

## Silver-catalyzed benzannulation, part 2: total synthesis of (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene and (1*R*,4*S*,11*S*)-8- hydroxyserrulat-14-en-19-oic acid

Nicholas Rudgley<sup>1</sup>, Taryn Lee March,<sup>1,2</sup> and Michael Victor Perkins<sup>1\*</sup>

<sup>1</sup>College of Science and Engineering, Flinders University, Adelaide, SA 5001, Australia

<sup>2</sup>Current address: Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Email: [mike.perkins@flinders.edu.au](mailto:mike.perkins@flinders.edu.au)

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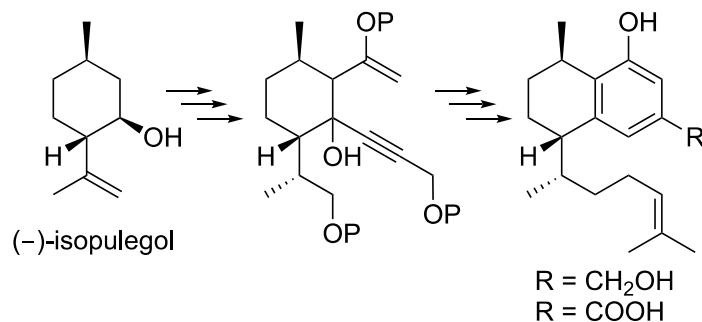
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### Abstract

This paper reports the total synthesis of the serrulatane natural products (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (5.0% yield) and (1*R*,4*S*,11*S*)-8-hydroxyserrulat-14-en-19-oic acid (3.8% yield) via a silver-catalyzed 6-*endo-dig* benzannulation of an (–)-isopulegol derived ene-yne-ol in 17 steps. Analysis of the spectroscopic data as well as the specific rotations allowed for the confirmation of the stereochemistry at C1, C4 and C11 as (1*R*,4*S*,11*S*) for both natural products 8,19-dihydroxyserrulat-14-ene and 8-hydroxyserrulat-14-en-19-oic acid that were reported from the Australian desert plant, *Eremophila neglecta*.

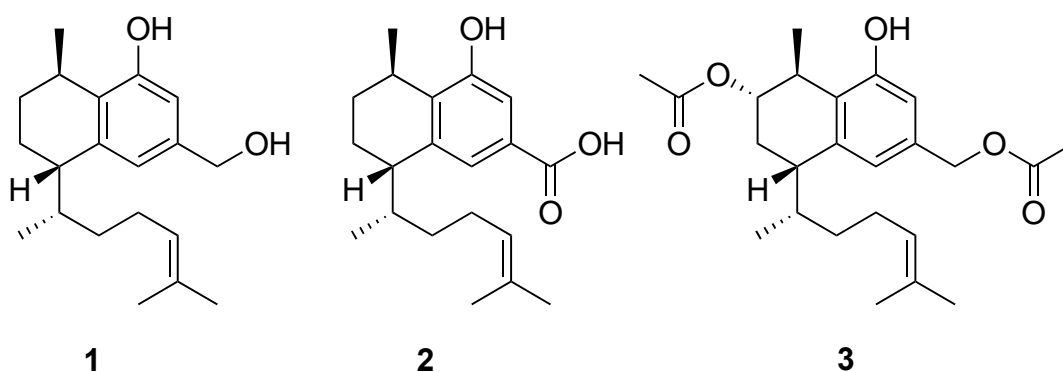


**Keywords:** Benzannulation, serrulatane, 5-alkoxy-1,5-enynes, 6-*endo-dig* cyclisation, tetrahydronaphthalene

## Introduction

The genus *Eremophila* consists typically of plant species that are woody shrubs and trees, with most producing attractive flowers or foliage. Due to the semi-arid to arid climates in which they are found, *Eremophila* species often produce waxy resins comprising up to 20% of the dry weight of the plant on their leaves. Extraction of the leaf material with an organic solvent has led to the isolation of a variety of secondary metabolites, with lipids, flavones and terpenes the most common constituents.<sup>1,2</sup> Amongst the most prolific terpenes isolated from *Eremophila* species are the serrulatanes, which are C<sub>20</sub> diterpenes. The location of these secondary metabolites in leaf cuticles indicates that they may serve a biological role in protection of the plant from grazing herbivores, as antimicrobial agents or possess insecticidal properties for defence of the plant.

Ndi *et al.*<sup>3</sup> took an ethnopharmacological approach, where they considered the species reportedly used in traditional medicines by Aboriginal peoples, in their investigation of the activity of 72 *Eremophila* species against streptococci and staphylococci.<sup>3</sup> Subsequently they isolated three serrulatane diterpenes **1-3** as well as the previously isolated biflorin from the endemic Australian plant *Eremophila neglecta* in 2007 (Figure 1).<sup>4</sup> Notably, **1** and **2** showed antimicrobial activity against Gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes*, and *S. pneumoniae*.

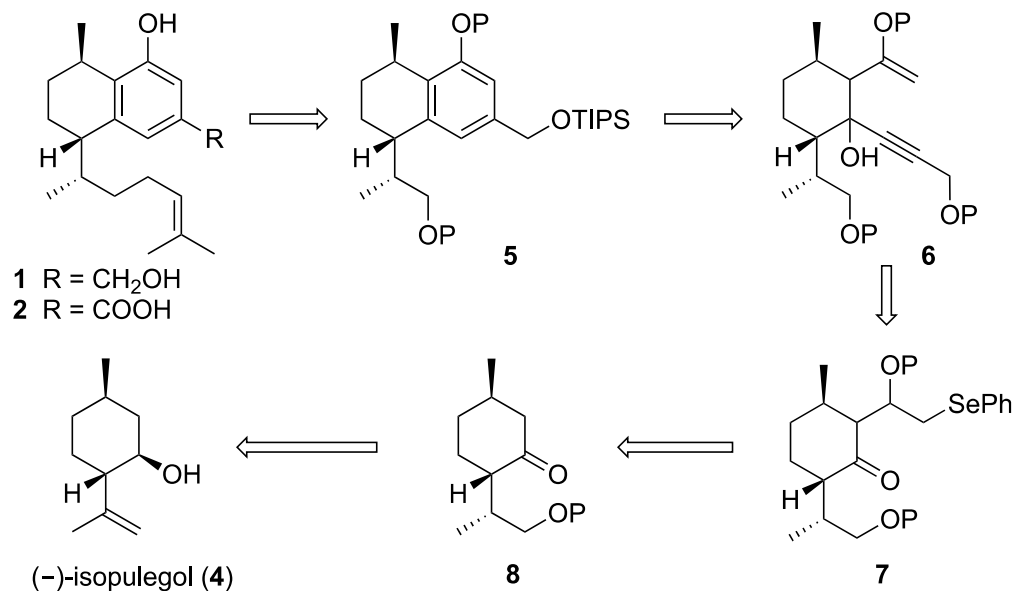


**Figure 1.** Serrulatane natural products from *Eremophila neglecta*.<sup>4</sup>

The structures, including stereochemistry, of the serrulatanes **1**, **2** and acetate **3** were determined by NMR spectroscopy.<sup>4</sup> The configurational assignments were assumed to be the same as previous serrulatane diterpenoids isolated from other plant species in the genus *Eremophila*. The biological activity and potential to confirm the absolute and relative configuration of the natural products **1** and **2** made them interesting synthetic targets in an extension of our previous synthesis of the related serrulatane natural product, leubethanol.<sup>5</sup> In this new approach we applied the silver nitrate catalyzed 6-*endo-dig* cyclisation developed for the synthesis of (1*R*,4*S*)-8,13-dihydroxycalamene, (1*R*,4*S*)-8-hydroxy-13-calamenenal and (1*R*,4*S*)-8-hydroxy-13-calamenenoic acid<sup>6</sup> to the synthesis of the tetrahydronaphthalene core present in **1** and **2**. Starting with (–)-isopulegol (**4**) enabled installation of the C1, C4 and C11 stereocenters early in the synthesis and allowed for incorporation of the prenyl side chain.

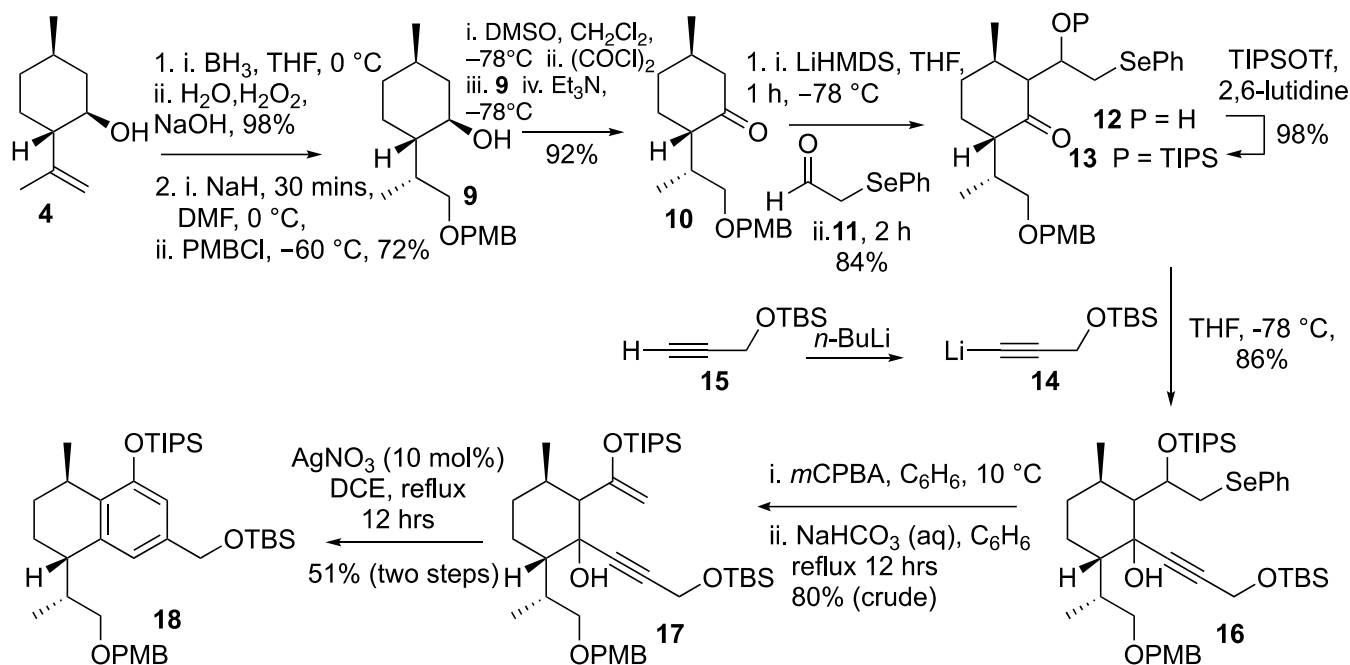
## Results and Discussion

From a retrosynthesis point of view, **1** and **2** could be synthesized from protected alcohol **5** through a chain extension and for **2**, an oxidation sequence. Tetrahydronaphthalene **5** would be synthesized using the silver-catalyzed benzannulation of enyne **6**, which in turn may be formed through acetylide addition to ketone **7** and selenoxide elimination (Scheme 1). Ketone **7** was proposed to be synthesized through TIPS protection of the corresponding  $\beta$ -hydroxy ketone obtained from aldol addition with ketone **8** and 2-(phenylselenanyl)-acetaldehyde. Protected ketone **8** could be obtained in three steps from the commercially available (–)-isopulegol (**4**) in a similar manner to leubethanol.<sup>5</sup>



