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

Jeremy J. Hans, Russell W. Driver, and Steven D. Burke*

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1369

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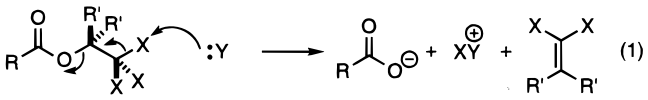
Amides and esters have been synthesized from 2,2,2-trihaloethyl esters in one pot using phosphorus(III) reagents as reductants, with resultant carboxylate activation as an acyloxyphosphonium intermediate, and in situ trapping by amine or alcohol nucleophiles. Secondary and tertiary amides were synthesized, including a dipeptide, in good yields using hexamethylphosphorous triamide, $(Me_2N)_3P$, 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.[1,2] Although the trichloroethyl ester has been the most widely used haloethyl protecting group,[1,3] other β-haloethyl esters have been used for this purpose, including tribromoethyl[4] and 1,1-dimethyl-2,2,2-trichloroethyl groups.[5] Trihaloethyl groups can be used to protect both carbon[1−4b] and phosphorus oxy acids,[4c,5] and the related trichloroethoxycarbonyl (TROC) protecting group has been used to protect alcohols and amines as carbonates or carbamates, respectively.[1]

Deprotection of trihaloethyl esters is achieved using reducing conditions to effect β-elimination, as shown in eq 1.[2] A variety of methods have been developed for the cleavage of these esters, with zinc being the most commonly used reductant.[3,6] Other transition-metal reagents have been employed for cleavage including zinc−copper[7] and zinc−lead couples,[8] as well as cobalt−phthalocyanine complex.[9] Selenium[10] and tellurium reagents,[11] as well as electrolysis,[4b,12] have also been used in trihaloethyl ester cleavage. Letsinger and co-workers have used tributylphosphine and $(Me_2N)_3P$ [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,[13] demonstrating the ability of phosphorus(III) reagents to reduce trihaloethyl esters.



(1)

Phosphorus(III) reagents are also used in the generation of phosphonium salts, which are mild and efficient reagents for condensation reactions.[14−19] These reactions can be described as "oxidation−reduction condensations"[19] 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,[19] and the reaction of phosphorus(III) reagents with halogenated alkanes such as carbon tetrachloride to effect condensations.[15,18]

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

* To whom all correspondence should be sent. Phone: (608) 262-4941. Fax: (608) 265-4534. E-mail: burke@chem.wisc.edu.

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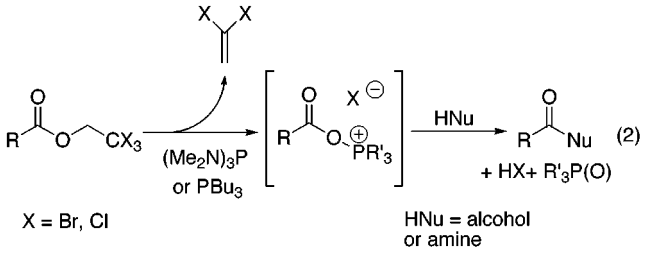
stepwise carboxylic acid deprotection followed by formation of an activated acyl species and treatment with an amine or alcohol nucleophile. Such a deprotection−condensation protocol requires two or more steps and can be attended by difficulties in working with the free carboxylic acid intermediate. 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,[14−27] 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.[28] 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[34] employed in these studies were synthesized from benzoyl chloride and the corresponding 2,2,2-trihaloethanol. Tribromoethyl esters of cyclohexanecarboxylic acid and *N*-Boc-alanine were synthesized using carbodiimide coupling conditions with diisopropylcarbodiimide (DIC) as the coupling reagent (Scheme 1).[29]

The conversion of 2,2,2-tribromoethyl benzoate (**2a**) to *N*-butylbenzamide (**7a**) using hexamethylphosphorous triamide [$(Me_2N)_3P$] 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 $(Me_2N)_3P$ was chosen for its high nucleophilicity.[14] Treatment of **2a** with 1.2 equiv of $(Me_2N)_3P$, 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.

