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Parallel synthesis of an ester library for substrate mapping of esterases and lipases

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Abstract—Use of solid-supported reagents simplified routine acylation of primary and secondary alcohols because it eliminated traditional purification. Using a parallel synthesizer, eight primary or secondary alcohols reacted with acid chloride in the presence of poly(4-vinylpyridine), which acted as a base and acylation catalyst. Filtration, subsequent addition of amino-functionalized silica gel to remove excess acid chloride and a second filtration affording the corresponding esters in high yield (70–98%), excellent chemical purity (93–99%). Acylation of enantiopure alcohols yielded enantiopure esters. Acylation of two tertiary alcohols gave esters in low yield (27–57%) and variable chemical purity (57–99%).

1. Introduction

Advances in genomics and molecular biology have greatly simplified the preparation of new enzymes. However, it is still slow and tedious to identify their favored substrates. This identification is essential to establish an enzyme's likely biochemical role and to identify potential application in biocatalysis. A key step in identifying the favored substrates of enzymes is substrate mapping, which measures the catalytic activity toward a broad range of substrates. In most cases, these substrates are not commercially available and must be synthesized. Herein, we report the application of modern parallel synthesis methodology to prepare an ester library suitable for substrate mapping of esterases and lipases.

Parallel synthesis makes individual compounds through simultaneous parallel reactions.[1] The two parallel synthesis methods are: solid-phase synthesis,[2] where soluble reagents act on a compound linked to a solid support, and solution-phase synthesis,[3] where solid-supported reagents react with soluble compounds.

Solid-phase synthesis has the advantages that an excess of reagents drives reactions to completion and that washing the support-bound product easily removes impurities and excess reagents. On the other hand, monitoring reaction progress is often difficult, extra steps are required for anchoring and removing the substrate from the solid-support, and synthetic procedures must be tediously optimized to act on compounds linked to the solid support. On the other hand, solution-phase synthesis retains the advantages of solid-support chemistry while eliminating some disadvantages. Traditional purification is avoided because filtration easily removes solid-supported reagents and solid-phase scavengers for impurities. However, one must know the nature of the impurity to chose a scavenger and avoid products containing functional groups that might react with the scavenger.

We required a parallel synthesis of simple esters in high yield, chemical purity, and conserved enantiomeric purity to map the substrate range and enantioselectivity of new hydrolases. For a typical substrate mapping experiment,[4] the slowest step is ester synthesis. The subsequent screening is fast using colorimetric screening in 96-well plates.[5]

Although several solid-phase synthesis methods exist for esters, we wanted to avoid anchoring and removing the

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product from solid support. For example, carbodiimide coupling (DMAP/DEC or DIC)[6] between resin-bound alcohol and carboxylic acid (and vice versa) yielded esters on solid support. Similarly, base-catalyzed addition of acid chloride to resin-bound alcohol (and vice versa) afforded resin-bound esters.[7] Finally, carboxylic acids added to trichloroacetimidate-activated Wang resin to form ester links.[8]

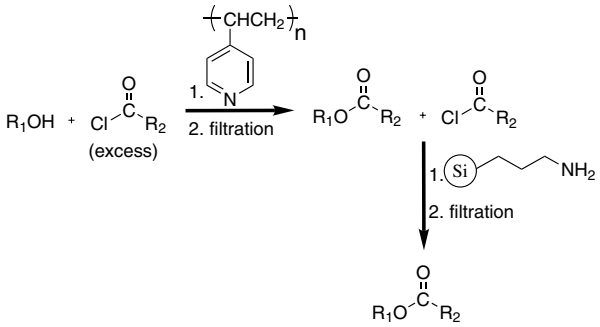
A number of groups have reported solution-phase synthesis of esters, but had not tested them for enantiopure esters. In the mid 1980's, Patchornik et al. used polymer-supported dimethylaminopyridine (PS-DMAP) as an acyl transfer agent to make two esters.[9] Treating PS-DMAP with excess acid chloride formed an *N*-acyl pyridinium salt. Washing the resin to remove excess acid chloride followed by addition of alcohol gave an 82–100% yield of soluble ester. However, our attempts to extend this method to a broader range of esters were disappointing.

