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De Novo Synthesis of Aceric Acid and an Aceric Acid Building Block

Mattie S. M. Timmer, Bridget L. Stocker, and Peter H. Seeberger*

Laboratory for Organic Chemistry, Swiss Federal Institute of Technology (ETH) Zürich, Wolfgang-Pauli Strasse 10, 8093 Zurich, Switzerland

seeberger@org.chem.ethz.ch

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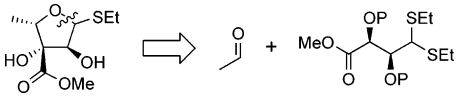

The de novo synthesis of an aceric acid thioglycoside building block and the total synthesis of the plant carbohydrate aceric acid are described via a highly convergent strategy. Aldol reaction of acetaldehyde and a protected tartaric acid derivative provided the open chain carbohydrate. Subsequent acid treatment yielded the aceric acid thioglycoside in 35% total yield over five steps. Oxidative cleavage of the thioketal in the open chain carbohydrate and basic hydrolysis of the methyl ester furnished fully deprotected aceric acid in 31% yield over six steps.

Rhamnogalacturonan-II (RG II) is a pectic polysaccharide[1] found in the cell walls of all higher plants and is one of the most complex carbohydrate structures found in nature.[2] Although only present in relatively small amounts, RG II is believed to play a pivotal role in plant cell wall stabilization. Defects in RG II production lead to growth inhibition and dramatic changes in cell wall architecture. Furthermore, RG II has been found in extracts used in traditional medicine and fermentation products such as red wine.[3] RG II consists of a (1 → 4)-linked galacturonic acid oligomeric backbone to which four distinct side chains (A−D) are attached (Figure 1). The side chains contain 12 different sugar monomers.

The complexity of RG II represents an enormous synthetic challenge despite significant advances in the field of oligosaccharide synthesis.[4] Methodology has been developed for the installation of even the most difficult glycosidic linkages and for the rapid automated synthesis of oligosaccharides.[5] As a result, the bottleneck for the synthesis of complex carbohydrates has shifted toward obtaining sufficient amounts of fully functionalized monosaccharide building blocks.[6]

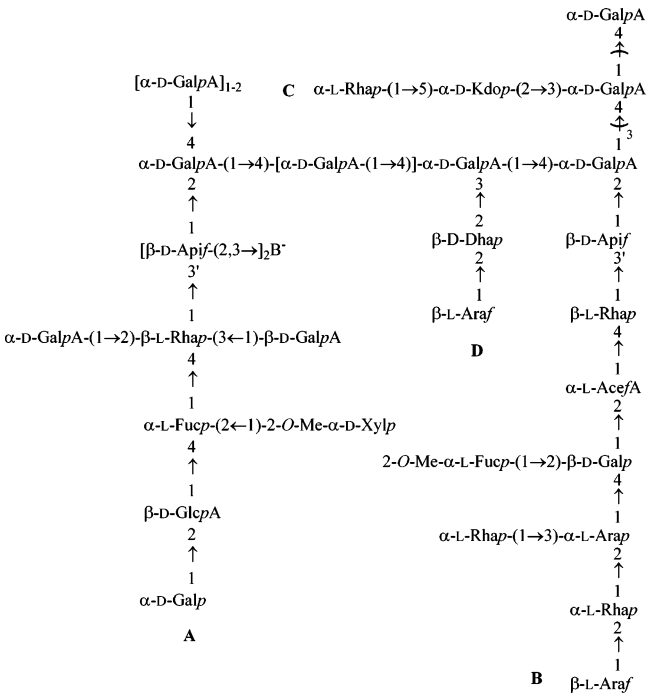

FIGURE 1. Structure of rhamnogalacturonan II.

For RG II, the incorporation of the unique sugar aceric acid (L-Ace*f*A, RG II chain B, Figure 1) requires the synthesis of such a building block. The C-3 branched acidic pentose (**1**, Scheme 1) was first isolated from the sycamore maple Acer *pseudoplantanus*.[7] The monosaccharide was recently synthesized by Jones et al.,[8] but thus far, no route to aceric acid building blocks has been reported. Herein, we present a short and efficient synthesis of an aceric acid building block.

