

HETEROCYCLES, Vol. 96, No. 2, 2018, pp. 219 - 232. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 24th June, 2017, Accepted, 29th December, 2017, Published online, 22nd January, 2018
DOI: 10.3987/COM-17-13770

HIGHLY REGIOSELECTIVE RING OPENING OF A COMMON *N,N*-DIALKYLAZIRIDINIUM ION BY CARBOXYLIC ACIDS

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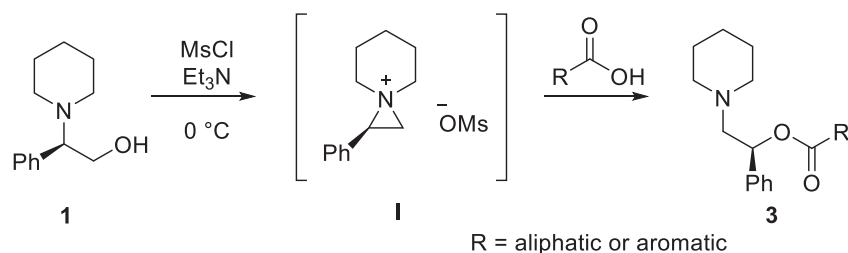
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Abstract – A variety of optically active amino esters were synthesized *via* ring-opening reaction of (*R*)-1-phenyl-3-azaspiro[2.5]octan-3-ium ion derived from (*R*)-2-phenyl-2-(piperidin-1-yl)ethan-1-ol in a highly regioselective manner. Ring-opening reaction with carboxylates series generated *in situ* proceeded smoothly and with excellent yields (85-98%).

INTRODUCTION

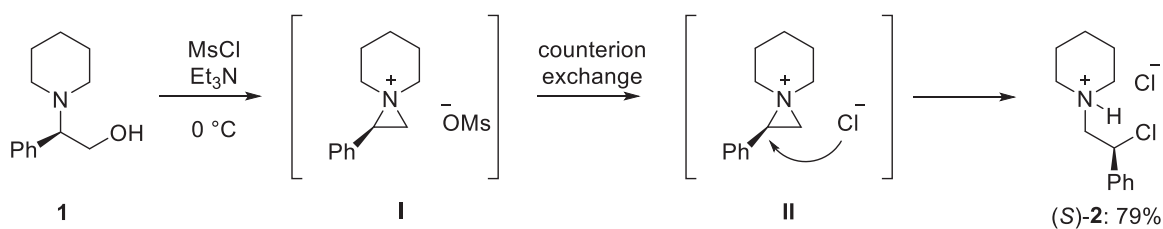
Aziridinium ions have received considerable attention as reactive intermediates in the asymmetric synthesis of natural products,¹⁻³ biologically active compounds⁴ and precursors in organic synthesis.⁵ Nucleophilic ring-opening of *N,N*-dialkylaziridinium ions have been recognized as efficient synthetic route to generate a variety of β -substituted amines including 1,2-diamines,⁶ 1,2-amino alcohols,⁷ β -amino ethers,⁸ and β -haloamines.⁹ The *N,N*-dialkylaziridinium ions are usually produced *in situ* from β -amino alcohols.¹⁰ Compared with aziridine congeners, the *N,N*-dialkylaziridinium ions show a strong electrophilic character, whereas the unactivated aziridines require activation by a Lewis acid and, therefore, always becomes aziridinium prior to nucleophilic ring-opening reactions.¹¹ Thus, *N,N*-dialkylaziridinium ions can be opened by a wide range of nucleophiles with or without rearrangement depending on the regioselectivity of the nucleophilic attack.¹⁰ Until now, opening reaction of aziridinium ions with carboxylate salts has been scarcely study.¹² In this sense, we herein report a high regiospecific ring-opening reaction of a common *N,N*-dialkylaziridinium ion **I** with a variety of aliphatic, aromatic and α,β -unsaturated carboxylic acids (Scheme 1).



Scheme 1. Ring-opening reaction of aziridinium ion **I** with various carboxylic acids

RESULTS AND DISCUSSION

Compound **1**¹³ was allowed to react with MsCl and TEA as a base in order to trap the corresponding β -chloropiperidinium chloride **2**. This intermediate was isolated as an air-stable white crystalline solid in 79% yield.¹⁴ The isolation of a single isomer, compound (*S*)-**2** is consistent with the inclusion of an aziridinium ion intermediate **II** (Scheme 2). The structure was fully ascertained by an X-ray diffraction analysis (Figure 1).



Scheme 2. Synthesis of β -chloropiperidinium chloride (*S*)-**2**

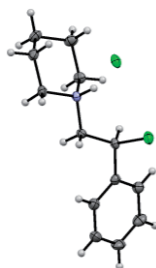


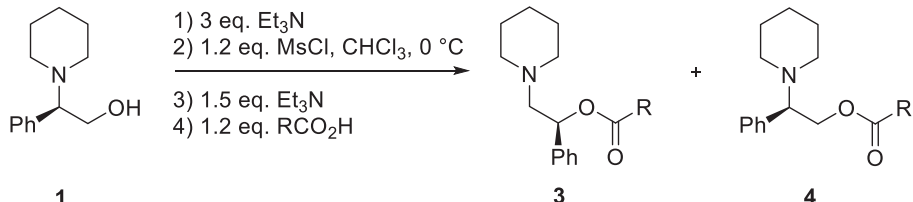
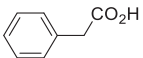
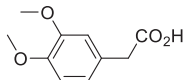
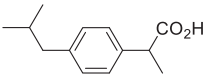
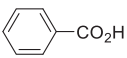
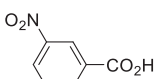
Figure 1. ORTEP of compound (*S*)-**2**

As we anticipate, this result shows clearly the more nucleophilic character of chloride anion than mesylate. According to the literature, opening of aziridinium ions usually occurs with a more nucleophilic species and no participation of chloride anion are present, but what is the competitive effect when a softer nucleophilic specie, like a carboxylate, are present in the medium reaction. For this precedent, we turned our attention to the opening reaction of aziridinium ions with diverse carboxylic acids using a modified version of O'Brien's method.⁶ We commence our investigation by the treatment of **I** with acetic acid.

