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Lipase-Catalyzed 1,6-Acylation of D-Mannitol

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The selective synthesis of 1,6-diacyl D-mannitols from 2,2,2-trifluoroethyl esters using transesterification, catalyzed by lipases, has been investigated, and the results have been compared with those obtained from a typical acid chloride procedure and a phenylboronic acid-assisted approach. Three commercially available lipases and five 2,2,2-trifluoroethyl esters were examined. In most cases, the yields obtained from the lipase reactions were superior to those produced from either of the other two methods.

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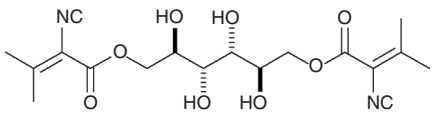
Introduction

1,6-Diacyl hexitols have several applications, including as components of industrial emulsifiers and non-ionic surfactants,[1] as precursors to chiral glycerides,[2] and as starting materials for chiral ligands for use in organometallic catalysis.[3] 1,6-Diacyl hexitols also have medicinal importance; the D-mannitol derivative and fungal metabolite A-32390A **1** (Scheme 1) has antimicrobial activity,[4] D-sorbityl salicylate is currently under investigation for the treatment of dermatological disorders,[5] and a naphthylpropanoate derived from D-mannitol has been used as intermediate in an enantioselective synthesis of (*S*)-(+)-Naproxen.[6] Our interest in the clean and facile synthesis of 1,6-diacyl mannitols relates to our investigation of their use in the formulation of organic-soluble borate esters as preventative agents for fungal and termite attack in wood.

The presence of six hydroxy groups in hexitols like D-mannitol makes selective acylation to give pure hexitol esters challenging. The lack of organic solubility of these polyols means that standard reactions that employ acylating agents dissolved in organic solvents often produce complex mixtures,[7] presumably because the low concentration of hexitols dissolved in the organic medium readily become over-acylated. The exception is the selective 1,6-aroylation of these compounds, which, although relatively low yielding, can be routinely achieved,[2,7,8] with triaroylation occurring to only a relatively low extent.[9] The steric hindrance around the secondary hydroxyls of the hexitols apparently limits further reactions with the less reactive aroylating agents, but does not prevent the formation of poly-alkanoates during alkanoylation.



A-32390A **1**

Scheme 1.

The contamination of poly-alkanoyl hexitols in industrial emulsifiers and surfactants is not generally seen as a major problem, except where they are used as food additives.[1] When the 1,6-dialkanoates are required for biological testing or as intermediates in pharmaceutical production, however, much higher purity and reaction selectivities are required. In our investigation of the detailed structure–activity relationships of wood preservatives derived from acylated mannitols, we also required high-purity 1,6-diacyl mannitol derivatives. To illustrate how such compounds have been previously prepared, it is instructive to examine the work of Schollkopf and coworkers. In their preparation of A-32390A **1** and its analogues, a multi-step approach was used to introduce esters at the 1- and 6-positions of D-mannitol, with a key step involving the displacement of mesylate groups from the dimesyl dibenzylidene **2** by a carboxylate salt **3** derived from *N*-formyldehydrovaline (Scheme 2).[10]

Koster and coworkers showed that selective protection of D-galactitol with triethylborane can lead to the production of 1,6-diesters in high yield.[11] We have recently investigated a similar strategy, in which phenylboronic acid (PBA) was used in the selective derivatization of D-mannitol (Scheme 3).[7] Using this approach, we found that pure D-mannitol diesters such as the 1,6-dioctanoate **7** can be prepared by a single-pot method in moderate yields without the need for chromatography or recrystallization. The simple

