# **Direct Transacylation of 2,2,2-Trihaloethyl Esters with Amines** and Alcohols Using Phosphorus(III) Reagents for Reductive **Fragmentation and in Situ Activation**

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Amides and esters have been synthesized from 2,2,2-trihaloethyl esters in one pot using phosphorus-(III) reagents as reductants, with resultant carboxylate activation as an acyloxyphosphonium intermediate, and in situ trapping by amine or alcohol nucleophiles. Secondary and tertiary amides were synthesized, including a dipeptide, in good yields using hexamethylphosphorous triamide, (Me<sub>2</sub>N)<sub>3</sub>P, as reducing agent. Optimal yields of esters derived from primary and secondary alcohols were obtained using tributylphosphine and DMAP. Tribromoethyl esters provided yields superior to those obtained with trichloroethyl esters.

# Introduction

2,2,2-Trihaloethyl esters are useful groups for the protection of carboxylic acids and other functional groups as a result of the mild, nonhydrolytic conditions used for their cleavage.<sup>1,2</sup> Although the trichloroethyl ester has been the most widely used haloethyl protecting group,<sup>1,3</sup> other  $\beta$ -haloethyl esters have been used for this purpose, including tribromoethyl<sup>4</sup> and 1,1-dimethyl-2,2,2-trichloroethyl groups.<sup>5</sup> Trihaloethyl groups can be used to protect both carbon<sup>1-4b</sup> and phosphorus oxy acids,<sup>4c,5</sup> and the related trichloroethoxycarbonyl (TROC) protecting group has been used to protect alcohols and amines as carbonates or carbamates, respectively.<sup>1</sup>

Deprotection of trihaloethyl esters is achieved using reducing conditions to effect  $\beta$ -elimination, as shown in eq 1.<sup>2</sup> A variety of methods have been developed for the cleavage of these esters, with zinc being the most commonly used reductant.<sup>3,6</sup> Other transition-metal reagents have been employed for cleavage including zinccopper<sup>7</sup> and zinc-lead couples,<sup>8</sup> as well as cobaltphthalocyanine complex.9 Selenium<sup>10</sup> and tellurium reagents,<sup>11</sup> as well as electrolysis,<sup>4b,12</sup> have also been used

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in trihaloethyl ester cleavage. Letsinger and co-workers have used tributylphosphine and (Me<sub>2</sub>N)<sub>3</sub>P [hexamethylphosphorous triamide, tris(dimethylamino)phosphine] to cleave 2,2,2-trichloroethyl and 1,1-dimethyl-2,2,2-trichloroethyl esters of phosphoric acids in their syntheses of oligonucleotides,<sup>13</sup> demonstrating the ability of phosphorus(III) reagents to reduce trihaloethyl esters.

$$\underset{R}{\overset{O}{\longrightarrow}} \underset{X}{\overset{R'}{\longrightarrow}} \underset{X}{\overset{R'}{\longrightarrow}} \underset{X}{\overset{(Y)}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{X}{\overset{O}{\longrightarrow}} \underset{X}{\overset{(Y)}{\longrightarrow}} \underset{R'}{\overset{(Y)}{\longrightarrow}} \underset{R'}{\overset{(Y)}{\overset}} \underset{R'$$

Phosphorus(III) reagents are also used in the generation of phosphonium salts, which are mild and efficient reagents for condensation reactions.<sup>14–19</sup> These reactions can be described as "oxidation-reduction condensations"<sup>19</sup> in which attack at a heteroatom by a phosphorus nucleophile results in oxidation of the latter to an electrophilic phosphonium salt. These salts then activate alcohol or carboxylic acid groups for condensation with various nucleophiles. Examples of the use of phosphorus-(III) reagents in coupling reactions include their combination with azodicarboxylates in the Mitsunobu reaction,14,16,17 the reaction of phosphines with disulfides in the Mukaiyama coupling method,<sup>19</sup> and the reaction of phosphorus(III) reagents with halogenated alkanes such as carbon tetrachloride to effect condensations.<sup>15,18</sup>

Preparation of amide and ester condensation products from protected carboxylic acids is usually achieved by

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stepwise carboxylic acid deprotection followed by formation of an activated acyl species and treatment with an amine or alcohol nucleophile. Such a deprotection-condensation protocol requires two or more steps and can be attended by difficulties in working with the free carboxylic acid intermediate. In light of the ability of phosphorus(III) reagents to cleave trihaloethyl esters and to act as efficient redox agents for condensation reactions, we believed the combination of these functions would produce a simple, one-pot procedure for the deprotection and condensation of trihaloethyl-protected acids. Although phosphonium salts have long been used to activate carboxylate functional groups in condensation reactions,<sup>14–27</sup> in situ formation of these species by reduction of trihaloethyl esters to effect condensation reactions has not been exploited. Toward this end, the amidation or transesterification of trihaloethyl esters using phosphorus(III) compounds, as generalized in eq 2, has been investigated.<sup>28</sup> This in situ deprotection, activation, and acyl-transfer sequence provides an operationally simple method for the title transformations.



# **Results and Discussion**

The 2,2,2-tribromoethyl and 2,2,2-trichloroethyl benzoate esters<sup>34</sup> employed in these studies were synthesized from benzoyl chloride and the corresponding 2,2,2trihaloethanol. Tribromoethyl esters of cyclohexanecarboxylic acid and *N*-Boc-alanine were synthesized using carbodiimide coupling conditions with diisopropylcarbodiimide (DIC) as the coupling reagent (Scheme 1).<sup>29</sup>

The conversion of 2,2,2-tribromoethyl benzoate (**2a**) to *N*-butylbenzamide (**7a**) using hexamethylphosphorous

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## Scheme 1





$ \begin{array}{c} O \\ H \\$					
	2a	NEt <sub>3</sub>	H 7a		
entry	solvent	<i>T</i> (°C)	% yield of <b>7a</b> <sup>a</sup>		
1	THF	0	36		
2	benzene	0	35		
3	CH <sub>3</sub> CN	0	70		
4	DMF	0	75		
5	DMF	-55	83		

<sup>a</sup> Isolated yields.

triamide [(Me<sub>2</sub>N)<sub>3</sub>P] was selected to determine the optimal reaction conditions for this transformation (Table 1). The tribromoethyl ester provides a softer, more reactive halogen electrophile than its trichloroethyl analogue, and (Me<sub>2</sub>N)<sub>3</sub>P was chosen for its high nucleophilicity.<sup>14</sup> Treatment of 2a with 1.2 equiv of (Me<sub>2</sub>N)<sub>3</sub>P, 1 equiv of butylamine, and 2.5 equiv of triethylamine in THF at 0 °C provided 7a in 36% yield (Table 1, entry 1). Use of benzene as a nonpolar solvent gave a similar yield (Table 1, entry 2), while more polar solvents such as acetonitrile (Table 1, entry 3) or dimethylformamide (DMF, Table 1, entry 4) facilitated the reaction, with DMF providing the best yield. Lowering the reaction temperature improved the yield of 7a to 83% (Table 1, entry 5). Small amounts of 2,2-dibromoethyl benzoate, and N,N-dimethylbenzamide were isolated as byproducts in these reactions.

