Antibacterial Galloylated Alkylphloroglucinol Glucosides from Myrtle (*Myrtus communis*)

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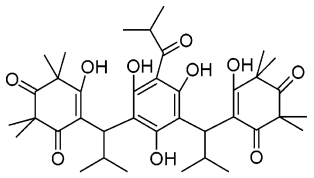
An investigation of the polar glycosidic fraction from the leaves of myrtle afforded four galloylated nonprenylated phloroglucinol glucosides (**3a**−**d**) related to the endoperoxide hormone G3 (**4**) in terms of structure and biogenesis. Despite their close similarity, significant antibacterial activity was shown only by one of these compounds (**3b**, gallomyrtucommulone B), while the G3 hormone (**4**) was inactive.

Myrtle (*Myrtus communis* L., Myrtaceae) is nowadays better known as a culinary herb rather than a medicinal plant, but holds an important place in Western culture because of its mythological associations[1] and its medicinal use as an antiseptic and an anti-inflammatory agent.[2] Over the past few years, liqueurs prepared from the berries of myrtle have become popular,[3] while its leaves have been used as a hop substitute in beer[4] and as a cosmetic ingredient in products against hair dandruff.[5] This has led to a renewed and general interest in myrtle, especially for its cultivation, since the collection from wild plants is becoming insufficient to satisfy the growing demand.[3] From a phytochemical standpoint, myrtle contains unique compounds, as exemplified by a series of oligomeric nonprenylated phloroglucinols related to myrtucommulone A (**1**).[6] This compound shows outstanding antibacterial[6] and anti-inflammatory[7] properties, while powerful antioxidant activity was demonstrated for its lower homologue, semimyrtucommulone (**2**).[8]



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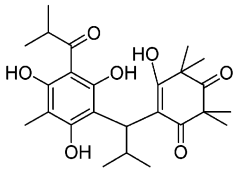

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Apart from these constituents, the leaves of myrtle are a rich source of flavonoids, and especially of myricetin glycosides.[9] Myricetin can enhance glucose utilization and lower plasma glucose,[10] and antidiabetic properties have been traditionally attributed to myrtle in the folk medicine of various parts of the Mediterranean area.[11] We therefore became interested in the characterization of the glycosidic fractions of the leaves. Apart from large amounts (ca. 0.2% from the dried plant material) of myricetin rhamnopyranoside, a fraction containing galloylated glucosides was also obtained. When thoroughly purified, this fraction turned out to be made up of a series of closely related galloylated glucosides of alkylphloroglucinols, an unprecedented type of natural product and whose characterization is presented here.

Results and Discussion

A glycosidic fraction was obtained from an acetone extract of leaves by vacuum-liquid chromatography (VLC) on RP-18 silica gel. The galloylated fraction was next separated from myricetin rhamnopyranoside by gravity column chromatography on silica gel, eventually obtaining a yellow powder in ca. 0.08% yield from the dried leaves. The ^{1}H NMR spectrum of this fraction showed the resonances typical of gallic acid and of a 6-acylated glucosyl residue, and a cluster of olefinic and oxymethine singlets grouped around δ ca. 5.0 and 3.90. The fine splitting of all signals and the complexity of the upfield part of the spectrum suggested a mixture of related compounds. Preparative HPLC separation on normal-phase silica gel resolved the mixture into four peaks, corresponding to compounds **3a**−**d**, named gallomyrtucommulones A−D to emphasize their origin. Compounds **3a**−**d** showed closely related NMR spectra, but could be sorted out by mass spectrometry into two pairs, differing in their molecular weight (570 for **3a**,**b** and 568 for **3c**,**d**). The structure elucidation will be detailed for **3d**, the major constituent of the mixture. For the remaining compounds, only the interpretation of the spectroscopic differences into structural terms will be described.

