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Synthesis of Arrays Using Low Molecular Weight MPEG-Assisted Mitsunobu Reaction

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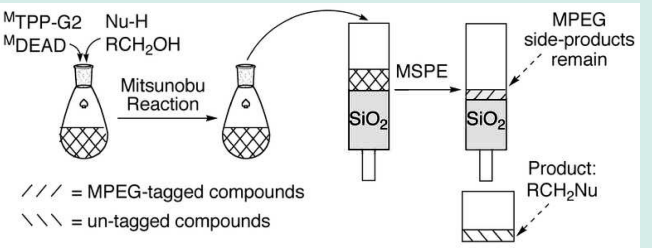
Supporting Information

ABSTRACT: Triphenylphosphine tagged with a short poly(ethyleneglycol)-ω-monomethyl ether chain (light MPEG, 10−16 ethylenoxy units, ^{M}TPP-G2) and an MPEG-tagged version of diethyl azodicarboxylate (^{M}DEAD) have been used to prepare a 20 member library of esters, ethers, and sulfonamides, with cLogP's in the range of 1.4−5.7 on a 0.1 mmol scale. Removal of MPEG-tagged side products was achieved by MPEG-assisted solid-phase extraction (MSPE) on prepacked silica columns to give the products in good yield and high purity.



KEYWORDS: triphenylphosphine, Mitsunobu reaction, cLogP, solid-phase extraction

INTRODUCTION

The Mitsunobu reaction is one of the most common ways of making a carbon-heteroatom bond in synthetic organic chemistry and is widely used in drug discovery.[1] Generally, a combination of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) is used to convert an alcohol **1** and a weak acid **2** into a substitution product **3**, triphenylphosphine oxide (TPPO) and dicarboethoxyhydrazine (DCEH, Scheme 1). The mechanism involves TPP and DEAD combining to give the betaine intermediate **4** (Scheme 2). Reaction between betaine **4**, the weak acid **2** and the alcohol **1** generates DCEH and the alkoxyphosphonium salt **5**. The nucleophilic anion of this salt then displaces the TPPO leaving group by a concerted mechanism to give the substitution product **3**. A range of phosphines and azodicarboxylates can be used, and tributylphosphine and di-isopropylazodicarboxylate (DIAD) are common alternatives to TPP and DEAD. The weak acid employed generally has a pK_a between 2 and 11, though there are examples of even weaker acids being successful, and can have O, N, S or C as the nucleophilic atom. The range of nucleophilies, the mild, near neutral reaction conditions, and the stereochemical control makes the Mitsunobu reaction an attractive synthetic method. However, purification of products after Mitsunobu reactions can be problematic, the TPPO and DCEH produced by the reaction are often difficult to remove from the desired product by chromatography, and there are potentially traces of four starting materials in the crude mixture.

There have been many attempts to overcome the purification problems associated with TPP, TPPO, DEAD, and DCEH, and these have been reviewed comprehensively.[1] The most popular approach is to use a solid-supported phosphine or azodicarboxylate, which can be removed after reaction by simple filtration, in polymer-assisted solution-phase synthesis.[2] The most obvious problem is that two solid-supported reagents cannot be used together as they are required to react with each other to form an intermediate analogous to betaine **4** (Scheme 2). Of course, a solid-supported phosphine can be combined with an azadicarboxylate removed by another method to avoid chromatography,[3,4] or vice versa,[5] but this requires additional manipulation. The heterogeneous nature of reactions can also be an issue as intrinsic reactivity of the supported reagent[6,7] in a given solvent depends on the nature of the polymer, the size of its cavities, bead size/shape and loading, and there can be mixing problems and mechanical damage to resins. In a direct comparison between solid-supported TPP (2.1 mmol g^{-1}, 1% cross-linked diphenylphosphinopolystyrene) and TPP itself in the bromination of 2,4-dimethoxybenzyl alcohol using carbon tetrabromide, it was found that while the initial rate of reaction was similar, the overall conversion was lower for solid-supported TPP, presumably because not all the phosphine groups were accessible.[8] Variability in the behavior of different batches of the same solid-supported reagents has also been noted as a problem,[7] and this is a particular issue because the chemical purity of solid-supported reagents are not easily checked.

