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Total synthesis 2-*epi*-α-cedren-3-one *via* a cobalt-catalysed Pauson-Khand reaction

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ABSTRACT

Herein we target the total synthesis of 2-*epi*-α-cedren-3-one, a natural compound isolated from the essential oil of *Juniperus thurifera*. Overall, our synthetic sequence presents an optimised and robust series of chemical transformations, with prominent features including a low temperature and highly (*Z*)-selective Wittig olefination reaction, which is vital for the establishment of the relative stereochemistry within the final natural product, and a microwave-assisted, catalytic, intramolecular Pauson-Khand cyclisation reaction, which is used to construct the intriguing tricyclic core of the target molecule. Our optimum cyclisation protocol utilises only 20 mol% of transition metal, and delivers the complex tricyclic structure in just 10 min. Further manipulations of the annulation product culminate in the first total synthesis of the described natural target.

1. Introduction

The synthetic chemistry community continually strives to develop methods to create complex, yet adaptable, molecular frameworks in a direct and effective manner. In this regard, the discovery and growth of metal-mediated transformations has vastly increased the spectrum of molecular architectures that are accessible *via* organic synthesis, often delivering simplification of synthetic routes with enhanced levels of efficiency.

A valuable, metal-mediated, method for generating molecular complexity in a single step is the Pauson-Khand reaction (PKR) [1]. Traditionally, this annulation technique has been mediated by cobalt, with the PKR bringing an alkene, alkyne (normally present as its hexacarbonyl dicobalt complex), and a carbon monoxide moiety together to construct a cyclopentenone ring system. Since its discovery, this organocobalt cyclisation process has been developed into an effective method, that has found increasing use as the key transformation in the synthesis of natural products and other cyclic compounds possessing an array of skeletal frameworks. Indeed, recent examples include Baran's development of an *N*-oxide/ethylene glycol-assisted intermolecular PKR towards the synthesis of axinellamines [2], and Sabitha's use of oxindole enynes to deliver interesting fused spiro-oxindole scaffolds [3]. In 2018, Xu elegantly utilised an intramolecular PKR in the construction of the rare, and highly congested, sesterterpenoid, astellatol [4]. Having stated all of this, in the main, many current examples make use of an intramolecular protocol to obtain bicyclic motifs, with the preparation of more elaborate, and more strained, structures remaining much less common. Furthermore, carrying out the PKR using sub-stoichiometric quantities of metal remains somewhat underdeveloped, with the scope, again, remaining limited and the majority of examples requiring an external source of toxic carbon monoxide gas under forcing reaction conditions [1,5].

As part of our ongoing endeavours to further develop the proficiency and applicability of this annulation process [6], we sought to establish a direct and efficient pathway for the synthesis of the structurally demanding natural target 2-*epi*-α-cedren-3-one [7]. (**1a**, Fig. 1) using the PKR as our central transformation. Isolated in 2000 from the essential oil of *Juniperus thurifera*, **1a** is part of a sesquiterpene family of continuing interest to our research laboratory. More specifically, in our previously reported syntheses of related natural species, α- and β-cedrene (**1b** and **1c**, respectively) [8] we have shown that the intriguing tricyclic core skeleton of such targets can be accessed expediently using a cobalt-mediated PKR strategy. As part of the programme of work described herein, we sought to develop a novel, *catalytic*, PKR, which would result in the construction of the core carbon skeleton of **1a** using sub-stoichiometric quantities of cobalt metal.

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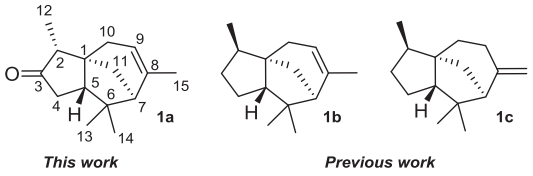
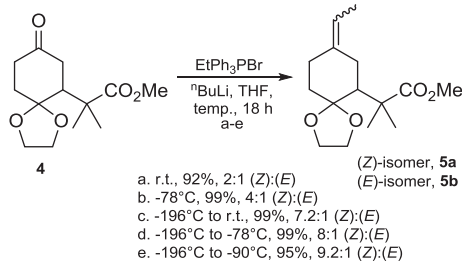


Fig. 1. 2-*epi*-α-Cedren-3-one and related sesquiterpenes.

2. Results and discussion

Our synthetic sequence began with the preparation of ketoester **4** (Scheme 1). Commercially available cyclohexanedione mono-ethylene acetal **2** was transformed to α,β-unsaturated ketone **3** (*via* the trimethylsilyl enol ether) using a palladium-mediated Saegusa oxidation protocol [9]. This reaction could also be carried out using sub-stoichiometric quantities [10] of palladium(II) acetate to deliver the desired unsaturated ketone in a very good yield. Following this, ketoester **4** was furnished directly *via* a conjugate addition reaction of the silyl ketene acetal of methyl isobutyrate, catalysed by ytterbium(III) triflate trihydrate [11].