Retrosynthetic analysis of aceric acid ethyl thioglycosides **A** (Scheme 1) reveals a ring formation that can take place in the final stage of the synthesis via an intramolecular substitution of an anomeric dithiane by the 4-hydroxyl. The dithiane can function as a protecting group for the anomeric center during the preceding reactions. Open chain carbohydrate **B** can in turn be formed via an aldol reaction between acetaldehyde (**C**) and an appropriately protected ester **D**.[9] The required stereocenters for the chiral ester can be derived from D-arabinose (**2**).

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(2) For a recent review, see: Paulsen, B. S.; Barsett, H. *Adv. Polym. Sci*. **2005**, *186*, 69.

(3) For biological functions, see: (a) Höfte, H. *Science* **2001**, *294*, 795. (b) O'Neill, M.; Eberhard, S.; Albersheim, P.; Darvill, A. G. *Science* **2001**, *294*, 846. (c) Ridley, B. L.; O'Neill, M. A.; Mohnen, D. A. *Phytochemistry* **2001**, *57*, 929. (d) O'Neill, M. A.; Ishii, T.; Albersheim, P.; Darvill, A. G. *Annu. Rev. Plant Biol.* **2004**, *55*, 109.

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(5) (a) Kanemitsu, T.; Kanie, O. *Trends Glycosci. Glycotechnol.* **1999**, *11*, 267. (b) Seeberger, P. H.; Haase, W. C. *Chem. Rev.* **2000**, *100*, 4349. (c) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523. (d) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344. (e) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545. (f) Seeberger, P. H. *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Wiley: New York, 2001. (g) Kanemitsu, T.; Kanie, O. *Comb. Chem. High Throughput Screening* **2002**, *5*, 339. (h) Plante, O. J.; Seeberger, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 521.

(6) Timmer, M. S. M.; Adibekian, A.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 7605.

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(8) Jones, N. A.; Nepogodiev, S. A.; MacDonald, C. J.; Hughes, D. L.; Field, R. A. *J. Org. Chem.* **2005**, *70*, 8556.

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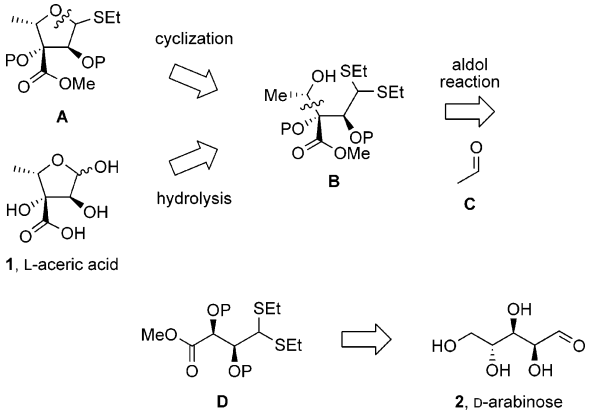
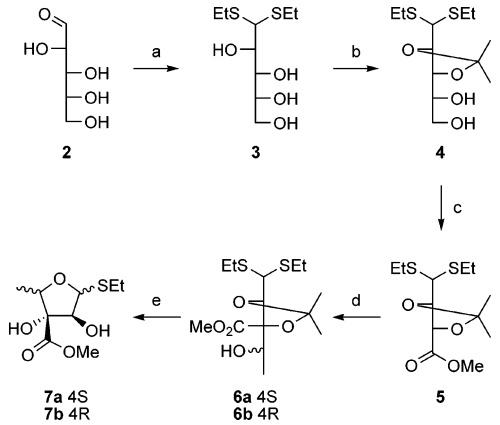
SCHEME 1. Retrosynthetic Analysis of Aceric Acid Thioglycosides



