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# PERROTTETINS E, F, AND G FROM Radula perrottetii (LIVERWORT)--ISOLATION, STRUCTURE DETERMINATION, AND SYNTHESIS OF PERROTTETIN E

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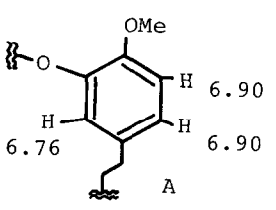
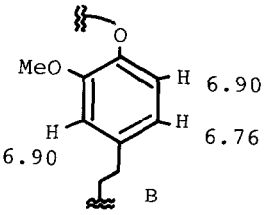
Abstract: Perrottetin E, a cytotoxic bis(bibenzyl) ether, was isolated from Radula perrottetii and its structure determined by spectroscopic methods and total synthesis. Perrottetins F and G were also isolated from the same source and fully characterized.

Liverworts are very rich sources of both terpenoids and aromatic compounds, some of which exhibit antifungal, antimicrobial, or cytotoxic activities.[1] We have been studying the chemical constituents of the liverworts and have previously reported that Radula perrottetii contains a number of aromatic compounds such as perrottetins A, B, C, and D, as well as unidentified substances, perrottetins E and F.[2] We now report the isolation and structure determination of perrottetins E, F, and G and the total synthesis of perrottetin E.

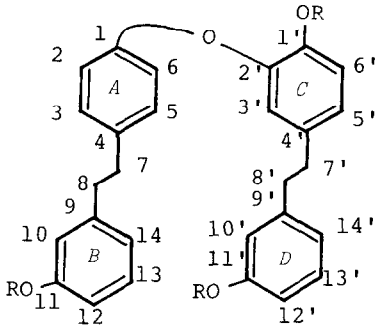
Perrottetin E (1)[3] was isolated from R. perrottetii following the published procedure.[2] The IR spectrum of 1 showed the presence of hydroxyl groups (3400 $cm^{-1}$) and the high resolution mass spectrum (HRMS) indicated the molecular formula, $C_{28}H_{26}O_4$. As the $^1H$ NMR spectrum suggested the presence of aryl groups and benzylic protons, 1 was deduced to be a member of the marchantin-series of compounds.[4] However, the degree of unsaturation of 1 was one less than that of marchantin A, a typical macrocyclic bis(bibenzyl).[4] Careful decoupling and NOE experiments revealed that there are four benzene rings (1,4-disubstituted, 1,2,4-trisubstituted, and two 1,3-disubstituted) as well as four benzylic groups (Table 1).[5] In order to assign the position of the hydroxyl groups, 1 was methylated using $MeI/K_2CO_3$ in acetone. The $^1H$ NMR resonances of the trimethyl ether 2,[7] $C_{31}H_{32}O_4$, are listed in Table 1. The

results of double resonance and NOE experiments concerning the protons of ring C were somewhat difficult to explain. When the higher-field benzylic protons were irradiated, an NOE was observed upon two broad singlet peaks (δ 6.76 and 6.90) as well as H-10' and H-14'. The singlet at δ 6.90 was enhanced, when the methoxyl group at δ 3.80 was saturated. These observations suggest that there are two possible structures for ring C. Chemical shifts are shown in the partial structures A and B. As the protons due to H-5' and H-6' have different chemical shifts in the case of B, they must exhibit mutual couplings, while in the case of A, it is possible that both H-5' and H-6' have the same chemical shifts by chance and show no coupling.

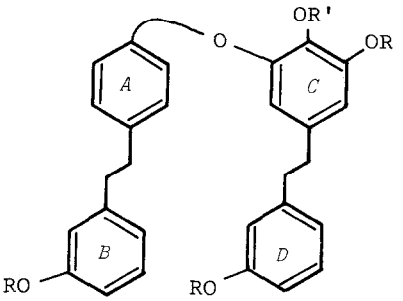



In order to clarify these points, we undertook a total synthesis of this compound. The strategy was to connect both rings B and D in simultaneous Wittig reactions to the diphosphonate corresponding to the ring A-C segment.




