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The Invention of Radical Reactions. Part XXXVIII.[1] Homologation of Carboxylic Acids with Acrylamide and Synthetic Studies of 3-Deoxy-D-*arabino*-2-heptulosonic Acid (DAH) and Its 4-Epimer

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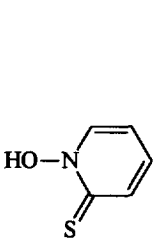
Abstract: Alkyl radicals generated from *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone added onto acrylamide at room temperature to form crystalline 2-(2-pyridylsulfanyl)-carboxamides. Desulfurization of the latter by nickel boride at room temperature afforded primary amides in quantitative yield. 3-Deoxy-D-*arabino*-2-heptulosonic acid (DAH), its 4-epimer, and their derivatives were effectively synthesized from commercial D-ribonolactone by similar radical chemistry. © 1997 Elsevier Science Ltd.

INTRODUCTION

Radical carbon-carbon bond formation reactions have been well recognized as an important tool for organic synthesis.[2] Numerous olefins have been used as radical traps to form carbon-carbon bonds.[3] The ever increasing use of radical chemistry by synthetic chemists is a result of the mild reaction conditions offered by an increasing number of convenient radical sources. This is well demonstrated in a recent review by Giese *et al.*[4] on radical cyclization reactions. The *O*-acyl derivatives (Barton esters) of *N*-hydroxy-2-thiopyridone **1**, as an important class of disciplined-radical sources,[5] have many other advantages besides the mild reaction conditions, such as facile accessibility, non-toxicity, and ease of handling. We have shown that this chemistry can be applied to the synthesis of many important classes of compounds such as halides, alcohols, chalcogenides, *inter alia*.[6] For example, radicals generated by this method can be trapped with disulfides,

diselenides, or ditellurides to form unsymmetrical thio-,[7] seleno-,[8] or telluro-ethers,[9] respectively. The utility of these reactions is well exemplified by the synthesis of two important selenoamino acids, L-selenomethionine and L-selenocystine.[8] Using acrylate esters as radical traps,[10] we applied this chemistry to the homologation of carboxylic acids, including the synthesis of biologically important α-keto acids.



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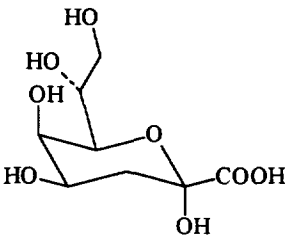

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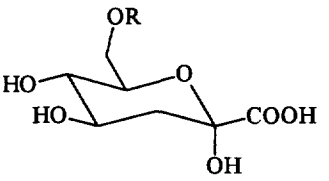

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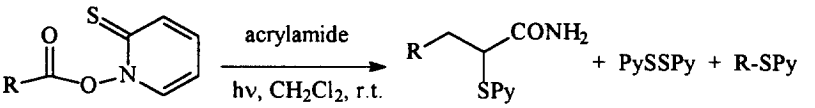
We also successfully applied a similar procedure to the construction of the 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **2**) skeleton and the synthesis of its phenylhydrazone derivatives.[11] The undesired lactonization of the ester group in the later deacetylation step prompted us to use acrylamide instead as a radical trap. The amide group would avoid lactonization under deacetylation conditions. Since this has not been examined before, we carried out some model studies, which showed that carboxylic acids can be readily converted to primary amides with two-carbon homologation by thiohydroxamate radical chemistry. It is known that the versatile amide function can be easily transformed into other derivatives.[12]

Recently in a short communication,[13] we reported the application of this radical chemistry to the synthesis of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **3**, R = H), another member of the biologically important class of carbohydrates, namely 3-deoxy-*glyc*-2-ulosonic acids. The 7-phosphate derivative of DAH, or DAHP (**3**, R = PO_3^{2-}), is the first intermediate of the shikimate pathway.[14] The latter is the common pathway leading to the biosynthesis of aromatic amino acids and other important compounds, such as folic acid and quinones, in plants and microorganisms.[15] All aromatic amino acids and related secondary metabolites in both plants and microbes must pass through dehydroquinate (DHQ) synthase, an enzyme which catalyzes the conversion of DAHP to DHQ and inorganic phosphate.[16] Therefore, the inhibition of this enzyme is of great value to the design and discovery of new herbicides. Because of the putative inhibiting abilities of DAHP analogues towards DHQ synthase,[17] enzymatic[18] and chemical[19] syntheses of precursor DAH have become of increasing interest in the discovery of potential herbicides.[20] In this manuscript, besides the homologation of carboxylic acids to primary amides, we also report in detail the novel radical approach towards DAH, its 4-epimer, and their derivatives.

RESULTS AND DISCUSSION

Two-carbon homologation of carboxylic acids to primary amides

The *N*-hydroxy-2-thiopyridone ester derivatives of primary, secondary, and tertiary carboxylic acids, **4a-e**, were readily synthesized in good yields as yellow crystals.[21] Due to the limited solubility of acrylamide in organic solvents, the radical chain reactions were carried out in dichloromethane at room temperature. The product yields are listed in Table 1.



4a-e **5a-e**

R = **a**: $Ph(CH_2)_2$; **b:** $(CH_3)_2CH$; **c**: *c*-C_6H_{11}; **d**: $(CH_3)_3C$; **e**: 1-adamantyl.

Table 1. Products and isolated yields of Barton-ester radical chain reactions.

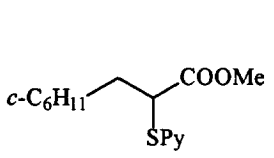
entry	substrate	acrylamide (eq.)	photolysis conditions	product (yield %)	PySSPy (%)	R-SPy (%)
1	**4a**	3	Q-beam, 6 min	**5a** (62)	14	17
2	**4b**	4	lab light, 7 h	**5b** (60)	5	2
3	**4b**	4	Q-beam, 5 min	**5b** (63)	9	2
4	**4c**	2	lab light, 7 h	**5c** (73)	10	10
5	**4c**	2	Q-beam, 5 min	**5c** (71)	12	9
6	**4d**	2	Q-beam, 20 min	**5d** (54)	trace	1
7	**4e**	2	Q-beam, 30 min	**5e** (56)	trace	trace

For comparison, the decarboxylation of thiohydroxamates in the presence of acrylamide was initiated with two different irradiation systems: a tungsten lamp (150 W, Q-beam) or the ordinary laboratory lighting. Although initiation with the latter required longer reaction times, the two methods eventually afforded the products in comparable yields (entries 2-5). As expected, all of the 2-(2-pyridylsulfanyl)-carboxamides **5a-e** were isolated as crystalline solids in reasonable yields; however, the latter were generally lower than those when acrylate esters were used as radical traps.[10] This might be due to the background rearrangement of the

thiohydroxamate esters or oligomerization of acrylamide, because these reactions were carried out at room temperature. The more reactive primary carbon radical, namely phenylethyl radical, resulted in a larger amount of rearrangement product (entry 1). The sterically hindered tertiary carbon radicals, such as *t*-butyl and 1-adamantyl radicals, were more likely to provoke oligomerization of the olefin and, correspondingly, gave lower yields (entries 6,7). The isolation of 2,2′-dipyridyl disulfide (PySSPy) and rearrangement products (RSPy) in relatively small amounts supported this hypothesis. The oligomers of acrylamide were presumably more polar and more soluble in water, and thus were lost during aqueous work-up. Considering these facts, we can conclude that acrylamide is an effective radical trap for radicals from Barton esters.