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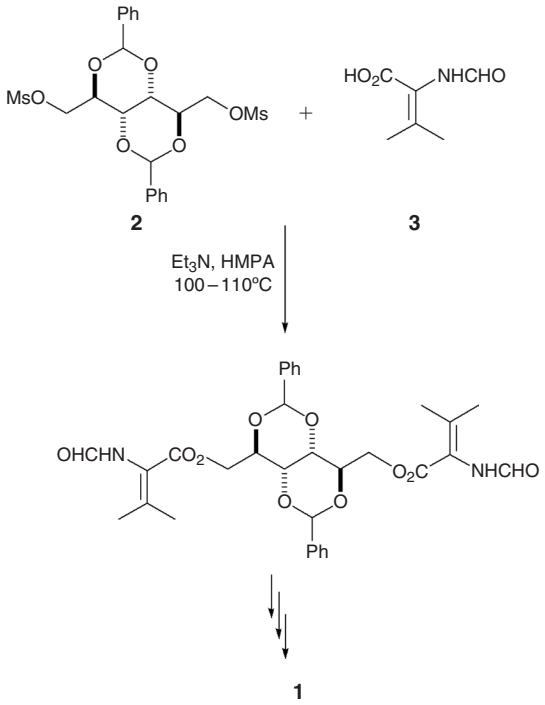
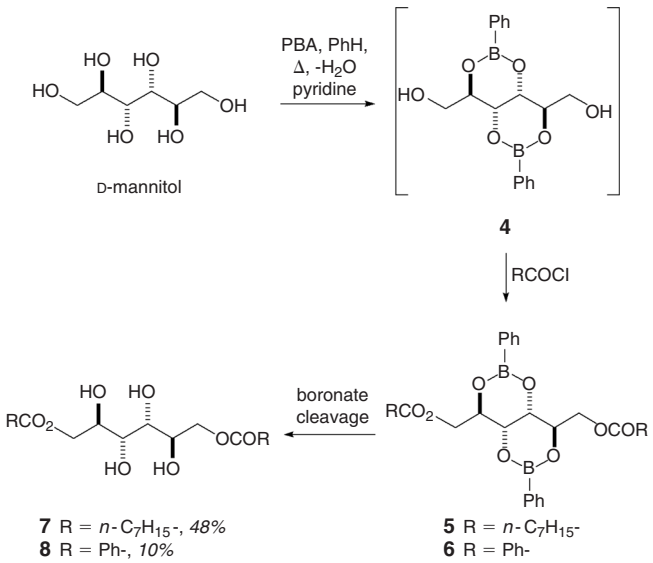
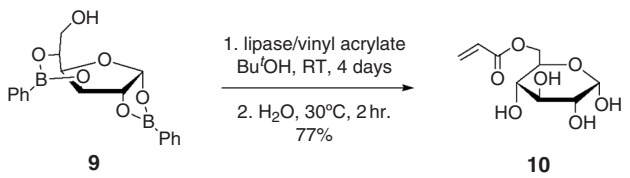
hydrolysis of the intermediate diboronate ester **5** with aqueous hydroxide allowed the recovery of the PBA. Lower yields of the 1,6-dibenzoate **8** were obtained with this method, and the intermediate diboronate **6**[12] was much more resistant to hydrolysis, so that oxidative conditions, which preclude the recycling of the boronic acid, were required to liberate **8**. Selective 1,6-dibenzylation[7] and disilylation[13] of D-mannitol has also been achieved in a similar way.



Scheme 2.



Scheme 3.



Scheme 4.

The use of enzymes in synthetic chemistry is now well established.[14] With the growing concern about the fate of chemicals in the laboratory and industry, the use of biological catalysts is an attractive alternative to traditional methods of synthesis. This is because enzymes usually catalyze specific reactions with particular functional groups without affecting other groups present in the substrate. They also act under mild conditions, can often be re-used, and are biodegradable. Lipases are particularly useful enzymes in this regard. Since many lipases are active in organic solvents, they can be used to catalyze esterification and transesterification reactions.[15] We describe here the results of a comparison of such lipase-catalyzed acylation reactions of D-mannitol with those obtained with a more traditional method, as well as our recently reported boronate-assisted approach.

Results and Discussion

The insolubility of polyols in organic media presents an apparent problem for their lipase-catalyzed acylation reactions. Ikeda and Klibanov, however, reported in 1993 that specific sugar and alditol acrylates could be produced in *t*-butanol in high yields from their more organic-soluble phenylboronate esters, by transesterification from vinyl acrylate in the presence of *Pseudomonas* sp. lipoprotein lipase.[16] Scheme 4 shows how 6-*O*-acryloyl-D-glucose **10** can be produced in this way from the diphenylboronate ester of glucose **9**. We thus initially set out to investigate similar reactions with the phenylboronate esters of D-mannitol (e.g. **4**). Unfortunately, all of the lipase-catalyzed reactions that we performed in the presence of PBA or its esters gave no acylated product. This might be because boronic acids have an inhibitory effect on lipases,[17] which could explain why Ikeda and Klibanov had to employ an enzyme-to-boronate ester mass ratio of approximately 3 : 1 in their lipase-promoted acylation reactions.

