Isoplagiochins C and D, New Type of Macrocyclic Bis(bibenzyls), Having Two Biphenyl Linkages from the Liverwort *Plagiochila fruticosa*

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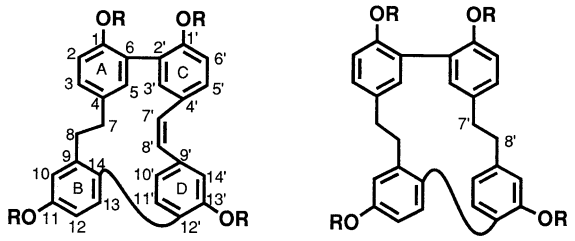
Two new type of macrocyclic bis(bibenzyls) named isoplagiochins C (**1**) and D (**2**) have been isolated from the liverwort *Plagiochila fruticosa*, and their structures established by a combination of two dimension NMR spectra and chemical degradation.

Plagiochila species (liverworts) are rich sources not only of sesquiterpenoids but also bibenzyl and cyclic bis(bibenzyl) derivatives with biological activities.[1-3] In our previous paper, we have reported on the isolation and structure elucidation of two novel macrocyclic bis(bibenzyls), named isoplagiochins A (**3**) and B (**4**) from the MeOH extract of *Plagiochila fruticosa*.[4] Further fractionation of the MeOH extract of *P. fruticosa* resulted in the isolation of two new type of macrocyclic bis(bibenzyls), named isoplagiochins C (**1**)[5] and D (**2**).[6] We now report on elucidation of their structures.

The MeOH extract (19.3 g) of fresh material (1.09 kg) of *P. fruticosa* collected in Tokushima in 1992 was subjected repeatedly to column chromatography using Sephadex LH-20 ($CHCl_3$: MeOH = 1 : 1) and silica gel ($CHCl_3$-MeOH, gradient) to afford isoplagiochins C (**1**) (91 mg) and D (**2**) (58 mg) along with isoplagiochins A (**3**) (365mg) and B (**4**) (194 mg).

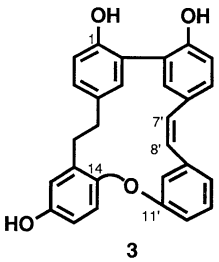
IR and UV spectra of isoplagiochin C (**1**)($C_{28}H_{22}O_4$) (HRMS: $[M]^+$ m/z 422.1485) indicated the presence of a phenolic hydroxyl group (ν 3223 cm^{-1}) and a benzene ring (ν 1607 cm^{-1}), which was conjugated with a double bond [λ_{max}287 nm (log ε=3.83)]. The ^1H and ^{13}C NMR spectra of **1** showed two benzyl methylene signals [δ_H2.67 (4H, m, 7 and 8-H_2); δ_c 38.4 (C-7), 39.3 (C-8)], *cis*-olefinic protons [δ_H 6.55, 6.65 (each 1H, d, J=11.5 Hz, 7' and 8'-H)], and twenty-four aromatic carbons including twelve methine and twelve quarternary carbons. These spectral data resembled those of isoplagiochin A (**3**) except for the signal patterns of D-ring, indicating that compound **1** possessed the same skeleton as that of compound **3**. The molecular formula of **1** was identical to that of **3**, suggesting that the former compound contained an additional phenolic hydroxyl group at D-ring, in place of an ether oxygen in compound **3**. This assumption was confirmed by the formation of a tetraacetate **5** from **1**, by acetylation (Ac_2O, pyridine). The location of the hydroxyl group at C-13' and the whole structure were deduced from careful analysis of the 2D NMR spectra including ^1H-^1H COSY, HMBC(Figure 2), HMQC and NOESY (Figure 3) of **1**.

