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ABSOLUTE CONFIGURATION AND SYNTHESIS OF GALLICADIOL

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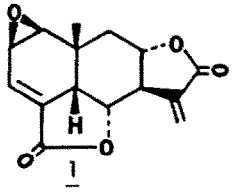
Abstract- A new cis-eudesmanolide, gallicadiol (3) was isolated and its structure was determined by spectroscopy, X-ray analysis and synthesis from vulgarin 6.

Gallicadiol (3), isolated from minor constituents of Artemisia maritima gallica Willd[1], is to the best of our knowledge[2], the first naturally-occurring cis-(10β,5β-OH)-eudesmanolide with a lactone ring at C-6/C-7 to be described. The only natural cis-(10β,5β)-eudesmanolide with lactone rings at C-6/C-15 and C-7/C-8 known to date is mykacynancholide (1) which was characterized by high field H-NMR spectroscopy[3] and its possible biogenetic relationship with myscandenin (2), a modified eudesmanolide the structure of which had been established by X-ray analysis[4]. These compounds are of particular interest in view of the biological activity[5] exhibited by many eudesmanolide sesquiterpene lactones.



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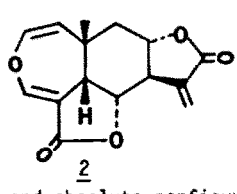

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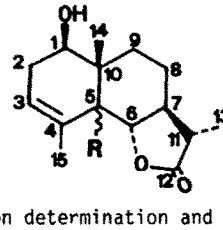


3 R=β-OH
4 R=α-OH
5 R=α-H

This paper reports the structure and absolute configuration determination and synthesis of gallicadiol (3).

RESULTS AND DISCUSSION

Gallicadiol was isolated as a crystalline compound: mp=219-221°(CH_2Cl_2-hexane); $[\alpha]_D$ -11.7°, c=0.2, $CHCl_3$); identified as 3 from its ^{1}H-NMR and ^{13}C-NMR spectral data (See tables 1 & 2) which were compared with those of its epimer 4[6] prepared by allylic oxidation of 5 as per Sharpless et al [7]. The axial (1R,β-OH) disposition of the 1-OH in 3 was established both by the $J_{1,2}$ (4.5 , 4.2 Hz) values and by the chemical shifts of the H-1 in 3 and 4[8]. The 5-OH was assigned a β(5S)configuration by comparing the chemical shifts of H-6 and H-14 in 3 and 4. The chemical shift of the C-1 in 3 and 4 (when compared with 5)is heavily dependent on the 5-OH disposition; if the 5-OH disposition is α as in 4, the C-1 is strongly shielded (ca 5 ppm, γ-effect)[9] but not, if it is β, as in 3. The ^{13}C-nmr spectra of 3,4 and 5 show this effect quite clearly [$\delta=\delta_5-\delta_3=-0.88$ ppm; $\delta=\delta_5-\delta_4=5.65$ ppm]. Following the guidelines laid down by Pregosin et al[10], the 11-H can be assigned a β disposition (11S) from the chemical shift of C-13.

The absolute configuration as 1R,5S,6S,7S,10S,11S was established by X-ray analysis and the final model for the correct enantiomer is shown in Figure 1. Ring A is in the half-chair $^1H_{10}$ conformation and ring B is a chair $^8C_5$. Ring C is an envelope with the apex at C-7 in accordance with Cremer's parameters[11] (Table 3). The A-B-C junction is cis-syn-trans. The OH groups on C-1 and C-5 are in a

1:3 diaxial relationship.The final atomic positional coordinates with e.s.d.'s in parentheses are listed in Table 4.The crystal structure is built by hydrogen bonds,one,intramolecular O(4)...O(1) with 2.75(2) Å distance and 125.6(9)° angle;the other,intermolecular O(1)...O(4) through symmetry operation X+½,-Y+1/2+1,-Z+2 with distance 2.73(2) Å and angle 169.4(8)°.