After 30 min, we obtained the corresponding regioisomeric mixture of esters **3a** + **4a** in a 99:1 ratio,¹⁵ which are consistent with previous reports, where the nucleophiles attacks were performed at the more electrophilic benzylic carbon in the intermediate ion (Table 1, entry 1).^{6,16}

Therefore, a series of carboxylic acids was tested in order to know the scope and limitation of this opening reaction. The use of aliphatic carboxylic acids afforded the desired amino ester **3** as a major regioisomer in excellent chemical yields (Table 1, entries 2-6). For aromatic carboxylic acids with electron-donating or electron-withdrawing groups on the phenyl ring compound **3** was obtained as a major regioisomer in good yields (Entries 7–14). Interestingly, carboxylic acids containing pyridine moiety was well tolerated and gave the desired product in good yield (Entry 15). In addition, aromatic olefinic acid gave good yield (Entry 16).

Table 1. Summary of regioselective synthesis of amino esters derivatives

				
Entry	RCO ₂ H	Product ^a	Regioselectivity ^b 3 : 4	3 Yield (%) ^c
1	AcOH	3a	99:1	93
2	Br-(CH ₂) ₄ -CO ₂ H	3b	98:2	94
3	Me-(CH ₂) ₂₄ -CO ₂ H	3c	98:2	95
4		3d	98:2	93
5		3e	97:3	90
6		3f	97:3	92
7		3g	97:3	91
8		3h	97:3	89

9		3i	97:3	87
10		3j	97:3	91
11		3k	97:3	90
12		3l	97:3	85
13		3m	97:3	94
14		3n	97:3	93
15		3o	97:3	91
16		3p	98:2	92

^aEnantiomeric purities were measurement by UHPLC normal phase; with an ULTRON ES-Pepsin Chiral column (all products show >99% ee). ^bRatio of regioisomeric amino esters **3** and **4** in the crude product mixtures determined by ¹H NMR spectroscopy. ^cIsolated yield after silica gel chromatography.

A single crystal of amino ester **3p** was obtained and X-ray crystallography analysis showed a (*S*) configuration for the new stereocenter and therefore a bimolecular nucleophilic ring opening reaction of aziridinium ion was proposed at this point (Figure 2).¹⁷

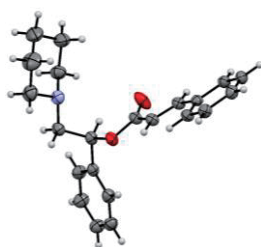
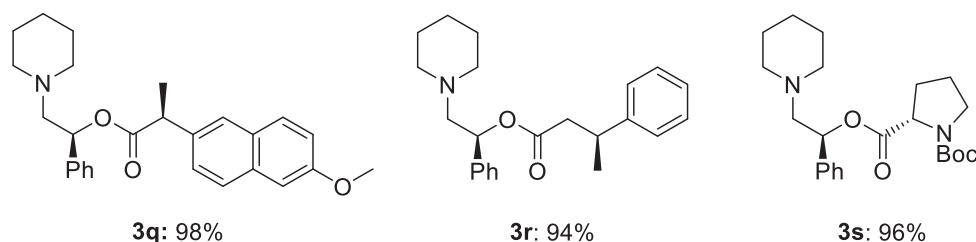


Figure 2. ORTEP of compound **3p**

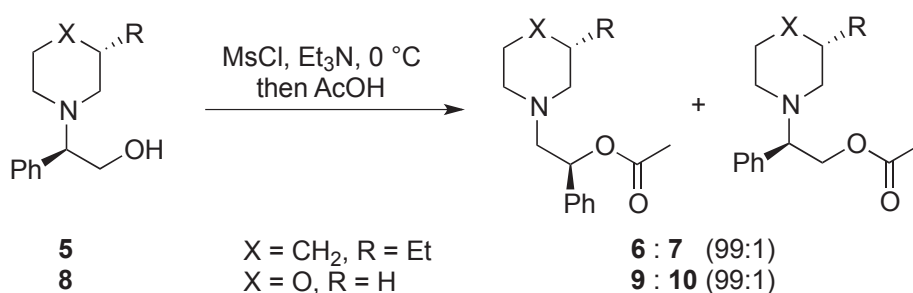
In line with the model proposed by Anderson,^{16a} the stereochemical outcome of the reaction is consistent with the participation of an aziridinium ion where competition between bimolecular and monomolecular substitution is possible, for this reason chiral acids were allowed to react with **1** (Scheme 3). The

corresponding amino esters, derived from (*S*)-Naproxen[®] **3q** and (*S*)-3-phenylbutyric acid **3r**, were obtained in good to excellent chemical yield. For both cases, the ¹H and ¹³C NMR spectra showed the presence of only one isomer, indicating a total stereoselectivity of the reaction, in consequence, no participation of carbocation intermediate was unambiguously confirmed. Finally, *L*-proline *N*-Boc protected was tested, affording the desired amino ester **3s** in 96% yield as a single diastereoisomer which exist in rotameric form.



