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BIOMIMETIC CYCLIZATION OF GALLICIN TO FORM GUAIANOLIDES[1]

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Abstract—A biomimetic-type cyclization of gallicineas carried out to form guaianolides. The possible mechanism is discussed and the stereoselectivity of the reaction explained by a preferred reacting conformation.

The 1,5-germacradienes have been considered the biogenetic precursors of eudesmane and guaiane sesquiterpenes.[2] The cyclization of *trans,trans*-germacradiene to form a guaiane requires an anti-Markovnikoff attack on the double bond system which has only been possible with some 1,5-cyclodecadiene derivatives;[3] on the other hand, 1-E-germacren-4α,5β-oxides are readily cyclized stereoselectivity, yielding, *cis*-guaiane (1α-H, 5α-H) derivatives.[4]

Gallicin (**1**) is a germacranolida isolated from *Artemisia maritima gallica* ssp Willd; its absolute configuration and conformation have been determined in this laboratory.[5,6] Its conversion to eudesmanolides has also been studied proving to be easy and completely stereoselective, giving *trans*-derivatives.[5] The subject of this paper is the biomimetic cyclization of gallicin to form guaiane derivatives.

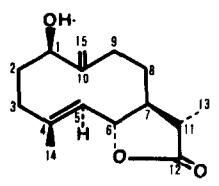
RESULTS AND DISCUSSION

Gallicin (**1**) possesses the perfect functionalization (1β-OH, $\Delta^{4,5}$ double bond) to be converted to guaitinolideas. A leaving group (mesylate or tolylate) must be introduced at C-1 and guaiane derivatives are produced by means of the $\Delta^{4,5}$ double bond attack on C-1.

1, when treated with mesyl chloride in pyridine at 0°, yielded four substances: **2**, **3**, **4** and **5**. Compounds **2** and **4** were obtained in miniscule amounts and structures have been proposed for them based on spectral data. Compounds **3** and **5** were isolated as oils and could not be crystallized. They have previously been reported[7,8] (1α-H, 5α-H), but, as the physical constants could not be compared directly, it was difficult to make a correct assignment for the configuration at C-1 and C-5.

To obtain indisputable proof of the stereochemistry of **3** and **5**, an authentic sample was synthesized according to the process described by Heathcock-Ratcliffe,[9] using vulgarin (**6**) as starting material. The catalytic hydrogenation of **6**, followed by reduction and tosylation under the usual conditions gave **9** which, by solvolysis with NaOAc–HOAc, led to the mixture of **3** and **10** reported earlier.[7]

Compound **3**, thus synthesized, proved identical to the cyclization product and when dehydrated, gave **5**, identical to the other cyclization product (superimposable NMR, IR and MS spectra in both cases).



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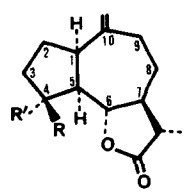
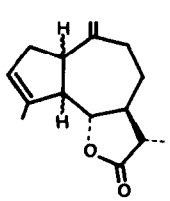


2 R=OH ; R′=CH_3
3 R=CH_3; R′=OH
4 R=CH_3; R′=OMs



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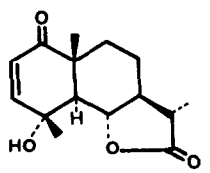

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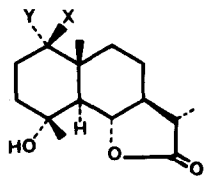
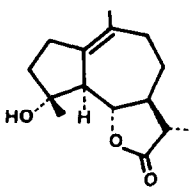