To overcome these difficulties, reagents that allow homogeneous reaction in solution and have properties that assist removal have been investigated.[1] Di-2-methoxyethyl azodicarboxylate has been introduced as a water-soluble reagent[9] and di-*tert*-butyl azodicarboxylate decomposes in aqueous acid into gaseous products.[10] Removal of the phosphine is more problematic: phosphines derived from pyridine or *N*,*N*-dimethylaniline can be washed away with aqueous acid after reaction,[11] but this process is less useful in drug discovery where many compounds contain a basic nitrogen atom. Alternatively, a precipitation tag can be

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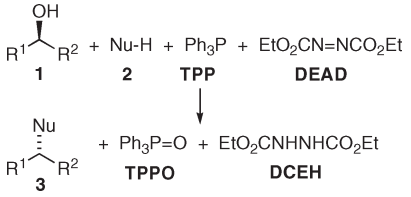
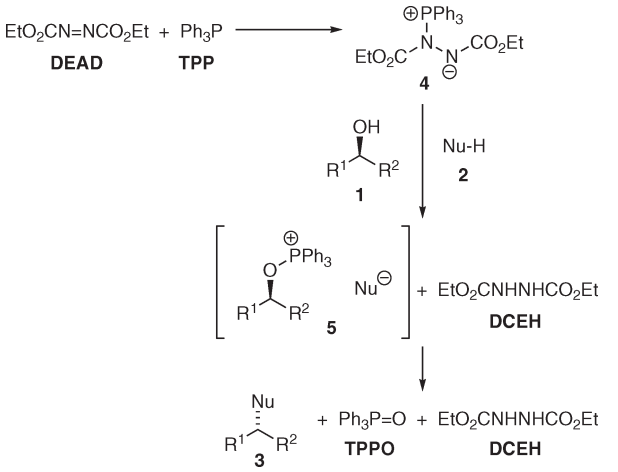
Scheme 1. Mitsunobu Reaction



Scheme 2. General Mechanism of Mitsunobu Reaction



used, so that the phosphine and phosphine oxide are precipitated upon switching to a nonpolar solvent such as diethyl ether, and are then removed by filtration.[12−15] However, coprecipitation of polar compounds can also occur. Very recently, Mitsunobu reactions in solution followed by a ring-opening metathesis reaction to scavenge the spent reagents onto a solid support has been reported.[16]

Fluorous technology, in which a perfluoroalkyl group acts as a "phase tag" assisting purification, is now very widely employed in solution-phase synthesis.[17,18] Fluorous DEAD and fluorous TPP have been used in the Mitsunobu reaction and these, together with the fluorous DCEH and TPPO arising from them, are conveniently removed by solid-phase extraction on fluorous silica gel (silica gel with a fluorocarbon bonded phase) eluting with methanol−water.[19] The use of two tagged reagents together and the simplicity of the purification procedure make this an attractive approach. The main problem is cost. Fluorous silica retails at about 15 times the price of ordinary silica,[20] and the fluorous tags themselves are also expensive.

Recently, we introduced light-MPEG-assisted organic synthesis (MPAOS) where reagents tagged with *low molecular weight* or "light" poly(ethyleneglycol)-ω-monomethyl ether (MPEG−OH, 8−19 ethylenoxy units, average MW 550) are used in homogeneous solution-phase reactions before being removed by solid-phase extraction on normal silica (MSPE) eluting with DCM or EtOAc to give pure products (Figure 1).[21] The MPEG-tagged reagents and biproducts remain attached to silica in the aprotic solvents, ethyl acetate and dichloromethane,[21,22] as MPEG has multiple hydrogen-bond acceptor sites that interact with multiple hydrogen-bond donors on the surface of the silica, but no hydrogen-bond donor sites to interact with aprotic solvents (Figure 2). In addition to the cost-saving of using normal silica, MPEG−OH is inexpensive even when purchased from a