R=H 1
R=Me 2




R=R'=H 8
R=R'=Me 9
R=H, R'=Me 10

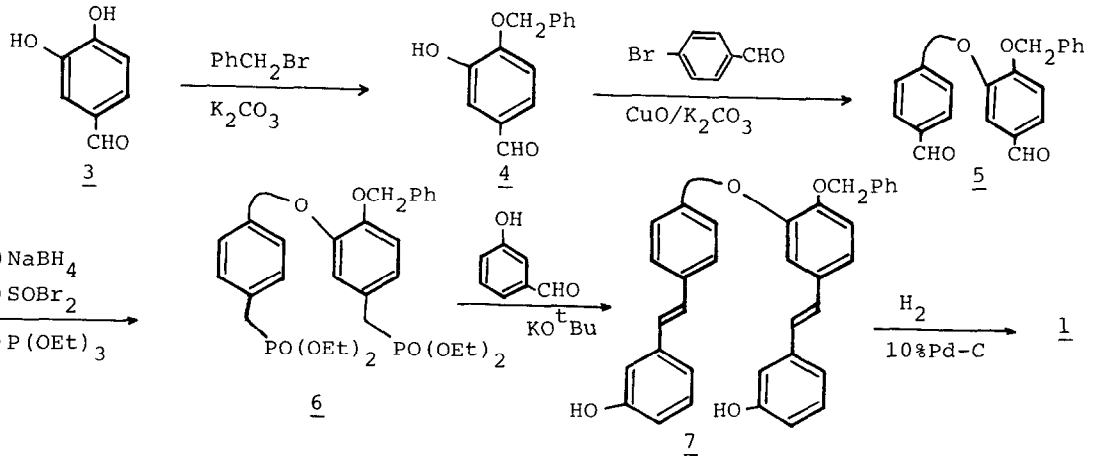


Table 1. $^1$H NMR Data of Compounds 1, 2, 8, 9, and 10.

| position | 1 | 2 | 8 | 9 | 10 |
|---|---|---|---|---|---|
| 2,6 | 6.86 d (8.7) | 6.83 d (8.6) | 6.84 d (8.5) | 6.85 d (8.6) | 6.82 d (8.6) |
| 3,5 | 7.10 d (8.7) | 7.09 d (8.6) | 7.08 d (8.5) | 7.09 d (8.6) | 7.06 d (8.6) |
| 7,8 | 2.88 brs | 2.88 s | 2.86 s | 2.88 s | 2.85 s |
| 10 | 6.63 * | 6.74 dd (2, 1) | 6.62 dd (2.5, 1.5) | 6.71 dd (2, 1) | 6.59 * |
| 12 | 6.65 * | 6.72 ddd (7.3, 2, 1) | 6.66 ddd (7.7,2.5,1.5) | 6.72 ddd (7.5,2,1) | 6.63 ddd(7.8,2.5,1) |
| 13 | 7.15 t (7.8) | 7.19 t (7.3) | 7.13 t (7.7) | 7.19 t (7.5) | 7.12 t (7.8) |
| 14 | 6.76 brd (7.8) | 6.79 ddd (7.3, 2, 1) | 6.74 brd (7.7) | 6.77 ddd (7.5,2,1) | 6.74 brd (7.8) |
| 3' | 6.61 d (2) | 6.76 brs | 6.19 d (2) | 6.39 d (1.9) | 6.23 d (2) |
| 5' | 6.83 dd (8, 2) | 6.90 brs | 6.57 d (2) | 6.48 d (1.9) | 6.59 d (2) * |
| 6' | 6.94 d (8) | 6.90 brs | ---- | ---- | ---- |
| 7',8' | 2.77 s | 2.81 brs | 2.72 m | 2.82 m | 2.73 m |
| 10' | 6.57 dd (2.5,1.5) | 6.67 t (2) | 6.58 dd (2, 1.5) | 6.67 t (2) | 6.59 * |
| 12' | 6.64 * | 6.72 ddd (7.3, 2, 1) | 6.66 ddd (7.5,2.5,1.5) | 6.72 ddd (7.5,2,1) | 6.74 brd (7.5) |
| 13' | 7.10 t (7.8) | 7.17 t (7.3) | 7.09 t (7.5) | 7.17 t (7.5) | 7.09 t (7.5) |
| 14' | 6.66 * | 6.73 ddd (7.3, 2, 1) | 6.66 ddd (7.5,2.5,1.5) | 6.73 ddd (7.5,2,1) | 6.67 brd (7.5) |
| 11-OMe | ---- | 3.75 | ---- | 3.77 | ---- |
| 1'-OMe | ---- | 3.80 | ---- | 3.80 | 3.87 |
| 6'-OMe | ---- | ---- | ---- | 3.85 | ---- |
| 11'-OMe | ---- | 3.76 | ---- | 3.76 | ---- |

