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Total Synthesis of (–)-aritasone via the ultra-high pressure hetero-Diels Alder dimerization of (-)-pinocarvone.

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Abstract

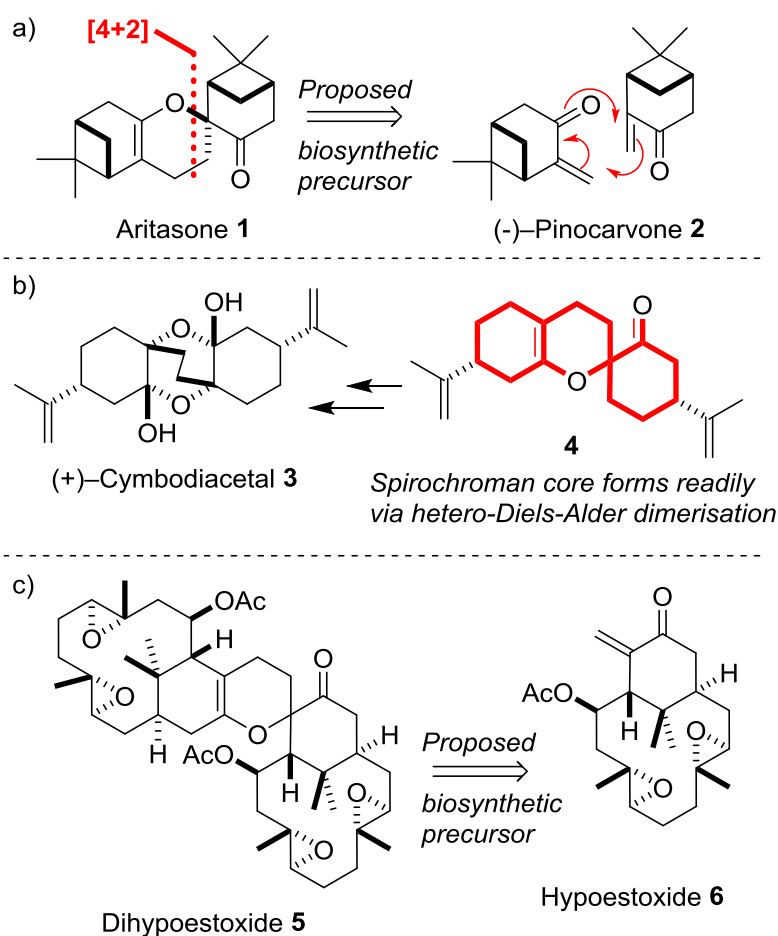
Introduction

As part of our ongoing interest in spirochroman-containing natural products,^{1, 2} our attention was drawn to aritasone (**1**), which has been isolated from *Chenopodium ambrosioides*.^{3, 4} It has been proposed that aritasone (**1**) is biosynthesised via a hetero-Diels Alder dimerization of (–)-pinocarvone (**2**) (Scheme 1a), which is an abundant component of the essential oil from the plant. Cedronellone, the enantiomer of aritasone (**1**), has been isolated from *Cedronella canariensis*,⁵ and similarly, this originates from the [4+2] dimerization of (+)-pinocarvone. During our total synthesis of (+)-cymbodiacetal (**3**),¹ we found that the spirochroman intermediate **4** (Scheme 1b), which is isomeric with aritasone (**1**), was formed by the spontaneous hetero-Diels-Alder dimerization of the corresponding enone precursor (**16**, Scheme 2), and we were intrigued by the fact that pinocarvone (**2**) appears to be resistant to [4+2] homodimerization (*vide infra*). It is interesting to note that this resistance to hetero-Diels-Alder dimerization is also displayed by hypoestoxide (**6**),⁶ which is the proposed biosynthetic precursor to dihydroestoxide (**5**) (Scheme 1c), and we felt that attempting to synthesise aritasone (**1**) via the proposed biomimetic [4+2] dimerization route would provide valuable insight into the factors controlling this type of hetero-Diels-Alder cycloaddition.

