# Structure Revision of Decurrensides A−E Enabled by the *RFF* Parametric Calculations of Proton Spin−Spin Coupling Constants

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S *Supporting Information*

ABSTRACT: Structure revision of the recently characterized natural products, decurrensides A−E, is described. The revision is aided by fast and accurate computations of proton spin−spin coupling constants. While the ^{13}C chemical shifts calculations could reveal the misassignment of the original structures, the calculated spin coupling constants possess much higher structural information content, informing and guiding the process of structure reassignment. Together, calculations of ^{13}C chemical shifts and spin coupling constants constitute a robust and now practical structure discovery tool.
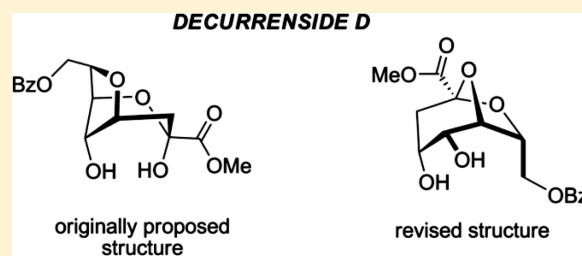
In 2012, five new derivatives of 3-deoxy-2-octulosonic acid were isolated by Kouno and co-workers from a plant *Solidago decurrens* and named decurrensides A−E (**1−5**), Figure 1.[1]
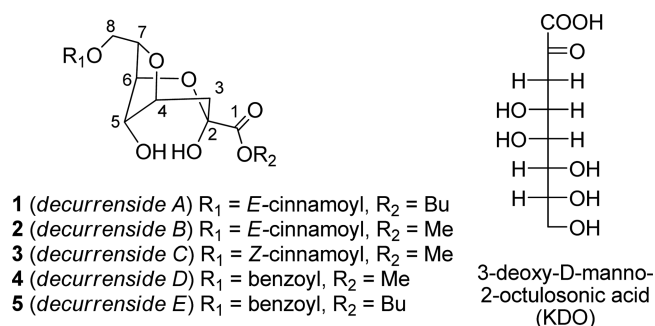

1 (*decurrenside A*) R₁ = E-cinnamoyl, R₂ = Bu
2 (*decurrenside B*) R₁ = E-cinnamoyl, R₂ = Me
3 (*decurrenside C*) R₁ = Z-cinnamoyl, R₂ = Me
4 (*decurrenside D*) R₁ = benzoyl, R₂ = Me
5 (*decurrenside E*) R₁ = benzoyl, R₂ = Bu

3-deoxy-D-manno-2-octulosonic acid (KDO)

Figure 1. Decurrensides A−E (**1−5**).

The structure assignment was based on an extensive NMR study. The authors identified a characteristic spin system across all five decurrensides, corresponding to the $C^3H_2-C^4H-C^5H-C^6H-C^7H-C^8H_2$ fragment, with a particularly peculiar chain of four consecutive 5 Hz spin−spin coupling constants (SSCCs) $J_{3-4} = J_{4-5} = J_{5-6} = J_{6-7} = 5$ Hz. However, the last year attempt to synthesize decurrenside D by Quintero and Sartillo-Piscil[2] produced material which did not match the original natural product. In this Note we present a computationally driven revision of the structure of decurrensides A−D.

We began with DFT GIAO ^{13}C chemical shifts computations for decurrenside D (**4**), which revealed poor correlation with the experimental values, especially for the hemiacetal carbon deviating by more than 10 ppm. Analysis of proton spin coupling constants, calculated with our *rff DU8c* method,[3] have revealed additional irreconcilable discrepancies. Most strikingly, the J_{6-7} for the proposed structure, with the experimental value

of 5 Hz, was calculated to be vanishingly small, less than 0.2 Hz. Based on the author's NMR data, our initial hypothesis was that the decurrensides contain the C1−C8 moiety of a 2-octulosonic acid. The remaining questions were as follows: (i) whether the core structure was 2-octulo*pyrano*sonic or octulo*furano*sonic acid; (ii) whether the cyclic core structure had hemiacetal or ketal's connectivity, and (iii) the stereochemistry of the parent 2-octulosonic acid. In their paper Kouno and coauthors designated decurrensides A−E (**1−5**) as derivatives 3-deoxy-D-*manno*-2-octulosonic acid (KDO), Figure 1. While KDO is relatively common, octulosonic acids possessing alternative sets of stereogenic centers, such as 3-deoxy-D-*gluco/altro/ido/talo/gulo/allo*-2 octulosonic acids,[4] are also known. Adding to confusion, Kouno's paper depicted the structure of **1−5** as shown in Figure 1, i.e. as a 2,6-hemiacetal of 3-deoxy-D-*altro*-2-octulosonic acid not *manno*-2-octulosonic acid. Quintero and Sartillo-Piscil[2] then attempted the synthesis of this *altro* derivative. They reported that the synthetic compound displayed "a mixture of α- and β-anomers," and suggested the bicyclo[3.3.0]octane glycosides in Figure 2 as their structures. We now confirm, based on the computed ^{13}C chemical shifts, that the synthetic products are indeed most likely α- and β- 2,5-hemiacetals of methyl ester of 8-O-benzoyl-3-deoxy-D-*altro*-2-octulosonic acid. NMR spectra of these
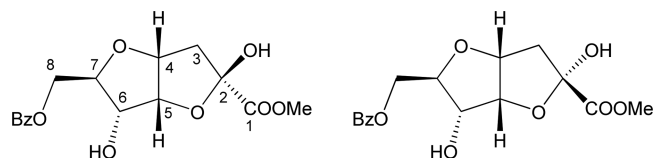

