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Structural revision of peribysins C and D

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Abstract—Structural revision of the cell-adhesion inhibitory eremophilane sesquiterpenoid peribysins C and D is reported. A CAST/CNMR system is utilized in the reinvestigation of ^{13}C NMR chemical shift values and structures, and geometric analyses with molecular and quantum mechanics calculations, and revalidation of NMR data support the revised structures.
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Peribysins A–G were isolated from a strain of *Periconica byssoides* OUPS-N133 that was originally separated from a sea hare *Aplysia kurodai* as an inhibitor of the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells.[1,2] Peribysins C (**1**) and D (**2**) were initially proposed as the diastereoisomers of the unique eremophilane sesquiterpenoids that possess a 4,6-dihydro-1*H*,3*H*-furo[3,4-*c*]furan system.[1] However, definite discrepancies were found in the ^{13}C NMR chemical shift values of the reported peribysins C and D from a data evaluation using a CAST/CNMR system,[3,4] which ensured highly accurate ^{13}C NMR chemical shift prediction effectively taking into account the stereochemistry. We wish to describe here the structural revision of peribysins C and D by revalidating the NMR data with conformational analysis.

The CAST/CNMR system predicts ^{13}C NMR chemical shifts based on the chemical shift data of carbon atoms in the same partial structure that are selected from a database. For the proposed structure of peribysin C (**1**), however, CAST/CNMR did not provide enough answers because of the 4,6-dihydro-1*H*,3*H*-furo[3,4-*c*]furan system that exists in **1**, which is a rare structure[5] and not stored in the database.[6] Making a comparison of the structural environments from each carbon atom between **1** and **2**, the CAST/CNMR system indicated that C-12 of **1** and **2** as well as C-13 of them should have shown close chemical shift values, because they had the same partial structures including configurational stereochemistry within three-bonds.[7] However, there were differences of about 20 ppm between **1** and **2** for both C-12 and C-13. Re-analyzing the 2D NMR spectral data[1] denied the possibility of misassignments. The observed chemical shift values for the 4,6-dihydro-1*H*,3*H*-furo[3,4-*c*]furan portion of C-6–C-8 and C-11–C-13 were as follows; 69.98, 136.72, 84.12, 131.02, 76.37, and 56.03 ppm for peribysin C, respectively, and 85.95, 136.6, 63.69, 132.82, 55.68, and 76.36 ppm for peribysin D, respectively, in $CDCl_3$.[1] There were also large differences in the chemical shifts for C-6 and C-8,[8] namely, high-field shifts were observed at C-6 and C-13 of peribysin C, and C-8 and C-12 of peribysin D, respectively. In order to explain the upfield-shifts, diol structures instead of dihydrofuran ether rings are reasonable.[9] We accordingly proposed 6,13-diol and 8,12-diol structures for peribysins C and D, respectively (Scheme 1).

In the EI-MS spectra of peribysins C and D, the true molecular ion was observed at *m*/*z* 252 in the original EI-MS spectra even though the intensity was small, although the dehydration ion at *m*/*z* 234 was recognized as the molecular ion in the original report.[1] For peribysin C, an authentic sample was available for EI-MS re-measurement, and the true molecular formula was confirmed with high resolution EI-MS data at *m*/*z* 252.1719 (M^+ 18% intensity, 252.1726 calculated for $C_{15}H_{24}O_3$). This MS data strongly supported the proposed diol structure.

For peribysin C, the A-ring conformation was established as a chair with the coaxial 5-methyl group, H-1β and H-3β, and the equatorial 4-methyl group and

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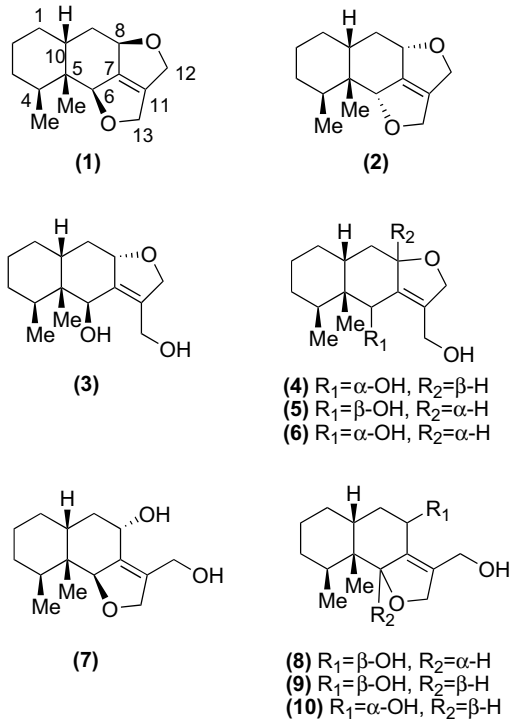

Scheme 1.