Compound	H-1	H-3	H-6	H-13	H-14	H-15
3	3.62 dd(J=4.7 & 4.2)	5.47 br s	4.25 d(J=10.8)	1.22 d(J=6.8)	1.36 s	1.82 br s
4	4.20 dd(J=7.1 & 6.4)	5.44 br s	4.06 d(J=10.4)	1.21 d(J=6.5)	0.92 s	1.82 br s
5	3.65 dd(J=7.8 & 7.3)	5.35 br s	3.95 dd(J=9.7 & 9.7)	1.22 d(J=6.9)	0.88 s	1.81 br s

Chemical shifts in ppm.Spectra were taken in Cl_3CD at 200 Mhz.Coupling constants in Hz.

Table 1- ^{1}H-n.m.r. for compounds 3,4 and 5

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
3	75.87	32.86	123.05	134.76	74.87	85.11	46.86	23.83
4	69.34	32.75	126.08	136.15	75.10	82.75	45.52	22.77
5	74.99	32.63	121.28	133.33	50.51*	81.40	53.56*	22.73

Compound	C-9	C-10	C-11	C-12	C-13	C-14	C-15
3	31.95	43.09	41.99	178.67	12.82	18.88	21.32
4	29.23	43.78	41.05	179.60	12.57	13.05	21.56
5	34.51	40.74	40.57	179.78	12.36	10.99	23.23

Chemicals shifts in ppm,$CDCl_3$ as solvent.Signals marked (*) are interchangeable.

Table 2-^{13}C-n.m.r. for compounds 3,4 and 5

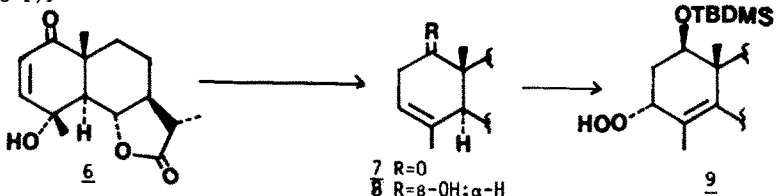
Ring	Φ_2(°)	θ_2(°)	Q_T(Å)	~ Conformation
A	144	134	.48	$^1H_{10}$
B	70	8	.62	$^8C_5$
C	70	--	--	Envelope (C_s)

Table 3- Cremer conformational parameters

ATOM	X/A	Y/B	Z/C	UEQ
O1	5275(6)	8587(6)	10067(2)	65(2)
O2	-1343(6)	10125(6)	7522(3)	67(2)
O3	422(5)	9499(5)	8335(2)	50(2)
O4	2258(6)	8815(6)	9575(2)	52(2)
C1	5883(9)	8807(9)	9371(3)	51(3)
C2	6319(10)	10520(9)	9292(3)	57(3)
C3	4878(10)	11497(8)	9195(3)	55(3)
C4	3436(9)	11004(8)	9013(3)	41(2)
C5	3074(8)	9261(7)	8947(3)	38(2)
C6	1999(7)	8796(8)	8341(3)	39(2)
C7	2699(7)	9223(7)	7641(3)	34(2)
C8	4156(7)	8213(8)	7510(3)	44(2)
C9	5331(7)	8519(8)	8104(3)	39(2)
C10	4621(8)	8267(7)	8841(3)	41(2)
C11	1224(8)	9047(7)	7181(3)	43(2)
C12	-54(9)	9616(8)	7665(4)	52(3)
C13	1254(9)	9921(9)	6485(3)	66(3)
C14	4320(9)	6518(8)	8959(3)	57(3)
C15	2101(10)	12134(8)	8952(4)	67(3)

Table 4- Non-hydrogen fractional coordinates ($x10^4$) and equivalent isotropic temperature factors ($x10^3$ Å^2) for gallicadiol.

Finally,gallicadiol (3) was synthesized from vulgarin (6) in ten stages.6 treated with Zn-HOAc and then $NaBH_4$ stereoselectively generated 5[6] which,by treatment with t-butyldimethylsilyl triflate followed by sensitized photo-oxygenation,gave hydroperoxide 9 with an overall yield of 47%.(Scheme I).