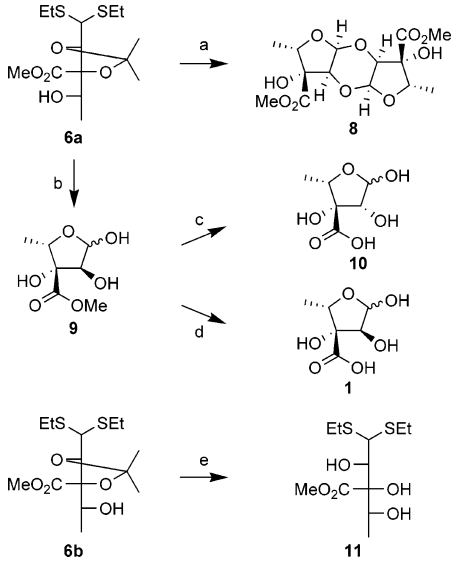
SCHEME 2. Synthesis of Aceric Acid Thioglycosides[a]



[a] Reagents and conditions: (a) EtSH, concentrated aq HCl, 10 min, 77%. (b) $(MeO)_2CMe_2$, *p*-TsOH (cat.), 2 h, then MeOH/H_2O (99:1), 50 °C, 3h, 75%. (c) 1: $NaIO_4$, THF/H_2O (9:1), 15 min, 0 °C to rt; 2: $AgNO_3$/NaOH, H_2O/dioxane (1:1); 3: CH_2N_2, ether, 82%. (d) LDA, THF, −78 °C, then $CH_3C(O)H$, −78 to −20 °C, 3 h, 92% (4:1 mixture of diastereoisomers); and (e) TFA/H_2O (1:1), 50 °C, 30 min, then TFA, 50 °C, 30 min, 99%.

With this strategy in mind, our studies commenced with the treatment of D-arabinose with concentrated hydrochloric acid and ethane thiol (Scheme 2).[10] The product crystallized from the reaction mixture, and ethyl mercaptane **3** was isolated in 77% yield. Selective protection of the 2- and 3-hydroxyl groups of **3** was accomplished via a two-step, one-pot, procedure. Mercaptane **3** was first transformed into its 2,3:4,5-bisacetonide by reaction with acetone in the presence of catalytic amounts of para-toluenesulfonic acid (*p*-TsOH). Evaporation of the solvent, redissolution in 99% aqueous methanol, and stirring at 50 °C led to the selective cleavage of the less stable 4,5-isopropylidine to furnish monoacetonide **4** in 76% yield.[11] At this stage, the transformation of the diol into a methyl ester was required, while avoiding oxidation of the mercaptane. First, the diol was cleaved using sodium periodate[6] in a water/THF mixture to give the crude aldehyde. Although few oxidizing

SCHEME 3. Total Synthesis of Aceric Acid[a]



[a] Reagents and conditions: (a) $PhI(C(O)CF_3)_2$, $MeCN/H_2O$ (85:15), 10 min, then TFA, 50 °C, 30 min, 52%. (b) $PhI(C(O)CF_3)_2$, $MeCN/H_2O$ (85:15), then TFA/H_2O (1:1), 50 °C, 30 min, 88%. (c) 1 M aq NaOH/MeOH (1:4), 1 h, quant. (d) LiOH (2 equiv), MeOH/H_2O (1:1), 0 °C to rt, 1.5 h, quant. (e) TFA/H_2O (1:1), rt, 2 h, quant.

agents leave thioethers unaffected, treatment of the crude aldehyde with silver oxide,[12] formed in situ by the combination of aqueous sodium hydroxide and silver nitrate solutions, resulted in the smooth formation of the acid. Moreover, extraction and back-extraction of the acid resulted in homogeneous material that was used without further purification. Finally, treatment of the acid with diazomethane[13] gave methyl ester **5** in an overall yield of 82%.

Having established an efficient synthetic route for the ester, the aldol reaction and cyclization were explored. Initial attempts to combine ester **5** with acetaldehyde using lithium hexamethyldisilazane yielded only the starting material. Apparently, a stonger base was required for effective enolization. Accordingly, deprotonation of **5** with lithium diisopropylamide and subsequent reaction with acetaldehyde gave a 4:1 diastereomeric mixture of *β*-hydroxy esters **6a** and **6b** in a combined yield of 85%. Further optimization of the aldol reaction was accomplished by using the lithium salt of 2,2,4,4-tetramethylpiperidine (LTMP) as the base. This reaction resulted in a 92% yield of esters **6**, also as a 4:1 mixture of diastereoisomers. Fortunately, the products were readily separable by column chromatography, and the individual diastereoisomers **6a** and **6b** were transformed into their respective thioglycosides. Subsequent treatment of **6a** or **6b** with 50% aqueous trifluoroacetic acid (TFA), to affect acetonide deprotection, and with pure TFA, to affect cyclization, gave the aceric acid ethyl thioglycosides **7a** and **7b** in near quantitative yields.