**Scheme 1.** Retrosynthetic analysis of **1** and **2**.

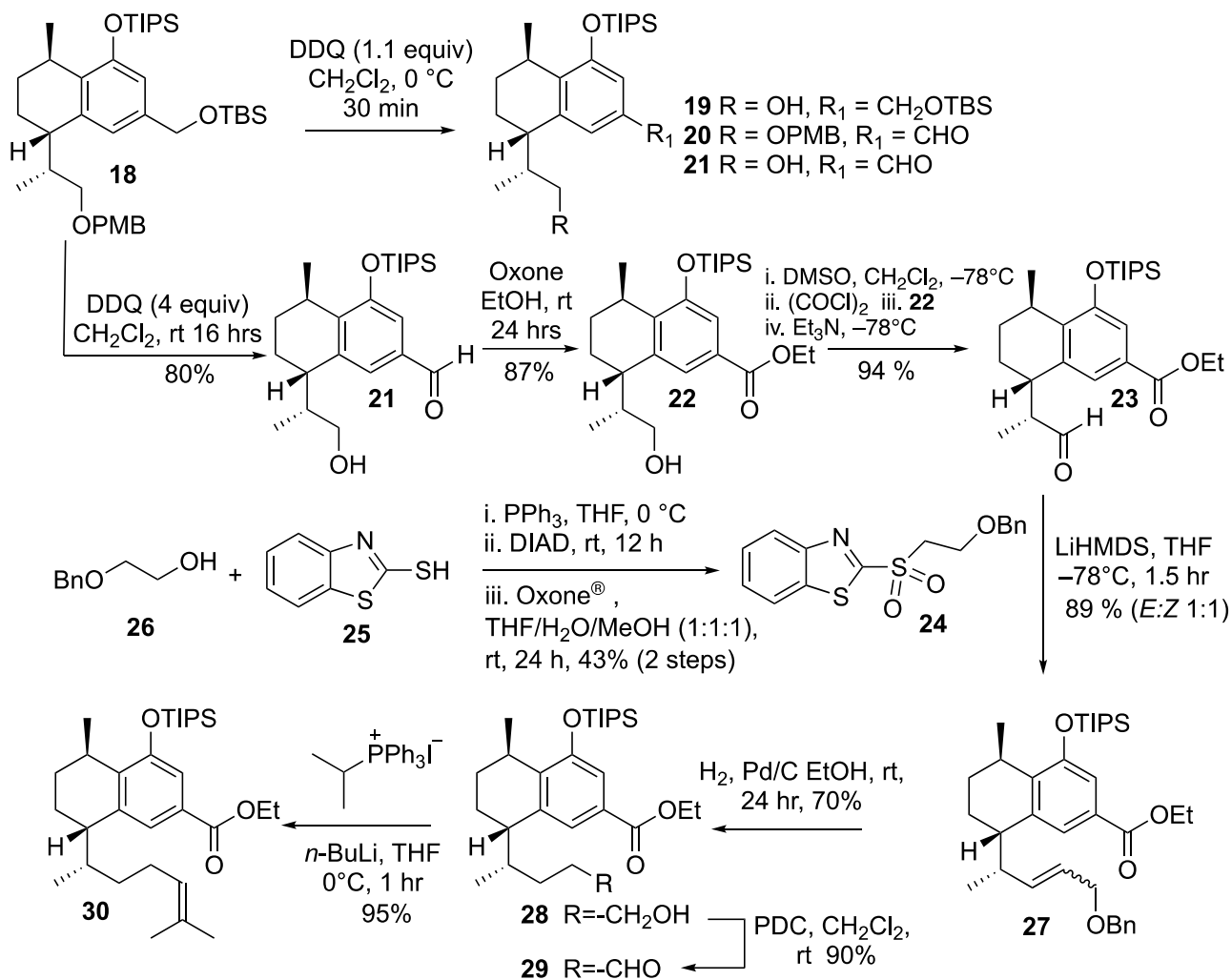
Synthetic studies towards **1** and **2** began with the substrate-directed hydroboration of (–)-isopulegol (**4**) (Scheme 2). Coordination of the secondary hydroxyl group at C1 with the borane, followed by subsequent addition to the alkene resulted in hydroboration occurring predominantly from one side of the alkene. This result was in accordance with the literature, with the hydroboration of isopulegol known to produce the 1*R*,2*S*,5*R*,7*R* stereochemistry.<sup>5,7,8</sup> Due to the similarities in *R<sub>f</sub>*, complete separation of the diastereomers was not achieved at this stage. Treatment of the diol intermediate with sodium hydride and benzyl bromide in DMF at –60 °C gave the primary mono-benzylated product **9** in good yield as well as a small amount of the dibenzylated side-product. Column chromatography afforded separation of ether **9** from the small quantity of bis-PMB ether and minor diastereomer. Swern oxidation afforded the ketone **10**, which was obtained in 65% yield over three steps from (–)-isopulegol. In contrast to the enolization of (–)-menthone with LDA in the synthesis of the 8-hydroxycalamenenes,<sup>6</sup> the preferred base was found to be LiHMDS. Enolization of ketone **10** with LiHMDS and treatment with (phenylselenanyl)acetaldehyde (**11**) afforded the desired hydroxyselenide **12** in an excellent 84% yield (Scheme 2). <sup>1</sup>H NMR spectroscopy indicated the presence of only one diastereomer, as did the <sup>13</sup>C NMR spectrum that contained an expected 22 carbon signals, but the stereochemistry was not assigned. Subsequent protection as the triisopropylsilyl ether **13** proceeded almost quantitatively (98% yield).



**Scheme 2.** Synthesis of silyloxy arene **18**.

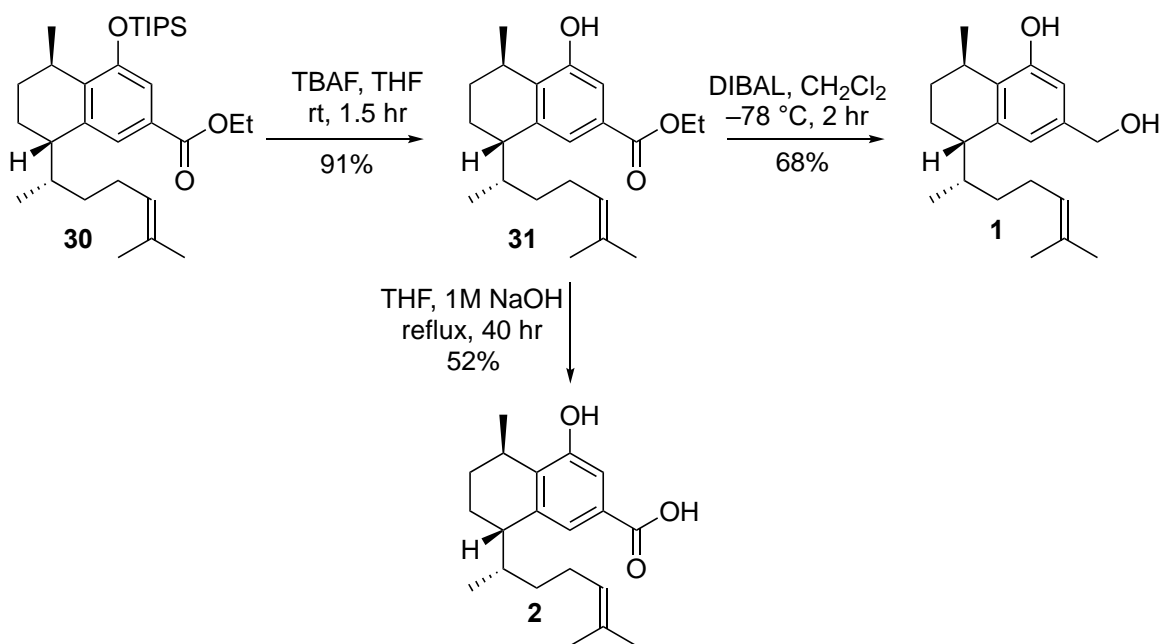
With the protected phenylselenide **13** in hand, the next step was the addition of lithium acetylide **14**. A large excess of alkyne (4 equiv) was used to ensure complete conversion and ease of purification. The TBS-alkyne **15** was deprotonated with freshly titrated *n*-butyl lithium, phenylselenide **13** added dropwise via cannulation at  $-78\text{ }^{\circ}\text{C}$  (Scheme 2), and the reaction stirred for 2 h. Notably, addition of lithium acetylide **14** to ketone **13** resulted in one distinguishable diastereomer of **16** based on analysis of the  $^1\text{H}$  NMR spectrum (See  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra in the supplementary information) and this addition occurred readily without DMPU, which was required for the analogous addition in the 8-hydroxycalamenenes synthesis.<sup>6</sup> To achieve elimination, phenylselenide **16** was first treated with *m*-chloroperbenzoic acid in anhydrous benzene for 20 min at  $10\text{ }^{\circ}\text{C}$ .<sup>9</sup> A saturated aqueous solution of  $\text{NaHCO}_3$  was then added, with the intermediate selenoxide heated at reflux overnight in the biphasic mixture to give crude **17**. The critical silver-catalyzed 6-*endo-dig* benzannulation procedure was then attempted using the previously developed conditions.<sup>6</sup> The enyne **17** was not purified, but simply dissolved in DCE and the resulting solution heated to reflux. A catalytic amount of  $\text{AgNO}_3$  (10 mol%) was then added and the solution heated at reflux in darkness for 12 h. Gratifyingly the arene **18** was isolated after column chromatography as a colorless oil in 51% yield over two steps from phenylselenide **16**.