7 X=Y=O
8 X=OH ; Y=H
9 X=OTs ; Y=H



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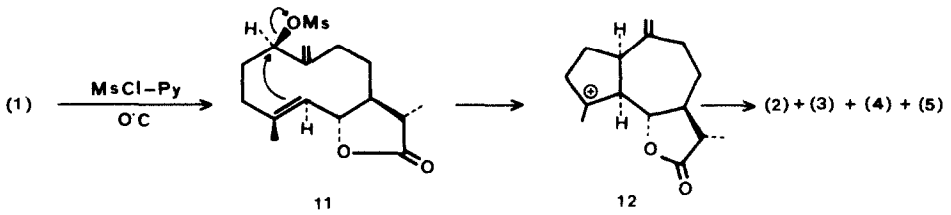
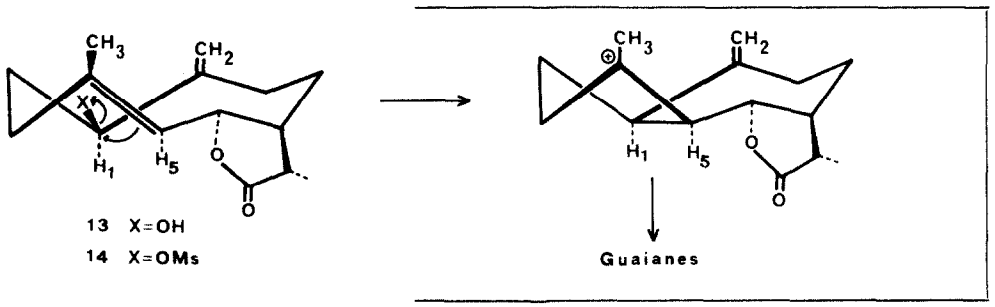
The transformation of gallicin (**1**) to guaiane derivatives lacking an A/B *trans* union is easy to perform with complete stereoselectivity and this fact coupled with the impossibility of isolating the intermediate sulfonic ester (**11**) strongly suggests that the cyclization is carried out in a concerted process with assistance of the $\Delta^{4,5}$ double bond producing the intermediate cation **12** which can develop without difficulty into the cyclization products.

This interpretation of the data is reinforced by the conformational analysis of gallicin[6] which was shown to



exist as a single CC conformer (**13**); assuming **14** to have the same conformation, the mesylate group would remain equatorial and so the $\Delta^{4,5}$ double bond attack on C-1 could be made on the dorsal face.

The stereoselectivity of the reaction may be due to the fact that the process takes place via a concerted mechanism through a preferred reacting conformation as has been suggested to explain *trans,trans*-1,5-germacradiene cyclizations forming eudesmane[10] and guaiane derivatives.[2]



As far as we know, this is the first time that a 1β-hydroxy-E-4(5),10(15)- germacradien-6,12-olide has been cyclized to form a guaianolide and it is interesting that the stereochemistry of the cyclization products is the same as is found in most natural guaianes.[11]

EXPERIMENTAL

M.ps were determined using a Kofler hot-plate apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 257, and NMR spectra were taken on a Perkin–Elmer R-12B in $CDCl_3$ with TMS as internal reference. Elemental analyses were performed by the Departamento de Microanalysis (Centro Nacional Química Orgánica), Madrid. Mass spectra were carried out on a Hewlett–Packard 5930A.

Cyclization of gallicin (**1**)

Compound **1** (340 mg) dissolved in Py (0.8 ml) were treated with MsCl (0.12 ml) at 0° for 24 hr, poured into sat $NaHCO_3$ aq and extracted with $CHCl_3$. The gross product was chromatographed on silica gel and eluted with benzene–EtOAc (7:3), yielding the following, in order of elution:

(a) 1α,5α,6β,7α,11α-H-*guaian*-3,10(15)-*dien*-6,12-*olide* (**5**): oil (104 mg); NMR δ 1.28 (3H, d, 6 Hz), 1.84 (3H, s), 3.99 (1H, dd, 9 and 10 Hz), 4.86 (2H, bs), 5.54 (1H, bs); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1760 (γ-lactone), 1630, 1600 (double bonds); MS, 232 (M$^+$).

