Pergamon

Tetrahedron: *Asymmetry* 14 (2003) 3973–3986

TETRAHEDRON: *ASYMMETRY*

# (–)-Daucic acid: Proof of D-*lyxo* configuration, synthesis of its D-*ribo*, D-*xylo*, L-*arabino* and L-*lyxo* analogs, and biosynthetic implications☆

Frieder W. Lichtenthaler,* Jürgen Klotz and Katsumi Nakamura

*Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, D-64287 Darmstadt, Germany*

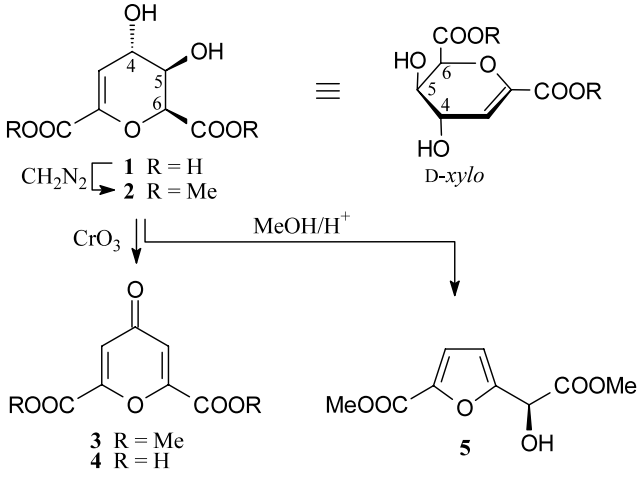
Received 26 September 2003; accepted 14 October 2003

**Abstract**—The dimethyl esters of the 2,6-anhydro-3-deoxy-hept-2-enaric acids with D-*xylo*, D-*lyxo*, L-*arabino*, L-*lyxo*- and D-*ribo*-configuration were synthesized from D-galactose and D-mannose, respectively, and further characterized by their di-*O*-acetyl and di-*O*-benzoyl derivatives. Comparison of their physical data with those of *Daucus carota* derived products revealed (–)-daucic acid to have D-*lyxo*-configuration **46** rather than the previously assigned D-*xylo* stereochemistry **1**. Dimethyl daucate **43** could be converted by acid-induced ring contraction and dehydration into naturally occurring (+)-osbeckic acid **47**, thereby proving its (*S*)-configuration. Configurational identity in the pyranoid rings of (–)-daucic acid and KDO, together with available biosynthetic evidence on chelidonic acid **4**, a leaf closing factor, suggests a joint, KDO 8-P-based pathway for their biosynthesis in plants.


## 1. Introduction

(–)-Daucic acid, a seven-carbon sugar–dicarboxylic acid widely distributed across a range of plant families such as carrots (*Daucus carota*), wheat, sunflower, sugar beet, and tobacco, was first isolated from mature carrots in 1971[2] and shown later to be a 2,6-anhydro-3-deoxy-D-hept-2-enaric acid of D-*xylo* configuration **1**.[3] The assignment of a dihydropyran structure was based on the oxidative conversion of its dimethyl ester into dimethyl chelidonate (**2**→**3**), its affiliation to the D-series of sugars, i.e. configuration at C-6, convincingly followed from the high positive rotation of the furanoid rearrangement product **5** (+79.3 in $CHCl_3$) which correlated well with the equally high negative rotation of the synthetically prepared L-enantiomer (Scheme 1).[3]

Less conclusive were the configurational assignments at C-4 and C-5, as they were inferred from low resolution (60 MHz) $^1$H NMR couplings for H-4 and H-5 in dimethyl daucate **2** and its di-*O*-acetyl derivative,[3] and comparisons with NMR data of certain 3,4-unsaturated hexuronates[4a] which on close inspection prove unreli-




**Scheme 1.** Reactions of *Daucus carota*-derived (–)-daucic acid leading to the structure of a 2,4-anhydro-2-deoxy-hept-2-enaric acid and, on the basis of 60 MHz $^1$H NMR data, to the D-*xylo* configuration.[3]

☆ Part 31 of the series 'Sugar-Derived Building Blocks'. For Part 30, see Ref. 1.

* Corresponding author. Fax: +49-6151-166674; e-mail: lichtenthaler@chemie.tu-darmstadt.de

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.10.007

able.[4b] In view of the proclivity of sugar-derived dihydropyrans to give complex, hardly predictable conformational equilibria between the respective half-chair forms, resulting in intricate coupling patterns with little bearing on the actual configuration, a verification of the stereochemistry at C-4 and C-5 of (−)-daucic acid appeared imperative.

These implications, together with the notion that daucic acid is a possible biosynthetic precursor of chelidonic acid **4**, a leaf-closing factor of *Cassia mimosoides*,[5] prompted us to devise a stereocontrolled synthesis, practical enough to furnish sufficient amounts for biological studies. Accordingly, we report herein expedient syntheses of the daucic acids with D-*xylo*, D-*ribo*, L-*arabino*, L-*lyxo*, and D-*lyxo* configuration, from D-galactose and D-mannose, respectively, entailing assignment of the D-*lyxo* stereochemistry to the *Daucus carota*-derived product.[6]

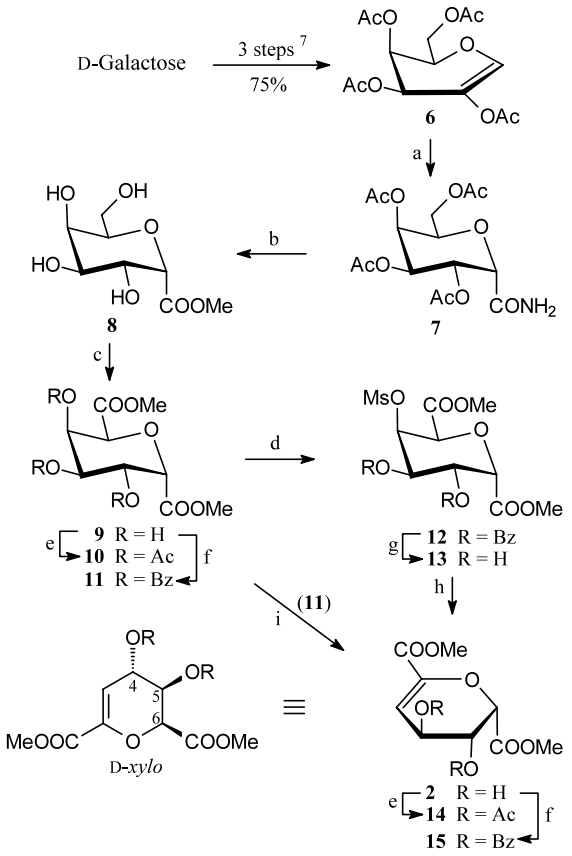
## 2. Results and discussion

Our conceptual approach for developing a stereochemically unambiguous access to the D-*xylo*-heptenaric acid **2**—as well as the three alternate configurations conceivable for **2**—was based on the anomeric one-carbon homologation of suitable D-hexoses, subsequent oxidation at either terminus to the respective pyranoid $C_7$-dicarboxylic acids, and controlled β-elimination into the pyranoid ring to be effected by the judicious choice of leaving groups.

### 2.1. D-*xylo*-Heptenarate 2

As outlined in Scheme 2, synthesis of **2** started from tri-*O*-acetyl-2-acetoxy-D-galactal **6**, readily accessible from D-galactose in a three-step/one-pot procedure involving acetylation, treatment with HBr/HOAc[7a] and dimethylamine-promoted elimination of HBr.[7b,c] The acetone-initiated photoaddition of formamide to **6**, albeit complex,[8] is α-selective to give heptonamide **7** as the major product (54%), which was then converted into methyl heptonate **8** by vigorous methanolysis. Oxidation of the primary hydroxyl was smoothly effected by oxygen in the presence of Adams catalyst to afford, after esterification with methanolic HCl, dimethyl heptarate **9**. Despite of its 5-OH group being axial suggesting a preferential 5,6-elimination in the tri-*O*-acetyl derivative **10**, exposure to NaOAc/$Ac_2O$ at 70°C led to complex mixtures. The tribenzoate **11**, however, when heated in NaOAc/$Ac_2O$ at 100°C, preferentially displaced the axial 5-benzoyloxy group to afford the $\Delta^{5,6}$-unsaturated dibenzoate **15** in fair yield (59%). Acid de-*O*-benzoylation then led to the D-*xylo*-heptenarate **2**.

An alternate possibility to generate **2** from dimethyl heptarate **9** comprised the introduction of a better leaving group at *O*-5, implemented by low temperature-benzoylation of the equatorial hydroxyls and subsequent treatment with methanesulfonyl chloride (→**12**). Now, 5,6-dimination could cleanly be effected, either in

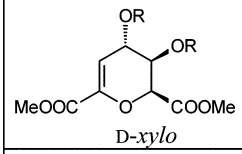
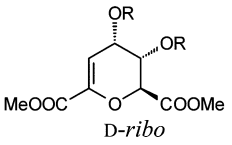
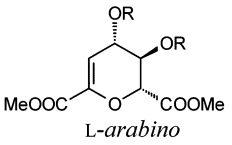
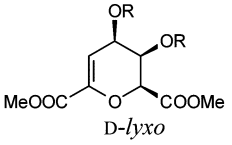



**Scheme 2.** Elaboration of D-*xylo*-heptenarates from D-galactose. *Reagents and conditions*: (a) $HCONH_2$, $Me_2CO$, *hv*, 3 days, rt, 54%;[8] (b) 8% HCl/MeOH, reflux, 3 h, 86%; (c) Pt/$O_2$, water (pH 8), 70°C, 4 h; then HCl/MeOH, rt, 1 h, 56%; (d) BzCl, pyridine, −40°C, 2 h; then MsCl, −40°C to rt, 2 h, 58%; (e) $Ac_2O$, pyridine rt, 14 h, 85%; (f) BzCl, pyridine, rt, 12 h, 87%; (g) HCl satd MeOH, reflux, 14 h, 73%; (h) 0.1N NaOMe/MeOH, rt, 1 h, 77%; (i) NaOAc/$Ac_2O$, 100°C, 1 h, 59%.

**12** by briefly heating in NaOAc/$Ac_2O$ to afford the dibenzoate **15** (79%), or, more smoothly, in its de-*O*-benzoylation product **13** through exposure to NaOMe/MeOH, which directly provided the OH-free dimethyl D-*xylo*-heptenarate **2** (77%). Except for the di-*O*-acetyl **14** and di-*O*-benzoyl derivatives **15**, all products of this reaction sequence were obtained in readily characterizable, crystalline form.

The melting point for **2** thus obtained proved to be close to that of the *Daucus carota*-derived product (cf. Table 1), yet its specific rotation, albeit similar in numerical value, was opposite in sign. The notion that the natural product could thus have the enantiomeric L-*xylo*-configuration, was clearly invalidated by the distinct differences in the $^1H$ NMR data of synthetic **2** and **15** as compared to those reported for the respective products of natural origin: chemical shifts for H-4, H-5 and H-6 are 0.3–0.6 ppm apart, and the $J_{3,4}$ and $J_{4,5}$ couplings have significantly different values (Table 1). Thus, a D-*xylo* or L-*xylo* configuration for natural (−)-daucic acid can unequivocally be dismissed.

**Table 1.** Relevant physicochemical data of dimethyl 2,6-anhydro-3-deoxy-hept-2-enarates of D-*xylo*, D-*ribo*, L-*arabino* and D-*lyxo* configuration and their diacetates as compared with those reported[3] for the carrot-derived daucic acid derivatives