Compound **3d** ($C_{27}H_{36}O_{13}$, HRMS) was obtained as an optically active yellowish powder. In the ^{1}H NMR spectrum (10% CD_3OD in $CDCl_3$, Table 1), the signals of a galloyl moiety (δ 7.07, s), as well as a glucose moiety acylated at the 6-hydroxyl (δ 4.52, m, H-1′; 3.25, dd, J = 8.0 and 7.8 Hz, H-2′; 3.45, m, H-3′; 3.42, m, H-4′; 3.48, m, H-5′; 4.53, m, H-6′a; 4.44, dd, J = 11.9, 4.7 Hz, H-6′b), an olefinic proton (δ 5.05, br s), an oxymethine (δ 3.81, s), two allylic methyls (δ 1.66 and 1.72, br s), and four quaternary methyls (δ 1.28, 1.28, 1.24, 1.17, s), were present. Apart from the protonated carbons corresponding to these resonances, the ^{13}C NMR spectrum (Table 2) showed a quaternary oxygenated carbon (δ 82.2, s), two ketone carbonyls (δ 215.4 and 211.4, s), and two quaternary carbons (δ 56.2 and 48.9, s). These signals were reminiscent of those observed in the endoperoxide G3 (**4**, Scheme 1), an antimalarial hormone constituent of various *Eucalyptus* species[12] that also occurs in myrtle.[6] Analysis of the HMBC correlations made it possible to evaluate the ^{1}H and ^{13}C NMR resonances in the dihydroxylated cyclohexadione structure **3d**. The *trans* configuration

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Table 1. ^{1}H NMR Data (500 MHz, 10% CD_3OD in $CDCl_3$) for Gallomyrtucommulones A (**3a**), B (**3b**), C (**3c**), and D (**3d**) [solvent signal of $CDCl_3$ (7.26 ppm) as reference, coupling constants (*J*) in Hz]

position	3a	3b	3c	3d
1	0.90 (d; 6.6)	0.88 (d; 6.6)	1.66 (s)	1.66 (s)
2	1.59 (m)	1.50 (m)		
3	0.73 (d; 6.6)	0.82 (d; 6.6)	1.66 (s)	1.72 (s)
4a	1.80 (dd; 6.4, 14.7)	1.89 (dd; 6.2, 14.7)	5.54 (br s)	5.05 (br s)
4b	1.28 (dd; 5.8, 14.7)	1.82 (dd; 5.0, 14.7)		
8		3.64 (s)		
10	3.73 (s)		3.70 (s)	3.81 (s)
11	1.22 (s)	1.32 (q)	1.22 (s)	1.28 (s)
12	1.21 (s)	1.07 (q)	1.19 (s)	1.24 (s)
13	1.18 (s)	1.15 (q)	1.18 (s)	1.17 (s)
14	1.15 (s)	1.09 (q)	1.18 (s)	1.28 (s)
1′	4.38 (d; 7.6)	4.36 (d; 7.8)	4.35 (d; 7.7)	4.52 (m)
2′	3.32 (m)	3.23 (m)	3.27 (m)	3.25 (dd; 8.0, 7.8)
3′	3.41 (m)	3.39 (m)	3.39 (m)	3.45 (m)
4′	3.38 (m)	3.40 (m)	3.37 (m)	3.42 (m)
5′	3.49 (m)	3.46 (m)	3.48 (m)	3.48 (m)
6′a	4.51 (dd; 1.6, 11.8)	4.55 (dd; 1.5, 11.9)	4.50 (dd; 1.5, 11.9)	4.53 (m)
6′b	4.37 (dd; 6.3, 11.8)	4.43 (dd; 5.3, 11.9)	4.36 ((dd; 5.3, 11.9)	4.44 (dd; 4.7, 11.9)
3″	7.03 (s)	7.06 (s)	7.02 (s)	7.07 (s)