The next step in our synthetic sequence involved the installation of the requisite alkene moiety. Experience from the syntheses α- and β-cedrene revealed that the stereochemical outcome of this olefination reaction has a direct impact upon the later stages in the synthetic programme. In this regard, and in contrast to our previous syntheses of the related natural sesquiterpenes [8], a (*Z*)-selective olefination reaction was required in order to establish the relative stereochemistry at C^2 in the final target and, more specifically, to align the methyl group (C^{12}) *syn* to the methylene bridge (C^{11}) in 2-*epi*-α-cedren-3-one, **1a**. Whilst the previous studies within our laboratories had allowed the preparation of desired (*Z*)-isomer, **5a**, the selectivity achieved had been, at best, moderate. As part of this programme of work, our preliminary efforts towards obtaining an enhanced isomeric ratio involved a standard Wittig protocol at room temperature (Scheme 2), which, pleasingly, delivered olefins **5a** and **5b** in an excellent 92% yield. In terms of selectivity, a modest 2:1 ratio in favour of the desired (*Z*) olefinic product was achieved (with olefin ratios being determined by ^{1}H NMR spectroscopy (see Section 4), based on that described in our previous work [8]). With this initial and encouraging result in hand, the temperature of the reaction was lowered to −78 °C in an attempt to improve the selectivity. This delivered a more appreciable 4:1 ratio of *Z*:*E* isomers, again in a very high yield. With this notable increase in selectivity, the reaction temperature was further reduced and, more specifically, with the mixture cooled to −196 °C and allowed to warm slowly to room temperature. Despite the reaction solvent being completely frozen at the initial reaction temperature, with the reaction perceived to be occurring during the slow melting process, a very good selectivity of 7.2:1 *Z*:*E* was achieved, in near quantitative yield. Accordingly, it was envisaged that cooling



a. r.t., 92%, 2:1 (*Z*):(*E*)
b. -78°C, 99%, 4:1 (*Z*):(*E*)
c. -196°C to r.t., 99%, 7.2:1 (*Z*):(*E*)
d. -196°C to -78°C, 99%, 8:1 (*Z*):(*E*)
e. -196°C to -90°C, 95%, 9.2:1 (*Z*):(*E*)

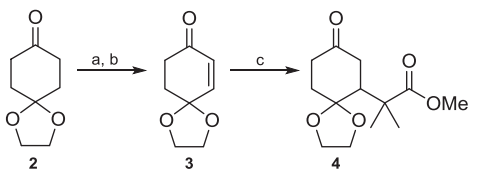
Scheme 2. Probing the stereoselectivity of the key olefination reaction.

to −196 °C and warming slowly to −78 °C would boost the selectivity even further. Using this modified method, further improvement in the selectivity was achieved. Furthermore, we were delighted to realise our optimised conditions upon cooling to −196 °C and warming to −90 °C, with this process delivering a 9.2:1 (*Z*):(*E*) alkene product ratio.

With the ethylidene functionality in place and based on previously published precedent from our laboratories [8a], attention was focused upon the preparation of the central Pauson-Khand annulation precursor, **7** (Scheme 3). At this stage, compounds **5a** and **5b** existed as an inseparable mixture, therefore, both geometrical isomers were used in combination in the following synthetic steps, with a view to separating the individual isomers at a later stage. In this vein, aldehydes **6a/b** were prepared *via* a two-step reduction/oxidation sequence in an overall yield of 90%. Following this, **6a/b** were treated with the Ohira-Bestmann reagent [12] (dimethyl acetyldiazomethylphosphonate) to install the alkyne moiety, delivering the key PKR precursors **7a/b** in an 80% yield.

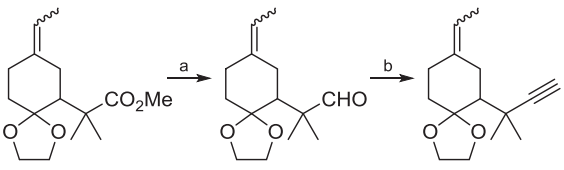
At this stage, with enynes **7a/b** in hand, the efficiency of the Pauson-Khand annulation, for the assembly of the core tricyclic skeleton, could now be investigated. Initially, sulfide-promoted conditions were examined for use within this cyclisation process. In particular, ^{n}butyl methyl sulfide, as first described by Sugihara and Yamaguchi [13], was used as a promoter within this attempted annulation (Scheme 4). Pleasingly, the desired cyclopentenone products **8a/b** were delivered in an excellent 83% yield following heating for 40 min.

Of course, the described Pauson-Khand annulation procedure involved a stoichiometric amount of transition metal. As alluded to previously, our aim was to establish a robust and efficient *catalytic* protocol within which the core tricyclic skeleton of the natural target could be constructed. Accordingly, a variety of methods employing sub-stoichiometric quantities of $Co_2(CO)_8$ were probed (Table 1). These included the use of tetramethylthiourea (TMTU) [14], employment of tributyl phosphine sulfide [15], and also the application of microwave technology in the presence of both amine and sulfide additives. In the case of TMTU (Entry 1) and Bu_3PS (Entry 2), not only did the protocols demand use of gaseous carbon monoxide, the desired cyclopentenone products were delivered in poor conversions. However, upon carrying out the PKR in a sealed



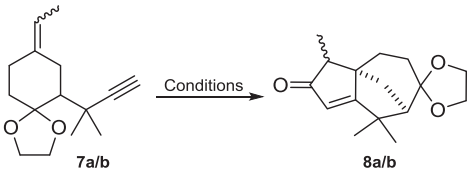
a. TMSOTf, Et_3N, DCM, **96%**; b. 1.05 eq. $Pd(OAc)_2$, MeCN, **92%** or $Pd(OAc)_2$ (5 mol%), 1,2-DPPE, diallylcarbonate, MeCN, **82%**; c. $Yb(OTf)_3.3H_2O$ (10 mol%), $Me_2CC(OMe)OTMS$, DCM, then Et_2O/oxalic acid 1:1, **75%**.

Scheme 1. Synthesis of ketoester **4**.



a. $LiAlH_4$, Et_2O, 1 h, then PCC, DCM, 18 h, **90%**; b. $AcC(N_2)PO(OMe)_2$, K_2CO_3, MeOH, 5 d, **80%**.

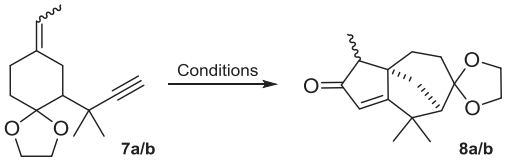
Scheme 3. Preparation of enyne **7**.



