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Microwave-Assisted Ester Formation Using *O*-Alkylisoureas: A Convenient Method for the Synthesis of Esters with Inversion of Configuration

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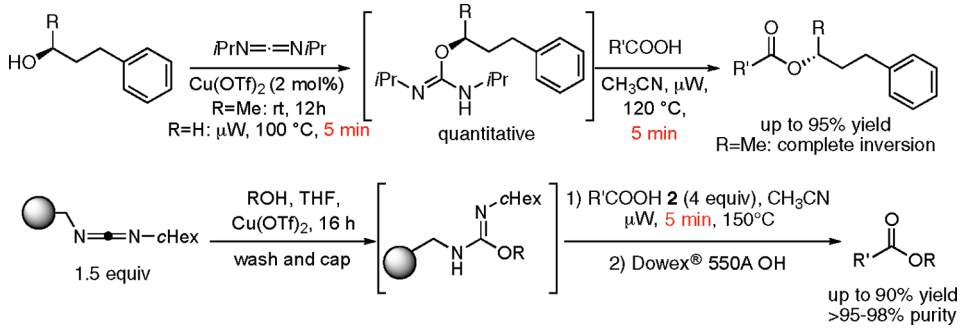

The formation of carboxylic esters *via* reaction of carboxylic acids with *O*-alkylisoureas proceeds in excellent yields with very short reaction times when conducted in a monomode microwave synthesizer. Efficient processes were developed using preformed or commercially available isoureas derived from primary and secondary alcohols, with a reaction time of only 5 min or less. It was demonstrated that under these microwave conditions, ester formation proceeded in good yields with clean inversion of configuration where appropriate. The process was validated using menthol, a hindered substrate for S_N2 reactions. In addition, starting from primary alcohols, ester formation was successfully accomplished using an in situ isourea formation procedure. A polymer-assisted solution-phase procedure was also developed by employing preformed solid-supported isoureas and by an efficient "catch and release" ester formation procedure whereby primary alcohols were caught on resin as isoureas by reaction with immobilized carbodiimide and released as esters by subsequent treatment with a carboxylic acids.

Introduction

The synthesis of carboxylic esters and lactones is a fundamental transformation and is used for a wide range of applications in very different areas and industries. From a synthetic point of view, requirements for simple alcohol or carboxylic acid protection as acetates or methyl esters are significantly different from those for the formation of esters where both the carboxylic acid and the alcohol unit are considered as "substrates" or are not commercially available. Cost, scale, time and ecological issues, as well as the desire to avoid toxic, explosive, or expensive reagents; excess reagents; and equilibrium reaction conditions and/or activation to unstable intermediates are all parameters of varying importance depending on the application. Hence, a wide range of methods has been developed for ester synthesis and transesterification,[1] and many novel methods are still being reported.[2] The formation of esters using solid-supported reagents[3−5] and reagents/catalysts that are linked to a soluble-phase label[5−7] has been reported. The use of microwave-assisted chemistry[8] has also proven to be useful for the rapid synthesis of esters,[9] including in combination with polymer-assisted solution phase (PASP) chemistry.[4]

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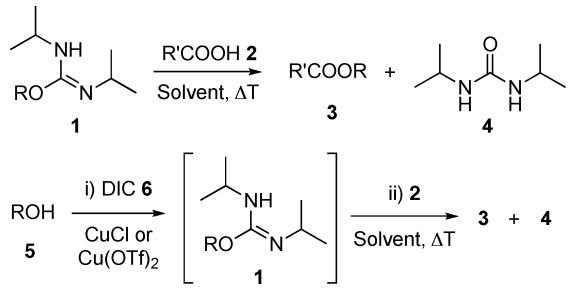
SCHEME 1. Isourea-Mediated Ester Formation Starting from *O*-Alkylisoureas 1 or via in Situ Formation of *O*-Alkylisoureas Starting from Alcohols 5



The reaction of carboxylic acids **2** (Scheme 1) with *O*-alkylisoureas **1** to give the corresponding alkyl esters **3** is well-established.[10,11] *O*-Alkylisoureas are easily prepared by the equimolar addition of an alcohol **5** to a carbodiimide (e.g., diisopropylcarbodiimide DIC **6**) under Cu(I) or Cu(II) catalysis,[12] with isolation achieved by filtration over Celite to remove copper salts. Alternatively, isoureas can be synthesized in situ. The synthetic utility of isoureas is not limited to ester formation.[10,13]

Isourea-mediated ester formation method has several advantages over the traditional carbodiimide-mediated coupling of an alcohol with a carboxylic acid. For example, the formation of *O*-acylisoureas, which are unstable structures that can undergo isomerization to the corresponding *N*-acylureas, is avoided.[1j,14] Kappe has shown that microwave-assisted solid-phase coupling using this method mainly led to the rearranged *N*-acylureas.[15] In addition, activation of α-chiral carboxylic acids also introduces a racemization or epimerization risk (this is more prominently the case in peptide synthesis where the formation of an oxazolone intermediate is possible).[14] The chemoselectivity of the *O*-alkylisourea-mediated ester formation is very good because alcohols[16] and even phenolic groups[17] do not react with these reagents under normal reaction conditions. An attractive feature for the isourea-mediated ester formation is that no additional reagent or catalyst (acid, base) is required for the reaction. Moreover, the reaction occurs with inversion of configuration[18] and is thus a potential alternative to the

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Mitsunobu reaction.[7,19] However, complete separation of the product from diisopropylurea **4** usually requires a chromatographic step, and the synthesis of *O*-alkylisoureas **1** from DIC **6**, as well as the actual ester formation step, are time-consuming even at elevated temperature.

In this context, we have reported dramatic rate acceleration when microwave irradiation is employed.[4b] Herein, our full results for the formation of carboxylic esters via reaction between carboxylic acids and preformed *O*-alkylisoureas under microwave irradiation conditions are reported. In addition, ester formation using complex alcohol substrates is discussed, exploiting a one-pot procedure starting from primary alcohols and carboxylic acids. We also describe an optimized procedure for the synthesis of esters using an isourea intermediate derived from chiral secondary alcohols as an alternative to the Mitsunobu reaction. Polymer-supported *O*-alkylisourea reagents derived from primary alcohols were also prepared and used to efficiently convert carboxylic acids into esters in which, apart from resin filtration and solvent evaporation, no further workup/purification was necessary to obtain pure compounds. A "catch and release" protocol was also developed.