Investigation of the choice of reductant and electrophile revealed the combination of (Me<sub>2</sub>N)<sub>3</sub>P and tribromoethyl protecting group to be the most effective for amide synthesis (Table 2). The reaction of (Me<sub>2</sub>N)<sub>3</sub>P with 2a proceeded rapidly at -55 °C to give **7a** (Table 2, entry 1). Use of tributylphosphine as the phosphorus reagent resulted in a slower reaction and provided 7a in reduced vield (Table 2, entry 2). Decreasing the nucleophilicity of the phosphorus reagent by using triphenylphosphine resulted in a markedly slower reaction at room temperature (Table 2, entry 3) and provided 7a in only 24% yield after 48 h. This yield is similar to that of the corresponding control experiment conducted in the absence of phosphine (Table 2, entry 4). Heating the triphenylphosphine reactions produced yields only marginally higher than controls. Use of the trichloroethyl ester necessitated higher temperatures for complete consumption of starting material, and lower yields were obtained (Table 2, entries 5 and 6). Using the optimized conditions, secondary and tertiary amides of aromatic (7b,c) and aliphatic (8a,b) acids, as well as a Boc-Ala-Ala-OEt dipeptide (9), have

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 Table 2. Effect of Phosphorus Nucleophile and Halogen on the Synthesis of 7a



entry	Х	phosphorus rgt	$T(^{\circ}C)$	time (h)	% yield of <b>7a</b> <sup>a</sup>
1	Br	(Me <sub>2</sub> N) <sub>3</sub> P	-55	0.5	83
2	Br	$PBu_3$	$-55 \rightarrow 0$	1.2	25
3	Br	$PPh_3$	rt	48	$24^{b}$
4	Br	none	rt	48	$17^{c}$
5	Cl	(Me <sub>2</sub> N) <sub>3</sub> P	rt	4.5	18
6	Cl	PBu <sub>3</sub>	90	3.5	39

 $^a$  Isolated yields.  $^b\!42\%$  of  ${\bf 2a}$  was recovered.  $^c\!66\%$  of  ${\bf 2a}$  was recovered.

Table 3. Conversion of Tribromoethyl Esters to Amides

O II	(Me <sub>2</sub> N) <sub>3</sub> P, amine, N	
	DMF, -55 °C	- н N - R"
2a (R=Ph) 5 (R=c-Hex) 6 (R=(S)-BocNH CH(CH <sub>3</sub> ))		7b (R=Ph, R'=R"=Et) 7c (R=Ph, R'=CH <sub>2</sub> CO <sub>2</sub> Et, R"=H) 8a (R=c-Hex, R'=Bu, R"=H) 8b (R=c-Hex, R'=R"=Et) 9 (R=( <i>S</i> )-BocNHCH(CH <sub>3</sub> ), R'=( <i>S</i> )-CH(CH <sub>3</sub> )CO <sub>2</sub> Et, R"=H)

entry	trihaloethyl ester	amine	product	% yield <sup>a</sup>
1	2a	HNEt <sub>2</sub>	7b	76
2	2a	HCl·GlyOEt	7c	77
3	5	BuNH <sub>2</sub>	<b>8</b> a	88
4	5	HNEt <sub>2</sub>	8b	57
5	6	HCl·AlaOEt	9	70

<sup>a</sup> Isolated yields.

been synthesized in good yields from the corresponding tribromoethyl esters (Table 3).

Modification of the amide synthesis conditions allowed for the synthesis of esters using this deprotectioncondensation strategy. Initial attempts to effect the transesterification of trihaloethyl esters by addition of (Me<sub>2</sub>N)<sub>3</sub>P to tribromoethyl esters failed to produce the desired products. The use of PBu<sub>3</sub> as phosphine reagent gave the ester products, albeit in low yield (Table 4, entry 1). Addition of 2 equiv of the acylation catalyst 4-(N,Ndimethylamino)pyridine (DMAP)<sup>30</sup> markedly improved vields in both (Me<sub>2</sub>N)<sub>3</sub>P- and tributylphosphine-induced reactions (Table 4, entries 2-5). Esterification protocols using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent<sup>25</sup> have appeared relatively recently.<sup>31</sup> In these studies, esterification of N-protected amino acids and phenylacetic acid proceeded in high yield, possibly via acylated hydroxybenzotriazole intermediates.<sup>25,26,31b</sup> This suggested the addition of 1-hydroxybenzotriazole (HOBt) as a transacylating agent in the (Me<sub>2</sub>N)<sub>3</sub>P-mediated reactions. In practice, HOBt-promoted esterification (Table 4, entry 6) but did not provide yields superior to the PBu<sub>3</sub>-DMAP reagent combination.

 
 Table 4. Effect of Phosphorus Nucleophile and Additive on Transesterification

		R <sup>L</sup> O <sup>O</sup>
₽ ₽ O CBr <sub>3</sub>	phosphorus rgt, additive, HOCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	10a (R=Ph) 11a (R= <i>c</i> -Hex) +
<b>2a</b> (R=Ph) 5 (R= <i>c</i> -Hex)	DMF,-55 °C	R N
		12 (R=Ph) 13 (R= <i>c</i> -Hex)

ntry	trihaloethyl ester	phosphorus reagent	additive	ester product	% yield <sup>a</sup>
1	2a	PBu <sub>3</sub>	none	10a	21
2	2a	$PBu_3$	DMAP	10a	69
3	2a	$(Me_2N)_3P$	DMAP	10a	50
					(18 of <b>12</b> )
4	5	PBu <sub>3</sub>	DMAP	11a	74
5	5	(Me <sub>2</sub> N) <sub>3</sub> P	DMAP	11a	44
					(28 of 13)
6	2a	$(Me_2N)_3P$	HOBt	10a	63
a Ico	lated violda				

<sup>*a*</sup> Isolated yields.

e

In contrast to the amidation reactions, tributylphosphine provided yields of ester products superior to those obtained with (Me<sub>2</sub>N)<sub>3</sub>P (Table 4). Substantial amounts of N,N-dimethylamide products were observed when (Me<sub>2</sub>N)<sub>3</sub>P was used as reductant (Table 4, entries 3 and 5).<sup>41,42</sup> This presumably results from attack of activated acyl intermediates by dimethylamine liberated in the alcoholysis of (Me<sub>2</sub>N)<sub>3</sub>P.<sup>32</sup> To substantiate this theory, the behavior of (Me<sub>2</sub>N)<sub>3</sub>P under similar reaction conditions in the absence of tribromoethyl ester was monitored by phosphorus NMR. After a solution of (Me<sub>2</sub>N)<sub>3</sub>P in DMF was stirred for 1.5 h, <sup>31</sup>P NMR analysis of an aliquot of this solution in  $CD_2Cl_2$  revealed a peak corresponding to (Me<sub>2</sub>N)<sub>3</sub>P (122.7 ppm, Figure 1) and a small amount of HMPA impurity (24.1 ppm, not shown). The (Me<sub>2</sub>N)<sub>3</sub>P solution was then treated with methanol (1.4 equiv), DMAP (1 equiv), and 4-(N,N-dimethylamino)pyridinium trifluoroacetate (DMAP·TFA, 0.4 equiv) as a surrogate

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Figure 1. (a) <sup>31</sup>P NMR spectrum (121 MHz,  $CD_2Cl_2$ ) of  $(Me_2N)_3P$ . (b) <sup>31</sup>P spectrum of aliquot 10 min after addition of MeOH, DMAP, and DMAP·TFA.

for the DMAP·HBr formed in these reactions. Analysis of an aliquot of this reaction mixture after 10 min showed no  $(Me_2N)_3P$  resonance and two downfield resonances that correspond to  $MeOP(NMe_2)_2$  (137.9 ppm) and  $(MeO)_2PNMe_2$  (147.6 ppm), indicating the rapid methanolysis of  $(Me_2N)_3P$ . A similar <sup>31</sup>P NMR spectrum was observed in the ethanolysis of  $(Me_2N)_3P$  by Houalla and co-workers.<sup>32e</sup> The reduced nucleophilicity of alcohols relative to amines allows attack by dimethylamine to become a competitive reaction pathway in the  $(Me_2N)_3P$ -mediated transesterifications.

