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ENT-KAURENOID METHYL ESTERS FROM *Viguiera stenoloba*, STRUCTURAL REVISION OF STENOLOBIN AND ITS BIOMIMETIC CONVERSION TO ZOAPATLIN

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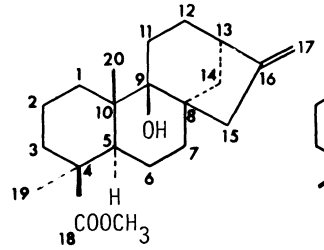
The structure of stenolobin, a diterpene from *Viguiera stenoloba*, was revised to 5. The new diterpene, 15α-angeloyloxy stenolobin, was also isolated from the same plant source. The biomimetic transformation of stenolobin (5) to zoapatlin is described.

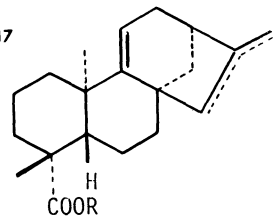
Several years ago, we proposed the structure of stenolobin by chemical and spectral methods and by comparison with a limited number of compounds as a phyllocladenoid diterpene (1)[1] (trans, syn, cis, stereochemical sequence of the A, B, and C rings). However, in recent years, the many other diterpenes isolated from the same[2] and related genera[3] with a trans, anti, cis stereochemical sequence of ent-kaurene diterpenes suggest that the proposed structure of stenolobin requires revision.

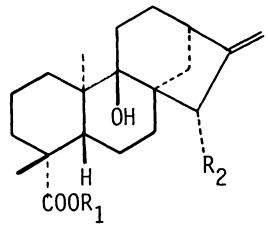
Aerial parts of *Viguiera stenoloba* were extracted and fractionated as previously described.[1] Stenolobin was isolated (0.025% of dry weight) and identified by its physical constants and direct comparison with an authentic sample still extant from the earlier work. Dehydration of stenolobin ($SOCl_2$-C_5H_5N, -20 °C, 90% yield) afforded methyl ent-kaur-9(11)-16-dien-19-oate (2), identical by direct comparison with the methyl ester of the natural product (3) obtained from *V. insignis*.[4] This result indicates that stenolobin belongs to the ent-kaurene series. The ^{13}C NMR data of stenolobin are in accord with the proposed structure.[5] In particular the chemical shift of C-5 (δ 50.2), C-9 (δ 77.3), and C-15 (δ 44.1), compared with the 9-unsubstituted diterpene (C-5: δ 56.9; C-9: δ 55.1; C-15: δ 49.1)[6] confirm the 9β-disposition of the tertiary hydroxyl group, previously proposed by chirooptical

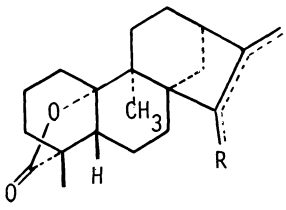
methods.[1] Therefore, the structure of stenolobin should be represented as methyl ent-9α-hydroxy-kaur-16-en-19-oate (5).

A minor constituent of this species was identified by their spectroscopic characteristics as 15α-angeloyloxy-stenolobin (6, 0.011% of dry weight), now isolated as natural product.[7] The ^{13}C NMR of this new diterpene agree with the proposed structure.[5] Furthermore, this substance was chemically correlated with stenolobin 5 via the 15α-hydroxy-derivative 7,[8] obtained by hydrolysis of 6 (KOH-MeOH, reflux, 95% yield) and by allylic oxidation (SeO_2-THF, room temp , 80% yield) of stenolobin 5, thus confirming its structure.