The only published research on either aritasone (**1**) or its enantiomer (cedronellone) reports an X-ray structure of cedronellone, although it was not recognised as a natural product by the authors.⁷

This pinocarvone dimer was produced as a side product (10% yield) during a research programme

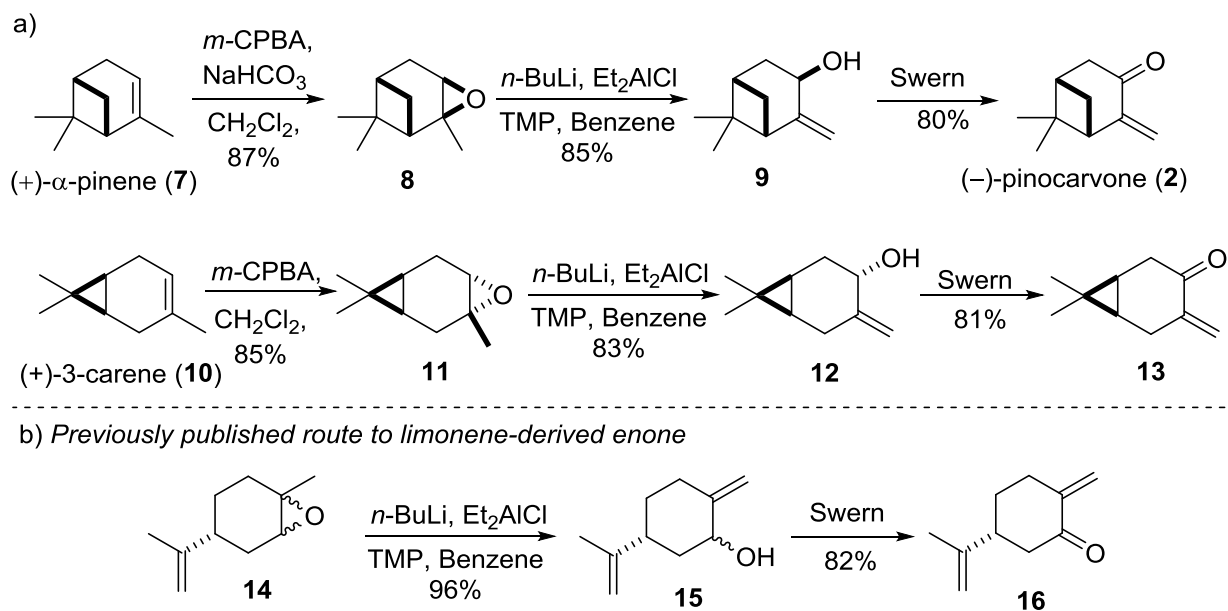
investigating the oxidation products of (-)- β -pinene, but very few synthetic details were given, as the primary focus of the paper was to report the X-ray structure. The paper indicated that (-)- β -pinene was first oxidised with selenium dioxide (no experimental details given), and stated that the [4+2] pinocarvone dimer (i.e. cedronellone) “was separated from the steam distilled reaction mixture by column chromatography”. It is unclear at which stage cedronellone was produced, i.e. before, during, or after the steam distillation process. Given the limited experimental information provided in this report, we decided to attempt to synthesise pinocarvone via a reliable route, and then separately study the hetero-Diels-Alder cyclodimerisation reaction.



Scheme 1

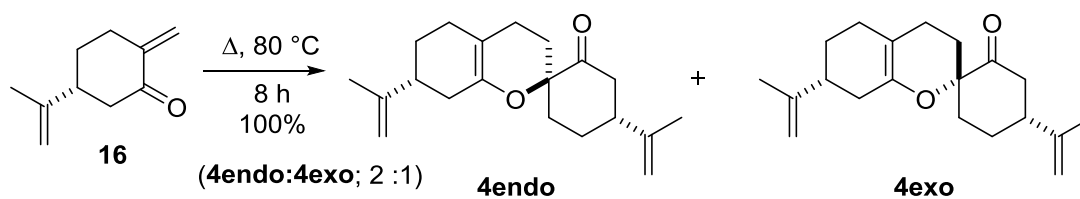
Thus, (+)- α -pinene (**7**) was treated with mCPBA to give the epoxide **8** (87%),⁸ and subsequent rearrangement with Yamamoto’s reagent⁹ provided allylic alcohol **9** (85%) as the only regioisomer. Swern oxidation¹⁰ of **9** then cleanly provided (-)-pinocarvone (**2**) in good yield (80%), which was

ready for assessment in the hetero-Diels-Alder reaction.¹¹ For comparison, we also synthesised the isomeric carene-derived enone **13** (Scheme 2a),¹² and prepared a fresh batch of the limonene-derived enone **16** (Scheme 2b) that we had used previously in our total synthesis of cymbodiacetal **3**.¹



