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Efficient One-Pot Formation of Amides from Benzyl Carbamates: Application to Solid-Phase Synthesis

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Abstract—A convenient one-pot protocol for the conversion of benzyl carbamates to amides is described. The general applicability of the procedure is illustrated using various types of substrates. This new method proceeds rapidly under mild conditions, in good yields, and without noticeable racemization. This protocol was applied to solid-phase synthesis to prepare amides and esters from Merrifield resin-bound carbamates and carbonates.

The selection of a protecting group is a key facet of modern organic and peptide synthesis. Significant progress has been made in the development of suitable protecting groups for a great number of functional groups.[1] Although a variety of protecting groups are available, certain synthetic processes require to chemoselective transformations of existing protecting group. The problem of selectivity in functional group transformations is especially acute in the design and construction of polyfunctional molecules such as peptides, polyketides and complex natural products. Therefore, the availability of methodologies to exchange protecting groups in a mild, straightforward, and preferably, one-pot procedure is of great benefit in terms of time and material savings.

The most useful amino protecting groups are the carbamates, developed for the protection of amino acids, and amides, and used more widely in the syntheses of alkaloids, peptides and nucleotides. Carbamates utilized in peptide and protein chemistry include the *N*-benzyloxycarbonyl (Cbz), *N*-fluorenylmethoxycarbonyl (Fmoc) and the *N*-*tert*-butoxycarbonyl (Boc). These groups exhibit contrasting chemical stabilities to catalytic hydrogenolysis, bases and acids.[1] The 9-fluorenylmethyl carbamates (Fmoc) are usually cleaved by organic bases. *N*-Boc groups are stable to bases but removed by acidic hydrolysis whereas benzyl carbamates (Cbz) are inactive to a variety of reagents and cleaved by catalytic hydrogenolysis. On the other hand, amides are exceptionally stable to hydrogenation, acidic or basic hydrolysis, and are classically hydrolyzed under harsh conditions by heating in strongly acidic or basic solution. To date, several reports have appeared dealing with the interconversion of carbamates, such as the transformation of a benzyl carbamate into the Boc group[2,3] and the reverse process[4,5] and the conversion of Fmoc into Cbz and Boc.[6,7] However, the transformation of carbamates into amides has not been previously documented.

In the course of the synthesis of the radiosumin[8,9] (Fig. 1), a trypsin inhibitor to be used in a combinatorial approach, we needed an efficient method of transforming benzyl carbamates into acetates in the presence of double bonds. Among the reported methods for removal of the benzyl carbamates, catalytic hydrogenolysis or reductive cleavage with a dissolving metal seemed unsuitable because of the combinatorial synthetic strategy and the structural limitations. We therefore sought to develop an efficient procedure for the Lewis acid catalyzed transformation of benzyl carbamates to the corresponding amides in high yields. We now describe a reagent system consisting of acetyl bromide (or benzoyl chloride) combined with tin(II) bromide and triethylamine and its practical applications (Scheme 1).

Reaction of benzyl carbamates with various Lewis acids, acetyl bromide and triethylamine (Table 1). Although several Lewis acids were reported to cleave benzyl

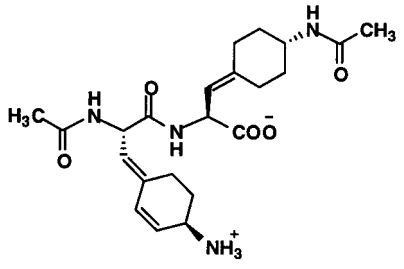

Figure 1. Radiosumin.

Keywords: benzyl carbamate; selective carbamate cleavage; benzyloxycarbonyl linker; Lewis acids; zinc(II) bromide; resin-bound carbamates and carbonates.

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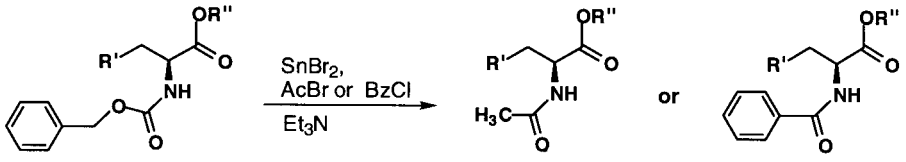


Scheme 1.

Table 1. Results obtained from the reaction of *N*-Cbz-Phe-OMe with acetyl bromide, triethylamine and 0.5 equiv. of various Lewis acids

Entry	Lewis acid	Time (h)	Yield (%)	*N*-Ac-L-Phe-OMe **1**	
				Mp (°C)	$[\alpha]_D^{25}$ (*c*, solvent)
1	$SnBr_2$	9	81	88–89	+101.2° (*c* 2.4, $CHCl_3$)
2	LiI	24	33	88–89	+101.5° (*c* 3.4, $CHCl_3$)
3	$SnCl_2$	24	70	88–89	+101.6° (*c* 3.5, $CHCl_3$)
4	$ZnCl_2$	10	70	89–90	+100.1° (*c* 3.4, $CHCl_3$)
5	$ZnBr_2$	10	71	89–90	+100.3° (*c* 5.7, $CHCl_3$)
6	$FeCl_3$	7	68	88–89	+102.3° (*c* 4.3, $CHCl_3$)
7	$AlCl_3$	24	52	89–90	+101.0° (*c* 2.9, $CHCl_3$)
8	$BF_3{\cdot}Et_2O$	24	31	88–89	+101.0° (*c* 3.0, $CHCl_3$)
9	TMSOTf	15	55	87–88	+101.2° (*c* 4.0, $CHCl_3$)

carbamates,[10,11] none of them has been known to convert carbamates to amides. Therefore, our initial efforts were directed at selecting the most suitable catalyst and reaction conditions for this transformation. As shown in Table 1, to convert benzyl carbamates into their corresponding *N*-acetates, the highest yields were obtained by treatment with acetyl bromide and tin(II) bromide in methylene chloride, followed by the addition of triethylamine. A lower yield of the desired products (monoamides) was observed by adding the triethylamine in one portion and this lower yield was attributed to the formation of diamides.