Scheme 1

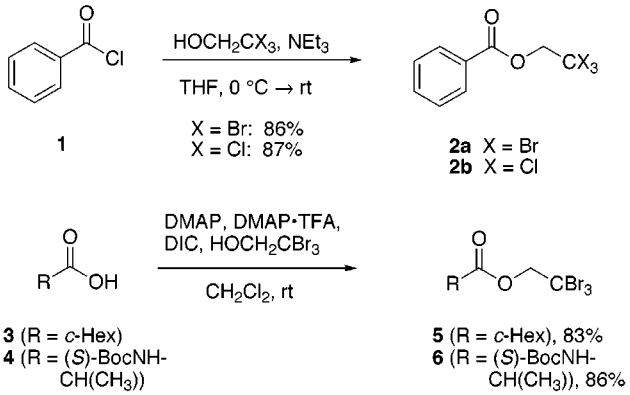
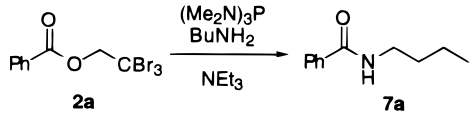


Table 1. Initial Studies of Amide Formation



entry	solvent	*T* (°C)	% yield of **7a**[a]
1	THF	0	36
2	benzene	0	35
3	CH_3CN	0	70
4	DMF	0	75
5	DMF	−55	83

[a] Isolated yields.

Investigation of the choice of reductant and electrophile revealed the combination of $(Me_2N)_3P$ and tribromoethyl protecting group to be the most effective for amide synthesis (Table 2). The reaction of $(Me_2N)_3P$ 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 yield (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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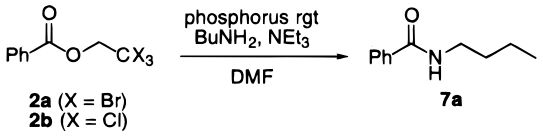
Table 2. Effect of Phosphorus Nucleophile and Halogen on the Synthesis of 7a



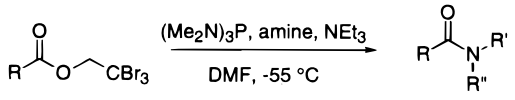
2a (X = Br)
2b (X = Cl)

7a

entry	X	phosphorus rgt	*T* (°C)	time (h)	% yield of **7a**[a]
1	Br	$(Me_2N)_3P$	−55	0.5	83
2	Br	PBu_3	−55 → 0	1.2	25
3	Br	PPh_3	rt	48	24[b]
4	Br	none	rt	48	17[c]
5	Cl	$(Me_2N)_3P$	rt	4.5	18
6	Cl	PBu_3	90	3.5	39

[a] Isolated yields. [b]42% of **2a** was recovered. [c]66% of **2a** was recovered.

Table 3. Conversion of Tribromoethyl Esters to Amides



2a (R=Ph)
5 (R=*c*-Hex)
6 (R=(*S*)-BocNH-CH(CH_3))

7b (R=Ph, R'=R"=Et)
7c (R=Ph, R'=CH_2CO_2Et, R"=H)
8a (R=*c*-Hex, R'=Bu, R"=H)
8b (R=*c*-Hex, R'=R"=Et)
9 (R=(*S*)-BocNHCH(CH_3), R'=(*S*)-CH(CH_3)CO_2Et, R"=H)

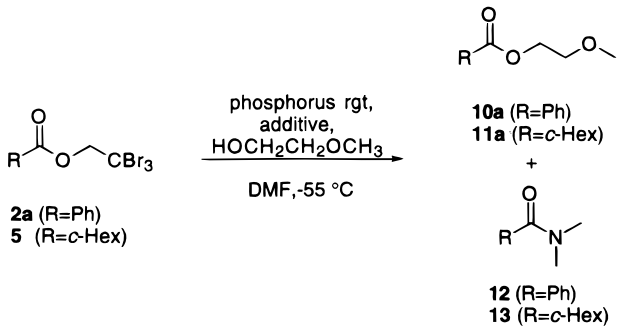
entry	trihaloethyl ester	amine	product	% yield[a]
1	**2a**	$HNEt_2$	**7b**	76
2	**2a**	HCl·GlyOEt	**7c**	77
3	**5**	$BuNH_2$	**8a**	88
4	**5**	$HNEt_2$	**8b**	57
5	**6**	HCl·AlaOEt	**9**	70