Conditions. 1.05 eq. $Co_2(CO)_8$, petrol, 2 h, then 1,2-DCE, ^{n}BuSMe, 40 min, 83°C, **83%.**

Scheme 4. Construction of the tricyclic core *via* the Pauson-Khand reaction.

Table 1
Optimisation studies for the key catalytic PKR. .



Entry	$Co_2(CO)_8$	Conditions[a]	Yield
1	10 mol%	TMTU, 1 atm. CO, PhH, 80 °C, 6 h	20%[b]
2	10 mol%	Bu_3PS, 1 atm. CO, PhH, 80 °C, 18 h	48%
3	20 mol%	$CyNH_2$, PhMe, MWI, 100 °C, 10 min	69%
4	20 mol%	^{n}BuSMe, 1,2-DCE, MWI, 100 °C, 10 min	65%
5	20 mol%	^{n}BuSMe, PhMe, MWI, 100 °C, 10 min	85%

[a] MWI: microwave irradiation.
[b] Conversion.

vessel under microwave irradiation, a protocol based on seminal outputs by Groth et al. [5c], we obtained the desired products in 69% yield and after only 10 min reaction time (Entry 3). Based on this result, we further optimised the annulation method by utilising ^{n}BuSMe as an additive (Entries 4 and 5). In toluene, the desired enone products were delivered in an 85% yield; this protocol required only 10 min under MWI and used 20 mol% of dicobalt octacarbonyl with no requirement for additional CO gas (Entry 5). It is important to note that, in line with that described previously [8], the ratio of stereoisomers generated *via* the Wittig olefination reaction corresponds directly to the ratio of cyclopentenone epimers **8a/b** obtained in every PKR described. In addition to this, from a practical perspective, purification was now trivial and it was possible to separate cyclopentenones **8a** (arising from the predominant Z-alkene, **7a**) and **8b**.

With the development of a new microwave-promoted technique for performing Pauson-Khand reactions with a sub-stoichiometric quantity of transition metal and no required external source of CO achieved, attention turned to the completion of the synthesis of the natural target. To this end, an efficient and completely facially selective, hydrogenation reaction was realised using palladium catalysis (Scheme 5). The resulting cyclopentanone **9** was treated with sodium borohydride, followed directly with sub-stoichiometric quantities of protic acid in acetone to furnish **10** in a good 82% overall yield, along with 10% of the diastereomeric alcohol. Following silyl protection, compound **11** was prepared in an appreciable 79% yield *via* treatment with freshly prepared methyllithium in refluxing ether. With the tertiary alcohol in hand, elimination was carried out, which provided compounds **12a** and **12b** in a combined yield of 60%. After partial separation, compound **12b** was taken through a deprotection and oxidation sequence to yield the final desired natural product in an overall 95% yield in these closing two steps.

The structure of 2-*epi*-α-cedren-3-one was confirmed by comparison to the literature isolation data [7], with matching infra-red, and proton and carbon NMR spectra being obtained. Further confirmation was also achieved *via* high resolution mass spectrometry. In order to completely authenticate the stereochemistry of the epimerisable C^2 stereocentre, NOE experiments were employed. Pleasingly, the key NOE interaction between the C^{12} methyl group and the C^{11} methylene bridge was clearly visible (Fig. 2), thereby corroborating the formation of exclusively the desired α-methyl epimer.

3. Conclusions

In summary, the first total synthesis of 2-*epi*-α-cedren-3-one has been completed in 17 steps. Amongst the salient features of this preparative approach is a highly efficient, low temperature *Z*-selective olefination protocol, which ultimately established the desired relative stereochemistry of the final natural target. In addition to this, the intriguing tricyclic core of this product was constructed in one step, from a relatively simple monocyclic precursor, utilising a cobalt-catalysed Pauson-Khand annulation process. Moreover, the optimum cyclisation protocol utilised 20 mol% of $Co_2(CO)_8$ (which also acted as the CO source), and delivered the desired tricyclic structure in just 10 min under microwave irradiation. The cyclopentenone so obtained was further elaborated to 2-*epi*-α-cedren-3-one, thus, delivering the first total synthesis of this natural target molecule.

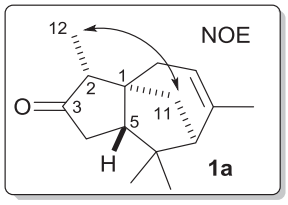
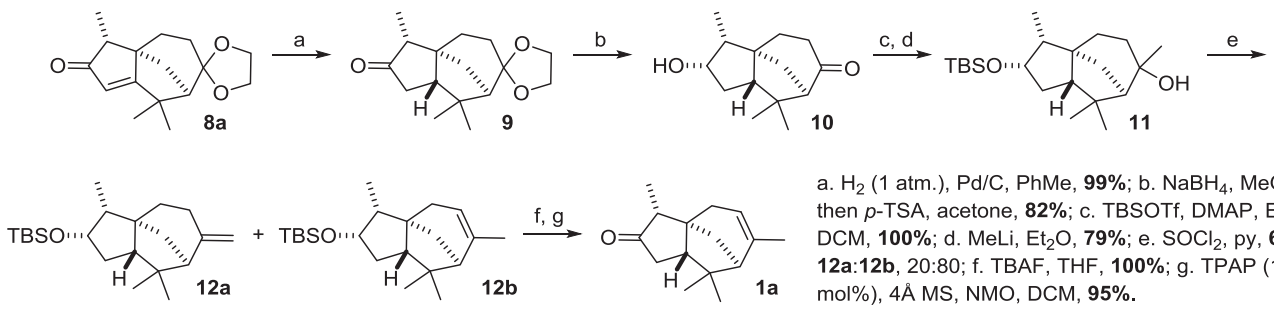


Fig. 2. Confirmation of the stereochemistry of **1a**.



a. H_2 (1 atm.), Pd/C, PhMe, **99%**; b. $NaBH_4$, MeOH, then *p*-TSA, acetone, **82%**; c. TBSOTf, DMAP, Et_3N, DCM, **100%**; d. MeLi, Et_2O, **79%**; e. $SOCl_2$, py, **60%**, **12a**:**12b**, 20:80; f. TBAF, THF, **100%**; g. TPAP (10 mol%), 4Å MS, NMO, DCM, **95%.**

Scheme 5. Towards the final natural target, 2-*epi*-α-cedrene-3-one, **1a**.

