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Article

A Novel Dihydroxy Nor-Guaiane Sesquiterpene: Synthesis and Crystal Structure Analysis

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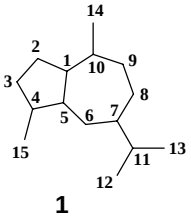
A epoxidação (H_2O_2, NaOH) de uma cicloeptenona-acetonilada forneceu um sesquiterpeno nor-guaiano bis-hidroxilado, através de uma seqüência inesperada de reações. Análise espectroscópica deste produto permitiu propor uma estrutura incluindo os grupos substituintes, porém a determinação tri-dimensional completa foi realizada por uma análise de difração de raio-X.

The epoxidation (H_2O_2, NaOH) of an acetonyl-cycloheptenone derived from (R)-(-)-carvone gives a dihydroxy-nor-guaiane sesquiterpene by way of an interesting sequence of reactions promoted by the basic reaction conditions. Although the major product could be identified spectroscopically with respect to functional groups, its complete three dimensional structure was determined by X-ray mono-crystal diffraction studies.

Keywords: nor-guaiane sesquiterpene, epoxidation, intramolecular aldol, β,γ-epoxy-ketone rearrangement, X-ray analysis

Introduction

Sesquiterpenes of the guaiane class **1** are encountered in plants of the *Compositae* family and less frequently in the *Umbelliferae*, *Magnoliceae* and *Lauraceae*[1]. Minor representatives of this class include the nor-guaianes **2** in which the C-15 methyl group is lost probably due to oxidative metabolism of the parent guaiane.



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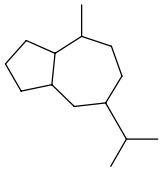

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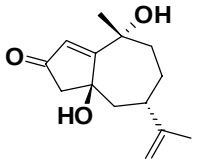

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Both these groups of natural products present various biologically important activities such as anti-tumoral, anti-ulcerogenic, cytotoxic and insecticide properties[1,2]. This diversity of biological activity together with their structural complexity makes these compounds very interesting targets for synthetic organic chemists.

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In this paper we describe a novel dihydroxy nor-guaiane sesquiterpene **3**, and its structure determination by spectroscopic and single crystal X-ray diffraction methods.

Experimental

2-Acetonyl-6-isopropenyl-3-methyl-cycloheptenone (**6**)

a) Allylation of cycloheptenone (**5**)

A solution of potassium *tert*-butoxide in *tert*-butanol was prepared from 1.231 g (31.48 mmol) of potassium and 62 mL of dry *tert*-butanol, under nitrogen, by heating at 70ºC until complete reaction of the potassium. After cooling to room temperature, 4.00 g (24.39 mmol) of 6-isopropenyl-3-methyl-2-cycloheptenone **5** (or its β,γ isomer; see reference 4) in 5 mL of dry *tert*-butanol was added and stirred for 20 min, with formation of a wine colored solution. 2.2 mL (26.7 mmol) of allyl chloride was added slowly at 5ºC and stirred for 1.5 h, followed by dilution with water and extraction with dichloromethane and ethyl ether. After drying the organic extracts with anhydrous magnesium sulfate, concentration and column chromatography on silica gel, 2.985 g (60%) of the mono-allylated cycloheptenone product was obtained, and used directly in the Wacker oxidation. ^{1}H NMR (200MHz, $CDCl_3$) δ 1.71 (broad s, 3H), 1.90 (s, 3H), 2.28-2.72 (m,

7H), 3.02-3.04 (d, 2H, *J* 6Hz), 4.72 (broad s, 2H), 4.86-4.96 (m, 2H), 5.65-5.81 (m, 1H); ^{13}C NMR (50MHz, $CDCl_3$) δ 204.1, 152.5, 147.8, 135.8, 114.3, 109.8, 46.6, 40.1, 33.8, 32.8, 30.0, 23.1, 21.0; IR ν_{max}/ cm^{-1} 3060, 2920, 1650, 1430, 1360, 880 (neat).