[a] 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 deprotection−condensation strategy. Initial attempts to effect the transesterification of trihaloethyl esters by addition of $(Me_2N)_3P$ to tribromoethyl esters failed to produce the desired products. The use of PBu_3 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*,*N*-dimethylamino)pyridine (DMAP)[30] markedly improved yields in both $(Me_2N)_3P$- and tributylphosphine-induced reactions (Table 4, entries 2−5). Esterification protocols using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent[25] have appeared relatively recently.[31] In these studies, esterification of N-protected amino acids and phenylacetic acid proceeded in high yield, possibly via acylated hydroxybenzotriazole intermediates.[25,26,31b] This suggested the addition of 1-hydroxybenzotriazole (HOBt) as a transacylating agent in the $(Me_2N)_3P$-mediated reactions. In practice, HOBt-promoted esterification (Table 4, entry 6) but did not provide yields superior to the PBu_3−DMAP reagent combination.

Table 4. Effect of Phosphorus Nucleophile and Additive on Transesterification



2a (R=Ph)
5 (R=*c*-Hex)

entry	trihaloethyl ester	phosphorus reagent	additive	ester product	% yield[a]
1	**2a**	PBu_3	none	**10a**	21
2	**2a**	PBu_3	DMAP	**10a**	69
3	**2a**	$(Me_2N)_3P$	DMAP	**10a**	50 (18 of **12**)
4	**5**	PBu_3	DMAP	**11a**	74
5	**5**	$(Me_2N)_3P$	DMAP	**11a**	44 (28 of **13**)
6	**2a**	$(Me_2N)_3P$	HOBt	**10a**	63

[a] Isolated yields.

In contrast to the amidation reactions, tributylphosphine provided yields of ester products superior to those obtained with $(Me_2N)_3P$ (Table 4). Substantial amounts of *N*,*N*-dimethylamide products were observed when $(Me_2N)_3P$ was used as reductant (Table 4, entries 3 and 5).[41,42] This presumably results from attack of activated acyl intermediates by dimethylamine liberated in the alcoholysis of $(Me_2N)_3P$.[32] To substantiate this theory, the behavior of $(Me_2N)_3P$ under similar reaction conditions in the absence of tribromoethyl ester was monitored by phosphorus NMR. After a solution of $(Me_2N)_3P$ in DMF was stirred for 1.5 h, ^{31}P NMR analysis of an aliquot of this solution in CD_2Cl_2 revealed a peak corresponding to $(Me_2N)_3P$ (122.7 ppm, Figure 1) and a small amount of HMPA impurity (24.1 ppm, not shown). The $(Me_2N)_3P$ 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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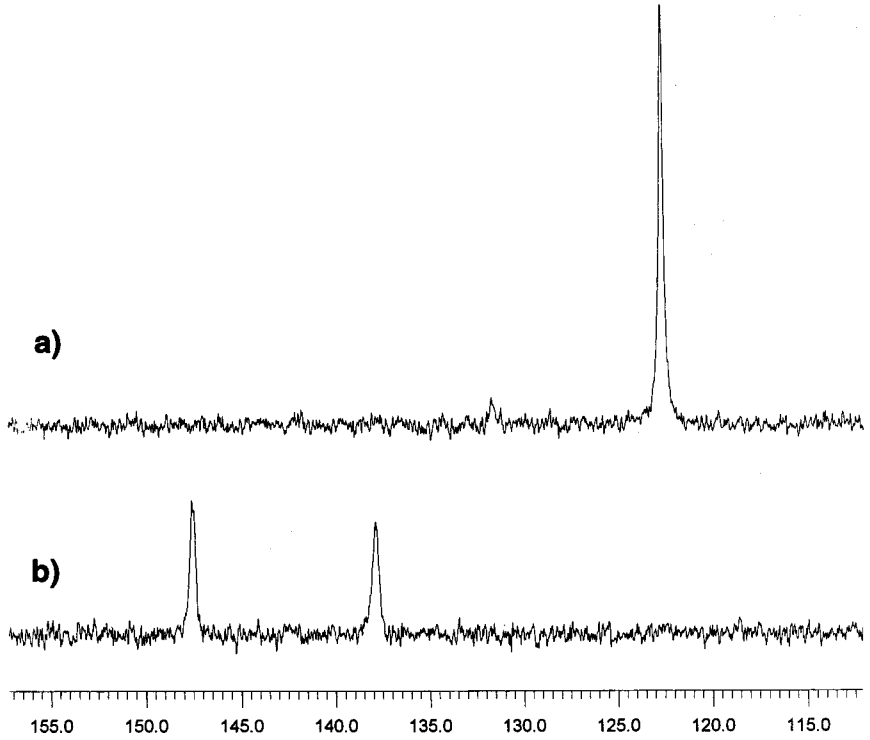


