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Prenylated alkylbisphenols from Grevillea whiteana

Abstract
Eleven new bisresorcinols including four mixtures each of two isomers and one resorcinol/phloroglucinol derivative, together with five known resorcinols have been isolated from the ethyl acetate extract of sterns of Grevillea whiteana. The new Compounds were identified as 4-(3-hydroxy-3-methylbutyl)grebustol-B (10a), 4'-(3-hydroxy-3-methylbutyl)grebustol-B (10b), 4-(4-hydroxy-3-methylbutyl)grebustol-B (2a) and 4'-(4-hydroxy-3-methylbutyl) rebustol-B (2b), 2,2-dimethyldihydropyrano grebustol-B (11a) and iso-2,2-dimethyldihydropyranogrebustol-B (11b), 2,2-dimethyl-3 xi-hydroxydihydropyranogrebustol-B (7a) and iso-2,2-dimethyl-3 xi-hydroxydihydropyranogrebustol-B (7b), 15-(2-(4-hydroxy-3-methylbutyl)-resorcinol-5-yl)-1-(phloroglucinolyl)-9(Z)pentadecen-one (whiteanone) (4), 5,5'-(hexadecan-diyl)bisresorcinol (12) and 2-methyl-5,5'-(8(Z)hexadecen-1,16-diyl)bisresorcinol (9). This is the first record of pyranobisresorcinols in the genus and the first report of a phloroglucinol terminal Phenolic unit in any Grevillea species.

Keywords
prenylated, grevillea, alkylbisphenols, whiteana

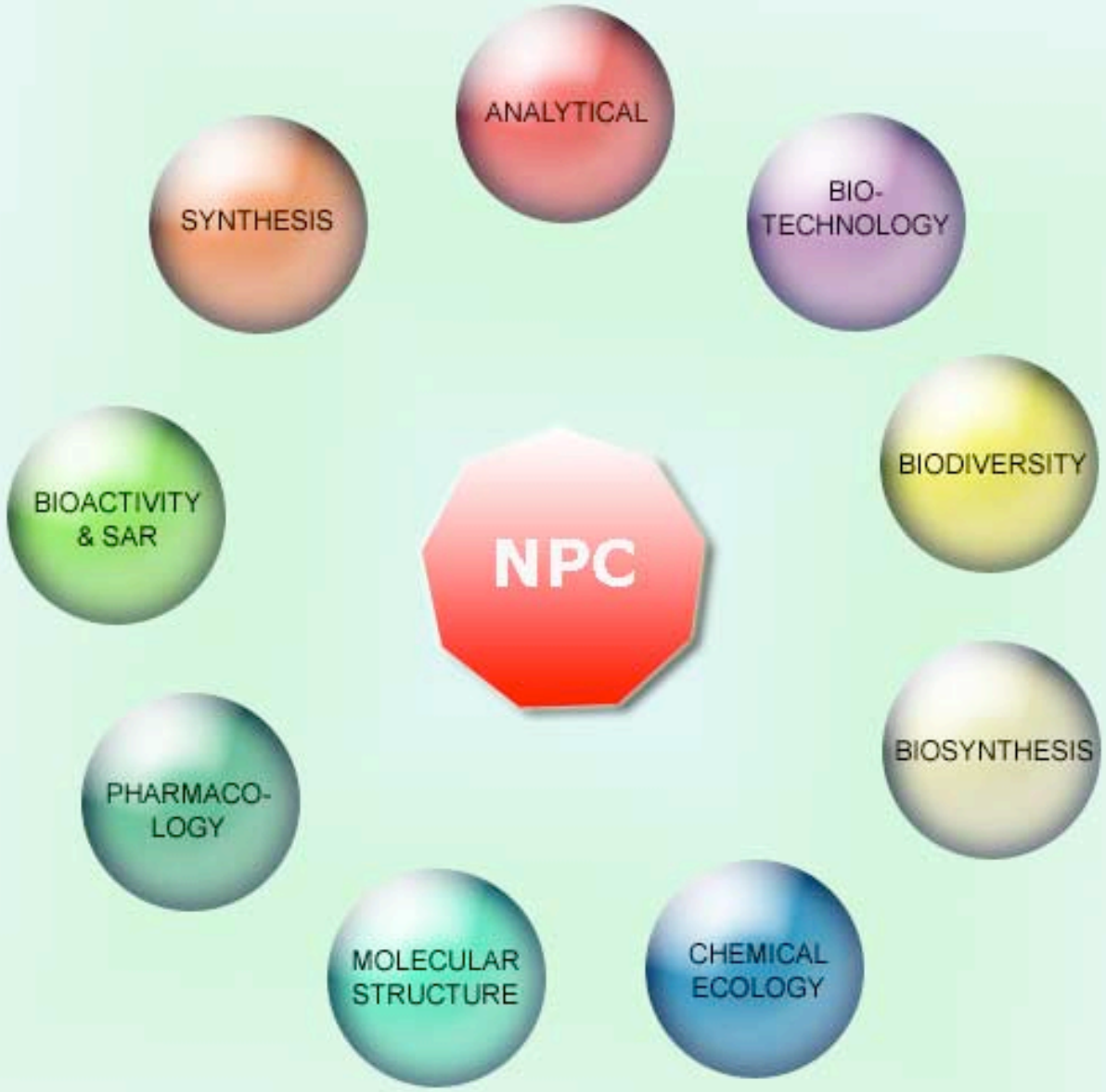
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Prenylated Alkyl*bis*phenols from *Grevillea whiteana*