With tetrahydronaphthalene **18** synthesized, installation of the prenyl side chain was attempted. The first step in this process was the removal of the 4-methoxybenzyl (PMB) protecting group. However, when arene **18** was treated with DDQ (1.1 equiv), a complex mixture of products was observed. Column chromatography afforded four major fractions. Two were the expected *p*-anisaldehyde and the desired primary alcohol **19** resulting from PMB deprotection, whilst the two other products were assigned as aldehydes **20** and **21**. The fact that aldehyde **20** with the PMB group still intact was isolated in conjunction with recovered starting material suggested that regioselective SET oxidative removal of PMB from **18** was not possible. But simultaneous removal of the PMB protecting group and oxidation of the benzylic C19 position could be achieved by treatment of the PMB ether **18** with excess DDQ (4.0 equiv), affording the deprotected aldehyde **21** in 80% yield (Scheme 3). Although it is not ideal to oxidize both positions, it does differentiate the two primary hydroxy groups, and C19 of compound **2** is in the carboxylic acid oxidation state.

Scheme 3. Synthesis of **30** (protected **2**).

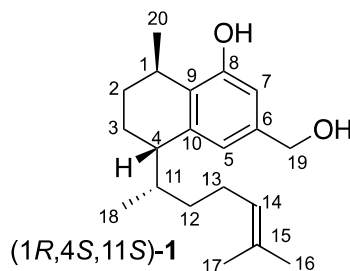
Selective oxidation and protection of the benzylic aldehyde was achieved using Oxone<sup>®</sup> esterification<sup>10</sup> to give aromatic ester **22** as a colorless oil in 87% yield. Swern oxidation<sup>11,12</sup> of aromatic ester **22** was conducted using the sterically hindered *N,N*-diisopropylethylamine as base to avoid epimerization. The aldehyde **23** was obtained in 94% yield as a colorless oil. Analysis of the <sup>1</sup>H NMR spectrum indicated one aldehyde signal and therefore no epimerization occurred. Considering that the tetrahydronaphthalene **23** has an ester functional group, the chain extension strategy should not employ reduction steps due to the obvious chemoselectivity issues. The ylides therefore had to possess the correct or lower oxidation state for chain extension. Julia-Kocienski olefination using a modified version of the Pospíšil and Markó<sup>13,14</sup> protocol with benzyl sulfone **24** ultimately provided an efficient path to the prenyl side chain. The sulfone **24** was prepared by Mitsunobu reaction of 2-mercaptobenzothiazole **25** and benzyl ether **26**, giving the sulfide in modest yield, which was oxidized to sulfone **24** using Oxone<sup>®</sup>. The sulfone **24** and aldehyde **23** were then dissolved together in THF and slow addition of base resulted in disappearance of the starting materials, giving the allylic benzyl ether **27** as an approximate 50:50 mixture of *E/Z* isomers in 89% yield. The saturation of the double bond as well as benzyl ether deprotection was then achieved using hydrogen and Pd/C. The double bond was removed easily, with the saturated benzyl ether observed after 2 h. The hydrogenation was continued for a further 12 h to remove the benzyl protecting group. Following purification through a plug of Celite and column chromatography, alcohol **28** was obtained in 70% yield as a colorless oil. Alcohol **28** was oxidized with PDC to aldehyde **29** in 90% yield.

Following column chromatography, the aldehyde was isolated as a colorless oil. The prenyl tail was introduced through a final Wittig olefination reaction, giving compound **30** in 95% yield. To minimize the total number of steps the silyl protecting group was to be removed first, and then from the free phenol both natural products could be accessed through either reduction or hydrolysis of the ester. Silyl ether **30** was deprotected with TBAF in THF (Scheme 4) giving the phenolic ester **31** in 91% yield. Reduction of **31** with DIBAL gave the first target compound (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (**1**) in 68% yield. Compound **31** was reasonably resistant to hydrolysis but treatment with 1 M sodium hydroxide in THF at reflux followed by acidification yielded the second target compound, (1*R*,4*S*,11*S*)-8-hydroxyserrulat-14-en-19-oic acid (**2**), in 52% yield.



**Scheme 4.** Synthesis of (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (**1**) and (1*R*,4*S*,11*S*)-8-hydroxyserrulat-14-en-19-oic acid (**2**).

The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data for the synthetic (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (**1**) and (1*R*,4*S*,11*S*)-8-hydroxyserrulat-14-en-19-oic acid (**2**) were totally consistent with that reported for the natural products **1** and **2** (Tables 1 and 2). Comparison of the optical rotations for the synthetic (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (**1**), [ $\alpha$ ]<sub>D</sub><sup>20</sup> -46.5 (c 0.19, MeOH), showed reasonable agreement with that reported<sup>4</sup> for natural **1**, [ $\alpha$ ]<sub>D</sub><sup>20</sup> -64.8 (c 0.216, MeOH), confirming the absolute configuration assigned to the natural product.

**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for natural natural product **1** reported by Ndi *et al.*<sup>4</sup> compared to the synthetic (**1R, 4S, 11S**)-**1**

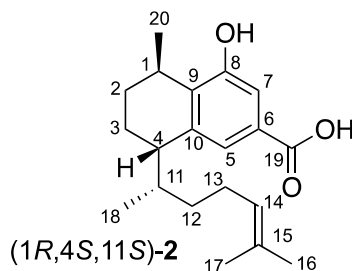
Carbon Number	Natural-1 <sup>a</sup>		Synthetic ( <b>1R, 4S, 11S</b> )-1 <sup>b</sup>		$\Delta\delta_{\text{c}}^{\text{d}}$
	$\delta_{\text{H}}^{\text{c}}$ ( <i>J</i> in Hz) <sup>c</sup>	$\delta_{\text{C}}^{\text{c}}$	$\delta_{\text{H}}^{\text{c}}$ ( <i>J</i> in Hz)	$\delta_{\text{C}}^{\text{c}}$	
8		153.6		153.4	0.19
10		141.5		141.5	-0.02
6		137.9		138.2	-0.33
15		131.2		131.2	-0.01
9		129.1		128.9	0.24
14	4.96 (t, 7)	124.9	4.98 (t, 7.1)	124.8	0.06
5	6.70 (br. d, 1.4)	120.3	6.74 (s)	120.4	-0.08
7	6.64 (br. d, 1.4)	111.1	6.63 (d, 1.6)	111.0	0.09
19	4.56 (br. s)	65.4	4.59 (s)	65.4	0.04
4	2.58 (dt, 5.6, 3)	42.5	2.61 (td, 5.6, 2.8)	42.5	0.01
11	1.86 (m)	38	1.86 (m)	38.0	-0.02
12	1.27 (dddd, 13, 10, 7, 3) 1.09 (dddd, 13, 10, 9.4, 5)	33.5	1.33–1.23 (m); 1.09 (dtd, 13.3, 9.7, 5.1)	33.5	0.03
2	1.88 (m) 1.48 (ddt, 13, 5, 3)	27.3	1.94 (ddd, 13.1, 6.0, 3.2) 1.51 (dq, 10.3, 2.6)	27.3	-0.01
1	3.09 (d. quin., 6.6, 3)	26.8	3.10 pd (6.8, 2.4)	26.8	0.05
13	a) 1.97 (m); b) 1.79 (m)	26.2	2.04–1.91(m) 1.79 (dd, 15.0, 7.7)	26.2	-0.04
16	1.63 (br. s)	25.7	1.65 (s)	25.7	0.02
20	1.18 (d, 6.6)	21	1.20 (d, 7.0)	21.0	-0.03
3	1.86 (m); 1.69 (ddt, 13.5, 5, 3)	19.4	1.86 (m); 1.74 (ddt, 13.7, 5.9, 3.1)	19.4	0.03
18	0.94 (d, 6.6)	18.7	0.96 (d, 6.8)	18.7	-0.04
17	1.53 (br. s)	17.6	1.55 (s)	17.6	-0.02

<sup>a</sup> Chemical shifts and coupling constants as reported by Ndi *et al.*<sup>4</sup>

<sup>b</sup> Chemical shifts and coupling constants for prepared compounds; Bruker 600 MHz NMR Spectrometer.

<sup>c</sup> Chemical shifts in ppm referenced to  $\text{CHCl}_3$  at 7.26 ppm and to  $\text{CDCl}_3$  at 77.00 ppm. Note the shifts reported here for synthetic compounds are referenced to 77.00 ppm for comparison with the natural products.

<sup>d</sup> This is the difference in the  $^{13}\text{C}$  chemical shift (ppm) of the synthetic isomer and that reported for the natural product.

**Table 2.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for natural product **2** as reported by Ndi *et al.*<sup>4</sup> compared to the synthetic (1*R*, 4*S*, 11*S*)-**2**

Carbon Number	Natural <b>2</b> <sup>a</sup>		Synthetic (1 <i>R</i> , 4 <i>S</i> , 11 <i>S</i> )- <b>2</b> <sup>b</sup>		$\Delta\delta_{\text{C}}^{\text{d}}$
	$\delta_{\text{H}}^{\text{c}}$ ( <i>J</i> in Hz)	$\delta_{\text{C}}^{\text{c}}$	$\delta_{\text{H}}^{\text{c}}$ ( <i>J</i> in Hz)	$\delta_{\text{C}}^{\text{c}}$	
19	-	172.1		170.9	1.21 <sup>e</sup>
8		153.2		153.1	0.05
10		141.7		141.7	0.02
9		136.5		136.3	0.21
15		131.4		131.4	-0.01
6		126.4		126.3	0.09
14	4.96, t (7.0)	124.6	5.00–4.94 (m)	124.6	-0.04
5	7.54 br d (1.4)	124.1	7.53 (br s)	124.1	0.02
7	7.29 br d (1.4)	113.2	7.27 (br s)	113.2	0.00
4	2.65 dt (5.7, 2.8)	42.5	2.72–2.63 (m)	42.4	0.07
11	1.89 m	38	1.85–1.95 (m)	38.1	-0.05
12	1.25 dddd (13.0, 9.9, 7.1, 3.0)	33.4	1.1–1.3 (m)	33.4	-0.01
	1.09 dddd (13.0, 10.0, 9.4, 5.0)		1.10 (dtd, <i>J</i> =13.5, 9.6, 5.0 Hz)		
2	1.95 m	27	2.05–1.84 (m)	27.0	0.05
	1.52 m		1.4–1.6 (m)		
1	3.18 d quint (7.0, 2.7)	27.3	3.18 (dtd, <i>J</i> =13.3, 6.6, 1.8 Hz)	27.3	0.03
13	1.96 m	26.2	2.05–1.74 (m)	26.2	0.02
	1.79 m				
16	1.62 br s	25.6	1.64 (s)	25.6	-0.04
20	1.20 d (7.0)	20.8	1.22 (d, <i>J</i> =7.0 Hz)	20.8	0.00
3	1.89 m	19.2	1.84–1.72 (m)	19.2	0.02
	1.73 m				
18	0.96 d (6.6)	18.7	0.97 (d, <i>J</i> =6.8 Hz)	18.7	0.05
17	1.524 br s	17.6	1.54 (s)	17.6	-0.02

<sup>a</sup> Chemical shifts and coupling constants as reported by Ndi *et al.*<sup>4</sup>

<sup>b</sup> Chemical shifts and coupling constants for prepared compounds; Bruker 600 MHz NMR Spectrometer.