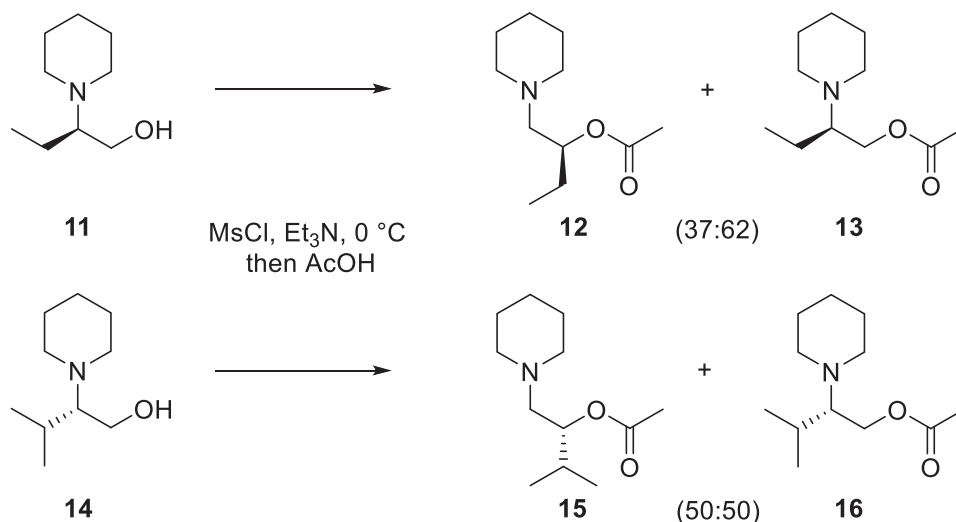
Scheme 3. Synthesis of amino esters coming from chiral acids

Finally, in order to examine reactions with more aziridinium ions derived from amino alcohols with different substituents at the ring nitrogen and/or other sites to show the scope and limitation of the present method, compounds **5**, **8**, **11** and **14** were subject to optimized reaction conditions using acetic acid as nucleophile. Compounds **5** and **8**, derived from (*R*)-(-)-2-phenylglycinol, afforded the regioisomeric mixture **6:7** and **9:10** in a 99:1 ratio respectively, in favor of the benzylic opening amino ester compound (Scheme 4).



Scheme 4. Synthesis of amino esters coming from heterocycles derived from phenylglycinol

Interestingly, when piperidine **11**, derived from (*R*)-(-)-2-amino-1-butanol, was allowed to react under the same conditions, the inseparable regioisomeric mixture **12:13** in 37:62 ratio in favor of the less substituted opening regioisomer **13** was obtained, while piperidine **14**, derived from (*S*)-(+)-2-amino-3-methyl-1-butanol, afforded the inseparable regioisomeric mixture **15:16** in 50:50 ratio (Scheme 5).



Scheme 5. Synthesis of amino esters coming from piperidines derived from other chiral amino alcohols

Notably, the reactions exhibit high regioselectivity in the opening of aziridinium ion when a benzylic position is present on the aziridinium ion despite we use a soft nucleophile.

In conclusion, aliphatic and aromatic carboxylic acids react with **1** to afford, *via* an aziridinium intermediate, the corresponding amino ester in good to excellent yield and high regioselectivity. In addition, we demonstrated opening reaction occurs preferentially at benzylic position following possibly a $\text{S}_{\text{N}}2$ type mechanism despite the soft nucleophilic character of carboxylate specie; the developed method is clean and efficient.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in CDCl_3 using a Bruker Avance III Spectrometer. Chemical shifts are given in ppm and reported to the residual solvent peak (CHCl_3 7.26 ppm and 77.16 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (J , Hz), and integration. Analytical TLC was performed on silica gel 60 F₂₅₄ plates. Column chromatography was carried out on silica gel 60 (63–200 μm). IR spectra were obtained using an FT-IR spectrometer, Spectrum One, Perkin Elmer. Mass spectra were recorded on JEOL The MStation JMS-700 at a voltage of 70 eV. X-Ray diffraction analysis was performed on a diffractometer Agilent Gemini Atlas fitted with an Atlas CCD detector, using $\text{Cu-K}\alpha$ ($\lambda = 1.54184$) radiation, and equipped with an Oxford Technologies Cryojet crystal cooling apparatus and a diffractometer STOE Stadivari using $\text{Ag-K}\alpha$ ($\lambda = 0.56083$) and equipped with a Pilatus-100 K detector. Optical rotations were measured on the Perkin-Elmer 341 polarimeter at room temperature. Enantiomeric purity measurements were performed by chiral UHPLC analysis in normal phase with an Agilent 1260

Infinity Analytical SFC System equipped with an Agilent 6120 quadrupole LC/MS, using an ULTRON ES-Pepsin chiral column (Shinwa Chemical Industries LTD, 4.6 x 150 mm, 5 μ m particle size).

Experimental procedure for intermediate 2.

