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Short communication

# Using NMR to determine the relative stereochemistry of 7,7-diaryl-8,8′-dimethylbutan-1-ol lignans

Samuel J. Davidson, Claire E. Rye, David Barker*

*School of Chemical Sciences, University of Auckland, 23 Symonds St., Auckland, New Zealand*

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ABSTRACT

Due to their linear, freely rotatable, structure many natural 7,7-diaryl-8,8′-dimethylbutan-7′-ol lignans are reported without any stereochemical assignment. Analysis of synthetic 8,8′-dimethylbutanol lignans and analogues reveals significant differences between the NMR data of *syn*- and *anti*-isomers. This information was then used to determine the relative stereochemistry of the C-8 and C-8′ methyl groups in previously undefined natural products.



Lignans are a broad class of plant secondary metabolites formed from the oxidative dimerization of two phenyl propanoid units. The different positions for oxidative coupling gives rise to the various structural classes of lignans. An interesting class of lignans, the 7,7-diarylbutanol seco-lignans, have been reported to have cytotoxic [1], anti-HIV-1 [2] and antioxidant [3] bioactivity (e.g. *Schisandra* lignan (**1**), Fig. 1) and synthetic analogues of these have shown even higher bioactivity [4]. Due to their acyclic structure with many freely rotatable bonds natural 7,7-diarylbutanol lignans are frequently reported in the literature with no relative stereochemical assignments and many of which are reported as having chirality. Kadangustin J (**2**), isolated from *Kadsura angustifolia* [5], has a reported $\alpha_D$ of +4.9° whereas a subsequent synthesis of the enantiomer of kadangustin J (**2**) found an $\alpha_D$ of −20.7° [6]. *Schisandra* lignan (**1**), isolated from *Schisandra propinqua* (Wall.) Baill. [1], also had dissimilar rotations from an asymmetrically prepared sample [7]. Syntheses of both *Schisandra* lignan (**1**) [7] and kadangustin J (**2**) [6,8] have allowed for the determination of a stereochemical relationship between the two methyl groups. Other lignans in this class, schilancifolignan D (**3**) – isolated from *Schisandra lancifolia* [9], marphenol G (**4**) – from *Schisandra wilsoniana* [10], and kadangustin K (**5**) – from *Kadsura angustifolia* [5], have been reported with undefined relative stereochemistry and have not been synthesised (Fig. 2). These lignans have three chiral centres compared to that of kadangustin J (**2**) and *Schisandra* lignan (**1**) which only have two chiral centres (Table 1). Therefore it would be helpful and important to understand the relative stereochemical relationship between the two methyl groups at C-8 and C-8′, as this would reduce the number of isomers required to determine the absolute stereochemistry of these interesting seco-lignans. Acetate forms of 7,7-diarylbutanol lignans have also been isolated, henricine B (**8**) – from *Schisandra henryi* [11], and lignan **9** – from *Schisandra sphenanthera* which has been reported as having anti-HSV and anti-adenovirus activity [12], and have been reported without stereochemical assignments (Table 2).

Previously, assignments of stereochemistry of these butanol type lignans have been achieved by chemical transformation to a known cyclic aryltetralone lignan (e.g. lignan **6** to lignan **6a**, Fig. 1) [13]. Others have used nOe analysis [14] and Newman projections [15] (lignan **7**), however due to the number of freely rotatable bonds in these butanol lignans, these methods of stereochemical analysis are non-reliable.

Our group has previously synthesised a range of *syn*-dimethyl-7,7-diarylbutanol lignans, including kadangustin J (**2**) [6]. During this previous work we observed that the NMR data from reported, but stereochemically undefined, lignans was significantly varied. This led us to speculate that these variations were due to the compounds being either *syn*- or *anti*-8,8′-dimethyl-7,7-diarylbutanols. We therefore theorized that if each stereoisomer was prepared it would allow for comparisons between the two isomers and perhaps differences could be seen that would allow for a simplified method of characterisation of isolated lignans.

The 7,7-diarylbutanol lignan analogues **10a–d** were synthesised following our reported procedure, which utilises the rearrangement of 1,4-diarylbutan-1,4-diols **11a–d** [16]. The *syn*-8,8′

* Corresponding author. Fax: +64 64 373 7422.
*E-mail address:* d.barker@auckland.ac.nz (D. Barker).