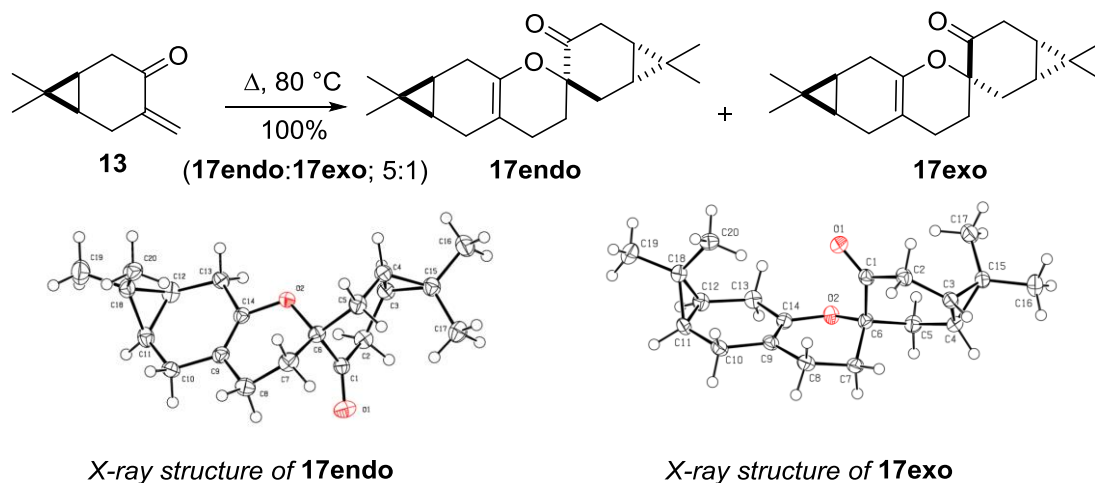
Scheme 2

With the isomeric enones **2**, **13** and **16** to hand, we then compared their performance in the hetero-Diels-Alder dimerization reaction. In our previous work,¹ we had found that the limonene-derived enone **16** underwent spontaneous room temperature [4+2] homodimerisation to give the spirochromans **4endo** and **4exo** as a 2:1 mixture of diastereoisomers, and we were able to confirm this result with our fresh batch of **16**. The reaction could be accelerated by heating **16** to 80 °C, and the spirochroman products could be isolated in quantitative yield in a 2:1 ratio after 8 hours (Scheme 3).



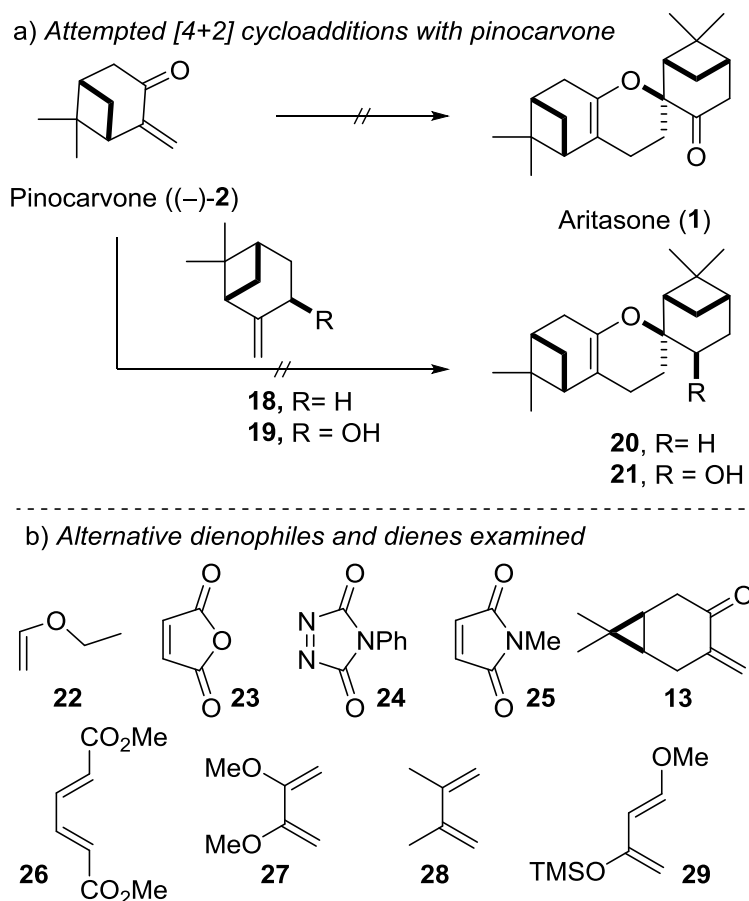
Scheme 3

With the successful dimerization of **16** providing the benchmark, we next exposed the isomeric carene-derived enone **13** and (–)-pinocarvone **2** to the same reaction conditions (neat, 80 °C). We found that the reactivity of the enone **13** was similar to that of **7**, and it underwent dimerisation to give a separable mixture of diastereoisomeric spirochromans **17endo** and **17exo** (5:1) in quantitative yield (Scheme 4). The diastereoisomers were both crystalline solids and X-ray crystallographic analysis confirmed their structures and the stereochemical assignment (Scheme 4).