Results and Discussion

Microwave-Assisted Synthesis of Esters Using *O*-Alkylisoureas. Simple isoureas such as *O*-methyldiisopropylisourea are commercially available or easily synthesized (see below). Initial investigations involved the formation of carboxylic esters using these simple isoureas. The reaction of carboxylic acids with isoureas was found to be dramatically accelerated when the reaction was performed at high temperature, achieved by microwave irradiation, in THF.[4b] A full set of results is listed in Table 1. Reaction at 120−130 °C for only 5 min led to the formation of ester products in good yields after chromatography (entries 3, 5, 8, 14, 18). An even shorter reaction time could be achieved by using acetonitrile as solvent, presumably because of the faster heating process in this solvent with a larger tan δ value. With *O*-alkylisoureas **1a**−**c**, very good yields were obtained with a reaction time of just 1−2 min. The esterification of sterically congested carboxylic acids (entries 11, 21, 23) was achieved in high yield, although a longer reaction time (5 min) was necessary for complete conversion. The reactions leading to **10a** and **10b** (entries 8, 9, 18−20) were very selective in that no alkylation of the phenolic OH was observed, despite the high temperature employed.[17] Reactions leading to *tert*-butyl esters (entries 27, 28) gave only moderate yields. A larger excess of **1d** was necessary because of an E1 side reaction leading to isobutene formation, though no excessive pressure increase in the microwave vial was observed. It should be noted that short-time microwave experiments tend to have reduced reproducibility due to the induction period for the reaction mixture to reach the maximum temperature (e.g., see entries 1, 2).

The very fast synthesis of methyl esters is noteworthy. It provides an excellent alternative to the corresponding diazomethane mediated process, without its associated hazards.

Isoureas are mildly basic species (pK_{aH} ∼6−10),[10b] and a brief investigation toward possible ester racemization under the above-mentioned microwave heating conditions was undertaken. For this purpose, the methylation of Cbz-Gly-Phe-Val-OH **15** to give (L,L)-**16** was investigated (Scheme 2). It is known that (L,L)-**16** can easily be distinguished (^{1}H NMR) from its diastereomer, which is exploited in the so-called Anteunis test to assess possible racemization during amide bond formation methods.[20] While the Anteunis test concerns the coupling of Cbz-Gly-Phe-OH with H-Val-OMe to give (L,L)-**16**, leading to the easily distinguishable (D,L)-**16** if racemization of the activated phenyl alanine moiety had occurred, methylation of (L,L)-**15** will lead to (L,D)-**16** if epimerization took place during the isourea-mediated reaction. The synthesis of **15** was achieved by coupling of Cbz-Gly-Phe-OH and H-Val-O*t*Bu using PS-DCC/1-hydroxybenzotriazole (HOBt) in DMF followed by deprotection using standard TFA/DCM (1:1) conditions. When *O*-methylisourea **1a** was used for the protection of the tripeptide Cbz-Gly-Phe-Val-OH **15**, ^{1}H NMR analysis indicated that **16** was obtained as a single (L,L)-epimer (see Supporting Information). Hence, though a slightly lower temperature was used, the long reaction time did not result in any observable epimerization.

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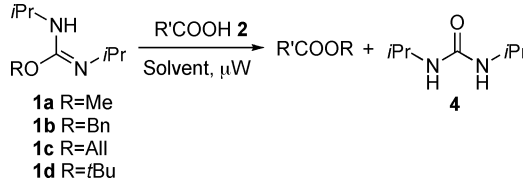
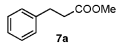
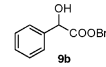
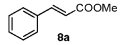
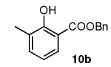
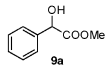
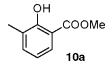
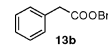
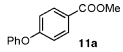
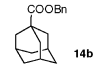
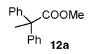
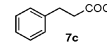
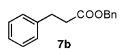
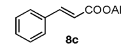
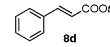
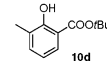
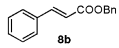
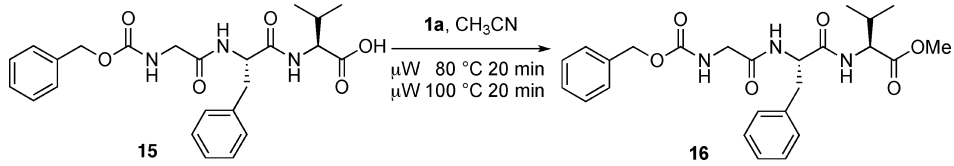
TABLE 1. Microwave-Assisted Synthesis of Carboxylic Esters with *O*-Alkylisoureas 1a−d



