Enantioselective Total Synthesis of (R,R)-Blumenol B and d9-(R,R)-Blumenol B

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Abstract: C13-norisoprenoids are of particular importance to grapes and wines, as these molecules influence wine aroma and have been shown to significantly contribute to the distinct character of various wine varieties. Blumenol B is a putative precursor to a number of important wine aroma compounds, including the well-known compounds theaspirone and vitispirane. The enantioselective synthesis of (R,R)-blumenol B from commercially available 4-oxoisophorone was achieved using a short and easily scaleable route, which was then successfully applied to the synthesis of poly-deuterated d9-blumenol B.

Keywords: wine aroma; C13-norisoprenoids; blumenol B; isotopic labelling

1. Introduction

Norisoprenoids are molecules found in grapes and wines that result from the direct degradation of carotenoids either photochemically, chemically or via oxidase-coupled mechanisms [1,2]. Those with 13 carbon atoms, i.e., C13-norisoprenoids, are of particular importance as these molecules, even at very low concentrations, are key contributors to the aroma profile of wine. C13-norisoprenoids are known to influence the distinctive sensory character of many wine varieties including Cabernet Sauvignon, Chenin blanc, Sauvignon blanc, Syrah and Riesling [3–5].

C13-norisoprenoids such as β-damascenone, α-ionol, β-ionol, α-ionone, β-ionone, vitispirane, actinidol, vomifoliol, and TDN (1,1,6-trimethyl-1,2-dihydronaphthalene) have been studied extensively not only in grapes and wines [6–9], but in other natural sources including honey, fruit and essential oils [1,10,11]; on the other hand, studies of blumenol B remain scarce.

Blumenol B 1 (also known as 7,8-dihydrovomifoliol), in its aglycone form, has been identified following the extraction and subsequent enzymatic hydrolysis of the non-volatile glycosylate precursor, icariside B5, which is present in the grapes and wines of Weisser Riesling [4], and also in Riesling grapevine leaves [3]. Blumenol B 1 has also been obtained via glycosylated precursor icariside B5 from other natural sources, including Pinus sylvestris and Picea abies needles [12], Casearia sylvestris leaves [13], and Sarcandra glabra Nakai [14]. Furthermore, blumenol B 1 has been directly isolated from the leaves of Podocarpus blumei [15], and Cannabis sativa [16].

Blumenol B 1 is reported to be a precursor for other important aroma compounds and, in its reduced and oxidised forms, has been reported to prompt the formation of other C13-norisoprenoids, including theaspirone 2 [17], vitispirane 3 [18], megastigm-4-ene-3,6,9-triol 4, 1,1,6-trimethyl-1,2-dihydronaphthalene (TDN) 5 [19], and Riesling acetal 6 (Scheme 1) [20]. Stereochemistry is important in these aroma compounds as the various stereoisomers of these compounds contribute to the distinct aroma profiles of various
grapes and wines [6,7,21–24]. For example, the (S,S)-stereoisomer of theaspirone 2 imparts an earthy scent, while the enantiomer gives off a sweet and tea-like odour [18,25,26]. The racemic mixture of vitispirane 3 is reported to have a woody, balsamic, resinous, and spicy aroma profile [18,27]. Pure isomers (R,R)- and (S,S)-vitispirane exert a floral and fruity aroma, while (S,R)- and (R,S)-vitispirane imparts a strong scent of exotic flowers and woody tone [6]. The aroma profile of another aroma compound, Riesling acetal 6, also differs between its enantiomeric forms, (+)-Riesling acetal imparts a subtle floral, fruity and woody scent, while (−)-Riesling acetal gives off a weak floral and camphoraceous aroma [1,19,28]. It is proposed that the stereochemistry of the precursor blumenol B 1 is important in the formation of the various isomers of 2, 3, and 6, and is thus important in the overall aroma profile of the wines.

![Scheme 1](image)

**Scheme 1.** Blumenol B (1) is a precursor in the formation of theaspirone (2) and other important C13-norisoprenoids including vitispirane (3), megastigm-4-ene-3,6,9-triol (4), TDN (5) and Riesling acetal (6) in grapes and wines.

To date, blumenol B 1 has only been synthesized via routes that were either non-stereospecific, lengthy (17-steps) or involved a semi-synthetic route from complex isolated natural products, such as the case of (S,R)- and (R,S)-blumenol B [17,25,29]. We wished to develop an efficient stereospecific synthesis of blumenol B from commercially available materials that would also be suitable for the preparation of isotopically labelled standards. Such standards could be employed for the identification and quantification of aglycones that are enzymatically and/or biochemically released from glycosidic precursors found in wine.

2. Results

A previous synthesis of structurally similar C13-norisoprenoids such as (±)-theaspirone and (±)-(Z)-vomifoliol utilized the coupling of an organometallic reagent with a cyclic ketone to form the key carbon–carbon bond at the tertiary alcohol center [17,25]. These previously endeavors were only able to form ring-opened derivatives such as 1 and 4 by an acidic ring cleavage of spiro-like molecules similar to 2. This not only resulted in ring-opened compounds but numerous rearranged and dehydrated species. We aimed to employ a similar organometallic strategy of addition to a ketone when attempting the racemic synthesis of blumenol B 1, but would avoid the formation of spiro-compounds enroute to 1. We began using the commercially available 4-oxoisophorone 7 as the substrate for coupling with a lithiated acetylide. The first step in this pathway was protection of the less hindered carbonyl in 4-oxoisophorone 7 to afford the known ketal 8, which was reacted with lithiated TMS-acetylene giving tertiary alcohol 9 in 65% yield across the two steps (Scheme 2) [30,31]. Removal of the TMS-group formed the free acetylide 10, which was reacted with acetaldehyde to afford diol 11 as an inseparable mixture of diastere-
omers. Acetylene 11 then underwent exhaustive hydrogenation of the exocyclic alkyne, followed by deprotection of the ketone acetal to give (±)-blumenol B 1 as an inseparable 2:1 diastereomeric mixture in 53% yield over two steps. It was found that hydrogenation for 20 h reaction time resulted in an exclusive reactive of the endocyclic alkene [32,33]. However, longer reaction times were found to result in unwanted over-reduction. The spectroscopic data of the mixture of isomers of (±)-1 were in agreement with those reported by Matsunami et al. [29] (Tables S1 and S2).