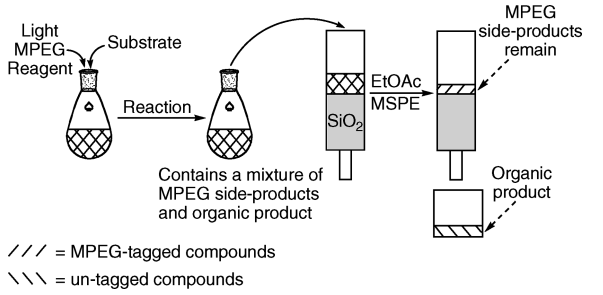


Figure 1

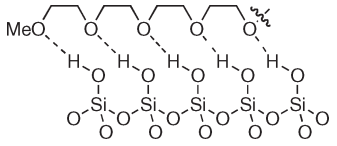


Figure 2. MPEG interactions with silica.

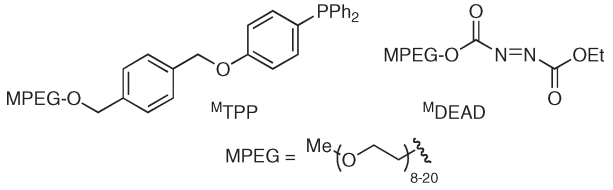


Figure 3. MPEG-tagged reagents for the Mitsunobu reaction.

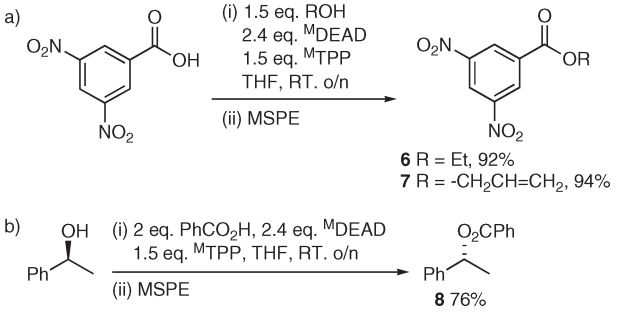
standard supplier of laboratory fine chemicals ($0.15 per mmol) and is prepared industrially from ethylene oxide on a very large scale for cosmetics and household uses (Carbowax). MPAOS does not rely on precipitation in nonpolar solvents with the danger of coprecipitation of polar compounds; indeed, the reagents are soluble in a wide range of solvents including nonpolar solvents like diethyl ether and *tert*-butyl methyl ether. Unlike batches of solid-supported reagents, the chemical purity of the MPEG-tagged compounds is easily checked by ^{1}H NMR spectroscopy using the methyl signal of the MPEG as an internal reference (δ 3.4), so potential failed arrays resulting from defective reagent are avoided.

Among the reagents we reported were MPEG-tagged TPP (^{M}TPP, Figure 3) and MPEG-tagged DEAD (^{M}DEAD, Figure 3) and we demonstrated that they could be used together in Mitsunobu reactions to give esters **6**-**8** in high yields and high purity following MSPE, and a wash with base in the case of ester **8** (Scheme 3).[21] MSPE was conducted using 10 g of silica for every 1 g of solvent-free unpurified material and eluting the product with EtOAc, leaving MPEG-tagged materials on the column. We now report the adaptation of this chemistry for the synthesis of arrays.

