Plant Acids

(−)-Daucic Acid: Revision of Configuration, Synthesis, and Biosynthetic Implications**

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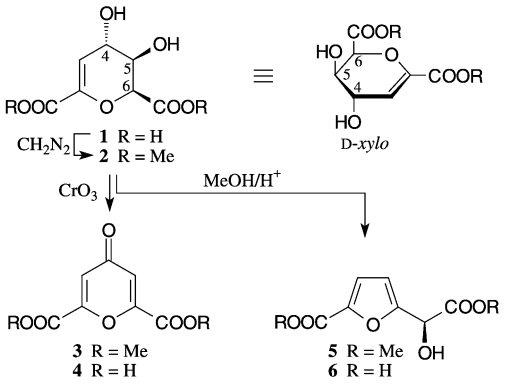
In memory of Friedrich Cramer

(−)-Daucic acid, a C_7-sugar dicarboxylic acid found in carrots (*Daucus carota*), sugar beet, wheat, sunflowers, and tobacco, was first isolated from mature carrots in 1971[1] and later assigned the structure of a 2,6-anhydro-3-deoxy-D-hept-2-enaric acid and D-*xylo* configuration with respect to the three chiral centers (Scheme 1, **1**).[2] The assignment of a dihydro-



Scheme 1. Reactions of (−)-daucic acid, isolated from *Daucus carota*, from which the structure of a 2,6-anhydro-2-deoxyhept-2-enaric acid was derived; the D-*xylo* configuration **1** was determined on the basis of ^{1}H NMR spectroscopic data (60 MHz).[2]

pyran structure was based on the oxidative conversion of its dimethyl ester into dimethyl chelidonate (**2**→**3**), and its affiliation to the D series of sugars (that is, its configuration at C6) followed convincingly from the high positive optical rotation of the furanoid rearrangement product **5** ($[\alpha]_D$ = +79.3 in $CHCl_3$), which correlated well with the equally high negative $[\alpha]_D$ value of the synthetically prepared L-enantiomer.[2] This assignment was later corroborated by the isolation of osbeckic acid **6** from *Osbeckia chinensis* L., the dimethyl ester of which proved to be fully congruent to **5**.[3]

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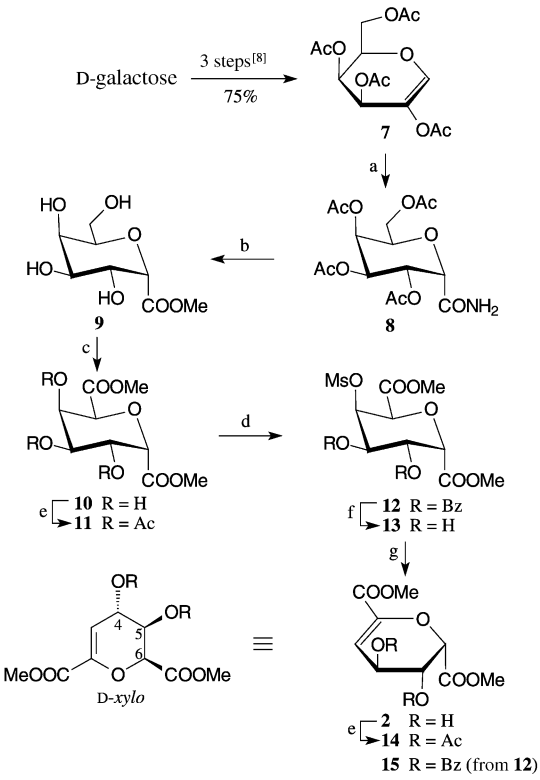
The assignment of the configuration at C4 and C5 was less conclusive (Scheme 1), as it was inferred from low-resolution (60 MHz) ^{1}H NMR spectroscopic data for dimethyl daucate (**2**) and its di-*O*-acetyl derivative, primarily from the coupling constants for 4-H and 5-H and comparison of these with analogous NMR spectroscopic data for certain 4,5-unsaturated hexuronates,[4] which on close inspection prove unreliable.[5] Moreover, the half-chair forms of sugar-derived dihydropyrans usually exist in complex conformational equilibria, which are virtually impossible to predict, thus resulting in coupling patterns that have little bearing on the actual configuration. Therefore, the verification of the stereochemistry at C4 and C5 of (−)-daucic acid was deemed imperative, particularly as reflections on its biosynthetic origin—its formation from 3-deoxy-D-*arabino*-heptulosonate 7-phosphate (DAHP), an early intermediate of the shikimic acid pathway,[6] is a likely possibility—would lead one to expect the D-*arabino* configuration.