Isoplagiochin D (**2**) ($C_{28}H_{24}O_4$) (HRMS: $[M]^+$ m/z 424.1654), has spectral data very similar to those of **1** except for four methylene signals (δ_c 36.1, 38.1, 38.5 and 39.1) in ^{13}C NMR spectrum. Compound **2** gave the tetraacetate **6** on acetylation and methylation affored the tetramethyl ether **7** indicating the presence of four phenolic hydroxyl groups. Hydrogenation (H_2 / 10%Pd-C) of compound **5** affored a tetraacetate **6** whose spectral data were identical to those of **6**. From the above chemical evidence, the HMBC NMR spectrum (Figure 4) of **2** and NOE experiments (Figure 5) on **7**, the structure of **2** was determined as $C_{7'}$, $C_{8'}$-dihydro



1 : R=H
5 : R=Ac

2 : R=H
6 : R=Ac
7 : R=Me



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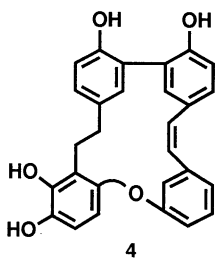

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Figure 1.

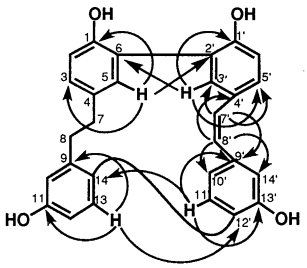

Figure 2. HMBC spectrum of 1.

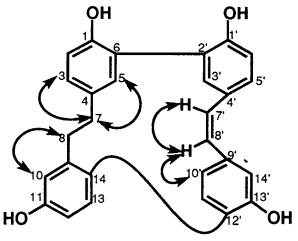

Figure 3. NOESY spectrum of 1.

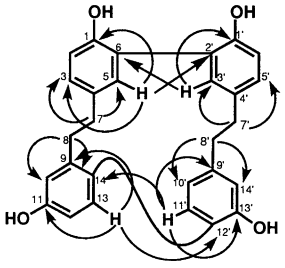

Figure 4. HMBC spectrum of 2.

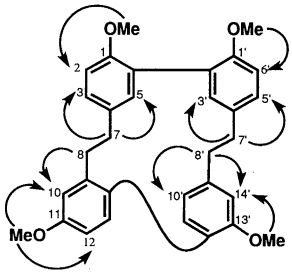

Figure 5. NOE difference spectrum of 7.

derivative of compound **1.**

Isoplagiochins A (**3**) and B (**4**) possess a C_{14}-$C_{11'}$ ether linkage and a C_6-$C_{2'}$ biphenyl bond, whereas isoplagiochins C (**1**) and D (**2**) possess two C_6-$C_{2'}$ and C_{14}-$C_{12'}$ biphenyl bonds. Isoplagiochins A~D might be biosynthesized from isoperrottetin A (**8**)[7] isolated from the liverwort *Radula perrottetii*, which was biosynthesized by a dimerization of lunularin (**9**) found in most of the liverworts as shown in Figure 6. This is the first report of the isolation of macrocyclic bis(bibenzyls), isoplagiochins C and D possessing two biphenyl linkage between rings A and C / rings B and D.

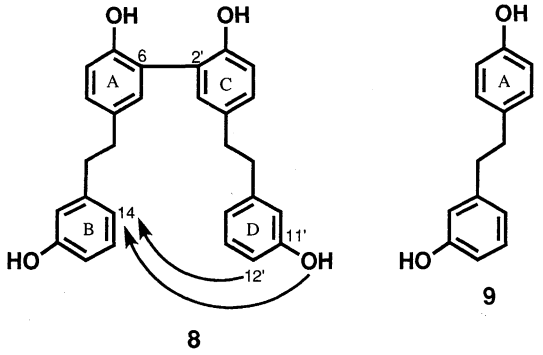

Figure 6.