The amount of by-products was catalyst-dependent, with aluminum(III) chloride and boron trifluoride etherate giving the most by-products. Iron(III) chloride, zinc(II) halides and tin(II) chloride afforded the product but the overall yields and the reaction rates were not as good as with tin(II) bromide. With catalysts, such as lithium iodide and trimethylsilyl triflate the reaction did not go to completion. Addition of tetrabutylammonium bromide or potassium iodide did not enhance the yield or reaction rate in this 'transprotection' with tin(II) bromide.

The transprotection: synthesis of amides (Table 2). A variety of substrates were examined to evaluate the scope of the reaction. The acetamides and benzamides were prepared from the corresponding benzyl carbamates using the method described in the general procedure. As shown in Table 2, the yields and the reaction rates of the various substrates show a definite pattern. Benzamides usually were obtained in better yields. Faster transprotection occurred with acetyl bromide (9–20 h) as compared to benzoyl chloride (24–36 h).

The ester groups, the sulfide bond and the peptide bonds were stable under these conditions. We also observed that the *tert*-butyldimethyl silyl ether was rapidly converted to the corresponding acetate (**3**) using $SnBr_2$/AcBr/Et_3N. This protocol complements the direct deprotection by fluoride, followed by acylation, and further illustrates the unexplored potential of this reagent system. In the present study, racemization was not detected after comparison of the optical rotations of the pure amides with those reported in the literature.

The catalyst and solvent effect (Table 3). When the reaction was carried out in the presence of tin(II) bromide (0.5 equiv.), the reaction rate increased and only 9 h were needed to reach total conversion. Screening various reaction conditions, we found that CH_2Cl_2 was the most suitable solvent. Other solvents such as Et_2O and DMF gave low yields and decreased the reaction rate. Therefore, this reaction does not seem to proceed in protic or lone pair electron rich solvents such as alcohols, *N*-methyl-2-pyrrolidinone (NMP) and acetone.

Table 2. One-pot conversion of benzyl carbamates into the corresponding amides

Entry	Substrate	Time (h)	Product	Yield (%)
1	*N*-Cbz-L-Phe-OMe	9	Ac-L-Phe-OMe (**1**)	81
2	*N*-Cbz-L-Met-OBn	12	Ac-L-Met-OBn (**2**)	79
3	*N*-Cbz-L-Ser(OTBDMS)-OMe	10	Ac-L-Ser(OAc)-OMe (**3**)	80
4	*N*-Cbz-L-Ala-L-Ile-OEt	20	Ac-L-Ala-L-Ile-OEt (**4**)	68
5	*N*-Cbz-L-Phe-L-Leu-OMe	15	Ac-L-Phe-L-Leu-OMe (**5**)	73
6	*N*-Cbz-L-Ala-OMe	36	Bz-L-Ala-OMe (**6**)	86
7	*N*-Cbz-L-Leu-OMe	34	Bz-L-Leu-OMe (**7**)	84
8	*N*-Cbz-L-Pro-OMe	24	Bz-L-Pro-OMe (**8**)	80
9	*N*-Cbz-L-Phe-L-Leu-OMe	36	Bz-L-Phe-L-Leu-OMe (**9**)	76

Table 3. Catalyst and solvent influence on the reaction of *N*-Cbz-Phe-OMe with acetyl bromide, tin(II) bromide and triethylamine

Entry	Equivalent of $SnBr_2$	Solvent	Time (h)	Yield (%)
1	0.02	CH_2Cl_2	48	46
2	0.1	CH_2Cl_2	48	61
3	0.5	CH_2Cl_2	9	81
4	0.5	DMF	48	14
5	0.5	THF	48	21
6	0.5	Et_2O	48	28
7	0.5	CH_3CN	24	66

Table 4. Results obtained from the cleavage of resin-bound carbamate of phenylalanine methyl ester with acetyl bromide, triethylamine and various Lewis acids

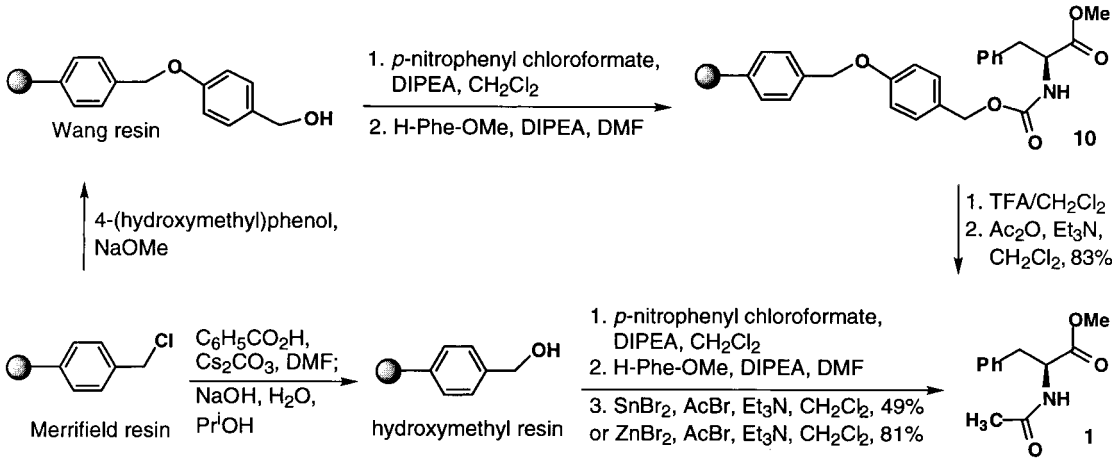
Entry	Lewis Acid	Time (h)	Yield of *N*-Ac-L-Phe-OMe **1** (%)
1	$ZnBr_2$	24	81
2	$SnBr_2$	24	49
3	$SnCl_2$	24	28
4	$FeCl_3$	20	42
5	$AlCl_3$	20	45
6	$BF_3{\cdot}Et_2O$	24	36
7	BBr_3	20	23
9	TMSOTf	15	25