Figure 1. (a) ^{31}P NMR spectrum (121 MHz, CD_2Cl_2) of $(Me_2N)_3P$. (b) ^{31}P spectrum of aliquot 10 min after addition of MeOH, DMAP, and DMAP·TFA.

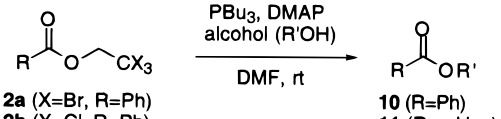
for the DMAP·HBr formed in these reactions. Analysis of an aliquot of this reaction mixture after 10 min showed no $(Me_2N)_3P$ resonance and two downfield resonances that correspond to $MeOP(NMe_2)_2$ (137.9 ppm) and $(MeO)_2PNMe_2$ (147.6 ppm), indicating the rapid methanolysis of $(Me_2N)_3P$. A similar ^{31}P NMR spectrum was observed in the ethanolysis of $(Me_2N)_3P$ by Houalla and co-workers.[32e] 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 ω-hydroxy and ω-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 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.

Table 5. Transesterification of Trihaloethyl Esters



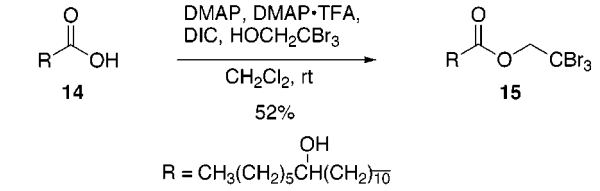
2a (X=Br, R=Ph)
2b (X=Cl, R=Ph)
5 (X=Br, R=*c*-Hex)

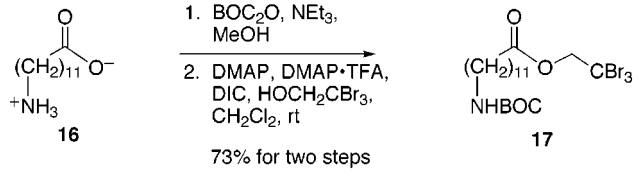
10 (R=Ph)
11 (R=*c*-Hex)

entry	trihaloethyl ester	alcohol (R′OH)	product	% yield[a]
1	**2a**	$CH_3O(CH_2)_2OH$	**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-cyclohexanol	**10f**	68
7	**5**	$CH_3O(CH_2)_2OH$	**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[b]	**10g**	11
13	**2b**	$CH_3O(CH_2)_2OH$	**10a**	44[c]

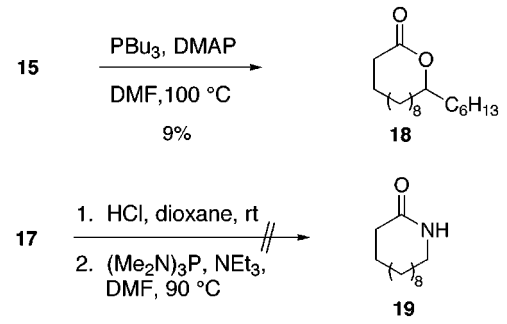
[a] Isolated yields. [b] 1:1 DMF/*t*-BuOH was used as solvent. [c] Reaction temperature = 100 °C.