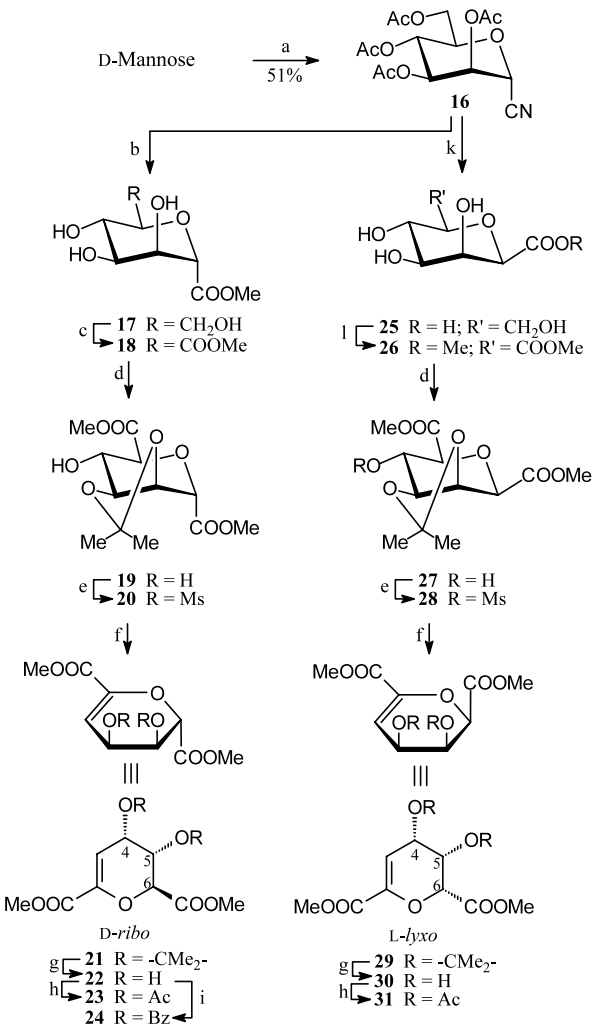
| Compound | | mp (°C) | $[\alpha]_D^{20}$ [a] | $^1$H NMR (δ, Hz) 4-H | 5-H | 6-H | $J_{3,4}$ | $J_{3,5}$ | $J_{4,5}$ | $J_{5,6}$ | solvent |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (-)-dimethyl daucate[3] | | 130-131 | −102[b] | 4.51 | 4.30 | 4.66 | 3 | 1 | ? | 2 | $CDCl_3$ |
| diacetate[3] | | oil | ? | – 5.73 – | | 4.82 | 2.3 | ? | ? | 1.8 | $CDCl_3$ |
| | | | | 5.63 | 5.85 | 4.35 | 2.6 | 1.5 | 4.4 | 1.8 | $C_6H_6$ |
|  D-*xylo* | **2** R = H | 133-135 | +106 | – 4.19 – | | 4.60 | 4.8 | 1.3 | ? | 1.5 | $CDCl_3$ |
| | **14** R = Ac | syrup | +146 | 5.13 | 5.38 | 4.61 | 5.3 | 1.5 | 2.2 | 1.4 | $CDCl_3$ |
| | | | | 5.20 | 5.57 | 4.41 | 5.3 | 1.5 | 2.2 | 1.0 | $C_6H_6$ |
|  D-*ribo* | **22** R = H | syrup | +150.4 | 4.32 | 4.12 | 4.63 | 4.4 | – | 4.3 | 7.6 | $CDCl_3$ |
| | **23** R = Ac | syrup | +171.1 | – 5.52 – | | 4.84 | 3.7 | – | ? | 6.8 | $CDCl_3$ |
| | | | | 5.62 | 5.71 | 4.74 | 3.8 | 0.7 | 4.2 | 6.3 | $C_6H_6$ |
|  L-*arabino* | **40** R = H | syrup | +30.0 | 4.25 | 4.19 | 4.73 | 4.3 | 0.9 | 2.2 | 5.4 | $CDCl_3$ |
| | **41** R = Ac | 104-106 | +72.1 | 5.14 | 5.44 | 5.06 | 5.4 | 1.5 | 2.1 | 2.2 | $CDCl_3$ |
| | | | | 5.22 | 5.58 | 4.89 | 5.3 | 1.5 | 2.3 | 2.6 | $C_6H_6$ |
|  D-*lyxo* | **43** R = H | 128-129 | −98.3 | 4.50 | 4.30 | 4.67 | 3.3 | 1.1 | 4.3 | 2.3 | $CDCl_3$ |
| | **44** R = Ac | syrup | −54.1 | – 5.74 – | | 4.84 | 2.2 | 1.7 | ? | 1.4 | $CDCl_3$ |
| | | | | 5.56 | 5.81 | 4.27 | 2.3 | 1.7 | 4.5 | 1.7 | $C_6D_6$ |

[a]Rotations for OH-free diesters in acetone; for diacetates in $CHCl_3$.
[b]$[\alpha]_D$ value at 24.5 °C.

### 2.2. Heptenarates of D-*ribo* and L-*lyxo* configuration

Of the remaining configurational possibilities for carrot-derived (−)-daucic acid—D-*ribo*, D-*lyxo* and D-*arabino*—the synthesis of the D-*ribo*-analog **22** was addressed next, taking advantage of the α-D-mannosyl-cyanide **16**, readily accessible from D-mannose by acetylation[9] and anomeric cyanation.[10] Acid hydrolysis followed by esterification with methanol smoothly provided the mannosyl-*C*-carboxylate **17**. As the $Pt/O_2$-oxidation of the primary hydroxyl group in **17** proved unusually capricious, its conversion into the 1,7-dicarboxylate was effected by TEMPO-catalyzed sodium hypochlorite oxidation—a reagent that had given excellent results in various other sugar oxidations[11]—to provide, upon esterification with methanolic HCl, the dimethyl heptarate **18** in high yield. Subsequent protection of *O*-3 and *O*-4 by acetonation (→**19**), followed by mesylation (→**20**) set the stage for 5,6-elimination of methanesulfonate, which was simply realized by brief exposure to $Al_2O_3$/lutidine at 40°C (→**21**). Finally, removal of the isopropylidene group in **21** with aqueous trifluoroacetic acid smoothly delivered the desired D-*ribo*-heptenarate **22**, and, after acetylation, its di-*O*-acetyl derivative **23**. Both were obtained as syrups of distinctly high positive rotation in contrast to the substantially smaller negative value for the *Daucus carota*-derived product. As distinct differences also prevail in the respective $^1$H NMR data (cf. Table 1), D-*ribo* as well as L-*ribo* stereochemistry for natural (−)-daucic acid can also be eliminated.

The α-D-mannosyl-cyanide **16**, unexpectedly, could also be used to generate the L-*lyxo*-heptenarates **29**–**31** (Scheme 3). Quite in contrast to its acidic hydrolysis leading to the *C*-mannosyl-α-carboxylate (**16**→**17**), alkaline saponification—sodium methoxide/methanol for deacetylation (1 h, rt) and 12.5% aqueous sodium hydroxide (4 h, reflux) for nitrile hydrolysis—was accompanied by an unprecedented epimerization at the pseudo-anomeric C-2, to provide the *C*-mannosyl-β-carboxylic acid 25 in high yield (90%). The subsequent oxidation and esterification **25**→**26** followed standard methodology, as did the introduction of a mesyl group at *O*-5 after prior protection of the 3,4-diol grouping (**26**→**27**→**28**). Aluminum oxide/lutidine-induced 5,6-elimination of mesylate in **28** proceeded smoothly (→**29**) and acid removal of the isopropylidene group gave the well-crystallizing dimethyl L-*lyxo*-heptenarate **30** with physicochemical data highly relevant to the configuration of daucic acid: melting point (127–128°C), $^1$H NMR chemical shifts and coupling patterns




**Scheme 3.** D-Mannose-derived D-*ribo* and L-*lyxo* heptenarates. *Reagents and conditions*: (a) $Ac_2O$, pyridine,[9] then $Me_3SiCN$, $BF_3{\cdot}Et_2O$, $CH_3NO_2$, 35°C, 2 h;[10] (b) 25% aqueous HCl, 50°C, 24 h; then HCl satd MeOH, rt, 2 h, 85%; (c) TEMPO/NaOCl, $H_2O/CH_2Cl_2$, 0°C, 20 h, then HCl/MeOH, rt, 2 h, 83%; (d) $Me_2CO/H_2SO_4$, rt, 4 h, 75%; (e) MsCl, pyridine, 0°C, 3 h, 94%; (f) Basic $Al_2O_3$, lutidine, 40°C, 30 min, 75%; (g) $CHCl_3$–TFA–$H_2O$ (50:10:1), rt, 1 h, 86%; (h) $Ac_2O$/pyridine, rt, 5 h, 90%; (i) BzCl, pyridine, rt, 12 h, 87%; (k) NaOMe/MeOH, 1 h, rt, then 12.5% aqueous NaOH, reflux, 4 h, 90%; (l) conc. $HNO_3$, 55°C, 1 h, then 8% HCl/MeOH, 67%.

(cf. Table 1, D-*lyxo* data) correlated exceedingly well with the carrot-derived dimethyl daucate, only the specific rotation (+96.7), albeit identical in magnitude, was of opposite sign. Similarly congruent proved to be the $^1$H NMR data of the diacetate **31** and the natural dimethyl daucate derivative (Table 1). The conclusion to be drawn is obvious: the L-*lyxo*-heptenarate **30** and **31** are enantiomers to the respective carrot-derived products, that is, (−)-daucic acid must have D-*lyxo* configuration.

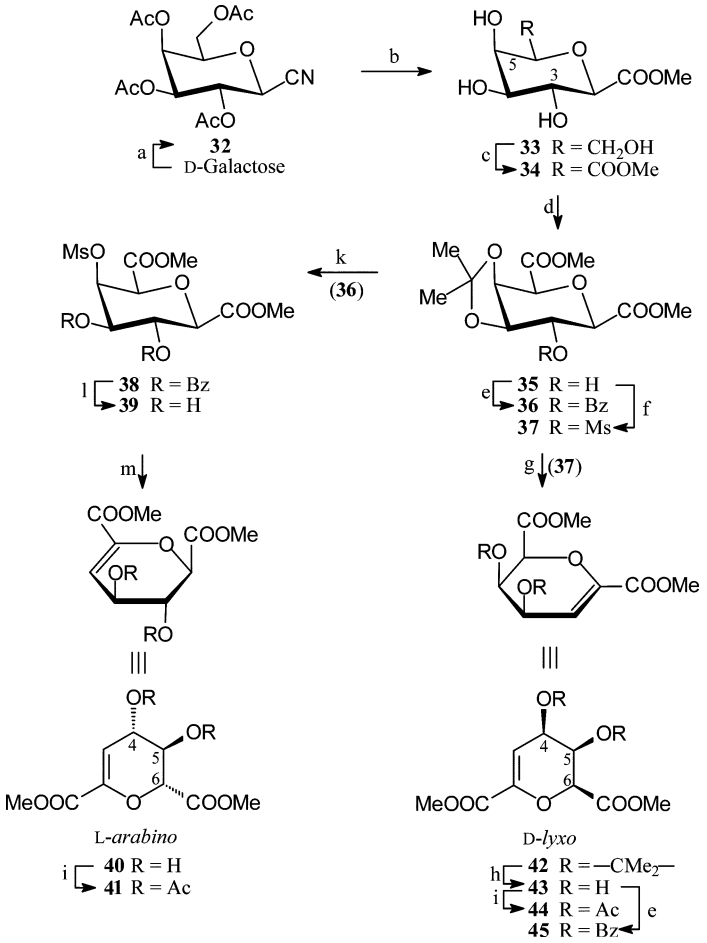
### 2.3. D-*lyxo*- and L-*arabino*-heptenarates

Finally to gain access to the D-*lyxo* configured (−)-daucic acid, we focused on a synthetic pathway starting from *C*-β-D-galactosyl-cyanide **32**, because it would also provide the respective L-*arabino* analogs by converting alternatively the 3-OH and the 5-OH in dimethyl heptarate **34** into displaceable leaving groups. The key intermediate **34** could straightforwardly be prepared by base hydrolysis of **32**, esterification (→**33**) and TEMPO/NaOCl oxidation, the three steps being performable in an overall yield of 64% (Scheme 4).

For generation of L-*arabino* analogs of daucic acid, the protocol used for the successful conversion of **9** into **12** was evaluated first, comprising selective 3,4-di-*O*-benzoylation and mesylation at *O*-5. In the case of **34**, however, this approach failed due to distinctly different OH groups reactitivites of **34** as compared to **9**: Reaction of **34** with 2.1 molar equiv. of benzoyl chloride in pyridine at −40°C resulted in mixtures mainly consisting of the 3,5- and 4,5-dibenzoates. This course was somewhat unexpected, as the dimethyl heptarates **9** and **34** are 2-epimeric *C*-(galacturonyl)carboxylates in which the axial 5-OH would anticipated to be least reactive towards acylation. As an alternate, albeit less direct route to the desired 3,4-di-*O*-benzoyl-5-*O*-mesylheptarate **38**, the *cis*-diol grouping in **34** was blocked by isopropylidenation (→**35**, the key intermediate for generation of the D-*lyxo* compounds, cf. below), followed by benzoylation (→**36**) and acid hydrolysis of the acetonide. The resulting 3-benzoate of **34**—unlike **34** itself—could readily be mono-acylated at the 4-OH by low temperature benzoylation, the ensuing in situ mesylation delivering the appropriately blocked **38** in a tolerable overall yield of 40% for the five steps from **34**. Introduction of the $\Delta^{5,6}$-unsaturation towards the L-*arabino* heptenarate was most readily effected in the de-*O*-benzoylated heptarate **39** to give **40**, the actual L-*arabino* analog of dimethyl daucate, as a syrup; its diacetate **41**, however, crystallized well. As anticipated, both, **40** and **41** had $^1$H NMR data (cf. Table 1) distinctly different in chemical shifts and coupling patterns from those observed for the carrot-derived products.

The D-*lyxo*-heptenarates **42**–**45**, all derivatives of natural (−)-daucic acid, were also prepared from the 4,5-*O*-isopropylidene-heptarate **35** by a similar sequence of reactions: mesylation (→**37**) and $Al_2O_3$/lutidine-induced elimination gave **42**, in which the isopropylidene group was removed by exposure to aqueous trifluoroacetic acid (→**43**).

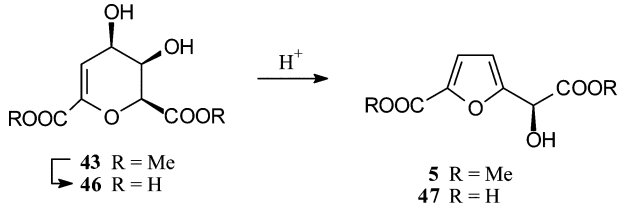
In their physicochemical data, **43** and its di-*O*-acetyl derivative **44** are in nearly perfect agreement with those of the carrot-derived products, not only in sign and magnitude of rotation but, most notably, in the chemical shifts and coupling patterns (Table 1). The slight deviations in the coupling constants undoubtedly result from comparing $^1$H NMR data obtained at different resolution (60[3] versus 300 MHz) and, conceivably, different temperatures which affect the $^5H_6 \rightleftharpoons {}^6H_5$ equi-




**Scheme 4.** Dimethyl heptenarates of L-*arabino* and D-*lyxo* configuration from D-galactose. *Reagents and conditions*: (a) NaOAc, $Ac_2O$, 100°C, 2 h,[12a] then $Me_3SiCN$, $BF_3{\cdot}Et_2O$ in $CH_3NO_2$, 35°C, 2 h,[12b] 79%; (b) (i) NaOMe/MeOH, 2 h, rt, (ii) 6N NaOH, 4 h, reflux, (iii) HCl–satd MeOH, rt, 2 h, 85%; (c) TEMPO/NaOCl, $H_2O/CH_2Cl_2$, 0°C, 20 h, then satd HCl/MeOH, rt, 2 h, 76%; (d) $Me_2CO$, $H_2SO_4$, rt, 4 h, 76%; (e) BzCl, pyridine, rt, 12 h, 90%; (f) MsCl/pyridine, 0°C, 3 h, 85%; (g) 0.2N NaOMe/MeOH, 15 min, rt, 77%; (h) $CHCl_3$–TFA–water (50:10:1), rt, 1 h, 83%; (i) $Ac_2O$/pyridine, rt, 12 h, 90%; (k) (i) TFA–$CHCl_3$–$H_2O$, rt, 30 min, (ii) BzCl (1.2 equiv.), pyridine, –40°C, 2 h, (iii) MsCl, pyridine, rt, 3 h, 53%; (l) HCl–satd MeOH, reflux, 24 h, 86%; (m) basic $Al_2O_3$–lutidine, 40°C, 30 min, 74%.