Esters of both primary and secondary alcohols were produced in good yields using the tributylphosphine-DMAP procedure (Table 5, entries 1-11). Acylation of primary alcohols (Table 5, entries 1-3, 7-9) proceeded in yields superior to that of sterically more hindered secondary alcohols (Table 5, entries 4-6, 10, and 11). Acylation of *tert*-butyl alcohol proved difficult, giving only 11% of the tert-butyl benzoate ester when tert-butyl alcohol was used as cosolvent (Table 5, entry 12). As a control, treatment of 2a with 2-methoxyethanol and DMAP in the absence of phosphine for 24 h at room temperature produced no product by TLC analysis. As with the amidation reactions, the use of the trichloroethyl ester derivatives required higher temperatures for starting material consumption and provided lower yields (Table 5, entry 13).

Preliminary investigations of the application of this method toward macrocyclization of  $\omega$ -hydroxy and  $\omega$ -amino carboxylic acids have been conducted. Tribromoethyl esters of 12-hydroxystearic acid (15) and *N*-Boc-protected 12-aminododecanoic acid (17) were synthesized as shown in Scheme 2. Subjecting ester 15 to the optimized esterification conditions modified slightly to allow for high dilution and temperature afforded only small amounts of macrolactone 18 (Scheme 3). Attempts to

Table 5. Transesterification of Trihaloethyl Esters

		e e
o II -	PBu <sub>3</sub> , DMAP alcohol (R'OH)	ĥ
R <sup>C</sup> O <sup>C</sup> CX <sub>3</sub>		
6	DMF, rt	
<b>2a</b> (X=Br, R=Ph)		10 (R=Ph)
2b (X=Cl, R=Ph)		11 (B=c-Hex)
5 (X=Br, R= <i>c</i> -Hex)		

entry	trihaloethyl ester	alcohol (R'OH)	product	% yield <sup>a</sup>
1	2a	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OH	10a	69
2	2a	BuOH	10b	81
3	2a	BnOH	10c	77
4	2a	2-pentanol	10d	62
5	2a	(–)-menthol	10e	61
6	2a	trans-2-phenyl-	10f	68
		cyclohexanol		
7	5	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OH	11a	74
8	5	BuOH	11b	65
9	5	BnOH	11c	70
10	5	2-pentanol	11d	63
11	5	(–)-menthol	11e	65
12	2a	t-BuOH <sup>b</sup>	10g	11
13	2b	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OH	10a	<b>44</b> <sup>c</sup>

<sup>*a*</sup> Isolated yields. <sup>*b*</sup>1:1 DMF/*t*-BuOH was used as solvent. <sup>c</sup>Reaction temperature = 100 °C.

convert **17** to macrolactam **19** using similarly modified amidation conditions failed to produce an observable amount of cyclized product. Other products isolated in these reactions include 2,2-dibromoethyl ester derivatives of the ester substrates and the free carboxylic acids. Further optimization of these conditions will be required to establish the applicability of this procedure for macrocyclic lactone and lactam synthesis.

The proposed mechanism for this deprotection—condensation reaction, as implied in eq 2, involves initial attack upon a halogen of the trihaloethyl ester protecting group by the phosphorus(III) reagent, resulting in release of a 1,1-dihaloethylene and the carboxylate nucleofuge.



Attack at the new electrophilic phosphorus(V) center by the carboxylate generates an acyloxyphosphonium intermediate. Acyloxyphosphonium species are believed to be common intermediates in condensation reactions that employ phosphonium salts as coupling reagents.<sup>14,15,19–27</sup> The activated ester shown in eq 2 then proceeds to the amide or ester product in the presence of an amine or alcohol nucleophile, respectively. The beneficial effect of catalytic DMAP observed in the transesterification reactions reflects the lower nucleophilicity of alcohols, relative to amines.<sup>30</sup>

Condensation by way of the proposed mechanism would produce a dihaloethylene byproduct. Formation of haloethylenes has been observed in the deprotection of trichloroethyl esters using NaHSe<sup>10b</sup> as well as in the reaction of triphenylphosphine with hexachloroethane (eq 3).<sup>15</sup> The release of 1,1-dibromoethylene has been verified in the current procedure by NMR analysis. Crude distillates of the reaction mixtures from the conversion of **2a** to **7a** and **2a** to **10a** showed <sup>1</sup>H ( $\delta$  = 6.26 ppm) and <sup>13</sup>C ( $\delta$  = 125.6, 94.6 ppm) resonances characteristic of 1,1-dibromoethylene.<sup>33</sup>

$$Ph_{3}P + CI \rightarrow CI + Ph_{3}PCI_{2}$$
 (3)

Proton NMR analyses of esters derived from chiral secondary alcohols also support the proposed mechanism. Menthol-derived esters **10e** and **11e**, as well as *trans*-2-phenylcyclohexanol-derived ester **10f**, display large coupling constants (10.5–10.9 Hz) for the acyloxy-bearing methine proton signals. This indicates the axial position of these protons (Figure 2) and the retention of configuration at the carbinol carbons that is consistent with



#### Figure 2.

hydroxyl group acylation. Ester formation therefore does not proceed by a Mitsunobu-type inversion in which the alcohol is activated by a phosphonium species and then displaced by a carboxylate anion.<sup>14,16,17</sup>

## Conclusion

In summary, tribromoethyl esters can be converted directly to secondary and tertiary amides in moderate to good yields by treatment with (Me<sub>2</sub>N)<sub>3</sub>P and an amine. Similarly, esters of primary and secondary alcohols have been prepared from tribromoethyl esters by treatment with tributylphosphine in the presence of DMAP. Trichloroethyl carboxylates gave lower yields of ester and amide products when subjected to these reaction conditions. The mechanism of this transformation involves reductive fragmentation, releasing a 1,1-dihaloethylene and formation of an acyloxyphosphonium activated ester intermediate, which is trapped by an amine or alcohol nucleophile. This method conveniently bypasses the carboxylic acid form of the substrate and provides an efficient, onestep conversion of tribromoethyl esters to amides or other esters.