To determine the absolute configuration of the isomers, we embarked upon the total synthesis of aceric acid (Scheme 3). A two-step procedure was applied for the deprotection of the dithioketal of **6a**. Oxidation of the sulfide using $PhI(C(O)CF_3)_2$ led to a diastereomeric mixture of sulfoxides,[14] but subsequent cleavage of both the thio and the isopropylidene ketals using

(9) For aldol reactions of tartrates and derivatives, see: (a) Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030. (b) Evans, D. A.; Trotter, B. W.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779. (c) Aggarwal, V. K.; Masters, S. J.; Adams, H.; Spey, S. E.; Brown, G. R.; Foubister, A. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 155. (d) Ladner, W. *Chem. Ber.* **1983**, *116*, 3413.

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(11) Procedure adapted from: Bozó, É.; Boros, S.; Kuszmann, J. *Carbohydr. Res.* **1997**, *302*, 149.

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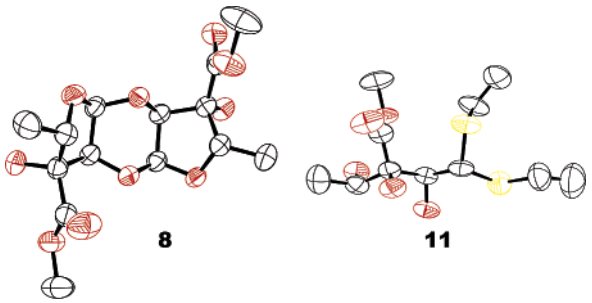

FIGURE 2. Ortep representation of the crystal structures of aceric acid dimer **8** and 4-epi-aceric acid diethyl dithio acetal **11**.

TFA did not lead to the expected methyl ester **9**. Instead, the self-condensation product **8** was isolated in modest 52% yield. X-ray crystallographic analysis of **8** (Figure 2) confirmed the absolute configuration of L-aceric acid. Conversely, milder deprotection of the sulfoxides using a 1:1 mixture of TFA and H_2O gave aceric acid methyl ester **9** in 88% yield. It is interesting to note that subjecting thioglycoside **7a** (Scheme 2) to NIS in acetone/H_2O (85:15) led to quantitative formation of ester **9**, but as depuration of the succinimide byproduct was strenuous, the oxidative deprotection of **6a** was preferred. Surprisingly, saponification of the methyl ester of **9** using NaOH in water/methanol did not lead to aceric acid but instead to complete epimerization of the 2-position, and it was the diastereoisomer 2-epi-aceric acid **10** that was isolated.[15] Deprotection under milder cleavage conditions (dilute LiOH at 0 °C) quantitatively yielded acid **1**, thereby completing the total synthesis of L-aceric acid in a total of six steps and 31% overall yield. All spectroscopic properties were in full accordance with the reported data[7,8] for aceric acid, revealing that the major isomer indeed had the desired 2*S*,3*R*,4*S* configuration.

The absolute configuration of the minor isomer **6b** was established from the crystal structure of the open chain triol **11** (Figure 2), synthesized in one step by treatment of the acetonide with a 1:1 mixture of TFA and H_2O. Here, it was found that the minor aldol product had the 2*S*,3*R*,4*R* configuration, epimeric to aceric acid at the 4-position.

The stereochemical outcome of the aldol reaction and the formation of the two diastereoisomers can be best explained by assuming a mixture of enolates **E** and **F**, an observation described earlier by Evans et al.,[9] that react via closed Zimmerman−Traxler transition states[16] **G** and **H**, respectively (Scheme 4).

Assuming that the aldehyde approaches from the least hindered side of the ester enolate, the methyl group of the aldehyde adopts an equatorial position, leading to the two isolated products. The product distribution can be explained by the preferential formation of the *trans*-enolate **E**.

