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A drimane sesquiterpenoid lactone from *Warburgia salutaris*

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Abstract

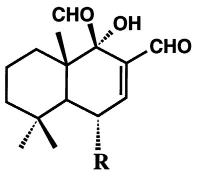
The stem bark of *Warburgia salutaris* collected in Zoutpansberg mountains yielded a new drimane sesquiterpenoid lactone, salutarisolide, along with four known drimane sesquiterpenoids warburganal, mukaadial, polygodial and isopolygodial. The structure of salutarisolide was fully characterized from its spectral data. The lactone is structurally related to muzigadial. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: *Warburgia salutaris*; Canellaceae; Salutarisolide; Warburganal; Muzigadial; Polygodial; Isopolygodial; NMR; INAPT; NOE; COSY

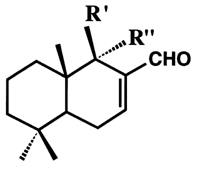
1. Introduction

Warburgia salutaris (Bertol. f.) Chiov. is a small tree, 5–10 m in height but reaching 20 m in some areas, which grows along the eastern seaboard of the province of KwaZulu-Natal and extend northwards through the Mpumalanga and the Northern Provinces of South Africa (Coates-Palgrave, 1977). The Venda people use the plant to treat soars and ulcer (Arnold, & Guluman, 1984). The antifungal, insect antifeedant, antiulcer and molluscicidal drimane sesquiterpenoid warburganal (**1**) (Kubo, Lee, Pettei, Pilkiewicz, & Nakanishi, 1976; Kubo, Matsomoto, Kakooko, & Mubiru, 1983; Mashimbye, Drewes, Appleton, & Cunningham, 1992) was previously isolated from the plant along with polygodial (**2**) (Mashimbye, 1993). This study was undertaken as part of our continuing interest in the medicinal plants of the Northern Province.

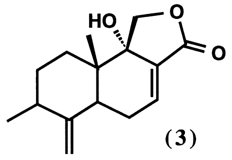
Further examination of the stem bark collected in Zoutpansberg mountains yielded, in addition to warbuganal (**1**) and polygodial (**2**), a new drimane sesquiterpenoid lactone salutarisolide (**3**) together with mukaadial (**4**) and isopolygodial(isotadeonal) (**5**). This paper describes the isolation and characterization of salutarisolide (**3**) a drimane sesquiterpenoid lactone isolated from *W. salutaris*.



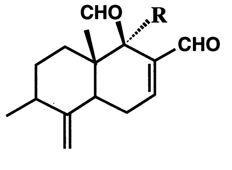
1, R = H
4, R = OH



2, R' = CHO, R'' = H
5, R' = H, R'' = CHO



(3)



6, R = OH
7, R = H

2. Results and discussion

Plants of the Canellaceae are sources of drimane

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sesquiterpenoids known to possess a wide range of biological activities (Jansen, & de Groot, 1991). Salutarisolide was obtained from the dichloromethane extract after repeated column chromatography using petroleum (40–60°) — ethyl acetate mixtures. The compound was obtained as an amorphous material, m.p. 139–140°, $[\alpha]_D = -52.29°$. The presence of the unsaturated lactone was indicated by the strong absorption at 1758 and 1683 cm^{-1}. The third oxygen was present as a hydroxyl group (broad band absorption at 3433 cm^{-1}). In addition, its IR spectrum exhibited absorption due to the exocyclic methylene group (1637 and 759 cm^{-1}) (Corbett, & Chee, 1976). The ^1H NMR spectrum exhibited NMR data similar to those of canellal (muzigadial) (**6**) (Kubo et al., 1977; El-Feraly, McPhail, & Onan, 1978), although the two aldehydes were replaced by one carbonyl group (δ 169) and the oxygen bonded methylene group (δ 75.0). The ^1H NMR spectrum showed two methyl groups, a singlet at δ 0.62 and a doublet at δ 1.1, which, together with the exocyclic methylene group at δ 4.9 (1H, s) and δ 4.7 (1H, s), clearly suggest ring A was similar to that of muzigadial (canellal) (Kubo et al., 1977; El-Feraly et al., 1978). The presence of the fragment CO–O–CH_2–COH- was indicated by a methylene group, δ 4.3 (2H, doublet, 9.7 Hz) and a hydroxyl peak, δ 2.6 (1H, broad), which disappeared in the deuterated ^1H NMR experiment. Furthermore the presence of the four methylene group, as indicated by the carbon magnetic resonance coupled with INAPT experiments suggest a methylene group at C-11. The three methine groups as indicated in the ^{13}C NMR Table 2, left C-9 as the only feasible position for the OH. Location of the OH group at C-9 is also based on the unusual low field chemical shift of H-11 (δ 4.3).