b) Wacker oxidation

To a two-necked round bottom flask, coupled to a small balloon inflated with dry oxygen, was added 0.018 g (0.10 mmol) of palladium chloride, 0.503 g (5.08 mmol) of cuprous chloride and 5.5 mL of aqueous dimethyl formamide (7:1 DMF:water) and stirred at room temperature for two h. The previously prepared allyl-cycloheptenone (0.250 g, 1.22 mmol) was added and stirred for seventeen hours. A cold 1.5 mol L^{-1} HCl solution was added and the mixture extracted five times with hexane. The organic phase was washed with 5% aqueous $NaHCO_3$, saturated NaCl, and dried over anhydrous $MgSO_4$. Concentration and preparative thick plate chromatography furnished 0.274 g (66%) of the diketone **6**. ^{1}H NMR (80MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.80 (s, 3H), 2.10 (s, 3H), 2.25-2.70 (m, 7H), 3.40 (s, 2H), 4.70 (broad s, 2H); ^{13}C NMR (20MHz, $CDCl_3$) δ 205.7, 203.4, 153.9, 147.6, 132.3, 109.8, 46.2, 43.8, 39.9, 33.8, 29.9, 29.2, 23.5, 20.8; IR ν_{max}/ cm^{-1} 3060, 2920, 1720, 1650, 1430, 1350, 880 (neat).

Di-hydroxy-nor-guaiane (**3**)

To a cooled solution (0 ^{o}C) of 95 mg (0.43 mmol) of diketone **6** in 9.0 mL of methanol and 0.18 mL of H_2O_2 30%, 0.05 mL of NaOH 6 mol L^{-1} was added, and stirred for 3 h at room temperature. The reaction mixture was then diluted with distilled water and extracted with ethyl acetate. After drying the organic layer with anhydrous Na_2SO_4 and evaporating the solvent, the resulting crude product (100 mg) was purified by silica gel column chromatography using hexane and ethyl acetate (40:60) as eluent, and furnished 48 mg (47% yield) of compound **3**: mp 129.1-130.6 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.46-1.58 (m, 2H), 1.50 (s, 3H), 1.69 (s, 3H), 1.69-1.77 (m, 1H), 1.93 (ddd, 1H, *J* 16.0, 8.0, 0.7 Hz), 2.04 (broad s, 1H), 2.19 (broad s, 1H), 2.24 (ddd, 1H, *J* 16.0, 4.0, 2.1 Hz), 2.27 (dd, 1H, *J* 16.0, 12.0 Hz), 2.45-2.52 (m, 1H), 2.60 (d, 1H, *J* 20.0 Hz), 2.73 (d, 1H, *J* 20.0 Hz), 4.69-4.71 (m, 2H), 6.26 (s, 1H); the two broad singlets at δ 2.04 and 2.19 disappeared on shaking with D_2O; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 188.0, 149.6, 130.0, 109.8, 79.6, 74.9, 55.8, 49.0, 45.3, 40.6, 33.2, 28.7, 20.4; UV λ_{max}/nm (MeOH) 232.5 (ε 11.500); IR ν_{max}/ cm^{-1} 3427, 3381, 3070, 2975, 2930, 2860, 1694, 1447, 1194, 1051, 888 (neat); Anal. Calcd. for C_{14} H_{22} O_4: C, 71.16; H, 8.53. Found: C, 71.16; H, 8.60.

X-ray structure determination of **3**

X ray data collection and refinement parameters are summarized in Table 1, the structure of the molecule with the atom-numbering is shown in Figure 1. Selected bond lengths and angles are given in Table 2. H atoms were placed in calculated positions, except those of the hydroxyl moieties, with fixed C—H distances (0.93 Å for Csp^2 and 0.96Å for Csp^3) each riding on a carrier atom, with an isotropic displacement parameter amounting to 1.5 (for methyl H atoms) or 1.2 (for the other H atoms) times the value of the equivalent isotropic displacement parameter of the atom they are attached. Programs used: cell determination and data collection: CAD4-Enraf-Nonius[6]; data reduction: Fair[7]; structure determination: SHELXS-86[8]; refinement: SHELXL-97[9]; graphic presentation ZORTEP[10]; calculus of the Cremer and Pople's[11] puckering parameters: CONFORMA[12].