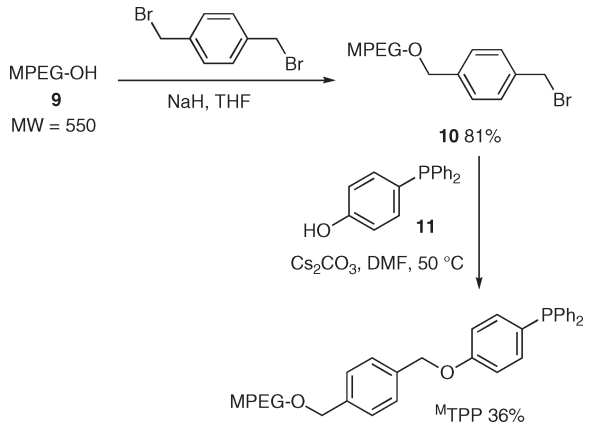
RESULTS AND DISCUSSION

The first stage in adapting the chemistry for array synthesis was to optimize the routes to the MPEG-tagged reagents for larger scale synthesis. Originally, ^{M}TPP had been prepared by reacting MPEG−OH **9** with excess α,α'-dibromo-*p*-xylene and then reacting the benzylic bromide **10** with the phenoxide derived from a phenolic analogue **11** of TPP, prepared by our adaptation[21] of the literature method[13] (Scheme 4). Thus, an extra xylyl unit was included, which effectively decreased the loading. We have now found

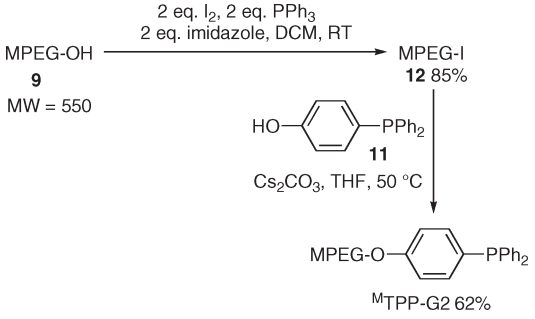
Scheme 3. MPEG-Assisted Mitsunobu Reaction



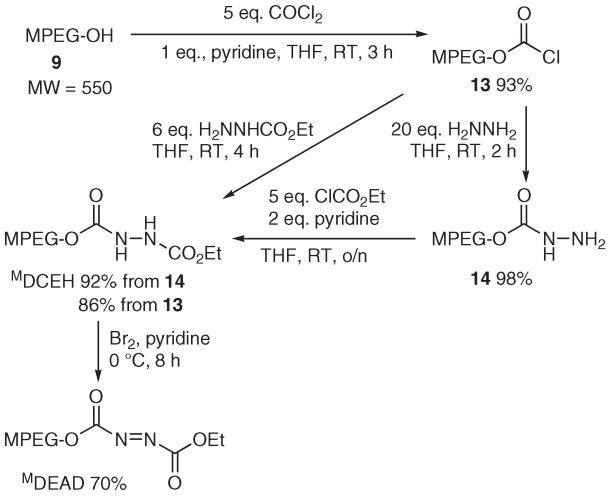
Scheme 4. Synthesis of ^{M}TPP



Scheme 5. Synthesis of ^{M}TPP-G2



Scheme 6. Synthesis of ^{M}DEAD



that a more scalable alternative is to make a compact second generation MPEG-tagged TPP (TPP-G2)[23] by converting MPEG−OH **9** into MPEG-I **12** and displacing the iodide (Scheme 5).

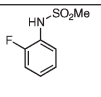
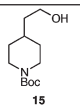
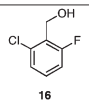
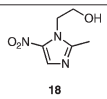
^{M}DEAD had originally been prepared by converting MPEG−OH **9** into the chloroformate **13**, and reacting the latter with a large excess of hydrazine to give amide **14** (Scheme 6).[21] Reaction with ethyl chloroformate then gave the ^{M}DCEH, which could be oxidized easily with bromine to give ^{M}DEAD itself. We have now optimized this route by converting chloroformate **13** directly into ^{M}DCEH with ethyl carbazate in good yield. The oxidation of ^{M}DCEH was also optimized and was found to be faster when an excess of pyridine and bromine were used.

The synthesis of arrays demands the standardization of reaction and purification conditions and of equipment, and the minimization of solvent. Although the best results for the Mitsunobu reactions are obtained when either the acid or alcohol is in excess and can easily be removed, e.g. a volatile alcohol or an acid that is removed by a wash with aqueous base, and such conditions are generally employed to illustrate new methods (see Scheme 3 above), we wished to use a more demanding test for our chemistry, bearing in mind that the two reacting components may be of equal value. Therefore, coupled products were obtained using a 1:1 ratio of reactants and without the inconvenience of an aqueous wash. Under these conditions, MSPE would remove the potential contaminants resulting from the reagents, but may leave contamination from starting alcohol or acid. We chose to synthesize 0.1 mmol of product and to use for purification commercially available prepacked columns of 5 g of silica with a 20 mL reservoir.