INAPT (Bax, Ferretti, Nashed, & Jerina, 1985) experiment at 993.6 Hz (which is the resonance frequency of H-7) shows peak enhancement at δ 169 (C-12), δ 129 (C-18), δ 76.9 (C-9), δ 39.9 (C-5) and δ 27.3 (C-6) which suggest a lactone with the carbonyl at C-12 and the oxygen bonded methylene, δ 75.00, at C-11. COSY reveal no correlation to the methylene group at δ 4.3 which further suggested that the two hydrogens were chemically nonequivalent consequently giving a geminal coupling (coupling constant 9.7 Hz).

^1H NMR data of our compound is almost similar to that of muzigadiolide (Kioy, Gray, & Waterman, 1990) however the optical rotations of the two compounds are different. Our compound gave the optical rotation, $[\alpha]_D$ −51°(MeOH, *c* 1.09) and $[\alpha]_D$ −57°($CHCl_3$, *c* 1.09) and muzigadiolide gave an optical rotation of $[\alpha]_D$ +380°; *c* 0.6) (Kioy et al., 1990). NOE experiments on H-15 protons gave positive enhancement on H-11 protons consequently the axial orientation of the OH group at C-9. Detailed NMR data comparison of salutarisolide, canellal (Kubo et al., 1977; El-Feraly et al., 1978) and 9-deoxymuzigadial (**7**) (Al-Said, El-Khawaja, El-Feraly, & Hufford, 1990) are compared in Tables 1 and 2.

3. Experimental

NMR spectra were recorded on a Varian Gemini 200 in $CDCl_3$, using TMS as internal standard (unless otherwise specified). TLC was performed on silica gel plates using petroleum (hexane) and ethyl acetate in different ratios. TLC plates were visualized under UV light or by using anisaldehyde reagent. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. The plant was collected in the Zoutpansberg mountains near Louis Trichardt, South Africa.

Table 1
^1H NMR of salutarisolide, canellal (muzigadial) and 9-deoxymuzigadial

H	Salutarisolide canellal		9-Deoxy muzigadial
1	2.3 (1H, m)		1.62 m
	1.3 (1H, m)		1.9 m
2	1.7 (1H, m)		1.71 m
	1.3 (1H, m)		1.15 m
3	2.1 (1H, m)		2.0 m
5	2.6 (1H, br)	2.5 (1H, ddd, $J = 9$, 7 and 0.5 Hz)	2.1 m
6	2.3 (2H, m)	6.1 (1H, dd, $J = 4$ and 3 Hz)	2.4 m
7	7.0 (1H, t, $J = 3.69$)		7.1 m
9			3.0 m
11	4.3 (2H, d, $J = 9.7$ Hz)	9.6 (1H, d, $J = 0.5$ Hz)	9.5 (1H, d, $J = 4.2$ Hz)
12		9.4 (1H, s)	9.4 (1H, s)
13	4.9 (1H, s) 4.4 (1H, s)	4.7 (dd, 0.5 Hz) and 4.4 (dd, 0.5 Hz)	4.9 (dd, 1.5 Hz) and 4.7 (dd, 1.5 Hz)
14	1.1 (3H, d, $J = 7.2$ Hz)	0.9 (3H, d, 6 Hz)	1.0 (3H, d, 6.3 Hz)
15	0.62 (3H, s)	0.7 (3H, s)	0.7 (3H, s)
OH at C-9	2.6 (1H, s)	4.08 (1H, d, $J = 0.5$ Hz)	

Table 2
^{13}C NMR of salutarisolide, canellal (muzigadial) and 9-deoxymuzigadial