In conclusion, a short and efficient synthesis of an aceric acid building block has been presented. Rapid access to large amounts of this monosaccharide will greatly facilitate the synthesis of larger oligosaccharides. Furthermore, this strategy is an expeditious means to synthesize aceric acid and its derivatives. Utilization of this methodology and the development of convergent routes for the synthesis of other carbohydrate building blocks are currently under investigation.

(15) All spectroscopic properties were in full accordance with the reported data (ref 8).

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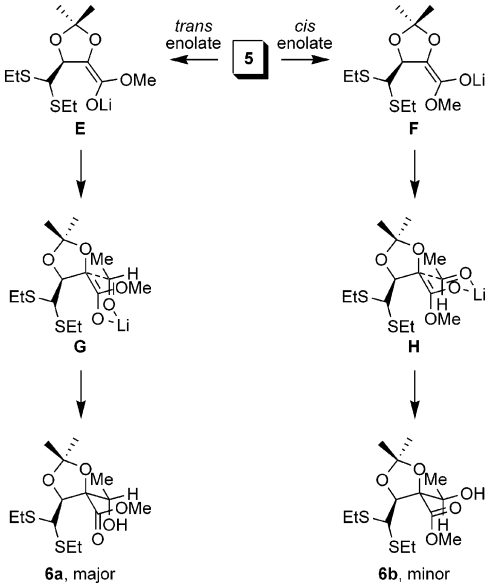
SCHEME 4. Mechanism Aldol Reaction



Experimental Section

2,3-*O*-Isopropylidine-D-arabinose Diethyl Dithio Acetal (4). 2,2-Dimethoxypropane (40 mL, 325 mL, 2.25 equiv) and *p*-toluenesulfonic acid (0.5 g, cat.) were added to a suspension of D-arabinose diethyl dithioacetal **3**[6] (36.8 g, 144 mmol) in acetone (500 mL). After obtaining a homogeneous solution and stirring for an additional hour, the mixture was concentrated, and the residue was dissolved in a mixture of MeOH (500 mL) and H_2O (5 mL). The solution was stirred for 2 h at 50 °C, saturated aqueous $NaHCO_3$ (100 mL) was added, and the mixture was concentrated to 150 mL. The residue was extracted with ethyl acetate (3 × 100 mL) and dried ($MgSO_4$) and concentrated. The resulting residue was triturated with dichloromethane and the solid D-arabinose diethyl dithioacetal (4.5 g, 17.6 mmol, 12%) collected by filtration. Concentration of the mother liquor and purification of the residue by column chromatography (hexanes → ethyl acetate/hexanes, 1:3, v/v) gave homogeneous diol **4** (32 g, 108 mmol, 75%) as a colorless oil. $\alpha_D^{20} = 59$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3606, 3421, 2991, 2931, 2873, 1602, 1455, 1385, 1374, 1248, 1161, 1052, 977, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.31 (dd, 1H, $J = 3.8$ Hz, $J = 6.9$ Hz), 4.08 (dd, 1H, $J = 6.9$, $J = 7.0$ Hz), 4.01 (d, 1H, $J = 3.8$ Hz), 3.81 (dd, 1H, $J = 2.8$ Hz, $J = 10.5$ Hz), 3.73 (ddd, $J = 2.8$ Hz, $J = 5.4$ Hz, $J = 7.0$ Hz), 3.67 (dd, 1H, $J = 5.4$ Hz, $J = 10.5$ Hz), 2.99 (bs, 2H), 2.77−2.65 (m, 4H), 1.43 (s, 3H), 1.36 (s, 3H), 1.25 (t, 1H, $J = 7.4$ Hz), 1.24 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.0, 83.2, 79.1, 73.0, 63.9, 53.1, 27.4, 27.1, 25.5, 25.2, 14.4; ESI-MS (*m*/*z*): 319.2 $[M + Na]^+$, 615.2 $[2M + Na]^+$, 341.0 $[M + HCO_2]^-$; HRMS(EI) *m*/*z* calcld for $C_{12}H_{22}O_4S_2^+$: 296.1111, obsd: 296.1109.