Other solution-phase syntheses of esters are extensions of procedures to make amide links. (Many procedures to make amides fail when applied to esters.) Carboxylic acids were linked to *N*-hydroxysuccinimide (NHS) or to pentafluorophenol using solid-supported EDAC (ethyl dimethylaminopropylcarbodiimide).[10] Similarly, Dendrinos and Kalivretenos made NHS esters via a capture–release method.[11] Carboxylic acids first coupled to polymer-bound 1-hydroxybenzotriazole using dicyclohexylcarbodiimide. Nucleophilic attack by NHS afforded the corresponding soluble esters. Although various carboxylic acids could be used, the only suitable alcohol was NHS. In our laboratory, these methods worked well to make soluble amides, but no esters formed using the less nucleophilic aliphatic alcohols or phenols.

To make three benzyl esters, Gayo and Suto used the basic ion-exchange resin Amberlite IRA-68 as both a reagent and scavenger.[12] Acid chloride acylated benzyl alcohol while the basic resin quenched liberated HCl. Addition of water hydrolyzed the excess acid chloride to the acid, which was also sequestered by the basic resin. The water-addition step requires additional work-up steps during product isolation.

A more general, but more complicated, method uses polystyrylsulfonyl chloride resin as a condensation reagent.[13] First, alcohol reacts with excess carboxylic acid in the presence of *N*-methylimidazole and the sulfonyl chloride resin. Second, addition of aminomethylated polystyrene resin and filtration removes excess acid. Third, addition of acidic ion-exchange resin Amberlyte 15 followed by filtration removes the *N*-methylimidazole. This method yielded high purities for a wide range of esters. Besides the complicated procedure, reaction times required optimization for different esters.

We report an efficient parallel solution-phase acylation of alcohols with excess acid chloride, using poly(4-vinylpyridine) as a catalyst and amino-functionalized silica gel to remove the excess acid chloride (Scheme 1). Our



Scheme 1. Parallel solution-phase synthesis of esters.

method affords enantiopure esters of primary and secondary alcohols in high yield and chemical purity. Successful alcohol acylation with five different acid chlorides demonstrates the versatility of this procedure. Flynn et al.[14] acylated amines using a similar method.

2. Results

First we optimized the scavenger. Amine-functionalized resins are traditionally used to sequester acid chlorides in solution-phase acylations.[15] However, Kim et al.[16] report increased yields for disubstituted guanine acylations when the scavenger is switched from polymer-bound trisamine to amino-functionalized silica (*Si*-Amine, Silicycle). Table 1 compares the efficiency of PS-Trisamine (commercial scavenger, Argonaut Technologies) and *Si*-Amine as acid chloride scavengers in our alcohol acylations. In these experiments, methyl (*R*)-3-hydroxy-2-methylpropionate reacted with excess 4-methylbenzoyl chloride (2.5 equiv)[17] in the presence of poly(4-vinylpyridine), followed by the addition of 1, 2, or 2.5 equiv of scavenger (with respect to excess acid chloride) upon acylation completion. We observed high ester yields (98–99%) and enantiomeric purity (99%) for all reactions, however product purity is significantly higher for the *Si*-Amine reactions (Table 1). PS-Trisamine matches *Si*-Amine with respect to acid chloride scavenging ability, but the presence of dimethylformamide (DMF) (presumably left over from scavenger syn-

Table 1. Evaluation of acid chloride scavengers in the acylation of alcohol **1** with 4-methylbenzoyl chloride

Scavenger	Equiv[a]	Yield (%)[b]	Purity (%)[b]	% Ee
PS-Trisamine[c]	1	98	88	99
	2	98	91	99
	2.5	99	87	99
Si-Amine[d]	1	98	92	99
	2	98	97	99
	2.5	99	98	99

[a] With respect to excess acid chloride.
[b] Determined by gas chromatography (flame ionization detector) using area % of peaks. *Si*-Amine reactions contained residual acid chloride as an impurity. PS-Trisamine reactions contained both residual acid chloride and DMF as impurities.
[c] Tris-(2-aminoethyl)amine polystyrene.
[d] Amino-functionalized silica.

thesis[18]) decreases reaction purity. Based on these observations, *Si*-Amine (2.5 equiv) is used as the scavenger in our parallel synthesis. To our knowledge this is the first application of *Si*-Amine as an acid chloride scavenger in alcohol acylation.