Application to solid-phase synthesis. Use of a carbamate linker to attach amines to Wang resin has been widely applied to prepare various compounds for biological testing.[12–19] The susceptibility of Wang resin-bound carbamate linker to cleave by mild acids limits the range of solid-phase chemistry which can be performed. Merrifield resin-bound carbamates, being much less labile towards acid than those linked to Wang resins, are more versatile in the solid-phase combinatorial synthesis. However, cleavage of these carbamates by acids is more difficult.[20–22] It is also desirable from a synthetic point of view that amines, released from the solid support, immediately react with acyl halides and provide amides in a one-pot reaction.[23,24] This type of 'traceless' cleavage method should find broad application in solid-phase synthesis and stimulate the wider use of the Merrifield resin. In order to enhance the acidic stability of Wang resin-bound carbamate linker and add another dimension to the strategy of solid-phase synthesis, we sought to develop a mild method which would allow an efficient one-pot formation of amides from Merrifield resin-bound carbamates and broaden the application of this resin. Because of the success of the solution method, we decided to apply the same protocol to combinatorial solid-phase synthesis. Unfortunately, several attempts to use tin(II) bromide to promote the conversion of Merrifield resin-bound carbamate to amide **1** suffered from incomplete cleavage and proceeded in poor yields (Scheme 2).

Our recent publication exploring the zinc(II) bromide assisted release of Merrifield resin-bound ethers prompted us to reinvestigate the catalyst effect on solid support.[25] Therefore, we examined reagents known to produce good results for the one-pot transformation of benzyl carbamates into amides in solution, including $ZnBr_2$, $SnCl_2$, $FeCl_3$, $AlCl_3$, and TMSOTf (Table 1). In search of a more efficient catalyst, investigations on the solid-phase were conducted on the resin-bound carbamate of phenylalanine methyl ester, to parallel the experiments in solution phase. As shown in Tables 1 and 4, a surprising solid-phase effect was observed.

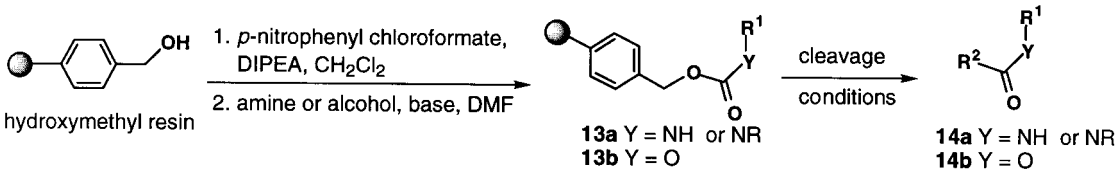
In the solution phase, *N*-Cbz-Phe-OMe was converted smoothly to the corresponding acetate with most of Lewis acids/acetyl bromide/triethylamine reagent systems. In contrast, on the solid-phase, the Merrifield resin-bound carbamate of phenylalanine methyl ester only reacted with the zinc(II) bromide catalyzed reagent system to give a high yield (81%) of the desired product **1**.[26] The precise mechanism of action of these reagent systems are unknown. However, the ability of tin bromide or zinc bromide to act as a Lewis acid in solution or solid-phase is probably an important factor. For comparison to the reported method,[12] Wang resin[27] was converted to an activated carbamate and treated with phenylalanine methyl ester to afford polymer **10** (Scheme 2). After trifluoroacetic acid cleavage and acetylation with Ac_2O/Et_3N, this protocol delivered *N*-Ac-L-Phe-OMe **1** in a similar overall yield.

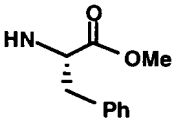
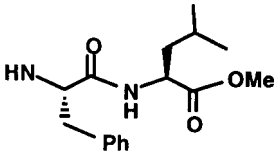
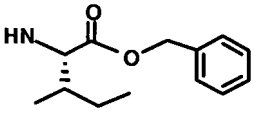
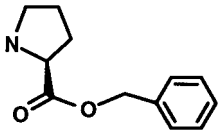
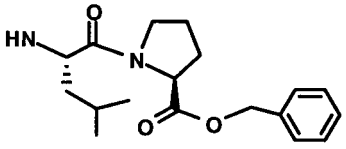
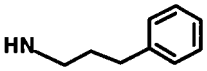
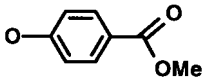
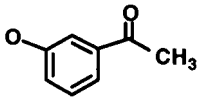
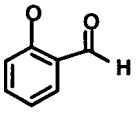
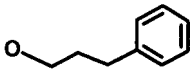
To verify the applicability of the method to solid-phase synthesis, we have synthesized Ac-L-Phe-L-Leu-OMe **5** (Scheme 3) and various amides listed in Table 5 on the Merrifield resin. As shown in Table 5, the *p*-nitrophenol



Scheme 2.

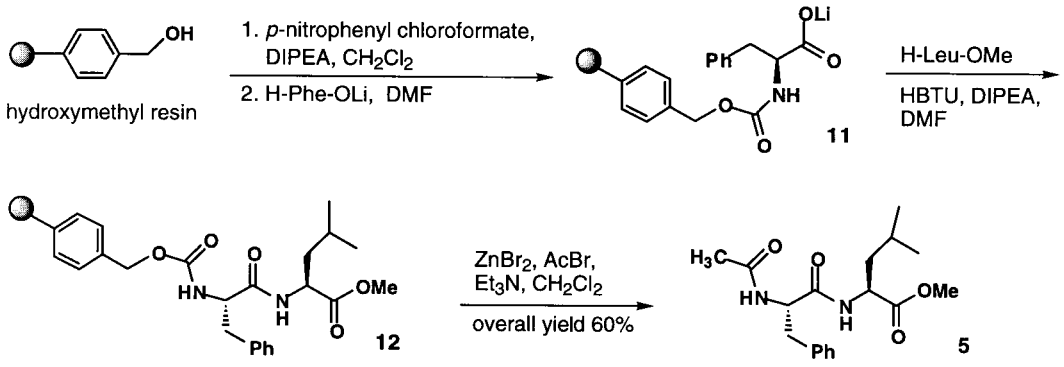
Table 5. Synthesis of amides **14a** and esters **14b** by Lewis acids assisted cleavage of resin-bound carbamates **13a** and carbonates **13b**