Scheme 4

In contrast to the enones **13** and **16**, pinocarvone **2** did not produce any of the corresponding spirochroman dimerization product (i.e. aritasone **1**) upon heating at 80 °C for 8 hours (Scheme 5a). Both increases in reaction time (24 hours), and/or reaction temperature (up to 220 °C), failed to induce [4+2] cycloaddition, and only decomposition of starting material was observed. In addition to heating neat samples, we also attempted the hetero-Diels Alder reaction of **2** at reflux in a variety of solvents (toluene, benzene, dichloromethane, methanol, acetic acid), and with microwave heating (water, dichloromethane), but no reaction occurred. We next tried to catalyse the dimerisation of **9** (ZnCl_2 , $\text{BF}_3 \cdot \text{OEt}_2$, *p*TSA, and proline), but in all cases the dimeric product **1** was not obtained.

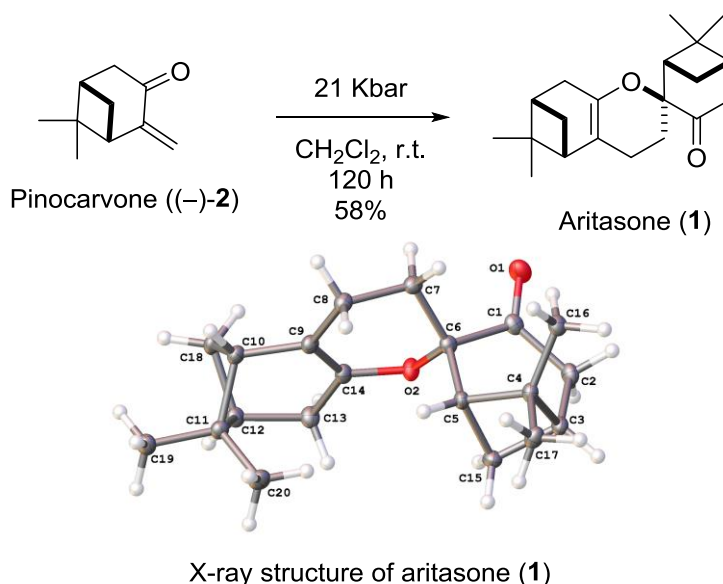


Scheme 5

As pinocarvone **2** proved refractory to hetero-Diels-Alder dimerization, we began to wonder whether the initial biosynthetic hypothesis was correct. As mentioned earlier, the only report of a pinocarvone-derived spirochroman dimer (i.e. either aritasone or cedronellone) emerged during a study on the allylic oxidation of β -pinene **18**.⁷ We wondered whether it was possible for the cycloaddition to occur between two pinene-derivatives at different oxidation levels (i.e. pinocarvone **2** and β -pinene **18**), with a post-cycloaddition oxidation providing the fully formed spirochroman product **1** (Scheme 5a). However, no cycloaddition products (**20** or **21**) were observed when pinocarvone **2** was treated with β -pinene **18** or pinocarveol **19**. In an attempt to achieve any type of [4+2] cycloaddition with pinocarvone **2**, we expanded the range of dienophile and diene reaction partners (Scheme 5b) to include both electron rich and electron deficient versions of both. In all cases, no cycloaddition was observed with **2** acting either as a heterodiene or dienophile, and the starting materials were recovered unchanged. In the example where **13** was

used, only **17endo** and **17exo** were produced, and no cross hetero-Diels-Alder cycloadducts were observed.

These results clearly show that the three isomeric enones **2**, **13** and **16** behave very differently in hetero-Diels-Alder reactions, with pinocarvone **2** being resistant to [4+2] cycloaddition under standard conditions with a range of reaction partners. As aritasone **1**, and its enantiomer (cedronellone) clearly exist as natural products, a route must exist for their formation. Although standard conditions did not facilitate the hetero-Diels-Alder dimerization, we postulated that the *gem*-dimethyl-substituted cyclobutane ring present in pinocarvone **2** was leading to steric hindrance in the [4+2] dimerization transition state. As a result, we decided to attempt the cycloaddition under ultra-high pressure¹³⁻¹⁷ to overcome this issue. Thus, a dichloromethane solution of (-)-pinocarvone (**2**) was subjected to 19 Kbar pressure at room temperature for 120 hours, after which time a new less polar compound (TLC analysis) had been produced (Scheme 6). Following chromatography, we were pleased to find that aritasone **1** had been formed (58%) as a crystalline solid. The NMR spectroscopic data for our synthetic material matched those previously reported,⁷ and the structure was unambiguously confirmed by X-ray crystallography.

