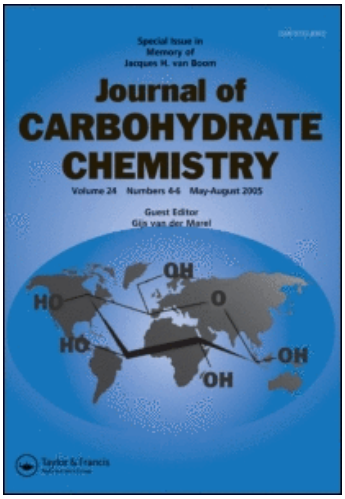

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COMMUNICATION

SELECTIVE MONOACYLATION OF ALDONOLACTONES BY LIPASE-CATALYZED TRANSESTERIFICATION

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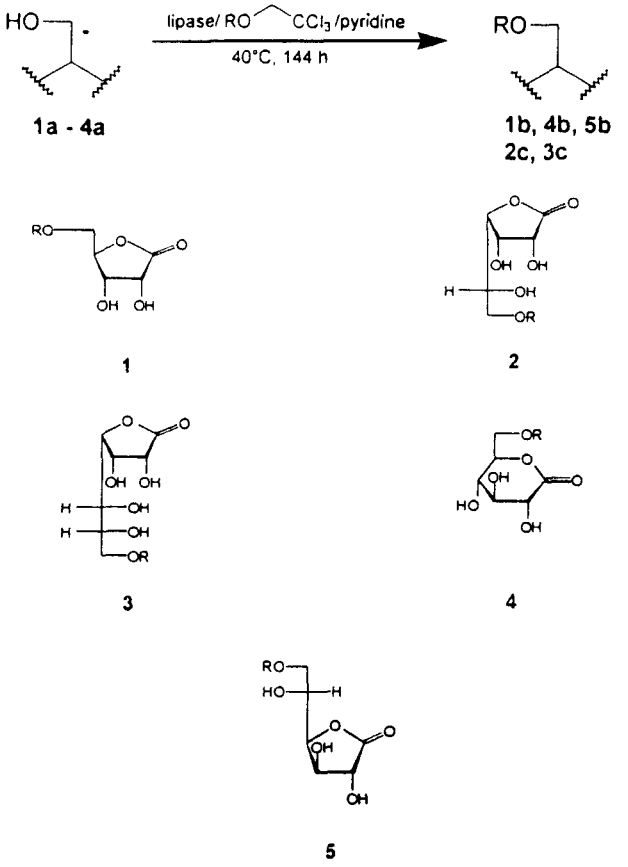
Facile esterification of carbohydrates can be accomplished using base catalyzed transesterification.[1] However, to achieve selective esterification this procedure is often inadequate, frequently leading to unwanted by-products.[2] The selective esterification of aldonolactones is further complicated by the tendency of some aldonolactones to form esters both by intermolecular self-condensation and by reaction with alcohol.[3] Consequently, as part of our study of carbohydrate based surfactants, we have investigated alternative approaches for the selective esterification of aldonolactones.

The selective esterification of pyranoses,[4] pyranosides,[5,6] furanosides,[7] and glucosides[8] at the primary hydroxyl has been accomplished by enzyme-catalyzed transesterification using various carboxylic esters. Here, we report the regiospecific esterification of the primary alcohol of several aldonolactones using 2,2,2-trichloroethyl alkanoates as the acyl donor.[6]



1 - 5	a	b	c
R	H	$-\overset{O}{\overset{\|}{C}}(CH_2)_{10}CH_3$	$-\overset{O}{\overset{\|}{C}}(CH_2)_8CH_3$

Scheme 1.

All the aldonolactones **1a-4a** were accepted as substrates by porcine pancreatic lipase (PPL) (Table 1). The enzyme displays a preference towards acylation of the primary alcohol for both δ- and γ-aldonolactones.

In the case of **4a**, however, GC-MS analysis of the reaction mixture identified the predominate product as the esterified 1,4-lactone, **5b**.[10] The production of **5b** proceeded via a 6-*O*-dodecanoylglucono-δ-lactone (**4b**) intermediate. The formation of **4b** was observed prior to the formation of **5b** during the course of the reaction (Figure 1).