4. Experimental

4.1. General

Chromatographic separations were performed either on Prolabo silica gel (230–400 mesh) or on prepacked Bond Elute® silica columns. Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator F254 and analysed using a Mineralight UVGL-25 lamp, or developed using potassium permanganate or vanillin dips. ^{1}H and ^{13}C NMR were recorded on a Bruker DMX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) and are referenced to the appropriate solvent peak. Coupling constants refer to $^{3}J_{H\text{-}H}$ interactions, unless otherwise stated, and are reported in Hz. Elemental analysis was obtained using a Carlo Erba 1106 CHN analyser. Melting points were obtained on a Büchi 545 using open capillaries and are uncorrected. High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at Swansea University, Wales. Reactions performed in the microwave were performed using a CEM Discovery apparatus.

4.2. Reagents

All reagents were obtained from commercial suppliers and were used without additional purification unless otherwise stated. Purifications were carried out according to standard laboratory methods, as detailed below [16].

Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by refluxing commercial solvents over sodium wire, with sodium benzophenone ketyl as an indicator, and then distilled under a nitrogen atmosphere. Dry dichloromethane (DCM) was obtained by refluxing over calcium hydride and then distilled under a nitrogen atmosphere. Petrol refers to the fraction of b.p. 30–40 °C and was distilled prior to use. 1,2-DCE, MeOH, and cyclohexylamine were distilled from CaH_2 immediately prior to use. Acetone was dried by refluxing over flame-dried potassium carbonate and then distilled prior to use. Triethylamine, thionyl chloride, and ^{n}BuSMe were all distilled prior to use. ^{n}BuLi, obtained as a solution in hexanes, was standardised using salicyldehyde phenylhydrazone [17]. $EtPh_3PBr$ was dried at 50 °C under high vacuum for 2 d prior to use. Molecular sieves were powdered and activated by heating in an oven (120 °C) before use. $NMO.H_2O$ was dried at 100 °C under vacuum for 3 h before use.

4.3. Intermediates

Compound **3** was prepared as delineated in our previous syntheses of α- and β-cedrene [8].

4.3.1. Methyl 2-(1,4-dioxaspiro[4,5]decan-8-on-6-yl)-2-methylpropanoate (*4*) [8]

To a stirring solution of 1,4-dioxaspiro[4,5]dec-6-en-8-one **3** (4.77 g, 31 mmol) in DCM (200 mL, bench grade) was added 1-methoxy-1-[(trimethylsilyl)oxy]-2-methylpropene [18]. (5.67 g, 32.5 mmol) and ytterbium(III) triflate trihydrate (1.92 g, 3.1 mmol). After stirring for 18 h at room temperature, the reaction mixture was filtered through a pad of silica (eluent: diethyl ether) and the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether (120 mL) and oxalic acid (2%, 120 mL) was added. Following vigorous stirring for 24 h, the organics were separated, washed with water (100 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was purified directly *via* column chromatography (eluent: 30% diethyl ether/petrol) to yield the desired compound **4** (5.96 g, 75%) as a colourless oil, which solidified on standing; melting point: 60–62 °C; IR (liq. film): 3343, 2974, 1728, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.05–3.92 (m, 4H, OCH_2CH_2O), 3.65 (s, 3H, OCH_3), 2.71–2.53 (m, 4H, ring), 2.52–2.47 (m, 1H, ring), 2.04–1.98 (m, 1H, ring), 1.79–1.71 (m, 1H, ring) 1.15 (s, 3H, CH_3), 1.12 (s, 3H, CH_3).

4.3.2. Methyl (*E*)/(*Z*)-2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate (*5a/b*) [8]

Scheme 2, reaction e. To a flame dried flask, under a nitrogen atmosphere, was added ethyl triphenylphosphonium bromide (0.297 g, 0.80 mmol) and THF (15 mL). To the resulting slurry was added freshly standardised ^{n}BuLi (0.36 mL, 2.25 M in hexanes, 0.80 mmol) dropwise. The resulting orange solution was then stirred for a further 1 h before cooling to −196 °C in a liquid N_2 bath (completely immersed). Once the solution had completely frozen, methyl 2-(1,4-dioxaspiro[4,5]decan-8-on-6-yl)-2-methylpropanoate, **4** (0.128 g, 0.50 mmol) was carefully added as a solution in THF (3 mL) down the wall of the flask to freeze the solution. The reaction was then warmed slowly to −90 °C and left for 18 h before the solvent was removed *in vacuo*. NOTE: as the mixture began to melt, the liquid N_2 bath was replaced with a liquid N_2/pentane bath. The crude residue was purified *via* column chromatography (eluent: 20% diethyl ether/petrol) to yield the desired compounds **5a/b** (0.127 g, 95%) as a clear liquid. The *Z*/*E* ratio was determined to be 9.2:1 by the integration of the ^{1}H NMR signals at δ 2.70–2.65 and δ 2.60–2.55 [8].