These considerations, together with the notion that daucic acid is a possible biosynthetic precursor of chelidonic acid (**4**), a leaf-closing factor in *Cassia mimosoides*,[7] prompted us to devise a stereocontrolled synthesis, which should be practical enough to furnish sufficient amounts for biological studies. Accordingly, herein we report expedient syntheses of the daucic acids with the D-*xylo*, D-*ribo*, L-*arabino*, and D-*lyxo* configuration. Our conceptual approach for developing stereochemically unambiguous access to the D-*xylo*-heptenaric acid **1** and the three alternate configurations of this acid was based upon the anomeric one-carbon-atom homologation of suitable D-hexoses (D-galactose or D-mannose), subsequent oxidation at both termini to the corresponding pyranoid C_7 dicarboxylic acids, and controlled β elimination into the pyranoid ring through the judicious choice of leaving groups.

The synthesis of the dimethyl D-*xylo*-dicarboxylate **2** started from tri-*O*-acetyl-2-acetoxy-D-galactal (**7**), readily accessible from D-galactose in a three-step, one-pot procedure[8] involving acetylation, treatment with HBr/HOAc, and dimethylamine-promoted elimination of HBr (Scheme 2). The acetone-initiated photoaddition of formamide to **7**, albeit complex,[9] is α selective to give the heptonamide **8** as the major product (54%), which can be converted into the methyl heptonate **9** by methanolysis under acidic conditions. Oxidation of the primary hydroxy group was effected smoothly with oxygen in the presence of the Adams catalyst to afford, after esterification with methanolic HCl, the dimethyl heptarate **10**. Although the axial orientation of the 5-OH group in **10** would suggest preferential 5,6-elimination from the corresponding tri-*O*-acetyl (**11**) or tri-*O*-benzoyl derivative, their exposure to a variety of suitable conditions (e.g. NaOAc/Ac_2O, 70°C or Al_2O_3/lutidine, 40°C) led to multicomponent mixtures. Thus, a better leaving group had to be introduced at C5. Low-temperature benzoylation of the equatorial hydroxy groups in **10** and subsequent treatment with methanesulfonyl chloride provided **12**. Now 5,6-elimination could be effected cleanly, either from **12** by briefly heating in NaOAc/Ac_2O to afford the dibenzoate **15** (59%), or from the debenzoylated product **13** through exposure to NaOMe/MeOH to deliver dimethyl D-*xylo*-heptenarate **2** (77%) directly. Gratifyingly, all products in this reaction sequence were obtained in readily



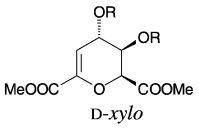
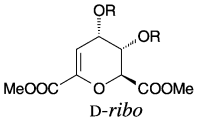
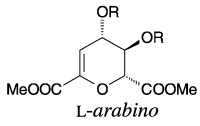
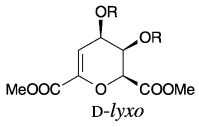
Scheme 2. Conversion of D-galactose into the D-*xylo*-heptenarate **2**: a) $HCONH_2$, Me_2CO, *hν*, 3 days, RT, 54%;[9] b) HCl (8%)/MeOH, reflux, 3 h, 86%; c) Pt/O_2, water (pH 8), 70°C, 4 h, then saturated methanolic HCl, RT, 1 h, 56%; d) BzCl, pyridine, −40°C, 2 h; then MsCl, −40°C→RT, 2 h, 58%; e) pyridine/Ac_2O (2:1), RT, 12 h, 85%; f) saturated methanolic HCl, reflux, 14 h, 73%; g) NaOMe (0.1 N)/MeOH, RT, 1 h, 77%. Ms = methanesulfonyl.

characterizable, crystalline form; only the di-*O*-acetyl and di-*O*-benzoyl derivatives **14** and **15** have so far resisted crystallization.