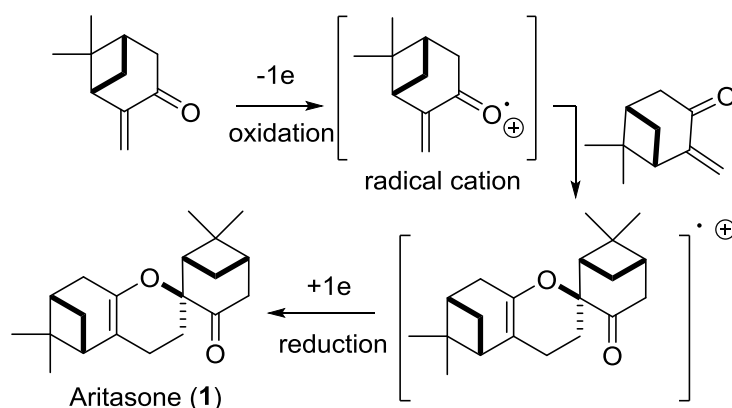


Scheme 6

Having successfully completed a synthesis of aritasone **1** via the hetero-Diels-Alder dimerization of pinocarvone **2**, we were struck by the extreme conditions required to achieve this proposed biomimetic transformation (19 Kbar pressure). It seems unlikely that these ultra-high pressures are accessible within a plant cell, and it seems sensible to consider alternative possibilities. Our work clearly shows that aritasone **1** (and by analogy cedronellone) are not simple artefacts of isolation that result from the spontaneous dimerization of pinocarvone **2**, which is much more abundant in the plant. Therefore, it seems likely that there is another process operating for the biosynthesis of aritasone **1**.

There has been much interest (and debate) regarding the existence (or not) of Diels-Alderase enzymes that are capable of catalysing cyclohexene formation *in vivo*,¹⁸⁻²⁰ and one possibility could be that there is a specific enzyme that catalyses the formation of aritasone **1** by lowering the activation barrier to cycloaddition. This obviously would also require an enzyme to catalyse the formation of cedronellone (the enantiomer of aritasone **1**), but no evidence currently exists for the presence of such enzymes, although hetero-Diels Alderases have been the source of some speculation.²¹ It is also possible that there is an alternative ‘chemical’ explanation for the formation of aritasone and cedronellone, and the previously-mentioned formation of cedronellone during the oxidation of β -pinene might afford a clue as to the nature of this process. From a purely theoretical point of view, the conjugated enone of pinocarvone **2** is required to act as both the hetero-diene and also the dienophile in the [4+2] cycloaddition, but it is well established that the ‘best’ cycloadditions occur when the HOMO-LUMO energy gap is as low as possible.²² In a dimerisation reaction, there is no possibility to affect this energy gap, other than by using catalysts, and we have already shown that a variety of common catalysts are ineffective in accelerating the reaction. An alternative approach, however, could involve the oxidation of the enone to form a transient radical cation, and this radical cation would have significantly altered HOMO and LUMO energies when compared to the neutral, unoxidised starting enone. The cycloaddition could then occur between a

radical cation and the enone,²³⁻²⁵ with the product being reduced to aritasone at a later stage (Scheme 7).



Scheme 7

This radical cation formation could explain the formation of cedronellone during Kohlemainer's β -pinene oxidation study,^{7,26} and this oxidative acceleration of [4+2] cycloaddition has been used to facilitate the dimerization of cyclohexadiene.²⁷ This methodology has recently been deployed in the total synthesis of the natural product kingianin A,^{28, 29} and could also have significance in the biosynthesis of dihydroestoxide 5.

Experimental

(1*S*,6*R*)-7,7-dimethyl-4-methylenebicyclo[4.1.0]heptan-3-one 13

A solution of DMSO (0.380 mL, 5.32 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred and cooled solution of oxalyl chloride (0.230 mL, 2.66 mmol) in CH_2Cl_2 (5 mL) at -78°C . After 1.5 h a solution of allylic alcohol **12**¹² (200 mg, 1.33 mmol) in CH_2Cl_2 (5 mL) was added. After a further 1.5 h, triethylamine (1.66 mL) was added and the mixture was left to stir for 2 h -78°C before the cooling bath was removed. Another 15 min of stirring allowed the mixture to warm to 0°C . TLC analysis showed full conversion of starting material into product. The reaction was quenched by saturated NaHCO_3 (30 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were washed with water (2×50 mL) and dried over MgSO_4 . The solvent was evaporated under vacuum at 20°C . Purification by column

