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Chromium-Mediated Stereoselective Synthesis of Carbohydrate-Derived (*E*)-α,β-Unsaturated Esters or Amides

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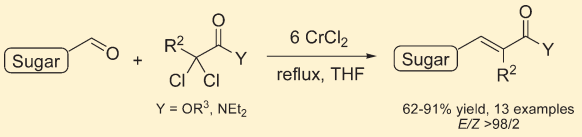
Supporting Information

ABSTRACT: A chromium-mediated novel synthesis of carbohydrate-derived di- and trisubstituted (*E*)-α,β-unsaturated esters or amides from a range of dichloroesters or amides and a variety of sugar aldehydes is reported. The process took place with total stereoselectivity and in high yields. A mechanism based on a sequential chromium-promoted aldol-type reaction and a completely stereoselective β-elimination reaction is proposed to explain these results.



Carbohydrate-derived α,β-unsaturated esters are intermediates of great synthetic utility and have been used in the synthesis of C2-symmetric cyclic ureas,[1] imino sugars,[2] β-amino acids,[3] and natural products such as tetronomycin,[4] muricatacin,[5] or callipeltin.[6] The most common synthetic procedure for the preparation of these enantiopure compounds is the Wittig reaction between the corresponding stabilized phosphonium ylides and sugar aldehydes. However, the synthetic utility of this Wittig reaction is often limited by the dependence on the stereochemical outcome of the reaction on the substrate and the reaction conditions.

When α-alkoxyaldehydes are used as starting materials, an important number of Wittig reactions take place through an abnormal stereochemistry course.[7] Although many efforts were made to overcome this problem, only limited success was achieved. To our knowledge, a Wittig reaction to obtain carbohydrate-derived α,β-unsaturated esters with complete stereoselectivity has not been reported to date. Apparently, the use of nonpolar solvents and high temperatures[8] increases the *E* selectivity of the product, whereas protic solvents promote *Z* selectivity. Nonetheless, this is not a general rule, and the selectivity is sometimes dependent on the structure of the aldehyde used as starting material. Catalytic amounts of a carboxylic acid,[9] tributylphosphoranes,[10] or bulky *O*-alkyl ester stabilized phosphoranes[11] have been also used to increase the *E* selectivity, but again, it is moderate and even reversed for some substrates.

Chromium dichloride has become an important reagent in synthetic organic chemistry as a consequence of its versatility in electron transfer reactions. In the last years, chromium dichloride has been applied to a multitude of organic transformations, which generally proceeded with high selectivity.[12] In this sense, we have previously reported the $CrCl_2$-mediated preparation of α,β-unsaturated esters[13] or ketones[14] from 2-halo-3-hydroxyesters or 2-chloro-3-hydroxyketones. We have also published a $CrCl_2$-promoted sequential reaction of various aldehydes with ethyl dibromoacetate[15] or dichloromethylketones[16] to afford α,β-unsaturated esters or ketones, respectively, and a halomethylenation of α-aminoaldehydes for the synthesis of enantiopure (*S*)-(*E*)-1-haloalk-1-ene-3-amines.[17]

As part of our interest in the development of new selective syntheses of synthetically interesting unsaturated compounds, the objective of this work is to prepare carbohydrate-derived α,β-unsaturated esters and amides with total stereoselectivity, through a sequential reaction from 2,2-dihaloesters and a variety of sugar-based aldehydes.

Our first attempts were performed using ethyl dichloroacetate and the protected aldehyde derived from glyceraldehyde **1a**. Accordingly, when a mixture of the aldehyde and ethyl dichloroacetate was refluxed in THF in the presence of a suspension of $CrCl_2$ (6 equiv) for 3 h, the corresponding (*E*)-α,β-unsaturated ester **3a** was obtained with total stereoselectivity and in high yield after hydrolysis (Table 1, entry 1).

Using these conditions, disubstituted (*E*)-α,β-unsaturated esters **3a**−**c** were obtained with total *E*-stereoselectivity and high yields (Table 1). Taking into account that the stereoselective preparation of trisubstituted alkenes is a challenging problem in organic chemistry,[18] we have also applied this methodology for synthesizing (*E*)-α,β-unsaturated esters in which the C═C bond is trisubstituted (Table 1, entries 4−9). To this end, 2,2-ethyl or isopropyl dichloropropanoate (R^2 = Me) or 2,2-dichloro-3-phenylpropanoate (R^2 = $PhCH_2$) were employed, using the above-mentioned reaction conditions.