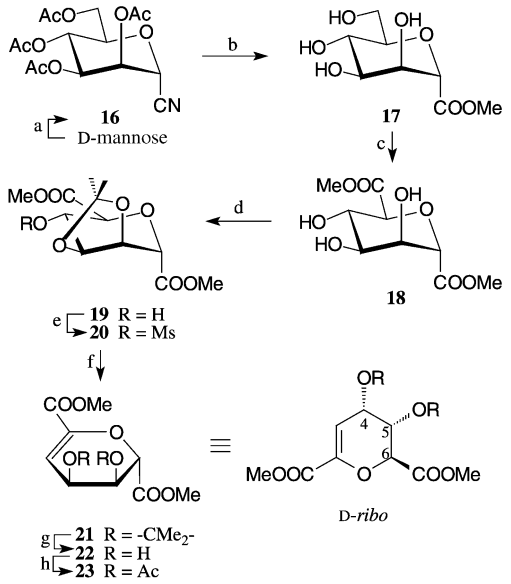
The melting point for the product **2** of this reaction sequence was close to that of the *Daucus carota* derived compound. However, its optical rotation, although similar in size, was opposite in sign (Table 1). The notion that the natural product might therefore have the enantiomeric (i.e. L-*xylo*) configuration was invalidated by the distinct differences in the ^{1}H NMR spectroscopic data of synthetic **2** and **14**, compared to those reported for the respective products of natural origin. The chemical shifts observed for 4-H, 5-H, and 6-H vary by $\delta = 0.3$–0.6 ppm in each case, and the coupling constants $J_{3,4}$ and $J_{4,5}$ have significantly different values (Table 1). Thus, a D-*xylo* or L-*xylo* configuration for natural (−)-daucic acid can be excluded unequivocally.

Of the remaining possible configurations—D-*ribo*, D-*lyxo*, and D-*arabino*—the synthesis of the D-*ribo* analogue **22**, the C5 epimer of **2**, was addressed next. We took advantage of the ready accessibility of heptononitrile **16** from D-mannose through a two-step, one-pot reaction comprising acetylation and anomeric cyanation (Scheme 3).[10] Acid hydrolysis followed by esterification with methanol then provided the mannosyl-*C*-carboxylate **17**. The Pt/O_2 oxidation of the primary hydroxy group in **17** proved unusually capricious,

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

Compound		M.p. [°C]	$[\alpha]_D^{20}$[a]	^{1}H NMR [ppm, Hz]							
				4-H	5-H	6-H	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$	$J_{5,6}$	solvent
(−)-dimethyl daucate[2]		130–131	−102[b]	4.51	4.30	4.66	3	1	?	2	$CDCl_3$
diacetate[2]		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*	**29** R = H	syrup	+30.0	4.25	4.19	4.73	4.3	0.9	2.2	5.4	$CDCl_3$
	30 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*	**35** R = H	128–129	−98.3	4.50	4.30	4.67	3.3	1.1	4.3	2.3	$CDCl_3$
	36 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