Scheme 2



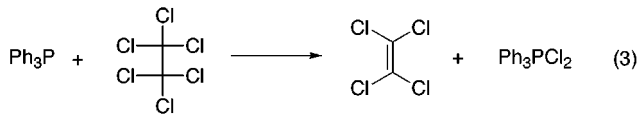


Scheme 3



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.[14,15,19−27] 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.[30]

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[10b] as well as in the reaction of triphenylphosphine with hexachloroethane (eq 3).[15] 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 ^{1}H (δ = 6.26 ppm) and ^{13}C (δ = 125.6, 94.6 ppm) resonances characteristic of 1,1-dibromoethylene.[33]



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

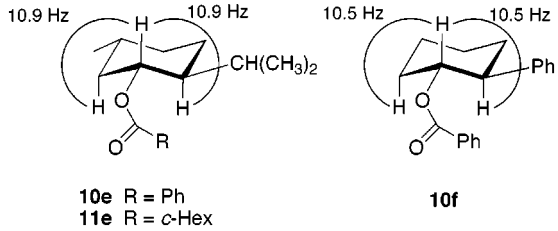


Figure 2.

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.[14,16,17]

Conclusion

In summary, tribromoethyl esters can be converted directly to secondary and tertiary amides in moderate to good yields by treatment with $(Me_2N)_3P$ 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, one-step conversion of tribromoethyl esters to amides or other esters.

Experimental Section

General Procedures. Infrared spectra (IR) are reported in wavenumbers (cm^{-1}) 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 (^{1}H NMR) spectra were recorded at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}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_3N), dichloromethane (CH_2Cl_2), butylamine, and diethylamine were distilled from calcium hydride prior to use. Acetonitrile (CH_3CN) 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_3) 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*; $CDCl_3$) 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 flame-dried 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 reac-

tion 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_{254} (250 μm layer thickness). TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or charring solution [*p*-anisaldehyde (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 2,2,2-tribromoethanol (3.50 g, 12.4 mmol) and NEt_3 (3.80 mL, 27.3 mmol) in 75 mL of THF at 0 °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 $NaHCO_3$, dried ($MgSO_4$), 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**: R_f 0.43 (10% EtOAc in hexanes); IR (thin film) 3066, 2941, 1732, 1263, 1111, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (m, 2H), 7.62 (tt, 1H, J = 7.4, 1.3 Hz), 7.50 (m, 2H), 5.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 133.5 (CH), 129.8 (CH × 2), 128.6 (C), 128.4 (CH × 2), 76.3 (CH_2), 35.5 (C); MS (EI) *m/e* (relative intensity, assignment) 385.8 (7.7, M^+), 306.9 (23.8, $M^+ - Br$), 105.0 (100, $M^+ - OCH_2CBr_3$); isotope pattern calculated for $C_9H_7Br_3O_2$ matches that observed.