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{14}H_{22}O_4$
Formula weight	254.32
Temperature	293(1) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	$P2_1/a$
Unit cell dimensions	*a* = 10.8224(7) Å *b* = 8.2680(10) Å *c* = 15.950(3) Å β = 102.780(10)^o
Volume	1391.8(3) Å^3
Z	4
Density (calculated)	1.214 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	552
Crystal size	0.25 x 0.20 x 0.20 mm
θ range for data collection	2.62 to 25.48^o
Index ranges	-13≤h≤0, -10≤k≤0, -18≤l≤19
Reflections collected	2727
Independent reflections	2577 [R_{int} = 0.0277]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2577 / 0 / 167
Goodness-of-fit on F^2	1.010
Final R indices [I>2σ(I)]	R1 = 0.0408, wR2 = 0.0940
R indices (all data)	R1 = 0.1166, wR2 = 0.1136
Largest diff. peak and hole	0.154 and -0.188 e.Å^{-3}

Table 2. Selected bond lengths [Å] and angles [^{o}].

O(1)-C(10)	1.435(2)
O(2)-C(3)	1.228(2)
O(3)-C(5)	1.421(2)
C(1)-C(2)	1.333(3)
C(11)-C(12)	1.341(3)
O(2)-C(3)-C(2)	126.80(19)
O(2)-C(3)-C(4)	125.5(2)
C(2)-C(1)-C(5)	110.91(17)
C(1)-C(2)-C(3)	110.90(18)
C(2)-C(3)-C(4)	107.64(17)
C(3)-C(4)-C(5)	104.24(16)
C(1)-C(5)-C(4)	102.09(16)

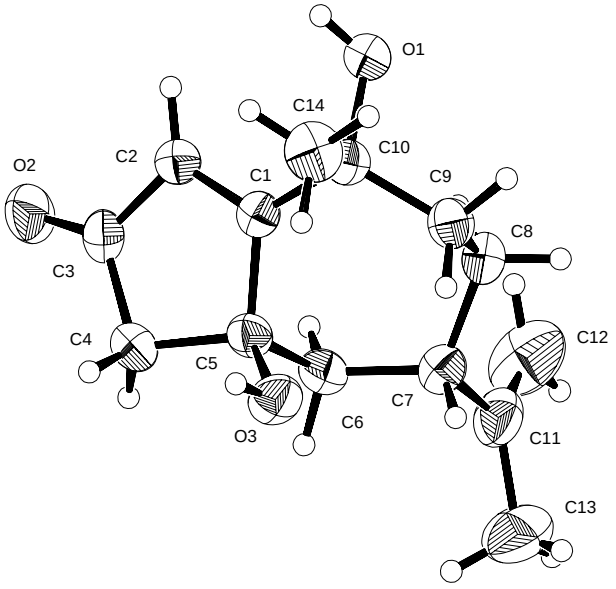


Figure 1. Projection of the molecular structure of **3** showing the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

Results

R-(-)-carvone (**4**) was used as starting material, and transformed[3,4] into the cycloheptenone **5**, which was mono-allylated and Wacker oxidized to the 1,4-diketone **6**. Our proposed next step was an intramolecular aldol reaction leading to the fused cyclopentenone ring of the nor-guaianes as in **7**, but as previous experience had demonstrated[3] this reaction is inhibited[5] by the sp^2 hybridization of the ring carbon (C-2 of compound **6**) linked to the side chain.