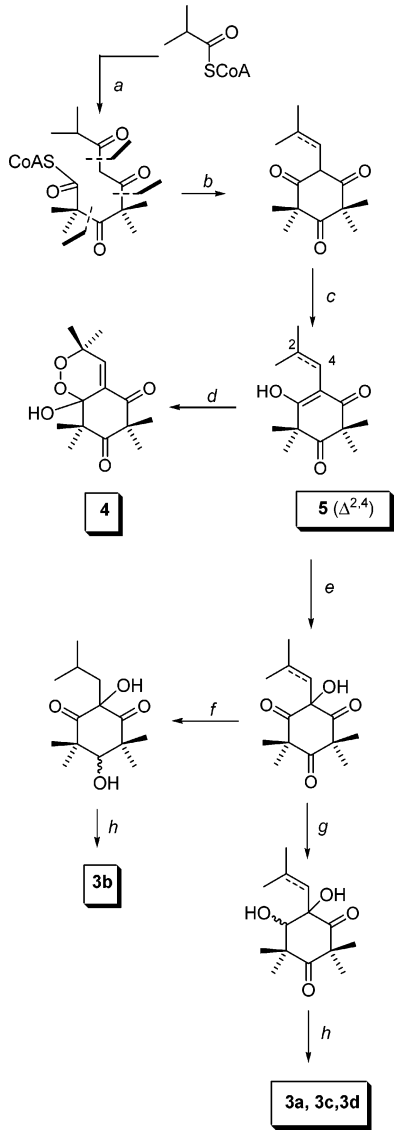
Table 2. ^{13}C (125 MHz, 10% CD_3OD in $CDCl_3$) NMR Data for Gallomyrtucommulones A (**3a**), B (**3b**), C (**3c**), and D (**3d**) [solvent signal of $CDCl_3$ (77.0 ppm) as reference, multiplicities from HMQC experiments]

position	3a	3b	3c	3d
1	24.3 (q)	23.7 (q)	26.8 (q)	27.1 (q)
2	23.6 (d)	24.2 (d)	144.2 (s)	145.6 (s)
3	23.7 (q)	23.8 (q)	18.9 (q)	19.6 (q)
4	38.9 (t)	44.1 (t)	117.8 (d)	116.6 (d)
5	82.3 (s)	84.1 (s)	80.3 (s)	82.2 (s)
6	212.3 (s)	211.8 (s)	209.9 (s)	211.1 (s)
7	55.3 (s)	50.1 (s)	55.4 (s)	56.2 (s)
8	215.1 (s)	85.1 (d)	215.0 (s)	215.4 (s)
9	49.3 (s)	48.8 (s)	49.5 (s)	48.9 (s)
10	86.9 (d)	213.1 (s)	86.8 (d)	87.8 (d)
11	25.8 (q)	22.6 (q)	25.0 (q)	25.6 (q)
12	23.1 (q)	25.4 (q)	24.6 (q)	24.8 (q)
13	29.0 (q)	24.4 (q)	28.8 (q)	27.1 (q)
14	22.3 (q)	26.1 (q)	22.7 (q)	28.1 (q)
1′	105.8 (d)	103.1 (d)	104.7 (d)	105.0 (d)
2′	74.2 (d)	74.0 (d)	74.0 (d)	76.5 (d)
3′	76.5 (d)	76.5 (d)	76.3 (d)	74.0 (d)
4′	69.9 (d)	70.0 (d)	69.8 (d)	69.8 (d)
5′	74.1 (d)	74.0 (d)	74.1 (d)	74.0 (d)
6′	63.5 (t)	62.9 (t)	63.2 (t)	63.2 (t)
1″	167.0 (s)	166.9 (s)	167.0 (s)	167.0 (s)
2″	120.3 (s)	120.4 (s)	120.3 (s)	120.5 (s)
3″	109.2 (d)	109.2 (d)	109.2 (d)	109.3 (d)
4″	144.4 (s)	144.4 (s)	144.5 (s)	144.4 (s)
5″	137.7 (s)	137.6 (s)	137.6 (s)	137.6 (s)