Interestingly, the selectivity and yield of these reactions were unaffected when the reaction was carried out with ethyl or isopropyl dichloroesters (Table 1, entries 1−5 and 6−9).

Considering the widespread use of the Wittig reaction for the preparation of carbohydrate-derived α,β-unsaturated esters, it was not surprising that fewer examples on the synthesis of

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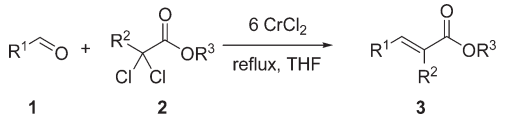
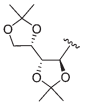
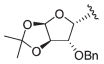
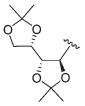
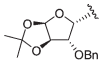
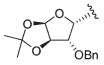
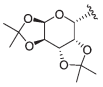
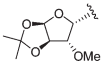
Table 1. Synthesis of Carbohydrate-Derived (*E*)-α,β-Unsaturated Esters 3



1 2 3

entry	3[a]	R^1	R^2	R^3	yield (%)[b]
1	**3a**		H	Et	91
2	**3b**		H	Et	90
3	**3c**		H	Et	87
4	**3d**		$PhCH_2$	Et	71
5	**3e**		$PhCH_2$	Et	66
6	**3f**		Me	*i*-Pr	68
7	**3g**		$PhCH_2$	*i*-Pr	68
8	**3h**		$PhCH_2$	*i*-Pr	63
9	**3i**		$PhCH_2$	Et	70

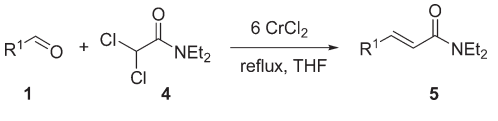
[a] *E*/*Z* > 98:2 was determined by 300 MHz ^{1}H NMR analysis of the crude products **3**. [b] Isolated yield of pure compounds **3** after column chromatography based on compounds **1**.

carbohydrate-derived α,β-unsaturated amides were reported in the literature.[19] Moreover, although procedures for the preparation of carbohydrate-derived α,β-unsaturated *N*-methoxy-*N*-methyl amides based on Wittig carbonyl olefination reactions[20] and Julia olefination protocols were developed,[21] these approaches have never been used to extend the chain on aldehydes from the carbohydrate domain.

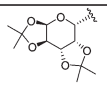
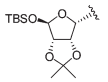
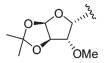
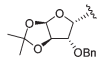
To synthesize (*E*)-α,β-unsaturated amides **5** we employed the same conditions as those previously developed for the synthesis of (*E*)-α,β-unsaturated esters **3**. Thus, when a mixture of the corresponding aldehyde **1** and *N*,*N*-diethyl dichloroacetamide **4** was refluxed in THF in the presence of 6 equiv of $CrCl_2$, the corresponding (*E*)-α,β-unsaturated amides **5** were obtained with total stereoselectivity and in high yields (Table 2).

The diastereoisomeric ratio of (*E*)-α,β-unsaturated esters **3** and amides **5** was determined by ^{1}H NMR spectroscopy (300 MHz) based on crude reaction products. In all cases, the (*E*)-stereoisomer was isolated as the only isomer, and the other isomers were not detected in the crude reaction.[22] The *E* stereochemistry of the C=C bond was assigned on the basis of the value of the ^{1}H NMR coupling constant between the olefinic protons of compounds **3a**−**c** and **5a**−**d** and by comparison of the NMR spectra for compounds **3a**[23] and **3c**[24] with those reported in the literature. In the case of trisubstituted (*E*)-α,β-unsaturated esters **3d**−**i**, a total stereoselectivity was again