Following the development of this short racemic synthesis of 1, the next goal was the stereoselective synthesis of (R,R)-blumenol B using enantiopure reagents to direct the stereochemistry of the two chiral centers (Scheme 3). The first enantiopure reagent employed was commercially available (R)-(−)-3-butyne-2-ol 12, which was protected with a TBDPS group giving 13 in quantitative yield [34]. The second enantiopure reagent used was 2R,3R-(−)-2,3-butanediol, which was used to protect the less-hindered carbonyl on 4-oxoisophorone 7, forming the known chiral ketal 14 [35]. Alkynylation of ketal 14 using lithium 13 afforded a 1:2:1 diastereomeric mixture of the R- and S-configuration at the newly formed tertiary alcohol stereocenter. Subsequent recrystallization using petroleum ether gave the major R-isomer 15 in 47% yield as a white solid and minor S-isomer 15a in 12% yield as a colourless oil, allowing for 15 to be easily separated. Similar facial selectivity, and solid versus oil for the two diastereoisomers, has been observed for the additional of alternative acetylenes with chiral ketone 14, which allowed for the determination of absolute stereochemistry in 15 [35]. This was further confirmed when crystals of d9-16 were formed (see below) and X-ray unequivocally determined the absolute stereochemistry. With 15 formed, both the acetal group and TBDPS-protecting group were removed to form propargyl alcohol 17 in 91% yield, across the two steps. The hydrogenation of propargyl alcohol 17 in the presence of Lindlar catalyst afforded (R,R)-blumenol B 1 in 57% yield, which exhibited identical $^1$H and $^{13}$C NMR data to reported values for (S,S)-blumenol B (Table S3) [29].

Following the successful synthesis of (R,R)-blumenol B 1, the next goal was to apply this methodology to synthesize isotopically labelled (R,R)-1, for possible use as an analytical standard for quantifying (R,R)-1. This would require the synthesis of an isotopically labelled precursor and it was decided to use the previously reported d9-8 in this study [36]. The synthesis began with treating 1,4-cyclohexanediol monoethylene acetal 18 with four equivalents of CD$_3$I, which afforded the target tri-substituted d9-19 in 77% (Scheme 4). Next, the α,β-unsaturated ketone was installed in two steps by converting d9-19 to the TMS-protected enol d9-20, which was then subjected to one-pot halogenation and elimination, using Br$_2$ followed by DBU to give the target enone d9-8 in 70% yield over the two steps.

**Scheme 2.** Synthesis of isomeric mixture of (±)-blumenol B 1. Reagents and conditions: (a) Ethylene glycol, p-TsOH, toluene, 24 h, 86%; (b) Trimethylsilylacetylene, BuLi, THF, −78 °C, 16 h, 75%; (c) K$_2$CO$_3$, MeOH, 1 h, 64%; (d) Acetaldehyde, LDA, THF, −78 °C, 14 h, 62%; (e) Lindlar catalyst, H$_2$, MeOH, 20 h then 2 M HCl, THF, 18 h, 52%.
Subsequent removal of the acetal group using 2M HCl afforded $d_9$-7, which could then be utilized for synthesis of $d_9$-($R,R$) blumenol B 1 via the aforementioned methods. In brief, $d_9$-7 was protected using 2R,3R(-)-2,3-butanediol to give chiral ketal $d_9$-14, which was then reacted with acetylide 13 affording $d_9$-15 in 44% yield over the two steps. Chiral acetal $d_9$-15 was removed using 2M HCl and subsequent TBDPS deprotection with TBAF gave $d_9$-17 in 94% yield. X-ray diffraction studies on TBDPS-protected $d_9$-16 intermediate confirmed the desired $R,R$ diastereomer had formed (Figure S1). Lastly, the alkyne motif was fully hydrogenated using H2 and Lindlar catalyst, forming $d_9$-($R,R$) blumenol B 1 in 44% yield.

Scheme 3. Synthesis of ($R,R$) blumenol B 1. Reagents and conditions; (a) TBDPS-Cl, imidazole, DMF, 0 °C, overnight, quant.; (b) 2R,3R(-)-2,3-butanediol, p-TsOH, toluene, overnight, 93%; (c) $^t$BuLi, THF, $-78$ °C, 14 h, 47% $15$ and 12% $15a$; (d) 2 M HCl, THF, 18 h, 95%; (e) TBAF, THF, 0 °C, 15 h, 96%; (f) Pd/BaSO4, H2, MeOH, 19 h, 57%.

Scheme 4. Synthesis of $d_9$-($R,R$)-blumenol B 1. Reagents and conditions; (a) NaH, CD3I, THF, 0 °C—reflux, overnight, 77%; (b) LDA, Et3N, TMS-Cl, THF, $-78$ °C—r.t., overnight, 82%; (c) 10% Br2 in CH2Cl2, DBU, CH2Cl2, 0 °C, overnight, 85%; (d) 2M HCl, THF, r.t., overnight, quant.; (e) 2R,3R(-)-2,3-butanediol, p-TsOH, toluene, overnight, 89%; (f) $^t$BuLi, THF, $-78$ °C, overnight, 51%; (g) 2 M HCl, THF, r.t., 18 h, 94%; (h) TBAF, THF, 0 °C, 15 h, quant.; (i) Pd/BaSO4, H2, MeOH, 8 h, 44%.
3. Materials and Methods