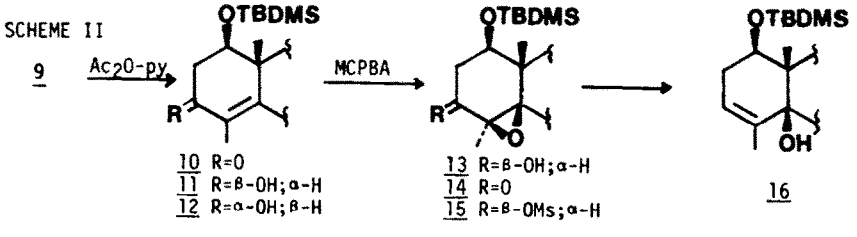
6 7 R=O 8 R=β-OH;α-H 9 R=β-OTBDMS;α-H 9

SCHEME I

Treatment of 9 with Ac_2O-py followed by $Zn(BH_4)_2$ reduction in ether afforded 11.The stereoselective epoxidation of 11[12],followed by oxidation,gave the keto-epoxide 14 (33%) which, when treated with NH_2-NH_2.H_2O in HOAc[13],yielded 16 (22%) which was deprotected to yield 3, identical to the natural product.

The overall yield of the conversion of 14 to 16 was low and so the methodology was changed and 13 was mesylated under the usual conditions and the mesylate 15 treated with NaI-Zn in glyme under reflux to give 16 directly (81%) (Scheme II).

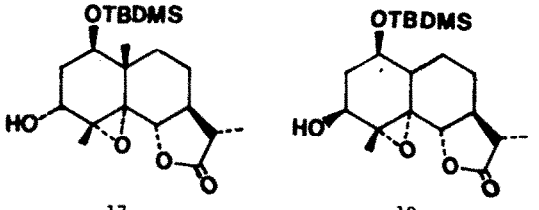
SCHEME II



10 R=O 11 R=β-OH;α-H 12 R=α-OH;β-H

13 R=β-OH;α-H 14 R=O 15 R=β-OMs;α-H

16



17 18

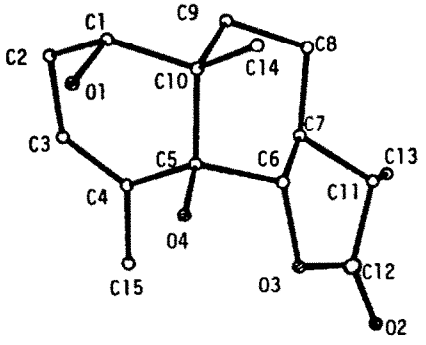


Figure 1

EXPERIMENTAL

Mp's were determined on a Kofler-type apparatus and are uncorr.The ir spectra were taken on a Perkin-Elmer 257 spectrophotometer with $CHCl_3$ as solvent.The ^1H and ^{13}C nmr spectra were collected on a Bruker WP-200SY at 200 MHz with $CDCl_3$ as solvent.The ms spectra were measured on a VG-Micromass ZAB-2F.Optical rotations were taken at 20-30° in $CHCl_3$ at 0.2-0.4% concentrations on a Perkin-Elmer 241 polarimeter.Unless otherwise stated,column chromatography was carried out using Merck silica gel (0.065-0.2 mm).

Isolation of gallicadiol (3) The aerial part of Artemisia maritima gallica (12 kg) was collected at Cabo Corbera (Valencia,Spain) between the months of May-July,triturated and exhaustively

extracted with hot EtOH.The EtOH extract was concd. in vacuo,yielding a syrupy liquid which was dissolved in hot EtOH (1 l) and boiling water (2 l) containing $Pb(OAc)_2$ (10 g).The soln was left for 24 h,then filtered and most of the alcohol was eliminated.The resulting extract was chromatographed (5 kg of adsorbent).The column was eluted with hexane and hexane-EtOAc mixtures and collected in 900 ml fractions.The 189-196 (4:6 hexane-EtOAc) fractions contained gallicadiol (3) (53 mg) which was crystallized with CH_2Cl_2-hexane,mp=219-221°;$[\alpha]_D$-11.7°.Ir:$\nu_{max}cm^{-1}$,3600,3500 (OH),1770(γ-lactone).H.r.m.s.,m/z 266.1514(M+,$C_{15}H_{22}O_4$);248.1394(M+ -H_2O,$C_{15}H_{20}O_3$);230.1300 (M+ -$2H_2O$,$C_{15}H_{18}O_2$).

