Efficient Solution-Phase Parallel Synthesis of 4-Substituted *N*-Protected Piperidines

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Practical conditions for the synthesis of 4-substituted *N*-protected piperidines through CuCN·2LiBr-catalyzed organozinc additions to 1-acylpyridinium salts and subsequent hydrogen-transfer hydrogenation have been established. The reaction sequence is performed at room temperature and provides 4-substituted *N*-protected piperidines in excellent overall yields without the isolation of intermediate dihydropyridines. In those cases in which the organozinc addition results in mixtures of 2- and 4-substituted dihydropyridines, the 2-substituted isomers are efficiently scavenged with maleic anhydride and subsequently removed by a mild extractive workup with $NaHCO_3$ (sat.). The *N*-acyl group can conveniently be exchanged from *N*-phenoxycarbonyl to *N*-*t*Boc, thus allowing orthogonal deprotection strategies.

Introduction

Substituted piperidines constitute one of the most studied heterocycles, owing to their ubiquitous nature in synthetically challenging alkaloids as well as in pharmaceutical research.[1−3] As a result, numerous methods for the synthesis of piperidine derivatives have been reported.[4−6] Goetz−Luthy reported an attractive synthetic strategy that takes advantage of the wealth of commercially available pyridines as starting materials, dihydropyridines being synthesized in low yields by direct alkylation of pyridines.[7] Recent work by Comins et al., however, has shown that activation of the pyridines through the formation of *N*-acyl pyridinium derivatives prior to the nucleophilic addition provides dihydropyridines in good yields and with good regioselectivities.[8,9] A wide range of organometallic reagents have also been used as nucleophiles in these reactions. Uncatalyzed Grignard[10] and organotin[11] reagents favor the formation of 2-substituted dihydropyridines, whereas the use of organotitanium reagents[12,13] and lithium dialkylcuprates[14] mainly results in 4-substituted dihydropyridines, which is also the case for Grignard reagents admixed with copper iodide.[15] Organozinc reagents are reported to give mainly mixtures of 4- and 2-substituted dihydropyridines.[16] Although not synthetically useful, owing to the formation of isomeric mixtures, the advantageous properties of organozinc reagents − such as their compatibility with a wide range of functional groups (e.g., chlorides, nitriles, esters, amides, and ketones) and the potential to perform the reactions at room temperature − makes their use attractive in parallel synthesis.[17−20] Therefore, to improve the regioselectivity it would be of great interest to investigate the possibilities of the use of organozinc reagents in combination with CuCN·2LiBr. A few scattered, individual examples of the use of organozinc reagents in combination with copper catalysis resulting in good regioselectivities have been reported.[21−24] Further investigation of the scope and limitations of these reactions is, however, necessary in the context of developing a reliable method for parallel synthesis. A practical Pd/C-catalyzed hydrogen-transfer reduction of the intermediate dihydropyridines, to provide the substituted piperidines efficiently, was also investigated. Here we report a practical and efficient procedure, also amenable for parallel synthesis, for the synthesis of 4-substituted N-protected piperidines.

Results and Discussion

To study the regioselective alkylation, a set of commercially available organozinc reagents, admixed with catalytic amounts (5 mol %) of CuCN·2LiBr were added to preformed *N*-acyl pyridinium salts (Table 1).

Both dialkylzinc reagents and secondary and primary alkylzinc halides almost exclusively gave the 4-addition products, with only trace amounts of the 2-substituted isomers being detectable by NMR spectroscopy (Table 1, entries 1−5). The tertiary alkylzinc nucleophile *tert*-butylzinc bromide similarly afforded a high isomeric ratio of 98% of the desired 4-substituted dihydropyridine **2**, and only 2% of

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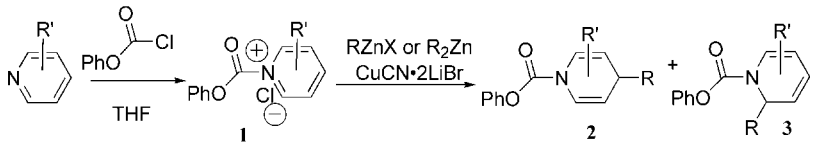
Table 1. Conversion of pyridines into dihydropyridines **2** and **3**



Entry	Pyridines	RZnX or R_2Zn[a]	Yield[b] (%)	Ratio[c] (**2**/**3**)
1	pyridine	$(CH_3)_2Zn$	96	>99:trace
2	pyridine	$(CH_3CH_2)_2Zn$	97	>99:trace
3	pyridine	$CH_3(CH_2)_3ZnBr$	91	>99:trace
4	pyridine	$(CH_2)_4CHZnBr$	95	>99:trace
5	pyridine	$(CH_3)_2CH(CH_2)_2ZnBr$	92	>99:trace
6	pyridine	$(CH_3)_3CZnBr$	90	98:2
7	pyridine	2-methoxyphenylZnI	72	65:35
8	pyridine	4-fluorophenylZnBr	84	75:25
9	pyridine	3,5-difluorophenylZnBr	94	>99:trace
10	pyridine	4-cyanophenylZnBr	95	>99:trace
11	pyridine	2-methylphenylZnBr	92	>99:trace
12	2-ethylpyridine	2-methylphenylZnBr	90	92:8
13	2-ethylpyridine	$(CH_3CH_2)_2Zn$	90	>99:trace
14	2-methoxypyridine	$CH_3(CH_2)_3ZnBr$	0	
15	2-methoxypyridine	2-methylphenylZnBr	0	
16	2-fluoropyridine	$(CH_3CH_2)_2Zn$	0	
17	3-fluoropyridine	$(CH_3CH_2)_2Zn$	87	97:3
18	2,3,5-collidine	$CH_3(CH_2)_3ZnBr$	90	85:15
19	2,3,5-collidine	$(CH_3CH_2)_2Zn$	84	83:17
20	2,3,5-collidine	$(CH_3)_3CZnBr$	82	73:27
21	2,3,5-collidine	2-methylphenylZnBr	92	70:30
22	2,6-lutidine	$CH_3(CH_2)_3ZnBr$	0	
23	2,6-lutidine	$(CH_3CH_2)_2Zn$	0	
24	4-picoline	$(CH_3CH_2)_2Zn$	94	trace:>99