1

2 R=CH_3,Δ^{16}
3 R=H,Δ^{16}
4 R=H,Δ^{15}

5 R_1=CH_3, R_2= H
6 R_1=CH_3, R_2=OAng
7 R_1=CH_3, R_2=OH
8 R_1=H, R_2=H

9 R=H_2,Δ^{16}
10 R=O,Δ^{16}
11 R=H,Δ^{15}

Stenolobin (5), an ent-9α-hydroxy kaurenoid (or its biosynthetic equivalent) may be the biogenetic precursor of zoapatlin (9),[9] 15-oxo-zoapatlin (10),[10] and similar diterpenoid lactones, as previously proposed.[11] Indeed, the recent biomimetic attempt to obtain a derivative of zoapatlin from an ent-kaurenoid epoxide was not successful,[12] but similar C-10 → C-9 methyl migrations,[13] followed by γ-lactonization of the -COOH group are described in the literature.[14] In this manner, stenolobin (5) was demethylated via O-alkyl cleavage[15] (n-PrSH, HMPA, Li, 100% yield) and the acid 8[16] was reacted (CH_3NO_2, -5 °C, 30 min) with BF_3OEt_2 (2.0 eq),[17] producing a biomimetic transformation to furnish a mixture of products (90% yield) from which zoapatlin (9),[9,18] iso-zoapatlin (11),[19] ent-kaur-9(11)-16-dien-19-oic acid (3)[9,18] and ent-kaur-9(11)-15-dien-19-oic acid (4)[18,20] were obtained in 24, 15, 12, and 11% yields, respectively.

The cis-relationship of the C-10 methyl group and the -COOH group in demethyl-stenolobin (8) indicates that the cyclization to form zoapatlin (9) and iso-

zoapatlin (11) is carried out in a non-concerted process. However, this transformation strongly suggests that the biogenesis of such diterpenoid lactones may proceed from ent-9α-hydroxy-kaurenoid diterpenes.

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References

1) L. A. Cuevas, F. García Jiménez, and A. Romo de Vivar, Rev. Latinoamer. Quím., 3, 22 (1972).

2) F. Bohlmann, Ch. Zdero, and P. Mahanta, Phytochemistry, 16, 1073 (1977); F. Bohlmann, J. Jakupovic, M. Ahmed, M. Grenz, H. Suding, H. Robinson, and R. M. King, ibid., 20, 113 (1981); G. Delgado, A. Romo de Vivar, J. Cárdenas, R. Pereda-Miranda, and E. Huerta, ibid., 23, (1984) in the press.

3) The closely related genus *Helianthus* also contains ent-kaurenoids: N. Ohno and T. J. Mabry, Phytochemistry, 19, 609 (1980); F. Bohlmann, J. Jakupovic, R. M. King, and H. Robinson, ibid., 19, 863 (1980); W. Herz, S. V. Govindan and K. Watanabe, ibid., 22, 2021 (1983).

4) G. Delgado, A. Romo de Vivar, A. Ortega, J. Cárdenas, and E. O. Schlemper, Phytochemistry, 22, 1227 (1983).

5) ^{13}C NMR of 5 : δ 37.9 (C-1), 19.2 (C-2), 34.4 (C-3), 44.1 (C-4), 50.2 (C-5), 21.9 (C-6), 40.6 (C-7), 49.4 (C-8), 77.3 (C-9), 44.0 (C-10), 29.7 (C-11), 32.4 (C-12), 42.4 (C-13), 36.6 (C-14), 44.1 (C-15), 155.2 (C-16), 103.1 (C-17), 17.4 (C-18), 178.1 (C-19), 28.9 (C-20), 51.0 (O-CH_3).

^{13}C NMR of 6 : δ 38.0 (C-1), 19.1 (C-2), 32.3 (C-3), 44.5 (C-4), 49.9 (C-5), 21.2 (C-6), 37.8 (C-7), 53.0 (C-8), 76.8 (C-9), 44.1 (C-10), 29.4 (C-11), 30.2 (C-12), 41.4 (C-13), 33.9 (C-14), 78.9 (C-15), 155.41 (C-16), 110.0 (C-17), 17.3 (C-18), 178.0 (C-19), 28.8 (C-20), 51.0 (O-CH_3), 167.9 (C-1'), 128.5 (C-2'), 137.0 (C-3'), 15.7 (C-4'), 20.6 (C-5').

All the ^{13}C NMR spectra were taken at 20 MHz for $CDCl_3$ solutions, and the assignments are based on the related compounds: I. Kubo, I. Miura, K. Nakanishi, T. Kamikawa, T. Isobe, and T. Kubota, J. Chem. Soc. Chem. Commun., 1977, 555. J. R. Hanson, M. Siverns, F. Piozzi, and G. Savona, J. Chem. Soc., Perkin Trans. 1, 1976, 114.

6) K. Yamasaki, H. Kohda, T. Kobayashi, R. Kasai, and O. Tanaka, Tetrahedron Lett., 1976, 1005.

7) The free acid has been previously reported as a natural product, but was characterized as its methyl ester (6): F. Bohlmann and N. Le Van, Phytochemistry, 16, 579 (1977); W. Herz, P. Kulanthaivel, and K. Watanabe, ibid., 22, 2021 (1983).