#### **Experimental Section**

**General Procedures.** Infrared spectra (IR) are reported in wavenumbers (cm<sup>-1</sup>) with broad signals denoted by "br". Mass spectra (MS) were obtained using electron impact (EI, 70 eV) or fast-atom bombardment (FAB, 8 kV, Xe carrier gas) techniques. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded at 300 MHz. Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded at 75 MHz. Carbon resonance assignments were made by DEPT 135 spectral analysis.

Tetrahydrofuran (THF) and benzene (PhH) were distilled from sodium/benzophenone ketyl immediately prior to use. Triethylamine (Et<sub>3</sub>N), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), butylamine, and diethylamine were distilled from calcium hydride prior to use. Acetonitrile (CH<sub>3</sub>CN) was distilled from calcium hydride and stored over 4 Å molecular sieves. N,N-Dimethylformamide (DMF) was distilled under reduced pressure from magnesium sulfate, twice dried over 4 Å molecular sieves, and stored over 4 Å molecular sieves. N,N-(Dimethylamino)pyridine (DMAP) was recrystallized from toluene. Tributylphosphine (PBu<sub>3</sub>) was distilled under reduced pressure from calcium hydride or used as received from the Aldrich Chemical Co. Butanol, 2-pentanol, and tert-butyl alcohol were distilled from sodium metal. Menthol was dried by azeotropic removal of water with benzene and further dried in vacuo. 2-Methoxyethanol (anhydrous, 99.8%) was used as received from Aldrich Chemical Co. Deuteriochloroform (chloroform-d; CDCl<sub>3</sub>) was stored over 4 Å molecular sieves. All other commercially obtained reagents and solvents were used as received without further purification unless otherwise indicated.

All moisture-sensitive reactions were performed in flamedried or oven-dried glassware under a positive pressure of nitrogen. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. Volatile solvents from reaction workups and chromatography solutions were concentrated using a Büchi rotary evaporator at reduced pressure. Residual solvents were removed by evacuation under high vacuum at approximately 1 mmHg. Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silica gel 60 F<sub>254</sub> (250  $\mu$ m layer thickness). TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or charring solution [*p*-anisal-dehyde (PAA)]. Flash chromatography was performed on EM Science silica gel 60 (230–400 mesh). Solvent mixtures used for TLC and flash chromatography are reported in  $V/V_{total} \times 100$ .

2,2,2-Tribromoethyl Benzoate (2a). To a solution of 2,2,2tribromoethanol (3.50 g, 12.4 mmol) and NEt\_3 (3.80 mL, 27.3 mmol) in 75 mL of THF at 0  $^\circ C$  was added benzoyl chloride (1.60 mL, 13.8 mmol) dropwise over 10 min. The cold bath was removed, and the reaction mixture stirred at ambient temperature for 6 h. The reaction mixture was filtered and diluted with diethyl ether (150 mL). This solution was washed with 2 M HCl and saturated NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (gradient elution, 1% to 2% EtOAc in hexanes) provided 4.1 g of 2a (10.6 mmol, 86%) as a colorless oil. Data for 2a: Rf 0.43 (10% EtOAc in hexanes); IR (thin film) 3066, 2941, 1732, 1263, 1111, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.17 (m, 2H), 7.62 (tt, 1H, J = 7.4, 1.3 Hz), 7.50 (m, 2H), 5.16 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  164.4 (C), 133.5 (CH), 129.8 (CH  $\times$  2), 128.6 (C), 128.4 (CH  $\times$  2), 76.3 (CH<sub>2</sub>), 35.5 (C); MS (EI) m/e (relative intensity, assignment) 385.8 (7.7, M<sup>+</sup>), 306.9 (23.8, M<sup>+</sup> – Br), 105.0 (100,  $M^{+}$  – OCH<sub>2</sub>CBr<sub>3</sub>); isotope pattern calculated for C<sub>9</sub>H<sub>7</sub>Br<sub>3</sub>O<sub>2</sub> matches that observed.

2,2,2-Tribromoethyl Cyclohexanecarboxylate (5). To a slurry of DMAP (0.93 g, 7.6 mmol), DMAP·TFA (4-(N,Ndimethylamino)pyridinium trifluoroacetate, 1.8 g, 7.6 mmol), and diisopropylcarbodiimide (DIC, 1.3 mL, 8.30 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was added a solution of cyclohexanecarboxylic acid (1.1 g, 8.6 mmol) and 2,2,2-tribromoethanol (2.23 g 7.9 mmol) in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> plus two 5 mL rinses via cannula. The reaction mixture was stirred at ambient temperature for 6 h. The reaction mixture was then washed with 2 M HCl. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organics were dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (5% EtOAc in hexanes) provided 2.57 g of 5 (6.54 mmol, 83%) as a colorless oil. Data for 5:  $R_f 0.36$  (5% EtOAc in hexanes); IR (thin film) 2931, 2854, 1747, 1153, 1124, 631 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.92 (s, 2H), 2.48 (tt, 1H, J = 11.0, 3.8 Hz), 2.02 (br d, 2H), 1.78 (m, 2H), 1.67 (m, 1H), 1.51-1.45 (m, 2H), 1.40-1.20 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) & 173.9 (C), 76.4 (CH<sub>2</sub>), 42.8 (CH), 36.2 (C), 28.8 (CH<sub>2</sub> imes 2), 25.6 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub> imes2); MS (EI) m/e (relative intensity, assignment) 392.8 (13.2), 306.9 (23.8), 264.8 (11.8,  $CH_2\dot{C}Br_3^+$ ) 127.0 (58.2,  $M^+$ CH<sub>2</sub>CBr<sub>3</sub>), 111.1 (100, M<sup>+</sup> –OCH<sub>2</sub>CBr<sub>3</sub>) 83.1 (60.7, C<sub>6</sub>H<sub>11</sub><sup>+</sup>); isotope pattern calculated for C9H13Br3O2 matches that observed.

*N*-(*tert*-Butoxycarbonyl)-L-alanine 2,2,2-Tribromoethyl Ester (6). To a slurry of DMAP (66 mg, 0.54 mmol), DMAP·TFA (125 mg, 0.529 mmol), and diisopropylcarbodiimide (90  $\mu$ L, 0.57 mmol) in 2.4 mL of CH<sub>2</sub>Cl<sub>2</sub> was added a solution of N-(tert-butoxycarbonyl)-L-alanine (101 mg, 0.534 mmol) and 2,2,2-tribromoethanol (178 mg, 0.629 mmol) in 1.0 mL of CH<sub>2</sub>Cl<sub>2</sub> plus two 0.5 mL rinses via cannula. The reaction mixture was stirred at ambient temperature for 17.5 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and washed with 2 M HCl. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organics were dried (MgSO4), filtered, and concentrated. Purification by flash chromatography (20% EtOAc in hexanes) provided 209 mg of 6 (6.54 mmol, 86%) as a yellow oil. Data for 6:  $R_f 0.47$  (20% EtOAc in hexanes);  $[\alpha]^{22}_{D}$  -30.8 (*c* = 1.86, EtOH); IR (thin film) 3364, 2978, 1760, 1708, 1507, 1158 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.07 (br s, 1H,), 4.98 (ABq, 2H,  $J_{AB}$  = 12.2 Hz,  $Δν_{AB}$  = 91.5 Hz), 4.48 (br quin, 1H, J = 7.2 Hz), 1.52 (d, 3H, J = 7.2 Hz), 1.46 (s, 9H);  $^{13}$ C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  171.6, (C), 155.0, (C), 80.1 (C), 77.0 (CH<sub>2</sub>), 49.3 (CH) 35.0 (C), 28.3 (CH<sub>3</sub>  $\times$  3), 18.4 (CH<sub>3</sub>); MS (FAB + NaI) m/e (relative intensity, assignment) 477.8 (51.2, M + Na<sup>+</sup>), 399.8 (35.2), 176.0 (100).