To exclude the possibility that acrylamide was involved in the initiation step of the radical chain reactions, we used a tungsten lamp to photolyze a dichloromethane solution of acrylamide in the absence of thiohydroxamate esters. Acrylamide was recovered unchanged after 30 minutes at room temperature. This confirms that the thiohydroxamates were the only radical sources in the chain reactions.

As a comparison, when **4c** was photolyzed in dichloromethane in the presence of methyl acrylate at 0°C, methyl 3-cyclohexyl-2-(2-pyridylsulfanyl)-propionate **6** and the double addition product **7** were obtained in 83 and 11% yields, respectively. This result supports the assumption that oligomerization of acrylamide was one of the reasons that resulted in lower yields than expected of the 2-(2-pyridylsulfanyl)-carboxamides when this amide was used as a radical trap.



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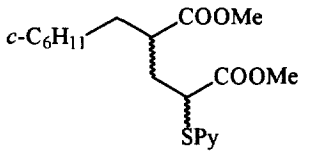

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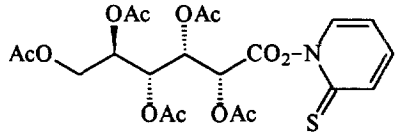

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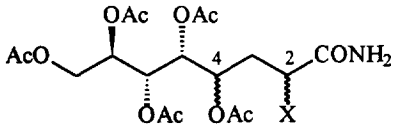
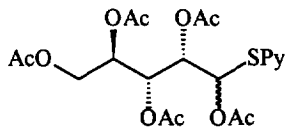


9 X = SPy

12 X = H



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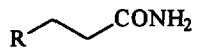


11a: R = c-C_6H_{11}

11b: R = 1-adamantyl

When the *N*-hydroxy-2-thiopyridone ester derivative **8** of 2,3,4,5,6-penta-*O*-acetyl-D-gluconic acid, prepared *in situ* by the DCC coupling method,[11] was photolyzed in the presence of acrylamide, the eight-carbon sugar derivative **9** was isolated in 40% yield as two fractions by column chromatography. The corresponding background rearrangement product **10**[22] was also obtained in 41% yield.

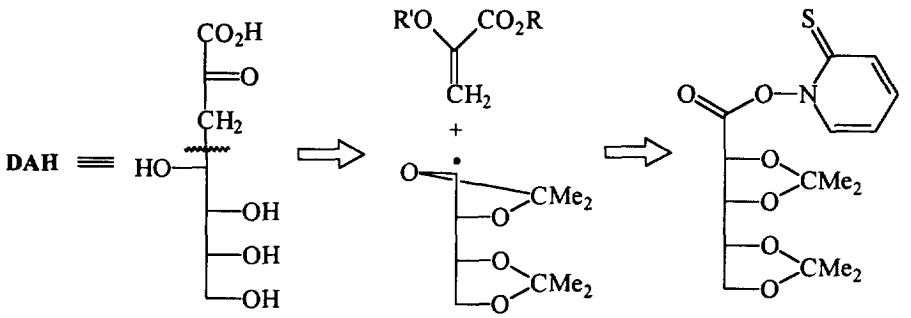
Since the sugar derivative **9** was isolated as two fractions, which theoretically contained four diastereoisomers, from the radical reaction, it was logical to eliminate one asymmetric center (C-2) by removal of the 2-pyridylsulfanyl group. Thus only two diastereoisomers should remain. After several attempts, we found that the combination of nickel(II) chloride and sodium borohydride ('nickel boride'[23]) was very effective for desulfurization of the pyridine sulfide compounds. When a mixture of **5c** and nickel(II) chloride in ethanol was treated with sodium borohydride in water-ethanol at room temperature, the 3-cyclohexyl-propionamide **11a** was obtained in quantitative yield after five hours. Under the similar conditions, the 3-adamantyl-propionamide **11b** was obtained in 94% yield from reduction of **5e**. When the two fractions of **9** were treated with nickel boride at room temperature, both of the two reactions afforded an identical mixture of two diastereoisomers, **12**, in 70-75% yields. This suggests that both of the two fractions of **9** contained two diastereoisomers, which have different configurations at the C-4 stereogenic center.

A hypothesis for the synthesis of DAH

In 1987,[24] we reported a decarboxylative alkylation reaction of tartaric acid based on thiohydroxamate radical chemistry. When the *N*-hydroxy-2-thiopyridone ester derivative of monomethyl 2,3-*O*-isopropylidene-tartrate was irradiated with visible light in the presence of methyl acrylate, the reaction afforded preferentially the alkylation product with the newly formed alkyl group *anti*- to the adjacent methoxycarbonyl group in a 96:4 ratio. This surprisingly high stereoselectivity has been explained by the relative steric hindrance on the two faces of the alkyl radical. This led to the utilization of the isopropylidene group in nucleoside chemistry with similarly satisfactory results.[25]

After having examined the stereochemistry of DAH, we conceived without difficulty that addition of an isopropylidene-protected D-erythrosyl radical **13** onto an olefin would yield preferentially the *trans*- addition product. The newly-formed stereogenic center at the C-4 position would exactly match the requirement of DAH synthesis. Furthermore, the so-designed radical would be readily produced by the *N*-hydroxy-2-thiopyridone ester derivative of either 2,3:4,5-di-*O*-isopropylidene-D-arabinonic acid or 2,3:4,5-di-*O*-isopropylidene-D-ribonic acid. The ready preparation of the latter **14** from the commercial D-ribonolactone[26] and its utilization in related radical reactions as described before[27] guaranteed us a seemingly easy approach to

the synthesis of DAH as follows (Scheme 1). The addition of the five-membered cyclic alkyl radical, generated from **14**, onto an olefin, such as ethyl 2-(trifluoroacetoxy)acrylate **15**,[10] would form the seven-carbon sugar derivative with the desired diastereoselectivity. Aqueous work-up and removal of the protecting groups from the *trans*-addition product would accomplish a short synthesis of DAH in a straightforward fashion.

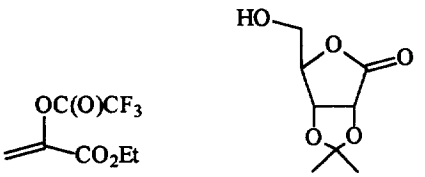


Scheme 1

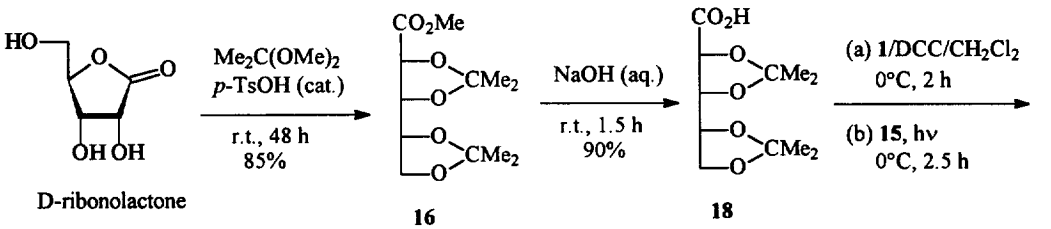
Synthesis of DAH through Barton-ester radical chemistry