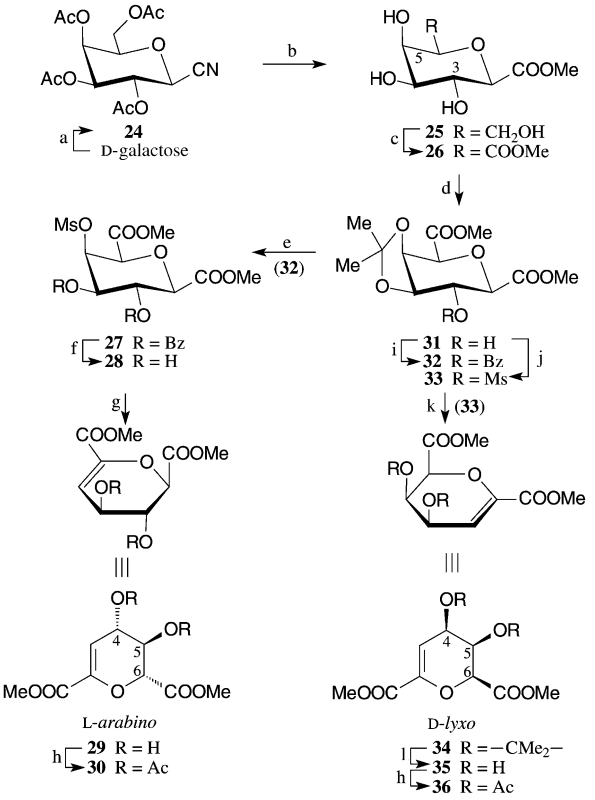
[a] Optical-rotation values for the free diols in acetone, for the diacetates in $CHCl_3$. [b] $[\alpha]_D$ value at 24.5 °C.



Scheme 3. Synthesis of the D-*ribo*-heptenarate **22** from D-mannose: a) pyridine/Ac_2O (1.3:1), 0 °C, 2 days,[10a] then Me_3SiCN, $BF_3{\cdot}Et_2O$, CH_3NO_2, 35 °C, 2 h;[10b] b) aqueous HCl (25%), 50 °C, 24 h, then saturated methanolic HCl, RT, 2 h, 85%; c) TEMPO/NaOCl, H_2O/CH_2Cl_2, 0 °C, 20 h, then saturated methanolic HCl, 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/water (50:10:1), RT, 1 h, 86%; h) pyridine/Ac_2O (2:1), RT, 5 h, 91%. TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxyl, TFA = trifluoroacetic acid.

and the conversion of this compound into the desired dicarboxylate was instead effected by a TEMPO-catalyzed oxidation with sodium hypochlorite,[11] to provide, upon esterification with methanolic HCl, the dimethyl heptarate **18** in high yield. Subsequent protection of the hydroxy groups at C3 and C4 through acetonide formation (→**19**), followed by mesylation (→**20**), set the stage for the 5,6-elimination of methanesulfonic acid, which was effected simply by briefly exposing **20** 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 dimethyl D-*ribo*-heptenarate **22**, which was acetylated to the di-*O*-acetyl derivative **23**. Both **22** and **23** were isolated as syrups with high positive optical-rotation values. Substantially smaller negative values were observed for the *Daucus carota* derived product. As distinct differences were also observed in the respective ^{1}H NMR spectroscopic data (see Table 1), the D-*ribo* and L-*ribo* stereochemistry for natural (−)-daucic acid can also be excluded.

To finally unravel the stereochemistry of the natural product—*arabino* or *lyxo* configurations were still possible—we investigated a convergent synthetic pathway from β-D-galactosyl cyanide **24**,[12] under the premise that $\Delta^{2,3}$ (or $\Delta^{5,6}$) unsaturation could be introduced selectively through an elimination reaction if the 3-OH (or, alternatively, the 5-OH) group in the C_7-dicarboxylate **26** was converted into a displaceable leaving group (Scheme 4). Indeed, this key intermediate was prepared in a straightforward manner by