Preparation of 5 5 was obtained from vulgarin (6) by the process described in [6].

Preparation of 4 A soln of SeO_2 (25 mg) in CH_2Cl_2 (2 ml) with HOO^tBu (80%;0.1 ml) was prepared and 5 (100 mg) in CH_2Cl_2 (5 ml) was then added.The mixture was left for 24 h at r.t. then poured onto water,dried over anhydrous Na_2SO_4 and the solvent was eliminated at reduced pressure.6:4 hexane-EtOAc chromatography yielded 4 (42 mg) which was crystallized in CH_2Cl_2-hexane:mp=168-170°; $[\alpha]_D$-3.2°.Ir:$\nu_{max}cm^{-1}$,3600,3500(OH),1760(γ-lactone).H.r.m.s.,m/z 266.1522(M+,$C_{15}H_{22}O_4$);248.1429 (M+ -H_2O,$C_{15}H_{20}O_3$);230.1312(M+ -$2H_2O$;$C_{15}H_{18}O_2$).

Protection of 5 TBDMSTf (1.9 ml) was added dropwise to a soln of 5 (2 g) in dry CH_2Cl_2 (10 ml) containing dry Et_3N (1.6 ml) and the mixture was stirred under argon for 4 h.A saturated soln of $NaHCO_3$ was then added,the mixture was extracted with CH_2Cl_2,washed with water,the organic phase dried with anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.The 8:2 hexane-EtOAc chromatography yielded the silyl ether 8 (2.75 g),which was crystallized with hexane :mp=123-125°; $[\alpha]_D$+28.7°.Ir:$\nu_{max}cm^{-1}$,1760(γ-lactone). H nmr:δ ppm 0.031,0.035 and 0.88 (-OTBDMS),3.57(1H,dd, J=6.7 and 6.4 Hz,H-1),5.30(1H,br s,H-3),3.93(1H,dd,J=9.7 and 8.5 Hz,H-6),1.21(3H,d,J=6.8 Hz,H-13), 0.90(3H,s,H-14),1.79(3H,s,H-15).H.r.m.s.,m/z 364.2449(M+,$C_{21}H_{36}O_3Si$);307.1729(M+ -^tBu,$C_{17}H_{27}O_3Si$).

Photo-Oxygenation of 8 Methylene blue (10 mg) was added to a soln of 8 (1.5 g) in absolute EtOH (100 ml) and irradiated for 26 h at r.t. with a quartz-halogen 1000w lamp while dry oxygen was bubbled through the mixture.After the solvent had been eliminated at reduced pressure,7:3 hexane-EtOAc chromatography yielded the hydroperoxide 9 (887 mg) and unreacted 8 (398 mg).9 was crystallized with CH_2Cl_2:mp=132-134°;$[\alpha]_D$ +35.5°.Ir:$\nu_{max}cm^{-1}$,3520(OOH),1770(γ-lactone). H nmr:δ ppm 8.00(1H,br s,-OOH,interchangeable with D_2O),3.74(1H,dd,J=3.6 and 3.7 Hz,H-1),4.23(1H,br s,H-3), 4.56(1H,d,J=11 Hz,H-6),1.21(3H,d,J=6.9 Hz,H-13),1.98(3H,d,J=1.4 Hz,H-14),1.05(3H,s,H-15).H.r.m.s., m/z 339.1645(M+ -^tBu,$C_{17}H_{27}O_5Si$).