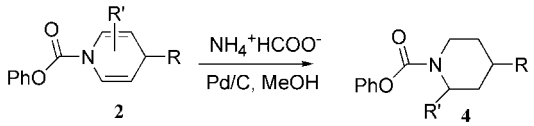
[a] Admixed with (5 mol%) CuCN·2LiBr. [b] Isolated yield. [c] Ratio determined by ^1H NMR spectroscopy of the crude isolate.

the 2-isomer **3** was isolated from a total yield of 90% (Table 1, entry 6). With the exceptions of the 2-methoxyphenyl- and the 4-fluorophenylzinc halides (Table 1, entries 7 and 8), high regioselectivities were observed for most of the aromatic zinc halides tested (Table 1, entries 9−11). Reduced yields − of 72% and 84%, respectively − were also noticed in the two former cases, whereas the yields in all the other examples were excellent (≥ 90%).

With these results in hand, the focus was turned to substituted pyridines as starting materials. Since the activated species **1** has to be formed in order for the nucleophilic addition to proceed, the anticipation was that the presence of substituents at the 2- and/or 6-positions in the pyridine ring could be problematic. Surprisingly, 2-ethylpyridine worked equally well as pyridine itself, resulting in a **2**/**3** ratio of 92:8 when 2-methylphenylzinc bromide was used (Table 1, entry 12) and of > 99:1 in favor of the 4-substituted product when diethylzinc was used (Table 1, entry 13). On the other hand, if the pyridine was substituted in both the 2- and 6-positions, as in 2,6-lutidine, no reaction took place (Table 1, entries 22 and 23). 2-Methoxypyridine and 2-fluoropyridine also afforded no product under these conditions (Table 1, entries 14−16). The presence of a 3-fluoro substituent, as in 3-fluoropyridine, gave excellent results in terms both of yield and of regioselectivity (Table 1, entry 17), affording mainly the 4-isomer (**2**/**3**, 97:3) in 87% yield. The presence of additional substituents in the ring, as exemplified by 2,3,5-collidine, caused reduced regioselectivity; when 2-methylphenylzinc bromide was used as nucleophile, for example, the **2**/**3** ratio went down to 70:30 (Table 1, entries 18−21), although the yields remained high. As would be expected, treatment of a 4-substituted pyridine with phenyl chloroformate, Et_2Zn, and CuCN·2LiBr resulted in exclusively the 2,4-disubstituted dihydropyridine **3**, with no 4,4′-disubstituted derivative **2** detectable (Table 1, entry 24).

Decomposition of the dihydropyridines occurred during storage in the freezer. Consequently, to accomplish high overall yields, it was important to reduce the dihydropyridines quickly to the corresponding piperidines. Previously, these substrates had mostly been reduced by hydrogenation with H_2 gas as the hydrogen source in the presence of a catalyst[25−27] (e.g. 10% Pd/C, 45 psi, 8−10 h or PtO_2, 6 h). Since parallel synthesis with pressurized hydrogen gas demands advanced equipment, the option to use a hydrogen-transfer reduction would be particularly attractive. Advantageously, both for avoiding the use of special equipment and for the time-saving aspect in the reduced reaction times, ammonium formate in absolute methanol reduced the dihydropyridines to piperidines within one hour at room temperature under Pd/C catalysis conditions (Table 2).[28,29] It should be noted, though, that restricting the reaction temperature to room temperature meant that aromatic substi-

Table 2. Conversion of 4-substituted dihydropyridines **2** into the corresponding piperidines **4**



Entry	Product	R	R′	(Pd/C, equiv.)	Yield[a] (%)
1	4.1	CH_3	H	0.05	95
2	4.2	CH_3CH_2	H	0.05	93
3	4.3	$CH_3(CH_2)_3$	H	0.05	92
4	4.4	$(CH_3)_3C$	H	0.05	92
5	4.5	$(CH_3)_2CH(CH_2)_2$	H	0.05	90
6	4.6	CH_3CH_2	2-CH_2CH_3	0.05	91[b]
7	4.7	$(CH_2)_4CH$	H	0.05	90
8	4.8	3,5-difluorophenyl	H	0.5	90
9	4.9	2-methylphenyl	H	0.5	92

[a] Isolated yield from pyridine. [b] Ca. 1:1 mixture of *cis* and *trans* isomers.

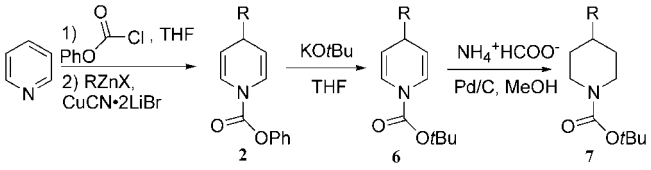
tuted dihydropyridines required 10 times more Pd/C than analogues with an aliphatic substituent (Table 2, entries 8 and 9). No reduction of the aromatic moiety was observed and the yields were excellent in all cases.

The outcome of the reduction of the 2,4-diethyl-1-acyldihydropyridine was hard to foresee, due to the possibility of forming a mixture of stereoisomers. The hydrogen-transfer reduction proved to be synthetically limited to monosubstituted dihydropyridines, since the reduction of **2.6** resulted in an almost 1:1 mixture of the *cis* and *trans* isomers **4.6** according to ^{1}H NMR spectroscopy.