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Eleven new bisresorcinols including four mixtures each of two isomers and one resorcinol/phloroglucinol derivative, together with five known resorcinols have been isolated from the ethyl acetate extract of stems of *Grevillea whiteana*. The new compounds were identified as 4-(3-hydroxy-3-methylbutyl)grebustol-B (**10a**), 4'-(3-hydroxy-3-methylbutyl)grebustol-B (1**0b**), 4-(4-hydroxy-3-methylbutyl)grebustol-B (**2a**) and 4'-(4-hydroxy-3-methylbutyl) rebustol-B (**2b**), 2,2-dimethyldihydropyrano grebustol-B (**11a**) and iso-2,2-dimethyldihydropyranogrebustol-B (**11b**), 2,2-dimethyl-3ξ-hydroxydihydropyranogrebustol-B (**7a**) and iso-2,2-dimethyl-3ξ-hydroxydihydropyranogrebustol-B (**7b**), 15-(2-(4-hydroxy-3-methylbutyl)-resorcinol-5-yl)-1-(phloroglucinolyl)-9(*Z*)pentadecen-one (whiteanone) (**4**), 5,5'-(hexadecan-diyl)bisresorcinol (**12**) and 2-methyl-5,5'-(8(*Z*)-hexadecen-1,16-diyl)bisresorcinol (**9**). This is the first record of pyranobisresorcinols in the genus and the first report of a phloroglucinol terminal phenolic unit in any *Grevillea* species.

Keywords: *Grevillea whiteana*, Proteaceae, bisresorcinol, grebustol-B, prenyl substituents.

With over 350 species, *Grevillea* R.Br. *ex* Knight is the largest genus in the family Proteaceae, and one of the largest plant genera of any family in Australia [1]. Early phytochemical work on the genus focused on the common and widespread species *G. robusta* and *G. striata* and most of the compounds isolated have been resorcinol derivatives [2-6].

Considering its size and ecological importance in Australia information on the chemistry of this genus is surprisingly scanty. Consequently we have undertaken a phytochemical survey of a number of species. As part of this survey we have already reported the profiles of compounds present in *G. robusta* [7], *G. banksii* [8] and *G. floribunda* [9]. In all those species the major classes of compounds were again bisresorcinols, together with arbutin derivatives.

We now wish to report the results of an investigation of a sample of *G. whiteana* McGillivray, a small tree up to 5 m tall of limited distribution in south-eastern Queensland from Boondooma northward to Mundubbera and also on Mt Walsh near Biggenden [1]. No previous studies have been reported for this species.

Through preparative HPLC of the methanol soluble fraction of an ethyl acetate extract, a total of sixteen phenols were isolated of which five were identified as the previously reported 2,2'-di(4-hydroxy-3-methylbutyl)grebustol-B (**1**) [8], 5,5'-(4(*Z*)-tetradecene-1,14-diyl)bisresorcinol (**3**) [10], grevirobstol-A (**5**) [6], mono-norstriatol, (**6**) [4] and striatol (**8**) [5]. Each was identified by comparison of their spectroscopic data with those reported in the literature. The remaining eleven compounds were novel and comprised four pairs of inseparable isomers (**2**, **10**, **11**, and **7**), together with three discrete compounds, **4**, **12** and **9**.

The mixture isolated as **2** was assigned the molecular formula $C_{31}H_{44}O_5$ based on HRESIMS. The ^{13}C-JMOD NMR (Table 1) and HSQC spectra defined

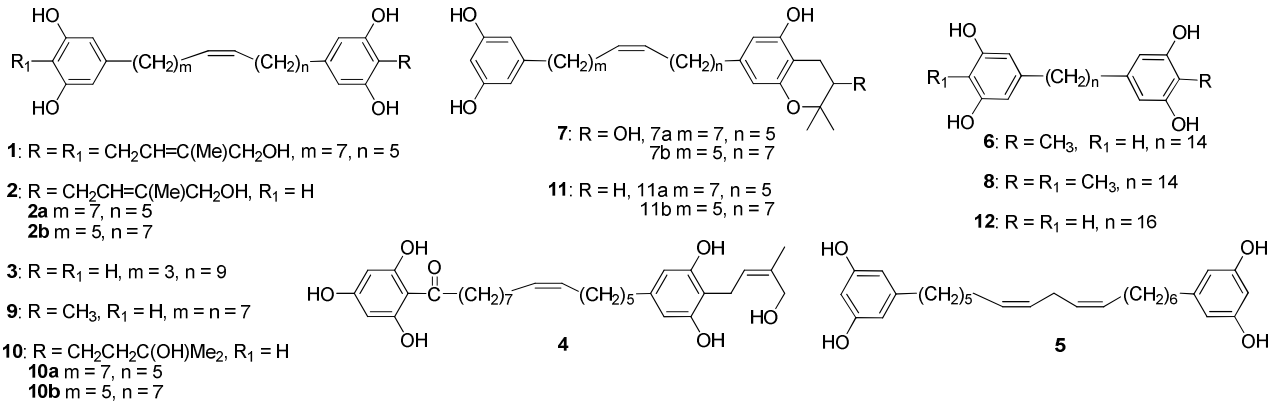


Table 1: ^{13}C and ^{1}H NMR assignments for **2**, **10** **11**, **7** and **4** (CD_3OD, 500 MHz).