Reduction of 9 $NaBH_4$ (5 mg) was added to a soln of 9 (40 mg) in EtOH (5 ml) at 0° and stirred for 30 min.HOAc (10%) to neutralization and NaCl saturated soln were added.The mixture was extracted with CH_2Cl_2,dried on anhydrous Na_2SO_4 and the solvent was eliminated at reduced pressure.From the 8:2 hexane-EtOAc chromatography,alcohol 12 (34 mg) was obtained but could not be crystallized. Ir:$\nu_{max}cm^{-1}$,3620(OH),1770(γ-lactone). H nmr:δ ppm 3.76(1H,dd,J=4.9 and 5.0 Hz,H-1),3.93(1H,br s, H-3),4.55(1H,d,J=11 Hz,H-6),1.19(3H,d,J=6.9 Hz,H-13),1.02(3H,s,H-14),1.96(3H,s,H-15).H.r.m.s.,m/z 380.2432(M+,$C_{21}H_{36}O_4Si$);323.1656(M+ -^tBu,$C_{17}H_{27}O_4Si$).

Preparation of 10 Ac_2O (0.5 ml) was added dropwise to a soln of hydroperoxide 9 (600 mg) in dry pyridine (2 ml) at 0° and then left for 1 h at r.t. Ice and a saturated soln of $NaHCO_3$ were added, the mixture was extracted with CH_2Cl_2 and washed with water.The organic phase was dried with anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.The 9:1 hexane-EtOAc chromatography gave ketone 10 (503 mg) which was crystallized with EtOAc-hexane:mp=148-150°;$[\alpha]_D$ +34.7°.Ir:$\nu_{max}cm^{-1}$,1765(γ-lactone),1650(ketone). H nmr:δ ppm 3.80(1H,dd,J=8.7 and 9.0 Hz,H-1),2.54 (1H,s,H-2),2.59(1H,s,H*-2),4.74(1H,d,J=11 Hz,H-6),1.26(3H,d,J=6.7 Hz,H-13),1.24(3H,s,H-14),1.99 (3H,d,J=1.5 Hz,H-15). H.r.m.s.,m/z 378.2261(M+,$C_{21}H_{34}O_4Si$);321.1515(M+ -^tBu,$C_{17}H_{25}O_4Si$).

Reduction of 10 $Zn(BH_4)_2$ (0.65 M;7 ml) in ether soln was added dropwise to ketone 10 (400 mg) dissolved in anhydrous Et_2O (10 ml) containing dry benzene (2 ml).The mixture was stirred for 12 h at r.t.,had HOAc (10%) added until neutralization,was extracted with CH_2Cl_2,washed with a saturated soln of $NaHCO_3$,water and dried on anhydrous Na_2SO_4,the solvent then being eliminated at reduced pressure.The 9:1 hexane-EtOAc chromatography gave the alcohols 12 (61 mg) and 11 (288 mg). 11 was crystallized with EtOAc-hexane:mp=157-158°;$[\alpha]_D$-5.0°.Ir:$\nu_{max}cm^{-1}$,3600(OH),1770(γ-lactone). H nmr:δ ppm 3.49(1H,dd,J=3.2 and 3.1 Hz,H-1),4.05(1H,dd,J=6.8 and 7.8 Hz,H-3),4.60(1H,d,J=11 Hz, H-6),1.22(3H,d,J=6.9 Hz,H-13),1.14(3H,s,H-14),1.94(3H,s,H-15).H.r.m.s.,m/z 323.1670(M+ -^tBu, $C_{17}H_{27}O_4Si$).