Table 2. Synthesis of Carbohydrate-Derived (*E*)-α,β-Unsaturated Amides 5

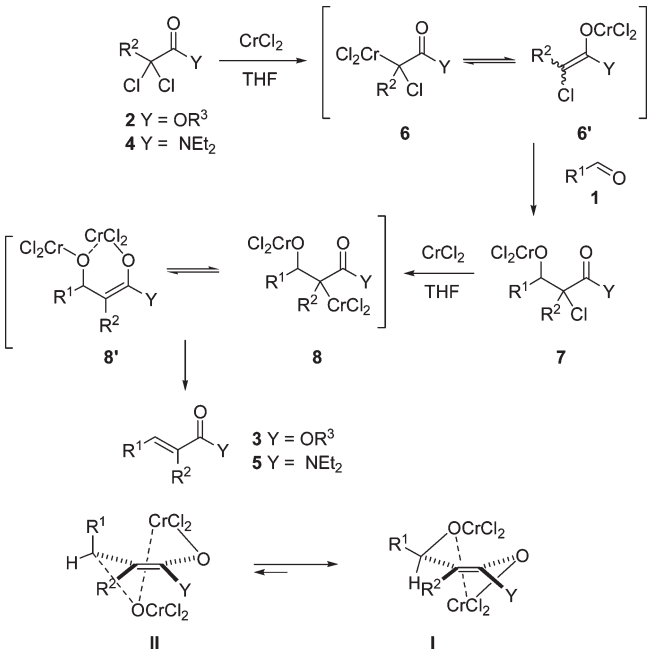


1 4 5

entry	5[a]	R^1	yield (%)[b]
1	**5a**		62
2	**5b**		68
3	**5c**		63
4	**5d**		67

[a] *E*/*Z* > 98:2 was determined by 300 MHz ^{1}H NMR analysis of the crude products **5**. [b] Isolated yield of pure compounds **5** after column chromatography based on compounds **1**.

Scheme 1. Mechanistic Proposal



observed, and the relative configuration of compounds **3d** and **3f** was assigned by NOESY experiments. The *E*-stereochemistry of other compounds **3** was assigned by analogy.

It is worth mentioning that this process tolerates a broad scope of sugar-derived aldehydes bearing different protection on the hydroxyl groups. Also, all reactions took place with total *E*-stereoselectivity and in high yields, under mild conditions, and in the absence of epimerization of any chiral center.

To explain the observed results, we propose a mechanism similar to those previously considered for other $CrCl_2$-promoted olefination reactions.[15,16] In this way, dichloroacetates **2** or dichloroacetamides **4** react with $CrCl_2$ to generate the chromium enolate **6**−**6′** (Scheme 1). The addition reaction of **6** to the

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corresponding sugar aldehyde **1** affords the corresponding 2-chloro-3-oxy ester or amide **7**. Metalation of **7** with two additional equivalents of chromium dichloride gives access to enolate intermediate **8**−**8′**, which would undergo a spontaneous elimination reaction rendering, after workup, the corresponding α,β-unsaturated esters **3** or amides **5**.

We assume that the elimination process takes place through a cyclic six-membered ring transition state **8′**, guided by coordination of the Cr^{III} center with the oxygen atom of the alcoholate function. Two conformations, **I** and **II**, are feasible for intermediate **8′**. Conformer **I** is presumably more stable than **II**, as the sugar moiety adopts a *pseudo*-equatorial orientation, thus avoiding unfavorable interactions with the chromium coordination sphere. Elimination from **I** renders (*E*)-α,β-unsaturated esters **3** or amides **5**.

In conclusion, we have described a novel and efficient chromium-mediated olefination protocol of aldehydes readily prepared from sugars directed toward the synthesis of carbohydrate-derived di- and trisubstituted (*E*)-α,β-unsaturated esters or amides. This process took place with total *E*-stereoselectivity and in high yields under mild conditions maintaining the stereochemical integrity of the sugar backbone.

EXPERIMENTAL SECTION

Synthesis of Compounds 3 and 5. To a stirred suspension of anhydrous $CrCl_2$ (6 mmol) in THF (10 mL) were added a solution of a 2,2-dichloroester or 2,2-dichloroamide (1 mmol) and the corresponding aldehyde (1 mmol) at room temperature and under an inert atmosphere. After stirring at 75 °C for three hours, the reaction mixture was quenched with HCl (0.1 M) and extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum. The organic layer was then filtered through a pad of Celite, and the solvents were removed in vacuo. Purification by column chromatography on silica gel (Hexane/EtOAc 5:1) afforded the corresponding α,β-unsaturated compound **3** or **5**.

Spectroscopic data for compounds **3a**[23] and **3c**[24] were previously reported in the literature.