	2		**10**		**11**		**7**		**4**	
C[a]	δ_C, m	δ_H, m, *J*	δ_C, m	δ_H, m, *J*	δ_C, m	δ_H, m, *J*	δ_C, m	δ_H, m, *J*	δ_C, m	δ_H, m, *J*
Resorcinol-1									Phloroglucinol	
1	157.1		157.0		156.5		157.0		166.0	
2	113.1		113.1		106.5		107.3		105.5	
3	157.1		157.0		156.5		156.5		166.0	
4	108.1	6.14 s	108.1	6.14 s	109.5	6.11 d 1.4	109.5	6.07 d 1.4	95.5	5.81 s
5	142.8		142.8		142.5		142.5		166.1	
6	108.1	6.14 s	108.1	6.14 s	107.5	6.18 d 1.5	107.5	6.16 d 1.5	95.5	5.81 s
4-Hydroxyprenyl			3-Hydroxy-isopentanyl		Pyran				Prenyl	
1	22.9	3.31 m	19.3	2.64 m	27.3	2.88 dd, 16.9, 5.6 2.52 dd, 16.9, 7.5	18.1	2.60 t 6.8	22.9	3.31 m
2	126.8	5.53 m	43.7	1.68 m	70.5	3.73 dd, 7.5, 5.6	33.7	1.76 t 6.8	126.8	5.52 m
3	134.7		72.1		77.7		74.8		134.7	
4	69.6	3.89 s	29.3 *q*	1.23 s	20.9 *q*	1.21 s	27.1 *q*	1.28 s	69.5 *q*	3.89 s
3-Me	14.0 *q*	1.80 s	29.3 *q*	1.23 s	26.0 *q*	1.30 s	27.1 *q*	1.28 s	14.0 *q*	1.80 s
Resorcinol-2									Resorcinol	
1, 3	159.4		159.4		159.4		159.4		159.4	
2	101.1	6.08 d 1.5	101.1	6.08 d 1.5	101.1	6.08 m	101.1	6.08 m	101.1	6.08 m
4, 6	108.0	6.13 d 2.2	108.1	6.13 d 2.2	108.1	6.13 d 2.2	108.1	6.13 d 2.2	108.1	6.13 d 2.2
5	146.5		146.5		146.5		146.5		146.5	
Tetradecene									9-Pentadecen-one	
1	36.9	2.41 t 7.6	36.9	2.41 t 7.6	36.9	2.43 m	36.9	2.41 m	207.8	
2	32.6	1.58 m	32.4	1.58 m	32.4	1.56 m	32.4	1.68 m	45.0	3.04 t 7.6
3	30.4[b]	1.34 m	30.5[b]	1.35 m	30.5[b]	1.31 m	30.5[b]	1.35 m	26.4	1.66 m
4	30.8[b]	1.34 m	30.4[b]	1.35 m	30.8[b]	1.31 m	30.9[b]	1.35 m	30.1[b]	1.33 m
5	28.2	2.02 m	28.3	2.02 m	28.3	2.02 m	28.3	2.03 m	30.2[b]	1.33 m
6	130.9	5.34 m	130.9	5.34 m	131.0	5.34 m	131.0	5.36 m	30.5[b]	1.33 m
7	131.1	5.34 m	131.1	5.34 m	130.9	5.34 m	130.9	5.36 m	30.8[b]	1.33 m
8	28.3	2.02 m	28.3	2.02 m	28.2	2.02 m	28.2	2.03 m	28.3	2.02 m
9	30.8[b]	1.34 m	30.9[b]	1.35 m	30.8[b]	1.31 m	30.8[b]	1.35 m	130.9	5.34 m
10	30.7[b]	1.34 m	30.8[b]	1.35 m	30.7[b]	1.31 m	30.6[b]	1.35 m	131.0	5.34 m
11	30.6[b]	1.34 m	30.7[b]	1.35 m	30.6[b]	1.31 m	30.6[b]	1.35 m	28.3	2.02 m
12	30.5[b]	1.34 m	30.4[b]	1.35 m	30.4[b]	1.31 m	30.5[b]	1.35 m	30.8[b]	1.33 m
13	32.6	1.58 m	32.6	1.58 m	32.5	1.56 m	32.5	1.58 m	30.1[b]	1.33 m
14	37.1	2.45 t 7.7	37.1	2.45 t 7.7	37.1	2.45 m	37.1	2.43 *m*	32.5	1.58 m
15									36.9	2.41 *t* 7.6

[a] Numbering of the resorcinol carbons follows the technical rather than the trivial name. Using the latter C-1 becomes C-3, C-2 = C-4, C-3 = C-5, C-4 = C-6, C-5 = C-1 and C-6 = C-2. Likewise the numbering for the prenyl unit is for the open chain, for the cyclized dihydropyran ring C-1 becomes C-4, C-2 = C-3, C-3 = C-2 and C-4 and 3-Me are the two methyl groups attached to C-2.