Methyl 2,3-*O*-Isopropylidine-D-threuronate Diethyl Dithio Acetal (5). A solution of $NaIO_4$ (6.34 g, 30 mmol, 1.4 equiv) in H_2O (25 mL) was added dropwise to a cooled (0 °C) and stirred solution of diol **4** (6.34 g, 21.4 mmol) in THF (75 mL). The ice bath was removed, and the suspension was stirred for 10 min before being quenched by the addition of concentrated aq sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed with brine (200 mL) and dried ($MgSO_4$), filtered, and concentrated. The resulting aldehyde was dissolved in dioxane (100 mL), and the solution was added to a stirred suspension of AgO, freshly made by the addition of a solution of NaOH (2.56 g, 64.2 mmol, 3.0 equiv) in H_2O (50 mL) to a vigorously stirred solution of $AgNO_3$ (7.28 g, 42.8 mmol, 2.0 equiv) in H_2O (50 mL). After 5 min, the reaction mixture was filtered over Celite, and the filter washed with water. The aqueous

solution was extracted with ether (2 × 100 mL), acidified with 1 M aq HCl to pH 2, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. KOH (3.42 g, 56.1 mmol, 2.8 equiv) was dissolved in a mixture of ether (15 mL), diethylene glycol monomethyl ether (30 mL), and H_2O (15 mL). This solution was placed in the distilling flask of a distillation setup equipped with a water bath at 70 °C, a Claisen adapter, a dropping funnel, water cooled condenser, and vacuum adapter for pressure relief, all without sharp edges or ground-glass joints. The acid was dissolved in ether (90 mL) and placed in the receiving flask. An ethereal solution of diazomethane[17] was distilled by the dropwise addition of a solution of *N*-methyl-*N*-(*p*-tolylsulfonyl)nitrosamide (11.9 g, 55.6 mmol, 2.6 equiv) in ether (90 mL). After complete addition of the ethereal solution, two additional portions of ether (10 mL) were added slowly, and the distillation continued until the distillate was colorless. After 1 h, the reaction was quenched by the addition of acetic acid (2 × 1 mL) in both the receiving and the distillation flasks. After stirring for an additional 16 h, the reaction mixture was concentrated, and the residue was purified by column chromatography (hexanes → CH_2Cl_2/hexanes, 1:1, v/v) to yield homogeneous methyl ester **5** (5.16 g, 18 mmol, 82%) as a colorless oil. $\alpha_D^{20} = 75$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 2993, 2931, 1750, 1439, 1376, 1263, 1163, 1109, 876, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.64 (d, 1H, $J = 6.8$ Hz), 4.56 (dd, 1H, $J = 4.4$ Hz, $J = 6.8$ Hz), 3.98 (d, 1H, $J = 4.4$ Hz), 3.79 (s, 3H), 2.77 (dq, 2H, $J = 12.4$ Hz, $J = 7.4$ Hz), 2.71 (dq, 2H, $J = 12.3$ Hz, $J = 7.4$ Hz), 1.50 (s, 3H), 1.42 (s, 3H), 1.27 (t, 3H, $J = 7.4$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 112.1, 82.2, 77.6, 52.8, 52.6, 52.6, 26.9, 25.9, 25.4, 25.0, 14.5, 14.4, 14.3; ESI-MS (*m*/*z*): 312.3 $[M + NH_4]^+$, 317.3 $[M + Na]^+$, 611.0 $[2M + Na]^+$; HRMS(EI) *m*/*z* calcld for $C_{12}H_{22}O_4S_2^+$: 294.0955, obsd: 294.0962.