N-Butylbenzamide (7a)<sup>35</sup> from 2a using (Me<sub>2</sub>N)<sub>3</sub>P. To a solution of 2a (141 mg, 0.364 mmol), butylamine (37 µL, 0.37 mmol), and NEt<sub>3</sub> (0.13 mL, 0.93 mmol) in 3.6 mL of DMF at -55 °C was added (Me<sub>2</sub>N)<sub>3</sub>P (73  $\mu$ L, 0.40 mmol) dropwise. The reaction mixture was stirred at -55 °C for 30 min. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with Et<sub>2</sub>O, and the combined organics were washed with saturated aqueous NaCl and H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (30% EtOAc in hexanes) provided 53.9 mg of 7a (0.304 mmol, 83%) as a colorless oil. Data for **7a**:  $R_f 0.43$  (50% EtOAc in hexanes, PAA); IR (thin film) 3313, 2958, 2871, 1638, 1543, 1308, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) & 7.77 (m, 2H), 7.46 (m, 3H), 7.38 (m, 2H), 6.57 (br s, 1H), 3.42 (m, 2H), 1.57 (m, 2H), 1.38 (m, 2H), 0.93 (t, J = 7.4 Hz);  $^{13}{\rm C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  167.5 (C), 134.8 (C), 131.1 (CH), 128.3 (CH  $\times$  2), 126.8 (CH  $\times$  2), 39.7 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 20.0 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); MS (EI) m/e (relative intensity, assignment) 177.1 (17.6, M<sup>+</sup>), 105.0 (100, M<sup>+</sup> - NHC<sub>4</sub>H<sub>9</sub>).

**General Procedure for the Synthesis of Amides using** (Me<sub>2</sub>N)<sub>3</sub>P. To a 0.1 M solution of tribromoethyl ester (1 equiv), amine or amine hydrochloride (1 equiv), and NEt<sub>3</sub> (2.5–3 equiv) in DMF at -55 °C was added (Me<sub>2</sub>N)<sub>3</sub>P (1.2 equiv) dropwise. The reaction mixture was stirred at -55 °C for 30 min. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with Et<sub>2</sub>O, and the combined organics were washed with saturated NaCl and H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (EtOAc-hexanes) afforded the amide product.

*N,N*-Diethylbenzamide (7b).<sup>36</sup> Amide 7b was obtained in 76% yield (38.5 mg) from 2a and diethylamine as a colorless oil (flash chromatography 40% EtOAc in hexanes). Data for 7b:  $R_f$ 0.32 (50% EtOAc in hexanes); IR (thin film) 2986, 2942, 1655, 1427, 1287, 1096 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.39–7.31 (m, 5H), 3.53 (br s, 2H), 3.23 (br s, 2H), 1.23 (br s, 3H), 1.09 (br s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  171.1 (C), 137.1 (C), 128.9 (CH), 128.2 (CH  $\times$  2), 126.1 (CH  $\times$  2), 43.1 (CH<sub>2</sub>), 39.0 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>); MS (EI) *m/e* (relative intensity, assignment) 177.1 (31.5, M<sup>+</sup>), 105.0 (100, C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>).

**N-Benzoylglycine Ethyl Ester** (7c).<sup>37</sup> Amide 7c was obtained in 77% yield (25.2 mg) from 2a and glycine ethyl ester hydrochloride as a colorless oil (flash chromatography 40% EtOAc in hexanes). Data for 7c:  $R_f$  0.36 (60% EtOAc in hexanes); IR (thin film) 3336, 3063, 2981, 2937, 1751, 1642, 1533, 1200 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.82 (m, 2H), 7.48 (tt, 1H, J = 7.4, 1.3 Hz), 7.41 (m, 2H), 6.76 (br s, 1H), 4.26 (q, 2H, J = 7.2 Hz), 4.23 (d, 2H, J = 5.0 Hz), 1.31 (t, 3H, J = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  170.1 (C), 167.4 (C), 133.7 (C), 131.7 (CH), 128.6 (CH  $\times$  2), 127.0 (CH  $\times$  2), 61.6 (CH<sub>2</sub>), 41.9 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>); MS (EI) *m/e* (relative intensity, assignment) 207.1 (14.8 M<sup>+</sup>), 134.1 (25.2, M<sup>+</sup> - CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>) 105.0 (100, C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>).

**N-Butylcyclohexanecarboxamide (8a).**<sup>38</sup> Amide **8a** was obtained in 88% yield (41.9 mg) from **5** and butylamine as a white solid (flash chromatography gradient elution 30% to 40% EtOAc in hexanes). Data for **8a**:  $R_f$  0.33 (40% EtOAc in hexanes); IR (thin film) 3295, 3083, 2930, 2854, 1642, 1551, 1447 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.85 (br s, 1H), 3.27–3.20 (br q, 2H, J = 7.2 Hz), 2.08 (tt, 1H, J = 11.8, 3.5 Hz), 1.90–1.16 (m, 14H), 0.92 (t, 3H, J = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  176.0 (C), 45.5 (CH), 38.9 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub> × 2), 25.7 (CH<sub>2</sub> × 3), 19.9 (CH<sub>2</sub>), 13.6 (CH<sub>3</sub>); MS (EI) *m/e* (relative intensity, assignment) 183.2 (46.4, M<sup>+</sup>), 168.1 (16.5, M<sup>+</sup> - CH<sub>3</sub>), 154.1 (17.8, M<sup>+</sup> - CH<sub>2</sub>CH<sub>3</sub>) 128.1 (82.4, C<sub>7</sub>H<sub>14</sub>-NO<sup>+</sup>), 111.1 (42.5, M<sup>+</sup> - NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 83.1 (100, C<sub>6</sub>H<sub>11</sub><sup>+</sup>).

*N*,*N*-Diethylcyclohexanecarboxamide (8b).<sup>38b</sup> Amide 8b was obtained in 57% yield (29.6 mg) from 5 and diethylamine as a colorless oil (flash chromatography 40% EtOAc in hexanes). Data for 8b:  $R_f$  0.22 (30% EtOAc in hexanes); IR (thin film) 2970, 2929, 2854, 1638, 1449, 1429 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.36 (q, 2H, J = 7.2 Hz), 3.32 (q, 2H, J = 7.2 Hz), 2.40 (tt, 1H, J = 11.4, 3.5 Hz), 1.85–1.45 (m, 7H), 1.35–1.20

(m, 3H), 1.18 (t, 3H, J = 7.0 Hz), 1.09 (t, 3H, J = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  175.3 (C) 41.6 (CH<sub>2</sub>), 40.7 (CH), 39.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub> × 2), 25.8 (CH<sub>2</sub> × 2), 25.7 (CH<sub>2</sub>), 14.9 (CH<sub>3</sub>), 13.0 (CH<sub>3</sub>).