[b] Assignments may be interchanged in each column

carbon signals for one methyl, 14 methylene, including one hydroxymethylene (δ 69.6), and two benzylic methylenes (δ 36.9 and 37.1), five aromatic methines (δ 101.1, 108.0 x 2 and 108.1 x 2), three vinyl methines (δ 126.8, 130.9 and 131.1), one olefinic quaternary (δ 134.7), and seven aromatic quaternary carbons (δ 113.1, 142.8, 146.5, 157.1 x 2 and 159.4 x 2). The ^{1}H NMR spectrum (Table 1), analyzed with the aid of the HSQC and COSY-45 spectra, showed signals attributable to a 4-hydroxy-3-methylbut-2-enyl unit. The remaining ^{1}H NMR resonances were for six methylenes at δ 1.34, two allylic methylenes at δ 2.02, two olefinic protons at δ 5.34, two methylene groups bonded to aromatic rings at δ 2.41 and 2.45, a set of A_2C aromatic protons at δ 6.13 and 6.08 and a pair of identical aromatic protons at δ 6.14.

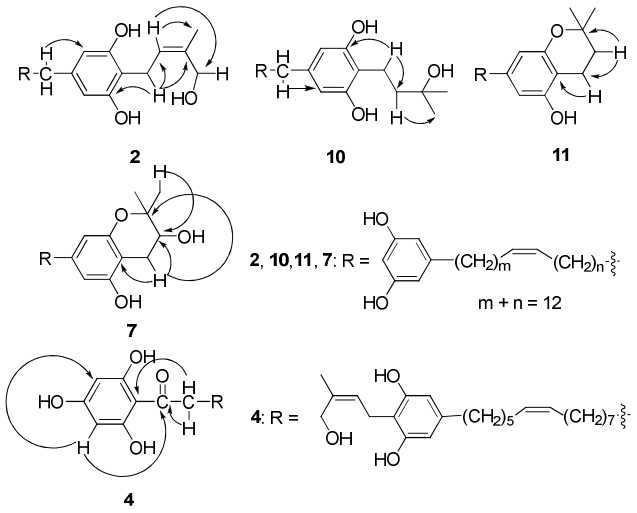


Figure 1: Key HMBC correlations of compounds **2**,**10**,**11**,**7** and **4**.

On the basis of these NMR spectroscopic data and comparison with previous studies [7,8] **2** appeared to be a tetradecene substituted with resorcinol groups at C-1 and C-14, similar to most compounds previously reported from *Grevillea*. HMBC correlations between the methylene groups at δ 2.41 and 2.45 and the two aromatic systems (Figure 1) confirmed their point of substitution between resorcinols and methylene chain was flanked by the methines resonating at δ 108.1 and 108.0, respectively. The olefinic bond must be placed somewhere near the centre of the 14 C chain as the olefinic carbons did not exhibit any HMBC correlations with the 1, 2, 13 or 14 methylenes, precluding placement at C-3, C-4, C-11 or C-12. The methylene at δ 3.31, part of the prenyl unit, exhibited ^3J correlations, revealing that it was flanked by the oxygenated carbons at δ 157.1. This required that it be placed at C-4 of one of the resorcinol units, *para* to the point of attachment of the alkene.

Placement of the double bond in the methylene chain was determined by the novel technique of Ozone Induced Dissociation (OzID) [14] of a sample of **2** that had been peracetylated. In the OzID spectrum of the $[M+Na]^+$ molecular ion (*m/z* 729), eight fragment ions were observed from the chemical cleavage of the tetradecenyl chain. These ions can be rationalized as shown in Figure 2 to indicate the presence of two compounds in which the double bond location on the tetradecenyl chain differs by two methylene units with respect to the two terminal aromatic units. The *Z*-configuration of the double bond was established by considering the chemical shifts (δ 28.2 and 28.3) of the allylic carbons. A lower field chemical shift

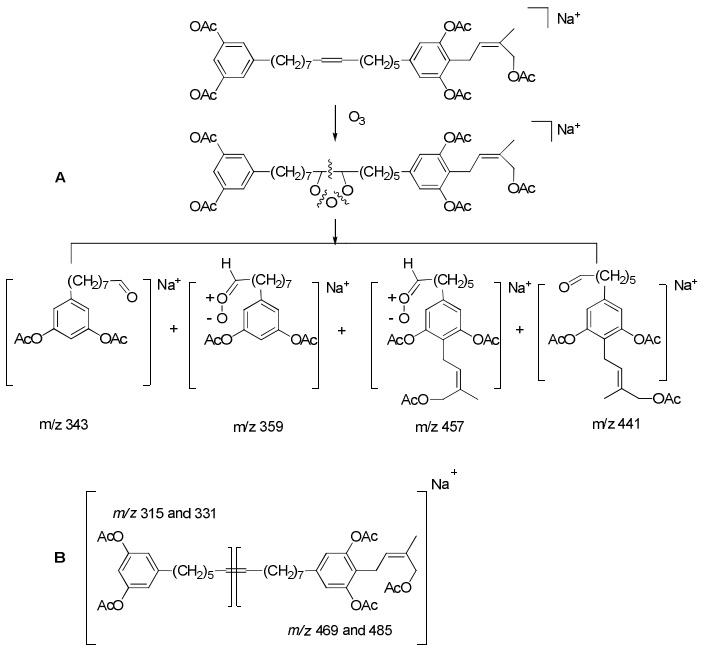


Figure 2: A: Mass fragmentation of acetylated **2a** with OzID.
B: Mass fragmentation of acetylated **2b** with OzID.

value would be expected for carbons allylic to a double bond with *E*-geometry [11]. A comparison with the data of analogous compounds [6] also confirmed the *Z*-form.