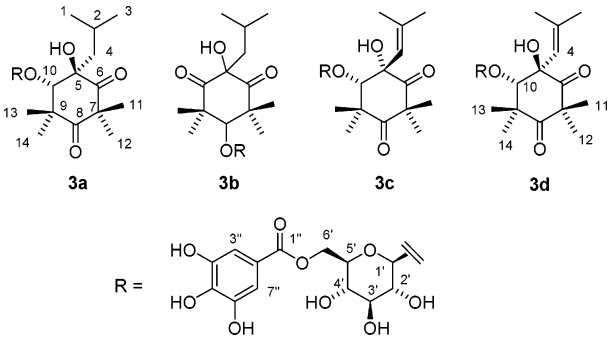
of the glycol moiety was indicated by the observation of NOE correlations between the vinylic proton (H-4) and the methyl protons H-12 and H-14, while H-10 correlated with the 13-methyl. In **3c**, a compound having the same molecular weight as **3d**, the vinylic proton was not NOE correlated to any methyl, indicating not only a different configuration at C-5 but also a different conformation of the cyclohexadienone ring. Since the NMR spectra of **3c** and **3d** showed the same ^{1}H spin systems and ^{13}C multiplicities, these compounds were assigned as a pair of *cis/trans* isomers.

The other pair of compounds (**3a** and **3b**) showed a molecular weight two units higher than **3c** and **3d.** This and the lack of the vinyl protons and allyl methyls in the ^{1}H NMR spectrum suggested saturation of the isobutenyl group. However, the HMBC correlations showed a substantially different connectivity for the cyclohexadione moiety between **3a** and **3b**. Thus, **3a** was simply the hydrogenation product of **3d**, while in **3b** the oxymethine and the quaternary oxygenated carbons were "*para*" (1,4) and not "*ortho*"(1,2) related. In **3a**, H-3 correlated with the 12-methyl, and H-10 with the 11- and 13-methyls, supporting this configurational assignment. Due to the lack of diagnostic NOE effects, it was not possible to assign the relative configuration of **3b**. On the other hand, since the glucose and the cyclohexane domains are spectroscopically isolated, only

Scheme 1. Possible Biogenetic Derivation of Gallomyrtucommulones (**3a**−**d**) and G3 (**4**)[a]



[a] Key: *a*: 3 × C2 elongation; *b*: intramolecular Claisen reaction; *c*: enolization; *d*: formal singlet oxygen cycloaddition; *e*: autoxidation; *f*: "*para*"-reduction; *g*: "*ortho*"-reduction; *h*: glucosidation and galloylation.



the relative configuration of the cyclohexadienone moiety of **3a**, **3c**, and **3d** could be assessed.

From a biogenetic standpoint, gallomyrtucommulones are presumably glycosidated polyketides, derived from an isobutyryl starter by three steps of C-2 homologation and two of geminal dimethylation (Scheme 1). After intramolecular Claisen cyclization and enolization, the enolic double bond is oxidized to a ketol, a known reaction for this type of compounds,[13] and then reduced and glycosidated. Compound **3c** (gallomyrtucommulone B) derives from a modification of this scheme, where the reduction step does not take place on one of the ketolic carbonyls, but on the "*para*" keto group. The endoperoxide hormone G3 (**4**) is presumably derived from the enolized trienone intermediate by reaction with a biological equivalent of singlet oxygen.