Removal of the *N*-phenoxycarbonyl group was achieved by treatment of the *N*-phenoxycarbonyl-protected piperidines with a mixture of KOH and $NH_2NH_2{\cdot}H_2O$ in ethylene glycol for one hour,[30] resulting in a series of 4-substituted piperidines **5.1**−**5.7** in 56−80% yield. Although this deprotection method turned out to work conveniently, for piperidines substituted either with aliphatic or with aromatic substituents, a milder procedure was preferable. *N*-*t*Boc-protected piperidines can easily be deprotected by various mildly acidic methods and are therefore attractive as target molecules. However, the organozinc addition is not compatible with the use of *t*BocCl or *t*Boc anhydride as activating agents, as would be required for the production of *t*Boc-protected piperidines. We therefore treated the *N*-phenoxycarbonyl derivatives **2** with KO*t*Bu, resulting in high yields of the *N*-*t*Boc-protected dihydropyridines **6** (Table 3).[31,32]

For the development of a procedure amenable for high-throughput organic synthesis it was necessary to perform the reactions without cumbersome purification steps. Reducing the number of time-consuming purification steps was achieved without complications, thanks to the fact that all reaction steps had been high-yielding and had delivered fairly pure crude products. Thus, conversion of the pyridines into a variety of *N*-*t*Boc-protected piperidines was performed with only quick aqueous washings of intermediates **2** and **6**, followed by a simple silica gel filtration after the final step, affording the desired 4-substituted *N*-*t*Boc-protected piperidines **7.1**−**7.10** in excellent overall yields (88−93% in three steps, Table 3) and purities > 95%.

Table 3. Synthesis of 4-substituted *N*-*t*Boc-protected piperidines **7**

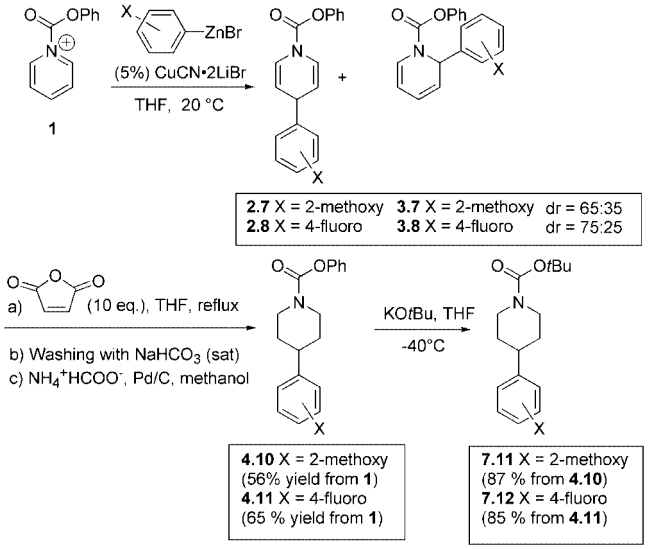


Entry	Product	R	Yield[a] (%)
1	7.1	2-methylphenyl-	90
2	7.2	$-CH(CH_3)CH_2CH_3$	92
3	7.3	$-CH(CH_2CH_3)_2$	93
4	7.4	$-CH_2(CH_2)_3CH_3$	88
5	7.5	$-CH(CH_2CH_3)(CH_2)_3CH_3$	91
6	7.6	$-CH(CH_2CH_3)(CH_2)_2CH_3$	89
7	7.7	$-C(CH_3)_2CH_2CH_3$	89
8	7.8	$-CH(CH_2CH_2CH_3)_2$	88
9	7.9	$-CH(CH_3)(CH_2)_3CH_3$	92
10	7.10	$-CH_2CH(CH_2CH_3)_2$	88

[a] Isolated yield from pyridine.

Another problem was the occasional occurrence of isomeric mixtures of the 2- and 4-substituted dihydropyridines. Even if excellent regioselectivities were observed in most of the examples, the exclusive isolation of the 4-substituted piperidine as the end product is necessary to make this procedure useful. Therefore, to avoid any substrate dependency, a scavenger step was added, demonstrated here by the 2-methoxyphenyl and the 4-fluorophenyl derivatives, in which the most pronounced mixtures of 4- and 2-isomers (65:35 and 75:25, respectively) had been formed (Table 1, entry 7 and 8). Maleic anhydride was added to remove the conjugated 2-substituted dihydropyridines **3.7** and **3.8** in a [4+2] reaction, followed by washing with $NaHCO_3$ (sat.) (Scheme 1). Although no experimental details had been re-

ported, this methodology had previously been used to remove unsubstituted conjugated dihydropyridines.[33] Owing to the more sterically demanding substituents in the current examples, heating of the reaction mixture at reflux for 10 h with 4 equivalents of maleic anhydride was initially tried. This long reaction time turned out to be detrimental for the outcomes of the reactions, giving low yields of the 4-substituted piperidines. A reduction of the reaction time to 2 h and an increase in the amount of maleic anhydride to 10 equivalents, however, afforded isomerically pure 4-substituted piperidines in excellent overall yields (Scheme 1). For the fluorine-containing derivative, ^{19}F NMR spectroscopy was used to monitor the disappearance of the 2-isomer.



Scheme 1. Synthesis of isomerically pure 4-substituted piperidines **7.11** and **7.12** by scavenging of the 2-substituted isomer by a [4+2] cycloaddition reaction with maleic anhydride followed by washing with $NaHCO_3$ (sat.)

Conclusions

A practical method suitable for the parallel synthesis of 4-substituted *N*-protected piperidines has been developed. Even though the substituted dihydropyridines were formed in high diastereomeric ratios, the developed strategy includes the option to remove undesired 2-substituted dihydropyridine to provide isomerically pure products. Furthermore, conditions for exchange of the *N*-phenoxycarbonyl to the *N*-*t*Boc protecting groups, which can be considered as orthogonal protecting groups, have been established. The high regioselectivities and yields achieved in the reaction, together with the practical synthetic and purification procedures, make this procedure attractive for library synthesis. The incorporation of these building blocks into more complex derivatives in a parallel manner will be reported in due course.