3.1. General Experimental Details

All reactions in non-aqueous solvents were carried out under an inert atmosphere using anhydrous AR grade solvents. Solvents used for reaction work up and purification were used as purchased, without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel F354 aluminium plates pre-coated with silica. Flash chromatography was carried out using Silica Gel 60 (40–63 µm, 230–430 mesh ASTM) utilising solvent systems defined in the experimental procedure for each synthesized molecule. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 series Fourier Transform Infra-Red ATR spectrometer. Melting points were measured using a Reicher-Koffer block and are uncorrected. NMR spectra were obtained using a Bruker Avance DRX 400 MHz spectrometer at ambient temperature. Chemical shifts are reported relative to the residual solvent peak of either CDCl$_3$ (δ 7.26 for $^1$H and δ 77.16 for $^{13}$C) or CD$_2$OD (δ 3.31 for $^1$H and δ 49.00 for $^{13}$C). $^1$H NMR data are reported in the following sequence: position (δ), relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; br s, broad singlet; br d, broad doublet), coupling constant (J, Hz), and proton assignment. $^{13}$C NMR data were reported in the following sequence: position (δ), multiplicity (d, doublet; q, quartet), coupling constant (J, Hz), and the carbon assignment. NMR assignments were made using a combination of $^1$H NMR, $^{13}$C NMR, HSQC and HMBC experiments. High-resolution mass spectroscopy (HRMS) was carried out using electrospray ionisation (ESI) on a MicroTOF-Q mass spectrometer.

3.2. Synthesis of Compounds

4,4-(Ethylenedioxy)-2,6,6-trimethylcyclohex-2-en-1-one (8): A mixture of 4-oxoisophorone (3.0 g, 19.7 mmol), ethylene glycol (1.46 mL, 26.2 mmol), and toluene-p-sulfonic acid monohydrate (0.09 g, 0.473 mmol) in toluene (14.8 mL) were heated at reflux overnight with a Dean-Stark trap. The solution was left to cool and quenched with sat. aq. NaHCO$_3$ (15 mL) and was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water and dried over anhydrous MgSO$_4$. The solvent was removed in vacuo and the crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the title compound 8 (3.325 g, 86%) as a yellow oil. $R_f$ (3:1 petroleum ether, ethyl acetate) = 0.54. $\delta_H$ (400 MHz; CDCl$_3$) 1.20 (6H, s, 6-(CH$_3$)$_3$), 3.90–3.95 (4H, m, 4H, m, OCH$_2$CH$_2$O), 6.30 (1H, br s, 3-H). The spectroscopic data were in agreement with the literature values [31].

4,4-(Ethylenedioxy)-2,6,6-trimethyl-1-trimethylsilyl-ethylcyclohex-2-en-1-ol (±)-9: To a stirred solution of trimethylsilylacetylene (0.29 mL, 2.03 mmol) in THF (3 mL) under an inert atmosphere at −78 °C was added $^8$BuLi (1.6 M in hexanes, 0.22 mL, 2.03 mmol). The reaction mixture was then stirred at −78 °C for 15 min and a solution of 8 (0.20 mg, 1.01 mmol) in THF (6 mL) was added dropwise to the previously prepared reaction mixture. The resultant mixture was then stirred under a nitrogen atmosphere for 1 h, and the reaction was quenched with sat. aq. NH$_4$Cl (5 mL), and was extracted with diethyl ether (3 × 5 mL), before the combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (14:1 hexanes, ethyl acetate) to yield the title compound (±)-9 (0.22 g, 75%) as a yellow oil. $R_f$ (14:1, 9:1 hexanes, ethyl acetate) = 0.39. $\delta_H$ (400 MHz; CDCl$_3$) 0.16 (9H, s, Si(CH$_3$)$_3$), 1.05 and 1.12 (each 3H, s, 6-(CH$_3$)$_3$), 1.89 (2H, s, 5-H), 1.91 (3H, s, 2-CH$_3$), 3.90–3.95 (4H, m, 4H, m, OCH$_2$CH$_2$O), 5.36 (1H, br s, 3-H). The spectroscopic data were in agreement with the literature values [31].

4,4-(Ethylenedioxy)-2,6,6-trimethyl-1-ethynylcyclohex-2-en-1-ol (±)-10: To a stirred solution of (±)-9 (1.80 g, 6.12 mmol) in methanol (50 mL), potassium carbonate (2.54 g, 18.8 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h. The precipitate was filtered, the solvent was removed in vacuo, and was extracted with diethyl ether (3 × 50 mL); then, the combined organic extracts were washed with water, dried over anhydrous MgSO$_4$ and the solvent removed in vacuo. The crude product was...
recrystallised from hexanes to yield the \textit{title compound} (±)-10 (1.85 g, 64%) as white needles. R\textsubscript{F} (9:1 hexanes, ethyl acetate) = 0.47. Melting point: 76–78 °C (lit. 78–80 °C). δ\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 1.10 (3H, s, 6-CH\textsubscript{3}), 1.16 (3H, s, 6-CH\textsubscript{3}), 1.88 (1H, d, J = 14.3 Hz, 5-H\textsubscript{A}), 1.93 (3H, d, J = 1.3 Hz, 2-CH\textsubscript{3}), 1.96 (1H, d, J = 14.2 Hz, 5-H\textsubscript{B}), 2.02 (1H, s, OH), 2.50 (1H, s, ethynyl CH), 3.90–3.96 (4H, m, O\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}O), 5.38 (1H, s, 3-H). The spectroscopic data and melting point were in agreement with the literature values [31].