More recently, Otero and coworkers have shown that D-sorbitol can be quantitatively converted into the corresponding 1,6-diesters by treatment with fatty acids in dry acetone containing immobilized *Candida antartica* lipase B (Novozym 435).[1] Precipitation of the products at lower temperature was thought to prevent over-acylation and a two-stage temperature regime resulted in a reduction of the reaction times to three days. Maugard et al. have used the same enzyme to prepare mono- and di-salicyl esters of D-sorbitol in relatively low yields by transesterification with methyl salicylate in *tert*-amyl alcohol.[5] A serine protease from *Bacillus licheniformis* (Optimase M-440) has also been used to prepare amino acid–D-sorbitol conjugates in pyridine by transesterification from 2,2,2-trifluorethyl esters of *N*-protected amino acid.[18]

Activated esters, such as 2,2,2-trifluoroethyl esters, are often used as substrates for enzyme-catalyzed transesterification reactions[19] because the weakly electron-withdrawing

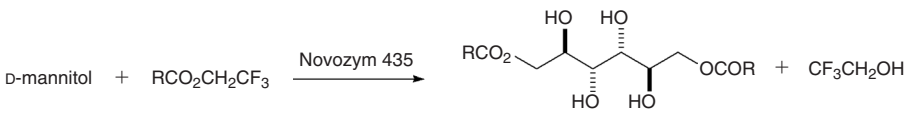
trifluoroethyl group activates the acyl group towards nucleophilic attack. The presence of the fluorines is also thought to shift the equilibrium of the reaction in favour of the product by destabilization of the starting ester relative to the alkyl ester product and reducing the nucleophilicity of the alcohol by-product. We thus set out to examine the acylation of D-mannitol by transesterification with a range of 2,2,2-trifluoroethyl esters, promoted by commercially available lipases. Five acyl sources, 2,2,2-trifluoroethyl octanoate **11**, isovalerate **12**, decanoate **13**, phenylacetate **14**, and benzoate **15**, were chosen. Three lipases, porcine pancreatic lipase, a lipase from *Pseudomonas*, and the immobilized *Candidia* enzyme Novozym 435, were considered.

In order to establish the appropriateness of the chosen enzymes for the planned transesterification reactions, a solution of 2,2,2-trifluoroethyl octanoate **11** and heptan-1-ol (4 : 1 molar ratio) in THF was stirred for 72 min at 30°C in the presence of each of the lipases. Gas chromatography was used to measure the extent of reaction. With Novozym 435 and the *Pseudomonas* enzyme, the reaction was found to go to completion, whereas with the porcine enzyme, only 25% of the heptanol was consumed. Given that Novozym 435 was more readily available than the *Pseudomonas* enzyme, all subsequent enzymatic reactions were performed with the immobilized enzyme (Novozym 435).

Next we performed experiments to determine the optimum solvent for the lipase-catalyzed acylation of D-mannitol. Dimethylformamide, *t*-butanol, pyridine, and THF were used in reactions that contained 2,2,2-trifluoroethyl octanoate **11** and Novozyme 435 (Scheme 5). As Table 1 shows, the best result was obtained with THF (entry 4), with a 38% yield of D-mannitol 1,6-dioctanoate **7** being produced, despite the marginal solubility of D-mannitol in that solvent. These reactions employed a simple workup procedure and **7** was the only product obtained from the reactions that used *t*-butanol, pyridine, and THF as the solvent (entries 2–4). Of all the solvents used, DMF solublizes D-mannitol the most effectively, but no acylated product was obtained from the reaction that used DMF (entry 1). This is consistent with the findings of Bergbreiter, Wong, and coworkers[20] who also found DMF to be a poor solvent for lipase-catalyzed reactions. Such reactions tend to work better in more non-polar solvents, with highly polar solvents thought to deactivate the enzyme.

Having established the best solvent and enzyme combination, we next set out to determine the generality of the reaction through variation of the acyl source. It was thus found that the only product from the transesterification reactions with **11**–**14** was the 1,6-acyl mannitol, with a low-to-moderate yield being obtained in these cases (Table 1, entries 4–7). The reaction with 2,2,2-trifluoroethyl benzoate produced no D-mannitol dibenzoate **8** (entry 8). The production of aryl esters through lipase-catalyzed transesterification reactions has previously been found to be low yielding,[21] so the latter result is not unexpected.