Experimental Section

General: All reactions were carried out under inert atmospheres with dry solvents under anhydrous conditions, unless otherwise stated. Pyridine was distilled before use. Methanol and ethylene glycol were dried over molecular sieves (3 Å) in a flask. THF was distilled from potassium. All the other chemicals were purchased from Aldrich and were used as received (it should be noted that some of the aliphatic zinc reagents contained traces of regioisomers, which was confirmed by treatment with benzoyl chloride followed by analysis by LCMS and NMR spectroscopy). TLC was performed on 60 F_{254} silica gel (Merck) with detection by UV light and by staining with solutions of potassium permanganate (3 g), potassium carbonate (20 g), 5% aqueous sodium hydroxide (5 mL) in water (300 mL), or of 2% Ninhydrin in EtOH 95%. Flash column chromatography (eluents given in brackets) was performed on silica gel (Matrex, 60 Å, 35−70 μm, Grace Amicon). The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 instrument on solutions in $CDCl_3$ [residual $CHCl_3$ (δ_H = 7.26 ppm) or $CDCl_3$ (δ_C = 77.00 ppm) as internal standard] or in [D_6]DMSO {residual [D_5]DMSO (δ_H = 2.50 ppm) or [D_6]DMSO (δ_C = 40.0 ppm) as internal standard} at 298 K. First-order chemical shifts and coupling constants were obtained from one-dimensional spectra. Proton and carbon resonances were assigned from appropriate combinations of COSY and ^1H-^{13}C HMQC. IR spectra were recorded on an ATI Mattson Genesis Series FTIR™ spectrometer. LCMS analysis was performed with a Waters micromass ZQ spectrometer [ES], and high-resolution mass spectra [EI or FAB] were recorded on a Jeol JMS-SX 102 spectrometer. All organic extracts were dried with solid Na_2SO_4 unless otherwise stated.

General Procedure for the Preparation of Substituted Phenyl Dihydropyridine-1-carboxylates 2 and 3: Pyridine (0.6 mL, 7.5 mmol), CuCN (45 mg, 0.5 mmol), and LiBr (86 mg, 1 mmol) were dissolved in THF (20 mL) at room temperature, which resulted in a yellow-green solution. Upon the dropwise addition of phenyl chloroformate (0.63 mL, 5 mmol) the color changed to orange-red and a lot of solid was formed. The zinc reagent was then added dropwise at room temperature. After one hour at room temperature, aqueous NH_4Cl (20%, 25 mL) and Et_2O (50 mL) were added. The water layer was separated and reextracted with Et_2O (2 × 7 mL). The organic layers were combined and washed with aqueous NH_4Cl (20%)/NH_4OH (20%) (1:1, 10 mL), water (2 × 10 mL), HCl (10% aq., 2 × 10 mL), water (2 × 10 mL), and brine (2 × 10 mL) and dried. Concentration at reduced pressure gave the crude products **2** and **3**. (See Table 1 for isolated yields).

General Procedure for the Synthesis of 4-Substituted Phenyl Piperidine-1-carboxylates by Removal of Undesired 2-Isomers by a [4+2] Cycloaddition with Maleic Anhydride: A mixture of the 2- and 4-substituted dihydropyridine (0.5 mmol) was added to a solution of maleic anhydride (490 mg, 5 mmol) in THF (1.5 mL). After the mixture had been heated at reflux for two hours, saturated aqueous $NaHCO_3$ (5 mL) was added. Et_2O (15 mL) was then added, and the water layer was separated and reextracted with Et_2O (2 × 5 mL). The organic layers were combined, washed with brine (2 × 5 mL), and dried. Concentration at reduced pressure gave the crude 4-substituted dihydropyridine, which was used immediately in the next step without further purification.

Phase-Transfer Reduction: The crude 4-substituted dihydropyridine, together with dry ammonium formate (20 mol equiv.), dissolved in a solution of absolute methanol/THF (11 mL, 10:1), were added to a slurry of activated 10% Pd/C (30 mg) in absolute meth-

anol (1 mL).[34] The resulting mixture was stirred at room temperature for half to one hour until all the starting material had been consumed (indicated by TLC, *n*-heptane/EtOAc, 6:1). The slurry was filtered through Celite and the Celite was thoroughly washed with Et_2O. The resulting organic solution was washed with water and brine to remove the residual ammonium formate and dried. Concentration at reduced pressure gave the crude product, which was purified by short silica gel flash chromatography (*n*-heptane/EtOAc, 6:1) to provide pure 4-substituted 1-(phenyloxycarbonyl)piperidine **4.10** (total yield 56%) and **4.11** (total yield 65%).

Phenyl 4-Methylpiperidine-1-carboxylate (4.1): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 9:1) gave **4.1** as a white solid (yield, 95%). m.p. 61−63 °C. Commercially available, registry number: 333444−36−3.

Phenyl 4-Ethylpiperidine-1-carboxylate (4.2): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 9:1) gave **4.2** as a colorless oil (yield, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.08 (m, 5 H), 4.35−4.19 (br. m, 2 H), 3.03−2.72 (br. m, 2 H), 1.75 (m, 2 H), 1.40 (m, 3 H), 1.20 (m, 2 H), 0.95 (t, 3 H) ppm. ^{13}C NMR: δ = 153.65, 151.55, 129.12, 125.00, 121.72, 44.83, 44.50, 37.51, 31.93, 31.52, 29.07, 11.13 ppm. IR (neat): $\tilde{\nu}$ = 3041, 2956, 2925, 2856, 1670 (C=O), 1425 (C=C), 1205 cm^{-1}. MS (EI): 234 [M + 1], 233 [M], 140 (100%), 112, 94, 77, 65.

Phenyl 4-Butylpiperidine-1-carboxylate (4.3): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **4.3** as a colorless oil (yield, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.07 (m, 5 H), 4.34−4.17 (br. m, 2 H), 3.03−2.72 (m, 2 H), 1.75−1.10 (m, 11 H), 0.91 (t, *J* = 6.68 Hz, 3 H) ppm. ^{13}C NMR: δ 153.55, 151.46, 129.03, 124.91, 121.63, 44.76, 44.41, 36.01, 35.70, 32.24, 31.82, 28.71, 22.72, 13.95 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2856, 1722 (C=O), 1423, 1199 cm^{-1}. MS (EI): 261 [M], 204, 168 (100%), 140, 112, 77, 65.