Epoxidation of 11 Solid $NaHCO_3$ (10 mg) and MCPBA (275 mg) were added to alcohol 11 (200 mg) dissolved in CH_2Cl_2 (10 ml) and the suspension was stirred for 12 h at r.t. A saturated soln of $NaHCO_3$ was added,the mixture was extracted with CH_2Cl_2 and washed with a 10% soln of $NaHSO_3$ and water.The organic phase was dried on anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.9:1 and 8:2 hexane-EtOAc chromatography gave a mixture of the epoxides 13 and 18 (196 mg). Fractionated crystallization of the mixture in EtOAc-hexane gave 13 (121 mg) and a 1:3 mixture of 13+18 (73 mg).13:mp=133-134°;$[\alpha]_D$-15.6°.Ir:$\nu_{max}cm^{-1}$,3550(OH),1750(γ-lactone). H nmr:δ ppm 3.29 (1H,dd,J=4.9 and 4.9 Hz,H-1),3.78(1H,dd,J=5.9 and 6.0 Hz,H-3),4.41(1H,d,J=11.5 Hz,H-6),1.23(3H,d, J=6.9 Hz,H-13),1.14(3H,s,H-14),1.67(3H,s,H-15).H.r.m.s.,m/z 396.2344(M+,$C_{21}H_{36}O_5Si$);339.1670 (M+ -^tBu,$C_{17}H_{27}O_5Si$).

18 could not be totally separated from 13 and its ^1H nmr data from the mixture are as follows: 3.62(1H,dd,J=4.2 and 4.1 Hz,H-1),3.92(1H,dd,J=8.7 and 8.7 Hz,H-3),4.31(1H,d,J=10.7 Hz,H-6),1.23 (3H,d,J=6.8 Hz,H-13),1.11(3H,s,H-14),1.62(3H,s,H-15).

Epoxidation of 12 Alcohol 12 was epoxidated under identical conditions to 11 yielding the epoxide 17 in 83% yield.17 crystallized in hexane:mp=99-101°;$[\alpha]_D$+36.5°.Ir:$\nu_{max}cm^{-1}$,3550(OH),1770 (γ-lactone). H nmr:δ ppm 3.69(1H,dd,J=4.7 and 4.7 Hz,H-1),3.82(1H,d,J=7.1 Hz,H-3),4.33(1H,d,J=10.7 Hz,H-6),1.22(3H,d,J=6.8 Hz,H-13),1.02(3H,s,H-14),1.68(3H,s,H-15).H.r.m.s.,m/z 396.2284(M+, $C_{21}H_{36}O_5Si$);339.1645(M+ -^tBu,$C_{17}H_{27}O_5Si$).

Oxidation of 13 PDC (145 mg) was added to the epoxyalcohol 13 (100 mg) in dry CH_2Cl_2 (2 ml) under argon atmosphere.After the suspension had been stirred for 12 h at r.t.,CH_2Cl_2 was added,and the mixture was filtered over dry $MgSO_4$ and the solvent evaporated.8:2 hexane-EtOAc chromatography yielded ketone 14 (76 mg) which was crystallized with CH_2Cl_2 -hexane:mp=123-125°;$[\alpha]_D$-15.6°.Ir: $\nu_{max}cm^{-1}$,1770(γ-lactone),1620(ketone). H nmr:δ ppm 3.52(1H,dd,J=3.4 and 3.5 Hz,H-1),3.10(2H,dd, J.12.2 and 12.3 Hz,H-2),4.49(1H,d,J=11.6 Hz,H-6),1.25(3H,d,J=6.9 Hz,H-13),1.28(3H,s,H-14),1.65

(3H,s,H-15).H.r.m.s.,m/z 394.2158(M+,$C_{21}H_{34}O_5Si$);337.1459(M+ -^tBu,$C_{17}H_{25}O_5Si$).