The results of the lipase-catalyzed acylation of D-mannitol were then compared with two alternative methods of preparing 1,6-diacyl mannitols, the conventional reaction using an acid chloride in hot pyridine, and our previously reported PBA-assisted method.[7] The results of these reactions are shown in Table 2. It had already been established[7] that the conventional acid chloride method for the acylation of D-mannitol is low yielding and the results shown in Table 2 support this assessment. With the exception of the preparation of the 1,6-dioctanoate **7**, the PBA-assisted reactions were



11 R = *n*-C_7H_{15}-
12 R = $(CH_3)_2CHCH_2$-
13 R = *n*-C_9H_{19}-
14 R = $PhCH_2$-
15 R = Ph-

7 R = *n*-C_7H_{15}-
16 R = $(CH_3)_2CHCH_2$-
17 R = *n*-C_9H_{19}-
18 R = $PhCH_2$-
8 R = Ph-

Scheme 5.

Table 1. Yields of D-mannitol esters from lipase-catalyzed reactions[A]

Entry	2,2,2-TFE ester	Solvent	Product	Yield [%][B]
1	Octanoate **11**	DMF	–	0
2	Octanoate **11**	Bu^{t}OH	1,6-Dioctanoate **7**	18
3	Octanoate **11**	Pyridine	1,6-Dioctanoate **7**	14
4	Octanoate **11**	THF	1,6-Dioctanoate **7**	38
5	Isovalerate **12**	THF	1,6-Diisovalerate **16**	11[C]
6	Decanoate **13**	THF	1,6-Didecanoate **17**	40
7	Phenylacetate **14**	THF	1,6-Diphenylacetate **18**	26
8	Benzoate **15**	THF	–	0

[A] Reaction mixtures were stirred at 50°C for 4 days. Lipase used was Novozym 435. Ratio of 2,2,2-TFE ester to D-mannitol was 4 : 1.
[B] Isolated yields based on D-mannitol.
[C] A 43% yield was obtained when ratio of 2,2,2-TFE ester to D-mannitol was 7.3 : 1.0.

Table 2. Yields of 1,6-D-mannitol esters from acid chloride/pyridine and PBA-assisted reactions

Entry	Product	Conventional method [%][A]	PBA method [%][A]
1	**7**	16[B]	48[B]
2	**17**	9	7
3	**18**	0	0
4	**8**	22[B]	10[B]

[A] Isolated yields based on D-mannitol.
[B] Results from reference 7.

also found to be low yielding. Thus, apart from the preparation of the 1,6-dibenzoate **8**, the lipase method reported here is superior to the two previously reported methods for the production of 1,6-diacyl mannitols, including the PBA-assisted method of preparing the dioctanoate **7**, which, although providing a higher yield of the acylated product (48% cf. 38% from the lipase method), suffers from the need to preform the di-PBA ester **4** and to recover the PBA after use.

Conclusions

We have found that lipases can be used to prepare pure 1,6-acylated D-mannitols by transesterification from a range of 2,2,2-trifluoroethyl alkanoates in organic solvents following a simple procedure. In line with previous findings,[21] this method was unsuccessful for the preparation of benzoate esters. In contrast to results described for the acylation of D-glucose,[16] however, the solubilization of D-mannitol in the organic solvent through the preformation of phenylboronate esters resulted in no acylated product; this suggests that inhibition of the enzyme-promoted transesterification reaction had occurred.

The maximum yields of the most successful lipase-catalyzed transesterification reactions were approximately 40%, which might reflect the position of the equilibrium between acylated mannitol and trifluoroethyl ester starting material. Otero and coworkers have previously shown that the removal of the by-product from similar lipase-catalyzed reactions of D-sorbitol, in that case water, through the use of molecular sieves, as well as the precipitation of the acylated product, resulted in quantitative conversion of D-sorbitol.[1] Similar approaches might improve the yield of the lipase-catalyzed reactions of D-mannitol. Despite the moderate yields of D-mannitol 1,6-alkanoates obtained here, though, the results obtained are still superior to those obtained from the traditional acid chloride/pyridine method and all but one PBA-assisted acylation reaction.

The wood preservation properties of borate esters derived from 1,6-diacyl mannitols will be described in a subsequent publication.