There is evidence that, under physiological conditions, the G-factors are present in plant tissues as inactive precursors, converted into the active hormones in response to damage or a biological stimulus. An oxidative deglucosidation would convert gallomyrtucommulones C and D (**3c** and **3d**) into the G3 precursor **5** (Scheme 1), making it of interest to evaluate the physiological relationship (if any) between G3 and these compounds. On the other hand, it was also interesting to investigate the antibacterial activity of gallomyrtucommulones, since powerful antibiotic activity has been shown for several phloroglucinols from myrtle.[6,15] All compounds were evaluated against a panel of resistant *Staphylococcus aureus* strains (Table 3), and these included MRSA strains XU212 (which also expresses the TetK efflux pump) and EMRSA-15 (which is an epidemic MRSA strain commonly encountered in the U.K.). Other isolates included the multidrug-resistant SA-1199B, which overexpresses the NorA MDR efflux transporter, and RN4220, which has a more specific macrolide efflux mechanism. Compounds **3c** and **3d** were inactive against the test panel of resistant staphylococci at a concentration of 256 μg/mL; however **3a** and **3b** had moderate antibacterial activities with minimum inhibitory concentration (MIC) values ranging from 64 to 256 μg/mL (Table 3). Compound **3b** showed significant (MIC =128 μg/mL) antibacterial activity against *Staphylococcus aureus* SA-1199B, but was ca. 4-fold less potent than the fluoroquinolone norfloxacin (MIC = 32 μg/mL), the reference compound for this type of activity. Compound **3b** was the most active analogue evaluated against RN4220, which expresses the MsrA macrolide transporter and is highly resistant to erythromycin (MIC > 128 μg/mL). Therefore, a surprising configurational dependence for the antibacterial activity of gallomyrtucommulones exists, an observation that suggests a specific biological target for these compounds. A similar dependence has been observed previously for myrtle phloroglucinols with respect to oligomerization.[6]

Taken together, the results of this study further qualify myrtle as a source of unique secondary metabolites. Nonprenylated acylphloroglucinols are common constituents of ferns,[16] but are otherwise very rare in higher plants, while alkylphloroglucinol glycosides are unknown as natural products.[17] It is therefore surprising that myrtle, despite the powerful and pleiotropic activity of its extracts and its medicinal, nutritional, and cultural relevance, has so long escaped the attention of phytochemists.

Table 3. Minimum Inhibitory Concentrations (MIC) of **3a** and **3b** (μg/mL)[a]

strain (resistance mechanism)	**3a**	**3b**	norfloxacin
ATCC 25923	128	64	1
SA-1199B (NorA)	256	128	32
RN4220 (MsrA)	128	128	2
XU212 (TetK, MecA)	256	128	4
EMRSA-15 (MecA)	128	128	0.5

[a] All MIC values were determined in duplicate.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 192 polarimeter equipped with a sodium lamp (589 nm) and 10 cm microcell. IR spectra were obtained on a Shimadzu DR 8001 spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained at room temperature with a Bruker DRX500 spectrometer with an inverse multinuclear 5 mm probehead equipped with a shielded gradient coil. The spectra were recorded in $CDCl_3$, and the solvent signals (7.26 and 77.0 ppm, respectively) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (J) in Hz. COSY, HMQC, and HMBC experiments were recorded with gradient enhancements using sine-shaped gradient pulses. For the 2D heteronuclear correlation spectroscopy the refocusing delays were optimized for $^1J_{CH} = 145$ Hz and $^nJ_{CH} = 10$ Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker XWIN NMR software (rev. 010101). Mass spectra (HRESI) were recorded with a Micromass Q-TOF microinstrument. Silica gel 60 (70−230 mesh) and Lichroprep RP-18 (25−40 mesh) were used for gravity column chromatography. HPLC in isocratic mode was performed on a JASCO Herculite apparatus equipped with a UV detector set at 254 nm and using a 250 × 21.2 × 10 mm Chromasyl column.

Plant Material. *M. communis* L. was collected in April, 2003 near San Basilio (CA, Sardinia), and was identified by M. B. A voucher specimen (CAG 504) is deposited at the Dipartimento di Scienze Botaniche, Università di Cagliari.