Ethyl (*E*)-2,3-Dideoxy-4,5:6,7-di-*O*-isopropylidene-L-*xylo*-hept-2-enonate (3b). Colorless oil; $[\alpha]^{20}_D = -2.3$ ($c = 1$ in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (dd, J = 15.8, 5.0 Hz, 1 H), 6.18 (d, J = 15.8 Hz, 1 H), 4.63 (t, J = 5.7 Hz, 1 H), 4.22 (q, J = 6.9 Hz, 2 H), 3.88−3.79 (m, 3 H), 3.74−3.70 (m, 1 H), 1.46 (s, 6 H), 1.43 (s, 6 H), 1.31 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (C), 145.2 (CH), 135.8 (C), 122.0 (CH), 110.0 (C), 80.6 (CH), 77.7 (CH), 72.3 (CH), 63.4 (CH_2), 60.6 (CH_2), 26.9 (2 × CH_3), 26.6 (2 × CH_3), 14.1 (CH_3). MS (ESI^+-TOF) m/z (%): 283 (100), 261 (17), 203 (16). HRMS (ESI^+) calcd for $[C_{15}H_{25}O_6]^+$ $[M^+ + H]^+$ 301.1651. Found 301.1645. IR (neat): 3414, 1714, 1266, 740 cm^{-1}. R_f = 0.19 (hexane/EtOAc 1:1).

Ethyl (*E*)-2,3-Dideoxy-4,5:6,7-di-*O*-isopropylidene-2-*C*-phenylmethyl-L-*xylo*-hept-2-enonate (3d). Yellow oil; $[\alpha]^{20}_D$ = −19.6 ($c = 1$ in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26−7.08 (m, 5 H), 6.73 (d, J = 8.8 Hz, 1 H), 4.70 (apparent t, J = 7.2 Hz, 1 H), 4.05 (apparent q, J = 7.0 Hz, 2 H), 4.11−3.61 (m, 4 H), 3.77 (d, J = 15.1 Hz, 1 H), 3.68 (d, J = 15.1 Hz, 1 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.23 (s, 3 H), 1.11 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (C), 138.0 (C), 138.0 (CH), 135.0 (C), 128.4 (2 × CH), 128.2 (2 × CH), 126.0 (CH), 110.3 (C), 109.6 (C), 81.5 (CH), 76.5 (CH), 76.1 (CH), 67.2 (CH_2), 60.8 (CH_2), 32.7 (CH_2), 27.1 (CH_3), 27.0 (CH_3), 26.6 (CH_3), 25.1 (CH_3), 14.0 (CH_3). MS (ESI^+-TOF) m/z (%): 413 $[M^+ + Na]^+$ (100), 233 (28), 211 (5), 187 (10). IR (neat): 3437, 1720, 1063, 750 cm^{-1}. HRMS (ESI^+) calcd for $[C_{22}H_{30}O_6Na]^+$ $[M^+ + Na]^+$ 413.1940. Found 413.1934. R_f = 0.40 (hexane/EtOAc 5:1).

Ethyl (*E*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-phenylmethyl-α-D-*xylo*-hept-5-enofuranuronate (3e). Yellow oil; $[\alpha]^{20}_D$ = −52.7 ($c = 1$ in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.12 (m, 10 H), 7.07 (d, J = 8.2 Hz, 1 H), 6.03 (d, J = 3.8 Hz, 1 H), 5.05 (dd, J = 8.2, 3.2 Hz, 1 H), 4.67 (d, J = 3.2 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.40 (d, J = 12.0 Hz, 1 H), 4.23 (c, J = 7.0 Hz, 2 H), 3.84 (d, J = 15.2 Hz, 1 H), 3.76 (d, J = 3.2 Hz, 1 H), 3.65 (d, J = 15.2 Hz, 1 H), 1.52 (s, 3 H), 1.33 (s, 3 H), 1.29 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 139.1 (C), 137.2 (C), 136.7 (CH), 134.2 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.6 (2 × CH), 126.1 (CH), 111.7 (C), 105.1 (CH), 83.5 (CH), 82.9 (CH), 76.9 (CH), 72.2 (CH_2), 60.9 (CH_2), 33.1 (CH_2), 26.8 (CH_3), 26.2 (CH_3), 14.1 (CH_3). MS (ESI^+-TOF) m/z (%): 439 $[M^+ + H]^+$ (100), 351 (10), 273 (13). IR (neat): 3058, 1712, 1076, 737 cm^{-1}. HRMS (ESI^+) calcd for $[C_{26}H_{31}O_6]^+$ $[M^+ + H]^+$ 439.2121. Found 439.2115. R_f = 0.30 (hexane/EtOAc 5:1).