4.3.3. (*E*)/(*Z*)-2-(8-Ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanal, (*6a/b*) [8]

To a stirred solution of methyl (*E*)/(*Z*)-2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate **5a/b** (2.66 g, 9.88 mmol) in diethyl ether (100 mL) was added lithium aluminium hydride (0.41 g, 10.9 mmol) portionwise. After stirring for 1 h, water (0.4 mL) was added, followed by 15% NaOH (0.4 mL), followed by water (1.2 mL). After stirring for a further 30 min the granular precipitate was removed by filtration through a pad of celite (eluent: diethyl ether). The filtrate was evaporated *in vacuo*, delivering the intermediate alcohol. The product was immediately dissolved in DCM (120 mL) and pyridinium chlorochromate (6.37 g, 29.6 mmol) added. After stirring for 18 h, the solid chromium residues were removed by filtration through celite and washed thoroughly with DCM. The crude products were then adsorbed onto silica and purified *via* column chromatography (eluent: 30% diethyl ether/petrol) to yield the desired compounds **6a/b** (2.11 g, 90%); IR (liq. film): 2819, 2710, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.34 (s, 1H, CHO), 5.27–5.22 (m, 1H, C=CHCH$_3$), 3.95–3.81 (m, 3H, OCH_2-CH_2O), 3.62 (m, 1H, OCH_2), 2.71–2.52 (m, 1H, ring), 2.30–2.22 (m, 2H, ring), 2.11–2.07 (m, 1H, ring), 2.03–1.91 (m, 1H, ring), 1.85–1.80 (m, 1H, ring), 1.63–1.59 (m, 3H, CH_3), 1.35–1.25 (m, 1H, ring), 1.02–0.98 (s, 6H, 2xCH_3).

4.3.4. (*E*)/(*Z*)-8-Ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane, (*7a/b*) [8]

To a stirring solution of (*E*)/(*Z*)-2-(8-ethylidene-1,4-dioxaspiro [4.5]decan-6-yl)-2-methylpropanal, **6a/b** (2.35 g, 9.93 mmol) in anhydrous methanol (60 mL) was added dimethyl 1-diazo-2-oxypropylphosphonate (2.92 g, 14.9 mmol) and potassium carbonate (2.09 g, 14.9 mmol). The reaction mixture was stirred for 24 h before the addition of more dimethyl 1-diazo-2-oxypropylphosphonate (0.70 g, 4.21 mmol) and potassium carbonate (0.59 g, 4.21 mmol). The reaction was stirred for a further 4 d with further dimethyl 1-diazo-2-oxypropylphosphonate (0.70 g, 4.21 mmol) and potassium carbonate (0.59 g, 4.21 mmol) being added every 24 h. The solvent was then removed *in vacuo* and the residue taken up in diethyl ether (100 mL) and washed with water

(100 mL). The organics were then dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a gummy residue, which was purified *via* column chromatography (eluent: 10% diethyl ether/petrol) to yield **7a/b** as a colourless liquid (1.86 g, 80%), and starting aldehydes **6a/b** (0.28 g, 12%); IR (liq. film): 2972, 2305, 1440 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.30–5.20 (m, 1H, C=C<u>H</u>CH$_3$), 4.05–3.95 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 2.95–2.90 (m, 1H), 2.50–2.39 (m, 1H), 2.20–2.04 (m, 3H), 1.87–1.84 (m, 1H), 1.77–1.70 (m, 1H), 1.63–1.56 (m, 3H), 1.41–1.33 (m, 7H).

4.3.5. Cyclopentenones (*8a/b*) [8]

To a stirring solution of (*E*)/(*Z*)-8-ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **7a/b** (1.05 g, 4.47 mmol) in petrol (90 mL) was added octacarbonyldicobalt (1.61 g, 4.69 mmol) in one portion. After stirring for 2 h, the solvent was removed *in vacuo* and the brown residue was filtered through a short pad of silica gel. The intermediate cobalt complex was then dissolved in 1,2-DCE (60 mL) and ^{n}BuSMe (2.25 mL, 18.5 mmol) was added. The resulting solution was heated to reflux (83 °C) for 40 min before cooling to room temperature and removing the solvent *in vacuo*. The residue was purified *via* column chromatography (eluent: 20% diethyl ether/petrol) to yield the desired cyclopentenone epimer **8a** (0.85 g) and the undesired cyclopentenone epimer **8b** (0.12 g) in a combined 83% yield.

Data for epimer **8a**: melting point: 90–92 °C; lit. value [8]: 90–91 °C; IR (liq. film): 3042, 2978, 1702, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.71 (s, 1H, C=C<u>H</u>), 4.01–3.80 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 2.19 (q, J = 7.5 Hz, 1H, OCC<u>H</u>CH$_3$), 2.04–1.87 (m, 4H), 1.82–1.71 (m, 2H), 1.48 (s, 3H, C<u>H</u>$_3$), 1.33–1.27 (m, 1H), 1.20 (s, 3H, C<u>H</u>$_3$), 1.00 (d, J = 7.5 Hz, 3H, CHC<u>H</u>$_3$).

Data for epimer **8b**: melting point: 87–89 °C; lit. value [8]: 87–88 °C; IR (liq. film): 3035, 2979, 1702, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.81 (s, 1H, C=C<u>H</u>), 4.02–3.82 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 2.27 (q, J = 7.2 Hz, 1H, OCC<u>H</u>CH$_3$), 1.97 (d, J = 5.0 Hz, 1H, C<u>H</u>), 1.86–1.71 (m, 4H), 1.48 (s, 3H, C<u>H</u>$_3$), 1.32–1.28 (m, 1H), 1.20 (s, 3H, C<u>H</u>$_3$), 1.18–1.15 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H, CHC<u>H</u>$_3$).