8-(3-Hydroxybut-1-yn-1-y1)-7,9-trimethyl-1,4-dioxaspiro [4.5]dec-6-en-8-ol \textit{(±)-11}: To a stirred solution of \textit{(±)-10} (0.85g, 3.8 mmol) in THF (25 mL) under an anhydrous atmosphere, LDA (5.71 mL, 11.4 mmol) was added at −78 °C, and the resultant mixture was stirred for 30 min. Acetaldehyde (0.327 mL, 5.85 mmol) in THF (12 mL) was added dropwise to the reaction mixture at −78 °C and was left to stir for 30 min; it was then further stirred at 0 °C under a nitrogen atmosphere overnight. The reaction mixture was quenched with sat. aq. NH\textsubscript{4}Cl (15 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous MgSO\textsubscript{4} and the solvent was removed in vacuo. The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the \textit{title compound} (±)-11 (0.624 g, 62%) as a white solid. R\textsubscript{F} (1:1 hexanes, ethyl acetate) = 0.3. Melting point: 135–138 °C. δ\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 1.09 (3H, s, 9-CH\textsubscript{3}), 1.14 (3H, s, 9-CH\textsubscript{3}), 1.45 (3H, d, J = 6.5 Hz, CH(OH)CH\textsubscript{3}), 1.91 (3H, s, 7-CH\textsubscript{3}), 2.03 (2H, br d, J = 7.6 Hz, 5CH\textsubscript{2}), 3.90–3.97 (4H, m, O\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}O), 4.54–4.57 (1H, m, CH(OH)CH\textsubscript{3}), 5.36 (1H, br s, 3-H). The \textit{1H} NMR spectroscopic data and melting point were in agreement with the literature values [25].

\textit{(±)-Blumenol B \textit{(+)}-1}: To a stirred solution of \textit{(±)-11} (300 mg, 1.13 mmol) in MeOH (30 mL), Pa/BaSO\textsubscript{4} (120 mg, 40% w/w) was added, and was stirred under a hydrogen atmosphere at room temperature for 18–20 h. The mixture was filtered through Celite\textsuperscript{®}, washed with MeOH and the solvent was removed in vacuo to yield the alkane (160 mg, 40% w/w) was added, and was stirred under a nitrogen atmosphere overnight. The reaction mixture was quenched with sat. aq. NaHCO\textsubscript{3} (15 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous MgSO\textsubscript{4} and the solvent was removed in vacuo.

The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the \textit{title compound (±)-1} (153 mg, 96%) as a colorless oil. R\textsubscript{F} (1:1 hexanes, ethyl acetate) = 0.15. δ\textsubscript{H} (400 MHz; CD\textsubscript{3}OD) 1.02 (3H, s, 1-H), 1.10 (3H, s, 12-H), 1.22 (3H, d, J = 6.0 Hz, 10-H), 1.40–1.48 (1H, m, 8-H), 1.68–1.72 (1H, m, 8-H), 1.75–1.83 (1H, m, 7-H), 1.92–1.99 (1H, m, 7-H), 1.97–1.98 (1H, m, 7-H), 2.04 (3H, s, 13-H), 2.16 (1H, d, J = 18.1 Hz, 2-H), 2.59 (1H, dd, J = 4.5, 18.2 Hz, 2-H), 3.66 (1H, qu, J = 5.7 Hz, 9-H), 5.83 (1H, s, 4-H). δ\textsubscript{C} (100 MHz; CD\textsubscript{3}OD) 21.8 (C-13), 23.7 (C-10), 24.0 (C-12), 24.5 (C-11), 35.3 (C-8), 35.7 (C-7), 43.0 (C-1), 51.1 (C-2), 69.3 (C-9), 79.2 (C-6), 126.6 (C-4), 171.8 (C-5), 200.8 (C-3). HRMS (ESI\textsuperscript{+}): Found (MNa\textsuperscript{+})\textsuperscript{+}: 249.1457 C\textsubscript{13}H\textsubscript{22}NaO\textsubscript{3} requires 249.1461. IR: \nu\textsubscript{max}(film)/cm\textsuperscript{-1}: 3405 (O-H), 2967 (C-H), 2927 (C-H), 2878 (C-H), 2530 (O-H), 1647 (C=O), 1417 (C=C). Other diastereomer: δ\textsubscript{H} (400 MHz; CD\textsubscript{3}OD) 1.02 (3H, s, 11-H), 1.10 (3H, s, 12-H), 1.22 (3H, d, J = 6.0 Hz, 10-H), 1.40–1.48 (1H, m, 8-H), 1.68–1.72 (1H, m, 8-H), 1.75–1.83 (1H, m, 7-H), 1.92–1.99 (1H, m, 7-H), 2.04 (3H, s, 13-H), 2.16 (1H, d, J = 18.1 Hz, 2-H), 2.59 (1H, dd, J = 4.5, 18.2 Hz, 2-H), 3.76–3.78 (1H, m, 9-H), 5.88 (1H, s, 4-H). δ\textsubscript{C} (100 MHz; CD\textsubscript{3}OD) 21.7 (C-13), 23.5 (C-10), 24.0 (C-12), 24.6 (C-11), 35.2 (C-8), 35.6 (C-7), 42.9 (C-1), 51.1 (C-2), 68.9 (C-9), 79.1 (C-6), 126.6 (C-4), 171.7 (C-5), 200.9 (C-3). HRMS (ESI\textsuperscript{+}): Found (MNa\textsuperscript{+})\textsuperscript{+}: 249.1457 C\textsubscript{13}H\textsubscript{22}NaO\textsubscript{3} requires 249.1461. IR: \nu\textsubscript{max}(film)/cm\textsuperscript{-1}: 3405 (O-H), 2965 (C-H), 2927 (C-H), 2878 (C-H), 2530 (O-H), 1647 (C=O), 1417 (C=C). The spectroscopic data were in agreement with the literature values [25,29].