Methyl 2,3:4,5-di-*O*-isopropylidene-D-ribonate **16** was synthesized by stirring D-ribonolactone in 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid at room temperature (Scheme 2). This is a modification of the literature method.[28] The by-product of this reaction, 2,3-*O*-isopropylidene-D-ribonolactone (**17**, 9%), was also readily transformed to **16** in 80% yield under similar conditions. This transformation makes D-ribose a valuable alternative as the starting material for this synthesis, since D-ribose could be converted to 2,3-*O*-isopropylidene-D-ribonolactone easily.[29, 30] The ester **16** gave the corresponding carboxylic acid in a moderate yield (58%) using lithium hydroxide in water-THF by following the literature method.[31] We found that it was more convenient to hydrolyze the ester with aqueous sodium hydroxide. The corresponding carboxylic acid **18** was obtained in 90% yield after 90 minutes at room temperature. A simple acid-base extraction procedure afforded the pure product. The acid **18** could be stored in a freezer for over two weeks without decomposition; however, it slowly decomposed to **17** at

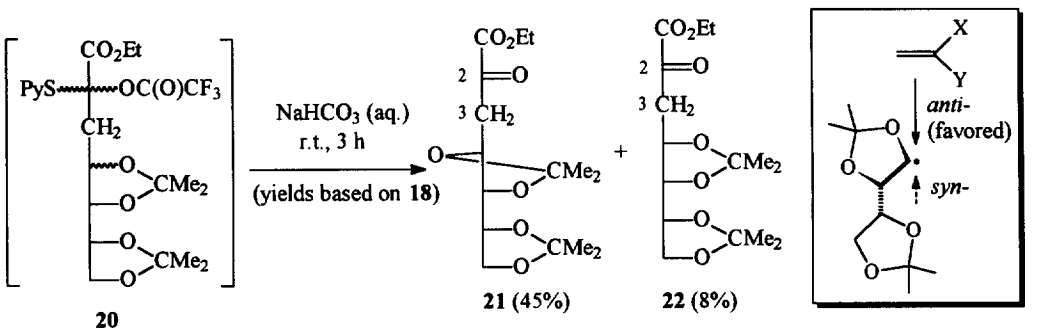
room temperature. As in the preparation of **16** from D-ribonolactone, the same procedure could also be used from a mixture of **17** and **18**.



15 **17** **19**



D-ribonolactone **16** **18**

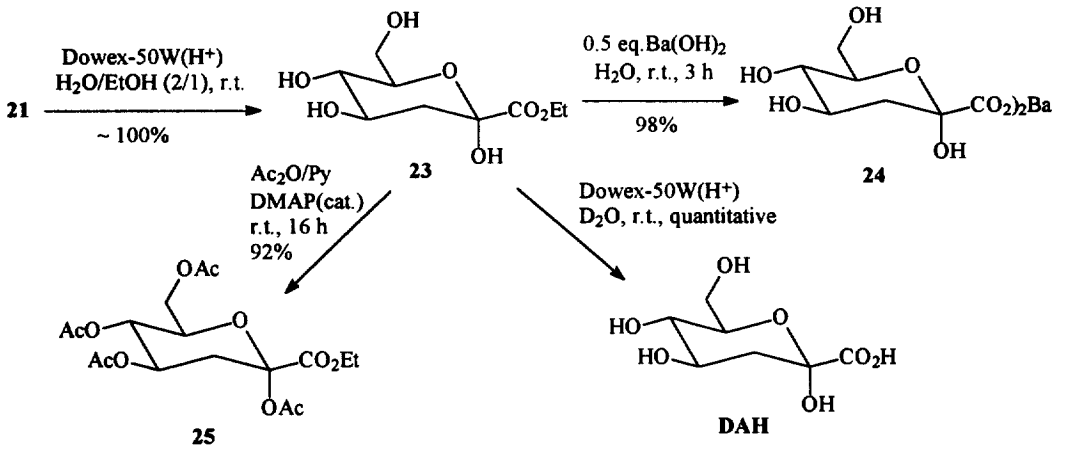


20 **21** (45%) **22** (8%)

Scheme 2

When we attempted to couple the acid **18** with 2,2′-dipyridyl disulfide 1,1′-dioxide **19** in the presence of tri-*n*-butylphosphine (Mukaiyama's method[21, 32]) followed by irradiation with **15**, only traces of the radical reaction products were detected. Because of the low solubility of **19** in dichloromethane at low temperature and the instability of the ester **14** at room temperature, the reaction conditions were not easily optimized. We

found that the conventional 1,3-dicyclohexylcarbodiimide (DCC) coupling method was more convenient for this purpose. Thus, the acid **18** was coupled to **1** in dichloromethane in the presence of DCC to form the ester. The latter, upon photolysis with a 150W tungsten lamp at 0°C and in the presence of **15**, afforded the expected adduct **20**. This intermediate was hydrolyzed by aqueous sodium bicarbonate to give ethyl 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*arabino*-2-heptulosonate **21** in 45% yield after column chromatography. The 4-epimer **22**, namely 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*arabino*-2-heptulosonate, which was contaminated by some DCC from the first isolation, was obtained in 8% yield after further purification by column chromatography. As expected, the desired compound **21** was the major product, since the olefin approached the substituted five-membered cyclic radical from the *anti*-face as a result of the steric hindrance at the *syn*-face (Scheme 2). The ^{1}H- and ^{13}C-NMR spectra showed that the two straight-chain compounds exist exclusively in the α-keto form in $CDCl_3$ (two C=O groups around 160 and 191 ppm in ^{13}C-NMR) and not in the tautomeric 2-enol form.



Scheme 3

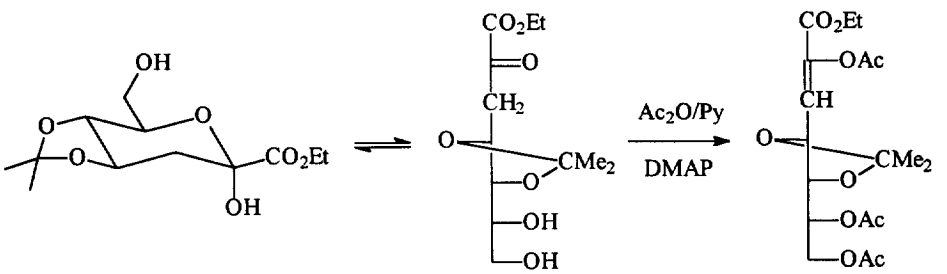
The removal of the isopropylidene groups was first attempted with TFA-ethanol on the minor product **22**. The reaction was sluggish and complex at room temperature. Then, we found that treatment of **21** with freshly activated Dowex-50W(H^+) resin in ethanol and water (neutral conditions) at room temperature cleanly afforded ethyl 3-deoxy-D-*arabino*-2-heptulopyranosonate **23** (Scheme 3). The latter was hydrolyzed with a

stoichiometric amount of barium hydroxide in water to give the corresponding DAH barium salt **24** quantitatively. Physical and spectroscopic data were in full agreement with those reported in the literature.[19]

To make the synthesis more practical, we also tried to skip the isolation step of the radical reaction products. The removal of the isopropylidene groups from the intermediates with Dowex-50W(H^+) yielded a mixture containing DAH ethyl ester as the major component in an overall 63% yield approximately. Hydrolysis of the mixture with barium hydroxide gave DAH barium salt. The latter was further converted to the corresponding ammonium salt in about 70% purity by exchange with ammonium sulfate followed by removal of the precipitate of barium sulfate.