Experimental

General Methods

Distillations were performed in a Buchi GRK 50 Kugelrohr apparatus. Quoted boiling points are approximate. Melting points were recorded with a Stuart Scientific SMP3 melting point apparatus. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier-transform instrument. Samples were analyzed as thin films (neat) or Nujol mulls mounted on NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer, referenced to tetramethylsilane (δ 0.00) when $CDCl_3$ was used as the solvent and to the residual protonated solvent peak (δ 2.62) when $(CD_3)_2SO$ was the solvent. Low-resolution mass spectra of methanol solutions were recorded with a Micromass Platform II API QMS electrospray mass spectrometer operating in the positive-ion mode. The lipase from *Pseudomonas* and porcine pancreatic lipase were both obtained as lipophilized powders from Sigma Aldrich. Novozym 435 (*Candidia antarctica* lipase immobilized on Accyrek EP-100) was a gift from Novo Nordisk A/S, Denmark. Gas chromatography was performed on a Varian gas chromatograph 3700 using a 20% SE-30, DMCS Chromosorb-W, 80/100 column, with dimensions of 1.8 m by 6 mm (O.D.).

General Procedure for the Preparation of 2,2,2-Trifluoroethyl Esters

A solution of 2,2,2-trifluoroethanol (730 μL, 10 mmol) and pyridine (3.2 mL, 40 mmol) in dry diethyl ether (4 mL) was cooled to 0°C and the acid chloride (12 mmol) was added dropwise, resulting in a yellow suspension. The mixture was then allowed to warm to room temperature, stirred for 5 h, then quenched with ice water, extracted with diethyl ether, the ether extracts were washed with 1 M HCl and brine, and dried over $MgSO_4$. Filtration and removal of the solvent under vacuum gave a crude oil that was distilled to afford a colourless oil.

*2,2,2-Trifluoroethyl Octanoate **11***

Yield 0.46 g (38%), bp 130°C/10 mmHg (lit.[22] 84°C/18 mmHg). ν_{max}/cm^{-1} (neat) 978, 1115, 1170, 1283, 1378, 1412, 1458, 1762, 2859, 2959. δ_H ($CDCl_3$) 0.88 (3H, t, *J* 6.6, CH_2CH_3), 1.31 (8H, m, CH_2), 1.64 (2H, m, $COCH_2CH_2$), 2.43 (2H, d, *J* 7.5, $OCOCH_2$), 4.49 (2H, q, *J* 8.5, CF_3CH_2). δ_C ($CDCl_3$) 14.5, 23.0, 25.1, 29.3, 32.0, 34.1, 60.5 (q, *J* 37), 123.3 (q, *J* 277), 172.3.

*2,2,2-Trifluoroethyl 3-Methylbutanoate **12***

Yield 0.48 g (24.6%), bp 85–90°C. ν_{max}/cm^{-1} (neat) 982, 1051, 1188, 1276, 1391, 1410, 1489, 1748, 2876, 2966. δ_H ($CDCl_3$) 0.98 (6H, d, *J* 6.6, $CH(CH_3)_2$), 2.14 (1H, m, $CH(CH_3)_2$), 2.28 (2H, d, *J* 7.0, $OCOCH_2$), 4.45 (2H, q, *J* 8.5, CF_3CH_2).

*2,2,2-Trifluoroethyl Decanoate **13***

Yield 1.36 g (50%), bp 180°C/10 mmHg (lit.[22] 139°C/18 mmHg). ν_{max}/cm^{-1} (neat) 978, 1115, 1170, 1285, 1378, 1412, 1458, 1762, 2856, 2929. δ_H ($CDCl_3$) 0.88 (3H, t, *J* 6.6, CH_2CH_3), 1.31 (12H, m, CH_2), 1.66 (2H, m, $COCH_2CH_2$), 2.42 (2H, d, *J* 7.5, $OCOCH_2$), 4.49 (2H, q, *J* 8.5, CF_3CH_2). δ_C ($CDCl_3$) 14.4, 15.3, 23.0, 29.3, 29.5, 29.5, 32.1, 34.0, 61.3 (q, *J* 35), 124.5 (q, *J* 278), 172.6.

*2,2,2-Trifluoroethyl Phenylacetate **14***

Yield 1.06 g (49%), bp 130°C/10 mmHg (lit.[22] 98°C/18 mmHg). ν_{max}/cm^{-1} (neat) 1051, 1411, 1455, 1497, 1604, 1758, 2974, 3034, 3091. δ_H ($CDCl_3$) 3.74 (2H, s, $OCOCH_2Ph$), 4.53 (2H, q, *J* 8.5, CF_3CH_2), 7.40 (5H, m ArH). δ_C ($CDCl_3$) 40.9, 60.9 (q, *J* 37), 123.2 (q, *J* 276), 127.7, 128.9, 129.4, 133.1, 170.1.