To a stirred solution of β -amino alcohol **1** (0.5 g, 2.43 mmol) in CHCl_3 (10 mL) at 0 °C in presence of triethylamine (1.01 mL, 7.30 mmol). Then, methanesulfonyl chloride (0.41 mL, 5.35 mmol) was added dropwise at a rate to keep the reaction temperature below 5 °C. After 30 min, the reaction was monitored by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5), indicating that the reactants were consumed. The reaction mixture was allowed to warm at room temperature for 16 h. Solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2 and washed with water and brine before drying over anhydrous sodium sulfate. Solvent was removed under vacuum and the crude product was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3) gave the desired β -chloropiperidinium chloride (**S**)-**2**.

Intermediate: (S)-1-(2-chloro-2-phenylethyl)piperidin-1-ium chloride (2). The desired pure product was obtained in 79% yield (500 mg) as white solid; mp 180 °C; $[\alpha]_{\text{D}}^{20} +23.6$ (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 12.69 (br s, 1H), 7.49-7.26 (m, 5H), 5.85-5.83 (dd, $J = 7.2, 4.5$ Hz, 1H), 3.88-3.41 (d, $J = 12.0$ Hz, 1H), 3.50-3.41 (m, 2H), 3.18-3.16 (d, $J = 12.1$ Hz, 1H), 2.80-2.74 (m, 1H), 2.64-2.56 (m, 1H), 2.29-2.13 (m, 2H), 1.86-1.80 (m, 2H), 1.71-1.69 (m, 1H), 1.53 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.3, 129.4, 129.2, 127.0, 64.6, 55.5, 54.7, 53.8, 22.5, 21.8; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{Cl}_2\text{N}$: 261.0973, found: 261.0970.

General procedure and compound characterization data for products 3a-s.

To a stirred solution of compound **1** (0.5 g, 2.43 mmol) in CHCl_3 (10 mL) at 0 °C in presence of triethylamine (1.01 mL, 7.30 mmol). Then, methanesulfonyl chloride (0.22 mL, 2.92 mmol) was added dropwise at a rate to keep the reaction temperature below 5 °C. After 30 min, the reaction was monitored by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5), indicating the reactants were consumed. Triethylamine (0.50 mL, 3.65 mmol) was added. Finally, the corresponding carboxylic acid (1.2 equiv.) was added and the reaction mixture was allowed to warm to room temperature for 16 h. After completion of the reaction as indicated by TLC, the crude product was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3) provided the corresponding product **3**.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl acetate (3a). The desired pure product was obtained in 93% yield (560 mg) as orange oil; $[\alpha]_{\text{D}}^{20} +52.9$ (c 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2932, 2858, 1736, 1230; ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (m, 5H), 5.97-5.94 (dd, $J = 9.0, 4.0$ Hz, 1H), 2.85-2.80 (dd, $J = 13.6, 9.0$ Hz, 1H), 2.54-2.49 (m, 3H), 2.42-2.41 (m, 2H), 2.09 (s, 3H), 1.56-1.51 (m, 4H), 1.42-1.37 (m, 2H); ^{13}C

