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Total synthesis of the proposed structure of decurrenside D

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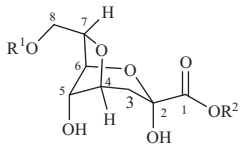
ABSTRACT

A chiron approach for the total synthesis of the proposed structure of decurrenside D is reported. The construction of the 3-deoxy-D-manno-2-octulosonic acid framework (KDO derivative) was achieved by the transformation of the respective *C*-allylated-*ribo*furanose derivative into its corresponding α-keto acid ester derivative. Accordingly, the crucial step of this total synthesis is the application of the stereoselective nucleophilic substitution at the anomeric position (NSAP) reaction to the 5-*O*-benzoyl *ribo*furanose derivative. Both optical rotation and NMR data of the synthesized decurrenside D are inconsistent with the proposed structure.

Decurrenside D, and also its four congeners (A, B, C, and E), were recently isolated from the methanolic extracts of the plant *Solidago decurrens* by Kuono and coworkers.[1] These plants have been used in Chinese traditional herbal medicine as diuretic, choleretic, antiseptic, and also for wound healing.[1] The molecular structure of decurrenside D possesses a unique dioxabicyclo [3.2.1] octane moiety fused on a KDO derivative skeleton at the C4 and C6 positions.[2] The molecular structure was established by 1D and 2D NMR spectra analyses and by comparison with spectroscopic data of known compounds. Furthermore, the bicyclic system was suggested by the degree of unsaturation in the molecular formula and by the presence of carbon acetal (δ_C 104.9 ppm). The HMBC correlation between H-4 and C-7 indicated an ether bond between C-4 and C-7, while the NOESY correlation between hydroxyl groups at C-2 and C-5 suggested *endo* orientation (Fig. 1).

As part of a project directed to the synthesis of biological important natural products which contains the furanoside ring,[3] we got interested, not only on the unique molecular structure of decurrensides but also in their probable biological activity. Consequently, decurrenside D was selected as the initial target. We planned to access to the KDO structure of decurrenside D by simple hydrolysis reaction of the α-keto acid ester (**1**), which would be prepared by selective oxidation of triple bond of *C*-propargylated *ribo*furanose derivative (**2**). Synthesis of **2** would be achieved from *C*-allylated ribofuranose derivative **3**, and this latter compound by a stereoselective nucleophilic substitution at the anomeric position (NSAP) of α-D-*ribo*furanose derivative **4** (Scheme 1).[3,4]

Ribofuranose derivative **4** was prepared in three steps from α-D-*allo*furanose **5**. Benzylation of **5** (benzyl bromide/NaH) gave *allo*furanose derivative **6**[5] (90% yield), which was submitted to a sequential hydrolysis–dehomologation–reduction procedure[6] to afford *ribo*furanose **7** in 75% overall yield. After benzoylation of **7** under standard conditions, the α-D-*ribo*furanose derivative **4** was obtained. Compound **4** was subjected to NSAP reaction (8–10 equiv of allyltrimethylsilane (ATMS), 6 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C), the expected allylated product **8** was obtained in low yield (8%) along with an unexpected allylated/debenzylated product **9**, as the



R^1 = *E*-Cinnamoyl; R^2 = Butyl: Decurrenside A
R^1 = *E*-Cinamoyl; R^2 = Methyl: Decurrenside B
R^1 = *Z*-Cinnamoyl; R^2 = Methyl: Decurrenside C
R^1 = Benzoyl; R^2 = Methyl: Decurrenside D
R^1 = Benzoyl; R^2 = Butyl: Decurrenside E

Figure 1. Proposed structures of decurrensides.

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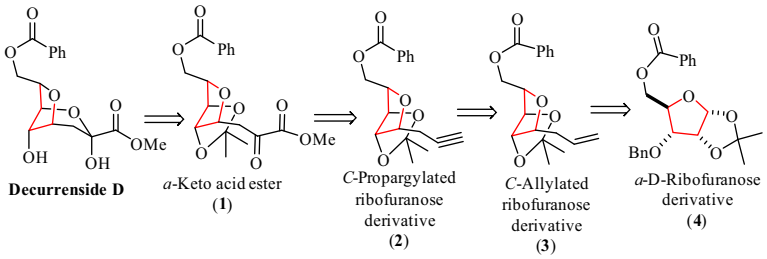


Scheme 1. Retrosynthetic plan for the proposed structure of decurrenside D.

major product.[3,4] Interestingly, by diluting the reaction mixture at 0.2 M the compound **9** resulted as the minor product (Scheme 2).