\textbf{(R)-(But-3-yn-2-yloxy)(lert-butyl)diphenylsilane (R)-13}: To a stirred solution of (R)-(+)\textsuperscript{-}3-butyn-2-ol (300 mg, 4.28 mmol) in DM\textsubscript{F} (15 mL) under an anhydrous atmosphere, imidazole (870 mg, 12.8 mmol) and TBDPSCl (1.66 mL, 6.40 mmol) was added at 0 °C, and was stirred for 2 h. The reaction mixture was quenched with sat. aq. NaHCO\textsubscript{3} (7 mL), and was extracted with ethyl acetate (3 × 15 mL), the combined organic extracts were washed with water (3 × 15 mL), dried over anhydrous MgSO\textsubscript{4} and the
solvent was removed in vacuo. The crude product was purified by flash chromatography (9:1 hexanes, ethyl acetate) to yield the title compound (R)-13 (980 mg, 99%) as a colourless oil. $R_f$ (9:1 hexanes, ethyl acetate) = 0.72. $\delta_1$ (400 MHz; CDCl$_3$) 1.09 (9H, s, Si(CH$_3$)$_3$), 1.40 (3H, d, $J = 6.5$ Hz, 1-C,H), 2.34 (1H, d, $J = 2.5$ Hz, 4-H), 4.47 (1H, qd, $J = 6.5$, 2.0 Hz, 2-H), 7.36–7.46 (6H, m, Ar-H), 7.60–7.81 (4H, m, Ar-H). $[\alpha]_D^{20} = +84.4^\circ$ (c = 1.00, MeOH). The spectroscopic data were in agreement with the literature values [34].

(2R,3R)-2,3,7,9,9-Pentamethyl-1,4-dioxaspiro [4.5]dec-6-en-8-one [4.5]dec-6-en-8-one (R,R)-14: To a stirred solution of 4-oxoisophorone 7 (300 mg, 1.97 mmol) in toluene (8 mL), 2,3R,3R-+2,3-butenediol (236 mg, 2.62 mmol) and p-toluenesulfonic acid (8.15 mg, 0.0473 mmol) was added. The reaction mixture was heated at reflux for 24 h with a Dean-Stark trap for the removal of excess water. The reaction mixture was cooled and quenched with sat. aq. NaHCO$_3$ (8 mL), and then extracted with diethyl ether (3 × 8 mL), dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (14:1 petroleum ether, ethyl acetate) to yield the title compound (R,R)-14 (280 mg, 93%) as a pale yellow oil. $R_f$ (3:1 petroleum ether, ethyl acetate) = 0.75. $\delta_1$ (400 MHz; CDCl$_3$) 1.17 (3H, s, 11-H), 1.22 (3H, s, 12-H), 1.27–1.30 (6H, m, 14 and 15-H), 1.79 (3H, d, $J = 1.5$ Hz, 13-H), 2.03–2.07 (1H, dd, $J = 14.0$, 1.5 Hz, 1H, 10-H), 2.10–2.13 (1H, d, $J = 14.0$ Hz, 10-H), 3.61–3.71 (2H, m, 2 and 3-H), 6.33 (1H, t, $J = 1.3$ Hz, 6-H). $[\alpha]_D^{20} = -16.1$ (c = 0.97, MeOH). The spectroscopic data were in agreement with the literature values [35].

(2R,3R,8R)-8-((R)-3-(tert-Butyldiphenylsilyloxy)but-1-yn-1-yl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro [4.5]dec-6-en-8-one (R,R)-15: To a stirred solution of (R)-13 (288 mg, 0.89 mmol) in THF (8 mL) under a nitrogen atmosphere, and tertBuLi (2 M in hexanes, 0.45 mL, 0.89 mmol) was added at −78 °C. The resultant mixture was stirred at −78 °C for 20 min and a solution of (R,R)-14 (100 mg, 0.45 mmol) in THF (4 mL) was added dropwise. The mixture was further stirred under a nitrogen atmosphere at room temperature overnight. The reaction was quenched with sat. aq. NH$_4$Cl (6 mL) and was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were washed with water (6 mL), brine (6 mL) and dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude product was recrystallised from petroleum ether to yield the title compound (R,R)-15 (112 mg, 47%) as a white solid. Melting point: 95–99 °C. $\delta_1$ (400 MHz; CDCl$_3$) 1.02 (3H, s, 11-H), 1.06 (12H, br s, 12-H and Si(CH$_3$)$_3$), 1.22 (6H, t, $J = 5.2$ Hz, 16 and 17-H), 1.41 (3H, d, $J = 6.5$ Hz, 10-H), 1.70 (3H, d, $J = 1.35$ Hz, 13-H), 1.76 (1H, d, $J = 14.1$, 2-H), 1.93 (1H, d, $J = 14.1$, 2-H), 1.86 (2H, dd, $J = 59.6$, 14.2 Hz, 2-H), 3.50–3.60 (2H, m, 14 and 15-H), 4.52 (1H, q, $J = 6.5$ Hz, 9-H), 5.30 (1H, s, 4-H), 7.36–7.46 (6H, m, Ar-H), 7.70 (2H, dd, $J = 8.0$, 2.0 Hz, Ar-H), 7.76 (2H, dd, $J = 8.0$, 2.0 Hz, Ar-H). $\delta_2$ (100 MHz; CDCl$_3$) 14.3 (C-13), 18.9 (C-16 and 17), 24.3 (C-11 and 12), 25.5 (C-10), 26.9 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 39.4 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 45.6 (C-2), 60.1 (C-9), 74.3 (C-7), 78.0 (C-14 and 15), 84.1 (C-8), 88.1 (C-6), 104.1 (C-3), 124.8 (C-4), 136.0 (Si(CH$_3$)$_2$), 140.4 (C-5). HRMS (ESI+): Found (MNa$^+$): 555.2989 C$_{33}$H$_{44}$NaO$_7$S requires 555.2901.