Entry	Resin **13**: R^1–Y group=	Base used	Cleavage conditions[a]	Product **14**: R^2 group	Overall yields[b] (%)
1		DIPEA	A	R^2=CH_3 (**1**)	81
		DIPEA	B	R^2=Ph (**15**)	86
2		DIPEA	A	R^2=CH_3 (**5**)	72
		DIPEA	B	R^2=Ph (**9**)	78
3		DIPEA	A	R^2=CH_3 (**16**)	72
		DIPEA	B	R^2=Ph (**17**)	74
4		DIPEA	A	R^2=CH_3 (**18**)	77
		DIPEA	B	R^2=Ph (**19**)	80
5		DIPEA	A	R^2=CH_3 (**20**)	70
		DIPEA	B	R^2=Ph (**21**)	75
6[c]		DIPEA	A	R^2=CH_3 (**22**)	74
7		Cs_2CO_3	C	R^2=CH_3 (**23**)	93
		Cs_2CO_3	D	R^2=Ph (**24**)	97
8		Cs_2CO_3	C	R^2=CH_3 (**25**)	75
9		Cs_2CO_3	C	R^2=CH_3 (**26**)	68
10		DMAP	C	R^2=CH_3 (**27**)	97
		DBU	C	R^2=CH_3 (**27**)	40
		NaH	C	R^2=CH_3 (**27**)	10

[a] Cleavage conditions: A. $ZnBr_2$/AcBr/Et_3N/CH_2Cl_2; B. $ZnBr_2$/BzCl/Et_3N/CH_2Cl_2; C. $ZnBr_2$/AcBr/CH_2Cl_2; D. $ZnBr_2$/BzCl/ CH_2Cl_2.
[b] Overall yields are isolated yields based on the loading of hydroxymethyl resin. All compounds gave satisfactory 200 MHz ^{1}H NMR spectra and the correct molecular ion by MS.
[c] Distilled technical grade 3-phenyl-1-propylamine was used.

was replaced by a variety of nucleophiles in the presence of different bases to afford resin-bound carbamates. Various types of the resin-bound carbamates were then cleaved with the zinc bromide/acyl halide/triethylamine reagent system to provide the corresponding amides in good yields. It is noteworthy that the cleavage proceeded faster with acetyl bromide but benzamides were obtained in better yield in both solid and solution reactions. The chemoselectivity of cleavage between benzyl carbamate and less reactive benzyl ester was excellent under the present conditions (entries 3–5).[28] No epimerization was observed when the cleavage of Merrifield resin-bound carbamates was



Scheme 3.

conducted with $ZnBr_2$/AcBr or BzCl/Et_3N reagent systems. The carbamide linkage was able to tolerate some stringent conditions such as LAH, NaOMe at room temperature, and therefore was a useful functionality in many aspects of organic synthesis. With these results in hand, we extended this protocol to the synthesis of acetates and benzoates from alcohol and phenols on solid support.[29] In contrast to the Merrifield resin-bound carbamate cleavage method, it was found that the triethylamine was not necessary to drive the reaction to completion when the resin-bound carbonates were cleaved (Table 5, entries 7–10). It should be noted that direct treatment of salicylaldehyde in CH_2Cl_2 with acetyl bromide in the absence of triethylamine for 24 h suffered incomplete acetylation (65% yield) and entry 9 also gave a moderate one-pot solid-phase synthesis of a *O*-acylated salicylaldehyde. This result is presumably due to hydrogen bonding between the carbonyl group and the hydrogen of the hydroxyl group, which retarded acylation of the alcohol.

In conclusion, we have developed novel and useful cleavage methods for the Merrifield resin based carbamates and carbonates which require no additional linker for anchoring amines, phenols, and alcohols to the resin other than the functional group constructed during the synthesis. This Merrifield resin-bound benzyloxycarbonyl linkage is stable to moderately strong bases such as piperidine, and it shows better stability against acids such as dilute trifluoroacetic acid. The direct transformation of benzyl carbamates and benzyloxycarbonyl resins into amides and esters has various advantages including mild and efficient reaction conditions, experimental convenience, and material efficiency. This methodology also gives high yields and purity, ensures total preservation of the stereochemistry, and therefore permits the construction of long chains of chiral amides and esters. The Merrifield resin-bound benzyloxycarbonyl linkers would also allow the construction of both peptide and organic combinatorial libraries in a bi-directional fashion. This protocol should expand the utility of commercially available Merrifield resin and hydroxymethyl resin and tremendously broaden the scope of the new synthetic procedure to the solid-phase combinatorial synthesis of natural products of pharmacological interest. Currently, we are in the process of using this Lewis acid catalyzed cleavage method to the combinatorial synthesis of radiosumin libraries and those results will be reported in due course.

Experimental

General procedures

All solvents were reagent grade and distilled before use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F_{254}) plates (0.25 mm). Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin, phosphomolybdic acid and anisaldehyde. Chromatography was carried out on Merck silica gel 60 (particle size 240–400 mesh). Melting points (mp) were determined with a Mel–Temp II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS) or chloroform as the internal standard. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Infrared spectra (IR) were obtained on a Bio-Rad FTS 155 spectrometer. Absorptions are reported in wave numbers (cm^{-1}) and the spectra are calibrated against the 1601 cm^{-1} band of a polystyrene film. Optical rotations (in degrees, °) were recorded on a Perkin–Elmer Model 343 polarimeter at the sodium D line. Concentrations were reported in g/100 mL. High resolution mass spectra (HRMS) were obtained on JEOL SX-102A, using either ammonia chemical ionization (CI) or electron impact (EI).