Isopropyl (*E*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-methyl-α-D-*xylo*-hept-5-enofuranuronate (3f). Yellow oil; $[\alpha]^{20}_D$ = −54.3 ($c = 1$ in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.19 (m, 5 H), 6.81 (dd, J = 7.5, 1.2 Hz, 1 H), 5.94 (d, J = 3.7 Hz, 1 H), 5.08−4.96 (m, J = 6.3 Hz, 1 H), 4.85 (dd, J = 7.5, 3.2 Hz, 1 H), 4.59 (s, 1 H), 4.58 (d, J = 12.2 Hz, 1 H), 4.39 (d, J = 12.2 Hz, 1 H), 3.87 (d, J = 2.5 Hz, 1 H), 1.73 (s, 3 H), 1.44 (s, 3 H), 1.27 (s, 3 H), 1.21 (d, J = 6.3 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C), 137.1 (CH), 134.9 (C), 131.2 (C), 128.4 (2 x CH), 127.9 (CH), 127.7 (2 x CH), 111.7 (C), 105.5 (CH), 83.0 (CH), 82.9 (CH), 77.2 (CH), 72.2 (CH_2), 68.0 (CH), 26.8 (CH_3), 26.1 (CH_3), 21.8 (2 × CH_3), 13.2 (CH_3). MS (ESI^+-TOF) m/z (%): 399 $[M^+ + Na]^+$ (100), 377 (23), 317 (17), 289 (29). IR (neat): 3414, 1710, 1254, 738 cm^{-1}. HRMS (ESI^+) calcd for $[C_{21}H_{29}O_6]^+$ $[M^+ + H]^+$ 377.1964. Found 377.1958. R_f = 0.19 (hexane/EtOAc 1:1).

Isopropyl (*E*)-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-phenylmethyl-β-D-*galacto*-oct-6-enopyranuronate (3g). Yellow oil; $[\alpha]^{20}_D$ = −96.6 (c = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.06 (m, 5 H), 6.88 (d, J = 8.0 Hz, 1 H), 5.51 (d, J = 4.4 Hz, 1 H), 4.95−4.87 (sx, J = 6.0 Hz, 1 H), 4.61 (d, J = 8.0 Hz, 1 H), 4.51 (d, J = 7.6 Hz, 1 H), 4.25 (dd, J = 4.8, 2.4 Hz, 1 H), 4.04 (d, J = 8.0 Hz, 1 H), 3.74 (d, J = 15.3 Hz, 1 H), 3.63 (d, J = 15.3 Hz, 1 H), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 1.11 (d, J = 6.2 Hz, 3 H), 1.09 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4 (C), 138.8 (C), 136.9 (CH), 134.4 (C), 128.3 (2 × CH), 128.2 (2 × CH), 126.0 (CH), 109.5 (C), 108.5 (C), 96.3 (CH), 72.7 (CH), 70.7 (CH), 70.1 (CH), 68.3 (CH), 65.1 (CH), 33.1 (CH_2), 25.9 (2 × CH_3), 24.7 (CH_3), 24.2 (CH_3), 21.6 (2 × CH_3). MS (ESI^+-TOF) m/z (%): 433 $[M^+ + H]^+$ (100), 375 (28), 315 (19), 257(15). IR (neat): 3433, 1713, 1066, 749 cm^{-1}. HRMS (ESI^+) calcd for $[C_{24}H_{33}O_7]^+$ $[M^+ + H]^+$ 433.2226. Found 433.222. R_f = 0.32 (hexane/EtOAc 5:1).