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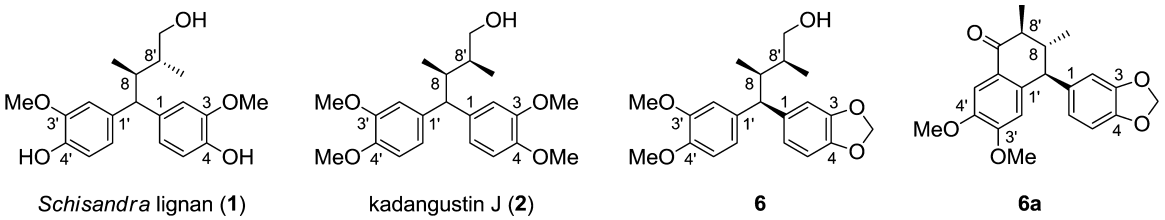



**Fig. 1.** Structures of 7,7-diaryl-8,8′-dimethylbutanol lignans: *anti-Schisandra* lignan, *syn*-kadangustin K, and lignan **6** with structure as determined via chemical transformation to give tetralone **6a**.

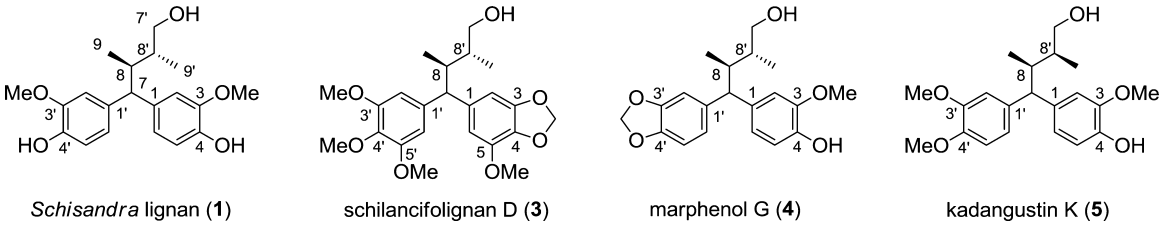


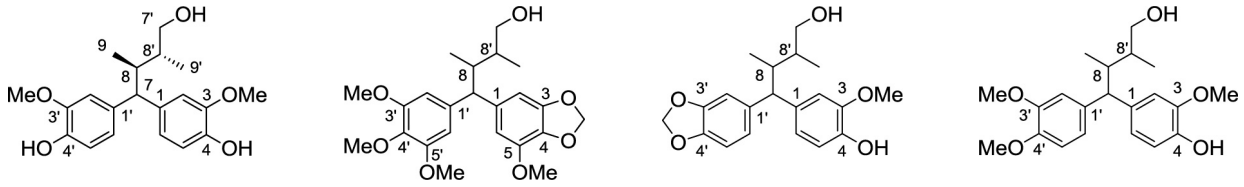

**Fig. 2.** Proposed relative stereochemistry of natural lignans based on NMR analysis.

stereochemistry in diols **11a**,**b** is provided by an acyl-Claisen rearrangement of *E*-crotyl morpholine (**12**) which gives only *syn*-amide **13**. Using a mixture of *E*- and *Z*-crotyl morpholine (**14**), prepared from commercial *E*/*Z*-crotyl chloride, in the acyl-Claisen rearrangement gave a mixture of *syn*-(major) and *anti*-(minor) amides **13** from which the *anti*-diastereomers of butanols **10c**,**d** were able to be obtained (Schemes 1–3).

*Syn*- and *anti*-isomers of *Schisandra* lignan (**1**) were prepared using an alternative method involving the Ireland-Claisen rearrangement which in this case favours the *anti*-product to give dimethylpentenoic acid **15** which was then coupled to morpholine to give *anti*-amide **13**, as the major isomer. From amide **13** our previously reported procedure was applied to give a mixture of *syn*- and *anti-Schisandra* lignan (**1**) [6].

