Highly oxygenated guaianolides from some compositae plants

Vivek Krishna, Pradeep K. Gupta, Sonakshi Jain and Pahup Singh*

Department of Chemistry, University of Rajasthan, Jaipur-302 004, India

Manuscript received 21 September 2001.

The isolation of twenty new highly oxygenated guaianolides along with several known guaianolides from Vernonia arkansana (aerial parts and roots), Pseudostiffia kingii (aerial parts), Dicoma anomala (roots), Hypochoris cretensis, Saussurea salicifolia, S. involucrata, S. candidans, Bishopanthus soliceps and Blainvillea latifolia (aerial parts) have been reviewed.

The sesquiterpene lactones are characteristic secondary metabolites of Compositae and their biological activities also make them of interest to pharmacologists. These lactones are formed by intramolecular cyclization of α- or ω-hydroxy acids and broadly termed as cyclic esters. The suffix ‘olide’ in their names refers to the lactone moiety in the molecule. The α,β-unsaturated-γ-lactones are cis- or trans-fused to the C6-C7 or C8-C7 positions of the carbocyclic skeleton. The structural variation of the basic sesquiterpene skeleton involves the incorporation of an epoxy ring, hydroxy groups, ester moieties and reduction or oxidation of certain groups or even opening of the rings. Acids generally involved in esterification are 4 and/or 5 carbon acids, viz. methacrylic, angelic, tiglic, senecioic, methylbutyric acids or their hydroxy and/or acetoxy derivatives. Guaianolides are derived from guaiane skeleton. In this short review, we present the results of structure elucidation of two guaianolides from Vernonia arkansana, the senecioate and the hydroxysenecioate guaianolides from Pseudostiffia kingii, a 9α-hydroxyguaianolide from Dicoma anomala sub sp. cirsiodioides, a guiaun-5,12-olide along with its precursor from Hypochoris cretensis, four 11α-13-dihydro derivatives from Saussurea salicifolia, an 8α-propionyl-oxydehydrocostus lactone from S. involucrata, three chlorojanerin derivatives from S. candidans, five highly oxygenated guaianolides from Bishopanthus soliceps and a pumilin derivative from Blainvillea latifolia.

Vernonia arkansana DC. has been investigated earlier. The re-investigation of roots afforded the known guaianolides 1-6, along with a new one 7. The structure of 7 was clearly arrived from the 1H NMR spectral data which were similar to that of dehydrosaluzalin C. The stereochemistry of C-8 was deduced from couplings observed for H-8 and from the typical downfield shift of H-13 proton. Its molecular formula C19H16O4 was established from high resolution mass spectrometry and identified as 8α-hydroxydehydroaluzalin C. The aerial parts on chemical examination gave marginatin, three bourbonenolides and a new methoxyguaianolide 8. Its 1H NMR data agree with its structure. From the signals of H-13, the presence of a methylene lactone was confirmed. However, the absence of signals for H-6, H-7 indicated a 6,7-double bond, its presence being supported by a downfield shifted doublet at δ 2.86, which was coupled with a broadenened doublet at δ 2.26. These signals probably were those of H-1 and H-5. A methoxy group was present at C-10 and an acetoxy group at C-8 position. The stereochemistry at C-4 and C-10 was assigned by analogy to that of bourbonenolides and characterized as 8α-acetoxy-4β-hydroxy-10α-methoxyguaian-6,7,11(13)-diene-6,12-olide. Probably lactone could be formed by fragmentation of bourbonenolide 9 by attack of methanol at C-10 as shown in Scheme 1. The bourbonenolide 9 has simultaneously been isolated from this plant.
Pseudostiffia is a monotypic genus and belongs to the subtribe Pseudostifftinae. Earlier work on Pseudostiffia kingii H. Robins led to the isolation of acetylenes and triterpenes. The re-investigation of its aerial parts reported the isolation of known guaianolides, viz. desacylcynaropicrin, arguerin, cynaropicrin, 8a-hydroxydehydrozaluzanin C, the corresponding 11,8,13-dihyderivative, as well as two further lactones, the senecioate and the hydroxysenecioate.