<sup>c</sup> Chemical shifts in ppm referenced to  $\text{CHCl}_3$  at 7.26 ppm and to  $\text{CDCl}_3$  at 77.00 ppm. Note the shifts reported here for synthetic compounds are referenced to 77.00 ppm for comparison with the natural products.

<sup>d</sup> This is the difference in the  $^{13}\text{C}$  chemical shift (ppm) of the synthetic isomer and that reported for the natural product.

<sup>e</sup> This large difference in chemical shift is attributed to a concentration effect for the carboxylic acid carbon.

## Conclusions

This paper has demonstrated the application of a novel method for the benzannulation of an (–)-isopulegol derived ene-yne **17** to give the aromatic ring, using silver nitrate as the catalyst. Deprotection and chain extension using a modified Julia-Kocienski olefination and Wittig reaction furnished the prenyl side chain, enabling the total syntheses of (1*R*,4*S*,11*S*)-8,19-dihydroxyserrulat-14-ene (**1**) (17 steps, 5.0%), and (1*R*,4*S*,11*S*)-8-hydroxyserrulat-14-en-19-oic acid (**2**) (17 steps, 3.8%) via a common intermediate. These total syntheses allowed confirmation of the absolute configurations of the natural products identified from the Australian desert plant, *Eremophila neglecta*.<sup>4</sup>

## Experimental Section

**General.** All reactions were carried out under an inert atmosphere of nitrogen unless otherwise specified. All glassware was either oven or flame-dried prior to use. Benzene, dichloromethane and triethylamine were distilled over CaH<sub>2</sub>. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone. All other reagents were used as received. Thin layer chromatography was performed with Merck silica gel 60 F<sub>254</sub> aluminium backed sheets and developed with KMnO<sub>4</sub> or anisaldehyde, or monitored by ultraviolet lamp. Column chromatography was performed with Merck silica gel (particle size: 0.04-0.063 mm), 230-400 mesh. When purifying compounds with acid sensitivity, column chromatography was performed on buffered silica as indicated. Buffered silica was prepared by spinning 100 g of silica gel 60 (mesh size 0.040-0.063 mm) with 10 mL of pH 7 phosphate buffer on a rotary evaporator overnight at atmospheric pressure.<sup>15</sup> <sup>1</sup>H NMR spectra were recorded using either a Bruker 400 MHz or Bruker 600 MHz spectrometer. Where CDCl<sub>3</sub> was used as the solvent and internal lock, it was referenced to CHCl<sub>3</sub> ( $\delta_{\text{H}}$  7.26) for <sup>1</sup>H NMR and CDCl<sub>3</sub> ( $\delta_{\text{C}}$  77.16) for <sup>13</sup>C NMR. Chemical shift values are reported in parts per million (ppm) and coupling constants are reported in hertz (Hz). Abbreviations used for assigning <sup>1</sup>H NMR spectra: Ar = aromatic, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, app. = apparent. Optical rotations were recorded on a Pola AR21 polarimeter referenced to the sodium D line (589 nm) at 20 °C. Concentrations are reported in g/100 mL using analytical grade solvents.

**(1*R*,2*S*,5*R*)-2-[(*R*)-1-Hydroxypropan-2-yl]-5-methylcyclohexan-1-ol (**32**).** The hydroboration was conducted according to a procedure by Correa and Moreira.<sup>8</sup> To a stirred solution of (–)-isopulegol (**4**) (15.98 g, 104 mmol) in THF (150 mL) at 0 °C was added BH<sub>3</sub> (1M in THF, 130 mL, 130 mmol) dropwise and the resulting solution stirred for 3 h at 0 °C. The reaction was quenched by addition of H<sub>2</sub>O (60 mL), H<sub>2</sub>O<sub>2</sub> (30%, 95 mL) and NaOH (30% w/v, 60 mL). The mixture was diluted with H<sub>2</sub>O (100 mL) until the solution was clear. The layers were separated and the aqueous layer extracted with Et<sub>2</sub>O (2 × 100 mL), with the combined organic extracts washed with brine (2 × 100 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Recrystallisation from cyclohexane gave the *title compound* **32** (17.4 g, 98%) as colorless needles with a trace impurity of minor diastereomer. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  3.66 (1H, dd, *J*=10.7, 5.6 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.60 (1H, dd, *J*=10.6, 3.4 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.47 (1H, td, *J*=10.5, 4.3 Hz, CHOH), 3.10 (2H, s, OH), 1.95 (1H, dtd, *J*=12.2, 3.8, 2.0 Hz), 1.89–1.82 (1H, m), 1.66–1.61 (1H, m), 1.56 (1H, dq, *J*=13.4, 3.5 Hz), 1.47–1.39 (1H, m), 1.40–1.32 (1H, m), 1.23 (1H, qd, *J*=13.0, 3.6 Hz), 0.96 (3H, d, *J*=7.3 Hz, C5CH<sub>3</sub>), 0.92 (3H, d, *J*=6.6 Hz, C2'CH<sub>3</sub>), 0.90–0.84 (1H, m); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  70.2, 67.2, 48.7, 44.7, 38.8, 34.7, 31.6, 29.7, 22.2, 12.0.

**(1R,2S,5R)-2-((R)-1-[(4-Methoxybenzyl)oxy]propan-2-yl)-5-methylcyclohexan-1-ol (9)**. To a stirred suspension of NaH (0.82 g, 34.2 mmol) in DMF (90 mL) at 0 °C was added diol **32** (2.9 g, 16.8 mmol) portionwise and the resulting suspension stirred for 1 h. The reaction mixture was cooled to –50 °C and PMBCl (2.28 mL, 16.8 mmol) added slowly over 10 min. The reaction mixture was stirred for 1.5 h at –50 °C then allowed to warm to room temperature overnight. The reaction was quenched by addition of NH<sub>4</sub>Cl (90 mL, sat. aq.) and the layers separated. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers washed with LiCl (5% aq., 3 × 100 mL), brine (2 × 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/hexane) afforded the *title compound 9* (3.54 g, 72%) as a colorless oil.  $[\alpha]_D^{20}$  –10.4 (c 0.96 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3420, 2998, 2949, 2920, 2866, 1613, 1586, 1514, 1455, 1364, 1302, 1248, 1174, 1041 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.27–7.21 (2H, m, Ar-H), 6.90–6.84 (2H, m, Ar-H), 4.47 (1H, d, *J*=11.5 Hz, OCH<sub>A</sub>H<sub>B</sub>PMP), 4.42 (1H, d, *J*=11.5 Hz, OCH<sub>A</sub>H<sub>B</sub>PMP), 3.80 (3H, s, OCH<sub>3</sub>), 3.69 (1H, s, CHOH), 3.47 (1H, dd, *J*=9.1, 6.3 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 3.42 (1H, td, *J*=10.5, 4.2 Hz, CHOH), 3.36 (1H, dd, *J*=9.1, 3.4 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 2.03 (1H, dtd, *J*=14.1, 6.9, 3.5 Hz), 1.96 (1H, dtd, *J*=12.4, 3.8, 2.1 Hz), 1.63 (2H, dp, *J*=12.6, 3.4 Hz), 1.55 (1H, dq, *J*=13.2, 3.4 Hz), 1.40 (2H, tdp, *J*=13.0, 6.5, 3.0 Hz), 1.30 (1H, ddt, *J*=12.6, 10.0, 3.1 Hz), 1.13 (1H, qd, *J*=13.0, 3.7 Hz), 0.94 (3H, d, *J*=7.3 Hz, C5CH<sub>3</sub>), 0.91 (3H, d, *J*=6.6 Hz, C2'CH<sub>3</sub>), 0.86 (1H, qd, *J*=12.9, 3.6 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 159.4, 130.0, 129.5, 114.0, 74.2, 73.1, 70.5, 55.4, 49.2, 44.1, 35.7, 34.9, 31.6, 28.2, 22.3, 13.6; HRESIMS calcd. for C<sub>18</sub>H<sub>28</sub>O<sub>3</sub>Na<sup>+</sup>, [M+Na]<sup>+</sup> 315.1936 found 315.1942.

**(2S,5R)-2-((R)-1-[(4-Methoxybenzyl)oxy]propan-2-yl)-5-methylcyclohexan-1-one (10)**. The oxidation was conducted according to a procedure by Mancuso and Swern.<sup>11,12</sup> To a stirred solution of DMSO (3 mL, 42.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (70 mL) at –78 °C was added oxalyl chloride (2 M in CH<sub>2</sub>Cl<sub>2</sub>, 9.4 mL, 18.8 mmol) dropwise and the solution stirred for 30 min. Alcohol **9** (3.54 g, 12.1 mmol) was added via cannula (CH<sub>2</sub>Cl<sub>2</sub>) and the solution stirred for 1.5 h. Et<sub>3</sub>N (10 mL, 71.7 mmol) was added dropwise and the solution maintained at –78 °C for a further hour. The reaction mixture was quenched through addition of NH<sub>4</sub>Cl (40 mL, sat. aq.) and allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/hexane) afforded the *title compound 10* (3.25 g, 92%) as a colorless oil.  $[\alpha]_D^{20}$  –10.9 (c 0.92 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2954, 2926, 2865, 1709, 1586, 1514, 1455, 1375, 1302, 1247, 1172, 1089, 823 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.26–7.21 (2H, m, Ar-H), 6.90–6.84 (2H, m, Ar-H), 4.40 (2H, AB quartet, 12.0 Hz, CH<sub>2</sub>PMP), 3.80 (3H, s, OCH<sub>3</sub>), 3.44 (1H, dd, *J*=9.1, 5.4 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 3.35 (1H, dd, *J*=9.1, 6.0 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 2.36–2.29 (2H, m, CH<sub>2</sub>C=O), 2.14 (1H, hept, *J*=6.6 Hz), 2.02 (1H, ddt, *J*=12.0, 5.5, 3.1 Hz), 1.97 (1H, t, *J*=13.0 Hz), 1.89–1.79 (1H, m), 1.41 (1H, qd, *J*=12.5, 2.8 Hz), 1.34 (1H, qd, *J*=12.5, 3.0 Hz), 1.00 (3H, d, *J*=6.4 Hz), 0.99 (3H, d, *J*=6.9 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 212.0, 159.1, 130.9, 129.2, 113.7, 72.8, 72.7, 55.3, 52.3, 51.1, 35.6, 34.2, 32.8, 29.6, 22.4, 15.6; HRESIMS calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub>Na<sup>+</sup>, [M+Na]<sup>+</sup> 313.1780 found 313.1779.