*Peaks are not resolved.

Mono-protection of 3,4-dihydroxy benzaldehyde ($PhCH_2Br/K_2CO_3$/acetone) followed by Ullmann coupling ($CuO/K_2CO_3$/Py) with p-bromobenzaldehyde smoothly afforded the dialdehyde ether 5 (in 60% yield).[8] The diphosphonate 6 was prepared from 5 in three steps [1)$NaBH_4$ 2)$SOBr_2$/PhH 3)$P(OEt)_3$] in 64% yield and then condensed in a Wittig reaction with m-hydroxybenzaldehyde using $KO^tBu$ as base to gave the stilbene-type ether 7. Hydrogenation ($H_2$/10%Pd-C/MeOH) afforded perrottetin E (1) (72% yield from 6). The synthetic material was identical with the natural product in all respects (TLC, MS, IR, $^1$H and $^{13}$C NMR). Furthermore, the corresponding trimethyl ether prepared from the synthetic sample was completely identical with 2.

From a more polar fraction, perrottetin F (8)[9] was isolated. It could be more conveniently purified as its tetramethyl ether.[2] Perrottetin F (8), $C_{28}H_{26}O_5$, posseses four hydroxyl groups (3330, 3550 $cm^{-1}$) since methylation gave the tetramethyl ether 9,[10] $C_{32}H_{34}O_5$. The $^1$H NMR spectrum of 8 suggested that one of the benzene rings (ring C) has one more hydroxyl group than in the case of 1. Double resonance and NOE experiments revealed that the 1' and 6' positions are hydroxylated, because the mutually coupled protons H-3' (d, J=2 Hz) and H-5' (d, J=2 Hz) both showed an NOE when the benzylic methylenes were irradiated. Careful separation of the minor components afforded perrottetin G (10),[11] $C_{29}H_{28}O_5$ , having one methoxyl group. It is clear that 10 is simply a monomethyl ether of 8, since permethylation afforded 9 ($CH_3I/K_2CO_3$/acetone). The position of the methoxyl group of 10 was determined to be 1', as no NOE was

observed on irradiation of the methoxyl group.[12]

Thus perrottetins E (1), F (8), and G (10) were established to have the structures shown. These compounds are of interest because they are the linear analogues of the macrocyclic bis(bibenzyl) ethers which are found in Marchantia species,[4] and hence are possible biogenetic precursors to marchantins and riccardins.