The structure of 13 was established from 1H NMR data. Its NMR clearly showed the presence of a zaluzanin C derivative, as most signals were similar to those of zaluzanin C. However, an additional seneciroyloxy residue was present. Spin decoupling showed that this group had to be placed at C-8 while from the coupling constants the a-orientation could be established. Acetylation afforded the acetate 14 and 13 was identified as 8a-seneciroyloxydehydrozaluzanin C. The 1H NMR spectral data of 15 indicated that a hydroxylated ester group was present. Since the signal of the olefinic methyl group was at δ 2.15, the stereochemistry was also clear. All other signals were similar to those of 13. Acetylation gave the diacetate 16 and its 1H NMR spectrum further established the structure. 15 was named as 8a-(4'-hydroxysenecioyloxy)dehydrozaluzanin C.

So far the results of chemical investigation of Dicoma species indicated the presence of characteristic oxygenated germacranolides. A re-investigation of the roots of Dicoma anomala Sond. subsp. cirsiiodes (Harv.) Willd. afforded in addition to stigmasterol, sitosterol, lupenone, eudesmanolides, a known guaianolide (dehydrozaluzanin C) 5 and a new guaianolide 17.

The 1H NMR spectrum of 17 was very similar to 5. The presence of a 9a-hydroxy group was deduced from the downfield shifts of H-14 (5.09 s, 4.67 d) and H-9 (4.63 ddd) and the value of coupling J_8,9. This was confirmed by spin decoupling which allowed the assignment of all signals. The corresponding 9-O-angelate was isolated from Zinnia species and as expected the couplings were nearly the same. It was characterized as 9a-hydroxy-dehydrozaluzanin C.

Earlier work on the genus Hypochoeris has shown that guaianolides related to lactucin may be characteristic for this genus. The chemical examination of the aerial parts of Hypochoeris cretensis Benth. showed the presence of taraxasterol, lupeol and its acetate, phytol, isoalantolactone and a new guaian-5,12-olide and the corresponding precursor.

The structure of 18, which on addition of diazomethane afforded the pyrazoline, was derived from the molecular formula and the high field 1H NMR spectrum.

The presence of a methylene lactone followed from the typical pair of downfield signals at δ 6.62 and 5.71. The IR band at 1740 cm⁻¹ indicated a δ-lactone. The chemical shifts of two olefinic methyls and a quartet at δ 6.18 showed that most likely a guaianolide with a keto group at C-2 and a 1(10) as well as a 3,4-double bonds were present. The absence of a H-5 signal and the results of spin decoupling clearly showed that a 5,12-guaianolide was present, which
required an equatorial orientation of H-7. Accordingly, this signal was narrowly split only as all couplings were small. Inspection of a model further showed that the angles H-7-H-13 supported the observed small couplings of H-13. The stereochemistry of the pyrazoline derivative 20 was deduced from the observed downfield shift of H-6β. The 1H NMR spectral data of 19 showed that a methyl ester was present. The conformation was clearly different from that of 18 since H-7 was now axial as followed from the couplings observed. Spin decoupling allowed the assignment of all signals. Guaian-5,12-olide 18 was named as hypocretenolide and its precursor 19 as methyl hypocretenoate.

The large genus \textit{Saussurea} (Compositae, tribe-cynareae) with more than 300 species\textsuperscript{23} has been investigated chemically for acetylenes\textsuperscript{24} as well as for sesquiterpene lactones. So far lactones are reported from nine species\textsuperscript{25-32}. Guaianolides related to cynaropicrin 12 are characteristic of this genus. Some other types of lactones were also reported from \textit{S. lappa}\textsuperscript{26}. Three species, namely, \textit{S. salicifolia}, \textit{S. involucrata} and \textit{S. candidans} have been examined. The aerial parts of \textit{S. salicifolia} (L.) DC. gave arctigenin, matairesinol, trachelogenin, cynaropicrin 12, 19-desoxyjanerin 21, janerin 22, desacyl-janerin-\textit{O}-hydroxytiglate 23, desacylexomethylene 24 and 11α,13-dihydro derivatives 25-28.

The polarity of lactones 25-28 was very similar, hence their separation was difficult. These could only be separated by TLC and HPLC.