Table 1, entry 1. To a stirring solution of (*E*)/(*Z*)-8-ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **7a/b** (0.060 g, 0.256 mmol) and tetramethylthiourea (0.020 g, 0.154 mmol) in benzene (7.5 mL) was added octacarbonyldicobalt (0.009 g, 0.026 mmol) in one portion. The reaction was then purged with CO (balloon) and heated to reflux (80 °C) for 6 h. After cooling to room temperature, the solvent was removed *in vacuo* and purification of the residue was attempted *via* column chromatography (eluent: 20% diethyl ether/petrol). The product was found to be contaminated with TMTU by ^1H NMR; the conversion of the desired cyclopentenones **8a/b** was calculated to be 20%.

Table 1, entry 2. To a stirring solution of (*E*)/(*Z*)-8-ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **7a/b** (0.060 g, 0.256 mmol) and tributylphosphine sulfide (0.036 g, 0.154 mmol) in benzene (3.6 mL) was added octacarbonyldicobalt (0.009 g, 0.026 mmol) in one portion. The reaction was then purged with CO (balloon) and heated to reflux (80 °C) for 18 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue purified *via* column chromatography (eluent: 50% diethyl ether/petrol) to yield the desired products **8a/b** (0.032 g, 48%).

4.3.6. General Procedure for microwave-assisted PKRs

To a 10 mL CEM microwave vessel, equipped with a stirrer bar, was added (*E*)/(*Z*)-8-ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **7a/b**, solvent, additive, and octacarbonyldicobalt. The tube was sealed immediately and was placed in the microwave. The reaction was then carried out at the allotted temperature for the specified time. Following this, the crude mixture was purified directly *via* column chromatography (eluent: 50% diethyl ether/petrol) to yield cyclopentenones **8a/b**.

The following experiments were carried out according to the above *General Procedure*. The data are presented as follows: (a) quantity of **7a/b**, (b) volume of solvent, (c) quantity of additive, (d) quantity of $Co_2(CO)_8$, (e) temperature, (f) time, and (g) reaction yield.

Table 1, entry 3. (a) 0.060 g, 0.256 mmol, (b) toluene, 3 mL, (c) $CyNH_2$, 0.035 mL, 0.307 mmol, (d) 0.018 g, 0.0512 mmol, (e) 100 °C, (f) 10 min, and (g) 0.046 g, 69%.

Table 1, entry 4. (a) 0.060 g, 0.256 mmol, (b) 1,2-DCE, 3 mL, (c) ^{n}BuSMe, 0.038 mL, 0.307 mmol, (d) 0.018 g, 0.0512 mmol, (e) 100 °C, (f) 10 min, and (g) 0.043 g, 65%.

Table 1, entry 5. (a) 0.060 g, 0.256 mmol, (b) toluene, 3 mL, (c) ^{n}BuSMe, 0.038 mL, 0.307 mmol, (d) 0.018 g, 0.0512 mmol, (e) 100 °C, (f) 10 min, and (g) 0.057 g, 85%.

4.3.7. Cyclopentanone (*9*)

To a stirred solution of cyclopentenone **8a** (0.75 g, 2.86 mmol) in toluene (50 mL) was added 10% palladium on charcoal (0.03 g) and the reaction purged twice with hydrogen and then placed under an atmosphere of hydrogen (balloon). The reaction was then stirred at room temperature for 1 h, before filtration through a pad of silica (eluent: diethyl ether). The volatiles were then removed *in vacuo* to yield the desired ketone **9** (0.75 g, 99%) as a white solid; Melting point: 95–96 °C; IR (CH_2Cl_2): 2966, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.99–3.79 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 2.43 (ddd, ^2J = 19.1 Hz, J = 11.9 Hz, ^4J = 1.8 Hz, 1H), 2.25–2.14 (m, 2H), 2.11–1.91 (m, 3H), 1.77 (dd, ^2J = 13.7 Hz, J = 6.0 Hz, 1H), 1.63–1.60 (m, 2H), 1.55–1.40 (m, 2H), 1.26 (s, 3H, C<u>H</u>$_3$), 0.96 (d, J = 7.1 Hz, 3H, CHC<u>H</u>$_3$), 0.92 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 219.8, 110.9, 64.9, 63.5, 55.3, 52.6, 52.1, 48.5, 42.3, 38.0, 35.8, 35.0, 31.1, 29.4, 27.0, 9.0; HRMS *m/z* (EI): $C_{16}H_{24}O_3$ (M^+) requires 264.1725, found: 264.1737.

4.3.8. Alcohol (*10*)

To a stirring solution of cyclopentanone **9** (0.74 g 2.79 mmol) in methanol (35 mL) was added sodium borohydride (0.127 g, 3.34 mmol) in one portion. After stirring for 2 h, a saturated aqueous solution of ammonium chloride (35 mL) was added and the product was extracted with diethyl ether (2 × 50 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The crude residue was then dissolved in acetone (30 mL) and *para*-toluenesulfonic acid (0.048 g, 0.279 mmol) was added. The reaction was then stirred for 4 h at room temperature, before the addition of a saturated, aqueous solution of sodium bicarbonate (30 mL), and extraction with diethyl ether. The organics were then dried over sodium sulfate and the solvent removed *in vacuo*. The crude residue was then purified by column chromatography (eluent: 25% diethyl ether/petrol) to yield the desired compound **10** (0.508 g, 82%), along with the diastereomeric alcohol (0.063 g, 10%); appearance: white solid; melting point: 174–176 °C; IR (CH_2Cl_2): 3609, 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.25–4.23 (m, 1H, C<u>H</u>OH), 2.57–2.52 (m, 1H), 2.47 (d, J = 8.1 Hz, 1H), 2.39 (q, J = 9.8 Hz, 1H, C<u>H</u>CH$_3$), 2.33–2.31 (m, 1H), 2.10 (dd, ^2J = 10.9 Hz, J = 4.3 Hz, 1H), 1.95–1.87 (m, 2H), 1.85–1.80 (m, 1H), 1.75–1.68 (m, 1H), 1.57–1.51 (m, 1H), 1.38–1.33 (m, 2H), 1.12 (s, 3H, C<u>H</u>$_3$), 1.02 (s, 3H, C<u>H</u>$_3$), 1.01 (d, J = 7.2 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 214.3, 79.0, 66.4, 56.3, 46.5, 43.9, 37.4, 36.9, 36.2, 34.2, 27.5, 27.1, 9.8; HRMS *m/z* (ES): $C_{14}H_{26}NO_2$ (M^++NH_4) requires 240.1958, found: 240.1959; elemental analysis: $C_{14}H_{22}O_2$ requires C, 75.63%; H, 9.97%, found: C, 75.72%; H, 10.13%.