Next we examined a range of alcohols. Table 2 shows the acylation results of 10 alcohols (Scheme 2) with octanoyl chloride, poly(4-vinylpyridine), and *Si*-Amine. We used a dual-sided parallel synthesizer (Quest 210, Argonaut Technologies) with 10 reaction vessels on each side. We used one side of the Quest 210 for alcohol acylation and then transferred reactions simultaneously via cannula to the other side for *Si*-Amine scavenging. Primary and secondary alcohols acylate in moderate to excellent yield (70–98%) with high purity (93–97%). Furthermore, acylation of all enantiopure alcohols occurs with conservation of enantiomeric purity.

Both tertiary alcohols **9** and **10** acylate in low yield (53–57%) and purity (57–60%). β-Keto esters of the corresponding alcohols form as byproducts in the acylation reactions. These byproducts likely arise from octanoyl chloride ketene formation, dimerization, and subsequent reaction between the alcohol and resulting diketene (Scheme 3). Bhushan et al. proposed a similar mechanistic pathway for byproducts observed in the acylation of tertiary alcohols with equimolar amounts of 4-dimethyl(amino)pyridine (DMAP) and acetic/propionic anhydride.[19] Furthermore, Sung and Wu reported the dimerization of octanoyl chloride with triethylamine, isolation of the resulting-lactone, and subsequent reaction with methanol to form the corresponding β-keto methyl ester.[20]

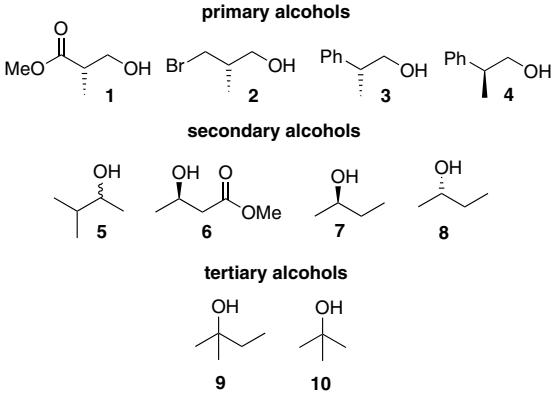
Table 2. Parallel acylation of alcohols **1**–**10** with octanoyl chloride and solid-supported reagents

Alcohol	Isolated yield (%)[a]	Purity (%)[b]	% Ee
1	98	96	>99
2	82	93	98
3	83	97	>99
4	98	97	>99
5	70	94	n.a.[c]
6	94	95	98
7	92	96	95
8	89	96	96
9	57	60	n.a.
10	53	57	n.a.

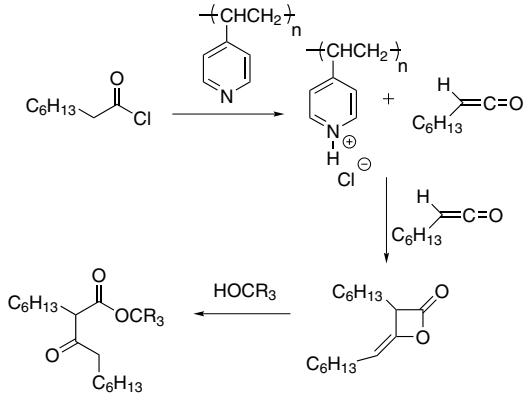
[a] Reaction conditions: (a) alcohol, poly(4-vinylpyridine), CH_2Cl_2, rt, 6 h; (b) *Si*-Amine, rt, 2 h.

[b] Determined by gas chromatography (flame ionization detector) using area % of peaks. Residual octanoyl chloride identified in reactions containing alcohols **1**–**8**. β-Keto esters identified as byproducts in reactions containing **9** and **10**.

[c] n.a. = not applicable because starting alcohol was either racemic or achiral.



Scheme 2. Primary, secondary, and tertiary alcohols acylated. Yields and purities were low for the tertiary alcohols.



Scheme 3. Proposed formation of β-keto tertiary alcohol esters.