**(3R,6S)-2-[1-Hydroxy-2-(phenylselanyl)ethyl]-6-((R)-1-[(4-methoxybenzyl)oxy]propan-2-yl)-3-methylcyclohexan-1-one (12)**. To a stirred solution of ketone **10** (2.02 g, 6.96 mmol) in THF (10 mL) at –78 °C was added LiHMDS (1 M in THF, 9 mL, 9 mmol) dropwise and the resulting solution stirred for 1 h. Aldehyde **11** (1.99 g, 9.99 mmol) was added dropwise over 10 min and the resulting solution stirred at –78 °C for 3 h. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL), quenched through addition of NH<sub>4</sub>Cl (10 mL) and extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were washed with NaHCO<sub>3</sub> (10 mL), H<sub>2</sub>O (10 mL) and brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/hexane) to afford the *title compound 12* (2.84 g, 83%) as a light-yellow oil.  $[\alpha]_D^{20}$  negligible rotation; IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3517, 3056, 2927, 2854, 1692, 1612, 1579, 1513, 1302, 1248, 1173, 1086, 1035, 820, 738, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.52–7.47 (2H, m, Ar-H), 7.28–7.20 (5H, m, Ar-H), 6.90–6.86 (2H, m, Ar-H), 4.42 (1H, d, *J*=11.7 Hz, CH<sub>A</sub>H<sub>B</sub>PMP), 4.37 (1H, d, *J*=11.7 Hz, CH<sub>A</sub>H<sub>B</sub>PMP), 3.81 (4H, m, OCH<sub>3</sub> and CHOH), 3.56 (1H,

s, OH), 3.37 (1H, dd,  $J=9.1, 4.5$  Hz,  $CH_AH_BOPMB$ ), 3.32 (1H, dd,  $J=12.5, 5.9$  Hz,  $CH_AH_BSePh$ ), 3.29 (1H, dd,  $J=9.2, 5.7$  Hz,  $CH_AH_BOPMB$ ), 3.09 (1H, dd,  $J=12.5, 8.9$  Hz,  $CH_AH_BSePh$ ), 2.46 (1H, dt,  $J=11.6, 1.4$  Hz,  $CHCHOH$ ), 2.29–2.22 (1H, m), 2.08–1.98 (2H, m), 1.85 (1H, dq,  $J=13.2, 3.4$  Hz), 1.43 (1H, qd,  $J=13.2, 3.6$  Hz), 1.34 (1H, qd,  $J=12.9, 3.4$  Hz), 1.00 (3H, d,  $J=6.4$  Hz,  $C3CH_3$ ), 0.93 (3H, d,  $J=6.9$  Hz,  $C6'CH_3$ );  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  217.3, 159.2, 133.0, 130.9, 129.7, 129.34, 129.26, 127.3, 113.9, 72.9, 72.4, 70.2, 59.2, 55.4, 54.6, 38.7, 34.7, 32.9, 32.3, 31.1, 20.3, 16.3; HRESIMS calcd. for  $C_{26}H_{34}O_4^{80}SeNa^+$ ,  $[M+Na]^+$  513.1520 found 513.1500.

**(3R,6S)-6-((R)-1-((4-Methoxybenzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-**

**[(triisopropylsilyl)oxy]ethyl)cyclohexan-1-one (13).** To a stirred solution of alcohol **12** (1.15 g, 2.35 mmol) in  $CH_2Cl_2$  (30 mL) at  $-78$  °C was added 2,6-lutidine (0.52 mL, 4.5 mmol) and TIPSOTf (0.89 mL, 3.3 mmol) sequentially. The resulting solution was stirred for 3 h at  $-78$  °C then warmed to room temperature. The reaction was quenched by addition of  $NaHCO_3$  (30 mL, sat. aq.), layers separated and the aqueous layer extracted with  $CH_2Cl_2$  (3  $\times$  20 mL). The combined organic layers were dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/hexane) gave the *title compound* **13** (1.49 g, 98%) as a light-yellow oil.  $[\alpha]_D^{20}$   $-13.4$  (c 0.97 in  $CHCl_3$ ); IR ( $CHCl_3$ ,  $cm^{-1}$ ) 3050, 2926, 2865, 1705, 1613, 1580, 1513, 1463, 1364, 1301, 1248, 1172, 1109, 1040, 883, 821, 736, 681  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.55–7.50 (2H, m, Ar-H), 7.27–7.19 (5H, m, Ar-H), 6.89–6.84 (2H, m, Ar-H), 4.61 (1H, br. s,  $CHOTIPS$ ), 4.40 (2H, AB quartet, 11.4 Hz,  $CH_AH_BPMP$ ), 3.79 (3H, s,  $OCH_3$ ), 3.44 (1H, dd,  $J=9.1, 4.8$  Hz,  $CH_AH_BOPMB$ ), 3.41–3.35 (1H, m,  $CH_AH_BSePh$ ), 3.32 (1H, dd,  $J=9.1, 6.2$  Hz,  $CH_AH_BOPMB$ ), 3.17 (1H, dd,  $J=11.7, 6.5$  Hz,  $CH_AH_BSePh$ ), 2.43 (1H, d,  $J=11.6$  Hz,  $CHCHOH$ ), 2.24 (1H, dt,  $J=13.3, 5.4$  Hz), 2.17 (1H, hept,  $J=6.7$  Hz), 2.04–1.94 (2H, m), 1.92–1.85 (1H, m), 1.49–1.34 (2H, m), 1.15 (3H, d,  $J=6.4$  Hz,  $C3CH_3$ ), 1.08–1.01 (21H, m,  $OTIPS$ ), 0.98 (3H, d,  $J=6.9$  Hz,  $C6'CH_3$ );  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  210.8, 159.2, 132.6, 131.6, 131.0, 129.3, 129.1, 126.8, 113.8, 72.9, 72.8, 70.8, 55.4, 53.6, 36.2, 35.3, 32.6, 32.2, 28.9, 21.7, 18.4, 17.8, 15.9, 13.0; HRESIMS calcd. for  $C_{35}H_{54}O_4^{80}SeSiNa^+$ ,  $[M+Na]^+$  669.2854 found 669.2825.

**(1R,3R,6S)-1-(3-((Tert-butyl)dimethylsilyl)oxy)prop-1-yn-1-yl)-6-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-[(triisopropylsilyl)oxy]ethyl)cyclohexan-1-ol (16).** The acetylide addition was conducted according to the procedure previously described.<sup>6</sup> To a stirred solution of OTBS-alkyne **15** (1.28 g, 7.51 mmol) in THF (40 mL) at  $-78$  °C was added *n*-BuLi (1.6 M in hexane, 4.5 mL, 7.2 mmol) dropwise and the resulting solution stirred for 1 h. Ketone **13** (1.18 g, 1.83 mmol) in THF (10 mL) was added via cannula and the reaction mixture stirred for 2 h at  $-78$  °C (monitored with TLC). The reaction was quenched through addition of  $NH_4Cl$  (30 mL, sat. aq.), layers separated and the aqueous layer extracted with  $Et_2O$  (3  $\times$  30 mL). The combined organic layers were dried ( $Na_2SO_4$ ) and concentrated *in vacuo*.  $^1H$  NMR analysis of the crude reaction mixtures revealed that there were no observable starting materials. Purification by column chromatography (5% EtOAc/hexane) afforded the *title compound* **16** (1.28 g, 86%) as a colorless oil.  $[\alpha]_D^{20}$   $+35.7$  (c 0.95 in  $CHCl_3$ ); IR ( $CHCl_3$ ,  $cm^{-1}$ ) 3335, 3057, 2928, 2863, 1613, 1581, 1515, 1463, 1362, 1303, 1251, 1160, 1083, 836  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.52–7.49 (2H, m, Ar-H), 7.28–7.24 (2H, m, Ar-H), 7.09–7.04 (3H, m, Ar-H), 6.86–6.82 (2H, m, Ar-H), 5.40 (1H, s, OH), 4.94 (1H, d,  $J=10.3$  Hz,  $CHOTIPS$ ), 4.52 (1H, d,  $J=11.6$  Hz,  $CH_AH_BPMP$ ), 4.46 (1H, d,  $J=11.5$  Hz,  $CH_AH_BPMP$ ), 4.22 (1H, d,  $J=15.9$  Hz,  $CH_AH_BOTBS$ ), 4.14 (1H, d,  $J=15.9$  Hz,  $CH_AH_BOTBS$ ), 3.94–3.88 (1H, m,  $CH_AH_BSePh$ ), 3.75 (3H, s,  $OCH_3$ ), 3.29 (1H, t,  $J=10.4$  Hz,  $CH_AH_BOPMB$ ), 3.21 (1H, dd,  $J=9.9, 3.2$  Hz,  $CH_AH_BOPMB$ ), 3.09 (1H, dd,  $J=12.7, 10.3$  Hz,  $CH_AH_BSePh$ ), 2.90 (1H, t,  $J=7.6$  Hz,  $C6'H$ ), 2.01–1.90 (1H, m), 1.77 (1H, dd,  $J=12.9, 3.5$  Hz), 1.59 (1H, d,  $J=11.4$  Hz,  $CHCHOTIPS$ ), 1.48–1.41 (2H, m), 1.40–1.34 (1H, m), 1.19 (3H, h,  $J=6.8$  Hz,  $OTIPS$ ), 1.13 (3H, d,  $J=6.1$  Hz,  $C3CH_3$ ), 1.06 (9H, d, 10.9 Hz,  $OTIPS$ ), 1.05 (9H, d, 10.9 Hz,  $OTIPS$ ), 0.91–0.86 [12H, m,  $Si(CH_3)_3$  and  $C6'CH_3$ ], 0.08 [6H, s,  $Si(CH_3)_2$ ];  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  159.5, 132.7, 130.7, 129.7, 129.2, 128.7, 125.2, 114.0, 89.1, 84.4, 75.8, 73.0, 72.4, 71.6, 59.4, 55.3, 54.0, 51.9, 36.7, 33.4, 32.8, 29.9, 28.2, 25.9, 22.0, 19.6, 18.7, 18.6, 18.5, 18.3, 13.0, 1.2,  $-5.06, -5.08$ ; HRESIMS calcd. for  $C_{44}H_{72}O_5Si_2(80)SeNa^+$ ,  $[M+Na]^+$  839.3987 found 839.3977.