C	Salutarisolide	Canellal	9-Deoxy muzigadial
1	32.4	31.7	39.4
2	31.7	30.8	31.6
3	38.5	38.1	38.5
4	152.2	151.8	151.3
5	39.9	40.1	45.8
6	27.3	27.7	27.0
7	139.8	139.6	152.9
8	129.9		137.9
9	76.9	77.4	58.3
10	40.6	42.2	38.2
11	75.0	201.3	201.1
12	169.6	192.7	193.3
13	105.7	106.0	106.0
14	15.9	15.1	18.4
15	18.5	18.1	13.5

3.1. Isolation of polygodial (**2**)

Dried powdered roots (1779.3 g) of *W. salutaris* was extracted with dichloromethane (ca. 7 l) for eight days at room temperature. Removal of the solvent under vacuum yielded 70 g of yellow material. Thirty-five grams was adsorbed onto silica gel and subjected to chromatographic separations using hexane–ethyl acetate solvent mixtures. Elution with hexane–ethyl acetate (98:2–95:5) yielded 500 mg of yellow mixture consisting of two compounds. Further separation using the chromatotron afforded 0.018 g of polygodial (**2**), $[\alpha]_D$ −73°, (*c* 0.176, CHCl$_3$), ^{1}H NMR (CDCl$_3$) δ: 9.55 (1H, d, H-11), 9.45 (1H, s, H-12), 7.15 (1H, m, H-7), 2.85 (1H, s, H-9), 1.0, 0.9 and 0.8 (each 3H, 3 Me) ^{13}C NMR: δ: 202 (d, C-11), 194 (d, C-12), 152.2 (d, C-7) 138.0 (s, C-8), 60.0 (d, C-9), 49.0 (d, C-5), 42.0 (t, C-3, 39.8 (t, C-1), 37.0 (s, C-10), 33.0 (s, C-4, 33.0 (q, C-13), 25.3 (t, C-6), 22.0 (q, C-14), 18.0 (t, C-2), 15.0 (q, C-15), MS: m/z: 219, 206, 163, 145, 121, 91, 77, 41.

3.2. Isolation of isopolygodial (**5**)

Isopolygodial (**5**) was isolated using the chromatotron from the 500 mg yellow mixture. 0.034 g of pure isopolygodial were collected, $[\alpha]_D$ −192° (*c* 0.166, CHCl$_3$), ^{1}H NMR (CDCl$_3$) δ: 9.85 (1H, d, H-11), 9.40 (1H, s, H-12), 7.10 (1H, m, H-7), 3.25 (1H, s, H-9), 0.98, 0.90 and 0.89 (each 3H, 3 Me). ^{13}C NMR: δ: 202 (d, C-11), 193 (d, C-12), 153.6 (d, C-7) 137.5 (s, C-8), 58.10 (d, C-9), 44.2 (d, C-5), 42.0 (t, C-3), 37.5 (t, C-10), 37.0 (s, C-1), 33.0 (s, C-4), 32.8 (q, C-13), 25.2 (t, C-6), 22.0 (q, C-14), 18.0 (t, C-2), 15.0 (q, C 15), MS: m/z: 234, 206, 163, 145, 121, 91, 77, 41.

3.3. Isolation of warburganal (**1**)

Elution with hexane–ethyl acetate (95:5) gave 0.72 g of pure compound which was further purified by crystalization to give pale yellow needles of warburganal (**1**) from hexane–ethyl acetate, ^{1}H NMR (CDCl$_3$) δ: 9.71 (1H, d, H-11), 9.39 (1H, s, H-12), 7.23 (1H, dd, H-7), 4.08 (s, OH), 2.59 (1H, dd, H-5), 1.08, 0.92 and 0.83 (each 3H, 3 Me). ^{13}C NMR: δ: 203.0 (d, C-11), 193.4 (d, C-12), 158.3 (d, C-7), 140.99 (s, C-8), 78.34 (d, C-9), 42.2 (d, C-5), 42.0 (t, C-10), 41.8 (t, C-3), 33.5 (s, C-4), 33.5 (q, C-13), 31.7 (s, C-1), 26.5 (t, C-6), 22.6 (q, C-14), 18.3 (t, C-2), 17.6 (q, C-15).