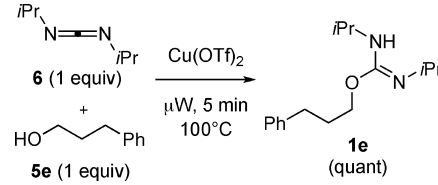
entry	isourea **1** (equiv.)	R'COOR	T (°C)	time (min) solvent	yield (%)	entry	isourea **1** (equiv.)	R'COOR	T (°C)	time (min) solvent	yield (%)
1	**a** (1.00)	 **7a**	120	1.5; ACN	48	17	**b** (1.05)	 **9b**	120	2.0; ACN	88
2	**a** (1.00)		120	2.0; ACN	93						
3	**a** (1.10)	 **8a**	130	5.0; THF	94	18	**b** (1.30)		130	5.0; THF	83
4	**a** (1.00)		120	1.5; ACN	94	19	**b** (1.30)	 **10b**	120	2.0; ACN	99
5	**a** (1.10)		130	5.0; THF	81	20	**b** (1.05)		120	2.0; ACN	96
6	**a** (1.05)	 **9a**	120	2.0; ACN	72	21	**b** (1.05)	 **12b**	120	5.0; ACN	80
7	**a** (1.05)		120	5.0; ACN	92						
8	**a** (1.10)	 **10a**	130	5.0; THF	89	22	**b** (1.05)	 **13b**	120	2.0; ACN	98
9	**a** (1.05)		120	2.0; ACN	82						
10	**a** (1.05)	 **11a**	120	2.0; ACN	98	23	**b** (1.05)	 **14b**	120	5.0; ACN	92
11	**a** (1.05)	 **12a**	120	5.0; ACN	96	24	**c** (1.10)	 **7c**	120	2.0; ACN	95
12	**b** (1.05)	 **7b**	120	1.0; ACN	88	25	**c** (1.05)	 **8c**	120	0.75; ACN	88
13	**b** (1.05)		120	2.0; ACN	95	26	**c** (1.05)			2.0; ACN	94
14	**b** (1.30)		130	5.0; THF	90	27	**d** (4.50)	 **8d**	120	2.0; ACN	63
15	**b** (1.30)		120	2.0; ACN	99	28	**d** (4.50)	 **10d**	120	2.0; ACN	49
16	**b** (1.05)	 **8b**	120	0.75; ACN	96						

SCHEME 2. Protection of L,L-Cbz-Gly-Phe-Val-OH Using *O*-Methylisourea 1a



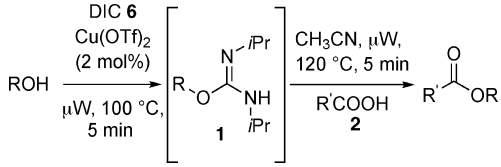
Microwave-Assisted One-Pot Ester Formation Using Primary Alcohols. Isourea-mediated ester formation starting from "substrate" alcohols was next investigated. A one-pot process was envisaged in which the isourea would be formed first, followed by addition of the carboxylic acid. In order to decrease reaction times for the isourea formation step, microwave conditions were investigated. Hence, both steps would take place in the microwave. Taking into account the limited volume of microwave vials and the convenience of adding the carboxylic acid as a solution after the first step, the isourea formation was investigated neat using 3-phenyl-1-propanol as test substrate (Scheme 3). Both CuCl and $Cu(OTf)_2$ are suitable Lewis acids, but it was found that lower catalyst loadings were possible with $Cu(OTf)_2$. The use of 2 mol % leads to complete conversion in only 5 min, as judged by the disappearance of the sharp carbodiimide band in the IR spectrum. Isourea formation in THF as solvent also gives excellent conversion (5 mol % $Cu(OTf)_2$, 120 °C, 5 min).

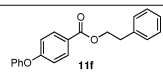
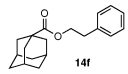
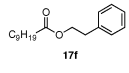
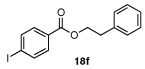
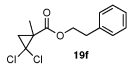
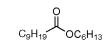
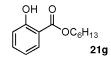
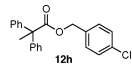
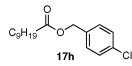
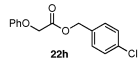
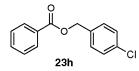
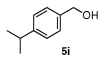
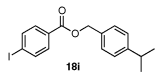
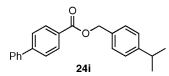
SCHEME 3. *O*-Alkylisourea Synthesis under Microwave Irradiation



With these results in hand, the solvent-free reaction of primary alcohols (1 equiv) with **6** (1 equiv) was undertaken with $Cu(OTf)_2$ catalysis (2 mol %) under microwave irradiation (100 °C, 5 min) to give isourea **1**. Subsequent cooling and addition of a solution of carboxylic acid (0.9 equiv) in acetonitrile followed by microwave irradiation (120 °C, 5 min) gave the

TABLE 2. One-Pot Isourea-Mediated Microwave-Assisted Ester Synthesis: Primary Alcohols



entry	5	R'COOR	yield (%)[a,b]
1			84
2	**5f**		70
3	**5f**		70
4	**5f**		87
5	**5f**		87
6	$C_6H_{13}OH$ **5g**		90
7	**5g**		74
8	**5g**		72
9	**5g**		87
10	**5g**		82
11			80
12	**5h**		80
13	**5h**		87
14	**5h**		90
15			83
16	**5i**		82

[a] Isolated yield. [b] Purity is >98% in all cases (determined by ELSD).

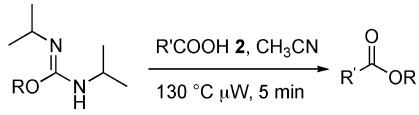
targeted ester (Table 2). Workup consisted of filtration of the diisopropylurea, followed by purification using a solid-phase extraction (SPE) reservoir filled with silica and alumina in order to remove the copper catalyst and excess isourea from the solution. A variety of carboxylic acids were selected in order to exemplify the use of the method. It was found that the esterification proceeded smoothly with simple aliphatic acids (entries 3, 7, 9, 12, 13) and substituted benzoic acids (entries 1, 4, 14−16). In addition, reaction with sterically hindered acids proceeded in good yields as well (entries 2, 5, 6, 8, 11), and again no etherification was observed with a phenolic OH (entry 10). However, the reaction failed when 3-phenylprop-2-yn-1-ol and 4-methoxy-benzyl alcohol were used (not shown).

Isourea-Mediated Ester Formation with Secondary Alcohols. The reaction of a carboxylic acid with an *O*-alkylisourea derived from a primary or a secondary alcohol is thought to proceed, after initial acid−base reaction, via an S_N2-displacement. Hence, this process is more challenging when secondary alcohols are used. A typical side reaction involves E2 chemistry, leading to the corresponding alkene. The usefulness of the microwave conditions for the isourea-mediated esterification of secondary alcohols was evaluated next. The investigation commenced by evaluating the reaction of two preformed *O*-alkylisoureas ***rac*-1j,k** derived from (racemic) secondary alcohols 2-octanol (**5j**) and 4-phenyl-2-butanol (**5k**), with a range of carboxylic acids (Table 3). The reaction mixture was purified by SPE (silica−alumina cartridge). Isolated yields were good to excellent in virtually all cases, except when a fatty acid was used (entries 2, 13). Interestingly, sterically hindered aliphatic and aromatic carboxylic acids gave excellent yields in many cases (entries 1, 3, 7, 16). Notably, ester formation from benzoic acids that possess electron-withdrawing substituents proceeded in very high yields (entries 6, 7, 15, 16). ^{1}H NMR of the isolated compounds showed no trace of the corresponding elimination products (presumably due to their volatility). However, a control experiment in which the reaction to give ***rac*-25j** was performed in CD_3CN permitted observation by ^{1}H NMR of the elimination products in the crude reaction mixture. A ratio of substitution vs elimination of 1:0.08 was found, confirming minimal levels of elimination.