The structures of 25 and 27 were followed from the 1H NMR spectra which indicated that these compounds only differed in the nature of the ester groups. The typical exomethylene signals in the spectrum of cynaropicrin were replaced by a methyl doublet at \(\delta 1.13\) and a doublet quartet at \(\delta 2.77\). Accordingly, these lactones were 11,13-dihydro derivatives of cynaropicrin and of the corresponding 4-hydroxytiglate. The configuration at C-11 was followed from the coupling \(J_{7,11}\) (7 Hz), while a very similar compound with a 11α-methyl showed as usual a large coupling\textsuperscript{25}. The 1H NMR spectral data of 26 and 28 were similar to that of janerin, the 4β,15-epoxide of cynaropicrin\textsuperscript{33} and with that of the corresponding 4-hydroxytiglate\textsuperscript{34}, respectively. However, again the signals of the exomethylene group (H-13) were replaced by a methyl doublet at \(\delta 1.14\) and a doublet quartet at 2.74. Subsequently, these lactones were 11,13-dihydro derivatives of the previously isolated methylene lactones. Again the coupling \(J_{7,11}\) exhibited the presence of 11β-methyl groups. The lactones 26 and 28 were identified as 11α,13-dihydrojanerin and 11α,13-dihydrodesacylexomethylene 4-hydroxytiglate, respectively.
Saussurea involucrata (Kar. et kir.) Sch. Bip. is used in the folk medicine by Mongolians and it is said to have activities similar to Ginseng. On examination it afforded costic acid, dehydrocostus lactone 2, its 11β,13-dihydro derivative 29, 8α-hydroxydehydrocostus lactone 30, its acetate 31 and the corresponding propionate 32 as new guaianolide.

The structure of propionate 32 could be easily deduced from the 1H NMR spectrum which was very close to that of the corresponding acetate 31. The acetate signal of the latter was replaced by a triplet and a quartet at δ 1.17 and 2.41, respectively, and named as 8α-propionyloxydehydrocostus lactone.

Previous work on *Saussurea cundicans* C.B. Clarke led to the isolation of acetylenes. The aerial part of this plant on re-investigation gave arctigenin and matairesinol, cynaropicrin 12, desacylcynaropicrin 10, aguerin-B 11, janerin 22, 19-desoxychlorojanerin 33, chlorojanerin 34, centaurepensin 35, repdiolide triol 36 in addition to tetrol 37, its 15-methoxy 38 and 15-acetoxy 39 derivatives.

The polarity of lactones 37-39 was very high and therefore their separation could be achieved by repeated preparative TLC and HPLC. The structure of 37 was established from 1H NMR spectral data which revealed that this compound differed from repdiolide triol 36 in the nature of the ester moiety at C-8 position. Methyl acrylate signals were replaced by its 3-hydroxy derivative and subsequently methyl signal was replaced by a broad singlet at δ 4.39 inte-
grated for two protons. The chemical shifts of the other protons remained unaltered. A similar compound with a 4-hydroxytiglate ester function at C-8 was reported from Centaurea imperialis. On acetylation it gave two tetracetates 40 and 41.

\[\text{Chemical shifts of the rest of protons of both the lactones remain unchanged. The lactones 37-39 were named as 1-1,1-14, 1-1,1-15, 1-1,1-19.} \]

\[\begin{align*}
\text{In the former case all the four hydroxyl groups acetylated and consequently H-3, H-15, H-19 were shifted downfield.} \\
\text{In the latter case (41), 3-hydroxymethacrylate ester group hydrolyzed prior to acetylation and signals of methacrylate ester function (\(\delta 6.33\) s, 5.97 q, 4.39 s br) replaced by an acetate singlet at \(\delta 2.19\). The } ^1\text{H NMR spectral data of 38 and 39 were very similar to that of repdiodiolide triol 36 with additional peaks for a methoxy (\(\delta 3.45\)) and an acetoxy (\(\delta 2.18\)) functions, respectively. The H-15, H-15' doublets were shifted slightly upfield at \(\delta 3.98\) and 3.67 in former and shifted downfield at \(\delta 5.03\) and 4.22 in the latter case. Chemical shifts of the rest of protons of both the lactones remain unchanged. The lactones 37-39 were named as 15-deschloro-15-hydroxychloroanerin, 15-deschloro-15-methoxychloroanerin and 15-deschloro-15-acetoxychloroanerin, respectively.}
\end{align*}\]

\[\text{Bishopanthus soliceps is a member of a new monotypic genus of the tribe Liliaceae of family Compositae. No work has been reported on this species.} \]