NMR (125 MHz, CDCl₃) δ 170.2, 139.8, 128.3, 127.8, 126.4, 72.9, 64.4, 54.6, 26.0, 24.2, 21.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₂₂NO₂: 248.1651, found: 248.1650.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 5-bromopentanoate (3b). The desired pure product was obtained in 94% yield (843 mg) as orange oil; $[\alpha]_D^{20}$ +41.5 (*c* 1.0, CH₂Cl₂); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2933, 2853, 1732, 1257, 698; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 6.00-5.97 (dd, *J* = 9.3, 3.7 Hz, 1H), 3.41-3.38 (m, 2H), 2.84-2.79 (dd, *J* = 13.6, 9.3 Hz, 1H), 2.55-2.49 (m, 3H), 2.43-2.37 (m, 4H), 1.93-1.87 (m, 2H), 1.82-1.77 (m, 2H), 1.55-1.52 (m, 4H), 1.42-1.39 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 139.5, 128.3, 127.8, 126.4, 72.7, 64.4, 54.6, 33.5, 33.1, 31.7, 25.9, 24.1, 23.5; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₂₇BrNO₂: 368.1225, found: 368.1222.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl hexacosanoate (3c). The desired pure product was obtained in 95% yield (1351 mg) as orange solid; mp 52 °C; $[\alpha]_D^{20}$ +10.4 (*c* 1.0, CH₂Cl₂); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2920, 2851, 1736, 1466, 1263, 1162; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.23 (m, 5H), 5.99-5.96 (dd, *J* = 9.1, 3.9 Hz, 1H), 2.83-2.78 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.53-2.50 (dd, *J* = 13.5, 3.9 Hz, 1H), 2.51 (m, 2H), 2.45-2.39 (m, 2H), 2.35-2.28 (m, 2H), 1.65-1.59 (m, 2H), 1.55-1.50 (m, 4H), 1.41-1.37 (m, 2H), 1.29-1.25 (br, 44H), 0.89-0.86 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.8, 139.8, 128.2, 127.6, 126.3, 72.5, 64.4, 54.6, 34.5, 31.8, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 26.0, 24.9, 24.2, 22.6, 14.0; HRMS (ESI): m/z [M+H]⁺ calcd for C₃₉H₇₀NO₂: 584.5407, found: 584.5401.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-phenylacetate (3d). The desired pure product was obtained in 93% yield (732 mg) as orange oil; $[\alpha]_D^{20}$ +48.6 (*c* 1.0, CH₂Cl₂); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2953, 2853, 1733, 1663, 1496, 1454; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.23 (m, 10H), 5.98-5.96 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.70-3.67 (d, *J* = 15.0 Hz, 1H), 3.65-3.62 (d, *J* = 15.0 Hz, 1H), 2.80-2.75 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.51-2.48 (dd, *J* = 13.6, 3.7 Hz, 1H), 2.46-2.45 (m, 2H), 2.34-2.33 (m, 2H), 1.50-1.45 (m, 4H), 1.38-1.35 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 139.5, 134.1, 129.3, 128.4, 128.3, 127.7, 126.9, 126.3, 73.4, 64.4, 54.6, 41.7, 26.0, 24.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₆NO₂: 324.1964, found: 324.1951.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(3,4-dimethoxyphenyl)acetate (3e). The desired pure product was obtained in 90% yield (840 mg) as orange oil; $[\alpha]_D^{20}$ +39.4 (*c* 1.0, CH₂Cl₂); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2933, 2834, 1732, 1141, 1026; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.25 (m, 5H), 6.83-6.77 (m, 3H), 5.98-5.95 (dd, *J* = 9.0, 3.8 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.63-3.60 (d, *J* = 14.8 Hz, 1H), 3.60-3.67 (d, *J* = 15.1 Hz, 1H), 2.81-2.77 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.53-2.50 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.47-2.45 (m, 2H), 2.36-2.34 (m, 2H), 1.50-1.46 (m, 4H), 1.38-1.34 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 148.7, 147.9, 139.5, 128.2, 127.7, 126.5, 126.3, 121.4, 112.2, 111.0, 73.4, 64.3, 55.8, 55.7, 54.5, 41.2, 25.9, 24.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₃H₃₀NO₄: 384.2175, found: 384.2188.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(4-isobutylphenyl)propanoate (3f). The desired pure product was obtained as diastereomer mixture in 92% yield (881 mg, **3f** = 1:1) as orange oil; FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2932, 2868, 1734, 1091, 1019; ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.04 (m, 18 H), 5.95-5.92 (m, 2H), 3.77-3.71 (m, 2H), 2.78-2.69 (m, 2H), 2.51-2.48 (m, 4H), 2.45-2.43 (m, 4H), 2.39-2.35 (m, 4H), 2.24-2.22 (m, 2H), 1.86-1.81 (m, 2H), 1.52-1.45 (m, 8H), 1.40-1.37 (m, 6H), 1.30-1.26 (m, 2H), 0.90-0.89 (m, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 173.5, 140.3, 139.8, 139.6, 137.6, 137.6, 129.1, 128.3, 128.1, 127.7, 127.5, 127.3, 127.3, 126.2, 126.0, 73.3, 73.0, 64.5, 64.2, 54.5, 54.2, 45.3, 45.2, 44.9, 44.9, 30.1, 30.1, 25.9, 25.8, 24.1, 24.0, 22.3, 22.3, 18.2, 18.2; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_2$: 394.2746, found: 394.2736.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl benzoate (3g). The desired pure product was obtained in 91% yield (685 mg) as orange oil; $[\alpha]_{\text{D}}^{20}$ -8.6 (c 1.0, CH_2Cl_2); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2933, 2853, 1717, 1266, 1069; ^1H NMR (500 MHz, CDCl_3) δ 8.10-7.25 (m, 10H), 6.20-6.18 (dd, J = 8.5, 3.9 Hz, 1H), 3.03-2.98 (dd, J = 13.8, 8.5 Hz, 1H), 2.74-2.70 (dd, J = 13.8, 3.9 Hz, 1H), 2.59-2.56 (m, 2H), 2.52-2.49 (m, 2H), 1.54-1.49 (m, 4H), 1.40-1.37 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 139.9, 132.8, 130.5, 129.6, 128.4, 128.3, 127.8, 126.3, 74.0, 64.5, 54.6, 26.0, 24.1; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2$: 310.1807, found: 310.1789.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-nitrobenzoate (3h). The desired pure product was obtained in 89% yield (768 mg) as yellow oil; $[\alpha]_{\text{D}}^{20}$ -2.3 (c 1.0, CH_2Cl_2); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2933, 2852, 1727, 1533, 1349; ^1H NMR (500 MHz, CDCl_3) δ 8.90-8.86 (m, 1H), 8.42-8.36 (m, 2H), 7.67-7.64 (m, 1H), 7.44-7.31 (m, 5H), 6.24-6.22 (dd, J = 8.9, 3.8 Hz, 1H), 3.03-2.98 (dd, J = 13.8, 8.9 Hz, 1H), 2.72-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.60-2.58 (m, 2H), 2.49-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.36 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.6, 148.2, 139.0, 135.3, 129.5, 128.5, 128.1, 127.2, 126.4, 125.7, 124.5, 74.9, 64.3, 54.7, 26.0, 24.0; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$: 355.1658, found: 355.1656.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 4-nitrobenzoate (3i). The desired pure product was obtained in 87% yield (751 mg) as yellow oil; $[\alpha]_{\text{D}}^{20}$ -11.0 (c 1.0, CH_2Cl_2); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2934, 2853, 1723, 1525, 1346; ^1H NMR (500 MHz, CDCl_3) δ 8.30-8.22 (m, 4H), 7.43-7.31 (m, 5H), 6.23-6.20 (dd, J = 9.0, 3.8 Hz, 1H), 3.00-2.96 (dd, J = 13.8, 9.0 Hz, 1H), 2.71-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.60-2.56 (m, 2H), 2.46-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.37 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.9, 150.4, 139.0, 136.0, 130.7, 128.5, 128.2, 126.4, 123.5, 74.9, 64.4, 54.7, 26.0, 24.1; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$: 355.1658, found: 355.1653.