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## References and Notes

1) Y. Asakawa, in "Progress in the Chemistry of Organic Natural Products", eds W. Herz, H. Griesebach, and G. W. Kirby, Springer-Verlag, Wien, 1982, vol. 42, p1.
2) Y. Asakawa, K. Takikawa, M. Toyota, and T. Takemoto, Phytochemistry, 21, 2481 (1982).
3) 1 shows cytotoxicity against KB cells at the concentration of 12.5 μg/ml. m/z 426 ($M^+$), 319 (base peak); $^{13}C$ NMR δ 155.5 (s X 2), 154.9 (s), 145.4 (s), 143.5 (s X 2), 143.4 (s), 136.8 (s), 134.2 (s), 129.8 (d X 2), 129.5 (d X 2), 124.4 (d), 121.0 (d X 2), 118.8 (d), 117.9 (d X 2), 115.9 (d), 115.5 (d X 2), 112.9 (d X 2), 37.8 (t), 37.7 (t), 36.8 (t), 36.7 (t).
4) Y. Asakawa, M. Toyota, R. Matsuda, K. Takikawa, and T. Takemoto, Phytochemistry, 22, 1413 (1983); Y. Asakawa, Rev. Latinoamer. Quim., 14-3, 109 (1984); Y. Asakawa, Journ. Hattori Bot. Lab., 56, 215 (1984).
5) Although we have already published a numbering system[4] for the marchantin and riccardin series, we have adopted a new systematic numbering for them[6] and have applied it to the closely related perrottetins.
6) M. Tori, M. Toyota, L. J. Harrison, K. Takikawa, and Y. Asakawa, Tetrahedron Lett., 26, in press.
7) m/z 468 ($M^+$), 347 (base peak); $^{13}C$ NMR δ 159.6 (s X 2), 156.0 (s), 149.5 (s), 145.1 (s), 143.4 (s), 143.1 (s), 135.8 (s), 134.7 (s), 129.4 (d X 2), 129.3 (d X 2), 124.2 (d), 120.9 (d X 2), 120.8 (d), 117.2 (d X 2), 114.2 (d X 2), 112.7 (d), 11.3 (d), 111.2 (d), 38.1 (t), 38.0 (t), 37.1 (t), 36.9 (t), 56.1 (q), 55.1 (q X 2).
8) M. Kodama, Y. Shiobara, K. Matsumura, and H. Sumitomo, Tetrahedron Lett., 26, 877 (1985).
9) m/z 442 ($M^+$), 335 (base peak); $^{13}C$ NMR δ 155.9 (s X 2), 155.2 (s), 145.1 (s), 143.8 (s), 143.2 (s X 2), 136.2 (s), 133.6 (s X 2), 129.5 (d X 2), 129.3 (d), 129.2 (d), 120.2 (d X 2), 117.3 (d X 2), 115.5 (d), 115.4 (d), 112.8 (d X 2), 111.2 (d X 2), 37.6 (q), 37.5 (q), 36.9 (q), 36.6 (q).
10) m/z 498 ($M^+$), 377 (base peak); $^{13}C$ NMR δ 159.6 (s X 2), 155.9 (s), 153.5 (s), 149.5 (s), 143.3 (s), 143.0 (s), 139.0 (s), 137.4 (s), 135.9 (s), 129.4 (d X 2), 129.3 (d X 2), 120.9 (d X 2), 117.4 (d X 2), 114.2 (d X 2), 113.1 (d), 111.3 (d), 111.2 (d), 108.1 (d), 38.1 (t), 37.8 (t), 37.6 (t), 37.0 (t), 61.1 (q), 56.1 (q), 55.1 (q X 2).
11) m/z 456 ($M^+$), 349 (base peak); $^{13}C$ NMR δ 155.5 (s X 2), 155.3 (s), 149.4 (s), 148.3 (s), 143.5 (s), 143.3 (s), 138.0 (s), 136.3 (s), 129.6 (d X 2), 129.5 (d X 2), 121.0 (d), 120.9 (d), 117.4 (d X 2), 115.5 (d), 115.4 (d), 112.9 (d X 2), 112.4 (d), 110.6 (d), 61.4 (q), 37.7 (t), 37.4 (q), 37.2 (q), 36.8 (q).
12) In the series of compounds having 1'- and 6'-OMe groups, when the 6'-OMe was irradiated, H-5' showed an NOE and when the 1'-OMe was saturated, no NOE was observed.

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