5-Deoxy-3-*C*-methoxycarbonyl-2,3-*O*-isopropylidine-L-xylose Diethyl Dithio Acetal (6a, Major) and 5-Deoxy-3-*C*-methoxycarbonyl-2,3-*O*-isopropylidine-D-arabinose Diethyl Dithio Acetal (6b, Minor). BuLi (10.1 mL 1.6 M in hexanes, 16.2 mmol, 2.0 equiv) was added to a cooled (−50 °C), stirred solution of tetramethyl piperidine (2.87 mL, 17.0 mmol, 2.1 equiv) in THF (100 mL). After 30 min, the reaction mixture was cooled further (−78 °C), and a solution of methyl ester **5** (2.38 g, 8.1 mmol) in THF (20 mL) was added dropwise. After another 30 min, acetaldehyde (2.26 mL, 40.4 mmol, 5.0 equiv) was added, and the reaction mixture was stirred for 2 h, allowing the temperature to rise to −20 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (hexanes → 5% ethyl acetate in hexanes) gave first **6b** (0.50 g, 1.5 mmol, 18%) and then **6a** (2.02 g, 6.0 mmol, 74%). **6a**: $\alpha_D^{20} = 70$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3578, 2988, 2931, 2873, 1750, 1720, 1455, 1435, 1382, 1259, 1143, 1101, 1034, 978, 894, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (d, 1H, $J = 3.0$ Hz), 4.13 (dq, 1H, $J = 9.9$ Hz, $J = 6.4$ Hz), 4.03 (d, 1H, $J = 3.0$ Hz), 3.74 (s, 1H), 2.74 (dq, 1H, $J = 12.4$ Hz, $J = 7.5$ Hz), 2.69 (dq, 1H, $J = 7.5$ Hz, $J = 12.4$ Hz), 2.69 (dq, 1H, $J = 7.4$ Hz, $J = 11.8$ Hz), 2.60 (dq, 1H, $J = 7.4$ Hz, $J = 11.8$ Hz), 2.01 (d, 1H, $J = 9.9$ Hz), 1.61 (d, 3H, $J = 0.5$ Hz), 1.43 (d, 3H, $J = 0.5$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz), 1.21 (t, 3H, $J = 7.5$ Hz), 1.20 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 110.7, 87.9, 83.0, 68.1, 52.4, 50.9, 26.9, 26.7, 25.9, 25.0, 18.9, 14.4, 13.7; ESI-MS (*m*/*z*): 699.0 $[2M + Na]^+$; HRMS(EI) *m*/*z* calcld for $C_{14}H_{26}O_5S_2^+$: 338.1217, obsd: 338.1217.

1-Deoxy-1-ethylthio-α,β-L-aceric Acid Methyl Ester (7a). Acetonide **6a** (100 mg, 0.30 mmol) was dissolved in a mixture of TFA (2.5 mL) and H_2O (2.5 mL). After stirring for 2 h at room temperature, the solvents were evaporated in vacuo, and the residue was taken up in pure TFA and stirred for an additional hour. Concentration of the reaction mixture and purification of the residue by column chromatography (ethyl acetate) gave thioglycoside **7a** (69 mg, 0.30 mmol, 99%) as a colorless oil. $\alpha_D^{20} = 4.7$ (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3520, 3007, 2931, 1732, 1602, 1439, 1380, 1264, 1147, 1063, 1012, 970, 909, 891 cm^{-1}. α-anomer: 1H NMR (300 MHz, $CDCl_3$): δ 5.55 (d, 1H, $J = 5.0$ Hz), 4.61 (q, 1H, $J = 6.3$ Hz), 4.28 (dd, 1H, $J = 5.0$ Hz, $J = 6.3$ Hz), 3.87 (s, 3H), 3.18 (bs, 1H), 2.96 (bd, 1H, $J = 6.3$ Hz), 2.77 (dq, 1H, $J = 12.7$ Hz, $J = 7.4$ Hz), 2.71 (dq, 1H, $J = 12.7$ Hz, $J = 7.4$ Hz), 1.32 (t, 3H, $J = 7.4$ Hz), 1.24 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 89.8, 83.4, 81.7, 77.3, 53.4, 25.8, 15.4, 12.8; *β*-anomer: ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (d, 1H, $J = 5.3$ Hz), 4.42 (q, 1H, $J = 6.4$ Hz), 4.12 (dd, 1H, $J = 5.2$ Hz, $J = 5.3$ Hz), 3.88 (s, 3H), 3.35 (bs, 1H), 2.90 (bd, 1H, $J = 5.2$ Hz), 2.70 (q, 2H, $J = 7.4$ Hz), 1.32 (t, 3H, $J = 7.4$ Hz), 1.29 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 87.3, 84.3, 83.2, 79.5, 53.4, 25.3, 15.1, 14.9; ESI-MS (*m*/*z*): 281.0 $[M + HCO_2]^-$; HRMS(ESI) *m*/*z* calcld for $C_9H_{16}O_5SNa^+$: 259.0611, obsd: 259.0613.