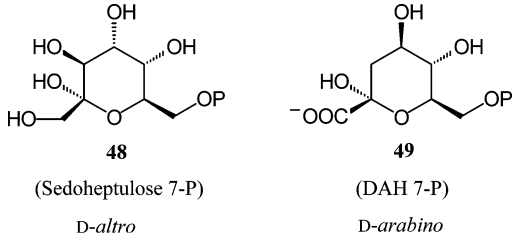
librium of the respective halfchair forms, and, hence, the NMR patterns. Notwithstanding, this evidence is cogent enough as to unambiguously assign carrot-derived (–)-daucic acid the D-*lyxo*-configuration.

The synthetic (–)-dimethyl daucate **43** could readily be de-esterified by aqueous trifluoroacetic acid to give the free acid **46** in crystalline form. Slightly more vigorous acid conditions elicited the pyran→furan rearrangement observed previously for the carrot-derived product:[3] when exposed to methanolic HCl, **43** was converted into **5** (60%), heating in water in the presence of a strongly acidic ion exchange resin gave the free acid **47** (81%). As **47** has been isolated from the shrub *Osbeckia chinensis* L., and hence named osbeckic acid,[13] it may well be generated from daucic acid in the plant.




## 2.4. Biosynthetic implications

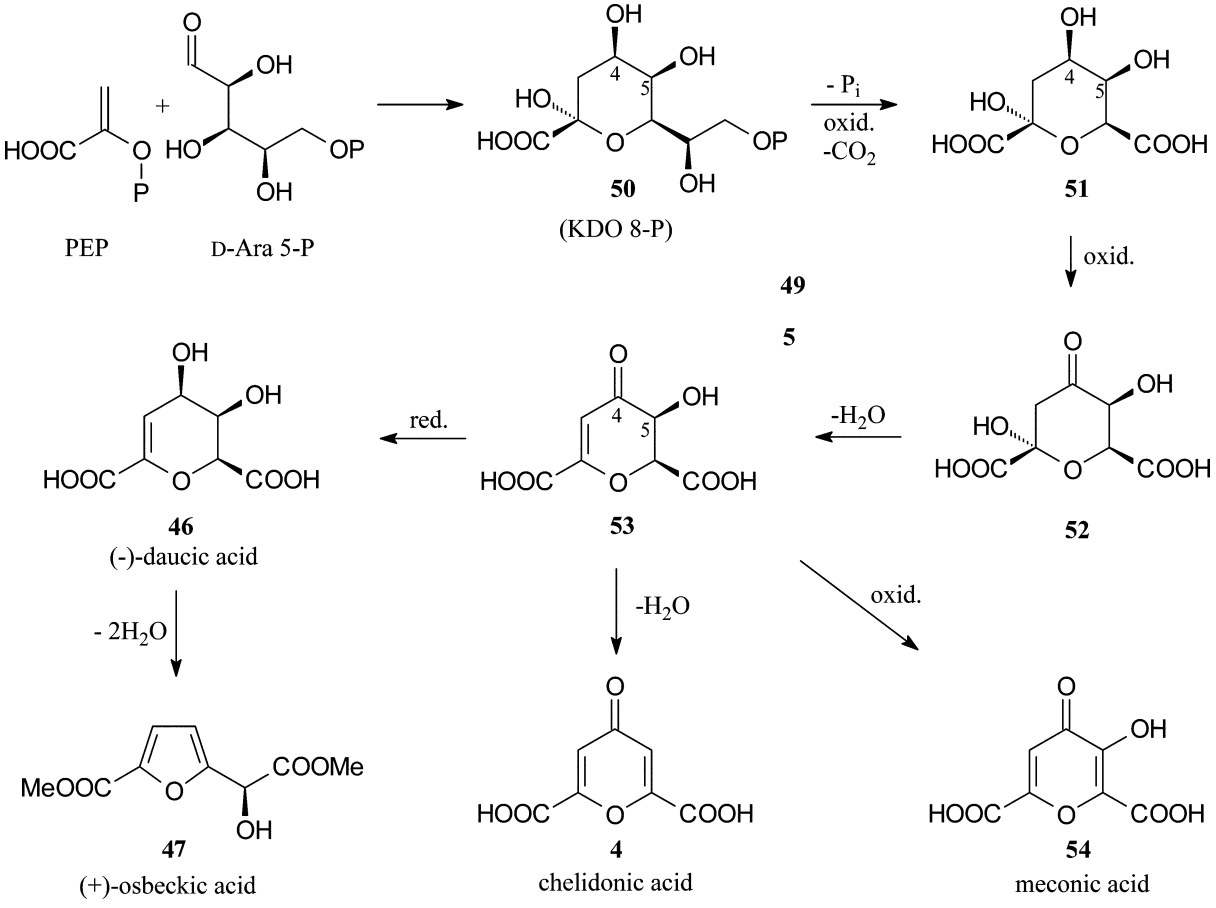
Not only is the biosynthetic origin of (–)-daucic acid intriguing—sedoheptulose-7-phosphate **48** and DAH 7-P **49**, both established intermediates of the pentose phosphate and shikimic acid pathways, respectively, may be conjectured as precursors—but the close structural analogy to chelidonic acid **4** with only oxidation of the allylic OH group in daucic acid and ensuing elimination of water being required to effect the chemical conversion.



$^{14}$C-Labeling studies on the biosynthesis of chelidonic acid have uniformly demonstrated that D-glucose and, still better, D-ribose is well incorporated,[14,15] whilst **48** is not.[14] The postulation, that, hence, DAH 7-P **49** is the likely precursor[15] persisted for 30 years, yet was convincingly disproved recently by quantitative carbon flux analyses of $^{13}$C-labeled sugars, suggesting a biosynthetic assembly of chelidonic acid from one molecule of pentose phosphate and phosphoenolpyruprate (PEP).[16] Such a biosynthetic process, de facto, is well established in Gram-negative bacteria, where PEP and D-arabinose 5-phosphate (D-Ara 5-P), in turn generated from D-ribulose 5-phosphate by isomerization, undergo an aldol-type condensation to 3-deoxy-D-*manno*-octulosonate 8-phosphate (KDO 8-P), **50**.[17,18] Thereby, the KDO 8-P synthase involved stereoselectively elaborates the 4*R* isomer, hence, D-*manno* configuration for **50**, as the aldol addition proceeds with exclusive *si* attack of PEP to the *re* face of the sugar carbonyl.[19] Although the existence of such a KDO 8-P-based mechanism has, as of now, not been detected in plants, the fact that DAH 7-P synthase—a key enzyme of the shikimic acid pathway[20] and abundantly present in higher plants—not only catalyzes aldol addition of PEP to its natural substrate, D-erythrose 4-phosphate, but to D-ribose 5-phosphate (D-Rib 5-P) and D-Ara 5-P as well,[21] may tentatively be taken as evidence that an octulosonate 8-phosphate-based pathway is also operative in plants.

Relying on the newly established D-*lyxo* stereochemistry of (–)-daucic acid—**48** and **49** as precursors would elaborate D-*arabino* configuration—and on the conjecture that daucic acid is a precursor of chelidonic acid, a biosynthetic pathway towards both readily unfolds as depicted in Scheme 5: D-Ara 5-P and PEP undergo an aldol-type condensation to KDO 8-P **50**, whose stereochemistry in the pyranoid ring, notably, correlates perfectly with the D-*lyxo* configuration of daucic acid. If D-Rib 5-P would be involved in the aldol addition step, the eight-carbon sugar phosphate would have D-*altro* configuration entailing an ('unnecessary') epimerization at some later stage.

Unlike bacterial systems where the eight-carbon chain of KDO 8-P is incorporated into cell wall lipopolysaccharides, here, the terminal carbon obviously is removed by dephosphorylation and oxidative decarboxylation. Although the resulting intermediate **51**




**Scheme 5.** Conceivable mechanism for the biosynthesis of $C_7$-dicarboxylic acids in plants from common precursors, based on the striking configurational identity of daucic acid **46** and KDO 8-P **50** in their pyranoid rings, the smooth chemical conversions of **46** into chelidonic **4** and osbeckic acid **47**, and available evidence on the biosynthesis of **4**. Meconic acid **54**, plentiful in the latex of Papaveracea, may be arrived at merely by oxidation of conjectural intermediate **53**.

requires only loss of water to reach daucic acid, a direct 3,2-elimination is unlikely—'cells obey the laws of chemistry'[22]—as the hydrogen atom involved (H-3) is not activated. This is usually effected by a vicinal carbonyl group—the D-glucose→kojic acid conversion[23] has been rationalized on this basis[24]—hence, oxidation of **51** at C-4 appears most plausible, the ensuing dehydration **52→53** now being readily comprehensible. From the central dihydropyranone intermediate **53**, elaboration of daucic acid merely requires a reduction, and generation of chelidonic acid the elimination of another molecule of water. Meconic acid may be conjectured to arise by a dehydrogenation step (**53→54**), the furanoid osbeckic acid **47** from daucic acid via ring contraction and twofold dehydration.

The tempting consistency of this metabolic scheme, most notably the configurational identity of KDO 8-P and daucic acid in their pyranoid rings, clearly calls for a systematic scrutiny of higher plants for the occurrence of an eight-carbon sugar phosphate pathway with the likely intermediates **51**–**53**, especially in those species, in which these $C_7$-dicarboxylic acids have been detected: daucic acid in carrots, sugar beet, wheat, sun flower, and tobacco,[3] osbeckic acid in *Osbeckia chinensis*,[13] meconic acid in Papaveraceae[25] and chelidonic acid in a plethora of plant families.[26] Also conducive towards unravelement of the biosynthesis of these plant acids will be the eleven-step-synthesis of (−)-daucic acid from D-galactose described since the first six from D-galactose to dimethyl D-*glycero*-L-*manno*-heptarate **34** can be performed in three consecutive one-pot operations on fairly large scale (51%). The synthesis is also flexible enough to readily prepare the postulated intermediates **51**–**53** in labeled form. Synthetic and biosynthetic studies along these veins are being implemented.

## 3. Experimental

### 3.1. General remarks

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20°C using a cell of 1 dm path length; concentration (*c*) in g/100 mL and solvent are given in parentheses. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ARX-300 spectrometer in the solvents indicated. Mass spectra were acquired on Varian MAT 311 and MAT 212 spectrometers. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 $F_{254}$) with detection by UV (254 nm) and/or spraying with $H_2SO_4$ (50%) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70–230 mesh) using the specified eluents.

### 3.2. D-Galactose→D-*xylo* analogs of dimethyl daucate

**3.2.1. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*gluco*-heptonamide [*C*-(tetra-*O*-acetyl-α-D-galactopyranosyl)formamide] 7**. 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol **6**, readily accessible from D-galactose by acetylation,[7a] treatment with HBr/HOAc[7b] and diethylamine-promoted elimination of HBr[7c] (75% overall yield on a 0.1 molar scale when refraining from purification of intermediates), was subjected to photoaddition of formamide to afford **7** in 54% yield;[8] mp 187–189°C; $[\alpha]_D^{20}=+57$ (*c* 0.9, $CHCl_3$) [lit.[8] mp 186–189°C; $[\alpha]_D^{20}=+53.3$ ($CHCl_3$)].

**3.2.2. Methyl 2,6-anhydro-D-*glycero*-L-*gluco*-heptonate [methyl *C*-(α-D-galactopyranosyl)formate] 8**. A suspension of **7** (5.42 g, 15 mmol) in 100 mL of 8% HCl in MeOH was refluxed for 3 h. The then clear solution was taken to dryness in vacuo and the resulting residue was purified by elution from a short silica gel column with $CHCl_3$–MeOH (4:1). Evaporation of the appropriate eluates left a syrup which crystallized from MeOH/$CHCl_3$: 2.87 g (86%) of **8**; mp 141–142°C; $[\alpha]_D^{20}=+106$ (*c* 0.7, MeOH). Anal. calcd for $C_8H_{14}O_7$ (222.2): C, 43.24; H, 6.35. Found: C, 62.07; H, 7.32.

