

Relative stereochemistries of the ether rings and sugar moieties in durinskiol A

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Abstract—Durinskiol A (**1**) is a long carbon-chain polyol compound with a molecular weight of 2128 mu isolated from the symbiotic dinoflagellate *Durinskia* sp. The relative stereochemistries of ether rings and sugar moieties in **1** were established based on 2D-NMR analysis and molecular modeling studies. Conformational analysis of the 6,5,6-bis-spiroacetal ring in **1** was also examined by using ab initio methods.

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In a previous paper, we reported isolation, planar structure, and biological activity of durinskiol A (**1**), a unique polyol compound with a molecular weight of 2128 mu.¹ The structural features of this molecule are a 6,5,6-bis-spiroacetal ring, α - and ω -olefins on the termini of the C₉₃ linear carbon-chain, two sugar units, and six- and seven-membered ether rings. We report here the relative stereochemistry of durinskiol A (**1**) determined by spectroscopic analysis and molecular modeling studies (Fig. 1).

The relative configurations of the ether rings and sugar units in durinskiol A (**1**) were analyzed using NOESY, ROESY, NOEDF and homonuclear *J*-resolved NMR spectra (Fig. 2). Regarding the ABC-ring, key NOEs were observed for H17/H19, H20b/CH₃99, and H25/H27a, which suggested that three ethereal oxygen atoms

faced each other. The large magnitude of $J_{17,18b}$, $J_{27a,28}$, and $J_{28,29a}$ (9.6–10 Hz) suggested that the four protons H17, H19, H27a, and H28 may be oriented in axial orientations with respect to the ether rings A and C with a chair conformation due to the minimization of steric repulsions between equatorial substituents, and by anomeric effects in an axial C–O conformation in the spiro[4.5] system. A molecular modeling study using a Merck molecular force field (MMFF) for the ABC-ring model compound **2** also indicated that the same conformation as above was appropriate (Fig. 3), and the calculated distances of all protons for which NOEs were observed in rings ABC in **1** were less than 2.7 Å. To obtain more reliable conformational energies, geometry optimization for the possible four conformers of **2** was conducted using B3LYP/6-31G(d) level of theory,² whose ethereal oxygen atoms were oriented in axial/equatorial (**i**), bis-axial (**ii**), bis-equatorial (**iii**), and equatorial/axial (**iv**), respectively (Fig. 4). Their having minimum energies were confirmed by frequency calculations. As a result, the axial/equatorial conformer (**i**) was found to be most stable, and conformers (**ii**), (**iii**), and (**iv**) were higher in energy by 3.8, 10.2, and 11.3 kcal/mol than conformer (**i**). Although conformer (**ii**) may incorporate the maximum amount of anomeric effects, 1,3-diaxial interactions between the axial substituent on C28 and the ethereal oxygen atom in the ring B

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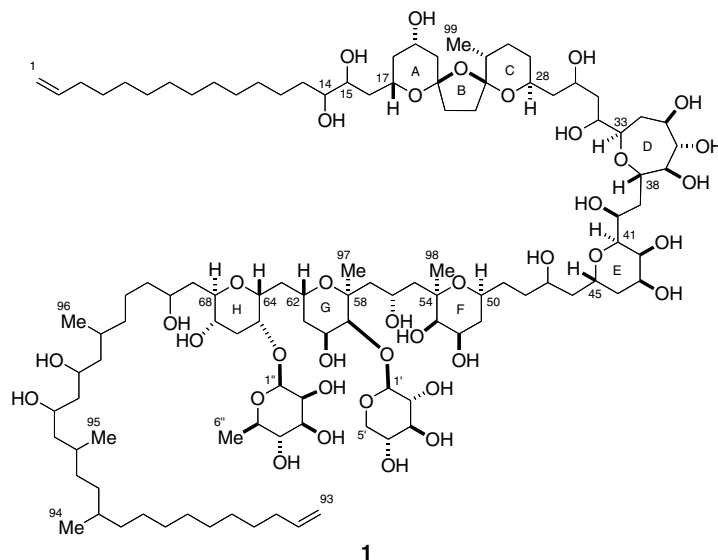


Figure 1. Structure of durinskiol A (**1**). The relative stereochemistry between rings C/D, E/F, G/xylose, and H/rhamnose has not been clarified.