Finally, we looked at two alkyl acid chlorides and two aryl acid chlorides. We observe high ester purity (94–99%) when we vary the acid chloride in the parallel acylation of primary **1** and secondary **6** alcohols (Table 3). Ester yields range from 71% to 96% depending on the acid chloride. We observed low ester yields (27–31%) for *tert*-butanol due to incomplete acylation with the aryl acid chlorides even after increasing the reaction time to 24 h. Nevertheless, with increased amounts of scavenger to remove acid chloride, the esters were

Table 3. Parallel acylation of primary alcohol **1**,[a] secondary alcohol **6**,[a] and tertiary alcohol **10**[b] with various acid chlorides

Alcohol	Chloride	Isolated yield (%)	Purity (%)[c]
1	CH_3COCl	75	94
1	C_3H_7COCl	83	96
1	C_6H_5COCl	80	95
1	4-MeC_6H_4COCl	94	95
6	CH_3COCl	71	99
6	C_3H_7COCl	88	94
6	C_6H_5COCl	87	99
6	4-MeC_6H_4COClC	96	99
10	C_6H_5COCl	27	99
10	4-MeC_6H_4COCl	31	93

[a] Reaction conditions: (a) acid chloride, poly(4-vinylpyridine), CH_2Cl_2, rt, 6 h; (b) *Si*-Amine (1.9 mmol, 2.5 equiv excess over acid chloride), 2 h.

[b] Reaction conditions: (a) acid chloride, poly(4-vinylpyridine), CH_2Cl_2, rt, 24 h; (b) *Si*-Amine (2.8 mmol, 2.5 equiv excess over acid chloride), 2 h.

[c] Determined by gas chromatography with a flame ionization detector using area % of peaks. The impurity was residual acid chloride.

Table 4. Hydrolase screening with esters containing 0–10% acetyl chloride

Ester	Hydrolase	Est. E[a]	Quick E[b]
Menthyl acetate	PCL	n.d.	1.1 (*R*)
Menthyl acetate + 5% acetyl chloride	PCL	n.d.	1.1 (*R*)
1-Phenylethyl acetate	PCL	>50 (*R*)	n.d.
1-Phenylethyl acetate + 10% acetyl chloride	PCL	>50 (*R*)	n.d.
1-Phenylethyl acetate	PFE	30 (*R*)	n.d.
1-Phenylethyl acetate + 10% acetyl chloride	PFE	29 (*R*)	n.d.

[a] The ratio of the initial rates of hydrolysis of the two enantiomers without competition.

[b] Calculated from the initial rates of hydrolysis of the two enantiomers in the presence of resorufin acetate. n.d. = not determined. Accurate measurement of high Quick E values requires a slower reacting reference compound to accurate compare to the slow reaction of the slow reacting enantiomer.

isolated in high purity (93–99%). Unreacted *tert*-butanol evaporated during solvent removal. Acylation with acetyl and butyryl chloride was not examined, but we expect significant β-keto ester byproducts for these reactions.

Although the purity of esters from primary and secondary alcohols is high (93–99%), the impurity, residual acid chloride, is a potential problem for using these products directly for screening. However, we found no detectable interference from this impurity and suspect that it hydrolyzed rapidly during preparation of the stock solution. As a test, we compared enantioselectivities measured using pure menthyl acetate with menthyl acetate containing 5% deliberately added acetyl chloride. In both cases, hydrolysis catalyzed by lipase from *Pseudomonas cepacia* (PCL) showed the same low enantioselectivity—$E = 1.1$ in favor of the (*R*)-enantiomer (Table 4). Similarly, we did not detect any interference from added acid chloride for reactions with higher E values. Using our method, we synthesized 1-phenylethyl acetate (99% purity) and compared it with 1-phenylethyl acetate containing 10% deliberately added acetyl chloride. Both measurements showed the same high estimated E values consistent with previous measurements.[21,22] The PCL-catalyzed hydrolysis showed $E > 50$ in favor of the (*R*)-enantiomer, while esterase from *Pseudomonas fluorescens* (PFE) showed E values of 30 and 29. Thus, in spite of the small amount of acid chloride impurities, the esters produced by this parallel synthesis method are suitable for use in enzyme screening without further purification.