Isopropyl (*E*)-6-*O*-Benzyl-2,3-dideoxy-4,5-*O*-isopropylidene-2-*C*-phenylmethyl-D-*erythro*-hex-2-enonate (3h). Yellow oil; $[\alpha]^{20}_D$ = +48.8 (c = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.04 (m, 10 H), 6.75 (d, J = 9.5 Hz, 1 H), 5.12−4.84 (m, 1 H), 4.53−4.48 (m, 1 H), 4.29−4.21 (m, 1 H), 3.71 (d, J = 15.2 Hz, 1 H), 3.56 (d, J = 15.2 Hz, 1 H), 3.47−3.25 (m, 4 H), 1.45 (s, 3 H), 1.31 (s, 3 H), 1.10 (t, J = 6.2 Hz, 3 H), 1.07 (t, J = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3 (C), 139.0 (C), 137.7 (C), 136.6 (CH), 134.7 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 126.1 (CH), 109.5 (C), 77.3 (CH), 73.7 (CH), 73.4 (CH_2), 69.0 (CH_2), 68.3 (CH), 32.7 (CH_2), 27.8 (CH_3), 25.3 (CH_3), 21.6 (2 × CH_3). MS (ESI^+-TOF) m/z (%): 447 $[M^+ + Na]^+$ (100), 442 (47), 367 (30), 307 (12). IR (neat): 3414, 1710, 1110, 738 cm^{-1}. HRMS (ESI^+) calcd for $[C_{26}H_{32}O_5Na]^+$ $[M^+ + Na]^+$ 447.2147. Found 447.2141. R_f = 0.42 (hexane/EtOAc 5:1).

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Ethyl (*E*)-3-*O*-Methyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-phenylmethyl-α-D-*xylo*-hept-5-enofuranuronate (3i). Yellow oil; $[\alpha]^{20}_D$= −34.6 (*c* = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−7.07 (m, 5 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 5.88 (d, *J* = 3.8 Hz, 1 H), 4.90 (dd, *J* = 7.6, 3.2 Hz, 1 H), 4.50 (d, *J* = 3.8 Hz, 1 H), 4.18−4.05 (m, 2 H), 3.81 (d, *J* = 15.2 Hz, 1 H), 3.59 (d, *J* = 15.2 Hz, 1 H), 3.37 (d, *J* = 3.2 Hz, 1 H), 3.19 (s, 3 H), 1.41 (s, 3 H), 1.24 (s, 3 H), 1.16 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (C), 139.3 (C), 136.6 (CH), 134.3 (C), 128.5 (2 × CH), 128.4 (2 × CH), 126.3 (CH), 111.7 (C), 105.0 (CH), 86.1 (CH), 82.1 (CH), 76.8 (CH), 61.0 (CH_2), 58.2 (CH_3), 33.2 (CH_2), 26.9 (CH_3), 26.2 (CH_3), 14.1 (CH_3). MS (ESI$^+$-TOF) *m*/*z* (%): 363 $[M^+ + H]^+$ (100), 317 (26), 259 (78). IR (neat): 3425, 1710, 1023, 744 cm^{-1}. HRMS (ESI$^+$) calcd for $[C_{20}H_{27}O_6]^+$ $[M^+ + H]^+$ 363.1808. Found 363.1802. R_f = 0.27 (hexane/EtOAc 5:1).

(*E*)-*N*,*N*-Diethyl-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-β-D-*galacto*-oct-6-enopyranosiduronamide (5a). Yellow oil; $[\alpha]^{20}_D$= +154.3 (*c* = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (dd, *J* = 15.0, 3.7 Hz, 1 H), 6.45 (dd, *J* = 15.0, 2.2 Hz, 1 H), 5.53 (d, *J* = 5.2 Hz, 1 H), 4.57 (dd, *J* = 7.7 Hz, 1 H), 4.44−4.39 (m, 1 H), 4.27 (dd, *J* = 5.0, 2.2 Hz, 1 H), 4.23 (dd, *J* = 7.7, 2.2 Hz, 1 H), 3.43−3.28 (m, 4 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H), 1.07 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3 (C), 139.2 (CH), 121.2 (CH), 109.2 (C), 108.4 (C), 96.2 (CH), 72.3 (CH), 70.6 (CH), 70.4 (CH), 67.2 (CH), 42.0 (CH_2), 40.5 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 24.6 (CH_3), 24.2 (CH_3), 14.6 (CH_3), 12.9 (CH_3). MS (ESI$^+$-TOF) *m*/*z* (%): 356 $[M^+ + H]^+$ (100). IR (neat): 3420, 1713, 1041, 752 cm^{-1}. HRMS (ESI$^+$) calcd for $[C_{18}H_{30}NO_6]^+$ $[M^+ + H]^+$ 356.2073. Found 356.2067. R_f = 0.25 (hexane/EtOAc 1:1).