Thus **2** was a mixture of 2-(4-hydroxy-3-methylbut-2-enyl)-5,5'(6(*Z*)-tetradecen-1,14-diyl)bisresorcinol (**2a**) and 2-(4-hydroxy-3-methylbut-2-enyl)-5,5'(8(*Z*)-tetradecen-1,14-diyl)bisresorcinol (**2b**). The unsubstituted bisresorcinol on which these structures are based is known and has been given the name grebustol-B [6]. Based on this, the trivial names 4-(4-hydroxy-3-methyl-but-2-enyl)grebustol-B (**2a**) and 4'-(4-hydroxy-3-methylbut-2-enyl)grebustol-B (**2b**) have been assigned to the two isomers.

Isolates **10**, **11** and **7**, based on their HRESIMS, exhibited the empirical formulae $C_{31}H_{46}O_5$, $C_{31}H_{44}O_4$ and $C_{31}H_{44}O_5$, respectively. NMR analysis comparable to that undertaken for **2** (Table 1) revealed that they were all based on the tetradecene bisresorcinol unit in which one of the resorcinol rings was substituted at C-4 by a prenyl group. In **10** the prenyl group was readily resolved to be 3-hydroxy-3-methylbutanyl, giving rise to the additional 2H in the empirical formula. In **11** the 5-carbon prenyl unit was again indicated, in this case as two adjacent methylenes at δ 1.76 and δ 2.60 (δc 33.7 and 18.1), a quaternary oxygenated sp^3 carbon (δc 74.8) and two

equivalent methyls at δ 1.28 (δc 27.1). As the empirical formula indicated 10 DBE's, of which only nine were accounted for by the two aromatic rings and the double bond in the tetradecene, the prenyl side chain had to be cyclized as a 2,2-dimethyldihyropyrano moiety. This argument was supported by HMBC correlations (Figure 1) and the non-equivalence of the resonances for the two methine protons of the prenyl-substituted resorcinol ring in comparison with the symmetry seen in **2** and **10**. Similarly, in **7** the calculation for **10** DBEs required cyclization of the prenyl group. The additional oxygen in the empirical formula of **7** was attributable to a hydroxymethine replacing one of the two methylenes in the dihydropyrano ring. This can be placed at C-3" (relative stereochemistry unresolved) on the basis of HMBC correlations (Figure 1).

In each case placement of the double bond in the methylene chain was again examined by MS analysis with OzID. For both **11** and **7** results were obtained comparable to those observed for **2**, confirming the presence of two isomers, in which the position of the double bond varied by two carbons. Surprisingly, the technique failed to give meaningful results for **10** and the paucity of material available made repeating the experiment impossible. While absolute proof is absent, there seems no reason not to assume that **10** is a mixture exactly as the other compounds are. Thus **11** was established as a mixture of 7-(14-(5-resorcinol-yl)-6(*Z*)-tetradecenyl)-5-hydroxy-2,2-dimethylchroman (**11a**) and 7-(14-(5-resorcinol-yl)-8(*Z*)-tetradecenyl)-5-hydroxy-2,2-dimethylchroman (**11b**). These two compounds have been given the trivial names 2,2-dimethyldihydropyranogrebustol-B and iso-2,2-dimethyldihydropyranogrebustol-B respectively. Likewise **7** was a mixture of 7-(14-(5-resorcinol-yl)-6(*Z*)-tetradecenyl)-3ξ,5-dihydroxy-2,2-dimethylchroman (**7a**) and 7-(14-(5-resorcinol-yl)-8(*Z*)-tetradecenyl)-3ξ,5-dihydroxy-2,2-dimethyl chroman (**7b**) with the trivial names 2,2-dimethyl-3ξ-hydroxydihydropyranogrebustol-B and iso-2,2-dimethyl-3ξ-hydroxydihydropyranogrebustol-B assigned to **7a** and **7b**, respectively. Isolate **10** is presumed to be a mixture of 4-(3-hydroxy-3-methylbutyl)grebustol-B (**10a**) and 4'-(3-hydroxy-3-methylbutyl)grebustol-B (**10b**).