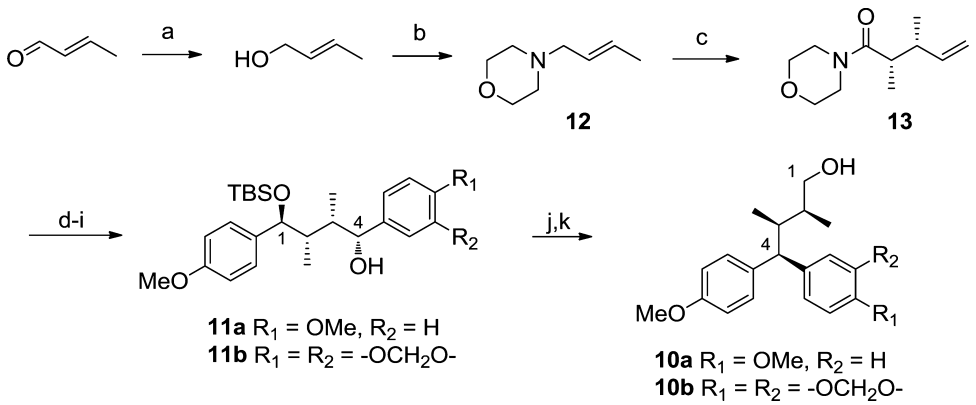
Comparison of the NMR data of synthetic compounds **1** and **10a-d** (Table 3) showed that four characteristic signals in the $^{1}$H NMR spectra and four characteristic signals from the $^{13}$C NMR spectra were found to vary significantly between *syn*- and *anti*-7,7-diaryl-8,8′-dimethylbutanol lignans and lignan analogues (full data can be found in the S.I.). In the $^{1}$H NMR spectra of *syn*-7,7-diaryl-8,8′-dimethylbutanols H-7 was observed in a range of $\delta$ 3.48–3.56 whereas in the *anti*-butanols the range was $\delta$ 3.61–3.77. Whilst the H-7 values are significantly different between *syn*- and *anti*-compounds they are not significantly different if C-7 is a chiral or achiral centre, thus the stereochemistry at this centre cannot be determined using NMR alone. The methyl groups at H-9 and H-9′ also showed significant differences between the *syn*- and *anti*-butanols with the signals arising from the *syn*-compounds showing a lower chemical shift compared to that of the *anti*-compounds. The H-7′ and selected signals arising from the $^{13}$C NMR also showed characteristic differences with observations recorded in Table 4. Combining these results and examining the $^{1}$H NMR values for H-7, H-7′, H-9 and H-9′ and the $^{13}$C NMR values for C-8, C-7′, C-8′ and C-9′ for *syn*- or *anti*- lignans one can define key differences in the chemical shift ranges (Table 4).

**Table 1**
Selected $^{1}$H and $^{13}$C NMR data of *Schisandra* lignan (**1**) and natural 7,7-diarylbutanol lignans of unknown stereochemistry.