Fragmentation of 14 A soln of HOAc in abs.MeOH (10%,0.3 ml) and NH_2-NH_2.H_2O (0.1 ml) was added to the epoxyketone 14 (85 mg) dissolved in abs. MeOH (5 ml) and after 10 min stirring at r.t.,a saturated NaCl soln was added,the mixture was extracted with CH_2Cl_2,washed with a saturated soln of $NaHCO_3$ and water,the organic phase dried with anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.8:2 hexane-EtOAc chromatography afforded 16 (18 mg) which was crystallized with CH_2Cl_2-hexane:mp=121-123°;$[\alpha]_D$-30.1°.Ir:$\nu_{max}$$cm^{-1}$,3460(OH),1760(γ-lactone). H nmr:δ ppm 3.62(1H,d, J=3.9Hz,H-1),5.36(1H,br s,H-3),4.22(1H,d,J=11 Hz,H-6),1.20(3H,d,J=6.9 Hz,H-13),1.26(3H,s,H-14), 1.82(3H,s,H-15).H.r.m.s.,m/z 323.1680(M+ -^tBu,$C_{17}H_{27}O_4Si$).

Mesylation of 13 Mesyl chloride (1 ml) was added to alcohol 13 (140 mg) dissolved in dry pyridine (1.5 ml) and the soln was stirred for 3 h at r.t.,after which a saturated $NaHCO_3$ soln was added, and the mixture was extracted with CH_2Cl_2,washed with water and the organic phase dried with anhydrous Na_2SO_4.The 8:2 hexane-EtOAc chromatography afforded mesylate 15 (153 mg) which was crystallized with CH_2Cl_2-hexane:mp=145-147°;$[\alpha]_D$-35.2°.Ir:$\nu_{max}$$cm^{-1}$,1770(γ-lactone). H nmr:δ ppm 3.08(3H,s,-OMs),3.25(1H,dd,J=3.2 and 3.2 Hz,H-1),4.88(1H,dd,J=5.1 and 5.2 Hz,H-3),4.39(1H,d, J=11.7 Hz,H-6),1.25(3H,d,J=6.9 Hz,H-13),1.13(3H,s,H-14),1.68(3H,s,H-15).H.r.m.s.,m/z 417.1416 (M+ -^tBu,$C_{18}H_{29}O_7SiS$);379.2284(M+ -OMs,$C_{21}H_{35}O_4Si$),321.1566(M+ -^tBu-OMs,$C_{17}H_{26}O_4Si$).

Preparation of 16 from 15 Water (0.5 ml),powdered zinc (206 mg) and NaI (228 mg) were added to mesylate 15 (150 mg) dissolved in glyme (10 ml) and the mixture was refluxed for 5 h and then chilled.Water was then added and the soln was extracted with CH_2Cl_2 and washed repeatdly with saturated $NaHCO_3$ and $Na_2S_2O_7$(5 %) solutions and water.The organic phase was dried with Na_2SO_4 and the solvent was eliminated at reduced pressure.The 8:2 hexane-EtOAc chromatography yielded 16 (105 mg).

Deprotection of 16 16 (50 mg) was dissolved in HOAc (3 ml) and water (1 ml) and the soln was stirred for 24 h at 60°,then chilled.A soln of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2,dried with anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.6:4 hexane-EtOAc chromatography gave gallicadiol (3) (32 mg).

X Ray Structure Determination of 3 Crystals of gallicadiol (3) are orthorhombic, $P2_12_12_1$, a=8.423(7) , b=8.618(3) , c=19.267(15) Å , V=1398 Å^3, Z=4 , μ =7.0 cm^{-1}.Diffraction maxima with 2θ<100° were collected on a computer-controlled four-circle Siemens AED diffractometer,using graphite monochromated CuKα radiation and w:θ scan mode;of 856 measured independent reflections,827(97%) with I>3σ(I) were treated as observed and corrected for Lorentz and polarization effects,no absorption correction being made.The structure was solved by direct methods[15].Most of the H atoms were located on a difference electron-density map and the others were placed in calculated positions[16].Final full-matrix l.s. refinement[17] with anisotropic displacement parameters for non-H atoms and fixed isotropic parameters for H atoms ,converged to a crystallographic residual of R=0.046.The absolute configuration was established by using 17 Bijvoet pairs with Fo>5σ(Fo) and ΔFc>0.08 in the ranges 5.<Fo<50. and .2<sinθ/λ<.5.The averaged Bijvoet differences are 0.239 for the correct enantiomer vs. 0.318 for the wrong one[18,19].

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