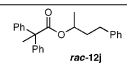
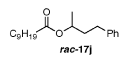
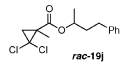
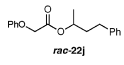
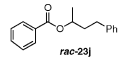
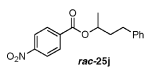
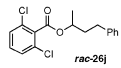
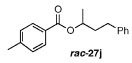
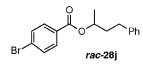
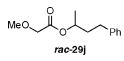
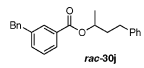
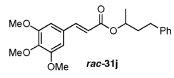
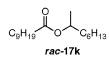
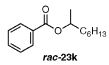
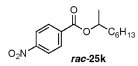
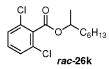
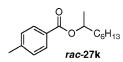
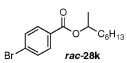
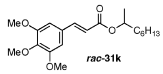
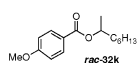
Hence, these results show that isourea-mediated ester formation starting from secondary alcohols using microwave heating is a very useful process, featuring short reaction times and high yields. As mentioned above,[18] the isourea-mediated ester formation can be used as an alternative to the Mitsunobu reaction.[21] It was subsequently investigated whether clean inversion of configuration could be obtained when microwave heating is employed. For this purpose, optically pure isoureas **(*S*)-1j** and **(*R*)-1k** were prepared from the corresponding enantiopure alcohols and subjected to ester formation with a set of carboxylic acids (Table 4). Again, high yields were obtained, and in all cases complete inversion of configuration was observed as shown by chiral HPLC analysis (Figure 1). With chiral acids, such as Mosher's acid and mandelic acid, only one diastereomer was observed (NMR). While *p*-nitrobenzoic acid would be the reagent of choice if a simple alcohol

(21) Examples of Mitsunobu-modifications/alternatives: (a) Boivin, J.; Henriet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1994**, *116*, 9739–9740. (b) Barrett, A. G. M.; Koike, N.; Procopiou, P. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1403–1404. (c) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273–6280. (d) Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053–1057. (e) Elson, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2003**, *1*, 2958–2965. (f) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4051–4054. (g) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *J. Org. Chem.* **2003**, *68*, 1597–1600. (h) Shintou, T.; Fukumoto, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1569–1579. (i) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590–5614. (j) Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 52–53. (k) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069–5072. (l) Poupon, J.-C.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1415–1420. (m) But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637. (n) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566–567.

TABLE 3. Microwave-Assisted Synthesis of Carboxylic Esters with *O*-Alkylisoureas 1j,k Derived from Secondary Alcohols

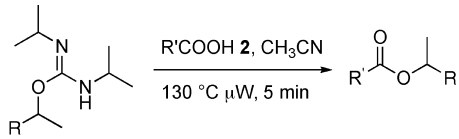


***rac*-1j** R= 4-phenyl-2-butyl-
***rac*-1k** R= 2-octyl-

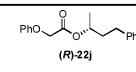
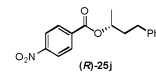
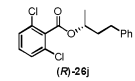
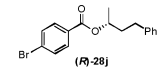
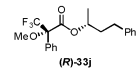
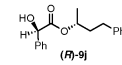
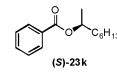
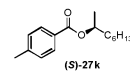
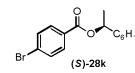
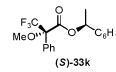
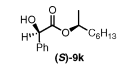
entry	isourea	R'COOR	yield (%)[a,b]
1	***rac*-1j**	 *rac*-12j	96
2	***rac*-1j**	 *rac*-17j	48
3	***rac*-1j**	 *rac*-19j	70[c]
4	***rac*-1j**	 *rac*-22j	90
5	***rac*-1j**	 *rac*-23j	90
6	***rac*-1j**	 *rac*-25j	95
7	***rac*-1j**	 *rac*-26j	96
8	***rac*-1j**	 *rac*-27j	80
9	***rac*-1j**	 *rac*-28j	87
10	***rac*-1j**	 *rac*-29j	82
11	***rac*-1j**	 *rac*-30j	85
12	***rac*-1j**	 *rac*-31j	47
13	***rac*-1k**	 *rac*-17k	60
14	***rac*-1k**	 *rac*-23k	80
15	***rac*-1k**	 *rac*-25k	95
16	***rac*-1k**	 *rac*-26k	90
17	***rac*-1k**	 *rac*-27k	78
18	***rac*-1k**	 *rac*-28k	72
19	***rac*-1k**	 *rac*-31k	74
20	***rac*-1k**	 *rac*-32k	74

[a] Isolated yield. [b] Purity is >98% in all cases (determined by ELSD). [c] Mixture of two diastereomers.