3. Discussion

In summary, we report a convenient method for the parallel acylation of primary and secondary alcohols using commercially available poly(4-vinyl)pyridine and *Si*-Amine. The procedure works well with alkyl and aryl acid chlorides and affords esters in high yield, chemical purity, and enantiomeric purity. We believe this will be an efficient method for the parallel synthesis of ester libraries to map the substrate range of lipases and esterases.

4. Experimental section

All reactions were carried out under nitrogen in anhydrous dichloromethane in a Quest 210 parallel synthesizer (Argonaut Technologies, Foster City CA, USA http://www.argotech.com). Poly(4-vinylpyridine) (Sigma-Aldrich Co., Oakville, ON) was dried under vacuum at room temperature for 24 h before use. Silica-supported amine (*Si*-Amine, Silicycle (Quebec City QC, http://www.silicycle.com) and polymer-supported amine (Trisamine, Argonaut Technologies) were used as received. Reactions were monitored by thin-layer chromatography using UV light as a visualizing agent or phosphomolybdic acid solution and heat as a developing agent. Gas chromatography was carried out with Chromopak Chiralsil-Dex CB column (25 m × 0.25 mm, Raritan, NJ). ^{1}H NMR spectra were acquired at 500, 400, or 300 MHz in $CDCl_3$.

4.1. Parallel acylation procedure

Ten 5-mL vessels (side A) of the Quest 210 parallel synthesizer were each loaded with poly(4-vinylpyridine) (0.250 g) and purged with nitrogen for 1 h. Dry dichloromethane (4 mL), alcohol (0.50 mmol), and acylating agent (1.25 mmol, 2.5 equiv) were added to each reaction vessel and the reaction mixtures were agitated for 6 h at room temperature. All reactions were simultaneously filtered and transferred via cannula to individual 5-mL reaction vessels of the Quest 210 (side B) containing *Si*-Amine (1.15 g, 1.9 mmol, 2.5 equiv excess over acid chloride). Side A reaction vessels were rinsed with dichloromethane (1 mL) and the rinse solutions were added to the reaction mixtures in Side B. After 2 h agitation at room temperature, each reaction was filtered through a 30 μm frit into a 25-mL test tube. The *Si*-Amine scavenger was rinsed with dichloromethane (3 × 5 mL) and rinse solutions were added to the 25-mL test tubes. The dichloromethane was removed by rotary evaporation yielding oils.

4.2. Octanoic acid (*S*)-2-methoxycarbonyl-propyl ester

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.28 (d, 3H), 1.36 (m, 8H), 1.64 (t, 2H), 2.34 (t, 2H), 2.84 (m, 1H), 3.76 (s, 3H), 4.28 (m, 2H).

4.3. (*S*)-3-Acetoxy-2-methyl-propionic acid methyl ester

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, 3H), 2.00 (s, 3H), 2.80 (m, 1H), 3.66 (s, 3H), 4.14 (dd, 1H), 4.20 (dd, 1H).

4.4. (*S*)-Butyric acid 2-methoxycarbonyl-propyl ester

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H), 1.22 (d, 3H), 1.60 (m, 2H), 2.28 (t, 2H), 2.80 (m, 1H), 3.66 (s, 3H), 4.14 (dd, 1H), 4.20 (dd, 1H).

4.5. (*S*)-Benzoic acid 2-methoxycarbonyl-propyl ester

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, 3H), 2.97 (m, 1H), 3.75 (s, 3H), 4.43 (dd, 1H), 4.52 (dd, 1H), 7.44 (2H), 7.55 (1H), 8.00 (2H).

4.6. (*S*)-4-Methyl-benzoic acid 2-methoxycarbonyl-propyl ester

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, 3H), 2.42 (s, 3H), 2.93 (m, 1H), 3.73 (s, 3H), 4.40 (dd, 1H), 4.48 (dd, 1H), 7.24 (d, 2H), 7.88 (d, 2H).