General procedure for the conversion of benzyl carbamates into amides

To a stirred solution of benzyl carbamates (0.46 mmol) in CH_2Cl_2 (2.3 mL) was added, under an argon atmosphere, tin(II) bromide (0.25 mmol) followed by acetyl bromide or benzoyl chloride (2.3 mmol) at room temperature. After the carbamates disappeared, a solution of triethylamine (0.69 mmol) in 2.5 mL CH_2Cl_2 was introduced dropwise and the mixture was then stirred at room temperature until the reaction was completed. The reaction was monitored by TLC using MeOH/CH_2Cl_2 (20:80) or EtOAc/hexane (30:70) as eluting system. After dilution with EtOAc, the mixture was washed with 5% $NaHCO_3$, 5% HCl and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude products were purified by column chromatography and eluted with a EtOAc/hexane system to afford the pure products.

General procedure for the synthesis of dipeptides such as *Z*-alaninylisoleucine ethyl ester

Isoleucine (1.17 g, 8.93 mmol) was dissolved in EtOH (40 mL) in a flame-dried flask equipped with a magnetic stirrer. To this stirred solution was added dropwise, under argon, a solution of thionyl chloride in EtOH (5 mL, 7 M). The reaction mixture was refluxed for 6 h, and then concentrated under reduced pressure. The resulting crude material was dissolved in CH_2Cl_2 (30 mL). To this solution was added triethylamine (1.8 mL, 13.39 mmol) at 0°C. The reaction was stirred for 15 min. and *Z*-alanine (1.99 g, 8.93 mmol) in CH_2Cl_2 (20 mL) was added via a cannula. 1,3-Diisopropylcarbodiimide (DIC) (1.53 mL, 9.82 mmol) was then added with stirring. After 24 h, the reaction mixture was concentrated, and the resulting solid was washed with cold EtOAc. The filtrate was concentrated under reduced pressure and diluted with ether (250 mL). The ether layer was washed with 10% HCl (40 mL), 5% $NaHCO_3$ (40 mL), and saturated NaCl (40 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/hexane (40:60). *Z*-alaninylisoleucine methyl ester (2.3 g, 92%) was obtained as a white solid.

Spectral data

Ac-L-Phe-OMe (1). Mp 88–89°C, lit.[30] 87–88.5°C; $[\alpha]_D^{25}=+101.2°$ (*c* 2.4, $CHCl_3$), lit.[30] $[\alpha]_D^{25}=+105.3°$ (*c* 1, $CHCl_3$), lit.[31] $[\alpha]_D^{25}=+96.4°$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν=3331, 3036, 2963, 1784, 1651, 1535, 1221 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.98 (s, 3H), 3.09–3.14 (m, 2H), 3.72 (s, 3H), 4.88 (m, 1H), 5.95 (br d, 1H, *J*= 6.0 Hz), 7.06–7.11 (m, 2H), 7.23–7.34 (m, 3H)[32]; ^{13}C NMR ($CDCl_3$/TMS) δ 23.11, 37.79, 52.30, 53.06, 127.10, 128.55, 129.19, 135.77, 169.57, 172.06; HRMS Calcd for $C_{12}H_{15}NO_3$ (M+) 221.1052, found 221.1036.

Ac-L-Met-OBn (2). $[\alpha]_D^{25}=-25.7°$ (*c* 1.7, MeOH); IR ($CHCl_3$): ν=3285, 3063, 2920, 1744, 1655, 1541, 1211 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.88–2.17 (m, 8H), 2.41–2.50 (m, 2H), 4.70–4.81 (m, 1H), 5.18 (d, 2H, *J*=1.9 Hz), 6.27 (br d, 1H, *J*=7.4 Hz), 7.32–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 15.44, 23.16, 29.83, 31.73, 51.68, 67.36, 128.34, 128.56, 128.64, 135.11, 169.84, 171.90; HRMS Calcd for $C_{14}H_{19}NO_3S$ (M+) 281.1086, found 281.1079.

Ac-L-Ser(OAc)-OMe (3). Mp 55–56°C; $[\alpha]_D^{25}=+68.4°$ (*c* 4.85, $CHCl_3$); IR ($CHCl_3$): ν =3299, 3063, 2949, 1744, 1657, 1543, 1375, 1227 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 6H), 3.78 (s, 3H), 4.30–4.51 (m, 2H), 4.82–4.90 (m, 1H), 6.25 (br d, 1H, *J*=6.0 Hz)[33]; ^{13}C NMR ($CDCl_3$/TMS) δ 20.47, 22. 79, 51.56, 52.66, 63.74, 169.97, 170.46; HRMS Calcd for $C_8H_{13}NO_5$ (M+) 203.0794, found 203.0784.

Ac-L-Ala-L-Ile-OEt (4). Mp 103–106°C; $[\alpha]_D^{25}=-19.3°$ (*c* 4.75, $CHCl_3$); IR ($CHCl_3$): ν=3285, 2963, 1744, 1643, 1543, 1448, 1259, 1024 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85–0.92 (m, 6H), 1.18–1.41 (m, 8H), 1.87–1.97 (m, 1H), 1.99 (s, 3H), 4.12–4.24 (m, 2H), 4.45–4.53 (m, 1H), 4.60–4.67 (m, 1H), 6.61 (br d, ^1H *J*=7.4 Hz), 7.02 (br d, 1H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 11.56, 14.14, 15.41, 18.49, 23.00, 25.00, 37.58, 48.70, 56.63, 61.14, 169.91, 171.53, 172.40; HRMS Calcd for $C_{13}H_{24}N_2O_4$ (M+) 272.1736, found 272.1755.