**Tert-butyl(5*R*,8*S*)-8-[(*R*)-1-[(4-methoxybenzyl)oxy]propan-2-yl]-5-methyl-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalen-2-yl)methoxydimethylsilane (18).** The selenoxide elimination was conducted according to a procedure by Engman.<sup>9</sup> To a stirred solution of phenylselenide **16** (1.08 g, 1.32 mmol) in benzene (20 mL) at 10 °C was added *m*CPBA (290 mg, 1.68 mmol) portionwise and the resulting solution stirred for 20 min. Benzene (40 mL) and NaHCO<sub>3</sub> (60 mL, sat. aq.) were added and the biphasic mixture heated at 90 °C for 12 h. The reaction mixture was allowed to cool to room temperature and the layers separated. The organic layer was washed with NaHCO<sub>3</sub> (30 mL) and brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude yellow enyne **17** (0.87 g, 80%) was used without further purification. The cycloisomerization was conducted according to a procedure published previously.<sup>6</sup> To a stirred solution of a portion of the crude enyne **17** (233 mg, 0.35 mmol) in 1,2-dichloroethane (10 mL) at reflux was added AgNO<sub>3</sub> (10 mg; 59 μmol) and the resulting yellow solution heated at reflux overnight in darkness. The reaction mixture was allowed to cool to room temperature then diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and quenched by addition of NaHCO<sub>3</sub> (10 mL). The organic layer was separated and washed with brine (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/hexane) afforded the *title compound* **18** [142 mg, 63%, (51% over 2 steps)] as a colorless oil. [α]<sub>D</sub><sup>20</sup> -21.3 (C 0.75 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2926, 2864, 1717, 1611, 1576, 1514, 1494, 1463, 1368, 1249, 1092, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.22 (2H, d, *J*=8.3 Hz, PMP-*H*), 6.87–6.83 (2H, m, PMP-*H*), 6.68 (1H, s, Ar-*H*), 6.60 (1H, s, Ar-*H*), 4.61 (2H, s, CH<sub>2</sub>OTBS), 4.38 (1H, d, *J*=11.6 Hz, CH<sub>A</sub>H<sub>B</sub>PMP), 4.33 (1H, d, *J*=11.6 Hz, CH<sub>A</sub>H<sub>B</sub>PMP), 3.80 (3H, s, OCH<sub>3</sub>), 3.31 (1H, dd, *J*=9.0, 4.3 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 3.24 (1H, t, *J*=8.6 Hz, CH<sub>A</sub>H<sub>B</sub>OPMB), 3.20–3.14 (1H, m, C1*H*), 2.71 (1H, t, *J*=5.5 Hz, C4*H*), 2.15–2.06 (1H, m), 1.90 (1H, tdd, *J*=13.7, 6.1, 3.2 Hz), 1.82–1.75 (1H, m), 1.73–1.66 (1H, m), 1.49 (1H, d, *J*=12.9 Hz), 1.31 (3H, dq, *J*=13.7, 6.9, 6.3 Hz, OTIPS), 1.15 (3H, d, *J*=6.8 Hz, C1CH<sub>3</sub>), 1.13 (9H, d, *J*=7.5 Hz, OTIPS), 1.09 (9H, d, *J*=7.5 Hz, OTIPS), 0.94 (3H, d, *J*=6.9 Hz, C11CH<sub>3</sub>), 0.93 [9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>], 0.08 [6H, s, Si(CH<sub>3</sub>)<sub>2</sub>]; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 159.2, 153.8, 139.6, 138.5, 131.9, 131.1, 129.2, 119.9, 113.8, 113.6, 74.0, 72.7, 65.1, 55.4, 40.1, 39.8, 27.2, 27.0, 26.1, 21.7, 20.7, 18.4, 18.3, 17.4, 13.3, -5.1; HRESIMS calcd. for C<sub>38</sub>H<sub>64</sub>O<sub>4</sub>Si<sub>2</sub>Na<sup>+</sup>, [M+Na]<sup>+</sup> 663.4241 found 663.4226.

**(5*R*,8*S*)-8-[(*R*)-1-Hydroxypropan-2-yl]-5-methyl-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (21).** To a rapidly stirred mixture of PMB ether **18** (41 mg, 64 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and pH 7 phosphate buffer solution (0.4 mL) at room temperature was added DDQ (60 mg; 0.26 mmol) and the resulting suspension stirred for 16 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL), quenched by addition of NaHCO<sub>3</sub> (10 mL, sat. aq.) and the layers separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and the combined organic layers washed with brine (10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (20% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>) afforded the *title compound* **21** (21 mg, 80%) as a colorless oil. [α]<sub>D</sub><sup>20</sup> -35.5 (c 0.87 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3379, 2945, 2868, 2727, 1697, 1598, 1574, 1464, 1430, 1385, 1370, 1341, 1283, 1205, 1177, 1140, 1067, 1034, 998, 923, 883, 847, 806, 729, 686 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 9.85 (1H, s, CHO), 7.26 (1H, s, Ar-*H*), 7.11 (1H, d, *J*=1.3 Hz, Ar-*H*), 3.55 (1H, dd, *J*=10.5, 4.7 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.48 (1H, dd, *J*=10.5, 7.5 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.28 (1H, p, *J*=6.6 Hz, C1*H*), 2.84 (1H, t, *J*=5.3 Hz, C4*H*), 2.10–2.02 (1H, m), 2.00–1.90 (1H, m), 1.89–1.76 (2H, m), 1.63–1.55 (1H, m), 1.36 (3H, hept, *J*=7.5 Hz, OTIPS), 1.18 (3H, d, *J*=7.0 Hz, C1CH<sub>3</sub>), 1.13 (9H, d, *J*=7.5 Hz, OTIPS), 1.10 (9H, d, *J*=7.5 Hz, OTIPS), 0.97 (3H, d, *J*=6.9 Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 192.4, 154.5, 141.5, 141.0, 134.3, 125.8, 114.1, 66.2, 42.1, 39.7, 27.8, 26.4, 21.2, 20.0, 18.22, 18.17, 16.7, 13.2; HRESIMS calcd. for C<sub>24</sub>H<sub>40</sub>O<sub>3</sub>SiNa<sup>+</sup>, [M+Na]<sup>+</sup> 427.2644 found 427.2642.

**Ethyl (5*R*,8*S*)-8-[(*R*)-1-hydroxypropan-2-yl]-5-methyl-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (22).** The oxidation was conducted according to a procedure from Borhan *et al*<sup>16</sup> To a stirred solution of aldehyde **21** (116 mg, 0.29 mmol) in EtOH (4 mL) at room temperature was added Oxone® (175 mg, 0.57 mmol) and the resulting mixture rapidly stirred for 16 h. The precipitate was

filtered and washed with ethanol, and the solution concentrated to ~1 mL *in vacuo*. The residue was taken up in EtOAc and H<sub>2</sub>O, and layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification through a plug of silica (20% EtOAc/hexane) afforded the *title compound 22* (112 mg, 87%) as a colorless oil.  $[\alpha]_D^{20} -32.3$  (c 0.99 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3427, 2945, 2868, 1718, 1603, 1575, 1464, 1421, 1368, 1341, 1289, 1228, 1174, 1111, 1065, 1035, 976, 922, 883, 848, 771, 685 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.45 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.30 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.38–4.27 (2H, m, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.54 (1H, dd, *J*=10.5, 4.7 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.46 (1H, dd, *J*=10.5, 7.7 Hz, CH<sub>A</sub>H<sub>B</sub>OH), 3.26 (1H, p, *J*=6.6 Hz, C1H), 2.80 (1H, t, *J*=5.4 Hz, C4H), 2.11–2.03 (1H, m), 1.98–1.88 (1H, m), 1.86–1.75 (2H, m), 1.62–1.53 (2H, m), 1.37 (3H, t, *J*=7.1 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.37–1.29 (3H, m, OTIPS), 1.17 (3H, d, *J*=7.0 Hz, C1CH<sub>3</sub>), 1.14 (9H, d, *J*=7.5 Hz, OTIPS), 1.10 (9H, d, *J*=7.5 Hz, OTIPS), 0.98 (3H, d, *J*=6.9 Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 167.0, 153.7, 140.2, 139.0, 127.7, 123.6, 116.1, 66.3, 60.9, 42.3, 39.8, 27.5, 26.6, 21.2, 19.8, 18.3, 18.2, 16.7, 14.5, 13.1; HRESIMS calcd. for C<sub>26</sub>H<sub>44</sub>O<sub>4</sub>SiNa<sup>+</sup>, [M+Na]<sup>+</sup> 471.2907 found 471.2899.

**Ethyl (5*R*,8*S*)-5-methyl-8-[(*R*)-1-oxopropan-2-yl]-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (23).** The oxidation was conducted according to a modified procedure by Mancuso and Swern.<sup>11</sup> To a stirred solution of DMSO (225 μL, 3.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.5 mL) at –78 °C was added oxalyl chloride (2.0M in CH<sub>2</sub>Cl<sub>2</sub>, 750 μL, 1.5 mmol) and the resulting solution stirred for 20 min. Alcohol **22** (157 mg, 0.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added *via* cannula and the solution stirred for 1 h at –78 °C. <sup>i</sup>Pr<sub>2</sub>NEt (1.1 mL, 6.3 mmol) was added and the resulting solution stirred for a further hour at –78 °C. The reaction mixture was quenched through addition of NH<sub>4</sub>Cl (5 mL, sat. aq.) and the biphasic mixture allowed to warm to room temperature. Layers were separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL), washed with brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/hexane) afforded the *title compound 23* (147 mg, 94%) as a colorless oil.  $[\alpha]_D^{20} -69.9$  (c 0.83 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2945, 2868, 1720, 1576, 1495, 1452, 1422, 1332, 1291, 1229, 1050 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 9.53 (1H, d, *J*=1.7 Hz, CHO), 7.48 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.35 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.39–4.29 (2H, m, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.29–3.20 (1H, m, CHCH<sub>3</sub>CHO), 3.18 (1H, t, *J*=6.3 Hz, C1H), 2.78 (1H, pd, *J*=6.9, 1.7 Hz, C4H), 2.04–1.96 (1H, m), 1.76–1.69 (2H, m), 1.59–1.55 (1H, m), 1.38 (3H, t, *J*=7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.36–1.30 (3H, m), 1.18 (3H, d, *J*=7.0 Hz, C1CH<sub>3</sub>), 1.14 (9H, d, *J*=7.5 Hz, OTIPS), 1.10 (9H, d, *J*=7.5 Hz, OTIPS), 1.10 (3H, d, *J*=6.9 Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 204.9, 166.7, 154.0, 138.9, 138.1, 128.2, 123.4, 116.7, 61.0, 52.6, 39.5, 29.9, 27.4, 25.8, 21.1, 20.0, 18.3, 18.2, 14.5, 13.1, 12.8; HRESIMS calcd. for C<sub>26</sub>H<sub>42</sub>O<sub>4</sub>SiNa<sup>+</sup>, [M+Na]<sup>+</sup> 469.2750 found 469.2740.