2,2,2-Tribromoethyl Cyclohexanecarboxylate (5). To a slurry of DMAP (0.93 g, 7.6 mmol), DMAP·TFA (4-(*N*,*N*-dimethylamino)pyridinium trifluoroacetate, 1.8 g, 7.6 mmol), and diisopropylcarbodiimide (DIC, 1.3 mL, 8.30 mmol) in 20 mL of CH_2Cl_2 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_2Cl_2 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_2Cl_2, and the combined organics were dried ($MgSO_4$), 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9 (C), 76.4 (CH_2), 42.8 (CH), 36.2 (C), 28.8 (CH_2 × 2), 25.6 (CH_2), 25.2 (CH_2 × 2); MS (EI) *m/e* (relative intensity, assignment) 392.8 (13.2), 306.9 (23.8), 264.8 (11.8, $CH_2CBr_3^+$) 127.0 (58.2, $M^+ - CH_2CBr_3$), 111.1 (100, $M^+ - OCH_2CBr_3$) 83.1 (60.7, $C_6H_{11}^+$); isotope pattern calculated for $C_9H_{13}Br_3O_2$ 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 μL, 0.57 mmol) in 2.4 mL of CH_2Cl_2 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_2Cl_2 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_2Cl_2 (15 mL) and washed with 2 M HCl. The aqueous phase was extracted with CH_2Cl_2, 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.07 (br s, 1H,), 4.98 (ABq, 2H, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 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 ($CDCl_3$, 75 MHz) δ 171.6, (C), 155.0, (C), 80.1 (C), 77.0 (CH_2), 49.3 (CH) 35.0 (C), 28.3 (CH_3 × 3), 18.4 (CH_3); MS (FAB + NaI) *m/e* (relative intensity, assignment) 477.8 (51.2, M + Na^+), 399.8 (35.2), 176.0 (100).

***N*-Butylbenzamide (7a)[35] from 2a using $(Me_2N)_3P$.** To a solution of **2a** (141 mg, 0.364 mmol), butylamine (37 μL, 0.37 mmol), and NEt_3 (0.13 mL, 0.93 mmol) in 3.6 mL of DMF at −55 °C was added $(Me_2N)_3P$ (73 μL, 0.40 mmol) dropwise. The reaction mixture was stirred at −55 °C for 30 min. The reaction mixture was diluted with Et_2O (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with Et_2O, and the combined organics were washed with saturated aqueous NaCl and H_2O, dried ($MgSO_4$), 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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}C NMR ($CDCl_3$, 75 MHz) δ 167.5 (C), 134.8 (C), 131.1 (CH), 128.3 (CH × 2), 126.8 (CH × 2), 39.7 (CH_2), 31.6 (CH_2), 20.0 (CH_2), 13.7 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 177.1 (17.6, M^+), 105.0 (100, $M^+ - NHC_4H_9$).

General Procedure for the Synthesis of Amides using $(Me_2N)_3P$. To a 0.1 M solution of tribromoethyl ester (1 equiv), amine or amine hydrochloride (1 equiv), and NEt_3 (2.5−3 equiv) in DMF at −55 °C was added $(Me_2N)_3P$ (1.2 equiv) dropwise. The reaction mixture was stirred at −55 °C for 30 min. The reaction mixture was diluted with Et_2O (20 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 ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (EtOAc−hexanes) afforded the amide product.

***N*,*N*-Diethylbenzamide (7b).[36]** 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1 (C), 137.1 (C), 128.9 (CH), 128.2 (CH × 2), 126.1 (CH × 2), 43.1 (CH_2), 39.0 (CH_2), 14.0 (CH_3), 12.8 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 177.1 (31.5, M^+), 105.0 (100, $C_6H_5CO^+$).

***N*-Benzoylglycine Ethyl Ester (7c).[37]** 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (C), 167.4 (C), 133.7 (C), 131.7 (CH), 128.6 (CH × 2), 127.0 (CH × 2), 61.6 (CH_2), 41.9 (CH_2), 14.1 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 207.1 (14.8, M^+), 134.1 (25.2, $M^+ - CO_2C_2H_5$) 105.0 (100, $C_6H_5CO^+$).

***N*-Butylcyclohexanecarboxamide (8a).[38]** 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0 (C), 45.5 (CH), 38.9 (CH_2), 31.7 (CH_2), 29.6 (CH_2 × 2), 25.7 (CH_2 × 3), 19.9 (CH_2), 13.6 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 183.2 (46.4, M^+), 168.1 (16.5, $M^+ - CH_3$), 154.1 (17.8, $M^+ - CH_2CH_3$) 128.1 (82.4, $C_7H_{14}NO^+$), 111.1 (42.5, $M^+ - NH(CH_2)_3CH_3$), 83.1 (100, $C_6H_{11}^+$).