Extraction and Isolation. Powdered, dried leaves (1156 g) were extracted with acetone at room temperature (2 × 5 L). The pooled extracts were filtered over Celite and concentrated to a small volume (bath temperature 35 °C). RP-18 silica gel (ca. 50 g) was then added, and evaporation was continued until a solid material was obtained. The latter was fractionated by VLC on RP-18 silica gel (bed size: 9 cm × 2 cm) using water−methanol mixtures. The fraction eluted with 1:1 methanol−water (4.4 g) contained a mixture of glycosides, which was fractionated by gravity column chromatography on silica gel (100 g, 1:1 petroleum ether−EtOAc as eluant) to afford 974 mg of a gallomyrtucommulone mixture and 2.185 g of myricetin rhamnopyranoside. A fraction (250 mg) of the gallomyrtucommulone mixture was purified by preparative HPLC to afford 12 mg of **3a**, 15 mg of **3b**, 11 mg of **3c**, and 25 mg of **3d**. The low final isolation yield was due to the difficulty of the separation and the fact that a baseline separation could not be achieved.

Gallomyrtucommulone A (3a): yellowish foam; $[\alpha]_D^{25}$ +56 (*c* 0.4, methanol); IR (KBr) ν_{max} 3356, 3320, 1654, 1557, 1354, 1287, 1210, 1151, 1071 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m*/*z* 593.2198, calcd for $C_{27}H_{38}O_{13}$ + Na, 593.2210.

Gallomyrtucommulone B (3b): yellowish foam; $[\alpha]_D^{25}$ +44 (*c* 0.4, methanol); IR (KBr) ν_{max} 3350, 3315, 1648, 1558, 1350, 1289, 1221, 1151, 1039 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m*/*z* 593.2208, calcd for $C_{27}H_{38}O_{13}$ + Na, 593.2210.

Gallomyrtucommulone C (3c): yellowish foam; $[\alpha]_D^{25}$ +38 (*c* 0.4, methanol); IR (KBr) ν_{max} 3352, 3321, 1641, 1513, 1287, 1217, 1154, 1079, cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m*/*z* 591.2061, calcd for $C_{27}H_{36}O_{13}$ + Na, 591.2054.

Gallomyrtucommulone D (3d): yellowish foam; $[\alpha]_D^{25}$ +31 (*c* 0.4, methanol); IR (KBr) ν_{max} 3356, 3320, 1647, 1658, 1351, 1284, 1221, 1156, 1069, cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m*/*z* 569.2211, calcd for $C_{27}H_{36}O_{13}$ + H, 569.2234.

Antibacterial Assays. *S. aureus* strain ATCC 25923 was the generous gift of E. Udo (Kuwait University, Kuwait). *S. aureus* RN4220 containing plasmid pUL5054, which carries the gene encoding the MsrA macrolide efflux protein, was provided by J. Cove.[18] Strain XU-212,

which possesses the TetK tetracycline efflux protein, was provided by E. Udo.[19] SA-1199B, which overexpresses the *norA* gene encoding the NorA MDR efflux protein, was provided by G. Kaatz.[20] EMRSA-15 is an epidemic strain of MRSA[21] and was the generous gift of P. Stapleton, School of Pharmacy, University of London. All *Staphylococcus aureus* strains were cultured on nutrient agar and incubated for 24 h at 37 °C prior to MIC determination. Bacterial inocula equivalent to the 0.5 McFarland turbidity standard were prepared in normal saline and diluted to give a final inoculum density of 5×10^5 cfu/mL. The inoculum (125 μL) was added to all wells, and the microtiter plate was incubated at 37 °C for 18 h. The MIC was recorded as the lowest concentration at which no bacterial growth was observed, as previously described.[19]

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References and Notes

(1) As a symbol of marital love, myrtle is one of the keys to two of the most famous and enigmatic paintings of the Renaissance, the *Venus of Urbino* by Titian and the *Two Court Ladies* by Carpaccio. (For a discussion, see: Romanelli, G. *Vittore Carpaccio. Le Due Dame Veneziane*; Silvana Editoriale: Cinisello Balsamo, 2003; pp 12−13)

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