**3.2.3. Dimethyl 2,6-anhydro-D-*glycero*-L-*gluco*-heptarate 9**. Freshly reduced Adams catalyst (1.0 g) was added to an aqueous solution of **8** (2.20 g, 10 mmol, in 50 mL), and $O_2$ was passed through the suspension with vigorous stirring for 4 h at 70°C, maintaining pH 8 by gradual addition of solid $NaHCO_3$. After filtration, the solution was taken to dryness in vacuo, the residue was suspended in methanolic HCl (40 mL of saturated solution), and stirred for 1 h at ambient temperature. Filtration of insolubles, removal of the solvent from the filtrate, purification of the resulting syrup by elution from a silica gel column (2×20 cm) with $CHCl_3$–MeOH (6:1), and evaporation of the eluates containing **9** gave 1.40 g (56%) of a colorless syrup, uniform by TLC ($R_f=0.42$ in $CHCl_3$–MeOH, 4:1); MS (FD) *m*/*z* 251 ($M^++1$), 250 ($M^+$). Anal. calcd for $C_9H_{14}O_8$ (250.2): C, 43.20; H, 5.64. Found C, 43.08, H, 5.60.

**3.2.4. Dimethyl 3,4,5-tri-*O*-acetyl-2,6-*anhydro*-D-*glycero*-L-*gluco*-heptarate 10**. A mixture of heptarate **9** (50 mg, 0.2 mmol), pyridine (2 mL) and $Ac_2O$ (1 mL) was kept at rt overnight, subsequently diluted with EtOAc and washed with satd aqueous $NaHCO_3$ and water, and dried ($Na_2SO_4$). Concentration of solution to dryness gave a crystalline mass, which was recrystallized from EtOH to afford 70 mg (90%) of **10**; mp 151–152°C; $[\alpha]_D^{20}=+173$ (*c* 0.7, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.02, 2.05, 2.10 (3 s, 3H each, 3 Ac), 3.76, 3.77 (two 3H-s, 2 OMe), 5.05 (d, 1H, $J=6.0$ Hz), 5.38 (d, 1H, $J=2.7$ Hz), 5.39 (dd, 1H, $J=2.9$, 9.8 Hz), 5.77 (dd, 1H, $J=2.7$, 2.9 Hz); MS (FD) *m*/*z* 378 ($M^++2$), 334 ($M^+$−Ac). Anal. calcd for $C_{15}H_{20}O_{11}$ (376.3): C, 47.88; H,5.36. Found: C, 47.79; H, 5.19.

**3.2.5. Dimethyl 3,4,5-tri-*O*-benzoyl-2,6-*anhydro*-D-*glycero*-L-*gluco*-heptarate 11**. Benzoyl chloride (1.8 mL, 15

mmol) was added to a solution of dimethyl heptarate **9** (150 mg, 0.6 mmol) in pyridine (12 mL), and the mixture was stirred at rt overnight. Dilution with EtOAc, successive washings with satd aqueous $NaHCO_3$ and water, drying ($Na_2SO_4$), and evaporation to dryness in vacuo gave a syrup which was purified by elution from a short silica gel column with *n*-hexane–acetone (2:1). Removal of the solvents from the product-containing eluates (TLC: $R_f = 0.28$ in *n*-hexane–acetone, 2:1) gave a solid residue which crystallized from EtOH: 295 mg (87%) of 11 as colorless crystals; mp 136–137°C; $[\alpha]_D^{20} = +217$ (*c* 1.1, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.63, 3.69 (two 3H-s, 2 OMe), 5.46 (d, 1H, $J = 5.5$ Hz), 5.57 (d, 1H, $J = 3.6$ Hz), 5.85 (dd, 1H, $J = 5.4$, 8.5 Hz), 6.04 (dd, 3.1, 8.5 Hz), 7.50, 7.95 (2 m, 9H and 6H, 3 $C_6H_5$); MS (FD) $m/z$ 563 ($M^+$+1). Anal. calcd for $C_{30}H_{26}O_{11}$ (562.5): C, 64.06; H, 4.66. Found: C, 63.96; H, 4.58.

**3.2.6. Dimethyl 2,6-anhydro-3,4-di-*O*-benzoyl-5-*O*-mesyl-D-*glycero*-L-*gluco*-heptarate 12**. A solution of heptarate **9** (810 mg, 3.2 mmol) in pyridine (10 mL) was cooled to −40°C and a mixture of benzoyl chloride (0.8 mL, 0.69 mmol) and pyridine (5 mL) was added dropwise with vigorous stirring. After 2 h at −40°C, methanesulfonyl chloride (0.25 mL, 3.2 mmol) was added and stirring was continued at −40°C (1 h) followed by allowing the mixture warm to rt (2 h). Subsequent extraction with satd aqueous $NaHCO_3$ and water, drying ($Na_2SO_4$), and removal of the solvent in vacuo gave a residue, which was purified by elution from a silica gel column with *n*-hexane–acetone (2:1). The first fraction ($R_f = 0.49$, TLC in *n*-hexane–acetone, 3:2) contained 320 mg (18%) of tribenzoate of **11**. The fractions eluted next, with product of $R_f = 0.39$, were combined and evaporated to a syrup which crystallized from EtOH: 930 mg (53%) of **12** as colorless crystals; mp 158–160°C; $[\alpha]_D^{20} = +174$ (*c* 0.5, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.04 (s, 3H, $SO_2Me$), 3.64, 3.85 (2 s, 3H each, 2 OMe), 5.22 (d, 1H, $J = 6.7$ Hz), 5.62 (d, 1H, $J = 1.8$ Hz), 5.76 (dd, 1H, $J = 1.8$, 2.9 Hz), 5.84 (dd, 1H, $J = 6.7$, 10.3 Hz), 5.93 (dd, 1H, $J = 2.9$, 10.3 Hz), 7.50, 8.00 (2 m, 2 $C_6H_5$); MS (FD) $m/z$ 537 ($M^+$+1). Anal. calcd for $C_{24}H_{24}O_{12}S$ (536.5): C,53.73; H, 4.51. Found: C,53.68; H, 454.

**3.2.7. Dimethyl 2,6-anhydro-5-*O*-mesyl-D-*glycero*-L-*gluco*-heptarate 13**. A suspension of 805 mg (1.5 mmol) of dibenzoate **12** in satd methanolic HCl (25 mL) was refluxed for 14 h. The clear solution was then taken to dryness in vacuo and the residue was purified on a short silica gel column by elution with aceton–$CHCl_3$ (1:1). Removal from the solvents in vacuo afforded a syrup, which crystallized from $CHCl_3$/*n*-hexane to yield 425 mg (73%) of **13**; mp 149–150°C; $[\alpha]_D^{20} = +92$ (*c* 0.7, $CHCl_3$); MS (FD) $m/z$ 388 ($M^+$). Anal. calcd for $C_{15}H_{16}O_{16}S$ (388.4): C, 46.39; H, 4.15. Found: C, 46.30; H, 4.03.

**3.2.8. Dimethyl 2,6-anhydro-3-deoxy-D-*xylo*-hept-2-enarate 2**. A methanolic solution of mesylate **13** (390 mg, 1 mmol, in 10 mL) was added to 20 mL of 0.1N methanolic NaOMe, the mixture was stirred for 1 h, and subsequently concentrated in vacuo. The amorphous residue was purified by elution from a short silica gel column with acetone–$CHCl_3$ (1:1). Eluates containing product of $R_f = 0.40$ (TLC in $CHCl_3$–acetone, 2:1) were concentrated to a syrup, which crystallized from EtOAc/hexane: 180 mg (77%) of **2**; mp 133–135°C; $[\alpha]_D^{20} = +106.0$ (*c* 0.6, acetone). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.85, 3.88 (two 3H s, 2 OMe), 4.19 (m, 2H), 4.60 (m, 1H), 6.20 (dd, 1H, $J = 1.3$, 4.8 Hz); MS (FD $m/z$ 232 ($M^+$), 233 ($M^+$+1). Anal. calcd for $C_9H_{12}O_7$ (232.2): C, 46.55; H, 5.21. Found C, 46.48; H, 5.25

**3.2.9. Dimethyl 4,5-di-*O*-acetyl-2,6-anhydro-3-deoxy-D-*xylo*-hept-2-enarate 14**. A solution of heptenarate **2** (60 mg, 0.26 mmol) in a mixture of $Ac_2O$ (1 mL) and pyridine (3 mL) was stirred at rt overnight and subsequently taken to dryness in vacuo. The resulting residue purified on a short silica gel column by elution with $CHCl_3$–MeOH (20:1) to give 68 mg (82%) of **14** as a clear syrup; $[\alpha]_D^{20} = +146.0$ (*c* 0.8, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.06, 2.11 (two 3H-s, 2 Ac), 3.84, 3.86 (two 3H-s, OMe), 4.61 (m, 1H), 5.13 (ddd, 1H, $J = 0.8$, 2.2, 5.3 Hz), 5.38 (ddd, 1H, $J = 1.4$, 1.5, 2.2 Hz), 6.23 (dd, $J = 1.5$, 5.3 Hz; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 1.49, 1.50 (two 3H-s, 2 Ac), 3.27, 3.34 (two 3H-s, 2 OMe), 4.41 (m, 1H), 5.20 (ddd, 1H, $J = 0.8$, 2.2, 5.3 Hz), 5.57 (ddd, 1H, $J = 1.4$, 1.5, 2.2 Hz), 6.38 (dd, 1H, $J = 1.5$, 5.3 Hz); MS (FD) $m/z$ 316 ($M^+$), 257 ($M^+$–COOMe).

**3.2.10. Dimethyl 4,5-di-*O*-benzoyl-2,6-anhydro-3-deoxy-D-*xylo*-hept-2-enarate 15**. (a) By benzoylation of **2**. Benzoyl chloride (0.2 mL, 0.7 mmol) was added solution of **2** (60 mg, 0.26 mmol) in pyridine (2 mL), and the mixture was stirred at rt overnight. Dilution with EtOAc, washing with satd $NaHCO_3$ and water, drying ($Na_2SO_4$), and removal of the solvent in vacuo left a syrup, which was purified on a short silica gel column (*n*-hexane–acetone, 2:1). Eluates with $R_f = 0.63$ (TLC, $CHCl_3$–EtOAc, 20:1) were concentrated to give 95 mg (83%) of **15** as colorless syrup; $[\alpha]_D^{20} = +127.0$ (*c* 0.9, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.82, 3.88 (two 3H-s, 2 OMe), 4.86 (m, 1H), 5.56 (ddd, 1H, $J = 0.8$, 2.4, 5.2 Hz), 5.78 (ddd, 1H, $J = 1.5$, 1.8, 2.4 Hz), 6.41 (dd, $J = 1.5$, 5.2 Hz), 7.46, 7.60, 8.03 (3 m, 10H, 2 $C_6H_5$); MS (FD) $m/z$ 440 ($M^+$). Anal. calcd for $C_{23}H_{20}O_9$ (440.4): C, 62.72; H, 4.58. Found: C, 62.65; H, 4.50.

(b) By elimination of benzoic acid from **11**. A solution of **11** (200 mg, 0.35 mmol) in $Ac_2O$ (5 mL) was heated in the presence of NaOAc (150 mg) at 100°C for 1 h. The reaction mixture was diluted with EtOAc, washed with water, satd aqueous $NaHCO_3$ and water, and then dried over $Na_2SO_4$. The solution was concentrated and purified on a silica gel column ($CHCl_3$–EtOAc, 30:1) to afford 90 mg (59%) of **15** as a syrup, identical with the product described above.

### 3.3. D-Mannose→products of D-*ribo* configuration (21–24)

**3.3.1. Methyl 2,6-anhydro-D-*glycero*-D-*talo*-heptonate [methyl *C*-(α-D-mannopyranosyl)formate] 17**. A solution of 4.0 g (11.2 mmol) of *C*-(tetra-*O*-acetyl-α-D-manno-

syl)cyanide **16**[10] in water (40 mL) and conc. HCl (80 mL) was stirred at 50°C for 24 h followed by concentration in vacuo and repeated coevaporation with MeOH. Drying in vacuo afforded the free heptonic acid (**17**, H instead of Me, 2.2 g) as a uniform syrup (TLC: $R_f$ = 0.49 in EtOAc–HOAc–water, 3:2:1), which was dissolved in anhydrous MeOH (20 mL) followed by addition of 20 mL of HCl–satd MeOH. The solution was stirred at rt for 2 h, followed by removal of the solvent to dryness in vacuo and three coevaporations with dry MeOH. Purification of the residue by elution from a silica gel column (3×30 cm) with $CHCl_3$–MeOH (5:1) and concentration of the eluates in vacuo gave 2.14 g (86%) of **17** as a syrup; $[\alpha]_D^{20}$ = +39.6 (*c* 1.1, MeOH); $R_f$ = 0.64 (TLC in EtOAc–EtOH–water, 14:6:3). $^1$H NMR (300 MHz, [D$_4$]MeOH) $\delta$ 3.45 (dd, 1H, *J* = 3.0, 8.9 Hz), 3.68 (m, 2H, H-5, H-6), 3.72 (m, 1H, H-7), 3.84 (dd, 1H, *J* = 1.8, 11.8 Hz, H-7), 4.28 (dd, 1H, *J* = 2.2, 3.0 Hz), 4.52 (d, 1H, *J* = 2.2 Hz); MS (FD) *m*/*z* 223 (M$^+$+1), 222 (M$^+$). Anal. calcd for $C_8H_{14}O_7$ (222.2) C, 43.23; H, 6.35. Found: C, 43.29; H, 6.41.