tert-Butyl 4-(((S)-1-phenyl-2-(piperidin-1-yl)ethoxy)carbonyl)phenylcarbamate (3j). The desired pure product was obtained in 91% yield (940 mg) as orange oil; $[\alpha]_{\text{D}}^{20}$ -36.6 (c 1.0, CH_2Cl_2); FT-IR $\nu_{\max}/\text{cm}^{-1}$ 2935, 2852, 1709, 1152, 1050; ^1H NMR (500 MHz, CDCl_3) δ 8.01-7.25 (m, 9H), 6.76 (br, 1H),

6.17-6.15 (dd, $J = 8.4, 3.9$ Hz, 1H), 3.01-2.96 (dd, $J = 13.8, 8.5$ Hz, 1H), 2.73-2.69 (dd, $J = 13.8, 4.0$ Hz, 1H), 2.56-2.48 (m, 4H), 1.52 (s, 9H), 1.50-1.48 (m, 4H), 1.38-1.35 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.3, 152.1, 142.6, 140.0, 130.9, 128.3, 127.7, 126.3, 124.7, 117.3, 81.1, 73.8, 64.5, 54.6, 28.2, 26.0, 24.1; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4$: 425.2440, found: 425.2428.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(4-chlorobenzoyl)benzoate (3k). The desired pure product was obtained in 90% yield (981 mg) as orange oil; $[\alpha]_{\text{D}}^{20} +20.0$ (c 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 2853, 1717, 1674, 1454, 1267; ^1H NMR (500 MHz, CDCl_3) δ 8.15-7.12 (m, 13H), 5.98-5.96 (dd, $J = 8.5, 4.2$ Hz, 1H), 2.68-2.64 (dd, $J = 13.6, 8.5$ Hz, 1H), 2.46-2.43 (dd, $J = 13.6, 4.2$ Hz, 1H), 2.38-2.37 (m, 2H), 2.30-2.25 (m, 2H), 1.50-1.38 (m, 4H), 1.36-1.25 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 195.5, 164.6, 141.2, 139.4, 138.8, 135.5, 132.4, 130.7, 130.4, 129.5, 129.0, 128.7, 128.2, 127.9, 127.3, 126.5, 74.6, 63.8, 54.5, 25.9, 24.0; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{27}\text{ClNO}_3$: 448.1679, found: 448.1681.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-methylbenzoate (3l). The desired pure product was obtained in 85% yield (669 mg) as yellow oil; $[\alpha]_{\text{D}}^{20} +11.0$ (c 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2932, 2853, 1719, 1455, 1251, 1075; ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.15 (m, 9H), 6.26-6.24 (dd, $J = 9.2, 3.3$ Hz, 1H), 3.13-3.08 (dd, $J = 13.8, 9.2$ Hz, 1H), 2.77-2.74 (dd, $J = 13.8, 3.4$ Hz, 1H), 2.70-2.64 (m, 2H), 2.60-2.56 (m, 2H), 2.57 (s, 3H), 1.62-1.58 (m, 4H), 1.45-1.40 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 140.3, 139.6, 131.8, 131.5, 131.2, 130.5, 128.5, 128.0, 126.4, 125.6, 125.3, 73.0, 63.9, 54.3, 25.4, 23.9, 21.7; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$: 324.1964, found: 324.1961.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-methylbenzoate (3m). The desired pure product was obtained in 94% yield (740 mg) as yellow oil; $[\alpha]_{\text{D}}^{20} -13.8$ (c 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2853, 1718, 1454, 1274, 1081; ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.24 (m, 9H), 6.20-6.17 (dd, $J = 8.4, 4.0$ Hz, 1H), 3.01-2.98 (dd, $J = 13.7, 8.4$ Hz, 1H), 2.74-2.70 (dd, $J = 13.7, 4.0$ Hz, 1H), 2.57-2.48 (m, 4H), 2.39 (s, 3H), 1.53-1.49 (m, 4H), 1.40-1.35 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.8, 140.0, 138.0, 133.5, 130.1, 128.3, 128.1, 127.7, 126.7, 126.3, 73.9, 64.5, 54.6, 26.0, 24.1, 21.2; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$: 324.1964, found: 324.1962.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 4-methylbenzoate (3n). The desired pure product was obtained in 93% yield (732 mg) as orange oil; $[\alpha]_{\text{D}}^{20} -14.8$ (c 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2853, 1715, 1543, 1266, 1019; ^1H NMR (500 MHz, CDCl_3) δ 7.99-7.22 (m, 9H), 6.19-6.16 (dd, $J = 8.4, 3.9$ Hz, 1H), 3.01-2.96 (dd, $J = 13.8, 8.5$ Hz, 1H), 2.73-2.70 (dd, $J = 13.8, 4.0$ Hz, 1H), 2.57-2.49 (m, 4H), 2.39 (s, 3H), 1.53-1.48 (m, 4H), 1.39-1.34 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 143.4, 140.0, 129.6, 129.0, 128.3, 127.8, 127.7, 126.3, 73.8, 64.5, 54.6, 26.0, 24.1, 21.6; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$: 324.1964, found: 324.1960.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl nicotinate (3o). The desired pure product was obtained in 91%