(8R)-6-Hydroxy-6-((R)-9-hydroxybut-7-yn-7-yl)-1,1,5-trimethylcyclohex-4-en-3-one (R,R)-17: To a stirred solution of (R,R)-15 (703 mg, 1.32 mmol) in THF (40 mL) under a nitrogen atmosphere, 2M HCl (6 mL) was added and the mixture stirred under an nitrogen atmosphere at room temperature overnight. The solvent was removed in vacuo and the remaining residue was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed brine (40 mL) and dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. This crude product was purified by flash chromatography (1:3 petroleum ether, ethyl acetate) to yield the title compound (R,R)-17 (270 mg, 91%) as a colourless oil. N.B. compound 17 was found to be very volatile and prone to evaporation if placed under strong vacuum. $R_f$ (1:1 petroleum ether, ethyl acetate) = 0.23. $\delta_1$ (400 MHz; CDCl$_3$) 1.09 (3H, s, 11-H), 1.19 (3H, s, 12-H), 1.47 (3H, d, $J = 6.5$ Hz, 10-H), 2.10 (3H, d,
Molecules 2022, 27, 7294
8 of 11

\[ J = 1.35 \text{ Hz}, 13\text{-H}), 2.38 (1H, d, J = 16.5 \text{ Hz}, 2\text{-H}), 2.51 (1H, d, J = 16.5 \text{ Hz}, 2\text{-H}), 4.58 (1H, q, J = 6.6, 9\text{-H}), 5.83 (1H, s, 4\text{-H}). \delta_{c} (100 \text{ MHz}; \text{CDCl}_{3}) 19.8 (C-12), 22.8 (C-11), 24.4 (C-10), 25.2 (C-13), 29.7 (C-1), 49.2 (C-2), 58.4 (C-9), 74.5 (C-7), 82.8 (C-5), 89.4 (C-8), 126.3 (C-4), 160.4 (C-5), 198.4 (C-3). \text{HRMS (ESI+):} \text{Found (MNa}^{+}) 245.2712 \text{C}_{13}\text{H}_{18}\text{NaO}_{3} \text{requires 245.2712.} \\
\text{[a]}^{22}\text{D} = -138.79^\circ (c = 0.66, \text{MeOH}). \text{IR:} \nu_{\max}(\text{film})/\text{cm}^{-1}; 3456, 3025, 2864, 1396, 1086.

(6R,9R)-Blumenol B (R,R)-1: To a stirred solution of (R,R)-17 (14 mg, 0.0629 mmol) in MeOH (5 mL), Pd/BaSO_{4} (1.4 mg, 20% w/w) was added, and the resultant mixture was washed with water (30 mL), brine (30 mL) and dried over anhydrous MgSO_{4} was washed with MeOH and the solvent was removed in vacuo. The crude product was purified by flash chromatography (12 petroleum ether, ethyl acetate) to yield the title compound (R,R)-1 (8 mg, 57%) as a colourless oil. \text{RF} (1:3 petroleum ether, ethyl acetate) = 0.26. \delta_{t}\text{(400 MHz; CDCl}_{3}) 1.02 (3H, s, 11\text{-H}), 1.09 (3H, s, 12\text{-H}), 1.16 (3H, d, J = 6.2 \text{ Hz}, 10\text{-H}), 1.40 (1H, dddd, J = 12.7, 11.5, 8.05, 5.12 \text{ Hz}, 8\text{-H}), 1.79 (1H, tt, J = 12.7, 4.0 \text{ Hz}, 7\text{-H}), 1.98 (1H, td, J = 12.7, 5.3 \text{ Hz}, 7\text{-H}), 2.04 (3H, d, J = 1.49 \text{ Hz}, 13\text{-H}), 2.16 (1H, ddd, J = 18.0, 1.02 \text{ Hz}, 2\text{-H}), 2.59 (1H, d, J = 18.1 \text{ Hz}, 2\text{-H}), 3.61–3.69 (1H, m, 9\text{-H}), 5.83 (1H, s, 4\text{-H}). \delta_{c} (100 \text{ MHz}; \text{CDCl}_{3}) 21.8 (C-13), 23.7 (C-14), 24.5 (C-12), 35.3 (C-7), 35.7 (C-8), 42.9 (C-1), 51.5 (C-2), 69.3 (C-9), 79.2 (C-6), 126.6 (C-4), 171.8 (C-5), 200.8 (C-3). \text{HRMS (ESI+):} \text{Found (MNa}^{+}) 249.3115 \text{C}_{13}\text{H}_{17}\text{NaO}_{3} \text{requires 249.3115.} \text{[a]}^{22}\text{D} = -1.25^\circ (c = 0.16, \text{MeOH}). \text{IR:} \nu_{\max}(\text{film})/\text{cm}^{-1}; 3469, 3068, 2956, 1410, 1097.

Compounds \text{ds}_{19}, \text{ds}_{20} and \text{ds}_{8} were prepared using the reported method [36].

2,6,6-Tris(methyl-d_{15})cyclohex-2-ene-1,4-dione-d_{9} \text{ds}_{7}: To a stirred solution of \text{ds}_{8} (61 mg, 0.297 mmol) in THF (7 mL) under a nitrogen atmosphere, 2M HCl (3.5 mL) was added, and the resultant mixture was stirred under a hydrogen atmosphere overnight. The mixture was filtered through Celite\textsuperscript{®}, washed with MeOH and the solvent was removed in vacuo. The crude product was purified by flash chromatography (4:1 petroleum ether, ethyl acetate) to yield the title compound \text{ds}_{7} (48 mg, quant.) as a colourless oil. \text{RF} (3:1 petroleum ether, ethyl acetate) = 0.61. \delta_{t}\text{(400 MHz; CDCl}_{3}) 2.70 (2H, s, 5\text{-H}), 6.55 (1H, s, 3\text{-H}). \delta_{c} (100 \text{ MHz}; \text{CDCl}_{3}) 44.9 (C-6), 51.8 (C-5), 137.2 (C-3), 149.0 (C-2), 197.9 (C-4), 203.7 (C-1). \text{HRMS (ESI+):} \text{Found (MNa}^{+}) 184.2413 \text{C}_{6}\text{H}_{9}\text{NaO}_{2} \text{requires 184.2412.} \text{IR:} \nu_{\max}(\text{film})/\text{cm}^{-1}; 3049, 2986, 2912, 1768, 1087.