\[\begin{align*}
\text{The } ^1\text{H NMR spectral data showed 42 and 43 were hydroperoxides (s br 8.38, 8.47 respectively). A pair of doublets at 6.22 and 6.34 in the spectrum of 42 with a 6 Hz coupling clearly revealed that a guaianolide with a 2,3-}
\end{align*}\]

\[\text{double bond was present. Most signals were close to those of one of the epimeric endoperoxides isolated from Tanacetum species. However, these compounds had no 8-O-acetate group. When the shifts of H-5 and H-6 were compared with those of epimeric tanaparthin peroxides it was obvious that 42 was the } 1\alpha,4\alpha-\text{isomer. Noe difference spectroscopy gave clear effects between H-14 and H-2 and H-9\alpha, between H-5 and H-7, between H-6 and H-8 and between H-15, and H-3 and H-5, which established the proposed configurations. Models indicated however that the orientation of H-15 cannot be assigned from these results. As the configuration of the isomeric endoperoxides from the Tanacetum species was established, the configuration at C-4 in 42 was clear. The spectrum of 43 was in part similar to that of 42. However, the olefinic signals were replaced by a pair of upfield shifted doublets which were due to epoxide protons. The } ^1\text{H NMR spectrum of 44 and 46 were again in part very similar. Both compounds were transformed by reduction with triphenylphosphine to the lactone 45 which was also present in the extract.} \]
differed from that of 42 by the presence of exomethylene proton signals. As the H-9 signals were shifted downfield, a 10 (14) – double bond was proposed. Compound 44 showed clear noe between H-6 and H-8, between H-15 and H-6 and H-3, between H-14 and H-2 and between H-14' and H-9a. These results required the proposed configuration for 44-46 and the relative position of the hydroperoxide groups followed from the downfield shift of H-5 in the spectrum of 46 if compared with that of 44 and 45. The lactone without an oxygen function at C-1 and C-4 was named bishopsolicepolide and consequently 44-46 were characterized as lα-peroxy-4α-hydroxybishopsolicepolide, lα,4α-dihydroxybishopsolicepolide and lα-hydroxy-4α-peroxy bishopsonicepolide, respectively.

So far two species of Blainvillea (Compositae, tribe-Heliantheae, subtribe-Ecliptinae) have been examined chemically and both gave melampolides and some other sesquiterpene lactones39.40. The aerial parts of Blainvillea latifolia afforded zoapatanolides A and B, subacaulin 47 and a new guaianolide 48.

The structure of 48 could easily be deduced from the 1H NMR spectrum which was close to that of dehydroleucodin41 and in part to that of 4742. The configuration at C-8 and C-9 followed from the observed couplings and the relative position of the ester group from the chemical shifts of H-8 and H-9. From spectral data it was characterized as 5-desoxyxypumilin.

Acknowledgement

The authors thank Dr. J Jakupovic and (Late) Prof. F. Bohlmann, Berlin, Germany, for helpful suggestions and recording high field 1H NMR, high resolution mass and noe spectra. One of the authors (P.K.G.) is grateful to C.S.I.R., New Delhi, for Junior Research Fellowship.