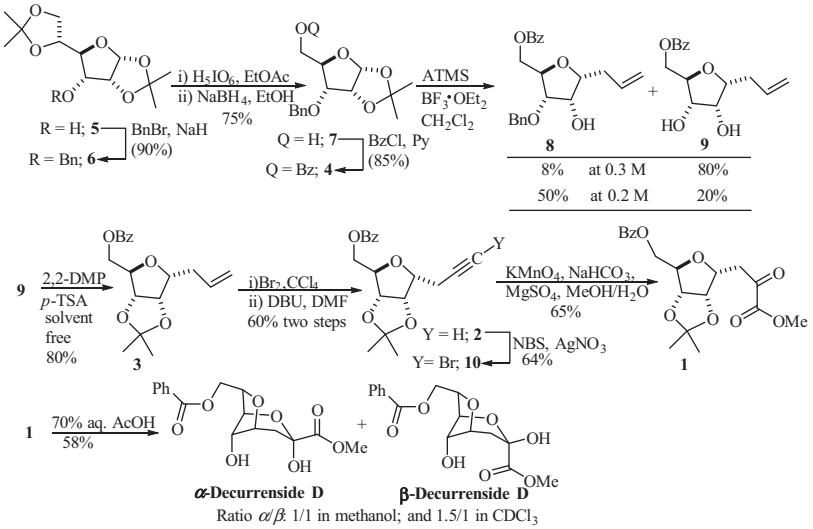
The stereochemical outcome of the NSAP follows the Woerpel's 'inside attack' model,[3e,7] whereby the 1,3-*cis* stereoisomer is the major product. Diol **9** was protected with 2,2-dimethoxypropane (2,2-DMP) to obtain the desired *C*-allylated *ribo*furanose derivative **3**. Transformation of **3** into the *C*-propargylated *ribo*furanose **2** was accomplished in two steps with good yields: dibromination with Br_2 in CCl_4 followed by double dehalogenation with DBU in DMF. The α-keto acid ester **1**, precursor of the proposed decurrenside D, was prepared following another two-step protocol: C–H bromination with NBS and $AgNO_3$, and selective triple bond oxidation with $KMnO_4$ in the presence of $NaHCO_3$, $MgSO_4$ and methanol.[8] Finally, acetonide hydrolysis of **1** with aqueous acetic acid gave a white solid (mp = 173–175 °C), which did not match neither the optical rotation value nor the NMR data (Scheme 2).

Whereas the natural compound shows the presence of a single anomer, the ^1H and ^{13}C NMR spectra of the synthetized compound displayed a mixture of two compounds, presumably a mixture of α-and β-anomers with an equimolar ratio in methanol and 1.5:1 in $CDCl_3$ (Scheme 2). Representative NMR data of both natural and synthetic decurrenside D is shown in Table 1. Although NMR data of synthetized decurrenside D do not match to that of the natural substance, the analysis of ^{13}C NMR of C1 and C2, and also coupling constants of geminal hydrogen atoms at C3 revealed the closest correlation. The major differences are manifested in the dioxabicyclo [3.2.1] octane skeleton. Interestingly, while the analysis of the ^1H–^{13}C HMBC spectrum showed correlation between C2