4.7. 2-Hexyl-3-oxo-decanoic acid *tert*-butyl ester

The byproduct was isolated by column chromatography using hexane/ethyl acetate (500:1) eluent: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H), 0.90 (t, 3H), 1.28 (m, 16H), 1.46 (s, 9H), 1.59 (m, 2H), 1.80 (m, 2H), 2.50 (m, 2H), 3.32 (t, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.41, 14.49, 22.91, 22.97, 23.03, 23.91, 27.72, 28.28, 28.49, 29.43, 29.47, 31.90, 32.02, 42.06, 60.57, 81.80, 169.31, 205.98; MS (FAB) *m/z* 327 (7, $[M+H]^+$), 271 (100), 253 (35), 127 (81).

4.8. 2-Hexyl-3-oxo-decanoic acid 1,1-dimethyl-propyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 9H), 1.28 (m, 16H), 1.46 (s, 6H), 1.59 (m, 2H), 1.80 (m, 4H), 2.50 (m, 2H), 3.32 (t, 1H). The ^{1}H NMR spectrum was nearly identical to that of the *tert*-butyl β-keto ester. Differences in integration values correspond to the dimethyl-propyl moiety of ester.

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References

1. (a) Ripka, W. C.; Barker, G.; Krakover, J. *Drug Discov. Today* **2001**, *6*, 471–477; (b) Plunkett, M. J.; Ellman, J. A. *Sci. Am.* **1997**, *69–73*; (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600.
2. (a) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157; (b) Gordon, K.; Balasubramanian, S. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 835–851; (c) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*, 411–448.
3. (a) Ley, S. V.; Baxendale, I. R. *Nature Rev. Drug Discov.* **2002**, *1*, 573–586; (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815–4195; (c) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324–337; (d) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320–336.
4. Liu, A. M. F.; Somers, N. A.; Kazlauskas, R. J.; Brush, T. S.; Zocher, F.; Enzleberger, M. M.; Bornscheuer, U. T.; Horsman, G. P.; Mezzetti, A.; Schmidt-Dannert, C.; Schmid, R. D. *Tetrahedron: Asymmetry* **2001**, *12*, 545–556.
5. Janes, L. E.; Kazlauskas, R. J. *J. Org. Chem.* **1997**, *62*, 4560–4561.
6. (a) Pon, R. T.; Yu, S. *Nucleic Acids Res.* **1997**, *25*, 3629–3635; (b) Branton, D. W.; Fields, C. G.; VanDrisse, V. L.; Fields, G. B. *Tetrahedron Lett.* **1993**, *34*, 4885–4888; (c) Apsimon, J. W.; Dixit, D. M. *Synth. Commun.* **1982**, *12*, 113–116.
7. Laursen, J. B.; de Visser, P. C.; Nielsen, H. K.; Jensen, K. J.; Nielsen, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 171–175; Panek, J. S.; Zhu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12022–12023.
8. Phoon, C. W.; Oliver, S. F.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 7959–7962.
9. (a) Shai, Y.; Jacobson, K. A.; Patchornik, A. *J. Am. Chem. Soc.* **1985**, *107*, 4249–4252; (b) Patchornik, A. *Chemtech* **1987**, 58–63.
10. Adamcyk, M.; Fishpaugh, J. R.; Mattingly, P. G. *Tetrahedron Lett.* **1995**, *36*, 8345–8346.
11. Dendrinos, K. G.; Kalivretenos, A. G. *Tetrahedron Lett.* **1998**, *39*, 1321–1324.
12. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513–516.
13. Zander, N.; Frank, R. *Tetrahedron Lett.* **2001**, *42*, 7783–7785.
14. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodward, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874–4881.
15. Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320–336.
16. McComas, W.; Chen, L.; Kim, K. *Tetrahedron Lett.* **2000**, *41*, 3573–3576.
17. Using less acid chloride resulted in incomplete reactions. For example, 10% unreacted alcohol remained when using 2 equiv of acid chloride.
18. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882–4886.
19. Bhushan, V.; Chakraborty, T. K.; Chandrasekaran, S. *J. Org. Chem.* **1984**, *49*, 3974–3978.
20. Sung, K.; Wu, S.-Y. *Synth. Commun.* **2001**, *31*, 3069–3074.
21. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531–5534.
22. Baumann, M.; Stürmer, R.; Bornscheuer, U. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4201–4204.