Phenyl 4-*tert*-Butylpiperidine-1-carboxylate (4.4): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 8:1) gave **4.4** as a white solid (yield, 92%). m.p.: 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.08 (m, 5 H), 4.43−4.26 (br. m, 2 H), 3.01−2.72 (br. m, 2 H), 1.74 (d, 2 H), 1.36−1.14 (m, 3 H), 0.89 (s, 9 H) ppm. ^{13}C NMR: δ = 153.58, 151.55, 129.15, 125.03, 121.73, 46.55, 45.30, 45.01, 32.25, 27.25, 26.96, 26.56 ppm. IR (neat): $\tilde{\nu}$ = 3052, 2948, 2921, 2861, 1710 (C=O), 1592, 1492, 1419, 1378, 1313, 1199, 1182, 1035, 740, 688 cm^{-1}. MS (EI): 261 (M), 204, 168 (100%), 113, 94, 77.

Phenyl 4-(3′-Methylbutyl)piperidine-1-carboxylate (4.5): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 5:1) gave **4.5** as a white solid (yield, 90%). m.p. 42−43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.07 (m, 5 H), 4.34−4.16 (br. m, 2 H), 3.02−2.73 (br. m, 2 H), 1.75 (d, 2 H), 1.55 (m, 1 H), 1.45 (m, 1 H), 1.40−1.20 (m, 6 H), 0.91 (d, *J* = 6.68 Hz, 6 H) ppm. ^{13}C NMR: δ = 153.58, 151.49, 129.06, 124.93, 121.65, 44.80, 44.46, 36.04, 35.81, 34.08, 32.32, 31.91, 28.06, 22.53 ppm. IR (neat): $\tilde{\nu}$ = 3066, 3014, 2950, 2925, 2900, 2867, 2846, 1704 (C=O), 1592, 1417 (C=C), 1367, 1274, 1240, 1191, 740 cm^{-1}. MS (EI): 275 (M), 182 (100%), 162, 126, 94, 77, 65.

Phenyl 2,4-Diethylpiperidine-1-carboxylate (4.6): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 5:1) gave **4.6** as a colorless oil (yield, 91%). ^{1}H NMR (400 MHz, [D_6]DMSO, 298 K): two isomers (1:1), 1st isomer: δ = 7.40−7.27 (m, 10 H), 4.30−4.08 (m, 1 H), 4.08−3.89 (m, 1 H), 3.78 (t, 1 H), 3.75−3.67 (m, 1 H), 3.22−3.11 (m, 1 H), 3.08−2.80 (m, 1 H), 1.91−1.62 (m, 6 H), 1.57−1.37 (m, 4 H), 1.37−1.26 (m, 2 H), 1.26−1.11 (m, 5 H), 1.06−1.93 (m, 1 H), 0.92−0.78 (m, 12 H) ppm. ^{1}H NMR (400 MHz, [D_6]DMSO, 408 K), 2nd isomer: δ = 7.39−7.02 (m, 10 H), 4.24 (m, 1 H), 4.05 (m, 1 H), 3.85 (t, 1 H), 3.80−3.70 (m, 1 H), 3.31−3.19 (m, 1 H), 3.97 (t, 1 H), 1.97−1.81 (m, 2 H), 1.81−1.67 (m, 4 H), 1.67−1.43 (4 H), 1.43−1.42 (m, 2 H), 1.32−1.17 (m, 5 H), 1.17−1.10 (m, 1 H), 0.97−0.83 (m, 12 H) ppm. IR (neat): $\tilde{\nu}$ = 2960, 2923, 2873, 1712 (C=O), 1594, 1494, 1415 (C=C), 1373, 1201(C−O), 1149, 1058, 744, 690 cm^{-1}. MS (EI): 262 (M), 168 (100%), 140, 112, 94, 77, 65.

Phenyl 4-(Cyclopentyl)piperidine-1-carboxylate (4.7): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 3:1) gave **4.7** as a white solid (yield, 90%). m.p.: 60−61 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43−7.07 (m, 5 H), 4.39−4.07 (br. m, 2 H), 3.09−2.73 (br. m, 2 H), 1.94−1.48 (m, 10 H), 1.32−1.07 (m, 4 H) ppm. ^{13}C NMR: δ = 153.47, 151.42, 128.97, 124.85, 121.57, 45.72, 44.72, 44.39, 41.52, 31.20, 30.80, 30.20, 25.01 ppm. IR (neat): $\tilde{\nu}$ = 3056, 2939, 2863, 1710 (C=O), 1590, 1494, 1417 (C=C), 1259, 1197 (C−O), 1162, 742, 688 cm^{-1}. MS (EI): 273 (M), 204, 180 (100%), 95, 77, 67, 65.

Phenyl 4-(3′,5′-Difluorophenyl)piperidine-1-carboxylate (4.8): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 5:2) gave **4.8** as a white solid (yield, 90%). m.p.: 88−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42−6.63 (m, 8 H), 4.53−4.34 (br. m, 2 H), 3.14−2.84 (br. m, 2 H), 2.71 (tt, 1 H, *J* = 12.08 Hz, 3.75 Hz), 1.89 (d, 2 H), 1.72 (dddd, 2 H, *J* = 38.24 Hz, 25.25 Hz, 12.62 Hz, 4.12 Hz) ppm. ^{13}C NMR: δ = 163.91 (dd, *J* = 248.25 Hz, 12.80 Hz), 153.39, 151.26, 149.16 (t, *J* = 8.76 Hz), 129.04, 125.04, 121.54, 109.44 (dd, *J* = 18.19 Hz, 6.40 Hz), 101.61 (t, *J* = 25.60 Hz), 44.60, 44.25, 41.93, 32.64, 32.23 ppm. ^{19}F NMR: δ −110.35 ppm. IR (neat): $\tilde{\nu}$ = 3095, 3060, 3005, 2933, 2902, 2867, 1702(C=O), 1625, 1594, 1496, 1452, 1421(C=C), 1290, 1197(C−O), 1110, 1047, 960, 856, 748, 682 cm^{-1}. MS (EI): 317 (M), 267, 224 (100%), 182, 153, 127, 112, 94, 77, 65.