*N*-*tert*-**Butoxycarbonyl-L-alanyl-L-alanine Ethyl Ester** (9).<sup>39</sup> Amide 9 was obtained in 70% yield (39.1 mg) from 6 and L-alanine ethyl ester hydrochloride as a white solid (flash chromatography 50% EtOAc in hexanes). Data for 9:  $R_f$  0.38 (60% EtOAc in hexanes);  $[\alpha]^{22}_D - 48.1$  (c = 1.0, EtOH); IR (thin film) 3332, 3261, 3075, 2948, 1752, 1688, 1656, 1540, 1521, 1269, 1167 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.73 (br s, 1H), 5.12 (br s, 1H), 4.55 (quin, 1H, J = 7.4 Hz), 4.23–4.16 (m, 3H), 1.45 (s, 9H), 1.40 (d, 3H, J = 7.2 Hz), 1.37 (d, 3H, J = 7.2 Hz), 1.28, (t, 3H, J = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  172.7 (C), 172.2 (C), 155.4 (C), 79.5 (C). 61.4 (CH<sub>2</sub>), 49.9 (CH), 48.0 (CH), 28.3 (CH<sub>3</sub> × 3), 18.5 (CH<sub>3</sub>), 18.3 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>); MS (EI) m/e (relative intensity, assignment) 288.2 (2.4, M<sup>+</sup>), 144.1 (100,  $C_4H_9O_2CNHCHCH_3^+$ ) 116.1 (43.4,  $C_4H_9O_2CNH^+$ ).

General Procedure for the Synthesis of Esters. To a 0.1 M solution of tribromoethyl or trichloroethyl ester (1 equiv), alcohol (1 equiv), and DMAP (2 equiv) in DMF was added tributylphosphine (1.5 equiv) dropwise. The reaction mixture was stirred at ambient temperature for 1-5 h. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with Et<sub>2</sub>O, and the combined organics were washed with saturated NaCl and H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (EtOAc-hexanes) and/or Kugelrohr distillation afforded the ester product.

**2-Methoxyethyl Benzoate (10a) from 2,2,2-Tribromoethyl Benzoate (2a).** Ester **10**a<sup>40</sup> was obtained in 69% yield (51.7 mg) from **2a** and 2-methoxyethanol as a colorless oil (flash chromatography 10% EtOAc in hexanes). Data for **10a**:  $R_f$  0.48 (40% EtOAc in hexanes); IR (thin film) 2986, 1736, 1704, 1515, 1246, 1167 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ 8.08 (m, 2H), 7.55 (tt, 1H, J = 7.4, 1.3 Hz), 7.43 (m, 2H), 4.48 (m, 2H), 3.73 (m, 2H), 3.43 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) d 166.4 (C), 132.8 (CH), 129.9 (C), 129.4 (CH × 2), 128.2 (CH × 2), 70.4 (CH<sub>2</sub>), 63.9 (CH<sub>2</sub>), 58.9 (CH<sub>3</sub>).

**2-Methoxyethyl Cyclohexanecarboxylate (11a).** Ester **11a** was obtained in 74% yield (33.8 mg) from **5** and 2-methoxyethanol as a colorless oil (flash chromatography 10% EtOAc in hexanes). Data for **11a**:  $R_f$  0.50 (20% EtOAc in hexanes); IR (thin film) 2932, 2855, 1734, 1171, 1129 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.22 (m, 2H), 3.59 (m, 2H), 3.39 (s, 3H), 2.35 (tt, 1H, J = 11.2, 3.6 Hz), 1.94–1.89 (m, 2H), 1.80–1.71 (m, 2H), 1.65 (m, 1H), 1.52–1.37 (m, 2H), 1.36–1.13 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  176.0 (C), 70.5 (CH<sub>2</sub>), 63.1 (CH<sub>2</sub>), 58.9 (CH<sub>3</sub>), 42.9 (CH), 28.9 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>); MS (EI) m/e (relative intensity, assignment) 186.1 (1.5, M<sup>+</sup>), 111.1 (64.0, C<sub>6</sub>H<sub>11</sub>CO<sup>+</sup>), 83.1 (87.8, C<sub>6</sub>H<sub>11</sub><sup>+</sup>) 58.0 (100 C<sub>3</sub>H<sub>6</sub>O<sup>+</sup>).

**Butyl Benzoate (10b).**<sup>43</sup> Ester **10b** was obtained in 81% yield (51.8 mg) from **2a** and 1-butanol as a colorless oil after flash chromatography (1.5% EtOAc in hexanes) followed by Kugelrohr distillation. Data for **10b**:  $R_f$  0.42 (10% EtOAc in hexanes); IR (thin film) 2958, 1720, 1274, 709 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.05 (m, 2H), 7.55 (tt, 1H, J = 7.4, 1.3 Hz), 7.43 (m, 2H), 4.33 (t, 2H, J = 6.7 Hz), 1.81–1.70 (m, 2H), 1.55–1.41 (m, 2H), 0.98 (t, 3H, J = 7.3 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  166.7 (C), 132.7 (CH), 130.5 (C), 129.5 (CH × 2), 128.3 (CH × 2), 64.8 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 19.2 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); MS (EI) m/e (relative intensity, assignment) 178.1 (3.2, M<sup>+</sup>), 123.0 (85.4, C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>H<sub>2</sub><sup>+</sup>), 105.0 (100, C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>).

**Benzyl Benzoate (10c).**<sup>44</sup> Ester **10c** was obtained in 77% yield (40.3 mg) from **2a** and benzyl alcohol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **10c**:  $R_f$  0.58 (20% EtOAc in hexanes); IR (thin film) 3063, 3033, 1719, 1271, 1109, 711 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.08 (m, 2H), 7.54 (tt, 1H, J = 7.3, 1.3 Hz), 7.47–7.30 (m, 7H), 5.36 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  166.4 (C), 136.0

(C), 133.0 (CH), 130.1 (C), 129.7 (CH  $\times$  2), 128.5 (CH  $\times$  2), 128.3 (CH  $\times$  2), 128.2 (CH), 128.1 (CH  $\times$  2), 66.6 (CH<sub>2</sub>); MS (EI) *m/e* (relative intensity, assignment) 212.1 (39.6, M<sup>+</sup>), 105.0 (100, C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>), 91.0 (55.4, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub><sup>+</sup>), 77.0 (34.6, C<sub>6</sub>H<sub>5</sub><sup>+</sup>).

**2-Pentyl Benzoate (10d).** Ester **10d** was obtained in 62% yield (31.4 mg) from **2a** and 2-pentanol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **10d**:  $R_f$  0.51 (10% EtOAc in hexanes); IR (thin film) 2960, 2925, 2854, 1718, 1278, 1118 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.05 (m, 2H), 7.55 (tt, 1H, J = 7.4, 1.3 Hz), 7.43 (m, 2H), 5.18 (m, 1H), 1.81–1.30 (m, 4H), 1.34 (d, 3H, J = 6.2 Hz), 0.94 (t, 3H, J = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  166.2 (C), 132.7 (CH), 130.9 (C), 129.5 (CH  $\times$  2), 128.3 (CH  $\times$  2), 71.5 (CH), 38.2 (CH<sub>2</sub>), 20.1 (CH<sub>3</sub>), 18.7 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); MS (EI) *m/e* (relative intensity, assignment) 192.1 (0.9, M<sup>+</sup>), 123.0 (41.9, C<sub>6</sub>H<sub>5</sub>-CO<sub>2</sub>H<sub>2</sub><sup>+</sup>), 105.0 (100, C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>).