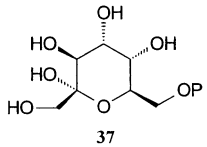
Scheme 4. Conversion of D-galactose into dimethyl heptenarates with the L-*arabino* (**29**) and the D-*lyxo* configuration (**35**); the stereochemistry of **35** corresponds to that of natural (−)-daucic acid: a) NaOAc/Ac_2O, 100 °C, 2 h,[12a] then Me_3SiCN, $BF_3{\cdot}Et_2O$ in CH_3NO_2, 35 °C, 2 h,[12b] 79%; b) 1. NaOMe/MeOH, 2 h, RT; 2. NaOH (6 N), 4 h, reflux; 3. saturated methanolic HCl, RT, 2 h, 85%; c) TEMPO/NaOCl, H_2O/CH_2Cl_2, 0 °C, 20 h, then saturated methanolic HCl, RT, 2 h, 76%; d) Me_2CO/H_2SO_4, RT, 4 h, 83%; e) $CHCl_3$/TFA/water (50:10:1), RT, 30 min, then BzCl (1.2 equiv), pyridine, −40 °C, 2 h, then MsCl, pyridine, RT, 3 h, 53%; f) saturated methanolic HCl, reflux, 24 h, 86%; g) NaOMe (0.1 N)/MeOH, 15 min, RT, 90%; h) pyridine/Ac_2O (2:1), RT, 14 h, 90%; i) MsCl, pyridine, 0 °C, 3 h, 85%; j) basic Al_2O_3, lutidine, 40 °C, 30 min, 74%; k) $CHCl_3$/TFA/water (50:10:1), RT, 1 h, 83%.

base hydrolysis of **24**,[12] esterification (→**25**), and TEMPO/NaOCl oxidation in an overall yield of 51%. Attempts to selectively benzoylate the equatorial OH groups in **26**, a protocol successful with its C2 epimer **10** in the synthesis of 5-*O*-mesylate **12**, failed as a result of the distinctly different reactivities of the hydroxy groups in **26** and **10**. As an alternate, albeit less direct route to the desired 3,4-di-*O*-benzoyl-5-*O*-mesylheptarate **27**, the 4,5-*cis*-diol in **26** was protected through isopropylidenation (→**31**, the key intermediate for the generation of the D-*lyxo* compounds; see below), which was followed by benzoylation and acid hydrolysis of the acetonide. The resulting 3-benzoate of **26**, unlike **26** itself, could be monobenzoylated readily at the 4-OH at low temperature, and subsequent in situ mesylation delivered **27** in a tolerable overall yield of 40% for the five steps from **26**. Introduction of the $\Delta^{5,6}$ unsaturation in the L-*arabino* heptenarate **29** was effected by brief exposure of the de-*O*-benzoylated heptarate **28** to NaOMe (0.1N)/MeOH. Whereas **29** was obtained as a syrup, its diacetate **30** crystallized well.

A similar sequence of reactions led from the isopropylidene-protected dimethyl heptarate **31** to the corresponding D-*lyxo* compounds **35** and **36**. Mesylation (→**33**) and Al_2O_3/lutidine-induced elimination gave **34**, which was then exposed to aqueous trifluoroacetic acid to remove the isopropylidene group.

Unlike the L-*arabino*-heptenarates **29** and **30**, whose ^{1}H NMR spectroscopic data differed markedly from those of the *Daucus carota* derived compounds,[2] the D-*lyxo* analogues **35** and **36** showed almost perfect agreement, not only in the sign and magnitude of their optical-rotation values, but most notably in the chemical shifts and coupling patterns in their ^{1}H NMR spectra (Table 1). The slight deviations observed in the coupling constants undoubtedly result from the different field strengths (60[2] versus 300 MHz) and, conceivably, from temperature differences. The temperature affects the equilibrium between the respective half-chair forms ($^5H_6 \rightleftarrows {}^6H_5$) and hence the NMR coupling patterns observed. This evidence is cogent enough to allow the unambiguous assignment of the D-*lyxo*-configuration to carrot-derived (−)-daucic acid.