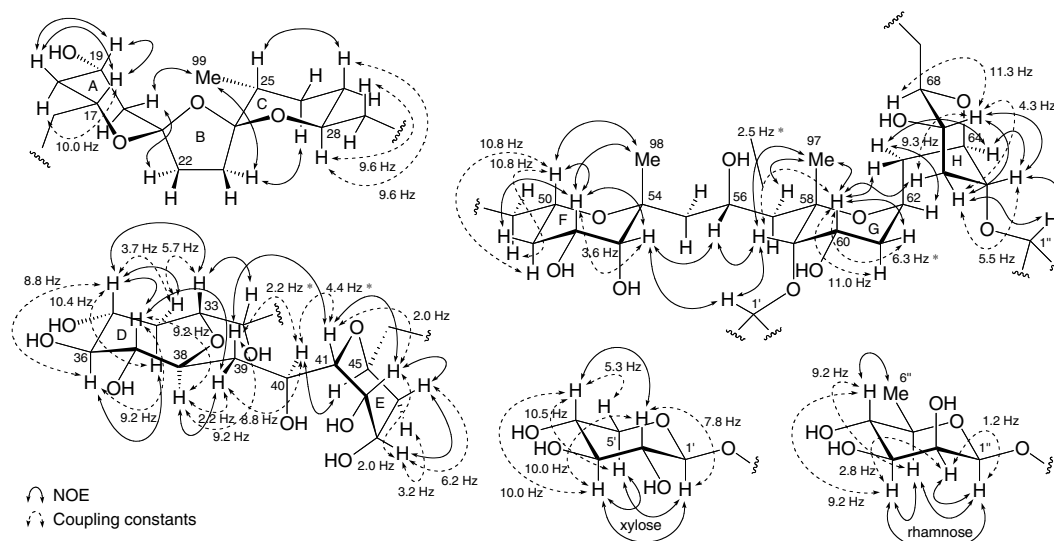


Figure 2. Relative stereochemistry of rings ABC, DE, FGH, and two sugar moieties for **1**. Asterisk indicates interchangeable values.

may be unfavorable.³ Thus, the relative stereochemistry in rings ABC was established to be $17S^*$, $19S^*$, $21R^*$, $24S^*$, $25R^*$, and $28S^*$.⁴

As for the D ring, the large magnitude of $J_{34a,35}$, $J_{35,36}$, $J_{36,37}$, $J_{37,38}$, and $J_{38,39a}$ (8.8–10.4 Hz) suggested that all of the five protons H34a, H35, H36, H37, and H38 were oriented in *anti* arrangements with respect to the D ring. Key NOEs H33/H35, H34a/H36, and H35/H37 indicated that the two alkyl substituents (C32 and C39) and three hydroxyl groups in the D ring should be oriented in pseudo-equatorial configurations with respect to the seven-membered ether ring with a chair conformation. Based on the molecular modeling study for the D-ring model compound **3**, all of the observed NOEs were applicable as with **2** (Fig. 3). Furthermore, the J values of vicinal protons (H34–H38) estimated from their dihedral

angles in the calculated model compound **3** mostly coincided with those of natural **1** (Table 1). Thus, the D-ring was confirmed to be a *trans*-fused ether.

Based on the NOEs observed for H40/H45, H42/H44a, H50/H52/ CH_3 98, H60/H63a/ CH_3 97, and H64/H65/H67, the F ring was found to be *cis*-2,6-dialkyltetrahydropyran, and the other three were *trans*. The large magnitude of $J_{50,51a}$, $J_{51a,52}$, $J_{60,61a}$, $J_{66a,67}$, and $J_{67,68}$ (9.3–11.3 Hz) suggested that the seven protons H50, H52, H60, H65, H66a, H67, and H68 were oriented in axial configurations with respect to the F, G, and H rings. Similarly, axial orientations for the two hydroxyl groups of C43 and C53 were established by the small magnitude of $J_{H42,H43}$ (2.0 Hz) and $J_{H52,53}$ (3.6 Hz), respectively. Thus, relative stereochemistry of each ethereal E–H ring part was confirmed.

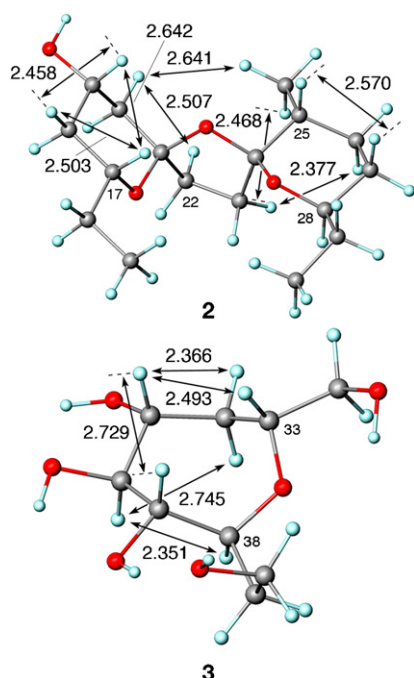


Figure 3. Three-dimensional structures of the ABC-ring model **2** and the D-ring model **3**. Each model was energetically minimized via iterative application of the MMFF (MacroModel 9.0). Values represent the calculated distances between two selected protons (Å). Substituent groups on C16 and C29 in **2** and on C33 and C39 in **3** were replaced with methyl groups and hydroxyl methyl groups, respectively.