Table 1. Porcine Pancreatic Lipase-Catalyzed Transesterification of Various Aldonolactones[9]

Substrate	Product	% Conversion of Aldonolactone	Actual Yield (% Yield)
1a	1b	85.0	0.90 g (40.4)
2a	2c	79.8	2.67 g (64.3)
3a	3c	81.9	2.47 g (54.5)
4a	5b 4b	82.4	1.98 g (44.1) 0.25 g (5.4)

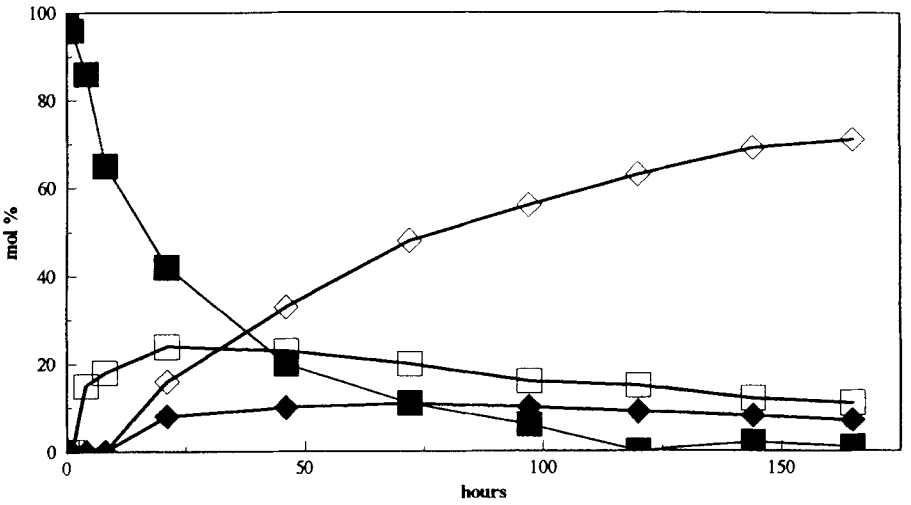


Figure 1. Time course for the lipase-catalyzed synthesis of 6-*O*-dodecanoylglucono-γ-lactone from glucono-δ-lactone and 2,2,2-trichloroethyl dodecanoate with porcine pancreatic lipase in pyridine. The reaction mixture was incubated at 40 °C for 165 h. A 100 μL aliquot of the reaction mixture was withdrawn for analysis by GC.[11] (■) **4a**, (□) **4b**, (◆) **5a**, (◊) **5b**.

Lipase from *Pseudomonas sp.* (Lipase PS and Lipase AK, Amano) also catalyzed the conversion of **4a** to **5b** via a **4b** intermediate albeit at a slower rate.[12] It is likely, however, that the conversion of **4b** to **5b** was not enzyme catalyzed since the rate of conversion of **4a** to **5a** was not enhanced in the presence of enzyme.[13]

Work-up from hexane yielded pure **5b**. However, conversion of **5b** to **4b** can occur during work-up from acetonitrile or 95% ethanol. The procedure reported here allows regiospecific acylation of aldonolactones without polymerization, however, rearrangement of hydrolytically sensitive lactones is still possible.

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9. Pyridine (Aldrich, anhydrous 99+%) containing aldonolactone (Aldrich) was stored over 3Å molecular sieve prior to use. Reactions were run in 50 mL of pyridine containing 12 g of PPL (Sigma, Type II), 12.5 mmoles of the aldonolactone and

2-fold molar excess of 2,2,2-trichloroethyl alkanoate. Reactions were run at 40 °C for 144 hours. Reactions were stopped by removing the enzyme by filtration. Solvent was removed by evaporation and product was precipitated from hexane. Purity of the product was established by GC using the conditions described in Note 11. The position of the acylation was determined for compounds by ^{13}C NMR in DMSO-d_6 using a Varian XL-300 spectrometer (75.4 MHz). The chemical shifts for the aldonolactone and the relevant chemical shifts for the alkyl chain are reported. The position of acylation was also confirmed by GC-MS using the conditions described in Note 10. High resolution mass spectrometry data for underivatized materials were obtained on a Finnigan-MAT 8230 mass spectrometer using positive ion direct chemical ionization (DCI). Isobutane was used as the reagent gas and protonated molecules of poly(ethylene glycol) oligomers were employed as exact mass standards for peak matching. Potonated molecules $(M+H)^+$ were found as the base peak for all samples.

1b : ^{13}C NMR (DMSO-d_6) C1, C2, C3, C4, C5 (δ 175.48, 68.70, 68.19, 81.84, 62.77). For the alkyl chain C2 and the carbonyl carbon C1 (δ 33.21, 172.35). MS (70eV EI) *m/z*: 474 (4.9), 459 (14.2), 327 (14.4), 231 (23.9), 246 (42.6), 204 (37.4), 147.2 (87.2), 129 (22.40), 73 (100.0). HRMS (CI, i-C_4H_{10}) calcd for $(M+H)^+$ $C_{17}H_{31}O_6$, 331.2121, found 331.2120.

2c : ^{13}C NMR (DMSO-d_6) C1, C2, C3 C4, C5, C6 (δ 175.75, 70.64, 69.18, 80.28, 67.24. 64.40). For the alkyl chain C2 and the carbonyl carbon C1 (δ 33.40, 172.77). MS (70eV EI) *m/z*: 548 (10.0), 533 (9.3), 243 (44.2), 287 (39.5), 204 (49.3), 155 (35.8), 129 (100.0), 73 (73.0). HRMS (CI, i-C_4H_{10}) calcd for $(M+H)^+$ $C_{16}H_{29}O_7$, 333.1913, found 333.1913.