TABLE 4. Microwave-Assisted Synthesis of Esters with Enantiopure Isoureas 1j,k



(*S*)-1j R= CH_2CH_2Ph
(*R*)-1k R= C_6H_{13}

entry	isourea	R'COOR	yield(%)[a,b] ret./inv.[c,d]
1	**(*S*)-1j**	 (*R*)-22j	90 ≤0.1/≥99.9[e]
2	**(*S*)-1j**	 (*R*)-25j	95 ≤0.1/≥99.9[e]
3	**(*S*)-1j**	 (*R*)-26j	95 ≤0.1/≥99.9[e]
4	**(*S*)-1j**	 (*R*)-28j	87 [d]
5	**(*S*)-1j**	 (*R*)-33j	78 ≤3/≥97[e]
6	**(*S*)-1j**	 (*R*)-9j	60 ≤5/≥95[e]
7	**(*R*)-1k**	 (*S*)-23k	80 ≤0.1/≥99.9[e]
8	**(*R*)-1k**	 (*S*)-27k	77 ≤0.1/≥99.9[e]
9	**(*R*)-1k**	 (*S*)-28k	70 ≤0.1/≥99.9[e]
10	**(*R*)-1k**	 (*S*)-33k	80 ≤3/≥97[e]
11	**(*R*)-1k**	 (*S*)-9k	90 ≤5/≥95[e]

[a] Isolated yield. [b] Purity is >98% in all cases (determined by ELSD). [c] Retention:inversion ratios measured by chiral liquid chomatography using an amylose-derivated ChiralpackAD-RH as stationary phase. [d] We were not able to determine the er. [e] Retention:inversion ratios measured by NMR.

inversion process is desired, the results in Table 4 show that this method is suitable for convenient synthesis of chiral, enantioenriched esters, even with hindered carboxylic acids (entries 3, 5, 10).

The isourea method was also compared with the microwave assisted Mitsunobu conditions described by Kappe, for the inversion of *S*-(+)-4-phenyl-2-butanol **5j** with phenoxy acetic acid (Scheme 4).[9h] As can be seen in Figure 1c, complete inversion of configuration was also confirmed by HPLC analysis.

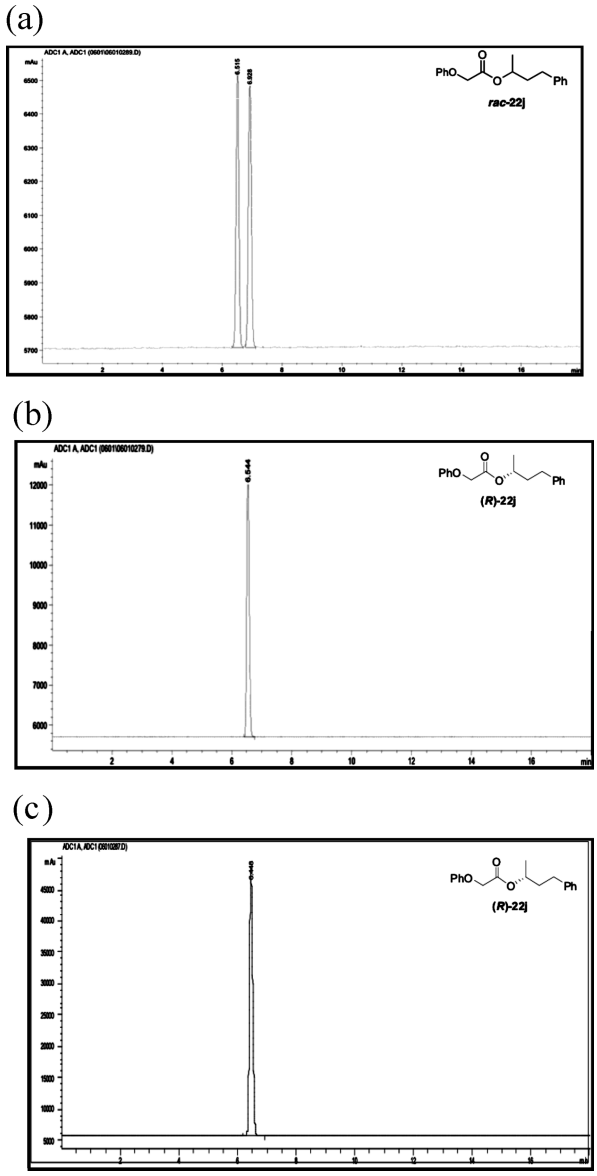
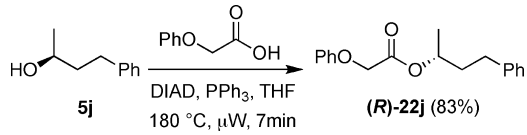


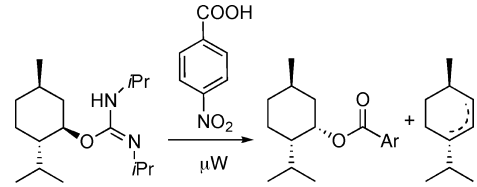
FIGURE 1. HPLC analysis of the isourea-mediated ester formation: (a) **rac-22j**, (b) **(*R*)-22j** (Table 4, entry 1), (c) **(*R*)-22j** (Scheme 4).

SCHEME 4. Microwave-Assisted Mitsunobu Reaction of 5j



The *O*-alkylisourea-mediated inversion of menthol[18a] was investigated as a test case for hindered secondary alcohols. *O*-(−)-Menthylisourea was synthesized using $Cu(OTf)_2$ as catalyst and subsequently treated with *p*-nitrobenzoic acid under microwave conditions. The crude reaction mixture was analyzed by GC−MS (Table 5). When using acetonitrile as solvent, it was found that elimination products 2- and 3-menthene were formed in substantial amounts (entry 1). Reducing the reaction time did not have a significant impact on the substitution/elimination ratio (entry 2). While the reactions showed complete conversion, lowering the temperature led to incomplete reaction, with an unchanged substitution/elimination ratio (entry 3). Changing the solvent to toluene had a huge impact in that the substitution reaction now became the dominant reaction pathway (entries 4, 5), with excellent isolated yield. Employing 2 equiv of isourea or *p*-nitrobenzoic acid surprisingly lowered the substitution/elimination ratio, and in the former case, an incomplete reaction was observed as well (entries 6, 7).