Synthesis of DAH derivatives

When **23** was treated with acetic anhydride, pyridine, and a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature, the DAH ethyl ester 2,4,5,7-tetra-*O*-acetate **25** was obtained in 92% yield (Scheme 3). The spectroscopic data and optical rotation were very close to those of the methyl ester congener.[18b,19d]



26 **27**

Scheme 4

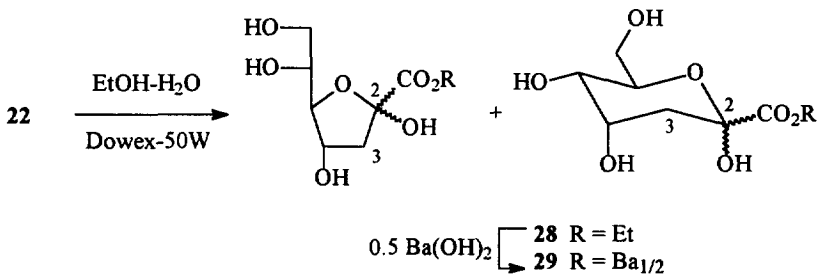
When a limited amount of Dowex-50W(H^+) resin was used in the deprotection step for a limited time, partial removal of the isopropylidene groups afforded **23** and ethyl 3-deoxy-4,5-*O*-isopropylidene-D-*arabino*-2-heptulosonate **26** (Scheme 4) in 1:1 ratio. When the mixture was further hydrolyzed with an ion exchange resin, the DAH ethyl ester became the sole product. The hydrolysis of the isopropylidene group was readily followed by ^{1}H-NMR spectroscopy when Dowex resin was added into an NMR tube containing **23** and **26** in

D_2O. It was observed that after removal of the isopropylidene group, indicated by the decrease of the isopropylidene group signals and the release of acetone, the hydrolysis of the ethyl ester group occurred, which was obviously judged by the appearance of a new diastereotopic CH_2 (C-3 of free DAH) signal and the formation of ethanol. After being left to stand at room temperature for 10 days, the hydrolysis was complete, and a single isomer, presumably the α-pyran form as deduced from the signal at 94.7 ppm (C-2) in the ^{13}C-NMR spectrum,[33] was observed. These studies proved the conformational stability of DAH in D_2O.

When a mixture of **23** and **26** reacted with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP, **25** and **27** were readily isolated by column chromatography.

Synthesis of 3-deoxy-D-*ribo*-2-heptulosonic acid (4-*epi*-DAH or DRH) and derivatives

Similarly, the deprotection of **22** with Dowex-50W(H^+) resin in ethanol-water at room temperature quantitatively gave the ethyl 3-deoxy-D-*ribo*-2-heptulosonate **28**. In contrast, this reaction afforded a mixture, presumably containing all isomers of pyanose and furanose forms as indicated by its complex ^1H and ^{13}C-NMR spectra. The mixture **28** was further hydrolyzed by barium hydroxide in water to afford the corresponding DRH barium salt **29** as a fluffy solid in quantitative yield after evaporation of the solvent to dryness.



Scheme 5

Once again, the ^1H- and ^{13}C-NMR spectra of the DRH barium salts confirmed the coexistence of the pyranose and furanose conformers indicated, respectively, by the 96 ppm and 104 ppm signals of their anomeric carbons (C-2) in the ^{13}C-NMR spectrum.[33] Furthermore, as expected, the IR spectrum of **29** is well comparable to that of DAH barium salt **24**.

CONCLUSIONS

Acrylamide can be used as an effective radical trap of thiohydroxamate esters for two-carbon homologation of carboxylic acids to primary amides. The desulfurization of pyridine sulfide compounds can be carried out with nickel boride under mild conditions. A diastereoselective synthesis of the biologically important sugar DAH was also readily achieved by a radical carbon-carbon bond formation reaction. The mild reaction conditions should find application in other related carbohydrate syntheses.

EXPERIMENTAL SECTION

General methods and starting materials

Melting points were determined with a Thomas hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 infrared spectrophotometer or on an ATI Mattson Genesis Series™ Fourier transform infrared (FT-IR) spectrophotometer. Optical rotations were determined on a Jasco DIP-360 digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were determined on a Varian XL-200E spectrometer at frequencies of 200 and 50 MHz, respectively, or on a Varian VXR-300 spectrometer at frequencies of 300 and 75 MHz, respectively. Chemical shifts are reported relative to tetramethylsilane (TMS, δ = 0.00 ppm). TLC analysis was performed on thin-layer aluminum or glass analytical plates covered with Merck Kieselgel silica gel $60F_{254}$. Column chromatography was carried out on Baxter S/P® brand silica gel (60 Å, 230-400 mesh). Microanalyses were performed by Atlantic Microlab, Inc. of Norcross, Georgia. *N*-Hydroxy-2-thiopyridone was isolated from its sodium salt (Sodium Omadine®), which was a kind gift of the Olin Corporation, Cheshire, Connecticut. D-Ribonolactone was purchased from Acros Organics, New Jersey. Other reference compounds and starting materials were purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin, or Fluka Chemika-BioChemika, Buchs, Switzerland. Solvents were used either as purchased or dried and purified by standard methodology under dry nitrogen.

General procedure for the synthesis of 2-(2-pyridylsulfanyl)-carboxamides

To a solution of acrylamide (2~4 mmol) in dry dichloromethane (20~40 mL) was added an appropriate Barton ester (**4a-e**, 1 mmol) under an argon atmosphere at room temperature. The yellow solution was irradiated with a tungsten lamp (150 W) or with the normal laboratory lighting for a certain period of time (see Table 1). The white suspension which resulted was filtered and the precipitate was washed with

dichloromethane. The filtrate was diluted with dichloromethane, washed with distilled water, and dried with magnesium sulfate. After removal of the solvent, isolation by a short column (Et_2O-hexanes 2:1) afforded the title compounds as white solids. The products were further recrystallized from hexanes-dichloromethane or hexanes-ethyl ether.

5-Phenyl-2-(2-pyridylsulfanyl)-pentanamide (5a, 62% yield): $C_{16}H_{18}N_2OS$ requires C 67.10, H 6.33, N 9.78; found C 67.13, H 6.39, N 9.70. m.p. 82-83°C (hexanes-CH_2Cl_2); IR (KBr) (cm^{-1}): 3408, 3191, 2942, 2917, 2851, 1651, 1579, 1453, 1420, 1403, 1249, 1127, 766; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 1.70-2.30 (m, 4H), 2.60-2.80 (m, 2H), 4.33 (m, 1H), 5.60 (br. s, 1H), 6.95-7.10 (m, 1H), 7.10-7.30 (m, 1H), 7.35 (br. s, 1H), 7.45-7.60 (m, 1H), 8.35-8.45 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 29.2, 29.9, 35.5, 45.5, 120.0, 122.6, 125.7, 128.25, 128.34, 136.4, 141.9, 149.2, 158.0, 174.9.