Phenyl 4-(2′-Methylphenyl)piperidine-1-carboxylate (4.9): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 8:1) gave **4.9** as a colorless oil (yield, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43−7.10 (m, 9 H), 4.54−4.39 (br. m, 2 H), 3.18−2.94 (br. m, 3 H), 2.39 (s, 3 H), 1.90−1.68 (m, 4 H) ppm. ^{13}C NMR: δ = 153.72, 151.44, 143.14, 135.02, 130.45, 129.19, 126.35, 126.13, 125.35, 125.16, 121.72, 45.37, 45.05, 38.12, 32.49, 32.11, 19.32 ppm. IR (neat): $\tilde{\nu}$ = 3045, 3018, 2937, 2854, 1716 (C=O), 1425(C=C), 1201(C−O), 1012, 750 cm^{-1}. MS (FAB): 296 [M + 1].

Phenyl 4-(2′-Methoxyphenyl)piperidine-1-carboxylate (4.10): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 9:1) gave **4.10** as a colorless oil (yield, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40−6.85 (m, 9 H), 4.50−4.36 (br. m, 2 H), 3.85 (s, 3 H), 3.19 (tt, 1 H, *J* = 12.08 Hz, 3.57 Hz), 3.06−2.93 (br. m, 2 H), 1.90 (d, 2 H), 1.75 (m, 2 H) ppm. ^{13}C NMR: δ = 156.72, 153.76, 151.55, 133.42, 129.20, 127.21, 126.47, 125.11, 121.77, 120.68, 110.39, 55.29, 45.42, 45.08, 35.23, 31.95, 31.47 ppm. IR (neat): $\tilde{\nu}$ = 3012, 2939, 2854, 1718(C=O), 1596, 1492, 1427, 1238, 1203 (C−O), 752 cm^{-1}. MS (EI): 312 [M + 1] (100%), 218, 175, 154, 77.

Phenyl 4-(4′-Fluorophenyl)piperidine-1-carboxylate (4.11): Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 9:1) gave 4.10 as a white solid (yield, 65%). m.p. 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42−7.06 (m, 9 H), 4.53−4.38 (br. m, 2 H), 3.21−1.85 (br. m, 2 H), 2.73 (tt, 1 H, *J* = 12.17 Hz, 3.57 Hz), 1.91 (d, 2 H), 1.72 (m, 2 H) ppm. ^{13}C NMR: δ = 161.38 (d, *J* = 244.21 Hz), 153.61, 151.40, 140.95 (d, *J* = 3.37 Hz), 129.16, 128.02 (d, *J* = 7.75 Hz), 125.12, 121.66, 115.20 (d, *J* = 20.88 Hz),

45.01, 44.68, 41.69, 33.43, 32.91 ppm. ^{19}F NMR: δ = −117.12 ppm. IR (neat): ṽ = 3073, 2996, 2950, 2919, 2850, 1716(C=O), 1598, 1508, 1425(C=C), 1274, 1193(C−O), 1160, 1112, 1047, 829, 744 cm^{-1}. MS (FAB): 300[M + 1].

General Procedure for the Preparation of 4-Substituted Piperidines (5): A mixture of phenyl piperidine-1-carboxylate **4** (1.5 mmol), KOH (2.1 g, 38 mmol), and 100% $NH_2NH_2{\cdot}H_2O$ (0.52 mL) in ethylene glycol (20 mL) was heated at reflux for 1 hour. The mixture was poured into water and extracted with CH_2Cl_2 (3 × 15). The organic solution was washed with NaOH (30%, aq.) and dried. Concentration at reduced pressure and purification by flash chromatography on silica gel (Et_2O:isopropylamine, 9:1) gave pure compound.

4-Methylpiperidine (5.1): Yield 56% Commercially available, registry number: 626−58−4.

4-Ethylpiperidine (5.2): Yield 60% Commercially available, registry number: 3230−23−7.[35,36]

4-Butylpiperidine (5.3): Yield 72% Spectral data as published.[35−37]

4-*tert*-Butylpiperidine (5.4): Yield 75% Commercially available, registry number: 1882−42−4.[35]

4-(3-Methylbutyl)piperidine (5.5): Yield 76% Commercially available, registry number: 372196−26−4.[38]

4-(2′-Methylphenyl)piperidine (5.6): Mixture of solid and oil. Yield 80% ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28−7.07 (m, 4 H), 3.2 (d, 2 H), 2.89−2.73 (m, 3 H), 2.35 (s, 3 H), 2.13 (s, 1 H), 1.77 (d, 2 H), 1.66 (m, 2 H) ppm. ^{13}C NMR: δ = 144.40, 134.91, 130.19, 126.16, 125.66, 125.44, 47.31, 38.57, 33.58, 19.22 ppm. IR (neat): ṽ = 3060, 3018, 2931, 2846, 2807, 2732, 1604, 1556, 1490, 1461, 1317, 1282, 1243, 752 cm^{-1}. MS (EI): 175 [M] (100%), 160, 117, 91, 83.