Compound **4** was assigned the molecular formula $C_{32}H_{44}O_7$ based on HRESIMS. The ^1H and ^{13}C NMR spectra (Table 1), when compared with those of **2**, showed the same partial structure in the 1-(4-hydroxy-3-methylbut-2-enyl)-resorcinolyl tetradecene moiety. However, there were differences in the resonances for the aryl substituent at the other end of the tetradecene chain. This revealed seven ^{13}C signals as two equivalent aromatic methines (δ 95.9), four aromatic quaternary carbons (δ 150.5, 160.0 x 2 and 160.1) and one carbonyl carbon (δ 207.8) in the ^{13}C-JMOD NMR spectrum and two equivalent aromatic protons (δ 5.81) in the ^1H NMR spectrum. This indicated the presence of a phloroglucinol ring attached to the methylene chain by the carbonyl. This was confirmed by the HMBC experiment, which revealed (Figure 1) intense correlations between the carbonyl carbon and the methylene protons at δ 3.04 (^2J) and between the methine protons and the ring junction carbon at δc 105.5 (^3J) and a surprisingly strong ^4J interaction between the methine protons and the carbonyl.

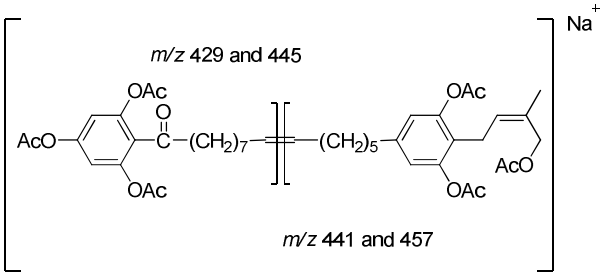


Figure 3: Mass fragmentation of acetylated **4** with OzID.

Again the OzID technique was applied to locate the double bond in the tetradecene chain. Two ozonolysis products were observed at *m/z* 441 and 457, which identified the location of the double bond at C-9 and C-10 of the tetradencyl chain (Figure 3). The *Z*-form of the double bond was again established by considering the chemical shifts (δ 28.3 and 28.2) of the allylic carbons [6]. On this basis, **4** was characterized as 15-(2-(4-hydroxyprenyl)-resorcinol-5-yl)-1-(phloroglu-cinolyl)-9(*Z*)-pentadecen-1-one, to which the trivial name whiteanone has been assigned.

The two remaining isolates (**9** and **12**) revealed, through ^1H and ^{13}C NMR spectra (Table 2), the typical bis-5-alkylresorcinol, but connected through a hexadecane chain. Compound **12** ($C_{28}H_{42}O_4$ by HREIMS) showed no additional features and therefore must be 5,5'-(hexadecan-1,16-diyl) bisresorcinol, an analogue of the known compound bisnorstriatol [4].

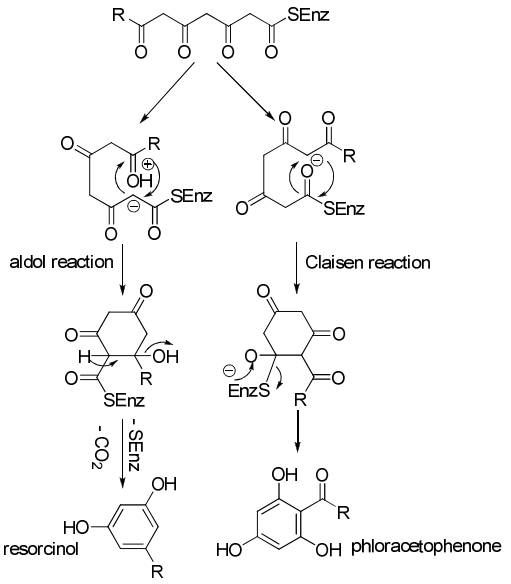
Table 2: ^{13}C and ^{1}H NMR assignments for **9** and **12** (CD_3OD, 500 MHz).

	9		**12**	
C[a]	δ_C, m	δ_H, m, *J*	δ_C, m	δ_H, m, *J*
Resorcinol-1				
1, 3	157.2		159.4	
2	110.0		101.1	6.08 t 2.2
4, 6	107.9	6.15 d 2.2	108.1	6.13 d 2.2
5	142.3		146.5	
CH_3	8.4	1.99 s		
Resorcinol-2				
1', 3'	159.4		159.4	
2'	101.1	6.08 t 2.2	101.1	6.08 t 2.2
4', 6'	108.1	6.13 d 2.2	108.1	6.13 d 2.2
5'	146.5		146.5	
Methylene chain				
1"	36.9	2.41 t 7.9	37.1	2.45 t 7.1
2"	32.5	1.56 brd, 5.6	32.5	1.56 m
3" - 5", 12" - 14"	30.4 – 30.6	1.31 m	30.4 – 30.6	1.31 m
6"	31.0[b]	1.31 m	30.7[b]	1.31 m
7"	28.3	2.03 brd 5.7	30.8[b]	1.31 m
8"	131.0	5.34 t 4.6	30.9[b]	1.31 m
9"	131.0	5.34 t 4.6	30.9[b]	1.31 m
10"	28.3	2.03 brd 5.7	30.9[b]	1.31 m
11"	31.0[b]	1.31 m	30.7[b]	1.31 m
15"	32.6	1.56 brd, 5.6	32.5	1.57 m
16"	37.1	2.45 t 7.9	37.1	2.45 t 7.1

[a] Numbering of the resorcinol carbons follows the technical rather than the trivial name. Using the latter C-1 becomes C-3, C-2 = C-4, C-3 = C-5, C-4 = C-6, C-5 -= C-1 and C-6 = C-2.
[b] Assignments may be interchanged in each column.