(b) 4β-*Hydroxy*-1α,5α,6β,7α,11α-*H-guaian*-10(15)-*en*-6,12-*olide* (**2**): oil (15 mg); NMR δ 1.21 (3H, d, 6 Hz), 1.42 (3H, s), 4.23 (1H, dd, 9 and 10 Hz), 4.94 (2H, bs); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3600 (OH), 1770 (γ-lactone), 1650; MS, 250 (M$^+$), 232 (M$^+$-18).

(c) 4α-*Hydroxy*-1α,5α,6β,7α,11α-H-*guaian*-10(15)-*en*-6,12-*olide* (**3**): oil (50 mg); NMR δ 1.21 (3H, d, 6 Hz), 1.27 (3H, s), 4.06 (1H, dd, 9 and 10 Hz), 4.95 (2H, bs); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3600 (OH), 1770 (γ-lactone), 1650; MS, 250 (M), 232 (M$^+$-18).

(d) 4α-*Hydroxy*-1α,5α,6β,7α,11α-H-*guaian*-10(15)-*en*-6,12-*olide mesylate* (**4**): oil (15 mg); NMR δ 1.21 (3H, d, 6 Hz), 1.27 (3H, s), 2.99 (3H, s), 4.06 (1H, dd, 9 and 10 Hz), 4.95 (2H, bs); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1770 (γ-lactone), 1630.

Hydrogenation of vulgarin (**6**)

Compound **6** (5 g) dissolved in EtOAc (50 ml) was hydrogenated at room temp and atmospheric pressure on C–Pd (10%) (0.8 g), then filtered over celite, concentrated *in vacuo* and crystallized with petroleum ether–EtOAc, yielding **7** (97%): m.p. 173–175° $\{\alpha\}_D$ – 39.3° ($CHCl_3$ 0.27) IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3525 (OH), 1770 (γ-lactone), 1710 (ketone); NMR δ 1.18 (3H, s), 1.22 (3H, d, 7 Hz), 1.51 (3H, s), 4.12 (1H, t, 10 Hz); MS, 266 (M$^+$). (Found: C, 67.31; H, 8.84. Calc.: C, 67.64; H, 8.33%).

Preparation of **8**. 200 mg $NaBH_4$ (EtOH, 10 ml) were added to 4.85 g of **7** dissolved in EtOH (25 ml) and stirred for 30 min at room temp. The soln was then concentrated at reduced pressure, poured over water, extracted with EtOAc, dried on Na_2SO_4 and chromatographed on silica gel. Elution with benzene–EtOAc yielded **8** (57.8%): m.p. 200–201° (EtOAc–hexane); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3505 (hydroxyl), 1780 (γ-lactone); NMR δ 0.99 (3H, s), 1.22 (3H, d, 7 Hz), 1.34 (3H, s) 3.40 (1H, complex), 4.12 (2H, complex); MS, 250 (M$^+$-18). (Found: C, 67.31; H, 8.84. Calc: C, 67.13; H, 9.01.)

Preparation of **9**. 2.50 g TsCl was added to 2.87 g of **8** dissolved in dry Py and the mixture was kept at 0° for 2 days, then poured over iced water, extracted with EtOAc, washed with sat NaCl-aq, dried on Na_2SO_4 and chromatographed on silica gel. Elution with benzene–EtOAc (1:1) produced **9** (85%): m.p. 165–167° (acetone–n-hexane), $\{\alpha\}_D$ +18.4° ($CHCl_3$ 0.22); IR ν_{max}^{KBr} cm^{-1} 3540 (hydroxyl), 1780 (γ-lactone); NMR δ 0.99 (3H, s), 1.20 (3H, d, 7 Hz), 1.29 (3H, s), 2.44 (3H, s), 4.13 (2H, complex), 7.34 (2H, d, 8 Hz), 7.81 (2H, d, 8 Hz); MS, 407 (M$^+$–15), 250 (M$^+$-172). (Found: C, 62.25; H, 7.07; S, 7.55. Calc.: C, 62.56; H, 7.11; S, 7.58.)