**2-(Benzyloxy)ethan-1-ol (26).** To a stirred solution of ethylene glycol (3 mL, 53.7 mmol) in THF (30 mL) at 0 °C was added NaH (0.76 g, 60% dispersion in mineral oil) portionwise. The resulting suspension was warmed to room temperature and stirred for 30 min. Benzyl bromide (1.94 mL, 16.3 mmol) was added dropwise followed by *n*-tetrabutylammonium iodide (0.66 g, 1.79 mmol) and the resulting mixture heated at reflux overnight. The reaction mixture was cooled to room temperature and quenched through slow addition of NH<sub>4</sub>Cl (30 mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (40% EtOAc/hexane) afforded the *title compound 26* (2.26 g, 91%) as a colorless oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.39–7.33 (4H, m, Ar-*H*), 7.32–7.27 (1H, m, Ar-*H*), 4.57 (2H, s, CH<sub>2</sub>Ph), 3.76 (2H, q, *J*=4.7 Hz, CH<sub>2</sub>OBn), 3.60 (2H, t, *J*=4.6 Hz, CH<sub>2</sub>OH), 2.10 (1H, s, OH). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 138.1, 128.6, 127.9, 127.9, 73.4, 71.5, 62.0.

**2-[[2-(Benzyloxy)ethyl]sulfonyl]benzo[*d*]thiazole (24).** To a stirred solution of benzyl ether **26** (2.25 g, 14.8 mmol), PPh<sub>3</sub> (5.8 g, 22.1 mmol) and benzo[*d*]thiazole-2-thiol (**25**) (5.1 g, 30.5 mmol) in THF (80 mL) at 0 °C was added DIAD (5.1 mL, 25.9 mmol) dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched through addition of H<sub>2</sub>O, layers separated and the aqueous layer

extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the crude sulfide (3.87 g, 87%) as a light-yellow oil.

To a stirred solution of the crude sulfide (3.87 g, 12.8 mmol) in THF/H<sub>2</sub>O/MeOH (1:1:1, 300 mL) at room temperature was added Oxone® (9.2 g, 30 mmol) and the resulting mixture stirred for 24 h at room temperature. The reaction mixture was filtered (Et<sub>2</sub>O), THF and MeOH removed *in vacuo*, and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H<sub>2</sub>O (30 mL) and brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude residue was recrystallized attaining separation of the dimeric by-product and affording the *title compound* **24** (2.1 g, 49%) as colorless needles. Mp 89.6–91.1 °C (Et<sub>2</sub>O); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.20 (1H, ddd, *J*=8.3, 1.2, 0.7 Hz, Ar-*H*), 7.94 (1H, ddd, *J*=8.1, 1.3, 0.7 Hz, Ar-*H*), 7.62 (1H, ddd, *J*=8.3, 7.2, 1.3 Hz, Ar-*H*), 7.57 (1H, ddd, *J*=8.3, 7.2, 1.2 Hz, Ar-*H*), 7.21–7.09 (3H, m, OCH<sub>2</sub>Ph-*H*), 7.01–6.97 (2H, m, OCH<sub>2</sub>Ph-*H*), 4.39 (2H, s, OCH<sub>2</sub>Ph), 4.00 (2H, t, *J*=5.8 Hz), 3.85 (2H, t, *J*=5.8 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.5, 152.8, 137.04, 136.98, 128.3, 128.0, 127.8, 127.7, 127.4, 125.6, 122.4, 73.4, 63.4, 55.2; HRESIMS calcd. for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>S<sub>2</sub>Na<sup>+</sup>, [M+Na]<sup>+</sup> 356.0391 found 356.0393.

**Ethyl (5*R*,8*S*)-8-[(*S*)-5-(benzyloxy)pent-3-en-2-yl]-5-methyl-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (27).** The olefination was conducted according to a modified procedure by Pospisil and Marko.<sup>13</sup> To a stirred solution of aldehyde **23** (48 mg, 0.11 mmol) and benzyl sulfone **24** (78 mg, 0.23 mmol) in THF (5 mL) at –78 °C was added LiHMDS (1 M, 0.25 mL, 0.25 mmol) dropwise over 5 min. The resulting red solution was allowed to stir at –78 °C for 1 h before warming to room temperature and quenching through addition of NH<sub>4</sub>Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/hexane) gave the *title compound* **27** (54 mg, 89%) as a colorless oil (50:50 mixture of *E/Z* isomers). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2944, 2867, 1718, 1575, 1494, 1454, 1421, 1368, 1289, 1228, 1066 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.47 (0.45H, d, *J*=1.6 Hz, Ar-*H*), 7.43 (0.53H, d, *J*=1.6 Hz, Ar-*H*), 7.36–7.23 (6H, m, Ar-*H*), 5.57–5.38 (2H, m, CH=CH), 4.49–4.26 (4H, m, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and OCH<sub>2</sub>Ph), 3.95–3.87 (1.4H, m, CH<sub>2</sub>OBn), 3.64–3.62 (0.6H, m, CH<sub>2</sub>OBn), 3.21 (1H, dp, *J*=12.5, 6.2, 5.7 Hz, C1*H*), 2.73–2.65 (1H, m, C4*H*), 2.65–2.53 (1H, m, C11*H*), 1.96–1.77 (2H, m), 1.51–1.44 (1H, m), 1.37 (3H, t, *J*=7.1 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.34 (3H, hept. of d, *J*=7.5, 1.9 Hz), 1.16 (1.7H, d, *J*=7.0 Hz, C1CH<sub>3</sub>), 1.15–1.13 (12H, m, OTIPS and C11CH<sub>3</sub>), 1.12–1.09 (9H, m, OTIPS and C11CH<sub>3</sub>), 1.02 (1.6H, d, *J*=6.7 Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 167.0, 166.9, 153.70, 153.66, 140.2, 139.9, 139.2, 139.0, 138.6, 138.5, 138.3, 137.9, 128.5, 128.4, 127.89, 127.87, 127.7, 127.6, 127.5, 127.2, 125.8, 125.5, 124.6, 124.0, 116.2, 116.1, 72.3, 71.9, 71.1, 66.2, 60.8, 43.3, 42.7, 42.2, 38.0, 27.6, 26.1, 26.0, 21.43, 21.35, 20.6, 19.8, 19.4, 19.2, 18.27, 18.25, 18.23, 18.21, 14.5, 13.1; HRESIMS calcd. for C<sub>35</sub>H<sub>52</sub>O<sub>4</sub>SiNa<sup>+</sup>, [M+Na]<sup>+</sup> 587.3501 found 587.3517.

**Ethyl (5*R*,8*S*)-8-[(*S*)-5-hydroxypentan-2-yl]-5-methyl-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (28).** To a stirred solution of alkene **27** (38 mg, 67 μmol) in EtOH (3 mL) at room temperature was added 10% Pd/C (11 mg, 10 μmol) and the heterogeneous mixture stirred under a H<sub>2</sub> atmosphere overnight. The mixture was filtered through Celite (EtOAc) and concentrated *in vacuo*. Purification by gradient elution chromatography (hexane then 10% EtOAc/hexane) afforded the *title compound* **28** (22 mg, 70%) as a colorless oil. [α]<sub>D</sub><sup>20</sup> –40.7 (c 0.98 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3446, 2942, 2868, 1719, 1575, 1494, 1464, 1368 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.45 (1H, s, Ar-*H*), 7.29 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.33 (2H, qd, *J*=7.1, 3.8 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.58–3.47 (2H, m, CH<sub>2</sub>OH), 3.30–3.21 (1H, m, C1*H*), 2.71–2.66 (1H, m, C4*H*), 1.94–1.83 (2H, m), 1.77–1.72 (1H, m), 1.66–1.50 (3H, m), 1.37 (3H, t, *J*=7.1 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.36–1.31 (4H, m), 1.29–1.24 (2H, m), 1.16 (3H, d, *J*=7.0 Hz, C1CH<sub>3</sub>), 1.14 (9H, d, *J*=7.5 Hz, OTIPS), 1.10 (9H, d, *J*=7.5 Hz, OTIPS), 0.97 (3H, d, *J*=6.8 Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 167.1, 153.6, 141.1, 139.4, 127.5, 123.2, 115.9, 63.3, 60.8, 42.5, 38.9, 31.3,

29.6, 27.7, 27.1, 21.3, 19.3, 19.1, 18.3, 18.2, 14.5, 13.1; HRESIMS calcd. for  $C_{28}H_{48}O_4SiNa^+$ ,  $[M+Na]^+$  499.3220 found 499.3213.

**Ethyl (5R,8S)-5-methyl-8-[(S)-5-oxopentan-2-yl]-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (29).** To a stirred solution of alcohol **28** (78 mg, 0.16 mmol) in  $CH_2Cl_2$  (3 mL) at room temperature was added finely ground PDC (95 mg, 0.25 mmol) and the resulting suspension stirred for 6 h. The reaction mixture was filtered through Celite ( $CH_2Cl_2$ ), concentrated *in vacuo* and passed through a plug of silica gel (10% EtOAc/hexane) to give the *title compound* **29** (70 mg, 90%) as a colorless oil.  $[\alpha]_D^{20}$   $-57.2$  (*c* 0.83 in  $CHCl_3$ ). IR ( $CHCl_3$ ,  $cm^{-1}$ ): 2927, 2868, 2715, 1721, 1575, 1464, 1368, 1341, 1289, 1227, 1065  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  9.64 (1H, t,  $J=1.8$  Hz, CHO), 7.43 (1H, s, Ar-H), 7.30 (1H, d,  $J=1.6$  Hz, Ar-H), 4.39–4.27 (2H, m,  $CO_2CH_2CH_3$ ), 3.32–3.21 (1H, m, C1H), 2.73–2.67 (1H, m, C4H), 2.41 (1H, dddd,  $J=17.1, 9.9, 5.4, 1.7$  Hz,  $CH_AH_BCHO$ ), 2.24 (1H, dddd,  $J=17.2, 9.7, 6.1, 2.1$  Hz,  $CH_AH_BCHO$ ), 1.97–1.83 (3H, m), 1.65–1.51 (4H, m), 1.37 (3H, t,  $J=7.2$  Hz,  $CO_2CH_2CH_3$ ), 1.35–1.31 (3H, m, OTIPS), 1.17 (3H, d,  $J=7.0$  Hz, C11 $CH_3$ ), 1.14 (9H, d,  $J=7.5$  Hz, OTIPS), 1.10 (9H, d,  $J=7.5$  Hz, OTIPS), 0.96 (3H, d,  $J=6.8$  Hz, C11 $CH_3$ );  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  202.8, 167.0, 153.7, 140.5, 139.3, 127.7, 123.2, 116.0, 60.9, 42.7, 42.3, 38.9, 29.9, 27.6, 27.0, 25.8, 21.2, 19.1, 18.9, 18.3, 18.2, 14.5, 13.1; HRESIMS calcd. for  $C_{28}H_{46}O_4SiNa^+$ ,  $[M+Na]^+$  497.3063 found 497.3050.