Compound **9** ($C_{29}H_{42}O_4$ by HRESIMS) revealed carbon signals (Table 2) for one methyl, 14 methylene carbons, including two benzylic methylenes (δ 36.6 and 37.0), five aromatic methines (δ 101.1-108.1), two equivalent olefinic methines (δ 131.0), and seven aromatic quaternary carbons (δ 110.0, 142.3, 146.5, 157.2 x 2 and 159.4 x 2). The ^{1}H NMR spectrum (Table 2), analyzed with the aid of the COSY-45 spectrum, showed signals for eight methylenes at δ 1.31, two methylenes at δ 1.56, two benzylic methylenes at δ 2.45 and 2.41, two allylic methylenes at δ 2.03, two olefinic protons at δ 5.34 and five aromatic protons at δ 6.15 x 2, 6.13 x 2 and 6.08. These data identified **9** as a bis-5-alkylresorcinol derivative with a hexadecene chain with one typical resorcinol terminal unit. The second terminal unit has one methine replaced with a C-methyl but retained symmetry in NMR resonances, allowing the methyl to be placed *para* to the alkyl group. The olefinic bond in the hexadecene chain can be placed at C-8/C-9 on the basis of the equivalence of the ^{13}C resonances for these carbons and in agreement with that reported for 5,5'-(8(*Z*)-hexadecene-1,16-diyl)bisresorcinol [12]. Hence, the structure of **9** was assigned as 2-methyl-5,5'-(8(*Z*)-hexadecen-1,16-diyl)bisresorcinol.

This study extends the range and structural diversity of prenyl substituents found in the bisphenols isolated from *Grevillea* species, the only previous example being that recorded by us from *G. banksii* [8]. It is somewhat surprising, given that the resorcinol nucleus is highly susceptible to the addition of prenyl substituents that these had not been recorded previously. Of considerable interest is the presence of the hitherto unrecorded phloroglucinol terminal unit found here in **4**. The phloroglucinol structure represents an alternate cyclisation of the polyketide chain to that occurring in the formation of resorcinol (Scheme 1) [13] and so finding the former is not unexpected. As is shown in Scheme 1, the formation of the phloroglucinol unit is thought to involve the loss of one less carbon from the polyketide precursor than does resorcinol and so the fact that the two phenols are separated by a 15-carbon chain in **4** whereas in the bisresorcinols based on grebustol-B they have a 14-carbon chain does not preclude the possibility that both have arisen from a common precursor.



Scheme 1: Possible route to resorcinol and phloroglucinol terminal units from a common precursor.
R = the remainder of the polyketide chain. Identical or different folding patterns at the two ends of the chain could be envisaged to lead to resorcinol or phloroglucinol terminal groups.

Experimental

General: NMR spectra were acquired on a Bruker AVANCE DRX500 (^{1}H, 500 MHz; ^{13}C, 125.77 MHz) spectrometer using CD_3OD and C_5D_5N as solvents and the residual solvent peak as reference. All experiments were run using the standard pulse sequences in the Bruker library. Mass spectra were recorded on an Agilent 1100 Series LC/MSD with binary pump, DAD, MS detector featuring

atmospheric pressure chemical ionization (APCI) and a Phenomenex Aqua C_{18} column (4.6×150 mm, 5 μm). HR-EIMS were obtained using a Kratos MS 25 RFA via direct insertion at 70 eV with PFK used as reference for magnet scan accurate mass data. Preparative isolations were performed on a Gilson HPLC system with 306 pump, UV/VIS-155 detector and FC 204 fraction collector using an Alltina C_{18} column (22 x 150mm, 5 μm). Semi-preparative isolations were performed on an Agilent 1100 system with quaternary pump and DAD using a Zorbax SB C_{18} column (9.4 x 250 mm, 5 μm).

Plant material: Fresh stems with leaves of *Grevillea whiteana* were collected at the Beeron Holding, Queensland, Australia, in March 2005, and identified by Dr Paul Forster. A voucher specimen (PIF 19596) was deposited at the Queensland Herbarium (BRI).

Extraction and isolation: The ground, air-dried stems (1.2 kg) were extracted by sonication with EtOAc (2 L x 2). The EtOAc extract (13 g) was partitioned between MeOH (10% H_2O) and *n*-hexane. The MeOH partition was applied to preparative HPLC with a solvent system of A (water) and B (acetonitrile, 0.05% TFA) with a gradient elution of 60% to 95% of B over 20 mins. to afford 23 fractions. Fraction 9 was subjected to semi-preparative HPLC, eluted with H_2O-acetonitrile (41:59), yielding compounds **1** (8.7 mg) and **2** (3.5 mg). Fraction 11 was separated by semi-preparative HPLC, eluted with H_2O-acetonitrile (40:60), giving **3** (2.7 mg) and **4** (1.8 mg). Fraction 13 was purified by semi-preparative HPLC, eluted with H_2O-acetonitrile (40:60), affording **5** (2.1 mg). Fraction 15 was purified by semi-preparative HPLC, eluted with H_2O-acetonitrile (10:90), yielding **6** (2.7mg). Fraction 16 was separated by semi-preparative HPLC, eluted with H_2O-acetonitrile (38:62), giving **7** (1.9 mg) and **8** (2.9 mg). Fraction 17 was purified by semi-preparative HPLC, eluted with H_2O-acetonitrile (36:64), yielding **9** (3.0 mg). Fraction 18 was separated by semi-preparative HPLC, eluted with H_2O-acetonitrile (36:64), giving **10** (1.9 mg) and **11** (1.6 mg). Fraction 22 was purified by semi-preparative HPLC, eluted with H_2O-acetonitrile (32:68), affording **12** (2.4 mg).