Data for the diastereomeric alcohol; appearance: white solid; melting point: 174–176 °C; IR (CH_2Cl_2): 3605, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.26–4.23 (m, 1H, CHOH), 3.80–3.74 (m, 1H), 2.52–2.46 (m, 1H), 2.36 (q, $J = 10.0$ Hz, 1H, $CHCH_3$), 2.25 (d, $J = 4.2$ Hz, 1H), 2.10–2.00 (m, 2H), 1.96–1.88 (m, 1H), 1.85–1.80 (m, 1H), 1.72 (br s, 1H), 1.63–1.57 (m, 1H), 1.40 (d, $J = 12.5$ Hz, 1H), 1.12 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.02–0.99 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 213.5, 79.0, 66.7, 53.6, 52.1, 48.7, 44.0, 36.9, 35.7, 34.0, 26.4, 25.1, 11.8; HRMS *m/z* (ES): $C_{14}H_{23}O_2$ (M^++H) requires 223.1689, found: 223.1689; elemental analysis: $C_{14}H_{22}O_2$ requires C, 75.63%; H, 9.97%, found: C, 75.58%; H, 9.78%.

4.3.9. 2-((tert-Butyldimethylsilyl)oxy)-3,8,8-trimethylhexahydro-1H-3a,7-methanoazulen-6(7H)-one

To a stirring solution of alcohol **10** (0.044 g, 0.196 mmol), DMAP (2 crystals), and triethylamine (0.055 mL, 0.392 mmol) in DCM (10 mL) was added *tert*-butyldimethlsilyl triflate (0.09 mL, 0.392 mmol). After stirring at room temperature for 18 h, 2 N HCl (10 mL) was added and the organics separated, washed with 2 N NaOH (10 mL), dried over sodium sulfate, and the solvent removed *in vacuo*. The crude residue was then purified *via* column chromatography (eluent: 0–10% diethyl ether in petrol) to yield the title compound (0.066 g, 100%); melting point: 70–72 °C; IR (CH_2Cl_2): 2958, 1693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.11 (t, $J = 4.8$ Hz, 1H, H), 2.51 (dt, $^2J = 12.3$ Hz, $J = 3.8$ Hz, 1H), 2.46–2.22 (m, 3H), 2.02 (dd, $^2J = 11.0$ Hz, $J = 3.7$ Hz, 1H), 1.89–1.69 (m, 3H), 1.60–1.56 (m, 1H), 1.47–1.44 (m, 1H), 1.24 (d, $J = 12.3$ Hz, 1H), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.88 (d, $J = 7.0$ Hz, 3H, $CHCH_3$), 0.84 (s, 9H, Si^tBu), 0.00 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$): δ 214.5, 79.4, 66.5, 56.6, 56.4, 47.1, 44.0, 37.5, 36.8, 35.9, 34.8, 27.9, 27.1, 26.4, 18.7, 10.5, −4.7; HRMS *m/z* (ES): $C_{20}H_{40}NO_2Si$ (M^++NH_4) requires 354.2823, found: 354.2819; elemental analysis: $C_{20}H_{36}O_2Si$ requires C, 71.37%; H, 10.78%, found: C, 71.52%; H, 10.72%.

4.3.10. Tertiary alcohol, (**11**)

To a flame dried flask, under an atmosphere of nitrogen, was charged diethyl ether (5 mL) and freshly prepared [19] MeLi (2.1 mL, 1.0 M in diethyl ether, 2.1 mmol). To this solution was added a solution of 2-((*tert*-butyldimethylsilyl)oxy)-3,8,8-trimethylhexahydro-1*H*-3a,7-methanoazulen-6(7*H*)-one (0.10 g, 0.30 mmol) in diethyl ether (5 mL) *via* syringe pump over 3 h. After stirring at reflux for a further 15 h, TLC analysis indicated that starting material remained, and, thus, a further quantity of MeLi (2.1 mL, 1.0 M in diethyl ether, 2.1 mmol) was added. After stirring for a further 30 h, a saturated, aqueous solution of ammonium chloride (5 mL) was added and the organics were extracted with diethyl ether (20 mL), dried over sodium sulfate, and the solvent removed *in vacuo*. The crude residue was then purified *via* column chromatography (eluent: 1:9 diethyl ether/petrol) to yield the desired product (0.083 g, 79%) as a white solid, along with returned starting material (0.017 g, 17%); melting point: 115–117 °C; IR (CH_2Cl_2): 3637, 2929, 1463 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.16–4.12 (m, 1H, SiOCH), 2.31–2.26 (m, 1H), 1.96–1.90 (m, 2H), 1.82–1.72 (m, 5H), 1.65–1.60 (m, 3H), 1.30 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.87 (overlapping s & d, 12H, Si^tBu and $CHCH_3$), 0.00 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$): δ 79.3, 75.3, 60.5, 56.5, 55.3, 47.3, 44.5, 37.0, 36.4, 36.2, 34.7, 30.7, 30.5, 28.4, 26.4, 18.7, 10.6, −4.2; HRMS *m/z* (ES): $C_{21}H_{40}O_2Si$ (M^+) requires 352.2790, found: 352.2792; elemental analysis: $C_{21}H_{40}O_2Si$ requires C, 71.53%; H, 11.43%, found: C, 71.62%; H, 11.66%.