Table 1
Representative NMR data of natural and synthetized decurrenside D

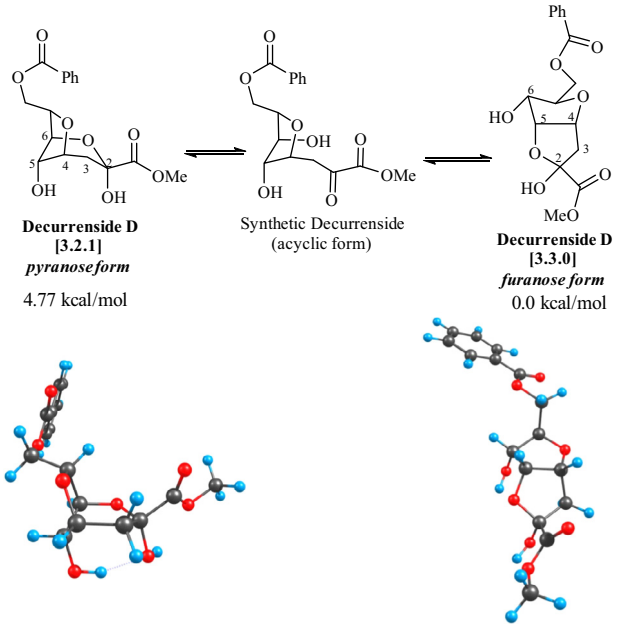
Position	Natural[a]		Synthetized[a]			
			α-Anomer		β-Anomer	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		169.60		172.10		172.0
2		104.90		105.50		105.60
3	2.25, dd (14.8, 5.0) 2.31, dd (14.8, 1.8)	40.40	2.25, d (14.5) 2.66, dd (14.5, 6.0)	45.10	2.55, dd (14.7, 2.9) 2.58, dd (14.6, 2.5)	46.40
4	4.14, t (5.0)	65.80	4.85, ddd (6.3, 4.4, 0.9)	83.10	4.89, dd (4.0, 2.7)	82.80
5	4.04, t (5.0)	69.50	4.69, t (4.6)	86.60	4.72, apparent t (4.0)	84.40
6	4.48, t (5.0)	78.40	4.08[b]	74.30	4.01[b]	74.20
7	4.42, ddd (8.4, 5.0, 3.2)	81.0	4.40, ddd (9.1, 5.6, 2.5)	80.0	4.08[b]	79.50
8	4.78, dd (12.4, 3.2) 5.02, dd (12.4, 8.4)	65.10	4.32, apparent d (12.0) 4.63, dd (12.0, 2.5)	65.30	4.33, apparent d (12.0) 4.59, apparent d (12.0)	65.60

[a] ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) data in CD_3OD.
[b] Overlapped signals.



Ratio *α*/*β*: 1/1 in methanol; and 1.5/1 in $CDCl_3$
Withe solid (Mp = 173-175 °C). $[\alpha]_D$ = +35.8 (*c* = 0.7, MeOH).
Lit.[1] Colorless gum. Single *α*-anomer. $[\alpha]_D$ = -11.7 (*c* = 0.1, MeOH).

Scheme 2. Synthesis of the proposed structure of decurrenside D.



Scheme 3. Molecular structures of the proposed decurrenside D, and optimized structures in methanol (ε = 32.613) using PCM at B3LYP/6-31+G(d,p) level theory.

and H5 for one of the 'anomers'; the correlation between C2 and H6 (evidence of which was observed in the natural product) was not observed (see Supplementary material). These lines of evidence suggest that the proposed decurrenside D could exist as a bicyclic [3.3.0] octane glycoside structure, and also as a mixture of epimers at the C2 position.[9] This is interesting because suggest that this unprecedented proposed structure (KDO derivative), prefers the furanose form over the pyranose form, even though the latter is considered as the thermodynamic structure.[10] This unexpected behavior might be attributed to the conformational strain imposed by the dioxabicyclo moiety, which according to DFT calculations [Geometry optimizations for conformers were performed at B3LYP/6-31+G(d,p)[11] with PCM[12] (methanol) using Gaussian 09[13]], the furanose form is 4.77 kcal/mol more stable than the pyranose form (Scheme 3).

To conclude, we have efficiently synthesized the proposed structure of decurrenside D by a chiron approach. Stereoselective substitution at the anomeric position could build the required furanose structure, and the conversion of the alkyne group to α-keto ester group provided the desired intermediate for acetal formation. A closer analysis of the optical rotation and NMR data indicated a mismatch of data of the synthesized molecule with that of the naturally isolated. Based on the current results, further synthetic studies directed to establish the correct molecular structure of decurreside D (and also the other congeners), are needed.

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Supplementary data

Supplementary data (experimental section and copies of spectra for new compounds and tables of atom coordinates of the minima obtained at B3LYP/6-31+G(d,p) level theory for proposed Decurrenside D in bicyclic [3.2.1] and [3.3.0] structural forms) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.003.

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