References

1. F. Bohlmann, P. Singh, N. Borthakur and J. Jakupovic, Phytochemistry, 1981, 20, 3379.
2. F. Bohlmann, P. Singh, R. M. King and H. Robinson, Phytochemistry, 1982, 21, 1171.
3. F. Bohlmann, P. Singh and J. Jakupovic, Phytochemistry, 1982, 21, 2029.
4. F. Bohlmann and P. Singh, Phytochemistry, 1982, 21, 2119.
5. F. Bohlmann, P. Singh, J. Jakupovic and S. Huneck, Planta Medica, 1984, 74.
6. P. Singh and M. Bhala, Phytochemistry, 1988, 27, 1203.
7. P. Singh, J. Jakupovic, F. Bohlmann, R. M. King and H. Robinson, Phytochemistry, 1985, 24, 2110.
8. P. Singh, M. Bhala, R. Jain and J. Jakupovic, Phytochemistry, 1988, 27, 609.
9. F. Bohlmann, J. Jakupovic, R. K. Gupta, R. M. King and H. Robinson, Phytochemistry, 1981, 20, 473.
10. Z. H. Abdel-Baset, L. Southwide, W. G. Padolina, H. Yoshoka, T. J. Mabry and S. B. Jones, Phytochemistry, 1971, 10, 2201.
11. N. H. Fischer, E. J. Oliver and H. D. Fisher, Prog. Chem. Org. Natural Prod., 1979, 38, 47.
12. H. Robinson, F. Bohlmann and R. M. King, Phytologie, 1980, 46, 421.
13. F. Bohlmann, C. Zdero, R. M. King and H. Robinson, Phytochemistry, 1980, 19, 2669.
14. A. G. Gonzales, J. Bermejo, G. M. Massanet and J. Perez, An. Quim., 1973, 1333.
15. A. G. Gonzales, J. Bermejo, I. Cabrera, G. M. Massanet, H. Mansilla and A. Galindo, Phytochemistry, 1978, 17, 955.
16. M. Suchy, V. Herout and F. Sorm, Collect. Czech. Chem. Commun., 1959, 24, 1542.
17. F. Bohlmann and N. Le Van, Phytochemistry, 1978, 17, 570.
18. F. Bohlmann, P. Singh and J. Jakupovic, Phytochemistry, 1982, 21, 2122.
19. F. Bohlmann, C. Zdero, R. M. King and H. Robinson, Phytochemistry, 1979, 18, 1343.
20. A. Gonzales, J. Bermejo, G. M. Massanet, J. H. Amaro and B. Dominguez, Phytochemistry, 1976, 15, 991.
21. F. Bohlmann and R. Bohlmann, Phytochemistry, 1980, 19, 2045.
22. F. Bohlmann, J. Jakupovic, W. R. Abraham and C. Zdero, Phytochemistry, 1981, 20, 2371.
23. M. Dittrich, "The Biology and Chemistry of the Compositae," eds. V. N. Heywood, J. B. Harborne and B. L. Turner, Academic, London.
24. F. Bohlmann, T. Burkhardt and C. Zdero, "Naturally Occurring Acetylenes", Academic, London, 1973.
Krishna et al.: Highly oxygenated guaianolides from some compositae plants

25. S. Das, R. N. Baruah, R. P. Sharma, J. N. Baruah, P. Kulanthaivel and W. Herz, Phytochemistry, 1983, 22, 1989.
26. S. V. Govindan and S. C. Bhattacharyya, Indian J. Chem., Sect. B, 1977, 956.
27. P. V. Chugunov, K. S. Rybalko and A. I. Shreter, Khim. Prir. Soedin., 1971, 7, 727.
28. I. Shamyanov, N. D. Abdullaev, G. P. Sidyakin and K. Taizhanov, Khim. Prir. Soedin., 1981, 17, 667.
29. P. S. Kalsi, S. Sharma and G. Kaur, Phytochemistry, 1983, 22, 1993.
30. O. A. Konovalova, K. S. Rybalko and M. G. Pimenov, Khim. Prir. Soedin., 1979, 15, 865.
31. N. V. Agafonova, L. E. Kushmir, A. D. Kuzovkov, A. I. Shreter and M. G. Pimenov, Aptechn. Delo, 1966, 15, 36.
32. S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kalkar and S. C. Bhattacharyya, Tetrahedron, 1965, 21, 3575.
33. A. Rustaiyan, L. Nazarians and F. Bohlmann, Phytochemistry, 1981, 20, 1152.
34. F. Bohlmann, D. Mahamadi and J. Jakupovic, Planta Med., 1984, 50, 192.
35. A. Ortega and E. Maldonado, Phytochemistry, 1984, 23, 1507.
36. A. Rustaiyan, Z. Sharif, A. Tajarodi, J. Ziesche and F. Bohlmann, Planta Med., 1984, 193.
37. H. Robinson, Phytologie, 1983, 54, 62.
38. F. Bohlmann and C. Zdero, Phytochemistry, 1982, 21, 2543.
39. P. Singh, A. K. Sharma, K. C. Joshi, J. Jakupovic and F. Bohlmann, Phytochemistry, 1985, 24, 2023.
40. F. Bohlmann, J. Ziesche, R. M. King and H. Robinson, Phytochemistry, 1981, 20, 263.
41. F. Bohlmann and C. Zdero, Tetrahedron Lett., 1972, 621.
42. W. Herz, S. V. Bhat and A. Srinivasan, J. Org. Chem., 1972, 37, 253.