**3.3.2. Dimethyl 2,6-anhydro-D-*glycero*-D-*talo*-heptarate 18**. To a mixture of **17** (2.14 g, 9.6 mmol) in satd aqueous $NaHCO_3$ (16 mL) containing KBr (90 mg) and *n*-Bu$_4$NCl (120 mg) was added a solution of 50 mg of 2,2,6,6-tetramethyl-1-piperidinyloxy ('TEMPO') in $CH_2Cl_2$ (20 mL). The mixture was cooled to 0°C and a solution of NaOCl (13%, 56 mL) and satd aqueous $NaHCO_3$ (8.8 mL) was added dropwise over 1 h. Stirring was continued at 0°C for 20 h, followed by separation of the two layers and washing of the organic phase with water (3×15 mL). The combined aqueous extracts were acidified with 2N HCl and concentrated in vacuo to a syrup which was dissolved in water and passed through an ion-exchanger column (Amberlite IR-120 H+, 3×30 cm). After removal of the solvent the syrup was dissolved in anhydrous MeOH (30 mL) and treated with a satd solution of dry HCl in anhydrous MeOH (30 mL) at ambient temperature for 2 h, and then concentrated. The residue was purified on a silica gel column (3×30 cm) by elution with $CHCl_3$–MeOH (5:1). Product-containing eluates ($R_f$ = 0.91, TLC in EtOAc–EtOH–water, 14:6:3) were concentrated to give 1.33 g (55%) of **18** as a colorless syrup; $[\alpha]_D^{20}$ = +61.4 (*c* 1.5, MeOH); $^1$H NMR (300 MHz, $D_2O$, 32°C) $\delta$ 3.74, 3.78 (two 3H-s, 2 OMe), 3.75 (dd, 1H, *J* = 2.9, 5.8 Hz), 4.11 (dd, 1H, *J* = 2.2, 3.0 Hz), 4.18 (dd, 1H, *J* = 4.5, 5.8 Hz), 4.11 (dd, 1H, *J* = 2.9, 5.8 Hz), 4.18 (dd, 1H, *J* = 4.5, 8.9 Hz), 4.29 (d, 1H, *J* = 4.5 Hz), 4.66 (d, 1H, *J* = 7.3 Hz). Anal. calcd for $C_9H_{14}O_8$ (250.2): C, 43.20; H,5.64. Found: C, 43,10; H, 5.62.

**3.3.3. Dimethyl 2,6-anhydro-3,4-*O*-isopropylidene-D-*glycero*-D-*talo*-heptarate 19**. A suspension of **18** (1.33 g, 5.3 mmol) in dry acetone (40 mL) and conc. $H_2SO_4$ (0.1 mL) was stirred at rt for 4 h. The reaction mixture was carefully neutralized with ion-exchange resin (Amberlite IR-400, OH–) and concentrated to syrup, which was dissolved in dry acetone (30 mL). After addition of 6 g of silica gel and removal of the solvent, the residue was applied to a silica gel column (3×30 cm) and eluted with toluene–EtOAc (1:1). Evaporation of the fractions with $R_f$ = 0.72 (TLC in EtOAc–EtOH–water, 30:3:1) and crystallization of the residue from EtOH–*n*-hexane gave 1.16 g (75%) of **19** as cubic crystals; mp 91°C; $[\alpha]_D^{20}$ = +12.5 (*c* 1.0, acetone); $^1$H NMR (300 MHz, [D$_4$]MeOH) $\delta$ 1.34, 1.45 (2 s, 3H each, $CMe_2$), 3.75, 3.77 (2 s, 3H each, 2 OMe), 4.14 (dd, 1H, *J* = 5.2, 5.4 Hz), 4.20 (dd, 1H, *J* = 5.4, 5.5 Hz), 4.31 (d, 1H, *J* = 5.2 Hz), 4.54 (dd, 1H, *J* = 4.3, 5.4 Hz), 4.67 (d, 1H, *J* = 4.3 Hz); MS (FD) *m*/*z* 291 (M$^+$+1), 290 (M$^+$). Anal. calcd for $C_{12}H_{18}O_8$ (290.3): C, 49.65; H, 6.25. Found: C, 49.66; H, 6.25.

**3.3.4. Dimethyl 2,6-anhydro-3,4-*O*-isopropylidene-5-*O*-mesyl-D-*glycero*-D-*talo*-heptarate 20**. To a cooled (0°C) solution of **19** (1.0 g, 3.4 mmol) in pyridine (12 mL) was added methanesulfonyl chloride (0.7 mL, 9 mmol), and the mixture was stirred for 3 h at 0°C. After addition of solid $NaHCO_3$ and stirring for another 30 min, the reaction mixture was diluted with satd aqueous $NaHCO_3$, extracted with EtOAc, dried ($Na_2SO_4$), and taken to dryness in vacuo: 1.19 g (94%) of **20** as colorless syrup; $[\alpha]_D^{20}$ = +9.7 (*c* 1.0, $CHCl_3$); $R_f$ = 0.57 (TLC in toluene–EtOAc, 1:1). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.32, 1.48 (two 3H-s, $CMe_2$), 3.08 (s, 3H, $SO_2Me$), 3.76, 3.77 (two 3H-s, 2 OMe), 4.30 (dd, 1H, *J* = 5.4, 5.7 Hz), 4.46 (d, 1H, *J* = 6.4 Hz), 4.52 (dd, 1H, *J* = 4.2, 5.4 Hz), 4.74 (d, 1H, *J* = 4.2 Hz), 4.99 (dd, 1H, *J* = 5.7, 7.4 Hz); MS (FD) *m*/*z* 369 (M$^+$+1), 368 (M$^+$). Anal. calcd for $C_{13}H_{20}O_{10}S$ (368.4): C, 42.39; H, 5.47. Found: C, 42.23; H, 5.38.

**3.3.5. Dimethyl 2,6-anhydro-4,5-*O*-isopropylidene-3-deoxy-D-*ribo*-hept-2-enarate 21**. To a solution of 1.0 g (2.7 mmol) **20** in 100 mL of lutidine was added 10 g of basic $Al_2O_3$ (Fluka type 5016A, basic) and the mixture was warmed to 40°C for 30 min, followed by evaporation to dryness in vacuo. The residue was applied to a silica gel column (3×30 cm) and eluted with $CH_2Cl_2$–acetone 110:1. Removal of the solvent from the eluates with $R_f$ = 0.74 (TLC in toluene–EtOAc, 1:1) in vacuo yielded 540 mg (73%) of **21** as a colorless syrup; $[\alpha]_D^{20}$ = +41.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.41, 1.48 (2 s, 3H each, $CMe_2$), 3.83, 3.84 (2 s, 3H each, 2 OMe), 4.46 (m, 2H, 5-H, 6-H), 4.63 (dd, 1H, *J* = 4.0, 4.9 Hz, 6.23 (d, 1H, *J* = 4.0 Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 25.9, 28.1 ($CMe_2$), 52.7, 52.9 (2 OMe), 67.2 (C-4), 71.7, 75.0 (C-5, C-6), 108.9 (C-3), 110.4 (*C*Me2), 144.6 (C-2), 161.9, 168.3 (2 CO). Anal. calcd for $C_{12}H_{16}O_7$ (272.3): C, 52.94; H, 5.92. Found: C, 53.06; H, 5.79.

**3.3.6. Dimethyl 2,6-anhydro-3-deoxy-D-*ribo*-hept-2-enarate 22**. Treatment of **21** (540 mg, 2.0 mmol) with 20 mL of a mixture of $CHCl_3$–TFA–water (50:10:1) at 30°C for 1 h and removal of the solvent afforded a syrup, which was purified by elution from a silica gel column (2×20 cm) with $CH_2Cl_2$–acetone (2:1). Concentration of the eluates gave 390 mg (85%) of **22** as a colorless syrup; $[\alpha]_D^{20}$ = +150.4 (*c* 1.0, acetone); $R_f$ = 0.57 (TLC in $CHCl_3$–acetone, 1:1). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.07, 3.45 (two 1H-d, 2 OH), 3.83, 3.84 (two 3H-s, 2 OMe), 4.12 (ddd, 1H, *J* = 4.3, 5.7, 7.6 Hz), 4.32 (ddd, 1H, *J* = 4.3, 4.4, 5.2 Hz), 4.63 (d, 1H, *J* = 7.6 Hz), 6.10 (d, 1H, *J* = 4.4 Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$)

$\delta$ 52.7, 53.0 (2 OMe), 61.5 (C-4), 66.7 (C-5), 74.7 (C-6), 109.9 (C-3), 143.8 (C-2), 162.1, 169.2 (2 CO); MS (FD) $m/z$ 233 ($M^+$+1), 232 ($M^+$). Anal. calcd for $C_9H_{12}O_7$ (232.2): C, 46.56; H, 5.21. Found: C, 44.91; H, 5.15.

**3.3.7. Dimethyl 4,5-di-*O*-acetyl-2,6-anhydro-3-deoxy-D-*ribo*-hept-2-enarate 23**. Stirring of **22** (63 mg, 0.27 mmol) in a mixture of $Ac_2O$ (2 mL) and pyridine (4 mL) for 5 h at rt, evaporation to dryness in vacuo, and elution of the residue from a silica gel column (1.5×20 cm) with $CH_2Cl_2$–acetone (60:1) afforded 78 mg (91%) of **23** as a colorless syrup; $[\alpha]_D^{20}=+171.1$ (*c* 0.9, $CHCl_3$); $R_f=0.69$ (TLC in toluene–EtOA*c* 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.08, 2.09 (two 3H-s, 2 Ac), 3.82, 3.85 (two 3H-s, 2 OMe), 4.84 (m, 1H), 5.52 (m, 2H), 6.01 (m, 1H); $^1$H NMR ($C_6H_6$): 1.68, 1.69 (two 3H-s, 2 Ac), 3.28, 3.25 (two 3H-s, 2 OMe), 4.74 (d, 1H, $J=6.3$ Hz), 5.62 (dd, 1H, $J=3.8$, 4.2 Hz), 5.71 (ddd, 1H, $J=0.7$, 4.2, 5.6 Hz), 6.02 (dd, 1H, $J=0.7$, 3.8 Hz); (FD) $m/z$ 317 ($M^+$+1), 316 ($M^+$). Anal. calcd for $C_{13}H_{16}O_9$ (316.3): C, 49.37; H, 5.10. Found: C, 48.95; H, 5.04.

**3.3.8. Dimethyl 2,6-anhydro-4,5-di-*O*-benzoyl-3-deoxy-D-*ribo*-hept-2-enarate 24**. A mixture of **22** (58 mg, 0.25 mmol), 4 mL of pyridine, and benzoyl chloride (0.1 mL, 0.86 mmol) was stirred for 4 h at 0°C and then diluted with EtOAc. The solution was successively washed with satd aqueous $NaHCO_3$ (3×10 mL) and water (10 mL), dried ($Na_2SO_4$), and then concentrated in vacuo. The residue was purified by elution from a silica gel column (1.5×20 cm) with $CH_2Cl_2$–acetone (60:1). Removal of the solvents from the eluates in vacuo gave 81 mg (74%) of **24** as a colorless syrup; $[\alpha]_D^{20}=+177.0$ (*c* 0.9, $CHCl_3$); $R_f=0.56$ (TLC in toluene–EtOAc, 1:1). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.75, 3.79 (two 3H-s, 2 OMe), 5.02 (m, 1H), 5.81 (m, 2H, H-4, H-5), 6.16 (m, 1H), 7.30, 7.45, 7.87 (3 m, 10 H, 2 $C_6H_5$); $^1$H NMR ($C_6H_6$) $\delta$ 3.23, 3.26 (two 3H s, 2 OMe), 4.93 (d, 1H, $J=6.4$ Hz), 5.98 (dd, 1H, $J=4.0$, 4.3 Hz), 6.09 (ddd, 1H, $J=0.9$, 4.2, 6.4 Hz), 6.22 (dd, 1H, $J=0.9$, 4.0 Hz), 6.94, 7.04, 7.99 (3 m, 10H, 2 $C_6H_5$). Anal. calcd for $C_{23}H_{20}O_9$ (440.4): C, 62.73; H, 4.58. Found: C, 62.72; H, 4.68.

### 3.4. D-Mannose→L-*lyxo* products 29–31 (*ent*-daucic acid derivatives)

**3.4.1. 2,6-Anhydro-D-*glycero*-D-*galacto*-heptonic acid [*C*-(β-D-mannopyranosyl)formic acid] 25**. To a solution of α-D-mannosyl-cyanide **16**[10] in MeOH (30 mL) was added 17 mL of 0.1N NaOMe in MeOH, and the mixture was kept at rt for 1 h followed by evaporation to dryness in vacuo. The residue was dissolved in 12.5% aqueous NaOH (50 mL) and refluxed for 4 h. Dilution with $H_2O$ (150 mL), neutralization by stirring with Amberlite IR-120 ($H^+$-form, 100 mL), filtration with several washings with water, and evaporation of the combined filtrates to dryness in vacuo gave a solid mass, which was purified by passing it, dissolved in 60 mL of water, through an Amberlite IR 120 column (100 mL) and rinsed with water. Evaporation of the combined eluates to dryness in vacuo gave 7.34 g (90%) of **25** as a syrup, which was directly used for the ensuing oxidation (→26); $R_f=0.34$ (TLC in EtOAc–HOAc–$H_2O$, 3:2:1); $[\alpha]_D^{20}=-2.4$ (*c* 1.0 MeOH); $^1$H NMR (300 MHz, $D_2O$) $\delta$ 3.41 (ddd, 1H, $J=2.3$, 6.4, 9.6 Hz, H-6), 3.59 (t, 1H, $J=9.6$ Hz), 3.72 (dd, 1H, $J=3.4$, 9.6 Hz), 3.75 (dd, 1H, $J=6.4$, 12.4 Hz), 3.93 (dd, 1H, $J=2.3$, 12.4 Hz), 4.31 (dd, 1H, $J=1.4$, 3.4 Hz), 4.37 (d, 1H, $J=1.4$ Hz); MS (FD) $m/z$ 208 ($M^+$).