When arrays are prepared for drug discovery, the library members generally have clogP's in the range of 1−5,[24] i.e. there are relatively polar members in the library. This presented us with a significant problem, EtOAc was insufficiently polar to elute the more polar compounds in this range in a reasonable volume of solvent (less than the reservoir volume). We scanned a variety of solvent combinations and found that EtOAc-MeOH (95:5), DCM-MeOH (95:5) and DCM-acetone (5:1) were all sufficiently polar. However, all caused some elution of the lighter fractions of MPEG. We noted that different chain lengths formed discrete spots on silica TLC plates when DCM-acetone (5:1) was used as the eluent, while solvent systems containing protic solvents led to streaking on TLC on silica. Clearly, acetone is sufficiently polar to overcome the entropic effect and allow elution of MPEG even though it is incapable of hydrogen-bonding to the MPEG, but the difference in behavior on TLC is consistent with different effects from aprotic and protic solvents.

Chromatography of ^{M}TPP-G2 removed both the lighter chain lengths and the heavier chain lengths to give ^{M}TPP-G2 with a narrower range of ethylenoxy units (10−16 by ESI-MS) and a loading of 1.04 mmol g^{-1} (by microanalysis). Similarly, narrow-MW-range ^{M}DCEH was obtained by chromatography and converted into ^{M}DEAD bearing 9−16 ethylenoxy units (by ESI-MS) having a loading of 1.22 mmol g^{-1}. Using these MPEG reagents, MSPE was effective on the crude mixtures produced by overnight reaction between 0.1 mmol of acid, 0.1 mmol of alcohol, 1.5 equiv of narrow-MW-range TPP-G2 and 1.8 equiv of narrow-MW-range ^{M}DEAD in THF. Following solvent evaporation, MSPE of the crude using 15 mL of EtOAc-MeOH

Table 1. Array Using a 1:1 Ratio of Alcohols and Weak Acids

	Yields[a] of library members with purities[b] in parenthesis. The clogP[25] appears below each yield (clogPs after removal of Boc group in parenthesis)				
Acid/ Alcohol	 A	 B	 C	 D	 E
 15	98 (>95) 5.67 (3.73)	62 (>95) 5.04 (3.10)	99 (91) 4.98 (2.56)	86 (>95) 4.42 (0.55)	95 (92) 3.61 (1.68)
 16	98 (>95) 5.66	48 (>95) 4.97	96 (83) 4.91	68 (>95) 4.36 (2.43)	95 (87) 3.55
 17	93 (>95) 4.72	58 (87) 4.09	96 (83) 4.03	94 (>95) 3.47 (1.54)	87 (>95) 2.66
 18	50 (>95) 3.05	20 (92) 2.42	62 (43) 2.36	29 (57) 1.99 (0.06)	68 (86) 1.41

[a] Yields are calculated by isolated mass/MW of desired product. [b] Purities are mass ratios derived from the mole ratios of starting materials and product determined by ^{1}H NMR spectroscopy. There are no significant side products.

(95:5) gave products with complete removal of MPEGylated compounds. A small array of compounds (Table 1) was produced in this way using alcohols **15**−**18** and weakly acidic compounds **A**−**E**. The library members had clogP's[25] in the range 1−6 and are arranged in Table 1 so that the least polar is top left and the most polar bottom right. There is a weak inverse relationship between polarity and yield, but all coupling partners gave product. The effectiveness of MSPE is well illustrated by the spectra of compound **17A** before and after MSPE (Figure 4).