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References and Notes

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5 Isoplagiochin C (**1**): amorphous powder; $[\alpha]_D^{21}$ ±0° (*c* 1.0, CH_3OH); HR-MS: M^+; m/z 422.1485, $C_{28}H_{22}O_4$ requires 422.1518; EI-MS: *m/z* 422 (M^+, 100), 211, 197, 165; IR (KBr) cm^{-1}: 3223 (OH), 1607, 1232; UV (EtOH)λ_{max}nm (logε): 287 (3.83), 204 (4.48); ^{1}H NMR (600 MHz, CD_3OD) δ 2.67 (4H, m, H-7 and 8), 6.55 (1H, d, J=11.7 Hz, H-7'), 6.60 (1H, d, J=2.2 Hz, H-5), 6.65 (1H, d, J=11.7 Hz, H-8'), 6.77 (1H, dd, J=2.4, 8.3 Hz, H-12), 6.78 (1H, d, J=8.1 Hz, H-2), 6.85 (1H, d, J=2.4 Hz, H-10), 6.88 (1H, dd, J=2.2, 8.1 Hz, H-10'), 6.89 (1H, d, J=2.2 Hz, H-14'), 6.90 (1H, d, J=8.3 Hz, H-6'), 6.98 (1H, dd, J=2.2, 8.1 Hz, H-3), 7.12 (1H, d, J=8.3 Hz, H-13), 7.15 (1H, dd, J=2.2, 8.3 Hz, H-5'), 7.16 (1H, d, J=8.1 Hz, H-11'), 7.28 (1H, d, J=2.2 Hz, H-3'); ^{13}C NMR (150 MHz, CD_3OD) δ 37.7 (t, C-7), 38.3 (t, C-8), 113.3 (d, C-12), 115.4 (d, C-14'), 115.9 (d, C-10), 116.8 (d, C-2), 120.3 (d, C-10'), 126.0 (s, C-2'), 126.8 (s, C-6), 127.2 (s, C-12'), 128.0 (d, C-3), 128.3 (s, C-14), 128.9 (d, C-8'), 129.6 (s, C-4'), 130.0 (d, C-7'), 130.5 (d, C-5'), 131.9 (d, C-13), 132.0 (d, C-11'), 133.4 (d, C-3'), 133.8 (d, C-5), 135.8 (s, C-4), 140.2 (s, C-9'), 144.0 (s, C-9), 150.8 (s, C-1), 152.4 (s, C-1'), 154.4 (s, C-13'), 156.7 (s, C-11).

6 Isoplagiochin D (**2**): amorphous powder; $[\alpha]_D^{21}$ ±0°(*c*1.0, CH_3OH); HR-MS: M^+; m/z 424.1654, $C_{28}H_{24}O_4$ requires 424.1675; EI-MS: *m/z* 424 (M^+, 100), 211, 197, 165; IR (KBr) cm^{-1}: 3223 (OH), 1607, 1232; UV (EtOH)λ_{max}nm (logε): 287 (3.83), 204 (4.48); ^{1}H NMR (600 MHz, acetone-d_6) δ 2.70~3.10 (8H, m, H-7, 8, 7' and 8'), 6.39 (1H, d, J=2.4 Hz, H-5), 6.51 (1H, d, J=2.2 Hz, H-3'), 6.72 (1H, dd, J=2.4, 8.1 Hz, H-12), 6.73 (1H, d, J=2.2 Hz, H-14'), 6.74 (1H, dd, J=2.2, 7.8 Hz, H-10'), 6.79 (1H, d, J=7.8 Hz, H-2), 6.84 (1H, d, J=2.4 Hz, H-10), 6.89 (1H, d, J=8.1Hz, H-6'), 6.99 (1H, d, J=8.1 Hz, H-13), 7.00 (1H, dd, J=2.4, 7.8 Hz, H-3), 7.07 (1H, d, J=7.8 Hz, H-11'), 7.13 (1H, dd, J=2.2, 8.1 Hz, H-5'), ^{13}C NMR (150 MHz, acetone-d_6) δ 36.1 (t, C-7'), 38.1 (t, C-7), 38.5 (t, C-8'), 39.1 (t, C-8), 113.3 (d, C-12), 116.0 (d, C-10), 116.1 (d, C-2), 117.0 (d, C-6'), 117.4 (d, C-10'), 121.5 (d, C-14'), 126.0 (s, C-2'), 127.2 (s, C-12'), 127.6 (s, C-6), 128.0 (d, C-3), 129.3 (d, C-5'), 129.5 (s, C-14), 131.9 (d, C-11'), 132.4 (d, C-13), 133.9 (d, C-3'), 133.9 (s, C-4'), 134.3 (d, C-5), 136.0 (s, C-4), 142.5 (s, C-9'), 144.0 (s, C-9), 151.6 (s, C-1), 152.2 (s, C-1'), 155.1 (s, C-13'), 157.3 (s, C-11).

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