yield (687 mg) as orange oil; $[\alpha]_{\text{D}}^{20} +3.4$ (*c* 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2931, 2853, 1721, 1590, 1419; ^1H NMR (500 MHz, CDCl_3) δ 9.29-9.23 (m, 1H), 8.78-8.77 (m, 1H), 8.33-8.31 (m, 1H), 7.43, -7.28 (m, 6H), 6.22-6.20 (dd, $J = 8.8, 3.8$ Hz, 1H), 3.00-2.96 (dd, $J = 13.8, 8.9$ Hz, 1H), 2.71-2.68 (dd, $J = 13.8, 3.8$ Hz, 1H), 2.59-2.55 (m, 2H), 2.48-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.35 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.4, 153.3, 150.9, 139.3, 137.1, 128.5, 128.1, 126.5, 126.4, 123.2, 74.5, 64.4, 54.7, 26.0, 24.1; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$: 311.1760, found: 311.1754.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl cinnamate (3p). The desired pure product was obtained in 92% yield (783 mg) as white solid (recryst. from *n*-hexane/ CH_2Cl_2); mp 82 °C; $[\alpha]_{\text{D}}^{20} -35.1$ (*c* 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2853, 1709, 1636, 978; ^1H NMR (500 MHz, CDCl_3) δ 7.70-7.67 (d, $J = 16.0$ Hz, 1H), 7.53-7.24 (m, 10H), 6.54-6.50 (d, $J = 16.0$ Hz, 1H), 6.11-6.08 (dd, $J = 8.8, 3.9$ Hz, 1H), 2.96-2.92 (dd, $J = 13.7, 8.8$ Hz, 1H), 2.64-2.60 (dd, $J = 13.7, 4.0$ Hz, 1H), 2.55-2.53 (m, 2H), 2.48-2.47 (m, 2H), 1.57-1.51 (m, 4H), 1.42-1.37 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.1, 144.8, 139.9, 134.3, 130.2, 128.8, 128.3, 128.0, 127.8, 126.4, 118.3, 73.2, 64.3, 54.6, 25.9, 24.1; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2$: 336.1964, found: 336.1951.

(2S)-(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(2-methoxynaphthalen-6-yl)propanoate (3q). The desired pure product was obtained in 98% yield (996 mg) as white solid; mp 71 °C; $[\alpha]_{\text{D}}^{20} +17.3$ (*c* 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 2852, 1730, 1605, 1154, 1031; ^1H NMR (500 MHz, CDCl_3) δ 7.69-7.10 (m, 11H), 5.96-5.94 (dd, $J = 9.0, 3.5$ Hz, 1H), 3.90-3.87 (m, 1H), 3.89 (s, 3H), 2.71-2.66 (dd, $J = 13.8, 9.0$ Hz, 1H), 2.48-2.45 (dd, $J = 13.8, 3.5$ Hz, 1H), 2.30-2.28 (m, 2H), 2.16-2.14 (m, 2H), 1.55-1.54 (d, $J = 7.2$ Hz, 3H), 1.28-1.23 (m, 4H), 1.20-1.17 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.5, 157.4, 139.7, 135.6, 133.5, 129.1, 128.8, 128.3, 127.7, 126.8, 126.4, 126.3, 126.0, 118.7, 105.4, 73.5, 64.2, 55.2, 54.3, 45.5, 25.8, 23.9, 18.3; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{32}\text{NO}_3$: 418.2382, found: 418.2374.

(3S)-(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-phenylbutanoate (3r). The desired pure product was obtained in 94% yield (804 mg) as red oil; $[\alpha]_{\text{D}}^{20} +62.5$ (*c* 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2852, 1733, 1494, 1452; ^1H NMR (500 MHz, CDCl_3) δ 7.22-7.11 (m, 10H), 5.87 (dd, $J = 9.2, 3.5$ Hz, 1H), 3.23-3.16 (m, 1H), 2.81-2.76 (dd, $J = 13.7, 9.3$ Hz, 1H), 2.64-2.60 (m, 1H), 2.53-2.49 (m, 1H), 2.48-2.41 (m, 3H), 2.40-2.35 (m, 2H), 1.44-1.41 (m, 4H), 1.32-1.29 (m, 2H), 1.19-1.17 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 145.7, 139.4, 128.4, 128.3, 128.3, 127.9, 126.8, 126.7, 126.4, 126.3, 126.0, 72.4, 63.4, 54.0, 42.9, 36.3, 25.3, 23.8, 21.9; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_2$: 352.2277, found: 352.2274.

(2S)-tert-Butyl (S)-1-phenyl-2-(piperidin-1-yl)ethyl pyrrolidine-1,2-dicarboxylate (3s). The desired pure product was obtained as a rotameric mixture (ratio 67:33) in 96% yield (941 mg) as yellow oil; $[\alpha]_{\text{D}}^{20} +32.5$ (*c* 1.0, CH_2Cl_2); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2802, 1747, 1698, 1157, 1087; (major rotamer) ^1H

NMR (500 MHz, CDCl₃) δ 7.36-7.24 (m, 5H), 6.07-6.03 (m, 1H), 4.29-4.26 (dd, J = 8.6, 3.5 Hz, 1H), 3.63-3.54 (m, 1H), 3.44-3.34 (m, 1H), 2.80-2.76 (dd, J = 13.4, 9.7 Hz, 1H), 2.56-2.46 (m, 3H), 2.35-2.29 (m, 2H), 2.24-2.14 (m, 2H), 2.02-1.93 (m, 1H), 1.90-1.82 (m, 1H), 1.53-1.50 (m, 4H), 1.41-1.38 (m, 2H), 1.22 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 153.7, 138.9, 128.1, 127.7, 126.4, 79.4, 72.3, 64.4, 58.9, 54.6, 46.1, 30.6, 28.2, 27.9, 24.0, 23.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₃H₃₅N₂O₄: 403.2597, found: 403.2587.