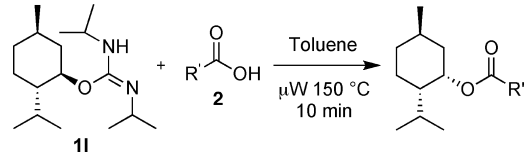
TABLE 5. Microwave-Assisted Synthesis of Neomenthyl-4-nitro Benzoate

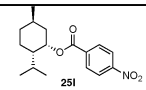
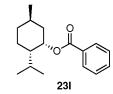
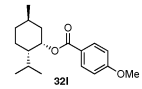


entry	*T* (deg); time (min)	solvent[a]	**1l**:acid (equiv)	ratio **25l**:**34**[b]
1	150;10	CH_3CN	1.06:1.00	58:42
2	150;5	CH_3CN	1.06:1.00	63:37
3	130;5	CH_3CN	1.06:1.00	60:40[c]
4	**150;30**	**toluene**	**1.06:1.00**	**92:8**[d]
5	150;10	toluene	1.06:1.00	90:10[e]
6	150;10	toluene	2.00:1.00	70:30[f]
7	150;10	toluene	1.00:2.00	72:28

[a] All reactions were carried out in 2 mL of solvent. [b] Product ratios determined by GC−MS analysis. [c] 25% starting material present. [d] 91% isolated yield. [e] 90% isolated yield. [f] 43% starting material present.

TABLE 6. Microwave-Assisted Synthesis of Neomenthyl Esters

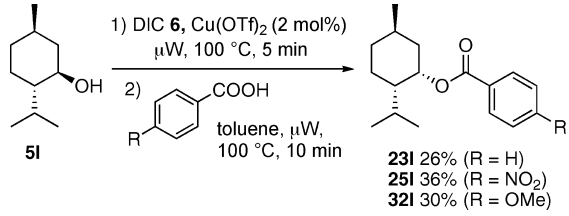


entry	Product	Yield(%)[a,b]
1		90
2		68
3		66
4		-[c]
5		31

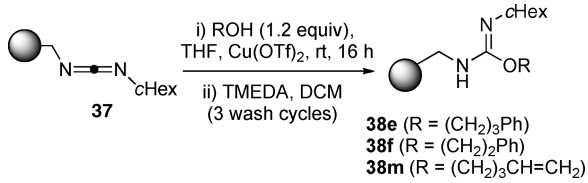
[a] Isolated yield. [b] Purity is >98% in all cases (determined by ELSD). [c] No reaction.

Following the optimized conditions for the synthesis of neomenthyl-4-nitro benzoate, the reaction was executed with benzoic acid and *p*-methoxy benzoic acid (Table 6, entries 2, 3). A somewhat reduced yield, with complete inversion of configuration, was observed. However, when acetic acid (entry 4) was used, the starting material was recovered and no product was isolated from the reaction mixture. Employing the more

SCHEME 5. One-Pot Isourea-Mediated Synthesis of Neomenthyl Esters



SCHEME 6. Synthesis of PS-*O*-Alkylisoureas



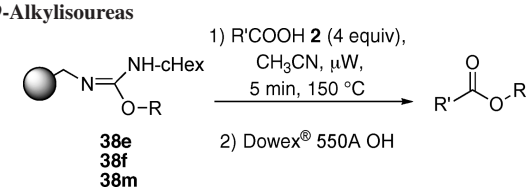
nucleophilic thioacetic acid led to a 31% yield of the inverted product (entry 5). Nevertheless, the isourea method for the formation of neomenthyl benzoates compares well with the Mitsunobu reaction itself[22] and with many alternatives,[21c,e−h,l] especially with regard to reaction time and ease of reaction workup.

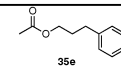
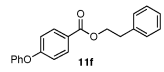
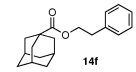
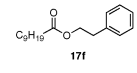
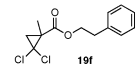
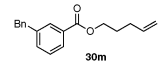
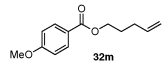
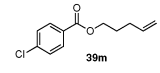
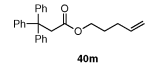
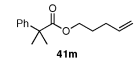
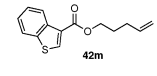
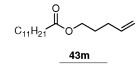
The synthesis of esters derived from secondary alcohols as a one-pot procedure where the isourea is synthesized in situ from the starting alcohol followed by reaction with a carboxylic acid directly was briefly investigated (Scheme 5). The viability of the microwave-assisted isourea formation from secondary alcohols using $Cu(OTf)_2$ as catalyst (5 mol %) had been demonstrated earlier.[13c] Hence, menthol was subjected to DIC **6**, followed by reaction with benzoic acids. In all cases, yields were roughly half compared to the yields obtained in the two-step process. However, complete inversion of stereochemistry was observed in all three cases (^{1}H NMR), suggesting that this one-pot method is still viable when starting from secondary alcohols.

PASP Synthesis of Esters Using PS-*O*-Alkylisoureas. The usefulness of polymer-supported isoureas (methyl, allyl, benzyl) for the protection of carboxylic acids has been demonstrated.[4b,c,e] These immobilized isoureas are easily synthesized, and react with carboxylic acids under microwave irradiation in short reaction times. The synthesis of immobilized isoureas using only a very small excess of more complex alcohols was equally possible, with complete conversion (as judged by IR spectroscopy) after 16 h at room temperature (Scheme 6). The copper salts were efficiently removed by three wash cycles with a 10% (v/v) solution of TMEDA in DCM.

Next, the isoureas **38e**, **38f**, and **38m** were investigated in ester formation reactions under microwave irradiation (Table 7). Using 2 equiv of carboxylic acid, 51% of the ester was obtained, which increased to 90% when 4 equiv of acid was used (entries 1, 2). After filtration of the resin, the resulting solution was treated with Dowex 550A OH resin in order to remove the excess of acid. Pleasingly, most ester products were formed in excellent yield, except when sterically hindered carboxylic acids were used (entries 4, 6). The purity of the obtained esters was excellent in all cases. Unfortunately, with secondary alcohols, elimination was a prominent side reaction,

TABLE 7. Microwave-Assisted Esterification Using PS-*O*-Alkylisoureas



Entry	Isourea	R'COOR	Yield(%)[a,b]
1	**38e**	 35e	51[c,d]
2	**38e**	**35e**	90[d]
3	**38f**	 11f	53
4	**38f**	 14f	56
5	**38f**	 17f	90
6	**38f**	 19f	68
7	**38m**	 30m	85
8	**38m**	 32m	80
9	**38m**	 39m	90
10	**38m**	 40m	90
11	**38m**	 41m	90
12	**38m**	 42m	90
13	**38m**	 43m	66

[a] Isolated yield. [b] Purity is >95% in all cases (determined by ELSD). [c] 2 equiv of AcOH. [d] Purity determined by ^{1}H NMR.

and though the use of toluene as a solvent significantly improved the substitution/elimination ratio, clean reaction products could not be obtained.

