. A.; Lawrence, N. J.; Liddle, J. *Synlett* **1996**, 55.
(6) Brown, K. M.; Jackson, D. A.; Lawrence, N. J.; Liddle, J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 6733.
(7) (a) Lawrence, N. J.; Davis, C. A.; Gray, M. *Org. Lett.* **2004**, *6*, 4957. (b) Cao, S.; Wu, J.; Li, L.; Zhu, L.; Zhang, J.; Yu, J.; Qian, X. *Org. Biomol. Chem.* **2008**, *6*, 1293.
(8) (a) Mąkosza, M.; Sienkiewicz, K.; Wojciechowski, K. *Synthesis* **1990**, 850. (b) Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488. (c) Mąkosza, M.; Białecki, M. *Synlett* **1991**, 181. (d) Tercel, M.; Lee, A. E.; Hogg, A.; Anderson, R. F.; Lee, H. H.; Siim, B. G.; Denny, W. A.; Wilson, W. R. *J. Med. Chem.* **2001**, *44*, 3511.
(9) Florio, S.; Lorusso, P.; Granito, C.; Luisi, R.; Troisi, L. *J. Org. Chem.* **2004**, *69*, 4961.
(10) Fedoryński, M.; Wojciechowski, K.; Matacz, Z.; Mąkosza, M. *J. Org. Chem.* **1978**, *43*, 4682.
(11) Escribano, A.; Pedregal, C.; González, R.; Fernández, A.; Burton, K.; Stephenson, A. *Tetrahedron* **2001**, *57*, 9423.
(12) (a) Mąkosza, M.; Tyrała, A. *Acta Chem. Scand.* **1992**, *46*, 689. (b) Kotovskaya, S. K.; Zhumabaeva, G. A.; Charushin, V. N.; Chupakhin, O. N. *Russ. Chem. Bull.* **2009**, *58*, 170.
(13) Conellon, J. M.; Rodriguez-Solla, H.; Diaz, P.; Liavona, R. *J. Org. Chem.* **2007**, *72*, 4396.
(14) Mąkosza, M. *Chem. Soc. Rev.* **2010**, *39*, 2855.

DOI: 10.1021/acs.joc.5b00204
J. Org. Chem. 2015, 80, 5436−5443