***N*,*N*-Diethylcyclohexanecarboxamide (8b).[38b]** 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3 (C) 41.6 (CH_2), 40.7 (CH), 39.9 (CH_2), 29.5 ($CH_2 \times 2$), 25.8 ($CH_2 \times 2$), 25.7 (CH_2), 14.9 (CH_3), 13.0 (CH_3).

***N-tert*-Butoxycarbonyl-L-alanyl-L-alanine Ethyl Ester (9).**[39] 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7 (C), 172.2 (C), 155.4 (C), 79.5 (C). 61.4 (CH_2), 49.9 (CH), 48.0 (CH), 28.3 ($CH_3 \times 3$), 18.5 (CH_3), 18.3 (CH_3), 14.1 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 288.2 (2.4, M^+), 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_2O (20 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 ($MgSO_4$), 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 **10a**[40] 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) d 166.4 (C), 132.8 (CH), 129.9 (C), 129.4 (CH × 2), 128.2 (CH × 2), 70.4 (CH_2), 63.9 (CH_2), 58.9 (CH_3).

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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0 (C), 70.5 (CH_2), 63.1 (CH_2), 58.9 (CH_3), 42.9 (CH), 28.9 (CH_2), 25.6 (CH_2), 25.3 (CH_2); MS (EI) *m/e* (relative intensity, assignment) 186.1 (1.5, M^+), 111.1 (64.0, $C_6H_{11}CO^+$), 83.1 (87.8, $C_6H_{11}^+$) 58.0 (100 $C_3H_6O^+$).

Butyl Benzoate (10b).[43] 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7 (C), 132.7 (CH), 130.5 (C), 129.5 (CH × 2), 128.3 (CH × 2), 64.8 (CH_2), 30.8 (CH_2), 19.2 (CH_2), 13.7 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 178.1 (3.2, M^+), 123.0 (85.4, $C_6H_5CO_2H_2^+$), 105.0 (100, $C_6H_5CO^+$).

Benzyl Benzoate (10c).[44] 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (m, 2H), 7.54 (tt, 1H, $J = 7.3$, 1.3 Hz), 7.47−7.30 (m, 7H), 5.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4 (C), 136.0 (C), 133.0 (CH), 130.1 (C), 129.7 (CH × 2), 128.5 (CH × 2), 128.3 (CH × 2), 128.2 (CH), 128.1 (CH × 2), 66.6 (CH_2); MS (EI) *m/e* (relative intensity, assignment) 212.1 (39.6, M^+), 105.0 (100, $C_6H_5CO^+$), 91.0 (55.4, $C_6H_5CH_2^+$), 77.0 (34.6, $C_6H_5^+$).

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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2 (C), 132.7 (CH), 130.9 (C), 129.5 (CH × 2), 128.3 (CH × 2), 71.5 (CH), 38.2 (CH_2), 20.1 (CH_3), 18.7 (CH_2), 14.0 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 192.1 (0.9, M^+), 123.0 (41.9, $C_6H_5CO_2H_2^+$), 105.0 (100, $C_6H_5CO^+$).

Menthyl Benzoate (10e).[45] 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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 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_2), 34.3 (CH_2), 31.4 (CH), 28.2 (CH), 26.6 (CH_2), 23.6 (CH_3), 22.0 (CH_3), 16.5 (CH_3).

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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 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_2), 32.4 (CH_2), 25.9 (CH_2), 24.8 (CH_2).

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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2 (C), 63.9 (CH_2), 43.3 (CH), 30.7 (CH_2), 29.0 (CH_2 × 2), 25.8 (CH_2), 25.5 ($CH_2 \times 2$), 19.1 (CH_2), 13.7 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 184.1 (1.5, M^+), 129.1 (100, $C_6H_{11}CO_2H_2^+$), 111.1 (73.1, $C_6H_{11}CO^+$), 83.1 (98.2, $C_6H_{11}^+$).