At this stage it was decided to investigate the use of more complex alcohols in a "catch and release" esterification procedure (Table 8), starting from the alcohol substrate. First the alcohol **5** was immobilized onto a resin as the corresponding isourea **38** using PS-DCC. It was decided to use an excess of carbodiimide (1.5 equiv), in order to maximize the yield based on alcohol starting material. However, as any unreacted carbodiimide will react with carboxylic acid, which is to be added next, unreacted carbodiimide needs to be removed by a capping procedure (Scheme 7). The capping was easily achieved by adding excess water to the resulting PS-isourea/PS-carbodiimide mixture, resulting in the conversion of the carbodiimide to the inert urea **44**. It was found that 45 min was sufficient to cap all

(22) (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236. (b) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth.* **1996**, *73*, 110–113.

SCHEME 7. Capping Procedure to Remove Excess PS-Carbodiimide

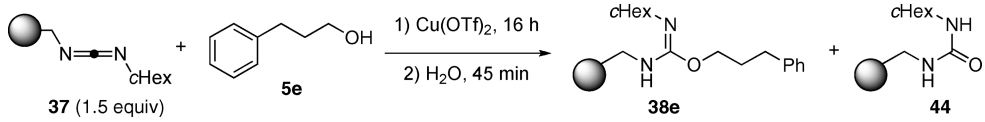
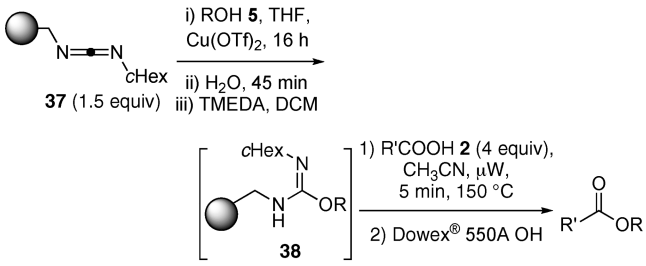
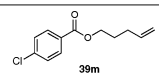
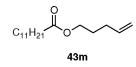
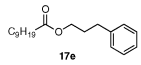
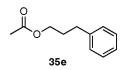
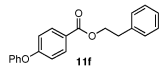
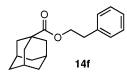
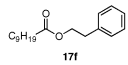
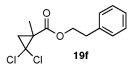
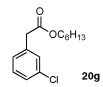
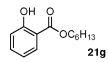


TABLE 8. Microwave-Assisted Catch and Release Synthesis of Esters



Entry	5	R'COOR	Yield (%)[a,b]
1	 5m	 39m	40
2	**5m**	 43m	70
3	**5e**	 17e	40
4	**5e**	 35e	90[c]
5	 5f	 11f	23
6	**5f**	 14f	40
7	**5f**	 17f	30
8	**5f**	 19f	30
9	$C_6H_{13}OH$ **5g**	 20g	80
10	**5g**	 21g	72

[a] Isolated yield. [b] Purity is ≥98% in all cases (determined by ELSD). [c] Purity >95% (determined by ^{1}H NMR).

positions as judged by IR analysis. The isourea did not hydrolyze under these conditions.

The "catch and release" process was investigated by reacting resin **37** with a limiting amount of alcohol (Table 8), followed by a capping and TMEDA-washing operation as described above. The immobilized isourea **38** was then reacted with an excess (4 equiv) of carboxylic acid. This second step resulted in the release of the ester product into solution, with any excess unreacted carboxylic acid easily removed using a basic ion exchange resin (DOWEX 550A OH). This process resulted in the isolation of the ester product in variable yield but in excellent purity, without recourse to any chromatography, which demonstrates the usefulness of this method for library synthesis.

Conclusions

We have demonstrated that rapid preparation of esters was possible using equimolar amounts of and *O*-alkylisoureas and carboxylic acid under microwave dielectric heating with no additional reagent or catalyst necessary to obtain good to excellent yields The method has also been applied successfully using in situ formed *O*-alkylisourea from primary alcohols and can be applied as a valid alternative to the Mitsunobu reaction. High yields were obtained using 2-octanol and 4-phenyl-2-butanol but also using a highly hindered alcohol such as L-(−)-menthol. The use of polymer supported *O*-alkylisourea for esterification of primary alcohols was also examined. Excellent yields and purities were obtained with preformed isoureas derived from primary alcohols without the need for chromatographic purification. A "catch and release" ester formation yielded very pure ester products in moderate yield. Unfortunately, ester formation with secondary alcohols mediated by immobilized carbodiimide proved not to work well due to excessive elimination side reactions. With the limitations of the method in mind, we have demonstrated that the microwave-accelerated isourea-mediated ester formation is a very useful method for many applications.

Experimental Section

General Procedure for the Esterifications Using *O*-Alkylisoureas 1a−d (Table 1). A microwave vial was charged with the carboxylic acid (2.0 mmol) and *O*-alkylisourea **1a−d** (2.1 mmol) followed by addition of CH_3CN or THF (4 mL). The vial was capped and heated at the reported temperature and time in a focused microwave oven. When isourea **1d** was employed, 4.5 mmol of isourea was used, and residual pressure was present in the vial after cooling. Hence it is recommended to release the gas present in the vial using a needle before decapping. The 1,3-diisopropylurea was removed by filtration, and the solvent was evaporated under vacuum. The residue was then further purified by column chromatography.

General Procedure for One-Pot Synthesis of Esters from Primary Alcohols (Table 2). The alcohol **5** (2.0 mmol) was added to a mixture of copper(II) triflate (14 mg, 0.04 mmol) in *N*,*N*′-diisopropylcarbodiimide **6** (2.0 mmol) in a microwave vial. The vial was capped, and the green mixture was heated at 100 °C for 5 min using a focused microwave oven. A solution of carboxylic acid (1.9 mmol) in CH_3CN (2 mL) was added to the oil, and subsequently the vial was capped and heated at 120 °C for 5 min using a focused microwave oven. The 1,3-diisopropylurea was filtered off, the solvent was evaporated, and the residue was purified by chromatography using SPE cartridges (20 mL) packed with silica and alumina.