*2,2,2-Trifluoroethyl Benzoate **15***

Yield 0.83 g (41%), bp 122°C/18 mmHg (lit.[22] 120°C/35 mmHg). ν_{max}/cm^{-1} (neat) 1051, 1411, 1455, 1497, 1604, 1758, 2974, 3034, 3091. δ_H ($CDCl_3$) 4.53 (2H, q, *J* 8.5, CF_3CH_2), 7.40 (5H, m ArH). δ_C ($CDCl_3$) 60.8 (q, *J* 38), 123.2 (q, *J* 278), 129.2, 129.4, 129.9, 133, 170.1.

General Procedure for Lipase-Catalyzed Acylation of D-Mannitol

D-Mannitol (27 mg, 0.15 mmol), the 2,2,2-trifluoroethyl ester (0.60 mmol), and Novozym 435 (20 mg) were added to the solvent (2 mL) and the resulting reaction mixture was stirred for 4 days at 50°C. The enzyme was then removed by vacuum filtration and the solvent evaporated under vacuum. The residue was taken up in ethyl acetate, then washed with saturated $NaHCO_3$ (replaced with 1 M HCl in the

case of the pyridine reaction), water, and brine. The organic layer was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The solid that remained was triturated with hexane.

D-Mannitol 1,6-Dioctanoate ***7***

This was obtained as a fine white powder (25 mg, 38%), mp 135–137°C (lit.[23] 132–136°C). δ_H [$(CD_3)_2SO/D_2O$] 0.91 (6H, t, *J* 6.9, 2 CH_3), 1.28 (16H, br s, 2 $(CH_2)_4CH_3$), 1.58 (4H, m, 2 $CO_2CH_2CH_2$), 2.35 (4H, t, *J* 7.3, 2 $CO_2CH_2CH_2$), 3.42 (2H, d, *J* 8.9, 2 $CH_2CH(OH)CH(OH)$), 3.58 (2 H, ddd, *J* 2.4, 6.4, and 8.9, 2 $CH_2CH(OH)CH(OH)$), 3.89 (2 H, dd, *J* 6.0 and 11.9, 2 $OCH^aH^bCH(OH)$), 4.71 (2H, dd, *J* 2.1 and 11.4, 2 $OCH^aH^bCH(OH)$). Other spectroscopic properties were identical to those previously reported.[7]

D-Mannitol 1,6-Di(3-methyl)butanoate ***16***

This was obtained as a fine white powder (6 mg, 11%) [repeated with 1.5 mmol D-mannitol and 10.9 mmol **12** to give a yield of 223 mg (43%)], mp 149–151°C. ν_{max}/cm^{-1} (Nujol) 1093, 1302, 1716, 2923, 3372. δ_H [$(CD_3)_2SO/D_2O$] 0.95 (6H, d, *J* 6.9, 2 CH_3), 2.04 (2H, m, 2 CO_2CH_2CH), 2.23 (4H, d, *J* 7.3, 2 CO_2CH_2CH), 3.65 (2H, d, *J* 8.9, 2 $CH_2CH(OH)CH(OH)$), 4.02 (2H, ddd, *J* 2.4, 6.4, and 8.9, 2 $CH_2CH(OH)CH(OH)$), 4.37 (2H, dd, *J* 6.0 and 11.9, 2 $OCH^aH^bCH(OH)$), 4.85 (2H, dd, *J* 2.1 and 11.4, 2 $OCH^aH^bCH(OH)$). δ_C [$(CD_3)_2SO$] 23.2, 26.1, 43.7, 67.8, 69.2, 70.1, 172.5. *m/z* 373.2 $[M + Na]^+$.