4-Methyl-2-(2-pyridylsulfanyl)-pentanamide (5b, 60-63% yield): $C_{11}H_{16}N_2OS$ requires C 58.89, H 7.19, N 12.49; found C 58.88, H 7.17, N 12.52. m.p. 95-96°C (hexanes-CH_2Cl_2); IR (KBr) (cm^{-1}): 3376, 3170, 2954, 2908, 1642, 1557, 1441, 1398, 1124, 1103, 757, 712, 643; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.92 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H), 1.55-2.05 (m, 3H), 4.39 (t, J = 7.7 Hz, 1H), 5.55 (br. s, 1H), 7.00-7.10 (m, 1H), 7.19-7.26 (m, 1H), 7.40 (br. s, 1H), 7.48-7.58 (m, 1H), 8.40-8.48 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 22.1, 22.5, 25.8, 38.8, 43.7, 119.9, 122.5, 136.4, 149.1, 158.2, 175.3.

3-Cyclohexyl-2-(2-pyridylsulfanyl)-propionamide (5c, 71-73% yield): $C_{14}H_{20}N_2OS$ requires C 63.60, H 7.62, N 10.60; found C 63.85, H 7.70, N 10.67. m.p. 141-142°C (hexanes-CH_2Cl_2); IR (KBr) (cm^{-1}): 3343, 3170, 2919, 2853, 1670, 1627, 1454, 1416, 706; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.85-2.05 (m, 13H), 4.42 (t, J = 7.8 Hz, 1H), 5.40 (br. s, 1H), 7.00-7.08 (m, 1H), 7.19-7.25 (m, 1H), 7.40 (br. s, 1H), 7.48-7.58 (m, 1H), 8.40-8.45 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 26.0, 26.1, 26.4, 32.8, 33.2, 35.1, 37.4, 42.9, 119.9, 122.5, 136.4, 149.2, 158.3, 175.3.

4,4-Dimethyl-2-(2-pyridylsulfanyl)-pentanamide (5d, 54% yield): $C_{12}H_{18}N_2OS$ requires C 60.47, H 7.61, N 11.76; found C 60.58, H 7.60, N 11.81. m.p. 88-89°C (hexanes-Et_2O); IR (KBr) (cm^{-1}): 3350, 3190, 2959, 1680, 1671, 1624, 1578, 1454, 1415, 1124, 760; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.97 (s, 9H), 1.57 (dd, J = 14.3, 4.6 Hz, 1H), 2.36 (dd, J = 7.6, 4.6 Hz, 1H), 4.40 (dd, J = 14.3, 7.6 Hz, 1H), 5.40 (br. s, 1H), 7.00-7.09 (m, 1H), 7.17-7.23 (m, 1H), 7.35 (br. s, 1H), 7.48-7.58 (m, 1H), 8.40-8.47 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 29.4, 31.4, 41.3, 43.2, 119.9, 122.4, 136.5, 149.2, 158.4, 175.5. GC-MS: 238 (M^+), 206, 181, 164, 138, 111, 78, 57.

3-(1-Adamantyl)-2-(2-pyridylsulfanyl)-propionamide (5e, 56% yield): $C_{18}H_{24}N_2OS$ requires C 68.31, H 7.64, N 8.85; found C 68.39, H 7.66, N 8.80. m.p. 170-171°C (hexanes-CH_2Cl_2); IR (KBr) (cm^{-1}):

3283, 3121, 2904, 1683, 1577, 1561, 1454, 1426, 1390, 1129, 762; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 1.43 (dd, J = 14.4, 4.4 Hz, 1H), 1.40-1.70 (m, 12H), 1.85-2.00 (m, 3H), 2.24 (dd, J = 14.4, 8.1 Hz, 1H), 4.44 (dd, J = 14.4, 8.0 Hz, 1H), 5.35 (br. s, 1H), 7.00-7.10 (m, 1H), 7.15-7.25 (m, 1H), 7.35 (br. s, 1H), 7.45-7.60 (m, 1H), 8.40-8.50 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 28.5, 33.2, 36.9, 39.6, 42.1, 44.0, 119.9, 122.3, 136.4, 149.1, 158.4, 175.6.

Cyclohexyl radical addition onto methyl acrylate

A solution of **4c** (1.187 g, 5 mmol) and methyl acrylate (0.9 mL, 10 mmol) in dry dichloromethane (20 mL) was irradiated with a tungsten lamp at 0°C under an argon atmosphere for one hour. After evaporation of the solvent, the residue was isolated by column chromatography (Et_2O-hexanes 1:4) to afford **6** and **7**.

Methyl 3-cyclohexyl-2-(2-pyridylsulfanyl)-propionate[10] (**6**, 83% yield): $C_{15}H_{21}NO_2S$, IR (neat) (cm^{-1}): 2924, 2851, 1731, 1577, 1446, 1413, 1272, 1257, 1157, 1120, 757, 723; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.80-2.00 (m, 13H), 3.72 (s, 3H), 4.63 (t, J = 7.9 Hz, 1H), 6.95-7.03 (m, 1H), 7.16-7.23 (m, 1H), 7.43-7.54 (m, 1H), 8.38-8.42 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 25.9, 26.0, 26.3, 32.8, 33.0, 35.4, 39.1, 44.1, 52.3, 119.7, 122.1, 136.0, 149.3, 157.4, 173.5.

Double addition product (7, 11% yield): IR (neat) (cm^{-1}): 2922, 2852, 1736, 1576, 1446, 1414, 1257, 1195, 1161, 1120, 1041, 759, 723; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.70-2.50 (m, 15H), 2.60-2.90 (m, 1H), 3.64 (s, 1.5H), 3.70 (s, 1.5H), 3.727 (s, 1.5H), 3.730 (s, 1.5H), 4.55-4.70 (m, 1H), 6.95-7.05 (m, 1H), 7.15-7.23 (m, 1H), 7.44-7.55 (m, 1H), 8.39-8.44 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 26.1, 26.5, 32.8, 33.0, 33.1, 33.3, 33.9, 34.6, 35.2, 35.4, 40.0, 40.2, 40.3, 40.7, 44.1, 44.6, 51.6, 52.5, 120.0, 122.27, 122.33, 136.16, 136.18, 149.3, 149.4, 156.66, 156.74, 172.6, 172.8, 176.0, 176.1; HRMS (FAB) 366.1745, $C_{19}H_{27}NO_4S$ (MH^+) requires 366.1739.

Synthesis of 4,5,6,7,8-penta-*O*-acetyl-2-(2-pyridylsulfanyl)-2,3-dideoxy-D-*manno(gluco)*-octonamide (9)

The ester **8**, prepared *in situ* from pentaacetyl-D-gluconic acid (813 mg, 2.00 mmol) according to the literature procedure,[11] was transferred into an acrylamide (284 mg, 4 mmol) solution in dry dichloromethane (20 mL), and the mixture was irradiated with a tungsten lamp at room temperature under an argon atmosphere for 20 minutes. After stirring for three hours, the reaction mixture was diluted with dichloromethane, washed with distilled water, and dried with magnesium sulfate. Removal of the solvent followed by flash chromatography (Et_2O to Et_2O-EtOAc 2:1) afforded the title compounds **9** as two fractions

accompanied by the rearrangement product **10**[22] (389 mg, 41%). **9** ($C_{23}H_{30}N_2O_{11}S$): the less polar fraction (containing two isomers, 190 mg, 18%): ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 1.80-2.00 (m, 1H), 2.00-2.20 (m, 15H), 2.35-2.60 (m, 1H), 4.00-4.30 (m, 2H), 4.35-4.45 (m, 1H), 5.00-5.15 (m, 1H), 5.25-5.35 (m, 1H), 5.40 (br. s, 1H), 5.40-5.50 (m, 2H), 7.00-7.10 (m, 1H), 7.15-7.25 (m, 1H), 7.35 (br. s, 1H), 7.45-7.60 (m, 1H), 8.35-8.45 (m, 1H); the more polar fraction (containing two isomers, 234 mg, 22%): ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 1.85-2.20 (m, 16H), 2.30-2.50 (m, 1H), 4.00-4.30 (m, 2H), 4.30-4.45 (m, 1H), 5.00-5.15 (m, 1H), 5.25-5.35 (m, 2H), 5.35-5.50 (m, 1H), 5.52 (br. s, 1H), 7.00-7.10 (m, 1H), 7.20-7.30 (m, 1H), 7.40 (br. s, 1H), 7.50-7.60 (m, 1H), 8.35-8.45 (m, 1H).