H-10 based on the NOE data.[1] It is well known that the conformation of 7(11)-eremophilene-12,8-olide analogues is controlled by C-8 stereochemitsry, i.e., when lactone oxygen O-8 is of the α orientation, the C-4 methyl group is equatorial, and when O-8 is of the β orientation, the C-4 methyl group is axial.[10–18] The same tendency should be found in the proposed dihydrofuran-type peribysin C, which has the same partial structure. Namely, it might possess H-8β. To confirm the stereochemistry of C-8 as well as C-6, conformational search and energy optimization were performed for all possible diastereoisomers **3**-**6** by using a MMFF force field and ab initio (6-31G**) quantum mechanics calculations, which resulted in geometric structures as shown in Figure 1.[19] Isomers **3** and **4** having H-8β stereochemistry were definitely optimized to geometries possessing the same A-ring conformation consistent with the NOE experiments, although isomers **5** and **6** with H-8α stereochemistry showed the flipped A-ring conformation having the axial 4-methyl group. Based on the evidences, we determined that the stereochemistry of C-8 was H-8β. In comparing the conformations of **3** and **4**, the isomer **3** was consistent with the NOE observed between H-4 and H-6, which suggested that H-6 was equatorial and of the α orientation.[1] This stereochemistry was supported by the absence of long-range coupling between H-6 and H-13 of the allylic methylene group.[11–18] Therefore, the structure of peribysin C was revised to 8α,12-epoxy-7(11)-eremophilene-6β,13-diol (**3**).

In the same way, conformational search calculations were performed for possible diastereoisomers **7**–**10** of peribysin D, from which results are shown in Figure 2. The optimized geometries of **7** and **8**, having H-6α stereochemistry, were consistent with the NOE data, which suggested that the A-ring existed in a chair form with the

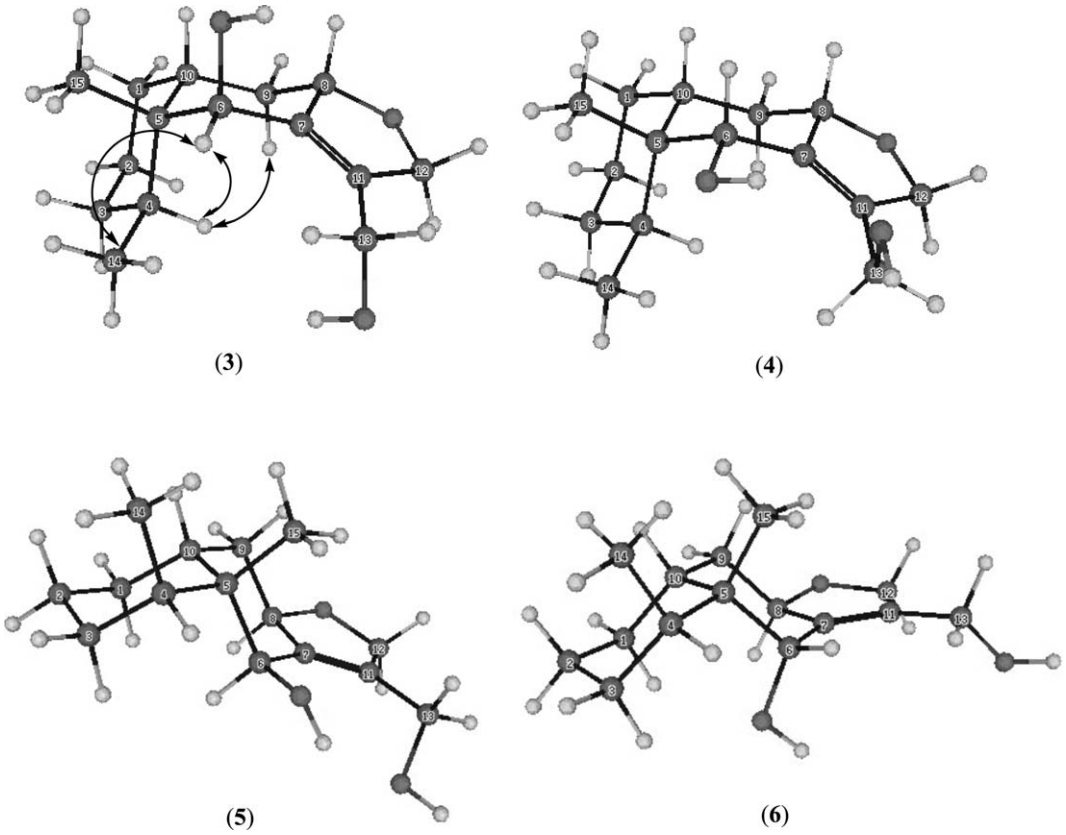

Figure 1. Optimized structures of **3**, **4**, **5**, and **6**, and the observed NOE data.