8) Methyl ent-9α,15β-dihydroxy-kaur-16-en-19-oate (7), colorless crystals mp : 177-180 °C, IR ($CHCl_3$): 3600, 3000, 2950, 2870, 1720, 1470, 1450, 1380, 1153, 998 cm^{-1}; EM, m/z (rel.intensity): 348 (M^+, 7), 330 (18), 312 (6), 271 (14), 270 (16), 230 (18), 201 (14), 148 (85), 123 (55), 91 (60), 79 (61), 55 (100), 42 (80); ^1H NMR ($CDCl_3$, 80 MHz): δ 5.20 (1H, br s, H-17), 5.08 (1H, br s, H-17'), 4.55 (1H, br s, H-15), 3.64 (3H, s, $-OCH_3$), 2.74(1H, m, H-13), 1.20 (3H, s, $18CH_3$), 0.99 (3H, s, $20CH_3$). In spite of the differences in physical states, these constants are similar to values reported in the literature: F. Bohlmann, J. Jakupovic, A. Schuster, R. M. King, and H. Robinson, Phytochemistry, 21, 2317 (1982).

9) Y. Caballero and F. Walls, Bol. Inst. Quím. Univ. Nac. Autón. Méx., 22, 79 (1970).

10) 15-oxo-zoapatlin (10) has recently been isolated from *Viguiera maculata*: G. Delgado, L. Alvarez, and A. Romo de Vivar, Phytochemistry, 23, (1984) in the press.

11) W. Herz, S. V. Govindan, and J. F. Blount, J. Org. Chem., 44, 2999 (1979).

12) T. Nakano, A. C. Spinelli, A. Martin, A. Usubillaga, A. T. Mc Phail, and K. D. Onan, Tetrahedron Lett., 1982, 3627.

13) N. J. Lewis and J. Mac Millan, J. Chem. Soc., Perkin Trans. 1, 1980, 1279.

14) W. Herz and H. J. Wahlborg, J. Org. Chem., 30, 1881 (1965); W. S. Hancok, L. N. Mander, and R. A. Massy-Westropp, ibid., 38, 4091 (1973); R. C. Cambie and W. A. Denny, Aust. J. Chem., 28, 1153 (1975); W. S. Hancok, L. N. Mander, and R. A. Massy-Westropp, ibid., 30, 1093 (1977).

15) P. A. Bartlett and W. S. Johnson, Tetrahedron Lett., 1970, 4459.

16) ent-9α-hydroxy-kaur-16-en-19-oic acid (8), colorless crystals mp : 109-110 °C, IR ($CHCl_3$) : 3620, 3510, 3300, 2500, 1735, 1700, 1660, 1470, 1450, 1380, 1365, 1265, 1120, 1030, 999, 970 cm^{-1}; EM, m/z (rel. intensity): 318 (M^+, 11), 301 (19), 300 (74), 285 (45), 257 (30), 240 (28), 211 (25), 159 (20), 147 (39), 121 (50), 118 (70), 109 (61), 105 (63), 93 (55), 91 (100), 79 (55), 43 (41), 41 (44).

^1H NMR ($CDCl_3$, 80 MHz): δ 4.77 (2H, br s, H-17, H-17'), 2.85 (1H, m, H-13), 2.65 (2H, br s, H-15, H-15'), 1.26 (3H, s, 18 CH_3), 1.10 (3H, s, 20 CH_3).

17) Reduced yields and minor relation lactonic/acidic products were obtained in ether and benzene.

18) All the products were characterized by spectral methods and identified by direct comparison with authentic samples.

19) Iso-zoapatlin (11), colorless crystals mp : 181-183 °C; IR ($CHCl_3$): 3040, 2990, 2935, 2860, 1755, 1444, 1380, 1350, 1276, 1185, 1152, 1141, 933 cm^{-1}; EM, m/z (rel. intensity): 300 (M^+, 99), 285 (22), 257 (41), 244 (28), 185 (17), 199 (19), 147 (25), 133 (36), 132 (32), 120 (58), 119 (93), 106 (86), 105 (63), 93 (55), 91 (100), 79 (48), 77 (47), 41 (38).

^1H NMR ($CDCl_3$, 80 MHz): δ 5.30 (1H, br s, H-15), 2.5 (1H, m, H-13), 1.55 (3H, br s, 17 CH_3), 1.18 (3H, s, 17 CH_3), 1.18 (3H, s, 18 CH_3), 1.07 (3H, s, 20 CH_3).

20) R. Neidlein and U. Stumpf, Arzneim-Forsch., 27, 999 (1977).

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