General procedure for nickel boride desulfurization reaction

To a mixture of the starting material (1 mmol) and nickel(II) chloride (1.3 g, 10 mmol) in ethanol (40 mL) was slowly added a solution of sodium borohydride (757 mg, 20 mmol) in ethanol-water (5 mL : 5 mL) over 20 minutes. After stirring at room temperature for two to five hours depending on substrates, the black mixture was filtered through Celite 545®, and the precipitate was washed with dichloromethane. After evaporation of the filtrate, the residue was dissolved in dichloromethane, washed with water, and dried with magnesium sulfate. Removal of the solvent afforded pure products by NMR.

3-Cyclohexyl-propionamide (**11a**, 100% yield): $C_9H_{17}NO$, m.p. 119-120°C (CH_2Cl_2-hexanes) (lit.[34] m.p. 119-120°C, MeOH); IR (KBr) (cm^{-1}): 3343, 3170, 2919, 2853, 1670, 1627, 1454, 1416, 1156, 706; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 0.80-1.40 (m, 7H), 1.40-1.80 (m, 6H), 2.15-2.30 (m, 2H), 5.60 (br. s, 1H), 5.95 (br. s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 26.2, 26.5, 32.9, 33.0, 33.4, 37.2, 176.4.

3-(1-Adamantyl)-propionamide (**11b**, 94% yield): $C_{13}H_{21}NO$ requires C 75.31, H 10.21, N 6.70; found C 75.40, H 10.29, N 6.71. m.p. 145-146°C (CH_2Cl_2-hexanes); IR (KBr) (cm^{-1}): 3434, 3190, 2899, 2847, 1665, 1451, 1404; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 1.38-1.50 (m, 8H), 1.66 (dd, J = 28.2, 11.7 Hz, 6H), 1.96 (br. s, 3H), 2.14-2.22 (m, 2H), 5.55 (br. s, 1H), 5.85 (br. s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 28.6, 29.5, 31.9, 37.0, 39.6, 42.1, 176.7.

4,5,6,7,8-Penta-*O*-acetyl-2,3-dideoxy-D-*manno(gluco)*-octonamide (**12**, two isomers, 70-75%): IR ($CHCl_3$ film) (cm^{-1}): 3461, 3364, 3203, 2935, 1738, 1667, 1430, 1368, 1217, 1044, 950, 919, 729; ^{1}H-NMR ($CDCl_3$, 200 MHz) (δ, ppm): 2.00-2.18 (m, 15H), 2.18-2.20 (m, 2H), 4.00-4.30 (m, 2H), 4.95-5.15 (m, 2H), 5.25-5.32 (m, 1H), 5.40-5.50 (m, 1H), 5.80 (br. s, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz) (δ, ppm): 20.5, 20.62, 20.65, 20.7, 20.8, 20.9, 26.0, 26.2, 29.6, 30.9, 31.0, 61.4, 61.8, 67.5, 68.0, 68.6, 68.7, 69.4, 69.7, 70.7, 70.9,

169.75, 169.83, 169.88, 169.94, 170.2, 170.6, 170.7, 173.9, 174.3; HRMS (FAB): 434.1672; $C_{18}H_{27}NO_{11}$ (MH^+) requires 434.1662.

Reaction of D-ribonolactone with 2,2-dimethoxypropane

To the suspension of D-ribonolactone (1.484 g, 10 mmol) in 2,2-dimethoxypropane (20 mL) was added *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol) under an argon atmosphere, and the reaction mixture was stirred at room temperature for 48 hours. Sodium bicarbonate (420 mg, 5 mmol) was added into the solution and the solvent was evaporated under reduced pressure. The residue was dissolved in saturated sodium bicarbonate solution and extracted with dichloromethane thrice. After being dried over magnesium sulfate, removal of the solvent from the combined organic extracts afforded a mixture of **16** and **17** in 9:1 ratio. Isolation by column chromatography (Et_2O-hexanes 1:2 to Et_2O) furnished **16** as a colorless oil and **17** as colorless crystals.

Methyl 2,3:4,5-di-*O*-isopropylidene-D-ribonate[27] (**16**, 85% yield): $C_{12}H_{20}O_6$, $[\alpha]_D^{28}$ −17.1 (c = 5.00, $CHCl_3$); IR (neat) (cm^{-1}): 2988, 2951, 2886, 1758, 1438, 1381, 1209, 1075, 850; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.30 (s, 3H), 1.37 (s, 3H), 1.40 (s, 3H), 1.55 (s, 3H), 3.76 (s, 3H), 3.89-3.96 (m, 1H), 4.03-4.12 (m, 2H), 4.20-4.28 (m, 1H), 4.71 (d, J = 6.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 25.3, 25.5., 26.8, 27.2, 52.0, 67.2, 73.7, 75.9, 78.4, 109.7, 110.9, 169.1.

2,3-*O*-Isopropylidene-D-ribonolactone (**17**, 9% yield): $C_8H_{12}O_5$, m.p. 137-138°C (CH_2Cl_2-hexanes) (lit.[35] 138-139°C); IR (KBr) (cm^{-1}): 3470, 2990, 2932, 1767, 1378, 1242, 1202, 1094, 1078, 976, 927, 867; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.39 (s, 3H), 1.48 (s, 3H), 3.82 (dd, J = 12.2, 1.8 Hz, 1H), 4.01 (dd, J = 12.2, 2.4 Hz, 1H), 4.64 (t, J = 2.1 Hz, 1H), 4.78 (d, J = 5.7 Hz, 1H), 4.84 (d, J = 5.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 25.4, 26.7, 61.9, 75.6, 78.2, 82.8, 113.1, 175.1.

Synthesis of 2,3:4,5-di-*O*-isopropylidene-D-ribonic acid (18):[27] To a flask containing the starting material (5.047 g, 19.39 mmol) was added 20 mL of distilled water and 1.96 g of NaOH pellets (48.53 mmol) at 0°C under an argon atmosphere. After being stirred at 0°C for 20 minutes and at room temperature for 70 minutes, the resultant colorless solution was diluted with water (~150 mL) and washed with dichloromethane (70 + 30 mL). The aqueous phase was acidified at 0°C with citric acid (15.42 g, 73.40 mmol). After complete dissolution of the citric acid, the aqueous solution was extracted with dichloromethane (4 × 65 mL). The aqueous solution was then salted with NaCl solid (5 g), and extracted again with dichloromethane (3 × 60 mL). The combined organic extracts were dried over magnesium sulfate. Removal of the solvent afforded

the pure acid (4.248 g, 90% yield). $C_{11}H_{18}O_6$, $[\alpha]_D^{26}$ −8.5 (c = 2.50, $CHCl_3$); IR (neat) (cm^{-1}): 3503, 2990, 2941, 1741, 1379, 1216, 1159, 1073, 847; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.33 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.57 (s, 3H), 3.97 (dd, J = 8.5, 4.9 Hz, 1H), 4.08 (dd, J = 8.5, 6.0 Hz, 1H), 4.19-4.26 (m, 1H), 4.33 (dd, J = 8.1, 6.6 Hz, 1H), 4.71 (d, J = 6.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 25.2, 25.4, 26.7, 27.0, 66.8, 73.7, 75.6, 78.2, 110.0, 111.2, 172.8.