General Procedure for the Synthesis of *O*-Alkyldiisopropylisoureas (Primary Alcohols). The respective alcohol (10.0 mmol) was added with stirring to a mixture of copper(II) triflate (0.20 mmol) in *N*,*N*′-diisopropylcarbodiimide **6** (10.0 mmol) in a microwave vial. The green mixture was heated under stirring at 100 °C for 5 min using a focused microwave oven. Hexane (10 mL) was added, and the solution was applied to a filter pad of a

neutral alumina. The product was eluted with a total volume of 50 mL of hexane; the solvent was evaporated under reduced pressure.

General Procedure for the Synthesis of *O*-Alkyldiisopropylisoureas (Secondary Alcohols). The respective alcohol (5.0 mmol) was added with stirring to a mixture of copper(II) triflate (0.14 mmol) in *N*,*N*′-diisopropylcarbodiimide **6** (5.0 mmol). The green mixture was stirred overnight at rt to ensure complete reaction. Hexane (5 mL) was added, and the solution was applied to a filter pad of a neutral alumina. The product was eluted with a total volume of 100 mL of hexane, at which time the IR spectrum indicates that all the isourea was removed from the alumina. The solvent was evaporated under reduced pressure.

General Procedure for Microwave-Assisted Synthesis of Carboxylic Esters with *O*-Alkylisoureas 1j,k Derived from Secondary Alcohols (Tables 3 and 4). A microwave vial was charged with the *O*-alkylisourea (0.50 mmol), the acid (0.47 mmol), and 1 mL of CH_3CN. The vial was capped, and the mixture was heated at 130 °C for 5 min using a focused microwave oven. The 1,3-diisopropylurea was filtered off, the solvent was evaporated, and the residue was purified by chromatography using SPE cartridges (20 mL) packed with silica and alumina.

General Procedure for the Synthesis of Neomenthyl Esters (Tables 5 and 6). A microwave vial was charged with isourea **1l** (0.50 mmol) and the acid (0.47 mmol) in 1 mL of toluene. The vial was capped, and the mixture was heated at 150 °C for 10 min using a focused microwave oven. The 1,3-diisopropylurea was filtered off, the solvent was evaporated, and the residue was purified by chromatography.

General Procedure for One-Pot Synthesis of Neomenthyl Esters (Scheme 5). L-(−)-Menthol **5l** (2.0 mmol) was added to a mixture of copper(II) triflate (14 mg, 0.04 mmol) in *N*,*N*′-diisopropylcarbodiimide **6** (2.0 mmol) in a microwave vial. The vial was capped, and the green mixture was heated at 100 °C for 5 min using a focused microwave oven. A solution of carboxylic acid (1.9 mmol) in toluene (2 mL) was added to the oil, and subsequently the vial was capped and heated at 150 for 10 min °C using a focused microwave oven. The 1,3-diisopropylurea was filtered off, the solvent was evaporated, and the residue was purified by chromatography using SPE cartridges (20 mL) packed with silica and alumina.

General Procedure for Synthesis of PS-*O*-Alkylisourea 38f,m (Scheme 6). *N*-Cyclohexyl-*N*′-methylpolystyrenecarbodiimide **37** (0.33 g, 0.7 mmol), alcohol (0.84 mmol), and copper(II) triflate (0.066 g, 0.182 mmol) were placed in a dry round-bottom flask. Anhydrous THF (5 mL) was added, and the mixture was stirred overnight. The resin was filtered and washed with a 10% (v/v) solution of TMEDA in DCM until the washing solution remained uncolored and then with DMF (3 × 20 mL), MeOH (3 × 20 mL), and DCM (5 × 20 mL). Resins **38f,m** were dried overnight under vacuum at 40 °C for 24 h.

General Procedure for Esterification Using PS-*O*-Alkylisourea 38f,m (Table 7). The acid (0.45 mmol) was dissolved in CH_3CN (2 mL), and the resulting solution was added to the resins **38f,m** (0.18 g, 0.30 mmol) in a microwave vial. The vial was capped and heated at 150 °C for 5 min using a focused microwave oven, and after cooling DOWEX 550A OH (0.750 g) was added. After shaking for 1 h, the resin was filtered and washed with DCM (3 × 5 mL). The combined filtrates were evaporated to afford the desired carboxylic esters. No purification was performed before NMR analysis.

General Procedure for Microwave-Assisted "Catch and Release" Synthesis of Esters (Table 8). *N*-Cyclohexyl-*N*′-methylpolystyrenecarbodiimide **37** (0.200 g, 0.38 mmol), alcohol (0.25 mmol), copper(II) triflate (0.010 g, 0.10 mmol) and, anhydrous THF (2 mL) were placed in a dry round-bottom flask. After the mixture was shaken overnight, water (110 μL, 6.0 mmol) was added, and shaking was continued for 45 min. The resin was filtered and washed with a 10% (v/v) solution of TMEDA in DCM until the washing solution remained uncolored and then with DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL). The resin was placed in a vial and swollen in CH_3CN (2 mL), and acid (1.00 mmol) was added. The resulting suspension was heated at 150 °C for 5 min using a focused microwave oven, and after cooling DOWEX 550A OH (0.750 g) was added. After shaking for 1 h, the resin was filtered and washed with DCM (3 × 5 mL). The combined filtrates were evaporated to afford the desired carboxylic esters. No purification was performed before NMR analysis.

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Supporting Information Available: Characterization data for product esters and isoureas **1j**, **1k**, **1l**, **38f**, and **38m**; synthesis of **16**, (*R*)-**22j** (Mitsunobu conditions); determination of the enantiopurities (chiral HPLC); copies of ^1H and ^{13}C NMR spectra of all esters. This material is available free of charge via the Internet at http://pubs.acs.org.

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