**3.4.2. Dimethyl 2,6-anhydro-D-*glycero*-D-*galacto*-heptarate 26**. Solid **25** (7.00 g, 33.7 mmol) was gradually added (30 min) to a stirred, warmed (55–60°C) mixture of conc. $HNO_3$–fuming $HNO_3$ (1:1, 12 mL) containing 9 mg of $NaNO_2$. Stirring at 55–60°C was continued for 1.5 h, followed by dilution with water (80 mL), neutralization with 25% aqueous NaOH (to pH 8) and filtration of insolubles. Removal of the solvent in vacuo left a syrup, which was dissolved in $H_2O$ (20 mL), then MeOH (200 mL) was added and the mixture was stored at 5°C for 12 h. The solid mass was separated, dissolved with $H_2O$ (80 mL) and applied to a column of Amberlite IR-120 ($H^+$-form) (140 mL). Acidic eluates were collected, treated with active carbon, and then taken to dryness in vacuo. Treatment of the residue with 8% HCl–MeOH (40 mL) at rt for 2 h and concentration to dryness gave a syrup, which was purified by elution from a silica gel column (4.5×30 cm) with $CHCl_3$–MeOH (6:1). Eluates of $R_f=0.40$ (TLC in $CHCl_3$–MeOH, 4:1) were evaporated to dryness in vacuo and the residue was crystallized from MeOH–$CHCl_3$: 4.65 g (55%) of **26** as needles; a second crop (0.98 g, 12%) was obtained from the mother liquor; mp 163°C; $[\alpha]_D^{20}=-22.7$ (*c* 1.0, MeOH); $^1$H NMR (300 MHz, $D_2O$) $\delta$ 3.76 (dd, 1H, $J=3.0$, 9.5 Hz), 3.81, 3.84 (two 3H-s, 2 OMe), 3.83 (dd, 1H, $J=9.2$, 9.5 Hz), 3.99 (d, 1H, $J=9.2$ Hz), 4.34 (dd, 1H, $J=1.2$, 3.0 Hz), 4.49 (d, 1H, $J=1.2$ Hz); MS (FD) $m/z$ 252 ($M_+$+2), 251 ($M^+$+1), 250 ($M^+$). Anal. calcd for $C_9H_{14}O_8$ (250.2): C, 43.20; H,5.64. Found: C, 42.98; H, 5.56.

**3.4.3. Dimethyl 2,6-anhydro-3,4-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptarate 27**. To a suspension of **26** (2.0 g, 8 mmol) in dry acetone (50 mL) containing 0.15 mL of conc. sulfuric acid was added. The reaction mixture was stirred for 4 h at 20°C followed by stirring with Amberlite IR-400 ($OH^-$-form), filtration washing with water and evaporation of the combined filtrates to dryness. The residue was applied to a silica gel column (3×30 cm) and eluted with toluene–EtOAc (1:1). Evaporation of the fractions with $R_f=0.72$ (TLC in EtOAc–EtOH–water, 30:3:1) left a syrup that crystallized from EtOH–*n*-hexane: 1.80 g (75%) of **27** as colorless needles; mp 139°C; $[\alpha]_D^{20}=-31.1$ (*c* 1.0, $Me_2CO$); $^1$H NMR (300 MHz, [$D_4$]MeOH) $\delta$ 1.32, 1.45 (2 s, 3H each, CMe2), 3.76, 3.77 (2 s, 3H each, 2 OMe), 3.98 (m, 2H, H-5, H-6), 4.23 (dd, 1H, $J=6.0$, 6.2 Hz), 4.55 (dd, 1H, $J=6.0$, 6.2 Hz), 4.67 (d, 1H, $J=2.4$ Hz); $^{13}$C NMR (75.5 MHz, [$D_4$]MeOH) $\delta$ 26.6, 27.9 ($CMe_2$), 52.9 (2 OMe), 70.6, 79.4 (C-5, C-6), 75.6 (C-2, C-3), 111.9 ($CMe_2$), 170.2, 171.5 (2 CO); MS (FD) $m/z$ 292 ($M^+$+2), 291 ($M^+$+1), 290 ($M^+$). Anal. calcd for $C_{12}H_{18}O_8$ (290.3): C, 49.65; H, 6.25. Found: C, 49.74; H, 6.28.

**3.4.4. Dimethyl 2,6-anhydro-3,4-*O*-isopropylidene-5-*O*-mesyl-D-*glycero*-D-*galacto*-heptarate 28**. To a cooled (0°C) solution of **27** (600 mg, 2 mmol) in pyridine (10 mL) was added methanesulfonyl chloride (0.4 mL, 5.2 mmol), and the mixture was stirred for 3 h at 0°C. Solid $NaHCO_3$ was then added and stirring was continued for another 30 min at 0°C. The reaction mixture was diluted with satd aqueous $NaHCO_3$, extracted with EtOAc, and dried over $Na_2SO_4$. Removal of the solvent in vacuo gave a crystalline mass, which was recrystallized from *i*-PrOH to afford 645 mg (85%) of **28** as colorless needles; mp 163°C; $[\alpha]_D^{20}=-17.9$ (*c* 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.37, 1.55 (2 s, 3H each, C*Me*$_2$), 3.14 (s, 3H, Ms*Me*), 3.83, 3.84 (2 s, 3H each, 2 OMe), 4.17 (d, 1H, $J=7.3$ Hz), 4.45 (dd, 1H, $J=6.0$, 6.2 Hz), 4.48 (d, 1H, $J=2.2$ Hz), 4.63 (dd, 1H, $J=6.0$, 6.2 Hz), 4.99 (dd, 1H, $J=6.2$, 7.3 Hz); MS (FD) *m*/*z* 369 ($M^+$+1), 368 ($M^+$). Anal. calcd for $C_{13}H_{20}O_{10}S$ (368.4): C, 42.39; H,5.47. Found: C, 42.03; H,5.42.

**3.4.5. Dimethyl 2,6-anhydro-4,5-*O*-isopropylidene-3-deoxy-L-*lyxo*-hept-2-enarate 29**. To a solution of 324 mg (0.9 mmol) **28** in 30 mL of lutidine was added 3 g of basic $Al_2O_3$ (Fluka type 5016 A basic) and the mixture was warmed to 40°C for 30 min followed by evaporation in vacuo to dryness. The residue was applied to a silica gel column (1.5×30 cm) and eluted with $CH_2Cl_2$–$Me_2CO$ (110:1). Removal of the solvent from the eluates with $R_f=0.53$ (TLC in vacuo yielded 165 mg (69%) as **29** as a syrup; $[\alpha]_D^{20}=+20.6$ (*c* 0.9, $CHCl_3$); $^1H$ and $^{13}C$ NMR data were identical to those of its D-*lyxo* enantiomer **41**. Anal. calcd for $C_{12}H_{16}O_7$ (272.3): C, 52.94; H, 5.92. Found: C, 51.44; H, 5.86.

**3.4.6. Dimethyl 2,6-anhydro-3-deoxy-L-*lyxo*-hept-2-enarate (*ent*-dimethyl daucate) 30**. Exposure of **29** to 6 mL of $CHCl_3$–TFA–$H_2O$ (50:10:1) for 1 h at 30°C and evaporation to dryness in vacuo gave a semi-crystalline residue, which was purified by elution from a silica gel column (2×20 cm) with $CH_2Cl_2$–$Me_2CO$ (2:1) Removal of the solvent and crystallization from EtOAc–*n*-hexane afforded 95 mg (73%) of **30**; mp 126°C; $[\alpha]_D^{20}=+94.1$ (*c* 0.3, acetone); $^1H$ and $^{13}C$ NMR data duplicated those of the enantiomeric (carrot-derived) (−)-dimethyl daucate 42 (vide infra). Anal. calcd for $C_9H_{12}O_7$ (232.2): C, 46.56; H, 5.21. Found: C, 45.92; H, 5.15.

**3.4.7. Dimethyl 4,5-di-*O*-acetyl-2,6-anhydro-3-deoxy-L-*lyxo*-hept-2-enarate 31**. Stirring of **30** (30 mg) in 4 mL of pyridine–acetic anhydride (4:1) for 5 h at rt, followed by work-up as described for the D-*lyxo* product **43** (cf. below) afforded **31** (27 mg, 88%) as a syrup of $[\alpha]_D^{20}=+53.6$ (*c* 1.0, $CHCl_3$). $^1H$ NMR data were identical to those of **44**.

### 3.5. D-Galactose→L-*arabino* analogs of daucic acid

**3.5.1. Methyl 2,6-anhydro-D-*glycero*-L-*manno*-heptonate [methyl *C*-(β-D-galactopyranosyl)formate] 33**. To a solution of 14.0 g (39.2 mmol) of *C*-(tetra-*O*-acetyl-β-D-galactosyl)cyanide **32**[12b] in dry MeOH (30 mL) was added 17 mL of 0.1N NaOMe–MeOH and the mixture was stirred at ambient temperature for 2 h, followed by removal of the solvent in vacuo. The residue was dissolved in 12.5% aqueous NaOH (50 mL) and the solution was refluxed for 4 h, subsequently diluted with water (150 mL) and neutralized by stirring with Amberlite IR-120 ($H^+$-form, 120 mL). Filtration, several washings with water and evaporation of the combined filtrates to dryness in vacuo gave the free heptonic acid (**33**, H instead of Me) as a crystalline mass, which was directly subjected to esterification by stirring with HCl–satd MeOH (50 mL) at rt overnight. The mixture was then taken to dryness in vacuo providing 7.4 g (85%) of **33** as a syrup, sufficiently pure ($^1H$ NMR) for the ensuing oxidation (→**34**).

Syrupy **33**, of $R_f=0.40$ (TLC in EtOAc–*i*-PrOH–water 5:2:1), can be crystallized by trituration with EtOAc:[27] mp 121–123°C, $[\alpha]_D^{20}=-32.0$ (*c* 0.2, $H_2O$).

**3.5.2. Dimethyl 2,6-anhydro-D-*glycero*-L-*manno*-heptarate 34**. To a solution of syrupy **33** as obtained above (7.2 g, 32 mmol) in satd aqueous $NaHCO_3$ (50 mL) containing KBr (300 mg) an $n$Bu$_4$NCl (350 mg) was added a solution of TEMPO in $CH_2Cl_2$ (150 mg in 60 mL) followed, after cooling to 0°C, by the dropwise addition of a mixture of aqueous 13% NaOCl (150 mL), satd aqueous NaCl (50 mL) and satd aqueous $NaHCO_3$ (25 mL) over the period of 1 h. Stirring was continued for 12 h at 0°C and the mixture was allowed to warm to ambient temperature. Separation of the two layers, washing of the organic phase with water (3×25 mL), acidification of the combined aqueous layer and extracts with 2N HCl, and concentration in vacuo left a syrup which was dissolved in water (80 mL) and passed through an Amberlite IR-120 column ($H^+$-form, 140 mL). Acidic eluates were collected, treated with active carbon, and then taken to dryness in vacuo. The resulting syrup was exposed to 8% HCl–MeOH (40 mL) for 2 h at ambient temperature. Removal of the solvent, purification of the residue by elution from a silica gel column with $CHCl_3$–MeOH (6:1) and evaporation of the combined eluates with $R_f=0.40$ in $CHCl_3$–MeOH (4:1) to dryness in vacuo gave a syrup which crystallized on trituration with MeOH–$CHCl_3$: 6.65 g (70%) of **34** as colorless needles; mp 163–164°C; $[\alpha]_D^{20}=+23.0$ (*c* 1.0, MeOH). $^1H$ NMR (300 MHz, $D_2O$) $\delta$ 3.76 (dd, $J=3.0$ Hz, 9.6 Hz, 1H), 3.81, 3.84 (2 s, 3H each), 3.83 (dd, $J=9.2$, 9.6 Hz, 1H), 4.00 (d, $J=9.2$ Hz, 1H), 4.34 (dd, $J=1.3$, 3.0 Hz, 1H), 4.50 (d, $J=1.3$ Hz, 1H); $^{13}C$ NMR (75.5 MHz, $D_2O$) $\delta$ 55.9, 56.0,70.6, 72.5, 75.7, 80.3, 80.8, 173.2, 173.7; MS (FD) *m*/*z* 251 ($M^+$+1), 250 ($M^+$). Anal. calcd for $C_9H_{14}O_8$ (250.2): C, 43.20; H,5.64. Found C, 43.24; H,5.60.

**3.5.3. Dimethyl 2,6-anhydro-4,5-*O*-isopropylidene-D-*glycero*-L-*manno*-heptarate 35**. A suspension of dimethyl heptarate **34** (3.40 g, 13.6 mmol) in dry acetone (70 mL) containing 0.2 mL of conc. $H_2SO_4$ was stirred for 4 h at ambient temperature, and subsequently neutralized with basic ion-exchange resin (Amberlite IR-400, $OH^-$). Evaporation to dryness gave a syrup which was applied to a silica gel column (4.5×30 cm) and eluted with toluene–EtOAc (1:1).

Evaporation of the fractions with $R_f = 0.72$ (TLC in EtOAc–EtOH–water 30:3:1) and crystallization of the residue from EtOH–*n*-hexane gave 3.25 g (83%) of **35** as colorless needles; mp 139°C; $[\alpha]_D^{20} = +38.7$ (*c* 0.7, $CHCl_3$). (300 MHz, $CDCl_3$) $\delta$ 1.31, 1.47 (2 s, 3H each), 3.49 (bs, 1H), 3.79, 3.80 (2 s, 3H each), 3.88 (d, $J = 8.2$ Hz, 1H), 4.04 (m, 1H), 4.20 (dd, $J = 5.8$, 5.8 Hz, 1H), 4.51 (m, 2H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 26.1, 27.4 ($CMe_2$), 52.7, 52.9 (2 OMe), 69.7, 73.4, 74.8, 76.7, 77.4, 110.9, 167.6, 169.9 (2 COOMe); MS (FD) *m*/*z* 291 ($M^+$+1), 290 ($M^+$), 275 ($M^+$–$CH_3$). Anal. calcd for $C_{12}H_{18}O_8$ (290.3): C, 49.65; H, 6.25. Found C, 49.71; H, 6.22.