Synthesis of ethyl 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*arabino(ribo)*-2-heptulosonate (21 & 22)

N-Hydroxy-2-thiopyridone (711 mg, 5.594 mmol) and DCC (1.212 g, 5.874 mmol, 1.05 eq.) were dissolved in dry dichloromethane (30 mL) in a two-necked flask (100 mL) at 0°C under an argon atmosphere. To the above mixture was added dropwise a solution of 2,3:4,5-di-*O*-isopropylidene-D-ribonic acid (1.3775 g, 5.594 mmol) in dichloromethane (10 mL) in the dark (protected by aluminum foil). After being stirred for two hours, the dichloromethane solution was transferred by an argon stream through a long needle to a 250 mL flask containing ethyl 2-(trifluoroacetoxy)acrylate (3 mL, ~3.56 g, 16.78 mmol) while photolyzed by a tungsten lamp at 0°C. The 1,3-dicyclohexyl urea (DCU) residue was washed with dichloromethane (3 × 5 mL) and the washings were also transferred to the olefin flask during irradiation. The reaction mixture was irradiated by a tungsten lamp for 2.5 hours at 0°C and then stirred at room temperature for another two hours. To the reaction mixture was added a $NaHCO_3$ (4.7 g, 56 mmol) solution (90 mL), and the reaction mixture was stirred at room temperature for three hours. After partitioned between dichloromethane and $NaHCO_3$ solution, the aqueous phase was extracted with more dichloromethane. The organic extracts were combined and dried with magnesium sulfate. After removal of the solvent, isolation over a short column (Et_2O-hexanes 1:3) afforded the products **21** and **22**. The latter was contaminated by some DCC, and the further purification by a short column furnished pure **22**.

Ethyl 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*arabino*-2-heptulosonate (21, 45% yield): $C_{15}H_{24}O_7$ requires C 56.95, H 7.65; found C 57.06, H 7.60. R_f (Et_2O-hexanes, 2:1): 0.23; $[\alpha]_D^{28}$ +26.0 (c = 1.02, $CHCl_3$); IR (neat) (cm^{-1}): 2987, 2936, 2905, 1730, 1372, 1240, 1216, 1156, 1066, 844; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.32 (s, 3H), 1.37 (s, 6H), 1.39 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H), 3.18 (dd, J = 16.8, 7.6 Hz, 1H), 3.25 (dd, J = 16.8, 4.6 Hz, 1H), 3.60 (t, J = 8.1 Hz, 1H), 3.90-4.18 (m, 3H), 4.33 (q, J = 7.1 Hz, 2H), 4.43 (td, J = 7.8, 4.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 14.0, 25.1, 26.6, 26.8, 27.0, 42.8, 62.5, 67.8, 75.6, 76.8, 80.7, 109.7, 109.8, 160.7, 191.3; HRMS (FAB) 317.1600, $C_{15}H_{24}O_7$ (MH^+) requires 317.1600.

Ethyl 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*ribo*-2-heptulosonate (**22**, 8% yield): $C_{15}H_{24}O_7$ requires C 56.95, H 7.65; found C 57.20, H 7.66. R_f (Et_2O-hexanes, 2:1): 0.29; $[\alpha]_D^{27}$ +26.3 (*c* = 1.00, $CHCl_3$); IR (neat): 2987, 2936, 1732, 1382, 1372, 1259, 1218, 1054, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.26 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.40 (s, 3H), 3.12 (dd, *J* = 7.8, 6.1 Hz, 1H), 3.47 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.86-4.14 (m, 4H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.74-4.83 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 14.0, 25.4, 25.5, 26.3, 28.0, 39.0, 62.4, 67.7, 72.6, 73.3, 77.7, 108.5, 110.1, 160.4, 191.0.

Ethyl 3-deoxy-D-*arabino*-2-heptulopyranosonate (**23**): To a solution of **21** (54 mg, 0.172 mmol) in water (2 mL) and ethanol (1 mL) under an argon atmosphere at room temperature, was added newly activated Dowex-50W(H^+) resin (250 mg) while stirring. (Dowex resin was washed in a Büchner filter funnel with water several times, 5% HCl once, and water again until the filtrate became neutral as tested by a pH paper.) TLC showed the disappearance of the starting material after eight hours. The ion exchange resin was removed by filtration and washed with some ethanol and water. Evaporation of the filtrate to dryness afforded a single product **23** (40 mg, 100%). $[\alpha]_D^{26}$ +37.0 (*c* = 0.62, H_2O); IR (neat) (cm^{-1}): 3405, 2932, 1734, 1626, 1446, 1373, 1302, 1270, 1141, 1108, 1069, 1025, 986; ^{1}H-NMR (D_2O, 300 MHz) (δ, ppm): 1.34 (t, *J* = 7.1 Hz, 3H), 1.88 (dd, *J* = 12.9, 7.1 Hz, 1H), 2.31 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.40-3.54 (m, 4H), 4.32 (q, *J* = 7.1 Hz, 2H); ^{13}C-NMR (D_2O, 75 MHz) (δ, ppm): 14.1, 39.4, 61.5, 64.4, 69.3, 71.5, 74.9, 96.0, 171.9; HRMS (FAB): 259.0804, $C_9H_{16}O_7$ (MNa^+) requires 259.0794.

Barium 3-deoxy-D-*arabino*-2-heptulopyranosonate (**24**):[19a-c] To a solution of **23** (38 mg, 0.16 mmol) in water (4 mL) was added barium hydroxide octahydrate (25 mg, 0.08 mmol), and the reaction mixture was stirred under argon at room temperature for three hours. Evaporation of the solvent until dryness afforded a pale yellow fluffy solid. The NMR showed as a single product DAH barium salt **24** (43 mg, 98%). $C_{14}H_{22}O_{14}Ba$: $[\alpha]_D^{26}$ +33.1 (*c* = 1.02, H_2O); m.p. 180-183°C (dec.); IR (KBr) (cm^{-1}): 3398, 2938, 1604, 1412, 1070; ^{1}H-NMR (D_2O, 300 MHz) (δ, ppm): 1.82 (dd, *J* = 13.0, 12.2 Hz, 1H), 2.23 (dd, *J* = 13.0, 5.2 Hz, 1H), 3.48 (t, *J* = 9.4 Hz, 1H), 3.74-4.02 (m, 4H); ^{13}C-NMR (D_2O, 75 MHz) (δ, ppm): 40.0, 61.5, 69.7, 71.5, 74.5, 97.1, 177.4.