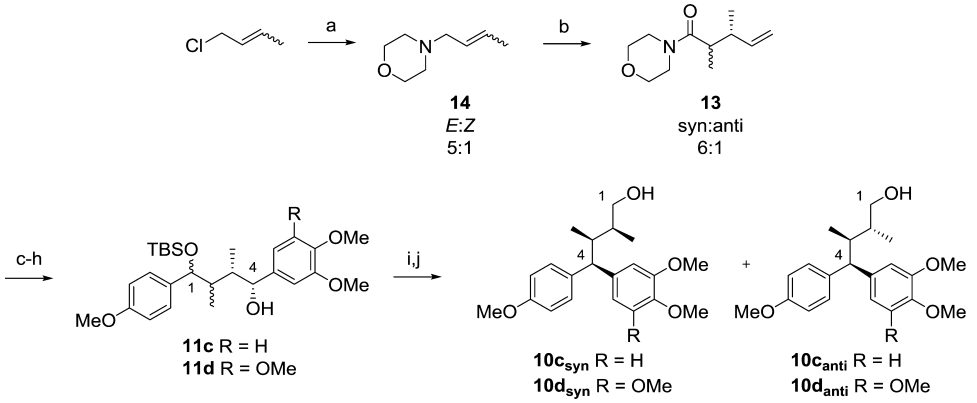


| | *Schisandra lignan* (1)[a] | Schilancifolignan D (3)[b] | Marphenol G (4)[b] | Kadangustin K (5)[a] |
|---|---|---|---|---|
| $^{1}$H | | | | |
| H-7 | 3.65, m | 3.99, d, 11.4 Hz | 3.83, d, 7.9 Hz | 3.53, d, 11.8 Hz |
| H-9 | 0.84, d, 7.2 Hz | 0.91, d, 6.9 Hz | 0.91, d, 7.9 Hz | 0.68, d, 6.8 Hz |
| H-7′α | 3.22, m | 3.79, d, 13.6 Hz | 3.73–3.81, m | 3.47–3.50, m |
| H-7′β | 3.69, m | 3.93, dd, 11.2, 6.6 Hz | | |
| H-9′ | 0.99, d, 6.4 Hz | 0.94, d, 7.1 Hz | 0.93, d, 7.9 Hz | 0.76, d, 7.0 Hz |
| $^{13}$C | | | | |
| C-8 | 36.1 | 36.7 | 36.5 | 35.9 |
| C-7′ | 63 | 66.8 | 66.5 | 67 |
| C-8′ | 40.7 | 36.6 | 36.8 | 36 |
| C-9′ | 15.6 | 10.2 | 12.3 | 9.6 |

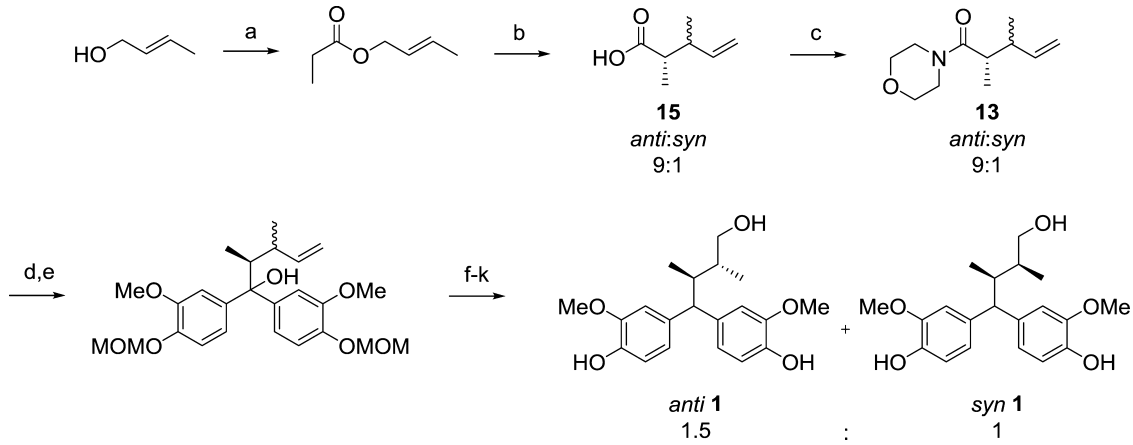
[a] Run in $CDCl_3$.
[b] Run in $C_5D_5N$.




**Scheme 1.** Reagents: (a) $LiAlH_4$, $Et_2O$, 0 °C, 15 min, 96%; (b) MsCl, $Et_3N$, morpholine, DCM, 0 °C, 21 h, 74%; (c) $AlCl_3$,*i*Pr2NEt, propionyl chloride, DCM, 24 h, 76%; (d) 4-bromoanisole, *t*BuLi, THF, −78 °C, 20 h, 73%; (e) $NaBH_4$, MeOH, -78 °C, 18 h, 90%; (f) TBDMSCl, imidazole, DMF, 0 °C, 48 h, quant.; (g) $OsO_4$ (1 mol%), NMO, *t*BuOH:$H_2O$ (1:1), 24 h, 83%; (h) $NaIO_4$, MeOH:$H_2O$ (3:1), 0 °C, quant.; (i) 4-bromoanisole (**11a**), 4-bromo-1,2-methylenedioxybenzene (**11b**), *t*BuLi, THF, −78 °C, 24 h, 33% (**11a**), 82% (**11b**); (j) MsCl, $Et_3N$, DCM, 0 °C, 2 h, 65% (from **11a**), 47% (from **11b**); (k) $NaBH_4$, MeOH, −78 °C, 24 h, 64% (**10a**), quant. (**10b**).