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^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9 (C), 136.3 (C), 128.5 (CH × 2), 128.0 (CH), 127.9 (CH × 2), 65.8 (CH_2), 43.2 (CH), 29.0 ($CH_2 \times 2$), 25.7 (CH_2), 25.4 ($CH_2 \times 2$); MS (EI) *m/e* (relative intensity, assignment) 218.1 (40.6, M^+), 111.1 (45.1, $C_6H_{11}CO^+$), 91.0 (100, $C_6H_5CH_2^+$), 83.1 (98.2, $C_6H_{11}^+$).

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^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8 (C), 71.1 (CH), 43.5 (CH), 38.1 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 20.0 (CH_3), 18.6 (CH_2), 13.9 (CH_3); MS (EI) *m/e* (relative intensity, assignment) 198.2 (0.35, M^+), 155.1 (7.4, $M^+ - C_3H_7$), 129.1 (88.3, $C_6H_{11}CO_2H_2^+$), 111.1 (92.2, $C_6H_{11}CO^+$), 83.1 (100, $C_6H_{11}^+$).

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^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7 (C), 73.5 (CH), 47.1 (CH), 43.5 (CH), 40.9 (CH_2), 34.3 (CH_2), 31.3 (CH), 29.1 (CH_2), 29.0 (CH_2), 26.1 (CH), 25.8 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 24.2 (CH_2), 23.3 (CH_3), 22.0 (CH_3), 16.1 (CH_3); MS (FAB + NaI) *m/e* (relative intensity, assignment) 289.3 (54.8, M + Na^+), 139.2 (100.0, $C_{10}H_{19}^+$).

***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_2O (20 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 ($MgSO_4$), 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^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00, (m, 2H), 7.52 (tt, 1H, J = 7.4, 1.4 Hz), 7.41 (m, 2H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5 (C), 132.4 (CH), 132.0 (C), 129.4 (CH × 2), 128.2 (CH × 2), 118 (C), 80.5 (C), 28.2 (CH_3 × 3); MS (EI) *m/e* (relative intensity, assignment) 178.1 (1.8, M^+), 123.0 (96.7, $C_6H_5CO_2H_2^+$), 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 2,2,2-tribromoethanol (2.35 g, 8.31 mmol) in 10 mL of CH_2Cl_2 was added a solution of diisopropylcarbodiimide (DIC, 0.29 mL, 1.85 mmol) in 7 mL of CH_2Cl_2 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_2Cl_2, and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (15% EtOAc in hexanes) provided 489 mg of **15** (0.865 mmol, 52%) as a yellow oil. Data for **15**: R_f 0.28 (10% EtOAc in hexanes); IR (thin film) 3324 (br), 3231 (br), 2922, 2851, 1750, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 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}C NMR ($CDCl_3$, 75 MHz) δ 172.0 (C), 76.7 (CH_2), 72.0 (CH), 37.5 (CH_2), 37.5 (CH_2), 36.0 (C), 34.0 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0, (CH_2) 25.6 (CH_2), 25.6 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); MS (FAB + NaI) *m/e* (relative intensity, assignment) 587.0 (100, M + Na^+).

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 CH_2Cl_2 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_2Cl_2. The reaction mixture was stirred at ambient temperature for 2.5 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 2 M HCl. The aqueous phase was extracted with CH_2Cl_2, and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (gradient elution, 20−10% hexanes in $CHCl_3$/5% methanol in $CHCl_3$) provided 720 mg of **17** (1.24 mmol, 73%) as a white solid. Data for **17**: R_f 0.53 ($CHCl_3$); IR (thin film) 3356 (br), 3231 (br), 2924, 2854, 1752, 1703, 1518, 1249, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0 (C), 156.0 (C), 79.0 (C), 76.7 (CH_2), 40.6 (CH_2), 36.0 (C), 34.1 (CH_2), 30.0 (CH_2), 29.5 (CH_2 × 2), 29.4, (CH_2) 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.4 (CH_3 × 3), 26.8 (CH_2), 24.8 (CH_2); MS (FAB + NaI) *m/e* (relative intensity, assignment) 602.0 (100, M + Na^+).

Lactone 18.[47] 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 ($MgSO_4$), 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); ^1H NMR ($CDCl_3$, 300 MHz) δ 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). ^1H and ^{13}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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