chromatography (pentane/Et₂O; 10/1) yielded pure enone **13** (125 mg, 63%) as a colourless oil; R_f 0.39 (pentane/Et₂O; 10/1); [α]_D²³ -278.9 (*c* 0.80 in CHCl₃); ν_{max}/cm⁻¹ (CHCl₃) 2948, 2865, 1709, 1620, 1457; δ_H (400 MHz; CDCl₃, 298K) 5.99 (1H, dd, *J* 2.1 and 0.7, H-8a), 5.18 (1H, br s, H-8b), 2.85 (1H, dd, *J* 16.6 and 7.1, H-2a), 2.65 (1H, dd, *J* 17.5 and 7.3, H-5a), 2.23 (1H, app ddt, *J* 16.6, 6.9 and 2.1, H-2b), 2.10 (1H, dd, *J* 17.5 and 5.7, H-5b), 1.09 (3H, s, CH₃), 1.06 (3H, s, CH₃), 0.94-0.84 (2H, m, H-1, H-6); δ_C (100 MHz; CDCl₃, 298 K) 201.5 (C), 142.2 (C), 121.2 (CH₂), 35.9 (CH₂), 28.3 (CH₃), 27.6 (CH₂), 20.9 (CH), 20.0 (C), 19.9 (CH), 14.8 (CH₃); *m/z* (ES⁺) 173.0948 (M + Na C₁₀H₁₄NaO requires 173.0919). These data were consistent to those previously reported.³⁰

(1R,2'R,5a'R,6S,6a'S) and **(1R,2'S,5a'R,6S,6a'S)-6',6',7,7-tetramethyl-4',5',5a',6',6a',7'-hexahydro-3'H-spiro[bicyclo[4.1.0]heptane-3,2'-cyclopropa[g]chromen]-4-one** **17endo** and **17exo**

The enone (+)-**13** (68 mg, 0.46 mmol) was heated in a sealed tube at 80 °C for 8 h in an oil bath in the absence of solvent. The ¹H NMR spectrum of the crude reaction mixture confirmed complete consumption of starting material (+)-**13**, and the residue was purified by column chromatography (pentane/Et₂O; 15/1) to afford **17endo** (55 mg, 81%) and **17exo** (10 mg, 16%), both as white solids. Analytical data for major dimer **17endo**; m.p. 95-96 °C; R_f 0.45 (pentane/Et₂O; 15/1); [α]_D²³ +29.1 (*c* 0.91 in CHCl₃); ν_{max}/cm⁻¹ (CHCl₃) 2926, 2835, 1720, 1602, 1453; δ_H (400 MHz; CDCl₃, 298 K); 2.82 (1H, dd, *J* 16.4, 9.2, H-13a), 2.40 (1H, dd, *J* 15.6, 9.6, H-10a), 2.35-2.22 (3H, m, H-2a, H-5a, H-13b), 2.10-1.95 (2H, m, H-2b, H-7a), 1.92 (1H, dd, *J* 7.3 and 3.5, H-8a), 1.82 (1H, br d, *J* 16.5, H-5b), 1.65-1.55 (1H, m, H-7b), 1.49 (1H, dd, *J* 15.6, 4.5, H-10b), 1.45-1.37 (1H, m, H-8b), 1.31 (1H, t, *J* 8.6, H-12), 1.02 (6H, s, C(CH₃)₂), 0.85-0.79 (7H, m, H-11, C(CH₃)₂), 0.77 (1H, t, *J* 8.81, H-3), 0.63 (1H, t, *J* 8.4, H-4); δ_C (100 MHz; CDCl₃, 298 K) 215.9 (C), 143.9 (C), 104.3 (C), 79.0 (C), 36.4 (CH₂), 34.8 (CH₂), 28.5 (CH₃), 28.5 (CH₃), 27.1 (CH₂), 25.4 (CH₂), 23.3 (CH₂), 23.2 (CH₂), 22.9 (CH), 20.0 (C), 19.5 (CH), 18.1 (CH), 17.3 (CH), 16.8 (C), 14.9 (CH₃), 13.5 (CH₃); *m/z*