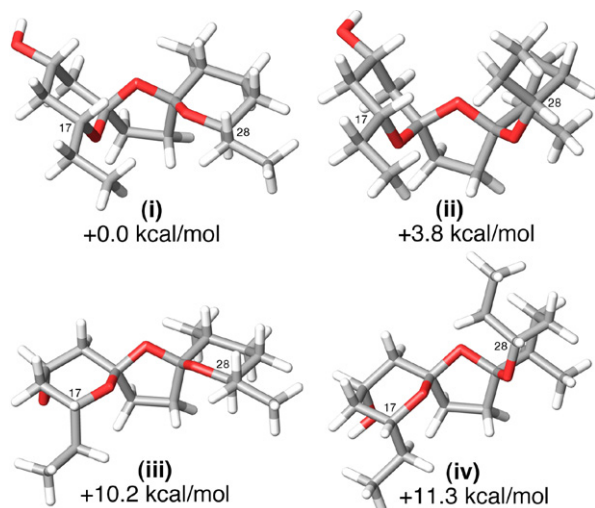


Figure 4. Optimized structures and relative energy of four conformers for **2** at the B3LYP/6-31G(d) level of theory.

Regarding the D/E linkage, the *anti* correlations for H38–C38–C39–H39a and H39b–C39–C40–H40 were established by the large magnitudes of $J_{\text{H38,H39a}}$ (9.2 Hz) and $J_{\text{H39b,H40}}$ (8.8 Hz). The obvious NOEs H37/H39b, H38/H39b, H39a/H41, and H40/45 strongly indicated that the hydroxyl group on C40 was oriented in a pseudoaxial configuration with a zigzag configuration from the carbon atom (C36) in D ring to the eth-

Table 1. Comparison of ^1H – ^1H coupling constants in the D-ring model compound **3** and natural **1**⁵

Coupling protons	Dihedral angles in 3 (deg)	Calculated coupling constants in 3 (Hz)	Observed coupling constants in 1 (Hz)
H33/H34a	–156.5	8.5	N.D.
H33/H34b	86.2	1.0	5.7
H34a/H35	179.3	11.2	10.4
H34b/H35	–65.6	3.5	3.7
H35/H36	163.5	6.4	8.8
H36/H37	179.7	9.4	9.2
H37/H38	–156.3	7.6	9.2

N.D.: Not determined.

real O atom in E ring, which alone satisfied all of the observed NOEs and J values. Thus, the relative stereochemistry in the DE rings was established to be 33*R*^{*}, 35*R*^{*}, 36*S*^{*}, 37*S*^{*}, 38*S*^{*}, 40*S*^{*}, 41*S*^{*}, 42*S*^{*}, 43*S*^{*}, and 45*S*^{*}. The strong NOEs observed for H53/H56/H59/H1' suggested that these four protons face each other with a zigzag conformation from carbons C54 to C58 between the F/G rings. The methylene protons H63a (δ 1.25) and H63b (δ 2.30) were clearly distinguished with each other. Key NOEs for H60/H63a, H60/H66a, H62/H63b, and H63b/H64 indicated that the free rotation of two sp^3 – sp^3 bonds, C62–C63 and C63–C64, was rather restricted and that only one configuration shown in Figure 2 could satisfy all of these data. Thus, the relative stereochemistry in the FGH rings was established to be 50*S*^{*}, 52*R*^{*}, 53*R*^{*}, 54*R*^{*}, 56*S*^{*}, 58*S*^{*}, 59*S*^{*}, 60*S*^{*}, 62*R*^{*}, 64*R*^{*}, 65*R*^{*}, 67*S*^{*}, and 68*R*^{*}.

The large magnitude of $J_{1',2'}$, $J_{2',3'}$, $J_{3',4'}$, $J_{4',5'a}$, $J_{3'',4''}$, and $J_{4'',5''}$ (7.8–10.5 Hz) suggested that all of the five hydroxyl groups on C2', C3', C4', C3'', and C4'' and a methyl group (C6'') were oriented in equatorial configurations. Meanwhile, an axial orientation for the hydroxyl group on C2'' was suggested by the small magnitudes of $J_{1'',2''}$ (1.2 Hz) and $J_{2'',3''}$ (2.8 Hz). Thus, two sugar moieties in **1** were unequivocally confirmed to be xylose and rhamnose.

In summary, a novel polyol compound with a molecular weight of 2128 mu, durinskiol A (**1**), was isolated from the dinoflagellate *Durinskia* sp., and its partial relative stereostructure was elucidated. Further chemical degradation studies and stereochemical assignment including the absolute stereochemistry of **1** are in progress.

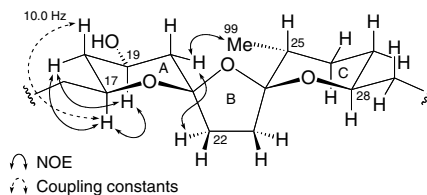
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4. Another stereoisomer ($17R^*$ and $19R^*$) whose A-ring was flipped was also conceivable (see below). However, the bis-equatorial C–O conformation in the 6,5,6-bis-spiroacetal ring may be unfavorable from the viewpoint of anomeric effects, and the lack of NOEs regarding H17/H22 and H19/H22 disagreed with such a conformation.



5. Coupling constants were calculated using the electronegativity-modified Karplus equation⁶ as implemented within MacroModel.
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