Figure 2. Plausible α and β forms of synthetic Decurrenside D.

compounds bear no resemblance to that of the natural decurrenside D.

Our predicted NMR spectra for both 2,5- and 2,6-hemiacetals of 3-deoxy-D-*manno*-2-octulofuranosonic acid did not give the desired match with the natural product either, so we directed our attention to two ketal forms of 3-deoxy-D-*manno*-2-octulofuranosonic acid, structures **6** and **7**, Figures 3
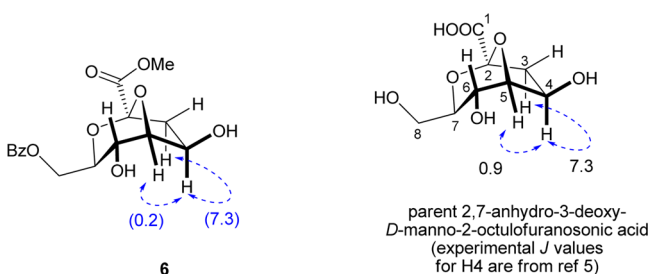
Figure 3. Ketal structure **6**: calculated *J*'s for H4, and experimental *J*'s for H4 in the parent 2,7-anhydro-3-deoxy-α-D-manno-2-octulofuranosonic acid.

and **4**. Detailed NMR analysis of the parent compound of the *furo* form **6**, i.e. 2,7-anhydro-3-deoxy-α-D-manno-2-octulofuranosonic acid, is described by Redmond,[5] Figure 3. *Rff*-computed spin−spin coupling constants for proton H4 in structure **6**, $J_{3'-4} = 7.3$ Hz and $J_{4-5} = 0.2$ Hz, match nicely Redmond's data for the parent octulofuranosonic acid ($J_{exp} = 7.3$ Hz, 0.9 Hz), but do not match the natural decurrenside D, in which $J_{4-5} = 5$ Hz. The *rff-DU8c*[3b] computed $^{13}C-^{1}H$ spin−spin coupling constants for structure **6** were also in conflict with the observed C2−H6 HMBC correlation reported by Kouno: for C2 in furanosonate **6** the computed constants were $J_{C2-H6} < 0.2$ Hz, $J_{C2-H5} = 8.2$ Hz, and yet the latter HMBC correlation (C2−H5) was not observed in the natural product, while the former (C2−H6) was reported.

At this point we shifted our focus to the 2,6-anhydro-3-deoxy-2-octulopyranosonic core. The *rff*-calculated *J*-coupling values, Figure 4, and GIAO mPW1PW91/6-311+G(d,p) ^{13}C chemical shifts for structure **7** matched the natural decurrenside D better than any other structure. Figure 3 shows the structures and the relative DFT energies (kcal/mol) of the four lowest energy conformers of structure **7**. Structure **7** is the only structure which has a chain of protons related to their vicinal neighbors by a dihedral angle of 40°−50° and, therefore, is compatible with the reported "chain" of the 5 Hz SSCCs.

Table 1 summarizes the result of conformer mixing according to their DFT energy, which produced a good match for the reported NMR data of natural decurrenside D: $RMSD_J = 0.56$ Hz and $RMSD_{C13} = 1.66$ ppm. One spin−spin coupling constant, J_{6-7}, deviated from the calculated value by >1 Hz. We do not believe that the stereochemistry at C-7 is incorrect. In the C-7 epimer, this J_{6-7} constant is even smaller; i.e. ΔJ is worse, >4 Hz.

The isotropic shielding values were scaled using the linear equation $180.8 − 0.976 \times \delta$. Additional linear correction of the calculated ^{13}C chemical shifts to match the experimental values, which is an acceptable practice, improves $RMSD_{C13}$ to a nearly perfect 1.04 ppm. The combination of matching ^{13}C chemical shifts and spin−spin coupling constants imparts confidence that decurrenside D is in fact 8-*O*-benzoylated methyl ester of 2,6-anhydro-3-deoxy-D-*manno*-2-octulopyranosonic acid. The C2−H6 HMBC correlation observed for the natural product is in keeping with this structure, in which C2 and H6 are separated by three bonds and are *anti*-vicinal. The *rff*-calculated $J_{C2-H6} = 6.6$ Hz, which normally shows as a clear HMBC cross peak.