(2R,3R)-2,3-dimethyl-7,9,9-tris(methyl-d_{15})-1,4-dioxaspiro [4.5]dec-7-en-8-one-d_{9} \text{ds}_{9} (R,R)-14: To a stirred solution of \text{ds}_{7} (1 g, 6.20 mmol) in toluene (15 mL), a solution of 2\text{M HCl} (3.5 mL) was added, and the resultant mixture was heated at reflux for 20 min and was quenched with sat. aq. \text{NaHCO}_{3} (15 mL), and was extracted with ethyl ether (3 \times 8 mL), dried over anhydrous MgSO_{4} and the solvent removed in vacuo. The crude product was purified by flash chromatography (14:1 petroleum ether, ethyl acetate) to yield the title compound \text{ds}_{9} (1.24 g, 89%) as a white solid. \text{RF} (9:1 petroleum ether, ethyl acetate) = 0.5. Melting point: 70–76 \text{°C}. \delta_{t}\text{(400 MHz; CDCl}_{3}) 1.28 (6H, s, J = 5.45 \text{ Hz}, 11- and 12-H), 2.02–2.13 (2H, m, 10-H), 3.61–3.71 (2H, m, 2 and 3-H), 6.32 (1H, s, 6-H). \delta_{c} (100 \text{ MHz}; \text{CDCl}_{3}) 16.7 and 16.9 (C-11 and 12), 47.5 (C-10), 78.5 (C-2 and 3), 103.0 (C-5), 141.5 (C-6), 204.6 (C-8). \text{HRMS (ESI+):} \text{Found (MNa}^{+}) 256.3423 \text{C}_{13}\text{H}_{17}\text{NaO}_{3} \text{requires 256.3428.} \text{[a]}^{22}\text{D} = + 5.50 (c = 0.4, \text{CHCl}_{3}). \text{IR:} \nu_{\max}(\text{film})/\text{cm}^{-1}; 3027, 2971, 1695, 1521, 1063.

(6R,14R,15R)-6-((((tert-Butyldiphenylsilyl)oxy)but-7-yn-7-yl)-14,15-dimethyl-1,15-tris(methyl-d_{15})-18,19-dioxaspiro [3.19]dec-4-en-6-ol-d_{8} \text{ds}_{10} (R,R)-15: To a stirred solution of (R,R)-13 (1.62 g, 5.04 mmol) in THF (30 mL) under a nitrogen atmosphere, \text{BuLi} (2 M in hexanes, 2.52 mL, 5.04 mmol) was added at \text{–78 °C}. The reaction mixture was further stirred at \text{–78 °C} for 20 min and \text{ds}_{10} (R,R)-14 (588 mg, 2.52 mmol) in THF (30 mL) was added dropwise. The resultant mixture was then further stirred at room temperature under a nitrogen atmosphere overnight. The reaction was quenched with sat. aq. \text{NaH}_{2}\text{Cl} (30 mL) and was extracted with ethyl acetate (3 \times 30 mL), the combined organic extracts were washed with water (30 mL), brine (30 mL) and dried over anhydrous MgSO_{4} and the
solvant was removed in vacuo. The crude product was purified by flash chromatography (9:1 petroleum ether, ethyl acetate) and recrystallised from petroleum ether to yield the title compound $d_9$-$(R,R)$-15 (1.98 g, 51%) as a white solid. $R_f$ (petroleum ether, ethyl acetate) = 0.41. Melting point: 111–115 °C. $\delta_{H1}$ (400 MHz; CDCl$_3$) 1.05 (9H, s, Si(CH$_3$)$_3$), 1.20–1.23 (6H, t, J = 4.8 Hz, 16 and 17-H), 1.41 (3H, d, J = 6.5 Hz, 10-H), 1.52 (1H, br s, OH), 1.74 (1H, d, J = 14.2 Hz, 2-H), 1.92 (1H, d, J = 14.1 Hz, 2-H), 3.50–3.60 (2H, m, 14 and 15-H), 4.52 (1H, q, J = 6.4 Hz, 9-H), 5.28 (1H, s, 4-H), 7.34–7.44 (6H, m, Ar-H), 7.68–7.75 (4H, m, Ar-H). $\delta_C$ (100 MHz; CDCl$_3$) 16.8 (C-16), 16.9 (C-17), 19.2 (2 x C$_2$D$_3$), 25.3 (C-10), 26.7 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 26.9 and 39.0 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 45.5 (C-2), 60.1 (C-9), 74.3 (C-7), 77.9 and 78.0 (C-14 and 15), 84.1 (C-8), 88.1 (C-6), 104.1 (C-3), 124.8 (C-4), 127.6–136.0 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 140.3 (C-5). HRMS (ESI+): Found (MNa$^+$): 564.8435 C$_{33}$H$_{35}$D$_9$NaO$_3$Si requires 564.8435. $|\alpha|^2_1^D = +2.27^\circ$ (c = 0.44, CHCl$_3$). IR: $\nu_{\text{max}}$(film)/cm$^{-1}$: 3574, 3058, 2871, 2133, 1739, 1524, 1088.