(*E*)-*N*,*N*-Diethyl-1-*O*-*t*-butyldimethylsilyl-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hept-5-enofuranosiduronamide (5b). Yellow oil; $[\alpha]^{20}_D$= +2.7 (*c* = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 14.9, 5.2 Hz, 1 H), 6.45 (d, *J* = 14.9 Hz, 1 H), 4.74 (dd, *J* = 5.2, 3.5 Hz, 1 H), 4.57 (apparent t, *J* = 3.5 Hz, 1 H), 4.51 (*J* = 6.2 Hz, 1 H), 3.48−3.28 (m, 5 H), 1.36 (s, 3 H), 1.23 (s, 3 H), 1.14 (t, *J* = 7.0 Hz, 3 H), 1.09 (t, *J* = 7.0 Hz, 3 H), 0.82 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (C), 137.5 (CH), 122.4 (CH), 112.4 (C), 101.0 (CH), 86.9 (CH), 80.8 (CH), 79.1 (CH), 42.1 (CH_2), 40.5 (CH_2), 25.9 (CH_3), 25.4 (3 × CH_3), 24.8 (CH_3), 17.7 (C), 14.7 (CH_3), 12.9 (CH_3), −4.7 (CH_3), −5.6 (CH_3). MS (ESI$^+$-TOF) *m*/*z* (%): 400 $[M^+ + H]^+$ (100), 284 (34). IR (neat): 2976, 1721, 1114 cm^{-1}. HRMS (ESI$^+$) calcd for $[C_{20}H_{38}NO_5Si]^+$ $[M^+ + H]^+$ 400.2519. Found 400.2517. R_f = 0.48 (hexane/EtOAc 1:1).

(*E*)-*N*,*N*-Diethyl-3-*O*-methyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-eno furanosiduronamide (5c). Yellow oil; $[\alpha]^{20}_D$= +33.4 (*c* = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (dd, *J* = 15.2, 4.2 Hz, 1 H), 6.52 (dd, *J* = 15.0, 1.8 Hz, 1 H), 5.91 (d, *J* = 4.0 Hz, 1 H), 4.70−4.75 (m, *J* = 4.2 Hz, 1 H), 4.56 (d, *J* = 4.0 Hz, 1 H), 3.72 (d, *J* = 3.3 Hz, 1 H), 3.47−3.34 (m, 4 H), 3.32 (s, 3 H), 1.45 (s, 3 H), 1.28 (s, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (C), 137.5 (CH), 122.4 (CH), 111.7 (C), 104.6 (CH), 85.3 (CH), 82.1 (CH), 79.6 (CH), 58.3 (CH_3), 42.1 (CH_2), 40.7 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 14.8 (CH_3), 13.0 (CH_3). MS (ESI$^+$-TOF) *m*/*z* (%): 300 $[M^+ + H]^+$ (100). IR (neat): 2989, 1717, 1033 cm^{-1}. HRMS (ESI$^+$) calcd for $[C_{15}H_{26}NO_5]^+$ $[M^+ + H]^+$ 300.1811. Found 300.1805. R_f = 0.33 (hexane/EtOAc 1:1).

(*E*)-*N*,*N*-Diethyl-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranosiduronamide (5d). Yellow oil; $[\alpha]^{20}_D$= −13.9 (*c* = 1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.19 (m, 5 H), 6.98 (dd, *J* = 14.9, 4.4 Hz, 1 H), 6.53 (dd, *J* = 14.9, 1.7 Hz, 1 H), 5.92 (d, *J* = 4.4 Hz, 1 H), 4.80−4.75 (m, 1 H), 4.57−4.44 (m, 3 H), 3.91 (d, *J* = 2.6 Hz, 1 H), 3.48−3.22 (m, 4 H), 1.43 (s, 3 H), 1.26 (s, 3 H), 1.09 (t, *J* = 6.6 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0 (C), 137.7 (CH), 137.1 (C), 128.4 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 122.4 (CH), 111.7 (C), 104.7 (CH), 82.9 (CH), 82.5 (CH), 79.7 (CH), 72.3 (CH_2), 42.1 (CH_2), 40.6 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 14.8 (CH_3), 13.0 (CH_3). MS (ESI$^+$-TOF) *m*/*z* (%): 376 $[M^+ + H]^+$ (100). IR (neat): 2982, 1713, 997 cm^{-1}. HRMS (ESI$^+$) calcd for $[C_{21}H_{30}NO_5]^+$ $[M^+ + H]^+$ 376.2124. Found 376.2118. R_f = 0.47 (hexane/EtOAc 1:1).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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