4.3.11. Alkenes (**12a/b**)

To a stirring solution of tertiary alcohol **11** (0.075 g, 0.212 mmol) in pyridine (5 mL) was added thionyl chloride (0.308 mL, 98%, 4.25 mmol) dropwise. After 1 h, diethyl ether (25 mL) and 2 N HCl (25 mL) were added, and the organics extracted with diethyl ether (50 mL). The organics were then washed with a further volume of 2 N HCl (2 × 25 mL) and the aqueous layers back-extracted with fresh diethyl ether (25 mL). The combined organics were dried over sodium sulfate and the solvent removed *in vacuo*. The resulting residue was purified *via* column chromatography (eluent: petrol) to yield the desired product (**12b**) as a mixture with the β-isomer (**12a**) of the double bond (0.041 g, 60%). The ratio of **12a**:**12b** was 20:80. Repurification of the mixture by column chromatography (eluent: petrol) allowed partial separation of **12a** and **12b**.

Data for **12b**: appearance: colourless oil; IR (liq. film): 2957, 1471 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.16 (br s, 1H, C=CH), 4.09–4.07 (m, 1H, SiOCH), 2.31–2.25 (m, 1H), 2.17 (dd, $^2J = 10.7$ Hz, $J = 3.6$ Hz, 1H), 1.73–1.69 (m, 3H), 1.63–1.61 (m, 3H, C=CCH_3), 1.59–1.52 (m, 2H), 1.46–1.43 (m, 1H), 1.08 (d, $^2J = 10.8$ Hz, 1H), 0.99–0.98 (2 overlapping singlets, 6H, CH_3), 0.87–0.84 (overlapping s & d, 12H, Si^tBu and $CHCH_3$), 0.00 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$): δ 141.6, 119.4, 79.4, 59.2, 55.6, 54.8, 48.8, 47.1, 43.2, 35.6, 34.5, 28.5, 27.6, 26.5, 25.2, 18.8, 10.4, −4.7; HRMS *m/z* (ES): $C_{21}H_{39}OSi$ (M^++H) requires 335.2765, found: 335.2760.

4.3.12. 3,6,8,8-Tetramethyl-2,3,4,7,8,8a-hexahydro-1H-3a,7-methanozulen-2-ol

To a stirring solution of alkene **12b** (0.136 g, 0.408 mmol) in THF (5 mL) was added TBAF (1.22 mL, 1 M in THF, 1.22 mmol) in one portion. After stirring for 3 days at room temperature, the solvent was removed *in vacuo*, and the residue purified directly *via* column chromatography (eluent: 0–20% diethyl ether in petrol) to yield the desired compound (0.09 g, 100%) as a colourless oil; IR (CH_2Cl_2): 3300, 2957, 1471 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 5.20 (s, 1H, C=CH), 4.21–4.17 (m, 1H, CHOH), 2.17 (dd, $J = 10.8$ Hz, $J = 4.0$ Hz, 1H), 1.86–1.77 (m, 3H), 1.68–1.67 (m, 4H), 1.64–1.55 (m, 3H), 1.19 (d, $J = 10.8$ Hz, 1H), 1.05 (s, 6H, CH_3), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: δ 141.5, 119.8, 79.8, 59.2, 55.2, 54.7, 48.6, 47.0, 43.0, 37.6, 34.5, 28.4, 27.5, 25.2, 10.2; HRMS *m/z* (EI): $C_{15}H_{24}O$ (M^+) requires 220.1822, found: 220.1823.

4.3.13. 2-Epi-α-Cedren-3-one (**1a**) [7]

To a stirred solution of 3,6,8,8-tetramethyl-2,3,4,7,8,8a-hexahydro-1*H*-3a,7-methanozulen-2-ol (0.0165 g, 0.074 mmol) and activated 4 Å molecular sieves (~0.05 g) in DCM (4 mL) was added NMO.H_2O (0.015 g, 0.112 mmol). After stirring for 30 min, TPAP (0.0026 g, 0.007 mmol) was added and the reaction stirred room temperature for 30 min. The reaction mixture was then filtered through a short pad of silica using DCM as the eluent to yield the desired compound **1a** (0.0155 g, 95%) as a colourless oil; IR (CH_2Cl_2): 2961, 1737, 1471, 1455 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 5.30 (s, 1H, C=CH), 2.54–2.40 (m, 2H), 2.17–2.07 (m, 2H), 1.98 (dd, $J = 12.4$ Hz, $J = 4.0$ Hz, 1H), 1.86 (d, $J = 17.1$ Hz, 1H), 1.77 (d, $J = 4.0$ Hz, 1H), 1.70 (apparent q, $^4J = 1.7$ Hz, 3H, C=CCH_3), 1.46 (dd, $^2J = 11.5$ Hz, $J = 3.5$ Hz, 1H), 1.32 (d, $^2J = 11.2$ Hz, 1H), 1.12 (s, 3H, CH_3), 0.97 (d, $J = 7.0$ Hz, 3H, $CHCH_3$), 0.91 (s, 3H, CH_3); ^{13}C (60 MHz, $CDCl_3$), δ 219.7, 140.4, 118.8, 52.5, 52.4, 51.7, 51.4, 48.7, 41.7, 38.0, 34.4, 27.8, 27.1, 24.7, 8.3; HRMS *m/z* (EI): $C_{15}H_{22}O$ (M^+) requires 218.1665, found: 218.1665.

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