3c : ^{13}C NMR (DMSO-d_6) C1, C2, C3, C4, C5, C6, C7 (δ 175.82, 70.84, 70.47, 79.13, 70.34, 68.23, 65.06). For the alkyl chain C2 and the carbonyl carbon C1 (δ 33.46, 172.86). MS (70eV EI) *m/z*: 650 (1.0), 517 (6.1), 317 (10.8), 287 (64.2), 217 (100.0), 155 (26.0), 143 (28.6), 147 (31.8), 73 (66.6). HRMS (CI, i-C_4H_{10}) calcd for $(M+H)^+$ $C_{17}H_{31}O_8$, 363.2019, found 363.2020.

4b : ^{13}C NMR (DMSO-d_6) C1, C2, C3, C4, C5, C6 (δ 175.32, 73.00, 72.48, 79.87, 66.38, 65.54). For the alkyl chain C2 and the carbonyl carbon C1 (δ 33.45 172.86). MS (70eV EI) *m/z*: 576 (6.9), 561 (13.6), 345 (23.8), 204 (29.0), 220 (45.9), 157 (61.0), 129 (26.6), 73 (100.0). HRMS (CI, i-C_4H_{10}) calcd for $(M+H)^+$ $C_{18}H_{33}O_7$, 361.2226, found 361.2226.

5b : ^{13}C NMR (DMSO-d_6) C1, C2, C3, C4, C5, C6 (δ 171.03, 71.74, 74.02, 68.35, 77.56, 62.80). For the alkyl chain C2 and the carbonyl carbon C1 (δ 33.28, 172.54). MS (70eV EI) *m/z*: 576 (38.8), 561 (26.2), 315 (100), 204 (46.5), 183 (27.6), 129 (28.4), 73 (84.0). HRMS (CI, i-C_4H_{10}) calcd for $(M+H)^+$ $C_{18}H_{33}O_7$, 361.2226, found 361.2226.

10. Lactone esters were analyzed as trimethylsilyl (TMS) ethers. A 5-10 mg sample was dissolved in 1.0 mL SilPrep (Alltech, Inc., Deer Park, IL) and allowed to react

at room temperature for a minimum of 30 minutes. A 1.0 μL aliquot was analyzed by gas chromatography-mass spectrometry (GC-MS), using a Finnigan TSQ-70 or SSQ-710 mass spectrometer equipped with a Hewlett-Packard 5890 Series II gas chromatograph and Finnigan A200S autosampler. GC analysis employed a DB-5 capillary column (30 m x 0.25 mm x 0.25 μm, J&W Scientific, Folsom, CA); split ratio was 50:1; column pressure was 12.0 psi; injector temperature, 250 °C; oven temperature, 70 °C for 2 minutes, ramped at 15 °C/minute to 300 °C; transfer line temperature, 275 °C. The mass spectrometer was scanned from 20-800 Dalton at 0.8 sec/scan. Electron ionization was employed at 70eV. Source temperature was 150 °C; collision dynode potential, -5 kV. The 6-*O*-dodecanoylglucono-γ-lactone showed a characteristic ion at *m/z* 315, the base peak of the spectrum.

11. Reactions were monitored by gas chromatography using a Hewlett Packard 5890 Series II gas chromatograph (Hewlett Packard, Palo Alto, CA) equipped with a HP1 capillary column (25 m x 0.2 mm x 0.33 μm, Hewlett Packard, Palo Alto, CA), a split injector (split ratio 167:1), and a flame ionization detector. Helium was used as the carrier gas, and the detector and injection port were set at 250 °C. Oven temperature was set at 140 °C for 2 minutes, then ramped at 8 °C/min to 250 °C and then held at 250 °C for 10 minutes. Reaction samples were dissolved in 1 mL of SilPrep (Alltech, Inc., Deer Park, IL) and allowed to react at room temperature for a minimum of 30 minutes before analysis. The retention times for **1b**, **2c**, **3c**, **4b** and **5b** were 22.2, 23.6, 31.8, 29.6 and 28.5 minutes respectively.

12. Under the same conditions as described in Note 9, a 61.9% conversion of glucono-δ-lactone was achieved in 166 h. using Lipase PS while a 40.2 % conversion of glucono-δ-lactone was achieved in 166 h. using Lipase AK.

13. The rate of isomerization of glucono-δ-lactone to glucono-γ-lactone was measured in 25 mL of pyridine containing 6.25 mM glucono-δ-lactone, and either 6.0 g of Lipase AK (which contained 3.43% H_2O by weight) or 0.71% H_2O. Isomerization was monitored by GC using the conditions described in Note 11. No difference in the rate of isomerization was found over the course of 100 hours.