3-Deoxy-D-*arabino*-2-heptulopyranosonic acid (DAH): To an NMR tube containing a mixture (18 mg) of **23** and **26** (1:1) in D_2O was added Dowex-50W(H^+) resin (100 mg) at room temperature, and the reaction was followed by NMR. The hydrolysis of the isopropylidene and ester groups went to completion in 10 days. $C_7H_{12}O_7$, ^{1}H-NMR (D_2O, 300 MHz) (δ, ppm): 1.88 (dd, J = 13.2, 11.7 Hz, 1H), 2.33 (dd, J = 13.2, 5.1 Hz, 1H), 3.49 (brt, J = 8.6 Hz, 1H), 3.80-3.96 (m, 3H), 3.96-4.08 (m, 1H); ^{13}C-NMR (D_2O, 75 MHz) (δ, ppm): 38.2, 60.1, 68.0, 70.1, 73.5, 94.7, 172.8.

Synthesis of acetylated DAH derivatives

Partial removal of acetone and acetylation: To the starting material **21** (95 mg, 0.30 mmol) in water (4 mL) and ethanol (2 mL) at room temperature was added Dowex-50W(H^+) resin (200 mg), and the reaction mixture was stirred for six hours. TLC showed the disappearance of the starting material. The ion exchange resin was removed by filtration and washed with ethanol and water. Removal of the solvents afforded a mixture (77 mg) of **23** and **26** in a 1:1 molar ratio. Then, to the mixture was added acetic anhydride (2 mL), pyridine (2 mL), and DMAP (10 mg) while stirring at room temperature. After 48 hours, the solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed successively with 5% HCl and saturated $NaHCO_3$, and dried over magnesium sulfate. After removal of the solvent, the residue was isolated by column chromatography (Et_2O/hexanes 1/2) to afford **25** (34 mg) and **27** (40 mg).

Full acetylation: To a flask containing **23** (59 mg, 0.25 mmol) was added acetic anhydride (2 mL), pyridine (2 mL), and DMAP (10 mg), and the mixture was stirred at room temperature for 16 hours. After evaporation of the solvents under reduced pressure, the residue was dissolved in dichloromethane, washed successively with 5% HCl and saturated $NaHCO_3$, and dried over magnesium sulfate. After removal of the solvent, the residue was isolated by column chromatography (Et_2O/hexanes 1/2) to afford **25** (93 mg, 92%).

Ethyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-D-*arabino*-2-heptulopyranosonate (25): $C_{17}H_{24}O_{11}$, $[\alpha]_D^{27}$ +59.0 (c = 0.85, $CHCl_3$); IR (neat) (cm^{-1}): 2982, 1741, 1444, 1369, 1227, 1170, 1101, 1081, 1052, 1009, 907, 859, 759; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.29 (t, J = 7.2 Hz, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.09 (dd, J = 13.6, 11.4 Hz, 1H), 2.17 (s, 3H), 2.66 (dd, J = 13.6, 5.2 Hz, 1H), 4.02-4.14 (m, 2H), 4.26 (qd, J = 7.2, 1.8 Hz, 2H), 4.35 (dd, J = 12.4, 4.2 Hz, 1H), 5.13 (t, J = 9.8 Hz, 1H), 5.25-5.35 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 13.9, 20.64, 20.74, 20.77, 20.84, 35.5, 61.7, 62.5, 68.3, 68.4, 71.5, 97.4, 98.6, 165.7, 168.3, 169.6, 170.1, 170.7; HRMS (FAB): 427.1224, $C_{17}H_{24}O_{11}$ (MNa^+) requires 427.1216.

Ethyl 2,6,7-tri-*O*-acetyl-4,5-*O*-isopropylidene-3-deoxy-D-*arabino*-2-enol-heptulosonate (27): $C_{18}H_{26}O_{10}$, R_f (Et_2O-hexanes, 2:1): 0.40; $[\alpha]_D^{27}$ +22.2 (c = 0.91, $CHCl_3$); IR (neat) (cm^{-1}): 2988, 2938, 1773, 1740, 1677, 1444, 1372, 1306, 1218, 1193, 1064, 935, 859; ^{1}H-NMR ($CDCl_3$, 300 MHz) (δ, ppm): 1.31 (t, J = 7.2 Hz, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.25 (s, 3H), 3.99 (t, J = 7.4 Hz, 1H), 4.11 (dd, J = 12.2, 6.1 Hz, 1H), 4.25 (qd, J = 7.2, 1.3 Hz, 2H), 4.49 (dd, J = 12.2, 2.7 Hz, 1H), 4.64 (dd, J = 8.8, 7.6 Hz, 1H), 5.14-5.22 (m, 1H), 6.41 (d, J = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) (δ, ppm): 14.0, 20.2, 20.7, 20.8, 26.79, 26.82, 62.0, 62.8, 71.3, 73.6, 78.2, 111.0, 126.0, 141.0, 161.2, 168.3, 170.1, 170.6); HRMS (FAB): 425.1437, $C_{18}H_{26}O_{10}$ (MNa^+) requires 425.1424.

Ethyl 3-deoxy-D-*ribo*-2-heptulosonate (28): To a solution of **22** (32 mg, 0.1 mmol) in ethanol (1 mL) and water (2 mL) was added Dowex-50W(H^+) resin (223 mg), and the mixture was stirred at room temperature for six hours. Removal of the ion exchange resin by filtration and evaporation of the solvent furnished a thick colorless oil (23 mg, 98%). $C_9H_{16}O_7$, $[\alpha]_D^{26}$ +35.5 (c = 0.30, H_2O); IR (neat) (cm^{-1}): 3417, 2941, 1740, 1645, 1304, 1268, 1071, 880; ^{1}H-NMR (D_2O, 300 MHz) (δ, ppm): 1.29-1.55 (m, 3H), 1.90-2.76 (m, 2H), 3.60-4.25 (m, 4H), 4.25-4.40 (m, 2H), 4.54-4.68 (m, 1H); ^{13}C-NMR (D_2O, 75 MHz) (δ, ppm): 14.3, 37.3, 44.5, 44.7, 62.1-75.6 (m), 96.0, 103.7, 169.3, 172.1, 172.3, 172.5, 176.7; HRMS (FAB): 259.0803, $C_9H_{16}O_7$ (MNa^+) requires 259.0794.

Barium 3-deoxy-D-*ribo*-2-heptulosonate (29): To a solution of **28** (15 mg, 0,064 mmol) in water (3 mL) was added barium hydroxide octahydrate (10 mg, 0.032 mmol). After stirring for five hours at room temperature, removal of the solvent to dryness resulted in the barium salt as a white solid (18 mg, 100%). $C_{14}H_{22}O_{14}Ba$, m.p. 165-180°C (dec), $[\alpha]_D^{26}$ +39.0 (c = 0.31, H_2O); IR (KBr) (cm^{-1}): 3388, 2940, 1605, 1419, 1221, 1158, 1102, 1073, 1026; ^{1}H-NMR (D_2O, 300 MHz) (δ, ppm): 2.08 (dd, J = 15.0, 2.8 Hz), 2.07-2.15 (m), 2.20 (dd, J = 15.0, 3.3 Hz), 2.30-2.48 (m), 2.58 (dd, J = 14.2, 7.5 Hz), 3.62-4.40 (m), 4.50-4.15 (m), 4.16-4.28 (m), 4.52-4.63 (m); ^{13}C-NMR (D_2O, 75 MHz) (δ, ppm): 36.9, 43.7, 44.4, 61.3, 62.5, 62.9, 66.3, 67.9, 69.5, 71.3, 71.9, 72.4, 72.6, 177.0, 177.06, 177.08; Mass of the negative ion (-FAB/DP): 207, $C_7H_{11}O_7$ requires 207.

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