To avoid this problem we decided to epoxidize compound **6** using H_2O_2 (30%) and NaOH 6 mol L^{-1} in methanol, simultaneously transforming the C-2 sp^2 carbon of compound **6** into an sp^3 carbon and temporarily protecting the endocyclic conjugated double bond as its epoxide. To our surprise the major reaction product **3**, obtained in 47% yield, was found to be a hydroxylated cyclopentenone of the nor-guaiane type, as determined by conventional spectroscopic methods including infrared and ultraviolet absorption spectra, nuclear magnetic resonance spectra of both ^1H and ^{13}C nucleii, and microanalytical data.

Thus the saturated and α,β-unsaturated carbonyl group absorptions of compound **6** in 1713 and 1653 cm^{-1} respectively, were replaced by an absorption in 1694 cm^{-1}, and most surprising two distinct hydroxyl group absorptions in 3427 and 3381 cm^{-1} can be observed. The ^{13}C NMR spectrum shows two new sp^2 carbon signals at δ 188.0 and 130.0, a unique carbonyl group carbon at δ 203.4, and also two carbinolic carbons at δ 79.6 and 74.9. The ^1H NMR spectrum shows a singlet at δ 6.26 (one H), a singlet at δ 1.50 (three H) and two exchangeable singlets at δ 2.04 and 2.19 (one H each).

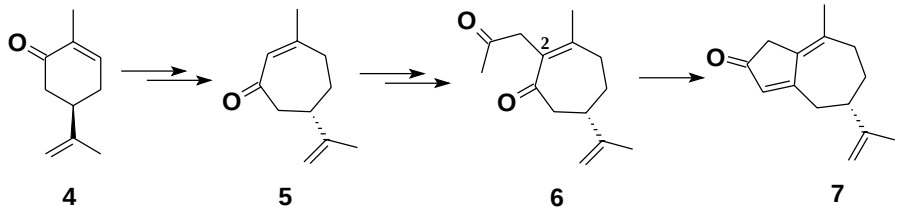
Our interpretation of these spectral data lead to a structure proposal for compound **3**, including a cyclopentenone nor-guaiane containing two independent hydroxyl groups. The first structure proposal was simply the 1-hydroxy-Δ-4 isomer of the true structure (usual guaiane numbering as in **1**). This structure could be proposed based upon the expected epoxidation, followed by an intramolecular aldol reaction with dehydration, and finally a simple hydrolytic opening of the resultant epoxide. However, as the spectroscopic data do not permit an unambiguous definition of structure even as to the two possible cyclopentenones, the position of the two hydroxyl groups, much less their relative configurations, a single crystal structure determination of **3** was undertaken.

Discussion

As can be seen in Figure 1 compound **3** is (5S,7S,10R)-5,10-dihydroxy-7-isopropenyl-10-methyl-bicyclo[5.3.0] dec-1-en-3-one.

The cyclopentenone ring adopts a distorted twist ($^2T_1$) conformation, as shown by the Cremer & Pople [11,12] parameters: q_2 = 0.203(2) Å and φ_2 = 61.0(6)º. The seven-membered ring has a conformation that approximates closely to a chair conformation as shown by the fact that the smallest torsion angle in the ring is adjacent to the exocyclic C1-C2 double bond: C9-C10-C1-C5 = 29.3(6)º. The Cremer & Pople [11] parameters are: q_2 = 0.456(2), q_3 = 0.650(2) Å, φ_2 = 160.6(2), φ_3 = 109.8(2)º.

The molecules are held together through hydrogen



Scheme 1.

bonds involving a crystallization water molecule as shown in Figure 2. The graph set method[13], a language for describing and analysing these kind of hydrogen bonds nets, was used. In this method the topologies of the hydrogen bond patterns are considered rather than their particular geometries. The water molecule is involved in three hydrogen bonds, as a donor the primary graph set is DD and as acceptor is D(2). The di-hydroxy-nor-guaiane acts as a donor through the hydroxyl groups and as an acceptor through atom O(1) of the C(10) hydroxyl group and the carbonyl oxygen atom O(2); these hydrogen bonds are designated D(2), according to the primary graph set method. The hydrogen bonds parameters are shown in Table 3 and the second level graph set is shown in Table 4.