**Menthyl Benzoate (10e).**<sup>45</sup> Ester **10e** was obtained in 61% yield (39.6 mg) from **2a** and (–)-menthol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **10e**:  $R_f$  0.63 (10% EtOAc in hexanes); IR (thin film) 2954, 1714, 1274, 710 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.05 (m, 2H), 7.55 (tt, 1H, J = 7.3, 1.5 Hz), 7.44 (m, 2H), 4.94 (td, 1H, J = 10.9, 4.2 Hz), 2.13 (m, 1H), 1.97 (sep d, 1H, J = 8.8, 2.6 Hz), 1.78–1.68 (m, 2H), 1.63–1.47 (m, 2H), 1.2–0.9 (m, 3H), 0.93 (d, 3H, J = 7.0 Hz), 0.92 (d, 3H, J = 7.0 Hz), 0.79 (d, 3H, J = 6.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  166.1 (C), 132.6 (CH), 130.8 (C), 129.5 (CH × 2), 128.2 (CH × 2), 74.8 (CH), 47.3 (CH), 41.0 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 31.4 (CH), 28.2 (CH), 26.6 (CH<sub>2</sub>), 23.6 (CH<sub>3</sub>), 22.0 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>).

**Benzoic Acid** *trans*-2-Phenylcyclohexyl Ester (10f). Ester 10f was obtained in 68% yield (43.0 mg) from 2a and *trans*-2-phenylcyclohexanol as a white solid (flash chromatography 3% EtOAc in hexanes). Data for 10f:  $R_f$ 0.32 (5% EtOAc in hexanes); IR (thin film) 3061, 3029, 2934, 2858, 1714, 1272, 1110, 711 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.82–7.77 (m, 2H), 7.48–7.41 (m, 1H), 7.35–7.18 (m, 6H), 7.14–7.07 (m, 1H), 5.18 (td, 1H, J = 10.5, 4.5 Hz), 2.85 (ddd, 1H, J = 11.0, 10.8, 3.6 Hz), 2.29 (m, 1H), 2.04–1.77 (m, 3H), 1.72–1.32 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  165.8 (C), 143.1 (C), 132.5 (CH), 130.6 (C), 129.3 (CH × 2), 128.3 (CH × 2), 128.1 (CH × 2), 127.4 (CH × 2), 126.4 (CH), 76.8 (CH), 49.8 (CH), 33.9 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 24.8 (CH<sub>2</sub>).

**Butyl Cyclohexanecarboxylate (11b).** Ester **11b** was obtained in 65% yield (40.4 mg) from **5** and 1-butanol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **11b**:  $R_f$  0.55 (10% EtOAc in hexanes); IR (thin film) 2858, 2932, 2856, 1733, 1171 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.06 (t, 2H, J = 6.6 Hz), 2.28 (tt, 1H, J = 11.0, 3.5 Hz), 1.95–1.84 (m, 2H), 1.79–1.69 (m, 2H), 1.68–1.54 (m, 3H), 1.50–1.13 (m, 7H), 0.93 (t, 3H, J = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  176.2 (C), 63.9 (CH<sub>2</sub>), 43.3 (CH), 30.7 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub> × 2), 25.8 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub> × 2), 19.1 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); MS (EI) m/e (relative intensity, assignment) 184.1 (1.5, M<sup>+</sup>), 129.1 (100, C<sub>6</sub>H<sub>11</sub>CO<sub>2</sub>H<sub>2</sub><sup>+</sup>), 111.1 (73.1, C<sub>6</sub>H<sub>11</sub>CO<sup>+</sup>), 83.1 (98.2, C<sub>6</sub>H<sub>11</sub><sup>+</sup>).

**Benzyl Cyclohexanecarboxylate (11c).** Ester **11c** was obtained in 70% yield (43 mg) from **5** and benzyl alcohol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **11c**:  $R_f$  0.22 (5% EtOAc in hexanes); IR (thin film) 2932, 2854, 1733, 1165 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.39–7.29 (m, 5H), 5.11 (s, 2H), 2.35 (tt, 1H, J= 11.2, 3.5 Hz), 1.98–1.87 (m, 2H), 1.80–1.70 (m, 2H), 1.68–1.59 (m, 1H), 1.54–1.38 (m, 2H), 1.36–1.13 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  175.9 (C), 136.3 (C), 128.5 (CH × 2), 128.0 (CH), 127.9 (CH × 2), 65.8 (CH<sub>2</sub>), 43.2 (CH), 29.0 (CH<sub>2</sub> × 2), 25.7 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub> × 2); MS (EI) *m/e* (relative intensity, assignment) 218.1 (40.6, M<sup>+</sup>), 111.1 (45.1, C<sub>6</sub>H<sub>11</sub>CO<sup>+</sup>), 91.0 (100, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub><sup>+</sup>), 83.1 (98.2, C<sub>6</sub>H<sub>11</sub><sup>+</sup>).

**2-Pentyl Cyclohexanecarboxylate (11d).** Ester **11d** was obtained in 63% yield (34.9 mg) from **5** and 2-pentanol as a colorless oil after flash chromatography (1.5% EtOAc in hexanes) followed by Kugelrohr distillation. Data for **11d**:  $R_f$ 

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0.28 (5% EtOAc in hexanes); IR (thin film) 2933, 2856, 1729, 1173 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.90 (m, 1H), 2.25 (tt, 1H, J = 11.0, 3.5 Hz), 1.94–1.83 (m, 2H), 1.80–1.21 (m, 12H), 1.18 (d, 3H, J = 6.2 Hz), 0.90 (t, 3H, J = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  175.8 (C), 71.1 (CH), 43.5 (CH), 38.1 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 20.0 (CH<sub>3</sub>), 18.6 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>); MS (EI) *m/e* (relative intensity, assignment) 198.2 (0.35, M<sup>+</sup>), 155.1 (7.4, M<sup>+</sup> – C<sub>3</sub>H<sub>7</sub>), 129.1 (88.3, C<sub>6</sub>H<sub>11</sub>CO<sub>2</sub>H<sub>2</sub><sup>+</sup>), 111.1 (92.2, C<sub>6</sub>H<sub>11</sub>CO<sup>+</sup>), 83.1 (100, C<sub>6</sub>H<sub>11</sub><sup>+</sup>).