(ES⁺) 301.2162 (M + H C₂₀H₂₉O₂ requires 301.2162). Data for minor dimer **17exo**; m.p. 87-90 °C; Rf 0.21 (pentane/Et₂O; 15/1); [α]_D²³ +46.5 (c 0.60 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃) 2922, 2963, 2899, 1715, 1602, 1448; δ_{H} (400 MHz; CDCl₃, 298 K) 2.73 (1H, dd, *J* 18.2, 8.8, H-13a), 2.50-2.18 (6H, m, H-13b, H-2a, H-10a, H-5a, H-7a, H-7b), 2.05 (1H, d, *J* 18.0, H-2b), 1.98-1.80 (3H, m, H-5b, H-8a, H-8b), 1.75 (1H, dd, *J* 14.6, 5.60, H-10b), 1.11 (1H, t, *J* 8.8, H-12), 1.03 (6H, s, C(CH₃)₂), 0.95 (1H, td, *J* 5.3 and 18.6, H-11), 0.88 (6H, s, C(CH₃)₂), 0.77 (1H, t, *J* 8.7, H-3), 0.64 (1H, t, *J* 8.3, H-4); δ_{C} (100 MHz; CDCl₃, 298 K) 211.8 (C), 145.1 (C), 101.4 (C), 80.5 (C), 35.5 (CH₂), 33.1 (CH₂), 28.9 (CH₂), 28.55 (CH₃), 28.2 (CH₃), 25.5 (CH₂), 23.3 (CH₂), 23.2 (CH), 22.7 (CH₂), 20.3 (C), 19.4 (CH), 18.7 (CH), 17.9 (CH), 17.1 (C), 15.2 (CH₃), 13.3 (CH₃); *m/z* (ES⁺) 301.2166 (M + H C₂₀H₂₉O₂ requires 301.2162).

(1*R*,3*S*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-ol 9

Freshly distilled tetramethylpiperidine (0.55 mL, 3.28 mmol) was diluted with benzene (5 mL) and the resulting solution was cooled to 0 °C. *n*-BuLi (1.49 mL, 3.28 mmol, 2.20 M solution in hexanes) was then added and the colourless solution turned yellow. After 30 min of stirring, diethylaluminiumchloride (3.77 mL, 3.77 mmol, 1 M solution in hexane) was added, the yellow colour disappeared and a turbid solution formed. After a further 40 min of stirring at 0 °C, the epoxide (–)-**8** (250 mg, 1.64 mmol) was added as a solution in benzene (3 mL). The reaction mixture was stirred for 45 min. at 0 °C and then for 2 h at room temperature. TLC analysis showed full conversion of starting material into product. The reaction was quenched by the slow addition of saturated NaHCO₃ (15 mL) at 0 °C. The solution was diluted with CHCl₃ (30 mL) and the aqueous phase was re-extracted with CHCl₃ (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. Purification by column chromatography (pentane/Et₂O; 4/1) yielded the pure allylic alcohol (–)-**9** (213 mg, 85%) as a colourless oil; [α]_D²⁶ –65.6 (c 0.71 in CHCl₃); δ_{H} (400 MHz; CDCl₃, 298K) 5.00 (1H, s, H-8a), 4.82 (1H, s, H-8b), 4.42 (1H, d, *J* 7.6 H-3), 2.52 (1H, t, *J* 5.50, H-1), 2.44-2.35 (1H, m, H-7a), 2.24

(1H, dd, J 14.6 and 7.6, H-4a), 2.00 (1H, dd, J 9.8 and 4.6, H-5), 1.85 (1H, dd, J = 14.6 and 4.2, H-4b), 1.72 (1H, d, J = 9.9, H-7b), 1.48 (1H, br s, OH), 1.28 (3H, s, CH₃), 0.50 (3H, s, CH₃); δ_C (100 MHz; CDCl₃, 298 K) 156.5 (C), 111.7 (CH₂), 67.4 (CH), 50.9 (CH), 40.7 (C), 40.2 (CH), 34.8 (CH₂), 28.3 (CH₂), 26.3 (CH₃), 22.3 (CH₃); HRMS m/z (ES⁺) found 153.1275 (M + H C₁₀H₁₈O requires 153.1279).

The same procedure was used for the synthesis of the enantiomer (+)-**9** [α]_D²³ +60.6 (c 1.96 in CHCl₃) H¹ NMR, ¹³C NMR, IR and MS data are in accordance with those of (–)-**9**.