Regioisomer: (R)-2-Phenyl-2-(piperidin-1-yl)ethyl acetate (4a). The desired pure product was obtained in 91% yield (548 mg) as yellow oil; [α]_D²⁰ -10.0 (c 1.0, CH₂Cl₂); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2929, 2853, 1740, 1226; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.25 (m, 5H), 4.51-4.48 (dd, J = 11.4, 6.3 Hz, 1H), 4.36-4.32 (dd, J = 11.4, 6.5 Hz, 1H), 3.63-3.60 (t, J = 6.4 Hz, 1H), 2.40-2.36 (m, 4H), 1.97 (s, 3H), 1.55-1.51 (m, 4H), 1.39-1.34 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.9, 138.5, 128.4, 128.0, 127.3, 68.3, 64.9, 51.7, 26.2, 24.4, 20.9; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₂₂NO₂: 248.1651, found: 248.1648.

Regioisomer: (R)-2-Phenyl-2-(piperidin-1-yl)ethyl benzoate (4g). The desired pure product was obtained in 89% yield (670 mg) as orange oil; [α]_D²⁰ -8.1 (c 1.0, CH₂Cl₂); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 2853, 1733, 1262; ¹H NMR (500 MHz, CDCl₃) δ 7.97-7.25 (m, 10H), 4.79-4.76 (dd, J = 11.4, 6.2 Hz, 1H), 4.62-4.59 (dd, J = 11.4, 6.3 Hz, 1H), 3.83-3.81 (t, J = 6.2 Hz, 1H), 2.62-2.47 (m, 4H), 1.59-1.57 (m, 4H), 1.42-1.35 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 166.3, 132.8, 130.1, 129.5, 128.5, 128.2, 128.2, 128.0, 127.5, 68.5, 65.5, 51.8, 25.9, 24.3, HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₄NO₂: 310.1807, found: 310.1803.

(S)-2-((S)-3-Ethylpiperidin-1-yl)-1-phenylethyl acetate (5). The desired pure product was obtained in 91% yield (537 mg) as orange oil; [α]_D²⁰ +53.3 (c 1.0, CH₂Cl₂); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 2851, 1737, 1231, 1026; ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.27 (m, 5H), 5.98-5.96 (dd, J = 8.9, 4.0 Hz, 1H), 2.91-2.82 (m, 2H), 2.88-2.84 (dd, J = 13.6, 9.0 Hz, 1H), 2.57-2.54 (dd, J = 13.6, 4.0 Hz, 1H), 2.12-2.03 (m, 1H), 2.09 (s, 3H), 1.74-1.68 (m, 2H), 1.64-1.50 (m, 2H), 1.43-1.35 (m, 1H), 1.25-1.17 (m, 2H), 0.88-0.85 (t, J = 7.5 Hz, 3H), 0.84-0.78 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.23, 139.67, 128.37, 127.86, 126.46, 73.00, 64.08, 59.90, 54.88, 37.62, 30.32, 27.10, 25.32, 21.37, 11.35. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₅NO₂: 276.1978, found: 276.1964.

(S)-2-Morpholino-1-phenylethyl acetate (8). The desired pure product was obtained in 93% yield (559 mg) as yellow oil; [α]_D²⁰ +70.1 (c 1.0, CH₂Cl₂); FT-IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2958, 2854, 1733, 1229, 1115, 1026; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.28 (m, 5H), 5.98-5.96 (dd, J = 9.2, 3.9 Hz, 1H), 3.71-3.64 (m, 4H), 2.86-2.82 (dd, J = 13.4, 9.3 Hz, 1H), 2.58-2.57 (m, 2H), 2.56-2.52 (dd, J = 13.4, 4.0 Hz, 1H), 2.48-2.47 (m, 2H), 2.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.23, 139.11, 128.41, 128.02, 126.44, 72.33, 66.94, 64.00, 53.71, 21.32; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₄H₁₉NO₃: 250.1443, found: 250.1437.

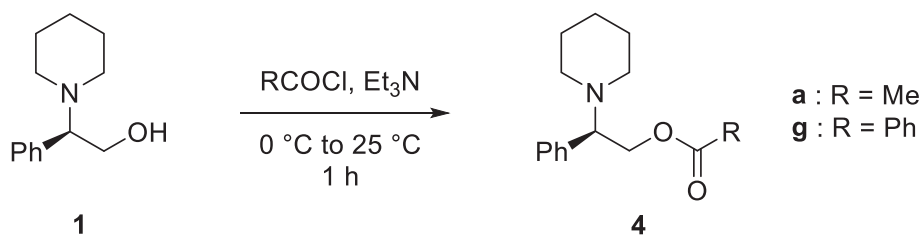
ACKNOWLEDGEMENTS

We are grateful to VIEP-BUAP for financial support, U.H.P and M.V.X thanks to CONACyT for the scholarships (297948 and 277416) and projects CONACyT (173585, 225041 and 268178), A. Mendoza and S. Bernès for the measurement of crystals in the X-ray Laboratories of CQ-ICUAP and IF-BUAP, respectively.

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