Ac-L-Phe-L-Leu-OMe (5). Mp 126–128°C; $[\alpha]_D^{25}=-18.2°$ (*c* 4.0, MeOH); IR ($CHCl_3$): ν=3285, 3077, 2963, 1744, 1657, 1549, 1200, 1153 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 6H, *J*=5.5 Hz), 1.46–1.59 (m, 3H), 1.96 (s, 3H), 3.06 (d, 2H, *J*=6.9 Hz), 3.69 (s, 3H), 4.48–4.55 (m, 1H), 4.60–4.81 (m, 1H), 6.34–6.43 (m, 2H), 7.23–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 21.87, 22.63, 23.08, 24.72, 38.28, 41.34, 50.90, 52.22, 54.30, 126.95, 128.56, 129.31, 136.42, 169.95, 170.71, 172.62; HRMS Calcd for $C_{18}H_{26}N_2O_4$ (M+) 334.1893, found 334.1895.

Bz-L-Ala-OMe (6). Mp 52–53°C; $[\alpha]_D^{25}=+38.6°$ (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): ν=3318, 2988, 1744, 1643, 1543, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 (d, 3H, *J*=7.2 Hz), 3.78 (s, 3H), 4.71–4.91 (m, 1H), 6.83 (br d, 1H, *J*=5.5 Hz), 7.39–7.51 (m, 3H), 7.78–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS) δ 18.56, 48.41, 52.52, 126.99, 128.51, 131.67, 133.82, 166.76, 173.65; HRMS Calcd for $C_{11}H_{13}NO_3$ (M+) 207.0895, found 207.0898.

Bz-L-Leu-OMe (7). Mp 102.5–103.5°C, lit.[34] 103–104°C; $[\alpha]_D^{25}=-22.7°$ (*c* 6.25, EtOH), lit.[34] $[\alpha]_D^{25}=-22°$ (*c* 3.6, EtOH); IR ($CHCl_3$): ν=3285, 3069, 2955, 1751, 1637, 1541, 1228, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96–1.01 (m, 6H), 1.62–1.81 (m, 3H), 3.78 (s, 3H), 4.84–4.88 (m, 1H), 6.55 (br d, 1H, *J*=7.3 Hz), 7.40–7.52 (m, 3H), 7.78–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS) δ 22.00, 22.79, 24.93, 41.80, 51.06, 52.34, 127.01, 128.52, 131.68, 133. 86, 167.05, 173.69; HRMS Calcd for $C_{14}H_{19}NO_3$ (M+) 249.1365, found 249.1364.

Bz-L-Pro-OMe (8). Mp 90–91°C, lit.[35] 89–91°C; $[\alpha]_D^{25}=-99.3°$ (*c* 5.85, MeOH), lit.[35] $[\alpha]_D^{25}=-100.1°$ (*c* 1.17, MeOH); IR ($CHCl_3$): ν=2951, 2878, 1742, 1624, 1572, 1448 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.81–2.34 (m, 4H), 3.50–3.71 (m, 2H), 3.77 (s, 3H), 4.36–4.68 (m, 1H), 7.36–7.59 (m, 5H)[36]; ^{13}C NMR ($CDCl_3$/TMS) δ 25.33, 29.34, 49.87, 52.20, 59.08, 126.46, 127.24, 128.18, 129.72, 130.13, 136.13, 169.62, 172.72; HRMS Calcd for $C_{13}H_{15}NO_3$ (M+) 233.1052, found 233.1063.

Bz-L-Phe-L-Leu-OMe (9). Mp 144–147°C, lit.[37] 163–166°C; $[\alpha]_D^{25}=-45.9°$ (*c* 4.35, MeOH); IR ($CHCl_3$): ν=3291, 3067, 2957, 1751, 1637, 1543, 1489, 1207 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.77 (d, 6H, *J*=5.14 Hz), 1.35–1.55 (m, 3H), 3.12 (m, 2H), 3.64 (s, 3H), 4.43–4.52 (m, 1H), 4.84–5.00 (m, 1H), 6.50 (br d, 1H, *J*=7.5 Hz), 6.64 (br d, 1H, *J*=8.8 Hz), 7.01–7.66 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ 21.84, 22.62, 24.72, 38.30, 41.29, 50.98, 52.28, 54.59, 127.02, 128.64, 129.45, 131.82, 133.71, 136.43, 167.20, 170.66, 172.66; HRMS Calcd for $C_{23}H_{28}N_2O_4$ (M+) 396.2049, found 396.2057.

Resin-bound phenylalanine lithium salt (11).[20,38] The hydroxymethyl resin[39] (300 mg, 0.48 mmol) was suspended in dry CH_2Cl_2 (1.9 mL) and treated with *p*-nitrophenyl chloroformate (290.3 mg, 1.44 mmol) and DIPEA

(0.26 mL, 1.44 mmol) under an argon atmosphere. The mixture was agitated for 8 h at room temperature, flushed and washed with DMF (2 mL×2) and CH_2Cl_2 (2 mL×2). The resulting resin was dried in vacuo to provide *p*-nitrophenyl carbonate resin. The carbonate resin (300 mg, 0.48 mmol) was then treated with freshly prepared phenylalanine lithium salt (246.5 mg, 1.44 mmol) in DMF (1.5 mL) at room temperature. The mixture was agitated for 24 h, filtered and washed with H_2O (2 mL×2), DMF (2 mL×2) and CH_2Cl_2 (2 mL×2) to afford the resin-bound phenylalanine lithium salt **11**.

Resin-bound phenylalaninylleucine methyl ester (12). To a suspension of resin-bound phenylalanine lithium salt **11** (200 mg, 0.32 mmol) in DMF (2.3 mL) was added HBTU (364.1 mg, 0.96 mmol) followed by leucine methyl ester (173.8 mg, 0.96 mmol) and DIPEA (0.366 mL, 1.92 mmol) under an argon atmosphere. The mixture was agitated for 3 h at room temperature. The resin was then flushed free of the liquids, washed with DMF (2×2 mL) followed by CH_2Cl_2 (2×2 mL) and DMF (2×2 mL) to afford the polymeric Phe-Leu-OMe **12**.