3.4. Isolation of salutarisolide (**3**)

Elution with petroleum–ethyl acetate (95:5–9:1) yielded 1.5 g of salutarisolide (**3**) which was isolated as an amorphous material, m.p. 139–140°, $[\alpha]_D$ −57°(CHCl$_3$, *c* 1.09), (found C, 72.02; H, 8.16 Calculated for $C_{15}H_{20}O_3$ C, 72.55; H, 8.11. ν_{max} 3433, 1758, 1725, 1683, 1637 and 759 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ: 2.3 (1H, m, H-1)); 1.3 (1H, m, H-1), 1.7 (1H, m, H-2); 1.3 (1H, m, H-2); 2.1 (1H, m, H-3); 2.6 (1H, br, H-5); 2.3 (2H, m, H-6); 7.0 (1H, t, $J=3.69$, H-7); 4.3 (2H, d, $J=9.7$ Hz, H-11); 4.9 (1H, s, H-13); 4.4 (IH, s, H-13); 1.1 (3H, d, $J=7.2$ Hz, H-14); 0.62 (3H, s, H-15); 2.6 (1H, s, OH). ^{13}C NMR: δ: 32.4 (t, C-1); 31.7 (t, C 2); 38.5 (d, C-3); 152.2 (s, C-4); 39.9 (d, C-5); 27.3 (t, C-6); 139.8 (d, C-7); 129.9 (s, C-8); 76.9 (s, C-9); 40.6 (s, C-10); 75.0 (t, C-11); 169.6 (s, C-12); 105.7 (t, C-13); 15.9 (q, C-14); 18.5 (q, C-15).

3.5. Isolation of mukaadial (**4**)

Further elution with 9:1 petroleum:ethyl acetate afforded mukaadial (**4**), 0.05 g, δ amorphous material, mp 193–198°, $[\alpha]_D$ −29.6° (*c* 0.132, DMSO), ^{1}H NMR (DMSO) δ: 9.59 (1H, d, H-11), 9.38 (1H, s, H-12), 6.99 (1H, d, H-7), 5.37 (1H, s, OH at C-6), 5.18 (1H, d, H-6), 4.34 (1H, s, OH at C-9), 1.08, 1.01 and 0.94 (each 3H, 3 Me). ^{13}C NMR (DMSO): δ: 2043 (d, C-11), 194.3 (d, C-12), 159.7 (d, C-7), 139.4 (s, C-8), 77.9 (s, C-9), 67.5 (d, C-6), 47.9 (d, C-5), 43.6 (s, C-10), 43.4 (t, C-1), 36.7 (s, C-15), 33.3 (t, C-2), 33.3 (s, C-4), 22.9 (q, C-14), 18.1 (t, C-3), 18.4 (q, C-13), MS: m/z: 248, 237, 219, 177, 149, 121, 109, 69.

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References

Al-Said, M. S., El-Khawaja, S. M., El-Feraly, F. S., & Hufford, C. D. (1990). *Phytochemistry*, *29* (3), 975.

Arnold, H. J., & Guluman, M. (1984). *Journal of Ethnopharmacology*, *12*, 35.

Bax, A., Ferretti, J. A., Nashed, N., & Jerina, D. M. (1985). *Journal of Organic Chemistry*, *50* (17), 3030.

Coates-Palgrave, K. (1977). In *Trees of southern Africa* (p. 618). Johannesburg: C. Struik.

Corbett, R. E., & Chee, T. L. (1976). *Journal of the Chemical Society, Perkin Trans*, *1*, 850.

El-Feraly, F. S., McPhail, A. T., & Onan, K. D. (1978). *Journal of the Chemical Society, Chem. Comm.*, 75.

Jansen, J. M., & de Groot, A. (1991). *Natural Products Reports*, 309.

Kioy, D., Gray, A. I., & Waterman, P. G. (1990). *Phytochemistry*, *29* (11), 3535.

Kubo, I., Lee, Y.-W., Pettei, M., Pilkiewicz, F., & Nakanishi, K. (1976). *Journal of the Chemical Society, Chem. Comm.*, 1013.

Kubo, I., Miura, I., Lee, Y.-W., Pettei, M., Pilkiewicz, F., & Nakanishi, K. (1977). *Tetrahedron Letters*, 4553.

Kubo, I., Matsomoto, T., Kakooko, A. B. &, Mubiru, N. K. (1983). *Chemistry Letters*, 979.

Mashimbye, M. J. (1993). Ph.D. thesis, University of Natal, South Africa.

Mashimbye, M. J., Drewes, S. E., Appleton, C. C., & Cunningham, A. B. (1992). *Journal of Medical and Applied Malacology*, *4*, 37.