**Ethyl (5R,8S)-5-methyl-8-[(S)-6-methylhept-5-en-2-yl]-4-[(triisopropylsilyl)oxy]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (30).** To a stirred solution of isopropyltriphenylphosphonium iodide (83 mg, 0.19 mmol) in THF (1 mL) at 0 °C was added *n*-BuLi (2.0M in cyclohexane, 90  $\mu$ L, 0.18 mmol) dropwise. The deep red solution was stirred for 30 min at 0 °C then aldehyde **29** (40 mg, 84  $\mu$ mol) was added *via* cannulation (THF). The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and quenched through addition of  $NH_4Cl$  (5 mL, sat. aq.). The layers were separated and the aqueous layer extracted with pentane (3  $\times$  10 mL). The combined organic layers were washed with brine (5 mL), dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. Purification by column chromatography (40%  $CH_2Cl_2$ /hexane) afforded the *title compound* **30** (40 mg, 95%) as a colorless oil.  $[\alpha]_D^{20}$   $-42.7$  (*c* 0.98 in  $CHCl_3$ ); IR ( $CHCl_3$ ,  $cm^{-1}$ ) 2926, 2867, 1721, 1606, 1575, 1494, 1453, 1421, 1288, 1226, 1065, 882  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.45 (1H, d,  $J=1.4$  Hz, Ar-H), 7.29 (1H, d,  $J=1.6$  Hz, Ar-H), 4.99–4.91 [1H, m,  $CH=C(CH_3)_2$ ], 4.33 (2H, qd,  $J=7.1, 3.3$  Hz,  $CO_2CH_2CH_3$ ), 3.30–3.20 (1H, m, C1H), 2.70–2.64 (1H, m, C4H), 1.97 (1H, ddd,  $J=14.7, 8.4, 4.0$  Hz), 1.92–1.83 (3H, m), 1.82–1.69 (2H, m), 1.63 [3H, d,  $J=1.3$  Hz,  $CH=C(CH_3)_A(CH_3)_B$ ], 1.52 [3H, s,  $CH=C(CH_3)_A(CH_3)_B$ ], 1.51–1.49 (1H, m), 1.42–1.30 (6H, m), 1.29–1.19 (1H, m), 1.16 (3H, d,  $J=7.0$  Hz, C11 $CH_3$ ), 1.14 (9H, d,  $J=7.5$  Hz, OTIPS), 1.10 (9H, d,  $J=7.5$  Hz, OTIPS), 0.96 (3H, d,  $J=6.8$  Hz, C11 $CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  167.1, 153.5, 141.2, 139.3, 131.3, 127.5, 124.9, 123.4, 115.8, 60.7, 42.5, 38.8, 33.8, 27.7, 27.0, 26.5, 25.8, 21.3, 19.3, 19.0, 18.3, 18.2, 17.7, 14.5, 13.1.

**Ethyl (5R,8S)-4-hydroxy-5-methyl-8-[(S)-6-methylhept-5-en-2-yl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (31).** To a stirred solution of **30** (19 mg, 38  $\mu$ mol) in THF (1 mL) at room temperature was added TBAF (1 M in THF, 0.4 mL) dropwise. The reaction mixture was stirred at room temperature for 1.5 h, then diluted with EtOAc (10 mL) and  $NH_4Cl$  (1 mL, sat. aq.) added. The layers were separated and the organic layer washed with  $H_2O$  (3 mL) and brine (3 mL). The organic layer was dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. Purification by column chromatography (buffered  $SiO_2$  gel (prepared according to the method of Gregg and Perkins),<sup>15</sup>  $CH_2Cl_2$ ) afforded the *title compound* **31** (12 mg, 91%) as a colorless oil.  $[\alpha]_D^{20}$   $-62.8$  (*c* 0.61 in  $CHCl_3$ ); IR ( $CHCl_3$ ,  $cm^{-1}$ ) 3436, 2957, 2925, 2856, 1718, 1694, 1608, 1582, 1494, 1452, 1423, 1372, 1293, 1235, 1051, 824  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.46 (1H, d,  $J=1.6$  Hz, Ar-H), 7.31 (1H, d,  $J=1.3$  Hz, Ar-H), 5.24 (1H, s, OH), 5.00–4.92 [1H, m,  $CH=C(CH_3)_2$ ], 4.41–4.29 (2H, m,  $CO_2CH_2CH_3$ ), 3.18 (1H, pd,  $J=6.9, 2.3$  Hz, C1H), 2.66 (1H, td,  $J=5.7, 2.7$  Hz, C4H), 2.03–1.83 (3H, m), 1.83–1.73 (2H, m), 1.66–1.60 (1H, m), 1.63 [3H, s,  $CH=C(CH_3)_A(CH_3)_B$ ], 1.54 [3H, s,  $CH=C(CH_3)_A(CH_3)_B$ ], 1.55–1.51 (1H, m), 1.38 (3H, t,  $J=7.1$  Hz,  $CO_2CH_2CH_3$ ), 1.30–1.21 (1H, m), 1.21 (3H, d,

$J=7.0$  Hz, C1CH<sub>3</sub>), 1.10 (1H, dtd,  $J=13.4, 9.7, 5.1$  Hz), 0.97 (3H, d,  $J=6.8$  Hz, C11CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  167.1, 153.4, 141.6, 135.4, 131.4, 127.8, 124.9, 123.4, 113.0, 61.0, 42.6, 38.3, 33.6, 27.3, 27.1, 26.4, 25.8, 21.0, 19.3, 18.8, 17.8, 14.5.

**(1R,4S,11S)-8, 19-Dihydroxyserrulat-14-ene (1).** To a stirred solution of **31** (5 mg, 15  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at  $-78$  °C was added DIBAL (1 M in toluene, 50  $\mu$ L, 50  $\mu$ mol) dropwise and the resulting solution stirred at  $-78$  °C for 2 h. The reaction mixture was warmed to 0 °C and quenched through addition of H<sub>2</sub>O dropwise. 1M HCl (5 mL) was added and the biphasic mixture diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The layers were separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (20% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>) afforded the *title compound* **1** (3 mg, 68%) as a colorless oil.  $[\alpha]_D^{20} -46.5$  (*c* 0.19 in MeOH); IR (MeOH, cm<sup>-1</sup>) 3368, 3018, 2925, 2861, 1709, 1610, 1494, 1452, 1430, 1377, 1051, 825 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  6.74 (1H, s, Ar-H), 6.63 (1H, d,  $J=1.6$  Hz, Ar-H), 4.98 [1H, t,  $J=7.1$  Hz, CH=C(CH<sub>3</sub>)<sub>2</sub>], 4.85 (1H, s, OH), 4.59 (2H, s, CH<sub>2</sub>OH), 3.10 (1H, pd,  $J=6.8, 2.4$  Hz, C1H), 2.61 (1H, td,  $J=5.6, 2.8$  Hz, C4H), 2.04–1.91 (1H, m), 1.94 (1H, ddd, 13.1, 6.0, 3.2), 1.83–1.90 (1H, m), 1.79 (1H, dd, 15.0, 7.7), 1.74 (1H, ddt, 13.7, 5.9, 3.1), 1.65 [3H, s, CH=C(CH<sub>3</sub>)<sub>A</sub>(CH<sub>3</sub>)<sub>B</sub>], 1.55 [3H, s, CH=C(CH<sub>3</sub>)<sub>A</sub>(CH<sub>3</sub>)<sub>B</sub>], 1.51 (1H, dq,  $J=10.3, 2.6$  Hz), 1.33–1.23 (1H, m), 1.20 (3H, d,  $J=7.0$  Hz, C1CH<sub>3</sub>), 1.09 (1H, dtd,  $J=13.3, 9.7, 5.1$  Hz), 0.96 (3H, d,  $J=6.8$  Hz, C11CH<sub>3</sub>), OH absent; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  153.6, 141.7, 138.4, 131.4, 129.0, 125.0, 120.5, 111.2, 65.5, 42.7, 38.2, 33.6, 27.5, 26.9, 26.4, 25.8, 21.2, 19.5, 18.9, 17.8. These spectra are consistent with those reported<sup>3</sup> for the natural product **(1R,4S,11S)-8,19-dihydroxyserrulat-14-ene**.

**(1R,4S,11S)-8-Hydroxyserrulat-14-en-19-oic acid (2).** To a stirred solution of **31** (4 mg, 12  $\mu$ mol) in THF (2 mL) was added 1 M NaOH (1 mL) and the resulting biphasic mixture heated under reflux for 40 h. The reaction mixture was allowed to cool to room temperature and acidified with 1 M HCl to pH ~2. The layers were separated and the aqueous layer extracted with EtOAc (3  $\times$  5 mL). The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography (20% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 1% Et<sub>3</sub>N) afforded the *title compound* **2** (1.9 mg, 52%) as a colorless oil. IR (thin film, cm<sup>-1</sup>) 3400, 2925, 2859, 1688, 1608, 1582, 1494, 1452, 1425, 1404, 1051, 875 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (1H, s, Ar-H), 7.27 (1H, s, Ar-H), 5.00–4.94 [1H, m, CH=C(CH<sub>3</sub>)<sub>2</sub>], 3.18 (1H, dtd,  $J=13.3, 6.6, 1.8$  Hz, C1H), 2.72–2.63 (1H, m, C4H), 2.05–1.74 (3H, m), 1.85–1.95 (1H, m), 1.84–1.72 (2H, m), 1.64 [3H, s, CH=C(CH<sub>3</sub>)<sub>A</sub>(CH<sub>3</sub>)<sub>B</sub>], 1.54 [3H, s, CH=C(CH<sub>3</sub>)<sub>A</sub>(CH<sub>3</sub>)<sub>B</sub>], 1.40–1.60, (1H, m), 1.22 (3H, d,  $J=7.0$  Hz, C1CH<sub>3</sub>), 1.10–1.30 (1H, m), 1.10 (1H, dtd,  $J=13.5, 9.6, 5.0$  Hz), 0.97 (3H, d,  $J=6.8$  Hz, C11CH<sub>3</sub>) phenol OH and carboxylic acid OH absent; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  171.1, 153.3, 141.8, 136.5, 131.6, 126.5, 124.8, 124.2, 113.4, 42.6, 38.2, 33.6, 27.4, 27.1, 26.4, 25.8, 21.0, 19.4, 18.8, 17.8. These spectra are consistent with those reported<sup>3</sup> for the natural product **(1R,4S,11S)-8,19-dihydroxyserrulat-14-ene**.

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## Supplementary Material

Copies of NMR Spectra for compounds **1, 2, 9, 10, 12, 13, 16, 18, 21, 22-24, 27-31**.

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