Our objective was to provide a methodology that would enhance the toolkit of procedures available to medicinal chemists.[26] This drove the selection of substrates including the incorporation of fluoroaromatics (fluorine is an important bioisostere of hydrogen for blocking metabolism[27]). The procedure was successful for carboxylic acids (**A** and **D**), phenols (**B** and **C**) and the sulfonamide **E**. The weak acids **A**, **C** and **D** are bifunctional, containing a potential site for palladium-catalyzed cross coupling and amination reactions,[28] a masked carboxylic acid, and a masked amine, respectively. Primary alcohols **15**-**18** were chosen to reflect a range of types of substrate: a masked amine, a hindered benzylic alcohol, a heterocyclic alcohol with potential for elimination, and a polar heterocyclic alcohol with a Lewis basic nitrogen atom, respectively. Although derivatives of alcohol **15** bearing a Boc protected amine are relatively nonpolar, the polarity of deprotected derivatives would be considerably lower (see clogP values in parentheses, Table 1), and the same is true of derivatives of acid **D**. Finally, the polar heterocyclic alcohol **18** was selected to demonstrate the utility of the method for the preparation of highly functionalized molecules with "drug-like" molecular properties.

In summary, we have demonstrated that light-MPEG-tagged reagents are useful and inexpensive tools for the synthesis of arrays by the Mitsunobu reaction.

EXPERIMENTAL PROCEDURES

General Comments on Synthesis and Characterization of MPEG Reagents[21]. Each MPEG-tagged compound is actually comprised of functionally identical compounds with different MPEG chain lengths. Thus, for each tagged compound the molecular ions appear as a series of peaks in the pneumatically assisted ESI-MS corresponding to $M + K^+$, $M + Na^+$, or $M + H^+$ with a difference of 44 amu between adjacent peaks in each series. The distribution of chain lengths was identified from such a series in each case and when reporting the ESI-MS, the 100% peak corresponds to the most intense peak in a series and all other intensities are reported relative to it. For each tagged compound, the HRMS was determined for the compound with twelve ethylene glycol units ($n = 12$). The average MW of the starting MPEG−OH **9** (i.e., 550) was used to calculate notional yields of the MPEG-tagged compounds, assuming no change in the distribution of chain lengths. The loadings of ^{M}TPP-G2 and ^{M}DEAD were determined by microanalysis from percentage phosphorus or nitrogen, respectively. The purity of each MPEG-tagged compound was established by ^{1}H NMR spectroscopy comparing the integration of the methyl