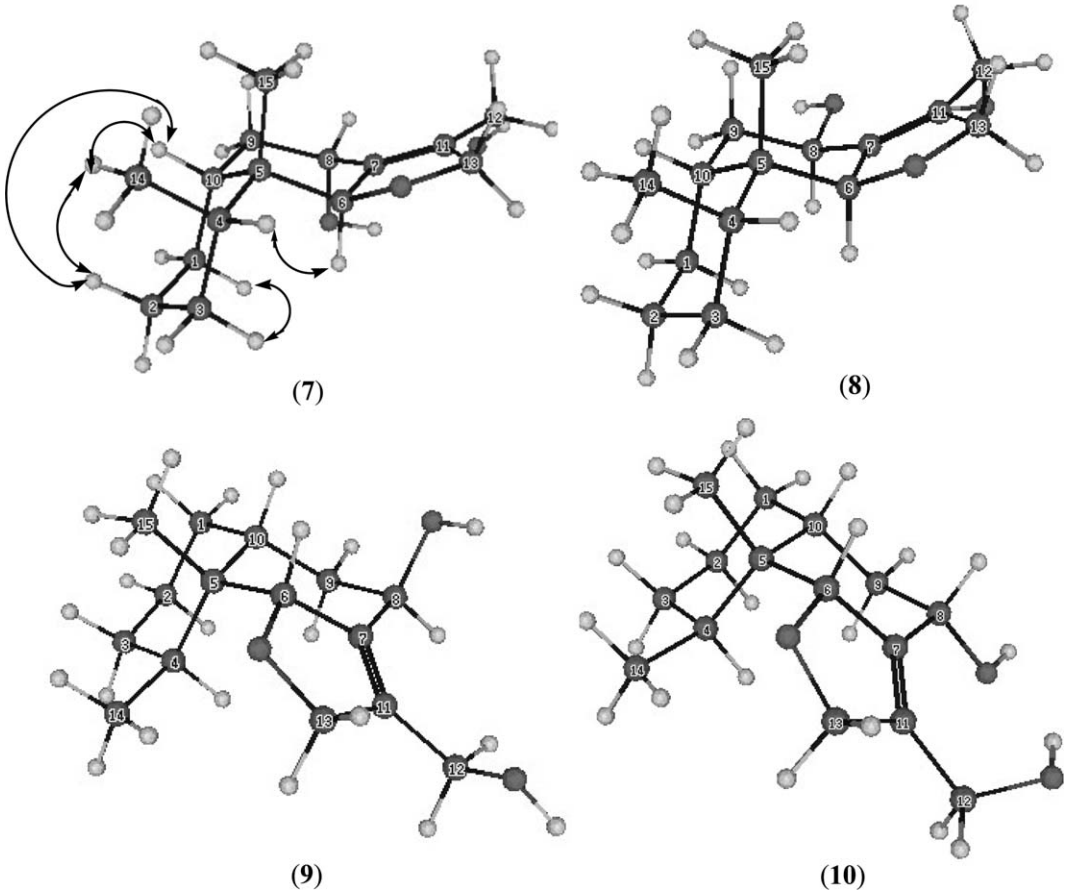

Figure 2. Optimized structures of **7**, **8**, **9**, and **10**, and the observed NOE data.

coaxial 4-methyl group, H-2β, and H-10,[1] although the flipped A-ring conformations were obtained for **9** and **10**, which had H-6β stereochemistry. The calculated stable conformations of the B-rings of **7** and **8** were chair-form, thus C-8 stereochemistry could be determined by the vicinal coupling constant values between H-8 and H-9. Small vicinal coupling but no long-range coupling was shown between H-8 of the oxygenated methine group at 4.77 (dd, $J = 4.8$ and 1.8 Hz) ppm[1] and H-12 of the allylic methylene group, which indicated that the stereochemistry of the hydroxyl group at C-8 was axial and of the α orientation. Therefore, the structure of peribysin D was revised to 6β,13-epoxy-7(11)-eremophilen-8α,12-diol (**7**).

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6. Suitable compounds for predicting C-6–C-8 and C-11–C-13 ^{13}C NMR chemical shifts for **1** and **2** were not available despite a *SciFinder* search, because the 4,6-dihydro-1*H*,3*H*-furo[3,4-*c*]furan system was quite unique and rare partial structure in natural products.
7. Considering conformational information, the CAST/CNMR system indicated that ^{13}C NMR chemical shifts of C-11–C-13 should be similar between **1** and **2**, respectively.
8. Environments for C-6 and C-8 were recognized to be the same in planar but different in the configuration between **1** and **2**.
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