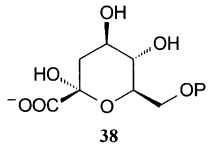
The synthetic (−)-dimethyl daucate (**35**) could be saponified readily by exposure to aqueous trifluoroacetic acid (4:1, 2 days, 25 °C), to provide the free acid in crystalline form (m.p. 87–88 °C, $[\alpha]_D^{20} = -85$ in MeOH, 80%). More vigorous acid conditions led to the pyran→furan rearrangement observed previously for the natural product (Scheme 1):[2] Heating **35** in methanolic HCl afforded dimethyl osbeckate (**5**) (60%), whereas heating **35** in water in the presence of a strongly acidic ion-exchange resin gave the free osbeckic acid (**6**; 81%).



37

(sedoheptulose 7-P)

D-*altro*



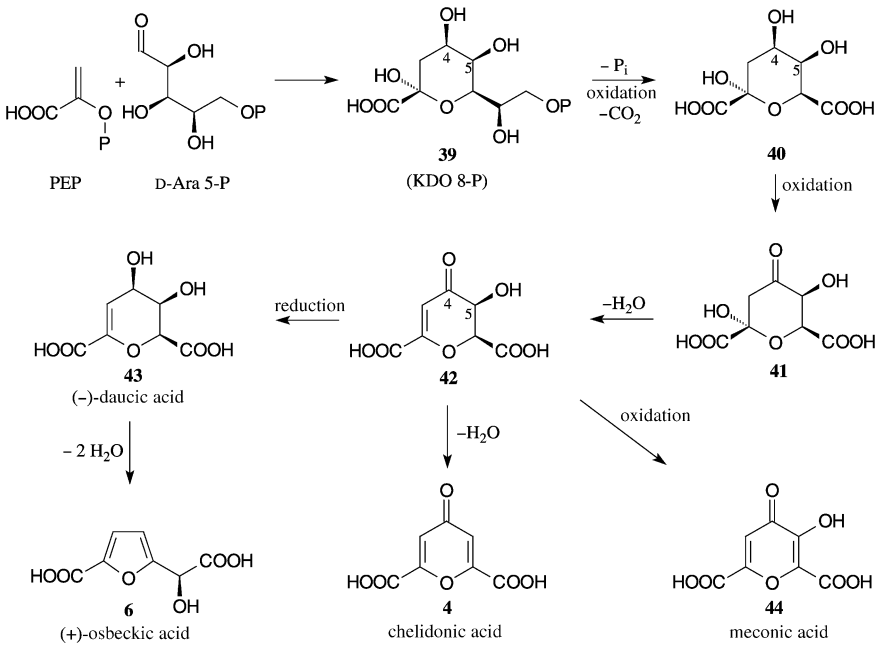
38

(DAH 7-P)

D-*arabino*

Not only is the biosynthetic origin of (−)-daucic acid intriguing—sedoheptulose 7-phosphate (**37**) and 3-deoxy-D-*arabino*-heptulosonate 7-phosphate (DAHP, **38**), both established intermediates of the pentose phosphate and shikimic acid pathways, respectively, are potential precursors—but also its close structural relationship with chelidonic acid (**4**). The elaboration of the γ-pyrone system would merely require oxidation of daucic acid at C4 and 5,6-elimination of water.

Studies on the biosynthesis of chelidonic acid with ^{14}C-labeled sugars have uniformly shown that D-glucose, and to an even greater extent D-ribose, are incorporated well,[13,14] whereas **37** is not.[13] Although the assumption that DAHP (**38**) is therefore the likely precursor[14] persisted for 30 years, it was convincingly disproved recently by quantitative carbon-flux analyses of ^{13}C-labeled sugars, which suggested a biosynthetic assembly of chelidonic acid from one molecule each of pentose phosphate and phosphoenolpyruvate (PEP;



Scheme 5. Possible mechanism for the biosynthesis of C_7 dicarboxylic acids in plants from common precursors. The suggestion is based on the identical configurations in the pyranoid rings of daucic acid (**43**) and KDO 8-P (**39**), the conjecture that the generation of the structurally similar daucic, chelidonic (**4**), and meconic acid (**44**) may occur via a common intermediate, and on studies[15] on the biosynthesis of **4**.