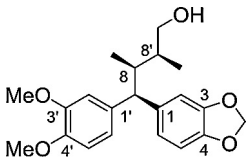
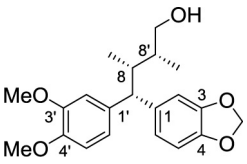
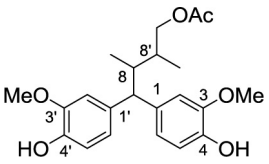
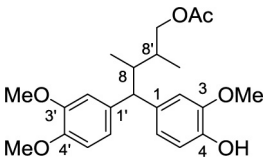



**Scheme 2.** Reagents: (a) morpholine, $Et_3N$, DCM, 0 °C, 24 h, 48%; (b) $AlCl_3$, *i*Pr2NEt, propionyl chloride, DCM, 24 h, 76%; (c) 4-bromoanisole, *t*BuLi, THF, −78 °C, 20 h, 73%; (d) $NaBH_4$, MeOH, −78 °C, 18 h, 90%; (e) TBDMSCl, imidazole, DMF, 0 °C, 48 h, quant.; (f) $OsO_4$ (1 mol%), NMO, *t*BuOH:$H_2O$ (1:1), 24 h, 83%; (g) $NaIO_4$, MeOH:$H_2O$ (3:1), 0 °C, quant.; (h) 4-bromoveratrole, *t*BuLi, (**11c**), 3,4,5-trimethoxyphenylmagnesium bromide (**11d**), THF, −78 °C, 24 h, 22% (**11c**), 52% (**11d**); (i) MsCl, $Et_3N$, DCM, 0 °C, 2 h, 63% (from **11c**), 58% (from **11d**); (j) $NaBH_4$, MeOH, −78 °C, 24 h, quant. (**10c**), 79% (**10d**).



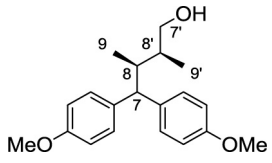
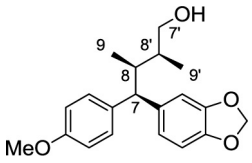
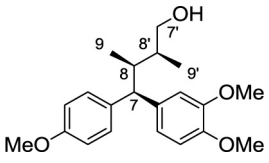
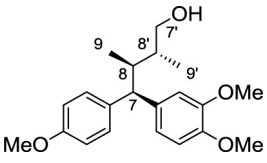

**Scheme 3.** Reagents: (a) propionyl chloride, pyridine, DCM, 0 °C, 18 h, 80%; (b) LDA, THF, −78 °C, 96%; (c) morpholine, DMAP, DCC, DCM, 22 h, 98%; (d) 1-bromo-3-methoxy-4-(methoxymethoxy) benzene, *t*BuLi, THF, −78 °C, 24 h, 73%; (e) 1-bromo-3-methoxy-4-(methoxymethoxy) benzene, *t*BuLi, THF, −78 °C, 24 h, 41%; (f) $Et_3SiH$, $BF_3{\cdot}OEt_2$, DCM, 0 °C, 30 min, 91%; (g) MOMCl, *i*Pr2NEt, DCM, 0 °C, 24 h, 79%; (h) $OsO_4$ (1 mol%), NMO, *t*BuOH:$H_2O$ (1:1), 48 h, 47%; (i) $NaIO_4$, MeOH:$H_2O$ (3:1), 0 °C, 20 min, 89%; (j) $NaBH_4$, MeOH, 5 h, 72%; (k) 2 M HCl, MeOH, 5 h, 86%.