D-Mannitol 1,6-Didecanoate ***17***

This was obtained as a fine white powder (28 mg, 40%), mp 102–106°C. ν_{max}/cm^{-1} (Nujol) 1078, 1172, 1292, 1747, 3327. δ_H [$(CD_3)_2SO$] 0.91 (6H, t, *J* 6.9, 2 CH_3), 1.28 (24H, br s, 2 $(CH_2)_6CH_3$), 1.50–1.52 (4H, m, 2 $CO_2CH_2CH_2$), 2.35 (4H, t, *J* 8.5, 2 $CO_2CH_2CH_2$), 3.55–3.65 (4H, m, 4 $CH_2CH(OH)CH(OH)$), 4.02 (2H, dd, *J* 2.0 and 11.4, 2 $OCH^aH^bCH(OH)$), 4.30 (2H, dd, *J* 2.0 and 9.0, 2 $OCH^aH^bCH(OH)$), 4.38 (2H, d, *J* 7.9, 2 $CH_2CH(OH)CH(OH)$), 4.85 (2H, d, *J* 6.1, 2 $CH(OH)CH(OH)$). δ_H [$(CD_3)_2SO/D_2O$] 0.82 (6H, t, *J* 6.9, 2 CH_3), 1.21 (24H, m, 2 $(CH_2)_6CH_3$), 1.48 (4H, m, 2 $CO_2CH_2CH_2$), 2.26 (4H, t, *J* 7, 2 $CO_2CH_2CH_2$), 3.92 (2H, dd, *J* 11.4, 7.0, $OCH^aH^bCH(OH)$), 4.22 (2H, br d, *J* 11.0, 2 $OCH^aH^bCH(OH)$); signals for $CH_2CH(OH)CH(OH)$ and $CH_2CH(OH)CH(OH)$ obscured by HOD/H_2O. δ_C [$(CD_3)_2SO$] 14.9, 22.9, 29.0, 29.1, 29.2, 29.3, 32.1, 34.4, 68.9, 69.8, 173.7. *m/z* 513.4 $[M + Na]^+$.

D-Mannitol 1,6-Di(phenyl)acetate ***18***

This was obtained as a fine white powder (16 mg, 26%), mp 151–153°C. ν_{max}/cm^{-1} (Nujol) 696.4, 723.6, 842, 980, 1052, 1169, 1282, 1604.1, 1759. δ_H [$(CD_3)_2SO/D_2O$] 3.71 (4H, s, 2 $PhCH_2CO_2$), 3.79 (2H, d, *J* 9.2, 2 $CH_2CH(OH)CH(OH)$), 4.07 (2H, m, 2 $CH_2CH(OH)CH(OH)$), 4.38 (2H, dd, *J* 1.4 and 11.0, 2 $OCH^aH^bCH(OH)$), 4.45 (2H, dd, *J* 6.0 and 11.0, 2 $OCH^aH^bCH(OH)$), 7.39 (4H, dd, *J* 1.5 and 8.5, 2 ArH), 7.48 (4H, m, 2 ArH), 7.62 (2H, m, 2 ArH). δ_C [$(CD_3)_2SO$] 41.9, 68.7, 71.08, 71.13, 127.7, 129.3, 130.4, 139.3, 172.0. *m/z* 441.2 $[M + Na]^+$.

General Procedure for the Conventional Acid Chloride Method

D-Mannitol (1.0 g, 5.5 mmol) was heated in pyridine (8 mL) under an inert atmosphere at 100°C for 15 min, after which time only about half of the D-mannitol was observed to dissolve. The acid chloride (11.0 mmol) was then added dropwise, with the reaction mixture becoming homogeneous once approximately half of the acid chloride had been added. The reaction mixture was then stirred and heated at reflux for 5 h, and then allowed to cool slowly to room temperature. The resulting reaction mixture was added to H_2SO_4 (10%, 50 mL) and further H_2SO_4 was added until a pH of 2 was attained. The reaction mixture was then left to stand overnight, resulting in the precipitation of a fine white solid. The precipitate was collected by vacuum filtration and then recrystallized from ethanol to yield a white powder. In this way, D-mannitol 1,6-didecanoate **17** (0.25 g, 9%) was obtained; the yield of D-mannitol 1,6-di(phenyl)acetate **18** obtained, however, was 0%.

Acylation of D-Mannitol Assisted by PBA

These reactions followed a previously reported procedure,[7] and employed D-mannitol (1.0 g, 5.5 mmol), PBA (1.33 g, 11.0 mmol), pyridine (40 mL), benzene (50 mL), and acid chloride (12 mmol). In this way, D-mannitol 1,6-didecanoate **17** (0.19 g, 7%) was obtained; the yield of D-mannitol 1,6-di(phenyl)acetate **18** obtained, however, was 0%.

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