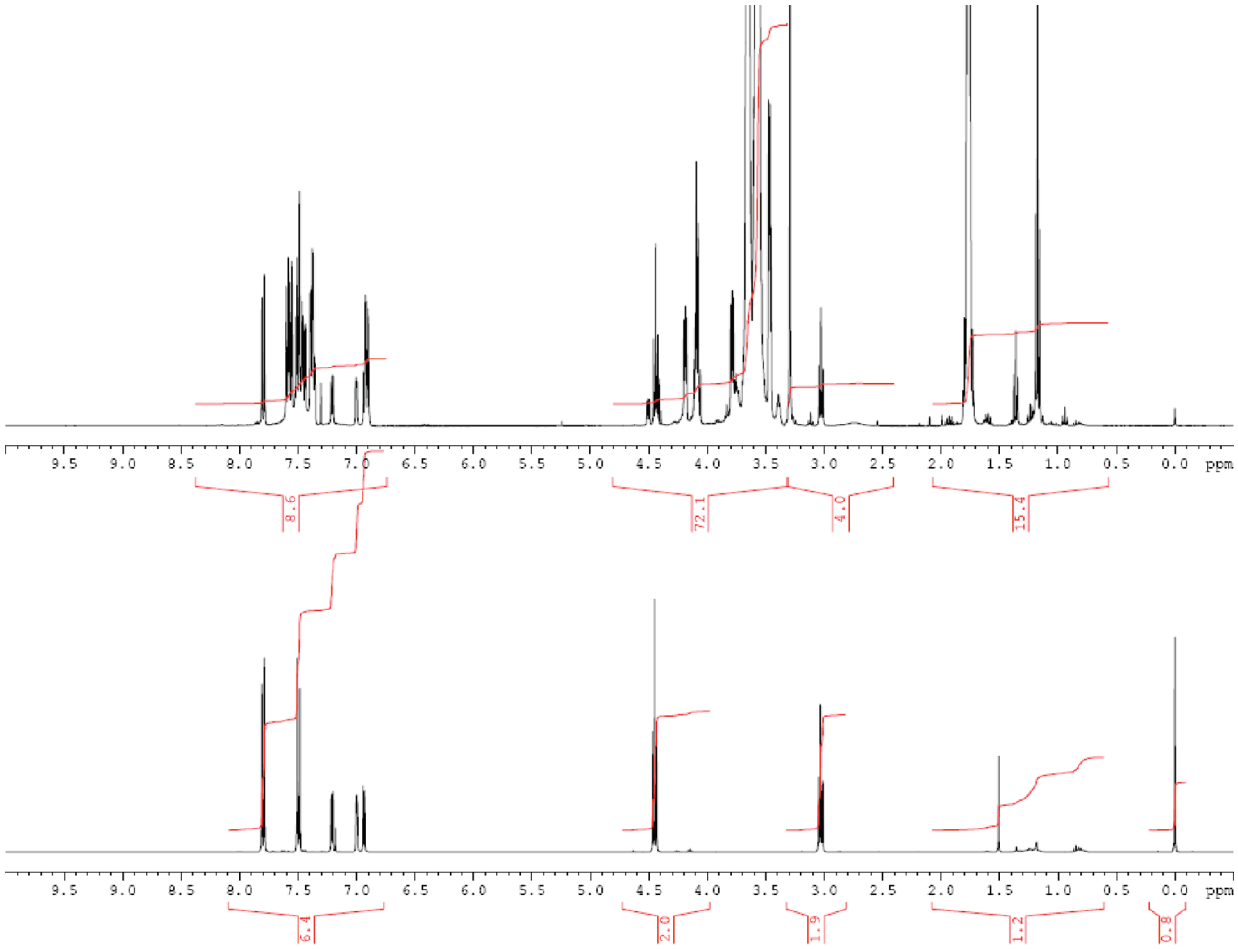


Figure 4. MSPE illustrated: ^{1}H NMR spectrum of ester **17A** before (top) and after MSPE (bottom).

group of the MPEG to signals for the tagged reagent, and from the absence of unexpected peaks in the ^{13}C NMR spectra.

General Procedure for the Preparation of Library Members. Narrow-MW-range MTPP-G2 (144 mg, 1.04 mmol g^{-1}, 0.15 mmol) in dry THF (0.25 mL) was added to a solution of an alcohol **15-18** (0.1 mmol) and an acid **A-E** (0.1 mmol) in dry THF (0.5 mL) followed by the ^{M}DEAD (151 mg, 1.19 mmol g^{-1}, 0.18 mmol) in dry THF (0.25 mL) under nitrogen. The mixture was stirred overnight (20 h). Solvent was evaporated and the residue dissolved in EtOAc-MeOH (95:5, 0.5 mL). The resulting solution was loaded onto a cartridge of silica [5 g, 20 mL reservoir volume, which had been prewashed with EtOAC (15 mL) prior to the use], washing onto the surface of the silica with a further 0.5 mL EtOAc-MeOH (95:5). The reservoir was filled and the product eluted by gravity under normal pressure. A total of 15 mL of eluent was collected from the cartridge (>16 mL should not be used as elution of MPEG-supported compounds may occur). Solvent was evaporated, the sample weighed and analyzed by ^{1}H NMR spectroscopy (data presented in Table 1). A pure sample was then obtained using an automated purification system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details for the preparation of MPEG-tagged compounds **12**, ^{M}DCEH, ^{M}DEAD and ^{M}TPP-G2 (including fractionation procedures), together with their characterization data and ^{1}H and ^{13}C NMR spectra, characterization data for all library members, together with their ^{13}C NMR spectra, and their ^{1}H NMR spectra after MSPE and when fully purified, and the ^{1}H NMR spectrum of a very impure sample of ester **17A**, prepared by employing the conditions used for the library generation but using DIAD and TPP instead of ^{M}DEAD and ^{M}TPP. This information is available free of charge via the Internet at http://pubs.acs.org/.

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