Scheme 5).[15] Such a biosynthetic process is well-established for Gram-negative bacteria, in which 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 form 3-deoxy-D-*manno*-octulosonate 8-phosphate (KDO 8-P, **39**).[16,17] As the KDO 8-P synthase catalyzed aldol addition proceeds with exclusive *Si* attack by PEP to the *Re* face of the sugar carbonyl group, the 4*R* isomer is formed stereospecifically, so that the product **39** has the D-*manno* configuration.[18] The existence of such a KDO 8-P based mechanism in plants has not yet been proved. However, the fact that DAH 7-P synthase, a key enzyme of the shikimic acid pathway[6] and abundant in higher plants, catalyzes the aldol addition of PEP not only 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,[19] may be regarded tentatively as evidence that an octulosonate 8-phosphate based pathway is also operative in plants.

Based on the newly established D-*lyxo* stereochemistry of (−)-daucic acid (**37** and **38** as precursors would lead to the D-*arabino* configuration), on the conjecture that the biosynthetic elaboration of daucic acid is closely related to that of chelidonic (**4**) and meconic acid (**44**), and on available evidence[15] about the biosynthesis of **4**, a biosynthetic pathway readily unfolds as depicted in Scheme 5: D-Ara 5-P and PEP undergo an aldol-type condensation to KDO 8-P (**39**), in which the stereochemistry of the pyranoid ring correlates with the D-*lyxo* configuration of daucic acid. If D-Rib 5-P was involved in the aldol addition step, the C_8-sugar phosphate would have the D-*altro* configuration, thus requiring an (unnecessary) epimerization at a later stage.

Unlike in Gram-negative bacteria, in which the C_8 chain of KDO 8-P is incorporated into the lipopolysaccharides of cell walls,[16] in this case the terminal carbon is removed by dephosphorylation and oxidative decarboxylation. Although only loss of water is formally required from the resulting intermediate **40** to give daucic acid, a direct 3,2-elimination is unlikely—"cells obey the laws of chemistry"[20]—as the hydrogen atom involved (3-H) is not activated. As activation is usually provided by a vicinal carbonyl group—the conversion of D-glucose into kojic acid by *Aspergillus oryzae* has been rationalized on this basis[21]—the oxidation of **40** at C4 appears plausible as the next step. Dehydration of the resulting ketodicarboxylic acid **41** is thought to proceed spontaneously to give the dihydropyranone **42**, a furcation point towards these C_7 dicarboxylic acids. Daucic acid is formed from **42** by reduction (**42**→**43**), chelidonic acid by elimination of water (**42**→**4**), and meconic acid, plentiful in Papaveraceae, by oxidation (**42**→**44**). The furanoid osbeckic acid is likely to be formed from daucic acid through ring contraction and double dehydration (**43**→**6**).

The alluring consistency of this proposed biosynthetic pathway, particularly the configurational identity of KDO 8-P and daucic acid in their pyranoid rings, clearly calls for the systematic investigation of higher plants for the occurrence of a C_8-sugar-phosphate pathway with the possible intermediates **40**–**42**, in particular in those species in which these C_7 dicarboxylic acids have been detected: daucic acid in carrots, sugar beets, wheat, sunflowers, and tobacco, osbeckic acid in *Osbeckia chinensis* L., meconic acid in Papaveraceae, and chelidonic acid in a plethora of plant families.

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materials III–V and VII–XI are identical, yet lead to different products, namely, to a β anomer VI and an α anomer X; moreover the coupling constants for the β (VI) and α compound (X) seem to have been interchanged, as only the latter can adopt a half-chair conformation with a H^2-C-C-H^3 torsion angle of ≈ 130°, and hence result in a coupling constant $J_{2,3} = 7.5$ Hz. Consequently, these data are not useful for comparative purposes.

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