**3.5.4. Dimethyl 2,6-anhydro-3-*O*-benzoyl-4,5-*O*-isopropylidene-D-*glycero*-L-*manno*-heptarate 36**. A solution of **35** (490 mg, 1.7 mmol) in pyridine (10 mL) containing 400 μL (3.5 mmol) of benzoyl chloride was stirred at rt overnight and then poured onto an approximate 1:1 mixture of ice and satd aqueous $NaHCO_3$. The solid material was filtered off, washed with water, and recrystallized from EtOH to afford 585 mg (90%) of **36**; mp 160–162°C; $[\alpha]_D^{20} = +6.3$ (*c* 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.36, 1.56 (two 3H-s, $CMe_2$), 3.76, 3.87 (two 3H-s, 2 OMe), 4.36 (d, 1H, $J = 5.4$ Hz), 4.57 (dd, 1H, $J = 5.4$, 6.4 Hz), 4.61 (d, 1H, $J = 2.3$ Hz), 4.68 (dd, 1H, $J = 2.3$, 6.4 Hz), 5.72 (t, 1H, $J = 5.4$ Hz), 7.55, 8.05 (2 m, 3H and 2H, $C_6H_5$); MS (FD) *m*/*z* 395 ($M^+$+1), 394 ($M^+$). Anal. calcd for $C_{19}H_{22}O_9$ (394.4): C, 57.87; H, 5.62. Found: C, 57.80; H, 5.55.

**3.5.5. Dimethyl 2,6-anhydro-3,4-di-*O*-benzoyl-5-*O*-mesyl-D-*glycero*-L-*manno*-heptarate 38**. A solution of **36** (320 mg, 0.8 mmol) in 6 mL of $CHCl_3$–TFA–water (50:10:1) was stirred at ambient temperature for 30 min, then concentrated to a syrup and purified on a silica gel column by elution with acetone–$CHCl_3$ (2:1). Eluates with $R_f = 0.26$ (TLC in acetone–$CHCl_3$, 2:1) were concentrated to a syrup, which was dissolved in pyridine (3 mL), cooled to −35 to −40°C, followed by addition of a mixture of benzoyl chloride (0.12 mL, 1 mmol) and pyridine (1 mL). Stirring at −40°C was continued for 2 h whereafter methanesulfonyl chloride (0.15 mL, 2 mmol) was then added, and the mixture was allowed to warm to rt (3 h). Subsequent dilution with EtOAc (20 mL), washing with satd aqueous $NaHCO_3$ and water, drying ($Na_2SO_4$), and concentration in vacuo gave a syrup which was purified on a silica gel column ($CHCl_3$–EtOAc, 5:1). Eluates with $R_f = 0.60$ (TLC in $CHCl_3$–acetone, 5:1) were concentrated to give a crystalline mass consisting of a 5:1 mixture ($^1H$ NMR) of **38** and its 4-*O*-mesylated isomer. Fractional crystallization from EtOH afforded 230 mg (53%) of **38**; mp 189–190°C; $[\alpha]_D^{20} = +89.0$ (*c* 0.6, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.05 (s, 3H, $SO_2Me$), 3.72, 3.86 (two 3H s, 2 OMe), 4.30 (d, 1H, $J = 10.0$ Hz), 4.55 (m, 1H), 5.55 (dd, 1H, $J = 3.1$, 10.2 Hz), 5.73 (dd, 1H, $J = 0.7$, 3.1 Hz), 5.91 (dd, 1H, $J = 10.0$, 10.2 Hz), 7.50, 8.00 (2 m, 6H and 4H, 2 $C_6H_5$); MS (FD) *m*/*z* 537 ($M^+$+1), 536 ($M^+$). Anal. calcd for $C_{24}H_{24}O_{12}S$ (536.5): C, 53.73; H, 4.51. Found: C, 53.63; H, 4.45.

Aside **38**, 40 mg (10%) of dimethyl 2,6-anhydro-3,5-di-*O*-benzoyl-4-*O*-mesyl-D-*glycero*-L-*manno*-heptarate was obtained from the fractional crystallization; mp 226–228°C; $[\alpha]_D^{20} = +104.8$ (*c* 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.05 (s, 3H, Ms*Me*), 3.72, 3.73 (two 3H-s, 2 OMe), 4.26 (d, 1H, $J = 9.9$ Hz), 4.52 (m, 1H, 6-H), 5.29 (dd, 1H, $J = 3.5$, 9.9 Hz), 5.76 (t, 1H, $J = 9.9$ Hz), 6.22 (dd, 1H, $J = 1.3$, 3.5 Hz), 7.35 and 8.10 (2 m, 6 and 4H, 2 $C_6H_5$); MS (FD) *m*/*z* 537 ($M^+$+1), 536 ($M^+$).

**3.5.6. Dimethyl 2,6-anhydro-5-*O*-mesyl-D-*glycero*-L-*manno*-heptarate 39**. A suspension of **38** (180 mg, 0.33 mmol) in 16% HCl–MeOH (10 mL) was refluxed for 2 days. The clear solution was concentrated to a syrup which was purified on a silica gel column ($CHCl_3$–acetone, 1:1). Product-containing eluates ($R_f = 0.25$, TLC in $CHCl_3$–acetone, 1:1) were concentrated to afford 95 mg (86%) of **39** as a crystalline mass; mp 144–145°C; MS (FD) *m*/*z* 329 ($M^+$+1), 328 ($M^+$).

**3.5.7. Dimethyl 2,6-anhydro-3-deoxy-L-*arabino*-hept-2-enarate 40**. To a solution of **39** in MeOH (80 mg in 2 mL) was added 1.7 mL of 0.1N NaOMe in MeOH and the mixture was stirred at rt for 15 min. Removal of the solvent in vacuo and purification by elution from a silica gel column with $CHCl_3$–acetone (1:1) afforded 52 mg (90%) of **40** as a syrup; $[\alpha]_D^{20} = +30.0$ (*c* 1.0, acetone); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.80, 3.85 (two 3H s, 2 OMe), 4.19 (m, 1H), 4.25 (m, 1H), 4.73 (dd, 1H, $J = 0.9$, 5.4 Hz), 6.13 (dd, 0.9, 4.3 Hz), MS (FD) *m*/*z* 233 ($M^+$+1), 232 ($M^+$). Anal. calcd for $C_9H_{12}O_7$ (232.2): C, 46.56; H, 5.21. Found: C, 46.50; H, 5.14.

**3.5.8. Dimethyl 4,5-di-*O*-acetyl-2,6-anhydro-3-deoxy-L-*arabino*-hept-2-enarate 41**. Exposure of **40** (23 mg, 0.1 mmol) to a mixture of $Ac_2O$ (0.3 mL) and pyridine (1.5 mL) for 12 h at rt, evaporation to dryness in vacuo and purification of the residual syrup by elution from a short silica gel column with *n*-hexane–acetone (2:1) gave 27 mg (90%) of **41** as a syrup, which gradually crystallized by standing at 5°C; mp 104–106°C; $[\alpha]_D^{20} = +72.0$ (*c* 0.6, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.01, 2.11 (two 3H-s, 2 Ac), 3.79, 3.88 (two 3H s, 2 OMe), 5.06 (dd, 1H, $J = 2.1$, 2.2 Hz), 5.14 (ddd, 1H, $J = 1.6$, 2.1, 5.4 Hz), 5.44 (m, 1H), 6.18 (dd, 1H, $J = 1.5$, 5.4 Hz); $^1H$ NMR ($C_6H_6$) $\delta$ 1.44, 1.46 (two 3H s, 2 Ac), 3.20, 3.25 (two 3H s, 2 OMe), 4.89 (dd, 1H, $J = 1.6$, 2.6 Hz), 5.22 (ddd, 1H, $J = 1.6$, 2.3, 5.3 Hz), 5.58 (m, 1H), 6.37 (dd, $J = 1.5$, 5.3 Hz); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 20.8 (2 Ac), 52.6, 52.9 (2 OMe), 62.5 (C-4), 66.9 (C-5), 73.2 (C-6), 104.6 (C-3), 145.2 (C-2), 161.9, 166.4, 169.9, 169.4 (4 CO); MS (FD) *m*/*z* 316 ($M^+$).

### 3.6. D-Galactose→(−)-dimethyl daucate and derivatives 42–45

**3.6.1. Dimethyl 2,6-anhydro-4,5-*O*-isopropylidene-3-*O*-mesyl-D-*glycero*-L-*manno*-heptarate 37**. To a cooled solution of **35** (1.0 g, 3.4 mmol) in pyridine (12 mL), methanesulfonyl chloride (0.7 mL, 9 mmol) was added. The mixture was stirred for 3 h at 0°C. After stirring with solid $NaHCO_3$ for 30 min at 0°C, the reaction

mixture was diluted with satd aqueous $NaHCO_3$, then extracted with EtOAc, and dried over $Na_2SO_4$. The solution was concentrated to give a crystalline mass, which was recrystallized from *i*-PrOH to afford 1.1 g (85%) of **37** as colorless needles; mp 163°C; $[\alpha]_D^{20}=+17.2$ (*c* 1.1, $CHCl_3$); $R_f=0.34$ (toluene–EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.37, 1.56 (2 s, 3H each, $CMe_2$), 3.15 (s, 3H, $SO_2Me$), 3.84, 3.85 (two 3H-s, 2 OMe), 4.17 (d, $J=7.4$ Hz, 1H), 4.46 (dd, $J=6.0$, 6.3 Hz, 1H), 4.49 (d, $J=2.3$ Hz, 1H), 4.64 (dd, $J=2.3$, 6.0 Hz, 1H), 4.98 (dd, $J=6.0$, 6.3 Hz, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 26.1, 27.1 ($CMe_2$), 39.0 ($SO_2Me$), 52.9, 53.1 (2 OMe), 73.7, 74.6, 75.3, 75.7, 77.2, 111.8 ($CMe_2$), 167.0, 167.1 (2 CO); MS (FD) *m*/*z* 369 ($M^+$+1), 368 ($M^+$), 353 ($M^+$−Me). Anal. calcd for $C_{13}H_{20}O_{10}S$ (368.4): C, 42.39; H, 5.47. Found: C, 42.48; H, 5.37.

**3.6.2. Dimethyl 2,6-anhydro-4,5-*O*-isopropylidene-3-deoxy-D-*lyxo*-hept-2-enarate (dimethyl 4,5-*O*-isopropylidene-daucate) 42**. To a solution of mesylate **37** (1.0 g, 2.7 mmol) in 100 mL of lutidine was added 10 g of basic $Al_2O_3$ (Fluka type 5016) and the suspension was stirred for 30 min at 40°C and subsequently evaporated to dryness. The residue was applied to a silica gel column (3×30 cm) and eluted with $CH_2Cl_2$–acetone (110:1). Removal of the solvent from the eluates with $R_f=0.51$ (TLC in toluene–EtOA*c* 1:1) in vacuo yielded 565 mg (77% of **42** as a syrup; $[\alpha]_D^{20}=-19.1$ (*c* 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.37, 1.41 (2 s, 3H each, $CMe_2$), 3.83, 3.90 (2 s, 3H each, 2 OMe), 4.67, (1H, d, $J=1.5$ Hz, H-6), 4.69 (1H, ddd, $J=1.3$, 1.5, 5.9 Hz), 4.89 (dd, 1H, $J=3.3$, 5.9 Hz), 6.08 (dd, 1H, $J=1.3$, 3.3 Hz). Anal. calcd for $C_{12}H_{16}O_7$ (272.3): C, 52.94; H, 5.92. Found: C, 53.10; H, 5.87.

**3.6.3. (−)-Dimethyl daucate (dimethyl 2,6-anhydro-3-deoxy-D-*lyxo*-hept-2-enarate) 43**. Exposure of **42** (475 mg, 1.7 mmol) to a stirred mixture of 20 mL of $CHCl_3$–TFA–water (50:10:1) gave after 1 h at rt and evaporation to dryness a semi-crystalline residue, which was purified by elution from a silica gel column (2×20 cm) with $CH_2Cl_2$–acetone (2:1). Concentration of the eluate and crystallization from EtOAc–*n*-hexane afforded 335 mg (83%) of **43** as a colorless powder; mp 128–129°C; $[\alpha]_D^{20}=-97.3$ (*c* 0.6, acetone); $R_f=0.38$ (TLC in $CHCl_3$–acetone 1:1). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.84, 3.86 (2 s, 3H each, 2 OMe), 4.30 (1H, ddd, $J=1.2$, 2.4, 4.4 Hz, H-5), 4.50 (1H, ddd, $J=0.7$, 3.3, 4.4 Hz, H-4), 4.67 (1H, dd, $J=0.7$, 2.4 Hz, H-6), 6.05 (1H, dd, $J=1.2$, 3.3 Hz, H 3; $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 52.8, 53.1 (2 OMe), 63.8 (C-4), 66.0 (C-5), 75.6 (C-6), 111.5 (C-3), 143.3 (C-2), 162.2, 168.8 (2*C*O); MS (FD) *m*/*z* 234 (4%, $M^+$+2), 233 (39%. $M^+$+1), 232 (100%, $M^+$); UV (EtOH) $\lambda_{max}$ 242 nm ($\varepsilon$ 5470). Anal. calcd for $C_9H_{12}O_7$ (232.3): C, 46.56; H,5.21. Found: C, 46.49; H, 5.19.