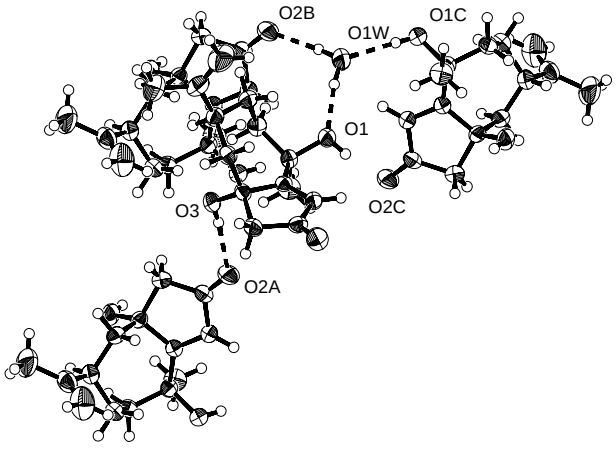


Figure 2. Hydrogen bond scheme.

Table 3. Hydrogen-bonding geometry (Å, º)

	D-H...A	H...A	D...A	D-H...A
a	O(1)-H1O1...O1W[i]	1.985	2.803(2)	176
b	O(3)-H1O3...O2[ii]	1.994	2.810(2)	173
c	O(1W)-H(1OW)...O(1)	1.895	2.858(2)	169
d	O(1W)-H(2OW)...O(2)[iii]	1.930	2.858(2)	175

Symmetry codes: (i)1.5-x, 0.5+y, 2-z; (ii) -0.5+x, 1.5-y, z; (iii) x-0.5, 0.5-y, z

Table 4. First and second-level hydrogen bond graph set motifs[a].

	a	b	c	d
a	D(2)	$C^2_2(16)$	$C^2_2(4)$	$C^2_2(9)$
b		D(2)	$C^2_2(16)$	$C^2_2(10)$
c			D(2)	$D^2_2(5)$
d				D(2)

[a]Rows and columns headings correspond to the hydrogen bonds as defined in Table 3.

Conclusion

We can now propose an interesting sequence of reactions leading from diketone **6** to the product nor-guaiane **3** involving the expected epoxidation of the endocyclic conjugated double bond, taking place from the a face as defined by the configuration of the future C-10 hydroxyl group. Cyclization promoted by the base present in the reaction medium leads to an aldol intermediate with a β hydroxyl group configuration. The basic medium promotes deprotonation and rearrangement of the β,γ epoxy-ketone to the γ hydroxy-cyclopentenone unit. The following scheme delineates a mechanistic route from diketone **6** to the major product **3**. As far as we can determine this cascade sequence has not been reported previously.

Acknowledgments

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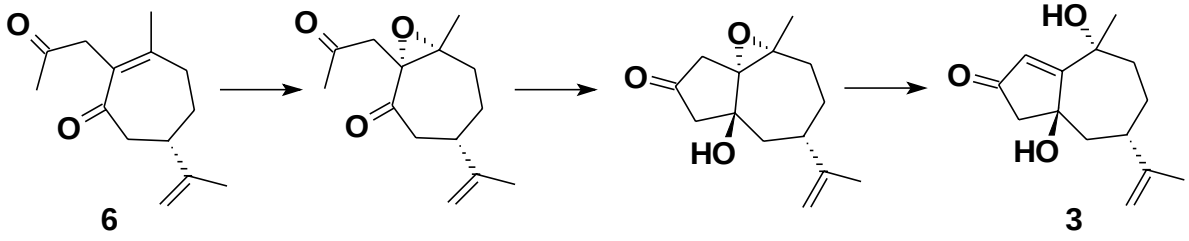
Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 139603. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



Scheme 2.

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