**Menthyl Cyclohexanecarboxylate (11e).** Ester **11e** was obtained in 65% yield (34.4 mg) from **5** and (–)-menthol as a colorless oil (flash chromatography 1.5% EtOAc in hexanes). Data for **11e**:  $R_f$  0.65 (30% EtOAc in hexanes); IR (thin film) 2931, 2856, 1728, 1172 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.65 (td, 1H, J = 10.8, 4.2 Hz), 2.26 (tt, 1H, J = 11.0, 3.7 Hz), 2.00–0.80 (m, 19H), 0.90, (d, 3H, J = 6.4 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.74 (d, 3H, J = 7.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  175.7 (C), 73.5 (CH), 47.1 (CH), 43.5 (CH), 40.9 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 31.3 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 23.3 (CH<sub>3</sub>), 22.0 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>); MS (FAB + Na1) m/e (relative intensity, assignment) 289.3 (54.8, M + Na<sup>+</sup>), 139.2 (100.0, C<sub>10</sub>H<sub>19</sub><sup>+</sup>).

tert-Butyl Benzoate (10g).46 To a solution of 2a (101 mg, 0.261 mmol) and DMAP (60.5 mg, 0.52 mmol) in 2.6 mL of 1:1 v/v tert-butyl alcohol/DMF was added tributylphosphine (0.13 mL, 0.52 mmol) dropwise. The reaction mixture was stirred at ambient temperature for 6.2 h. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with Et<sub>2</sub>O, and the combined organics were washed with saturated NaCl and H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (1.5% EtOAc in hexanes) followed by Kugelrohr distillation afforded 5.0 mg of 10g (0.028 mmol, 11%) as a colorless oil. Data for **10g**:  $R_{f}$  0.59 (20% EtOAc in hexanes); IR (thin film) 2964, 2928, 2871, 1729, 1275 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.00, (m, 2H), 7.52 (tt, 1H, J = 7.4, 1.4 Hz), 7.41 (m, 2H), 1.60 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$ 165.5 (C), 132.4 (CH), 132.0 (C), 129.4 (CH imes 2), 128.2 (CH imes2), 118 (C), 80.5 (C), 28.2 (CH<sub>3</sub>  $\times$  3); MS (EI) *m*/*e* (relative intensity, assignment) 178.1 (1.8, M<sup>+</sup>), 123.0 (96.7, C<sub>6</sub>H<sub>5</sub>- $CO_2H_2^+$ ), 105.0 (100,  $C_6H_5CO^+$ ).

2,2,2-Tribromoethyl 12-hydroxystearate (15). To a slurry of DMAP (202 mg, 1.65 mmol), DMAP·TFA (402 mg, 1.70 mmol), 12-hydroxystearic acid (504 mg, 1.68 mmol), and 2,2,2tribromoethanol (2.35 g, 8.31 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was added a solution of diisopropylcarbodiimide (DIC, 0.29 mL, 1.85 mmol) in 7 mL of CH<sub>2</sub>Cl<sub>2</sub> via cannula over 1 h. The reaction mixture was stirred at ambient temperature for an additional 4 h. The reaction mixture was then washed with 2 M HCl. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organics were dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (15% EtOAc in hexanes) provided 489 mg of 15 (0.865 mmol, 52%) as a vellow oil. Data for **15**:  $R_f 0.28$  (10% EtOAc in hexanes); IR (thin film) 3324 (br), 3231 (br), 2922, 2851, 1750, 1152 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.92 (s, 2H), 3.57 (m, 1H), 2.47 (t, 2H, J = 7.8 Hz), 1.80–1.65 (m, 2H), 1.49–1.25 (m, 27 H), 0.88 (m, 3H);  $^{13}\mathrm{C}$  NMR (CDCl\_3, 75 MHz)  $\delta$  172.0 (C), 76.7 (CH2), 72.0 (CH), 37.5 (CH2), 37.5 (CH2), 36.0 (C), 34.0 (CH2), 31.8 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 29.0, (CH<sub>2</sub>) 25.6 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 24.8 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>); MS (FAB + NaI) m/e (relative intensity, assignment) 587.0 (100, M + Na<sup>+</sup>).

12-tert-Butoxycarbonylaminododecanoic Acid 2,2,2-Tribromoethyl Ester (17). A slurry of 12-aminododecanoic acid (364 mg, 1.69 mmol) and di-tert-butyl dicarbonate (790 mg, 3.62 mmol) in 2.5 mL of 10% v/v triethylamine in methanol was refluxed until the reaction mixture became homogeneous (10 min). The reaction mixture was then concentrated to afford 578 mg of the crude triethylammonium N-BOC-12-aminododecanoate salt as a white solid. This solid and 2,2,2-tribromoethanol (586 mg, 2.07 mmol) were dissolved in 6.0 mL of CH2-Cl<sub>2</sub> and added dropwise via cannula to a slurry of DMAP (206 mg, 1.68 mmol), DMAP·TFA (437 mg, 1.85 mmol), and DIC (0.30 mL, 1.90 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was stirred at ambient temperature for 2.5 h. The reaction mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organics were dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (gradient elution, 20-10% hexanes in CHCl<sub>3</sub>/5% methanol in CHCl<sub>3</sub>) provided 720 mg of 17 (1.24 mmol, 73%) as a white solid. Data for 17:  $R_f 0.53$  (CHCl<sub>3</sub>); IR (thin film) 3356 (br), 3231 (br), 2924, 2854, 1752, 1703, 1518, 1249, 1172 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) & 4.93 (s, 2H), 4.48 (m, 1H), 3.09 (br q, 2H, J = 6.9 Hz), 2.48 (t, 2H, J = 7.8 Hz), 1.71 (quin, 2H J = 7.5 Hz), 1.50–1.23 (m, 16 H), 1.44 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) & 172.0 (C), 156.0 (C), 79.0 (C), 76.7 (CH<sub>2</sub>), 40.6 (CH<sub>2</sub>), 36.0 (C), 34.1 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub> × 2), 29.4, (CH<sub>2</sub>) 29.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub> × 3), 26.8 (CH<sub>2</sub>), 24.8 (CH<sub>2</sub>); MS (FAB + NaI) m/e (relative intensity, assignment) 602.0 (100, M + Na<sup>+</sup>).

**Lactone 18.**<sup>47</sup> To DMAP (118 mg, 0.966 mmol) and tributylphosphine (0.10 mL, 0.40 mmol) in 10 mL of DMF at 100 °C was added a solution of **15** in 40 mL of DMF via syringe pump over 10 h. The reaction solution was stirred at 100 °C for an additional 12 h and then allowed to cool. The reaction mixture was diluted with  $Et_2O$  (100 mL) and washed with 2 M HCl. The aqueous phase was extracted with  $Et_2O$ , and the combined organics were washed with saturated NaCl and  $H_2O$ , dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by flash chromatography (gradient elution 3–20% EtOAc in hexanes) afforded 2.5 mg of **18** (0.088 mmol, 9%) as a colorless film. Data for **18**:  $R_f$  0.54 (10% EtOAc in hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.88 (br quin, 1H, J = 5.5 Hz), 2.28 (m, 2H), 1.74–1.38 (m, 6H), 1.35–1.17 (m, 22H), 0.90–0.84 (m, 3H).

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**Supporting Information Available:** Experimental procedures for **2b**, **7a** (Table 2, entries 2 and 6), **10a** (Table 4, entry 3, and Table 5, entry 13), and **11a** (Table 4, entry 5). <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **2a,b**, **5**, **6**, **7a–c**, **8a,b**, **9**, **10a–e**, and **11a–e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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