(R)-6-((R)-9-[(tert-Butyldiphenylsilyloxy)but-7-yn-7-yl]-6-hydroxy-1,1,5-tris(methyl-d$_3$)cyclohex-4-en-3-one-d$_9$ $d_9$-$(R,R)$-16: To a stirred solution of $d_9$-$(R,R)$-15 (1.98 g, 3.71 mmol) in THF (40 mL) under a nitrogen atmosphere, 2M HCl (10 mL) was added, and the reaction mixture was stirred under an nitrogen atmosphere at room temperature overnight. The solvent was removed in vacuo and was extracted with ethyl acetate (3 x 40 mL); the combined organic extracts were washed with brine (40 mL), dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (3:1 petroleum ether, ethyl acetate) to yield the title compound $d_9$-$(R,R)$-16 (1.60 g, 94%) as white crystals. $R_f$ (3:1 petroleum ether, ethyl acetate) = 0.51. Melting point: 105–107 °C. $\delta_{H1}$ (400 MHz; CDCl$_3$) 1.05 (9H, s, Si(CH$_3$)$_3$), 1.46 (3H, d, J = 6.5 Hz, 10-H), 2.25 (1H, d, J = 16.5 Hz, 2-H), 2.34 (1H, d, J = 16.5 Hz, 2-H), 4.57 (1H, q, J = 6.5 Hz, 9-H), 5.73 (1H, s, 4-H), 7.36–7.46 (6H, m, Ar-H), 7.70 (4H, dt, J = 20.4, 6.1, 1.5 Hz, Ar-H). $\delta_C$ (100 MHz; CDCl$_3$) 19.2 (C-1), 25.2 (C-10), 26.8 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 41.2 (C-2), 59.9 (C-9), 74.2 (C-6), 82.4 (C-8), 89.7 (C-7), 126.1 (C-4), 127.7 and 127.9 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 130.0 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 135.8 and 136.0 ([OSi(Ph-C)(C$_2$H$_3$)$_3$]), 198.3 (C-3). HRMS (ESI+): Found (MNa$^+$): 492.2878 C$_{29}$H$_{35}$D$_9$NaO$_3$Si requires 492.2891. $|\alpha|^2_1^D = -2.35^\circ$ (c = 0.34, CHCl$_3$). IR: $\nu_{\text{max}}$(film)/cm$^{-1}$: 1369, 3056, 2863, 1786, 1121.

((R)-6-Hydroxy-4-((R)-3'-hydroxybutyl-1-yn-1-yl)-3,5,5-tris(methyl-d$_3$)cyclohex-2-en-1-one-d$_9$ $d_9$-$(R,R)$-17: To a stirred solution of $d_9$-$(R,R)$-16 (69 mg, 0.15 mmol) in THF (7 mL) under a nitrogen atmosphere, TBAF (0.09 mL, 0.30 mmol) was added at 0 °C, and the resultant mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was quenched with water (7 mL), the solvent was removed in vacuo and extracted with ethyl acetate (3 x 7 mL), the combined organic extracts were washed with brine (7 mL) and dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (1:2 petroleum ether, ethyl acetate) to yield the title compound $d_9$-$(R,R)$-17 (35 mg, quant.) as a colourless oil. N.B. compound 17 was found to be very volatile and was prone to evaporation if placed under a strong vacuum. $R_f$ (1:1 petroleum ether, ethyl acetate) = 0.26. $\delta_{H1}$ (400 MHz; CDCl$_3$) 1.46 (3H, d, J = 6.5 Hz, 10-H), 2.37 (1H, d, J = 16.4 Hz, 2-H), 2.49 (1H, d, J = 16.4 Hz, 2-H), 2.83 (OH), 4.58 (1H, q, J = 6.6 Hz, 9-H), 5.83 (1H, s, 4-H). $\delta_C$ (100 MHz; CDCl$_3$) 24.4 (C-10), 49.2 (C-2), 58.4 (C-9), 74.4 (C-6), 82.7 (C-7), 89.3 (C-8), 110.2 (C-4), 198.5 (C-3). HRMS (ESI+): Found (MNa$^+$): 254.1704 C$_{13}$H$_{13}$D$_4$NaO$_3$ requires 254.1713. $|\alpha|^2_{20}^D = -150.51^\circ$ (c = 0.78, MeOH). IR: $\nu_{\text{max}}$(film)/cm$^{-1}$: 3594, 2861, 2256, 1811, 1067.

(6R,9R)-Blumenol-B $d_9$-$(R,R)$-1-I: To a stirred solution of $d_9$-$(R,R)$-17 (54 mg, 0.23 mmol) in MeOH (7 mL), Pd/BaSO$_4$ (10 mg, 20% w/w) was added, and was stirred under a hydrogen atmosphere for 6 h. The mixture was filtered through Celite®, washed with MeOH and the solvent was removed in vacuo. The crude product was purified by flash chromatography (1:3 petroleum ether, ethyl acetate) to yield the title compound $d_9$-$(R,R)$-1 as (24 mg, 44%) as a colourless oil. $R_f$ (1:3 petroleum ether, ethyl acetate) = 0.24. $\delta_{H1}$ (400 MHz; CD$_3$OD) 1.17 (3H, d, J = 6.2 Hz, 10-H), 1.34–1.44 (1H, m, 8-H), 1.64–1.82 (2H, m, 8-H), 1.94–2.02 (1H, m, 7-H), 2.15 (1H, dd, J = 18.1, 0.98 Hz, 2-H), 2.59 (1H, d, J = 18.1 Hz, 2-H), 3.62–3.69
(1H, m, 9-H), 5.83 (1H, s, 4-H). δC (100 MHz; CD3OD) 23.7 (C-10), 35.3 (C-7), 35.7 (C-8), 50.9 (C-2), 69.4 (C-9), 79.2 (C-6), 126.6 (C-4), 171.7 (C-5), 200.9 (C-3). HRMS (ESI+): Found (MNa+): 258.2018 C13H13D9NaO3 requires 258.2026. [α]D = −2.272° (c = 0.22, CHCl3). IR: νmax (film)/cm−1: 3412.1 (broad OH), 2850.9, 2917.2 and 2961.0 (C-H), 1650.9 and 1729.3 (C=O).

4. Conclusions

In summary, we developed a six-step enantioselective route for the synthesis of (R,R) blumenol B 1. The synthesis is high-yielding, efficient, and significantly shorter than previously reported methods. Furthermore the method can be applied to the synthesis of d9-labelled (R,R)-blumenol B d9-(R,R)-1. The enantioselective synthesis involving the use of two readily available chiral reagents allowed for the selective formation and easy separation of respective stereoisomers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27217294/s1.

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