General procedure for the preparation of resin-bound carbamates 13a and carbonates 13b

(A) Amines. The hydroxymethyl resin (200 mg, 0.32 mmol) was swelled with CH_2Cl_2 (1.5 mL) and treated with *p*-nitrophenyl chloroformate (193.5 mg, 0.96 mmol) and DIPEA (0.17 mL, 0.96 mmol) under an argon atmosphere. The mixture was agitated for 8 h at room temperature, flushed and washed with DMF (2 mL×2) and CH_2Cl_2 (2 mL×2). The resin was dried in vacuo to provide *p*-nitrophenyl carbonate resin. The resulting carbonate resin (300 mg, 0.48 mmol) in DMF (1.9 mL) was added to the desired substrate hydrochloride amine salt (1.44 mmol) and *N*, *N*-diisopropylethylamine (0.5 mL, 2.88 mmol) and left to shake at room temperature for 6 h. The resin was then washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3). *(B) Phenols.* Same as condition A, except DIPEA was changed to Cs_2CO_3 and the mixture was agitated for 24 h. (*C*) *Aliphatic alcohol*. Same as condition B, except Cs_2CO_3 was changed to DMAP.

General procedure for the cleavage of resin-bound carbamates 13a and carbonates 13b

(A) Carbamates. To the carbamate resin (200 mg, 0.32 mmol), swelled in CH_2Cl_2 (1.6 mL), was added dry zinc(II) bromide (36 mg, 0.16 mmol) and acetyl bromide or benzoyl chloride (0.07 mL, 0.96 mmol) under an argon atmosphere. The mixture was stirred for 24 h at room temperature, then a solution of triethylamine (0.07 mL, 0.48 mmol) in 0.38 mL CH_2Cl_2 was added dropwise. After the reaction was completed, the resin was collected by filtration. The filtrate was washed with 5% $NaHCO_3$, 5% HCl and saturated NaCl solutions. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel to yield the desired amides **14a**. *(B) Carbonates.* Same as condition A, except the addition of triethylamine was omitted.

Spectral data

Bz-L-Phe-OMe (15). $[\alpha]_D^{25}=+80.5°$ (*c* 1.89, CH_2Cl_2); IR (CH_2Cl_2): ν=3318, 3063, 3030, 2952, 1744, 1643, 1535, 1489, 1217, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.13–3.38 (m, 2H), 3.76 (s, 3H), 5.09 (q, 1H, *J*=7.50 Hz), 6.62 (d, br, *J*=7.25 Hz), 7.12–7.74 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ 37.76, 52.28, 53.46, 126.92, 127.06, 128.48, 128.50, 129.21, 131.64, 133.77, 135.81, 166.763, 171.97; HRMS Calcd for $C_{17}H_{17}NO_3$ (M+) 283.1208, found 283.1214.

Ac-L-Ile-OBn (16). $[\alpha]_D^{25}=+144.5°$ (*c* 0.87, CH_2Cl_2); IR (CH_2Cl_2): ν=3306, 3065, 2870, 1670, 1543, 1460, 1211 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J*=7.4 Hz), 0.87 (t, 3H, *J*=7.0 Hz), 1.13–1.38 (m, 2H), 1.85–1.95 (m, 1H), 2.01 (s, 3H), 4.66 (dd, 1H, *J*=4.92 Hz), 5.08–5.23 (m, 2H), 6.33 (d, 1H, *J*=8.54 Hz), 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 11.31, 15.21, 22.77, 24.85, 37.63, 56.26, 66.66, 128.06, 128.17, 128.32, 135.11, 169.95, 171.99; HRMS Calcd for $C_{15}H_{21}NO_3$ (M+) 263.1521, found 263.1521.

Bz-L-Ile-OBn (17). $[\alpha]_D^{25}=+268.3°$ (*c* 0.87, CH_2Cl_2); IR (CH_2Cl_2): ν=3331, 3065, 3033, 2966, 2935, 2877, 1739, 1644, 1603, 1185, 712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J*=7.31 Hz), 0.96 (t, 3H, *J*=3.85 Hz), 1.21–1.49 (m, 2H), 2.00–2.06 (m, 1H), 4.89 (dd, 1H, J=4.85, 4.89 Hz), 5.13–5.29 (m, 2H), 6.78 (d, 1H, *J*=8.42 Hz), 7.37–7.82 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ 11.47, 15.41, 25.13, 38.15, 56.72, 66.97, 126.93, 128.24, 128.33, 128.44, 128.47, 131.55, 134.00, 135.148, 167.05, 171.93; HRMS Calcd for $C_{20}H_{23}NO_3$ (M+) 325.1678, found 325.1676.

Ac-L-Pro-OBn (18). $[\alpha]_D^{23}=-64.4°$ (*c* 1.79, CH_2Cl_2); IR (CH_2Cl_2): ν=3466, 2959, 1741, 1634, 1451, 1172 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.92–2.07 (m, 2H), 2.10 (s, 3H), 2.15–2.20 (m, 2H), 3.49–3.68 (m, 2H), 4.52–4.57 (m, 1H), 5.16–5.53 (m, 2H), 7.30–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 22.15, 24.66, 29.28, 47.65, 58.52, 66.63, 127.94, 128.44, 128.69, 169.36, 172.10; HRMS Calcd for $C_{14}H_{17}NO_3$ (M+) 247.1208, found 247.1209.