(1R,5R)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-one ((–)-pinocarvone 2)

A solution of DMSO (0.36 mL, 5.12 mmol) in CH₂Cl₂ (3 mL) was added dropwise to a stirred and cooled solution of oxalyl chloride (0.22 mL, 2.56 mmol) in CH₂Cl₂ (5 mL) at –78 °C. After 1.5 h a solution of allylic alcohol (–)-**9** (195 mg, 1.28 mmol) in CH₂Cl₂ (5 mL) was added, maintaining the temperature at –78 °C. After a further 1.5 h triethylamine (1.60 mL) was added and the mixture was left to stir for 2 h before the cooling bath was removed. Another 15 min stirring allowed the mixture to warm to 0 °C. The reaction was quenched by saturated NaHCO₃ (30 mL), then diluted with CH₂Cl₂ (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic phases were washed with water (2 × 50 mL) and dried over MgSO₄. After filtration, the solvent was evaporated under reduced pressure at 20 °C. Purification of the crude product by column chromatography (pentane/Et₂O; 10/1) yielded pure enone (–)-**2** (165 mg, 85%) as a colourless oil; [α]_D²⁷ –63.8 (c 0.75 in CHCl₃); (lit³¹ [α]_D –64.7 (neat); δ_H (400 MHz; CDCl₃, 298 K) 5.97 (1H, d, J 1.7, H-8a), 5.01 (1H, d, J 1.7, H-8b), 2.77 (1H, t, J 6.0, H-1), 2.73-2.63 (2H, m, H-4a, H-4b), 2.53 (1H, dd, J 19.3 and 3.1, H-7a), 2.24-2.17 (1H, m, H-7b), 1.4 (3H, s, CH₃), 0.88 (1H, t, J 6.9, H-5), 0.80 (3H, s, CH₃); δ_C (100 MHz; CDCl₃, 298 K) 200.1 (C), 149.1 (C), 117.5 (CH₂), 48.3 (CH), 42.5 (CH₂), 40.8 (C), 38.6 (CH), 26.0 (CH₃), 21.6 (CH₃); HRMS m/z (ES⁺) 301.1421 (2M + H C₂₀H₂₉O₂ requires 301.2162).

The same procedure was used for the synthesis of the enantiomer (+)-**2** $[\alpha]_{\text{D}}^{24} +63.4$ (c 0.7 in CHCl_3); (lit $[\alpha]_{\text{D}}^{24} +51.8$ (c 0.94 in MeOH)); ^1H NMR, ^{13}C NMR, IR and MS data are in accordance with those of (–)-**2**.

Aritasone (**1**)

A solution of pinocarvone ((–)-**2**) (100 mg, 0.66 mmol) in dichloromethane (5 mL) was pressurized to 19 kBar for 120 h. The ^1H NMR spectrum of the crude reaction mixture showed significant change in the composition as compared to the starting material. The solvent was evaporated and the residue was purified by column chromatography (pentane/ Et_2O ; 25/1) to afford aritasone (**1**) (20 mg) as a white solid; mp 101-103 °C; (lit³ mp 105-106 °C); $[\alpha]_{\text{D}}^{26} -26.1$ (c 0.40 in CHCl_3); (lit³ $[\alpha]_{\text{D}}^9 -118$); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3) 2926, 2359, 1722, 1689, 1601, 1467, 1372, 1305, 1152; δ_{H} (400 MHz; CDCl_3 , 298 K) 2.67 (2H, app dd, J 4.8, 2.5, H-2a, H-2b), 2.45-2.32 (3H, m, H-7a, H-15a, H-3), 2.15-2.01 (4H, m, H-10, H-12, H-15b, H-16a), 1.91-1.80 (2H, m, H-4, H-16b), 1.66 (1H, ddd, J 13.8, 6.4, 3.4, H-7b), 1.38 (3H, s, CH_3), 1.29-1.22 (7H, br s, CH_3 , H-13a, H-13b, H-8a, H-8b), 0.90 (3H, s, CH_3), 0.80 (3H, s, CH_3); δ_{C} (100 MHz; CDCl_3 , 298 K) 209.5 (C), 142.9 (C), 112.8 (C), 80.8 (C), 45.2 (CH), 44.3 (CH), 43.7 (CH_2), 40.9 (CH), 40.5 (C), 39.4 (CH), 38.3 (C), 33.2 (CH_2), 32.7 (CH_2), 27.7 (CH_3), 27.3 (CH_2), 27.3 (CH_3), 26.3 (CH_3), 22.5 (CH_2), 22.1 (CH_2), 20.9 (CH_3); HRMS m/z (ES^+) found 301.2162 (M + H) $\text{C}_{20}\text{H}_{29}\text{O}_2$ requires 301.2162 and 323.1981 (M + Na) $\text{C}_{20}\text{H}_{28}\text{O}_2\text{Na}$ requires 323.1982. These data were consistent to those previously reported.^{5,7}

Supporting Information Available

Copies of the ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at

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