Peracetylation: Reactant (0.5 mg) was placed in a 10 mL capped tube with 1 mL acetic anhydride and 3 mL pyridine. The solution was stirred at 60°C for 90 min. The reaction was stopped by adding 2 mL water, then partitioned against 2 mL CH_2Cl_2. The CH_2Cl_2 phase was washed with water (2 x 2 mL), then analyzed by LC-MS to check the completeness of peracetylation.

Ozonolysis of mass selected ions – Ozone Induced Dissociation (OzID): Ozone Induced Dissociation (OzID) is a novel approach for the identification of double bond position using mass spectrometry [14]. In OzID, ions are mass-selected and allowed to react with ozone to produce chemically induced fragment ions. The mass-to-charge of these fragment ions allows for the assignment of double bond position. OzID was performed on a modified ThermoFinnigan LTQ ion-trap mass spectrometer (San Jose, CA). The instrument modification involved by-passing the helium splitter to make a direct connection between the helium supply and the ion trap with the helium flow rate controlled using a metering flow valve. High concentration ozone was generated using a HC-30 ozone generator (Ozone Solutions, Sioux Center, Iowa, USA). Ozone was collected in a plastic syringe and introduced into the flow of helium through a PEEKsil tubing restrictor (100 mm L x 1/16" OD x 0.023 mm ID, SGE). Samples were prepared in MeOH with 100 μM NaOAc and ionized by Electrospray Ionisation (ESI). To acquire OzID spectra, $[M+Na]^+$ ions were mass-selected and trapped in the presence of ozone for 10 seconds per scan. At least 50 scans were acquired for each spectrum.

Mixture of 4- and 4'-(4-hydroxy-3-methylbut-2-enyl)grebustol-B (2a/2b)

Brown gum.
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
OzID-EIMS: *m/z* $[M + Na]^+$ 441 and 457 indicative of **2a** (Figure 2) and 469 and 485 indicative of **2b** (Figure 2).
HRESIMS *m/z* 519.3083 $[M + Na]^+$ (calcd for $C_{31}H_{44}O_5Na$, 519.3086).

Whiteanone (4)

Brown gum.
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
OzID-ESIMS of acetylated **4**: *m/z* $[M + Na]^+$ 441 and 457 indicative of structure shown in Figure 3. HRESIMS *m/z* 563.2990 $[M + Na]^+$ (calcd for $C_{32}H_{44}O_7Na$, 563.2985).

Mixture of 2,2-dimethyl-3ξ-hydroxy-dihydro pyran)grebustol-B and iso-2,2-dimethyl-3ξ-hydroxy-dihydropyranogrebustol-B (7a/7b)

Brown gum.
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
OzID-EIMS: *m/z* [M + Na]$^+$ 315, 331, 427 and 443 indicative of **7b** and 343, 359, 399 and 415 indicative of **7a**.
HRESIMS: *m/z* 519.3080 [M + Na]$^+$ (calcd for $C_{31}H_{44}O_5Na$, 519.3086).

2-Methyl-5,5'-(8(*Z*)-hexadecen-1,16-diyl) bisresorcinol (9)

Brown gum.
^{1}H NMR: Table 2.
^{13}C NMR: Table 2.
HRESIMS: *m/z* 477.2979 [M + Na]$^+$ (calcd for $C_{29}H_{42}O_4Na$, 477.2981).

Mixture of 4-(3-hydroxy-3-methylbutyl)grebustol-B and 4'-(3-hydroxy-3-methylbutyl)grebustol-B (10a/10b)

Brown gum.
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
HRESIMS: *m/z* 521.3243 [M + Na]$^+$ (calcd for $C_{31}H_{46}O_5Na$, 521.3243).

Mixture of 2,2-dimethyldihydropyranogrebustol-B and iso2,2-dimethyldihydro pyranogrebustol-B (11a/11b)

Brown gum.
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
OzID-EIMS: *m/z* [M + Na]$^+$ 315, 331 and 385 indicative of **11b** and 343, 359, 341 and 357 indicative of **11a**.
HRESIMS: m/z 503.3136 [M + Na]$^+$ (calcd for $C_{31}H_{44}O_4Na$, 503.3137).

5,5'-(Hexadecan-diyl)bisresorcinol (12)

Brown gum.
^{1}H NMR: Table 2.
^{13}C NMR: Table 2.
HRESIMS: *m/z* 465.2914 [M + Na]$^+$ (calcd for $C_{28}H_{42}O_4Na$, 465.2918).

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