The remaining decurrensides (A−C, E) have very similar reported NMR spectra, as they differ only in the C8−O-acyl substitution (benzoyl, *E*-cinnamoyl, and *Z*-cinnamoyl) and C1 esters (methyl, butyl); see Figure 1. The bicyclic core for all these sugars is undoubtedly 2,6-anhydro-3-deoxy-D-*manno*-2-octulopyranosonate. While this particular set of natural
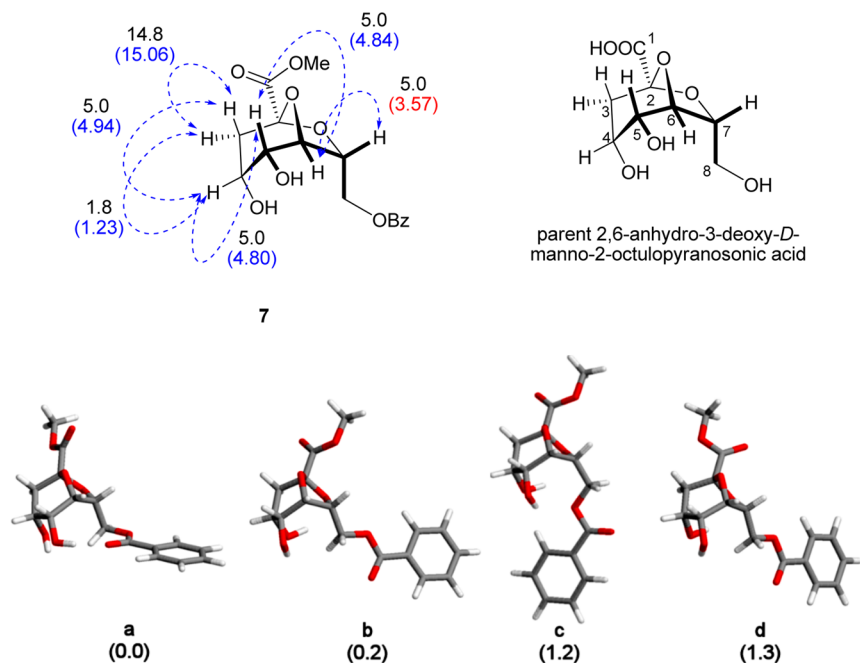
Figure 4. Second ketal structure **7** with the parent 2,6-anhydro-3-deoxy-D-manno-2-octulopyranosonic acid (experimental *J*'s for decurrenside D are in black, calculated *J*'s are in parentheses; four lowest energy conformers **a**−**d** are shown with their relative DFT energies, kcal/mol.

Table 1. Calculated J, Hz and δ_C, ppm for Revised Structure 7

Proton Spin Coupling Constants

J	Exp	Calc	Δ
J_{3a-3b}	14.8	15.06	-0.26
J_{3a-4}	1.8	1.23	0.57
J_{3b-4}	5	4.94	0.06
J_{4-5}	5	4.80	0.2
J_{5-6}	5	4.84	0.16
J_{6-7}	5	3.57	1.43
$J_{2'-3'}$	7.5	7.94	-0.44
$J_{2'-4'}$	1.5	1.29	0.21
$J_{3'-4'}$	7.5	7.32	0.18

rmsd = 0.56Hz (N=9)

^{13}C *chemical shifts*

	Exp	Calc	Δ
C1	169.6	168.54	1.06
C2	104.9	102.55	2.35
C3	40.4	37.48	2.92
C4	65.8	65.80	0.00
C5	69.5	68.71	0.79
C6	78.4	77.39	1.01
C7	81	79.58	1.42
C8	65.1	63.19	1.91
C-CO	167.9	167.4	0.50
C1'	131.4	129.15	2.25
C2'(6')	130.6	131.97	-1.37
C3'(5')	129.5	128.12	1.38
C4'	134.2	134.43	-0.23
C(OMe)	53.3	50.67	2.63

rmsd = 1.66ppm (N=14)

products was not described previously, other derivatives of 2,6-anhydro-3-deoxy-D-*manno*-2-octulopyranosonic are known. For example, mono-, di-, and trisubstituted caffeoyl derivatives of 2,6-anhydro-3-deoxy-D-*manno*-2-octulopyranosonic acid or its methyl ester were recently isolated from Roman chamomile.[6]

In conclusion, the structure of decurrensides A−E is revised from 2,6-hemiacetal of methyl 3-deoxy-D-*altro*-2-octulosonate to 2,6-anhydro-3-deoxy-D-*manno*-2-octulopyranosonate. The revision is facilitated by fast and accurate *rff*-calculations of nuclear spin−spin coupling constants, which allows for rapid screening of potential candidate structures and helps guide the chemically intuitive process of structural assignment based on the knowledge of predicted SSCCs. The dual criteria of matching both the computed SSCCs and ^{13}C chemical shifts improves the confidence level of such assignments.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01855.

> Computational details, Cartesian coordinates, computed chemical shifts, and nuclear spin coupling constants (PDF)

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Notes

The author declares no competing financial interest.

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