**Table 2**
Selected $^{1}H$ and $^{13}C$ NMR data of natural 7,7-diarylbutanol lignans (**6** and **7**) of proposed stereochemistry and selected $^{1}H$ and $^{13}C$ NMR data of natural 7,7-diarylbutanol acetates (**8** and **9**) of unknown stereochemistry.

| |  |  |  |  |
|---|---|---|---|---|
| | **6**[a] | **7**[a] | Henricine B (**8**)[b] | **9**[a] |
| $^{1}H$ | | | | |
| H-7 | 3.53, d, 11.9 Hz | 3.4–3.7, m | 3.52, d, 11.6 Hz | 3.50, d, 11.2 Hz |
| H-9 | 0.70, d, 6.9 Hz | 0.66, d, 7.0 Hz | 0.69, d, 6.8 Hz | 0.76, d, 6.8 Hz |
| H-7′α | 3.47, dd, 10.4, 6.5 Hz | 3.4–3.7, m | 3.70, d, 11.2 Hz | 3.82, d, 10.8 Hz |
| H-7′β | 3.51, dd, 10.4, 8.2 Hz | | 4.04, d, 10.8, 4.8 Hz | 4.15, dd, 10.8, 4.8 Hz |
| H-9′ | 0.76, d, 6.9 Hz | 0.73, d, 7.0 Hz | 0.88, d, 7.2 Hz | 0.99, d, 6.8 Hz |
| $^{13}C$ | | | | |
| C-8 | 36.1 | 35.6 | 42.1 | 41 |
| C-7′ | 67.2 | 66.5 | 67.2 | 65.9 |
| C-8′ | 36.3 | 35.6 | 34.5 | 32.9 |
| C-9′ | 9.8 | 9.3 | 17.2 | 17.1 |

[a] Run in $CDCl_3$.
[b] Run in $CD_3OD$.

**Table 3**
Selected $^{1}H$ and $^{13}C$ NMR data of synthetic 7,7-diarylbutanols in $CDCl_3$.

| |  |  |  |  |
|---|---|---|---|---|
| | **10a** | **10b** | **10c**$_{syn}$ | **10c**$_{anti}$ |
| $^{1}H$ | | | | |
| H-7 | 3.56, d, 11.6 Hz | 3.54, d, 12.8 Hz | 3.54, d, 12.0 Hz | 3.75, d, 11.6 Hz |
| H-9 | 0.68, d, 6.7 Hz | 0.70, d, 6.7 Hz | 0.69, d, 6.8 Hz | 0.79, d, 7.1 Hz |
| H-7′α | 3.45, dd, 10.6, 6.7 Hz | 3.44, dd, 10.6, 6.7 Hz | 3.45, dd, 10.6, 6.6 Hz | 3.36, dd, 10.8, 7.7 Hz |
| H-7′β | 3.50, dd, 10.6, 8.1 Hz | 3.49, dd, 10.6, 8.2 Hz | 3.51, dd, 10.6, 8.2 Hz | 3.67, dd, 10.8, 5.6 Hz |
| H-9′ | 0.75, d, 6.9 Hz | 0.74, d, 6.9 Hz | 0.75, d, 7.0 Hz | 0.99, d, 7.1 Hz |
| $^{13}C$ | | | | |
| C-8 | 36.1 | 36.0 | 36.0 | 40.8 |
| C-7′ | 67.1 | 67.0 | 67.1 | 64.8 |
| C-8′ | 36.1 | 36.0 | 36.1 | 36.5 |
| C-9′ | 9.5 | 9.5 | 9.5 | 16.6 |