Bz-L-Pro-OBn (19). $[\alpha]_D^{25}=-56.9°$ (*c* 2.21, CH_2Cl_2); IR (CH_2Cl_2): ν=3466, 3036, 1742, 1624, 1570, 1495, 787 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.81–2.07 (m, 2H), 2.23–2.34 (m, 2H), 3.49–3.84 (m, 2H), 4.70–4.76 (m, 1H), 5.02–5.29 (m, 2H), 7.26–8.08 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ 25.13, 29.16, 49.77, 59.11, 66.65, 127.053, 127.90, 128.07, 128.16, 129.80, 130.04, 133.06, 135.89, 169.67, 171.88; HRMS Calcd for $C_{19}H_{19}NO_3$ (M+) 309.1365, found 309.1363.

Ac-L-Leu-L-Pro-OBn (20). $[\alpha]_D^{24}=-83.3°$ (*c* 2.07, CH_2Cl_2); IR (CH_2Cl_2): ν=3466, 3063, 2961, 2866, 1742, 1632, 1537, 1441, 1373, 1169, 1093, 738 cm^{-1}; ^1H NMR (200 MHz, CDCl3) δ 1.04 (dd, 6H, *J*=6.834, 7.026 Hz), 1.60–1.64 (m, 2H), 1.75–1.84 (m, 1H), 1.88 (s, 3H), 2.04–2.28 (m, 4H), 3.73–3.92 (m, 2H), 4.69 (t, 1H, *J*=5.24 Hz), 4.92 (q, 1H, *J*=8.43 Hz), 5.16–5.31 (m, 2H), 6.37 (d, 1H, *J*=8.54 Hz), 7.37–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 22.02, 22.93, 24.72, 24.85, 28.98, 41.46,

46.90, 49.14, 59.00, 66.79, 128.05, 128.22, 128.51, 135.87, 169.78, 171.59, 171.70; HRMS Calcd for $C_{20}H_{28}N_2O_4$ (M+) 360.2049, found 360.2049.

Bz-L-Leu-L-Pro-OBn (21). $[\alpha]_D^{25}=-53.6°$ (*c* 0.75, CH_2Cl_2); IR (CH_2Cl_2): ν=3425, 2958, 1744, 1579, 1450, 1170 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (dd, 6H, *J*=6.438, 6.350 Hz), 1.58–1.76 (m, 3H), 1.99–2.10 (m, 2H), 2.23–2.25 (m, 2H), 3.68–3.91 (m, 2H), 4.61 (m, 1H), 5.06–5.25 (m, 3H), 7.26–7.45 (m, 10H), 8.09 (d, 1H, *J*=6.87 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 21.83, 23.37, 24.71, 28.98, 41.74, 46.97, 49.34, 58.98, 66.96, 127.14, 128.15, 128.32, 128.55, 130.00, 131.58, 133.80, 135.45, 167.19, 171.62, 171.82; HRMS Calcd for $C_{25}H_{30}N_2O_4$ (M+) 422.2206, found 422.2205.

***N*-(3-Phenylpropyl)acetamide (22).** IR (CH_2Cl_2): ν=3430, 3301, 3092, 2930, 2863, 1637, 1556, 1495, 1448, 1292, 744, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.76–1.98 (m, 2H), 1.94 (s, 3H), 2.65 (t, 2H, *J*=7.36 Hz), 3.28 (q, 2H, *J*=6.24 Hz), 5.64 (br, 1H), 7.16–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 23.33, 31.19, 33.37, 39.40, 126.06, 128.39, 128.52, 141.47, 140.19; MS Calcd for $C_{11}H_{15}NO$ (M+) 177.1, found 177.1.

4-Acetoxybenzoic acid methyl ester (23). IR (CH_2Cl_2): ν=3499, 3028, 1755, 1707, 1439, 1277, 1163, 1117, 914, 860, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.91 (s, 3H), 7.14–7.20 (m, 2H), 8.04–8.10 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS) δ 21.19, 52.24, 121.65, 127.74, 131.20, 154.32, 166.34, 168.91; HRMS Calcd for $C_{10}H_{10}O_4$ (M+) 194.0579, found 194.0583.

4-Benzoyloxybenzoic acid methyl ester (24). IR (CH_2Cl_2): ν=1718, 1597, 1502, 1282, 1265, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.28–7.33 (m, 2H), 7.48–7.65 (m, 3H), 8.09–8.22 (m, 4H); ^{13}C NMR ($CDCl_3$/TMS) δ 52.12, 121.68, 127.68, 128.59, 129.01, 130.15, 131.14, 133.80, 154.54, 164.54, 166.25; HRMS Calcd for $C_{15}H_{12}O_4$ (M+) 256.0736, found 256.0732.

1-(3-Acetoxyphenyl)ethanone (25). IR (CH_2Cl_2): ν=3520, 3077, 3003, 1761, 1680, 1591, 1489, 1435, 1360, 1283, 1005, 929 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.57 (s, 3H), 7.27–7.82 (m, 4H); ^{13}C NMR ($CDCl_3$/TMS) δ 20.78, 26.42, 121.19, 125.54, 126.22, 129.43, 138.25, 150.59, 169.02, 196.64; HRMS Calcd for $C_{10}H_{10}O_3$ (M+) 178.0630, found 178.0621.

2-Acetoxybenzaldehyde (26). IR (CH_2Cl_2): ν=2918, 2850, 1769, 1697, 1603, 1456, 1368, 1188 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.15–7.89 (m, 4H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS) δ 20.78, 123.42, 126.06, 131.28, 134.61, 135.28, 151.10, 169.26, 188.83; HRMS Calcd for $C_9H_8O_3$ (M+) 164.0473, found 164.0420.

3-Phenylpropyl acetate (27). IR (CH_2Cl_2): ν=3059, 3027, 1736, 1495, 1446, 1389, 1367, 1238, 1036, 742, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.91–1.99 (m, 2H), 2.05 (s, 3H), 2.69 (t, 2H, *J*=7.69 Hz), 4.08 (t, 2H, *J*=6.56 Hz), 7.16–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS) δ 20.90, 30.10, 32.09, 63.75, 125.93, 128.32, 128.36, 141.12, 171.01; HRMS Calcd for $C_{11}H_{14}O_2$ (M+) 178.0994, found 178.1007.

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