Solvolysis of **9**. 3.48 g of **9** dissolved in a 0.1 N soln (60 ml) KOAc in glacial HOAc was refluxed for 50 hr under inert atmosphere. The mixture was neutralized with sat $NaHCO_3$ aq, poured over water, extracted with EtOAc, dried on Na_2SO_4 and chromatographed on silica gel impregnated with 20% $AgNO_3$. Elution with petroleum ether–EtOAc (7:3) gave, in order of appearance: (1) 4α,hydroxy - 5α,6β,7α,11β-H-guaian - 1(10) - en - 6,12-olide (**10**; 25%): m.p. 123–124° (Et_2O–n-hexane), $\{\alpha\}_D$ –8° ($CHCl_3$ 0.25) IR ν_{max}^{KBr} cm^{-1} 3490 (OH), 1750 (γ-lactone); NMR δ 1.25 (3H, d, 6 Hz), 1.31 (3H, s), 1.70 (3H, s), 3.70 (1H, t, 9 Hz); MS, 250 (M$^+$), 232 (M$^+$-18). (Found: C, 71.66; H, 8.65. Calc.: C, 71.97; H, 8.86.); (2) 4α - hydroxy-1α,5α,6β,7α,11β - H - guaian - 10(15)-en-6,12-olide (**3**) oil, (11%): IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3560 (OH), 1760 (γ-lactone), 1640 (double bonds); NMR δ 1.23 (3H, d, 6 Hz), 1.29 (3H, s), 4.04 (1H, dd, 9 and 10 Hz), 4.95 (2H, bs); MS, 250 (M$^+$), 232 (M$^+$-18).

Preparation of **5**. 1.5 ml $SOCl_2$ (recently distilled) was added drop by drop of 160 mg of **3** dissolved in dry Py (0°, 3 ml) while stirring, then stirred for 15 min. The mixture was poured over

iced water, sat $NaHCO_3$aq was added, the mixture was extracted with EtOAc, dried on Na_2SO_4 and chromatographed on silica gel. Elution with benzene–EtOAc (7:3) yielded **5** (48.5%) as an oil.

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REFERENCES

[1]Part 43 in the series *Chemistry of the Composites*. For Part 42, see: A. G. González, A. Galindo, H. Mansilla and A. Alemany, *Tetrahedron Letters* 3769 (1979).

[2a]L. Ruzicka, *Experientia* **9**, 357 (1953); [b]D. H. R. Barton and P. De Mayo, *J. Chem. Soc.* 150 (1957); J. B. Hendrickson, *Tetrahedron* **7**, 82 (1959); [d]W. Parker, J. S. Roberts and R. Ramage, *Quart. Rev.* **21**, 331 (1967).

[3]K. Nishimura, N. Shinoda and Y. Hirose, *Tetrahedron Letters* 3097 (1967).

[4]E. D. Brown, J. K. Sutherland and T. W. Sam, *J. Chem. Soc.* Perkin I, 2332 (1975).

[5]A. G. González, J. Bermejo, H. Mansilla, A. Galindo, J. M. Amaro and G. M. Massanet, *Ibid.* Perkin I, 1243 (1978).

[6]See Ref. 1.

[7]M. Ogura, G. A. Cordell and N. R. Farnsworth, *Phytochemistry* **17**, 957 (1978).

[8]J. N. Marx and S. M. McGaughey, *Tetrahedron* **28**, 3583 (1972).

[9]C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.* **93**, 1746 (1971).

[10]E. D. Brown, T. W. Sam, J. K. Sutherland and A. Torre, *J. Chem. Soc.* Perkin I, 2326 (1975).

[11]W. Herz, *Israel J. Chem.* **16**, 32 (1977).