**3.6.4. Dimethyl 4,5-di-*O*-acetyl-2,6-anhydro-3-deoxy-D-*lyxo*-hept-2-enarate 44**. Stirring of dimethyl daucate **43** (40 mg, 0.17 mmol) with $Ac_2O$ (1 mL) and pyridine (4 mL) at 20°C for 5 h, evaporation to dryness in vacuo, and elution of the syrupy residue from a silica gel column (1.5×20 cm) with $CH_2Cl_2$–acetone (60:1) gave 50 mg (91%) of **44** as a colorless syrup, uniform by TLC ($R_f=0.60$ in toluene–EtOAc, 1:1); $[\alpha]_D^{20}=-54.1$ (*c* 0.6, $CDCl_3$); $^1H$ NMR (300 MHz, $CHCl_3$) $\delta$ 2.05, 2.10 (2 s, 3H each, 2 Ac*Me*), 3.82, 3.86 (2 s, 3H each, 2 OMe), 4.84 (1H, d, $J=1.4$ Hz, H-6), 5.73 (2H, m, H-4, H-5), 5.98 (1H, dd, $J=1.7$, 2.3 Hz, H-3). $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 1.65, 1.66 (2 s, 3H each, 2 AcMe), 3.31 (s, 6H, 2 OMe), 4.27 (1H, d, $J=1.7$ Hz, H-6), 5.56 (1H, ddd, $J=1.2$, 2.3, 4.5 Hz, H-4), 5.81 (1H, ddd, $J=1.2$, 1.7, 1.7 Hz, H-5), 6.00 (1H, dd, $J=1.7$, 2.3 Hz, H-3); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 20.5, 20.6 (2 AcMe), 52.8, 53.0 (2 COOMe), 63.5, 64.2 (C-4, C-5), 74.5 (C-6), 107.5 (C-3), 144.6 (C-2), 161.4, 166.4, 169.8, 169.9 (4 CO); MS (FD) *m*/*z* 316 ($M^+$). Anal. calcd for $C_{13}H_{16}O_9$ (316.3): C, 49.37; H, 5.10. Found: C, 49.31; H, 5.03.

**3.6.5. Dimethyl 2,6-anhydro-4,5-di-*O*-benzoyl-3-deoxy-D-*lyxo*-hept-2-enarate 45**. Dimethyl daucate **43** (21 mg, 0.09 mmol) was benzoylated with benzoyl chloride (0.1 mL, 0.86 mmol) and 3 mL of pyridine. The reaction mixture was stirred for 4 h at ambient temperature and then diluted with EtOAc. The solution was washed with satd aqueous $NaHCO_3$ (3×10 mL) and $H_2O$ (10 mL), dried ($Na_2SO_4$), and concentrated in vacuo to a residue, which was purified by elution from a silica gel column (1.5×20 cm) with $CH_2Cl_2$–acetone (60:1). Removal of the solvent from the eluates in vacuo and trituration of the syrup with little MeOH resulted in crystallization: 30 mg (76%) of **45**; mp 112–113°C [lit.[3] mp 112°C for the carrot-derived product]; $[\alpha]_D^{20}=-88.9$ (*c* 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.76, 3.90 (2 s, 3H each, 2 OMe), 5.06 (1H dd, $J=1.4$, 2.0 Hz, H-6), 6.07 (2H, m, H-4, H-5), 6.21 (1H, dd, $J=1.6$, 3.0 Hz, H-3), 7.26–8.14 (10 H, m, 2 $C_6H_5$); $^1H$ NMR (300 MHz, $C_6H_6$) $\delta$ 3.17, 3.32 (2 s, 3H each, 2 OMe), 4.31 (1H, dd, $J=1.2$, 1.7 Hz, H-6), 5.83 (1H, ddd, $J=1.2$, 1.7, 4.3 Hz, H-4), 6.11 (1H, ddd, $J=1.5$, 1.7, 4.3 Hz, H-5), 6.17 (1H, dd, $J=1.5$, 2.8 Hz, H-3), 6.8-7.1, 7.9 −8.1 (2 m, 10 H, 2 $C_6H_5$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 53.0, 53.1 (2 OMe), 64.6, 64.9 (C-4, C-5), 74.3 (C-6), 107.5 (C-3), 128.5–133.9 (12 C, 2 $C_6H_5$), 145.1 (C-2), 161.7, 165.3, 165.6, 166.7 (4 CO); MS (FD) *m*/*z* 440 ($M^+$). Anal. calcd for $C_{23}H_{20}O_9$ (440.4): C, 62.72; H, 4.58. Found: C, 62.66; H, 4.49.

**3.6.6. (−)-Daucic acid [2,6-anhydro-3-deoxy-D-*lyxo*-hept-2-enaric acid; IUPAC: (2*S*,3*R*,4*R*)-3,4-dihydro-3,4-dihydroxy-2*H*-pyran-2,6-dicarboxylic acid] 46**. To an aqueous solution of dimethyl daucate **43** (60 mg, 0.3 mmol, in 4 mL) was added TFA (1 mL) and the mixture was stirred for 3 days at 30°C. Evaporation of the solution to dryness in vacuo afforded a syrup, which gave a crystalline mass on trituration with acetone–*n*-hexane: 42 mg (79%) of **46**; mp 87–88°C; $[\alpha]_D^{20}=-85.0$ (*c* 1.2, MeOH); $R_f=0.25$ (TLC in EtOAc–HOAc–water, 3:2:1); [lit.[3] mp 85–87°C]. $^1H$ NMR (300 MHz, [$D_4$]MeOH) $\delta$ 4.28 (dt, 1H, $J=1.6$, 1.6, 4.5 Hz, H-5), 4.60 (ddd, 1H, $J=0.9$, 2.0, 4.5 Hz, H-4), 4.74 (dd, 1H, $J=0.9$, 1.6 Hz), 5.93 (dd, 1H, $J=1.6$, 2.0 Hz); $^{13}C$ NMR (75.5 MHz, [$D_4$]MeOH) $\delta$ 67.4 (C-4), 68.2 (C-5), 79.6 (C-6), 115.4 (C-3), 145.7 (C-2), 166.8, 173.4 (2 CO). Anal. calcd for $C_7H_8O_7$ (204.1): C, 41.14; H, 3.95. Found: C, 41.12; H, 3.87.

**3.6.7. (+)-Dimethyl osbeckate [methyl 2*S*-hydroxy-2-(5-carbomethoxy-2-furyl)acetate] 5**. Refluxing **43** (50 mg, 0.21 mmol) in methanol satd. with HCl (5 mL) for 4 h was followed by evaporation to dryness in vacuo and several coevaporations from MeOH. Purification of the residue by elution from a silica gel column (1×15 cm) with $CH_2Cl_2$–MeOH (20:1), removal of the solvents from the eluates and trituration of the residues with acetone–*n*-hexane yielded 28 mg (62%) of **5** as colorless crystals; mp 134°C; $[\alpha]_D^{20}=+78.9$ (*c* 0.5, acetone) [lit.[13] for the *Osbeckia chinensis*-derived product: mp 134–135°C; $[\alpha]_D^{20}=+79.3$ (*c* 0.2, acetone)]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.56 (bs, 1H, OH), 3.82, 3.87 (two 3H-s, 2 OMe), 5.25 (s, 1H), 6.48, 7.13 (2 d, $J=3.5$ Hz); MS (FD) *m*/*z* 215 $(M+1)^+$, 214 $(M^+)$. Anal. calcd for $C_9H_{10}O_6$ (214.2): C, 50.47; H, 4.71. Found: C, 50.50; H, 4.74.

**3.6.8. (+)-Osbeckic acid [2*S*-hydroxy-2-(5-carboxy-2-furyl)acetic acid] 47**. A solution of dimethyl daucate **43** (50 mg, 0.2 mmol) in water (5 mL) was stirred with Amberlite IR-120 ($H^+$-form, 1 g) and the mixture was refluxed for 5 h. Filtration and evaporation of the combined filtrate and washings to dryness in vacuo gave 35 mg (85%) of **47** as a colorless syrup; $R_f=0.59$ (TLC in EtOAc–HOAc–water, 3:2:1); $[\alpha]_D^{20}=+79.6$ (*c* 0.8, MeOH) [lit.[13] oil, $[\alpha]_D^{20}=+83.5$ (*c* 0.2, MeOH)]; $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.47 (s, 1H), 6.70 (d, $J=3.5$ Hz), 7.31 (d, 1H, $J=3.5$ Hz); $^{13}$C NMR (75.5 MHz, $D_2O$) $\delta$ 69.4 (C-2), 114.4, 122.9 (C-3′, C-4′), 147.5, 158.1, 164.8, 176.2 (C-2′, C-5′, 2 CO).

## Acknowledgements

We are pleased to acknowledge the support of this investigation by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Alexander von Humboldt Foundation (fellowship to K.N.)

## References

1. Peters, S.; Lichtenthaler, F. W.; Lindner, H. J. *Tetrahedron: Asymmetry* **2003**, *14*, 2475–2479.
2. Keys, A. J.; Leaver, C. J.; Barton, D. H. R.; Brown, B. D.; Widdowson, D. A. *Nature* **1971**, *232*, 423–424.
3. Barton, D. H. R.; Brown, B. D.; Ridley, D. D.; Widdowson, D. A.; Keys, A. J.; Leaver, C. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2069–2076.
4. (a) Kiss, J.; Arnold, W. *Helv. Chim. Acta* **1975**, *58*, 297–302; (b) A scrutinous evaluation of the $^1$H NMR data on 4,5-unsaturated hexopyranuronates reported therein disclosed serious inconsistencies: the formulae for educts III–V and VII–XI are identical, yet lead to different products, i.e. a β-anomer VI and an α-anomer X; moreover the coupling constants for the β-(VI) and α-compound (X) seem to be interchanged, because only the latter can adopt a half-chair conformation with a $H^2$-C-C-$H^3$ torsional angle of ~130°, and hence, a $J_{2,3}$ of 7.5 Hz. By consequence, the utility of these data for comparative purposes is futile.
5. (a) Miyoshi, E.; Shizuri, Y.; Yamamura, S. *Chem. Lett.* **1987**, 511–514; (b) Ueda, M.; Shigemori, H.; Sata, N.; Yamamura, S. *Phytochemistry* **2000**, *53*, 39–44.
6. For a preliminary report of part of this work, see: Lichtenthaler, F. W.; Nakamura, K.; Klotz, J. *Angew. Chem., Int. Ed.* **2003**, *43*, in press.
7. (a) Jeanloz, R. W.; Stoffyn, P. J. *Methods Carbohydr. Chem.* **1962**, *1*, 224–225; (b) Maurer, K.; Müller, A. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2069–2073; (c) When refraining from purification of the two intermediates, the yield over the three steps amounts to 75%.
8. Chmielewski, M.; BeMiller, J. N.; Ceretti, D. P. *J. Org. Chem.* **1981**, *46*, 3903–3908.
9. (a) Fischer, E.; Oetker, R. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 4029–4040; (b) Irani, R. K.; Bose, J. L. *Indian J. Chem.* **1975**, *13*, 529.
10. Kini, G. D.; Petrie, C. R.; Hennen, W. J.; Dalley, N. K.; Wilson, B. E.; Robins, R. K. *Carbohydr. Res.* **1987**, *159*, 81–94.
11. (a) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181–1184; (b) DeNooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 165–166; *Tetrahedron* **1995**, *51*, 8023–8032; (c) Györgydeák, Z.; Thiem, J. *Carbohydr. Res.* **1995**, *268*, 85–92.
12. (a) Erwig, E.; Koenigs, W. *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 2207–2215; (b) De las Heras, F. G.; Fernández-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903–907.
13. Su, J.-D.; Osawa, T.; Kawashiki, S.; Namiki, M. *Agric. Biol. Chem.* **1987**, *51*, 2449–3450.
14. Bohm, B. A. *Arch. Biochem. Biophys.* **1966**, *115*, 181–186.
15. Malcolm, M. J.; Gear, J. R. *Can. J. Biochem.* **1971**, *49*, 412–416.
16. Shen, Z.-W.; Fisinger, U.; Poulev, A.; Eisenreich, W.; Werner, I.; Pleiner, E.; Bacher, A.; Zenk, M. H. *Phytochemistry* **2001**, *57*, 33–42.
17. Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 378–388.
18. Bednarski, M. D.; Crans, D. C.; Dilosimo, R.; Simon, E. S.; Stein, P.-D.; Whitesides, G. M.; Schneider, M. J. *Tetrahedron Lett.* **1988**, *29*, 427–430.
19. Dotson, G. A.; Nanjappan, P.; Reily, M. D.; Woodard, R. W. *Biochemistry* **1993**, *32*, 12392–12397.
20. Haslam, E. *Shikimic Acid: Metabolism and Metabolites*; Wiley: Chichester, 1993.
21. (a) Sheflyan, G. Y.; Howe, D. L.; Wilson, T. L.; Woodard, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 11027–11032; (b) Duewel, H. S.; Woodard, R. W. *J. Biol. Chem.* **2000**, *275*, 22824–22831.
22. Dictum attributed to Sir Robert Robinson.
23. Béelik, A. *Adv. Carbohydr. Chem.* **1956**, *11*, 145–183.
24. Lichtenthaler, F. W. *Pure Appl. Chem.* **1978**, *50*, 1358ff.
25. Fairbairn, J. W.; Williamson, E. M. *Phytochemistry* **1978**, *17*, 2087–2089.
26. Ramstadt, E. *Pharm. Acta Helv.* **1953**, *28*, 45–57.
27. BeMiller, J. N.; Yadav, M. P.; Kalabokis, V. N.; Myers, R. W. *Carbohydr. Res.* **1990**, *200*, 111–126.