α,β-L-Aceric Acid Methyl Ester (9). Bis(trifluoroacetoxy)-iodobenzene (66 mg) and sodium bicarbonate (34.7 mg) were added to a mixture of acetonide **6a** (32 mg, 0.11 mmol) in H_2O (1 mL) and acetonitrile (4 mL). After stirring for 10 min, the reaction mixture was concentrated, and the residue was dissolved in a mixture of TFA (5 mL) and H_2O (5 mL). After stirring for 30 min at 50 °C, the solvents were evaporated in vacuo, and the residue was purified by column chromatography (hexanes → hexanes/ethyl acetate, 1:2) to give methyl ester **9** (16 mg, 0.083 mmol, 88%) as a colorless oil. $\alpha_D^{20} = 54.6$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3600, 3528, 3415, 3031, 2957, 2921, 2854, 1726, 1439, 1383, 1264, 1156, 1063, 1013, 970, 908 cm^{-1}; ^1H NMR (300 MHz, MeOD): α-anomer: δ 5.42 (d, 1H, $J = 4.2$ Hz), 4.64 (q, 1H, $J = 6.3$ Hz), 4.05 (d, 1H, $J = 4.2$ Hz), 3.77 (s, 3H), 1.16 (d, 3H, $J = 6.3$ Hz); *β*-anomer: δ 5.02 (d, 1H, $J = 2.1$ Hz), 4.52 (q, 1H, $J = 6.4$ Hz), 3.94 (d, 1H, $J = 2.1$ Hz), 3.76 (s, 3H), 1.24 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, MeOD): α-anomer: δ 172.2, 95.6, 82.4, 80.5, 76.9, 53.5, 13.6; *β*-anomer: δ 171.5, 102.8, 83.3, 81.8, 79.5, 53.6, 14.4; ESI-MS (*m*/*z*): 237.3 $[M + HCO_2]^-$; HRMS(ESI) *m*/*z* calcld for $C_7H_{12}O_6Na^+$: 215.0526, obsd: 215.0523.

α,β-L-Aceric Acid (1). LiOH (0.125 mL 1 M in H_2O, 125 μmol, 2 equiv) was added to a solution of methyl ester **9** (12 mg, 62 μmol) in H_2O (1 mL) and methanol (1 mL) at 0 °C. After stirring for 90 min, allowing the mixture to warm to room temperature, the reaction was neutralized by the addition of Amberlite IR 120, H^+-form. Filtration and concentration gave aceric acid **1** (11 mg, 62 μmol, quant.) as a colorless oil. $\alpha_D^{20} = -35.6$ (*c* 1.0, CH_3OH); IR (neat): 3375, 2927, 2854, 1722, 1439, 1385, 1270, 1163, 1060, 1012, 895, 853 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 5.49 (d, 1H, $J = 4.4$ Hz), 5.19 (d, 1H, $J = 2.8$ Hz), 4.69 (q, 1H, $J = 6.4$ Hz), 4.56 (q, 1H, $J = 6.5$ Hz), 4.16 (d, 1H, $J = 4.4$ Hz), 4.05 (d, 1H, $J = 2.8$ Hz), 1.26 (d, 1H, $J = 6.5$ Hz), 1.19 (d, 1H, $J = 6.4$ Hz);); 13C NMR (75 MHz, D_2O): δ 176.6, 176.6, 104.0, 98.4, 86.2, 85.4, 85.0, 80.9, 80.9, 79.6, 16.6, 15.3; ESI-MS (*m*/*z*): 177.0 $[M - H]^-$, 195.0 $[M + OH]^-$, 223.0 $[M + HCO_2]^-$; HRMS(ESI) *m*/*z* calcd for $C_6H_9O_6^-$: 177.0405, obsd: 177.0407.

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Supporting Information Available: Full experimental details and characterization data for all described compounds, including **7b**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Caution: diazomethane is both explosive and carcinogenic and should always be treated with care. For the preparation and use of diazomethane, see ref 13.