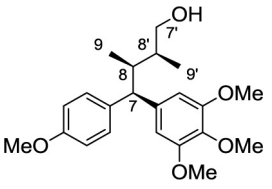
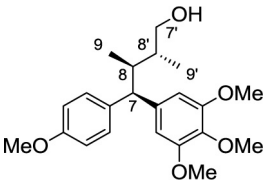
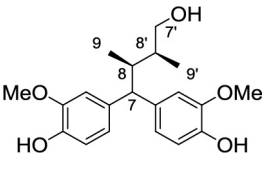
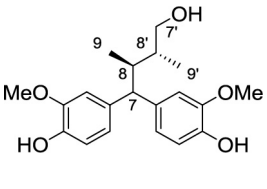
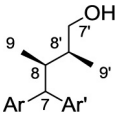
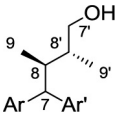
| |  |  |  |  |
|---|---|---|---|---|
| | **10d**$_{syn}$ | **10d**$_{anti}$ | **1**$_{syn}$ | **1**$_{anti}$ |
| $^{1}H$ | | | | |
| H-7 | 3.52, d, 11.5 Hz | 3.72–3.77, m | 3.48, d, 11.7 Hz | 3.61, d, 11.7 Hz |
| H-9 | 0.71, d, 6.8 Hz | 0.80, d, 6.8 Hz | 0.69, d, 6.6 Hz | 0.76, d, 6.6 Hz |
| H-7′α | 3.46–3.53, m | 3.36, dd, 10.7, 7.6 Hz | 3.90, dd, 10.8, 7.2 Hz | 3.80, dd, 10.9, 8.6 Hz |
| H-7′β | | 3.66, dd, 10.7, 6.0 Hz | 3.96, dd, 10.8, 7.4 Hz | 4.15, dd, 10.9, 5.0 Hz |
| H-9′ | 0.74, d, 7.0 Hz | 0.98, d, 6.9 Hz | 0.79, d, 7.0 Hz | 0.99, d, 7.0 Hz |
| $^{13}C$ | | | | |
| C-8 | 36.0 | 40.6 | 36.9 | 41.0 |
| C-7′ | 67.0 | 64.5 | 68.6 | 65.9 |
| C-8′ | 36.1 | 37.6 | 32.6 | 32.9 |
| C-9′ | 9.5 | 16.5 | 9.8 | 17.1 |

**Table 4**
Characteristic NMR signals for *syn*- and *anti*-dimethyl 7,7-diaryl-8,8′-dimethylbutanol lignans.

| |  |  |
|---|---|---|
| | syn | anti |
| $^{1}$H | | |
| H-7 | 3.48–3.56 | 3.61–3.77 |
| H-9 | 0.68–0.71 | 0.76–0.80 |
| H-7′ | 3.44–3.96 (α-β close/overlapped) | 3.36–4.15 (α-β separated) |
| H-9′ | 0.74–0.79 | 0.98–0.99 |
| $^{13}$C[a] | | |
| C-8 | ~36.5 | ~40.8 |
| C-7′ | ~67.7 | ~65.2 |
| C-8′ | ~36.0 | ~37.0 |
| C-9′ | ~9.6 | ~16.8 |

[a] Values given are averages of numerous example compounds.

Based on these descriptors we have assigned the relative stereochemistry of the two methyl groups present in natural 7,7-diarylbutanols. One of these natural lignans has been made synthetically as both the *syn*- and the *anti*-isomers by Yamauchi et al. (*Schisandra* lignan (**1**)) and our assignments based on NMR data are in agreement with this study [7]. Schilancifolignan D (**3**) showed H-9 of δ 0.91 and H-9′ of δ 0.94 as well as other signals that are in agreement with the *anti*-descriptors with similar results observed for marphenol G (**4**) therefore suggesting that these compounds have an *anti*-relationship between the two methyl groups. Kadangustin K (**5**) showed H-9 of δ 0.68 and H-9′ of δ 0.76 which are in agreement with the *syn*-descriptors suggesting that **5** is a *syn*-7,7-diaryl-8,8′-dimethylbutanol. These descriptors are also in agreement with the assignment of **6** and **7** as having a *syn* relationship between the two methyl groups. These NMR descriptors of *syn*- and *anti*-7,7-diarylbutanol lignans cannot be directly used for the characterisation of butanol acetate lignans (e.g. henricine B (**8**)) as the chemical shifts of these lignans are sufficiently different that they do not fall within the same ranges as the deacetyl compounds. However acetate lignans could be hydrolysed to give butanol lignans and then characterised using these descriptors shown above.

In summary the analysis of the $^{1}$H and $^{13}$C NMR of synthetic 7,7-diaryl-8,8′-dimethyl-butan-1-ol lignans and analogues in both *syn* and *anti* form has revealed significant differences in the chemical shifts in a number of resonances. Analysis of reported NMR data for the previous stereochemically undefined lignans schilancifolignan D (**3**), marphenol G (**4**) and kadangustin K (**5**) has determined the stereochemical relationship between the 8 and 8′-methyl groups to *anti* for **3** and **4** and *syn* for **5**.

## Supplementary data

Supplementary data associated with this article can be found, in the online version. These include the full NMR data for butanols **1** and 10**a**–**d**.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2015.09.014.

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