4-Cyclopentylpiperidine (5.7): Yield 63% Commercially available, registry number: 123812−47−5.[39]

General Procedure for the Preparation of 4-Substituted *tert*-Butyl Piperidine-1-carboxylates (7): Crude **4** (5 mmol) was added dropwise at −40 °C to a solution of KO*t*Bu (1.4 g, 12.5 mmol) in THF (15 mL), resulting in a red solution. The mixture was kept for one hour at −40 °C and then for 30 min at room temperature. Water (30 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 25 mL). The organic layers were combined, washed with water (2 × 15 mL) and brine (2 × 15 mL), and dried. Concentration at reduced pressure and purification by short flash chromatography on silica gel (*n*-heptane/EtOAc, 6:1) gave **7.11** (87%, from **4.10**) and **7.12** (85%, from **4.11**). Compounds **6.1**−**6.10** were prepared by the same procedure, starting from the corresponding 4-substituted 1-phenyloxycarbonyl-dihydropyridine (**2**). These were reduced without prior purification, by the phase-transfer hydrogenation described above, to 4-substituted 1-*tert*-butoxycarbonylpiperidines **7.1**−**7.10**.

***tert*-Butyl 4-(2′-Methylphenyl)piperidine-1-carboxylate (7.1):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.1** as a colorless oil (yield, 90%). ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.20−7.09 (m, 4 H), 4.31−4.17 (br. s, 2 H), 2.92−2.75 (m, 3 H), 2.36 (s, 3 H), 1.76 (d, 2 H), 1.63 (m, 2 H), 1.51 (s, 9 H) ppm. ^{13}C NMR: δ = 154.76, 143.51, 134.95, 130.31, 126.21, 125.91, 125.29, 79.28, 44.31 (br. s), 38.26, 32.31, 28.40, 19.24 ppm. IR (neat): ṽ = 3006, 2973, 2937, 2852, 1695 (C=O), 1423, 1365 (C=C), 1280, 1232, 1170 (C−O), 1114, 752 cm^{-1}. MS (EI): 275 (M), 219 (100%), 204, 160, 117, 105, 91, 70.

***tert*-Butyl 4-(1′-Methylpropyl)piperidine-1-carboxylate (7.2):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.2** as a colorless oil (yield, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15−3.96 (br. s, 2 H), 2.64−2.47 (br. s, 2 H), 1.48 (d, 2 H), 1.38 (s, 9 H), 1.35 (m, 1 H), 1.29−1.00 (m, 5 H), 0.84−0.72 (m, 6 H) ppm. ^{13}C NMR: δ = 154.68, 78.88, 44.20(br. s), 40.65, 38.89, 29.59, 27.95, 28.32, 26.24, 15.43, 11.53 ppm. IR (neat): ṽ = 2962, 2931, 2856, 1695 (C=O), 1421, 1365, 1282, 1234, 1174 cm^{-1}. MS (EI): 242 [M + 1], 241, 186 (100%), 168, 140, 84.

***tert*-Butyl 4-(1′-Ethylpropyl)piperidine-1-carboxylate (7.3):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.3** as a colorless oil (yield, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21−3.89 (br. s, 2 H), 2.65−2.43 (br. s, 2 H), 1.46 (d, 2 H), 1.38 (m, 10 H), 1.36 (m, 2 H), 1.21−1.03 (m, 4 H), 0.91 (m, 1 H), 0.83−0.72 (m, 6 H) ppm. ^{13}C NMR: δ = 154.64, 78.83, 45.54, 44.34 (br. s), 37.88, 28.94, 28.30, 22.15, 11.58 ppm. IR (neat): ṽ = 2962 cm^{-1}, 2931, 2873, 1697 (C=O), 1423, 1366, 1234, 1174 cm^{-1}. MS (EI): 255 [M], 200 (100%), 182, 126, 84, 71.

***tert*-Butyl 4-Pentylpiperidine-1-carboxylate (7.4):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.4** as a colorless oil (yield, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14−3.88 (br. s, 2 H), 2.69−2.52 (br. s, 2 H), 1.58 (d, 2 H), 1.40 (s, 9 H), 1.32−1.10 (m, 9 H), 1.08−0.93 (m, 2 H), 0.83 (t, 3 H) ppm. ^{13}C NMR: δ = 154.67, 78.86, 43.87 (br. s), 36.42, 35.90, 32.16, 31.94, 28.36, 26.18, 22.53, 13.94 ppm. IR (neat): ṽ = 2956, 2925, 2856, 1698 (C=O), 1421, 1365, 1278, 1245, 1172 cm^{-1}. MS (EI): 255 [M], 200 (100%), 182, 154, 140, 126, 84.

***tert*-Butyl 4-(2′-Ethylhexyl)piperidine-1-carboxylate (7.5):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.5** as a colorless oil (yield, 91%). ^{1}H NMR (400 MHz, $CDCl_3$), δ = 4.14−3.86 (br. s, 2 H), 2.70−2.51 (br. s, 2 H), 1.55 (d, 2 H), 1.39 (s, 9 H), 1.38(m, 1 H), 1.30−1.11 (m, 9 H), 1.09−0.91 (m, 4 H), 0.83 (t, *J* = 7.04 Hz, 3 H), 0.77 (t, *J* = 7.41 Hz, 3 H) ppm. ^{13}C NMR: δ = 154.71, 78.89, 43.87(br. s), 40.64, 35.22, 33.31, 32.91, 32.55, 32.44, 28.65, 28.33, 25.87, 23.00, 14.01, 10.46 ppm. IR (neat): ṽ = 2958, 2921, 2858, 1697 (C=O), 1465, 1421, 1365, 1278, 1243, 1172, 1151 cm^{-1}. MS (EI): 297 [M], 242 (100%), 224, 196, 168, 129, 84.

***tert*-Butyl 4-(1′-Ethylbutyl)piperidine-1-carboxylate (7.6):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.6** as a colorless oil (yield, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21−3.88 (br. s, 2 H), 2.67−2.42 (br. s, 2 H), 1.50−0.90 (m, 21 H), 0.89−0.64 (m, 6 H) ppm. ^{13}C NMR: δ = 154.52, 78.72, 44.33 (br. s), 43.62, 38.14, 32.15, 28.85, 28.72, 28.21, 22.67, 20.37, 14.23, 11.51 ppm. IR (neat): ṽ = 2958, 2931, 2869, 1697 (C=O), 1465, 1423, 1365, 1236, 1174, 1145 cm^{-1}. MS (EI): 269 [M], 213 (100%), 196, 168, 129, 126, 84.

***tert*-Butyl 4-(1′,1′-Dimethylpropyl)piperidine-1-carboxylate (7.7):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.7** as a colorless oil (yield, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18−3.82 (br. s, 2 H), 2.58−2.29 (br. s, 2 H), 1.55−1.20 (m, 11 H), 1.20−0.86 (m, 5 H), 0.81−0.47 (m, 9 H) ppm. ^{13}C NMR: δ = 154.44, 78.71, 44.35 (br. s), 43.85, 34.17, 32.10, 28.20, 26.18, 23.74, 7.78 ppm. IR (neat): ṽ = 2962, 2858, 1695 (C=O), 1465, 1448, 1423, 1365, 1241, 1162, 1116 cm^{-1}. MS (EI): 255 [M], 200 (100%), 182, 129, 126, 84, 71.

***tert*-Butyl 4-(1′-Propylbutyl)piperidine-1-carboxylate (7.8):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.8** as a colorless oil (yield, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21−3.87 (br. s, 2 H), 2.67−2.37 (br. s, 2 H),

1.51−1.27 (m, 12 H), 1.27−0.96 (m, 11 H), 0.79 (t, 6 H) ppm. ^{13}C NMR: δ = 154.62, 78.83, 44.41 (br. s), 41.82, 38.56, 32.80, 28.75, 28.25, 20.42, 14.28 ppm. IR (neat): ṽ = 2956, 2929, 2861, 1693 (C=O), 1454, 1423, 1365, 1234, 1172 (C−O), 1145. MS (EI): 283 [M], 227 (100%), 210, 182, 14o, 129, 84.

***tert*-Butyl 4-(1′-Methylpentyl)piperidine-1-carboxylate (7.9):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.9** as a colorless oil (yield, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15−3.95 (br. s, 2 H), 2.65−2.41 (br. s, 2 H), 1.55−1.31 (m, 11 H), 1.31−0.94 (m, 10 H), 0.87−0.68 (m, 6 H) ppm. ^{13}C NMR: δ = 154.64, 78.84, 44.24 (br. s), 41.03, 37.17, 33.42, 29.58, 29.42, 28.32, 27.91, 22.86, 15.93, 13.96 ppm. IR (neat): ṽ = 2956, 2929, 2856, 1697 (C=O), 1465, 1421, 1365, 1280, 1234, 1174 (C−O), 1145 cm^{-1}. MS (EI): 269 [M], 214 (100%), 196, 128, 84.

***tert*-Butyl 4-(2′-Ethylbutyl)piperidine-1-carboxylate (7.10):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 6:1) gave **7.10** as a colorless oil (yield, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13−3.84 (br. s, 2 H), 2.71−2.45 (br. s, 2 H), 1.61−1.43 (br. s, 2 H), 1.43−1.26 (br. s, 10 H), 1.26−1.09 (m, 5 H), 1.09−0.84 (m, 4 H), 0.84−0.60 (br. s, 6 H) ppm. ^{13}C NMR: δ = 154.62, 78.80, 43.83 (br. s), 40.11, 36.65, 33.26, 32.46, 28.29, 25.34, 10.48 ppm. IR (neat): ṽ = 2962, 2917, 2859, 1693 (C=O), 1421, 1365, 1278, 1243, 1172 (C−O), 1151 cm^{-1}. MS (EI): 269 [M], 213 (100%), 196, 184, 140, 129, 84.

***tert*-Butyl 4-(2′-Methoxyphenyl)piperidine-1-carboxylate (7.11):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 5:1) gave **7.11** as a colorless oil (yield, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22−7.11 (m, 2 H), 6.96−6.83 (m, 2 H), 4.33−4.12 (br. s, 2 H), 3.83 (s, 3 H), 3.09 (tt, 1 H, *J* = 12.26 Hz, 3.57 Hz), 2.82 (bt, 2 H, *J* = 12.62 Hz), 1.76 (d, 2 H), 1.58 (m, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR: δ = 156.72, 154.93, 133.87, 127.03, 126.48, 120.62, 110.34, 79.27, 55.28, 44.46 (br. s), 35.32, 31.81, 28.49 ppm. IR (neat): ṽ = 3004, 2960, 2933, 2852, 1693 (C=O), 1492, 1423, 1365, 1236, 1170 (C−O), 1016, 752 cm^{-1}. MS (FAB): 292 [M + 1].

***tert*-Butyl 4-(4′-Fluorophenyl)piperidine-1-carboxylate (7.12):** Purification by short flash chromatography on silica (*n*-heptane/EtOAc, 9:1) gave **7.12** as a colorless oil (yield, 85%). ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.18−7.11 (m, 2 H), 7.07−6.94 (m, 2 H), 4.32−4.14 (br. s, 2 H), 2.78 (br. m, 2 H), 2.62 (tt, 1 H, *J* = 12.26 Hz, 3.75 Hz), 1.79 (d, 2 H), 1.64−1.51 (m, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR: δ = 161.32 (d, *J* = 244 Hz), 154.83, 141.44 (d, *J* = 3.37 Hz), 128.07 (d, *J* = 7.75 Hz), 115.21 (d, *J* = 21.22 Hz), 78.48, 44.35 (br. s), 42.00, 33.35, 28.47 ppm. ^{19}F NMR: δ −117.51 ppm. IR (neat): ṽ = 3008, 2975, 2933, 2852, 1693 (C=O), 1511, 1425, 1365, 1280, 1228, 1168 (C−O), 1122 cm^{-1}. MS (EI): 280 [M], 224 (100%), 154, 136, 107, 77.

Supporting Information Available: ^{13}C NMR spectra of all purified compounds (see also the footnote on the first page of this article).

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