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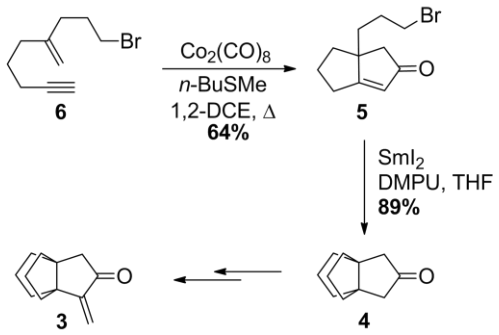

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Synthesis of α-Methylene Propellanone via the Strategic Employment of Metal-mediated Cyclisation Chemistry

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ABSTRACT

Biologically active α-methylenene propellanone has been synthesised in 12 steps in an overall yield of 11%. The key step of the synthesis, an intramolecular Pauson–Khand reaction, proceeds in good yield under alkyl sulfide promotion conditions, to furnish the 5,5-fused moiety within the target. Samarium diiodide-induced intramolecular conjugate addition onto the resulting cyclopentenone was used to complete the intriguing [3.3.3] propellanone skeleton.

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1. Introduction

Both naturally occurring and synthetic α-methylene cyclopentanones and cyclopentenones have been the subject of much study due to their interesting biological activity. Simple, representative examples of this class of compound are sarkomycin[1] **1** and methylenomycin B[2] **2**, which possess anti-tumour and anti-microbial activity, respectively (**Figure 1**). In a related series, α-methylene propellanone **3**, synthesised by Kakiuchi and co-workers,[3] has been identified as an appreciably potent cytotoxic agent within a range of tumour cell lines.

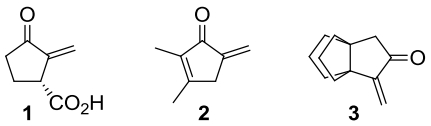
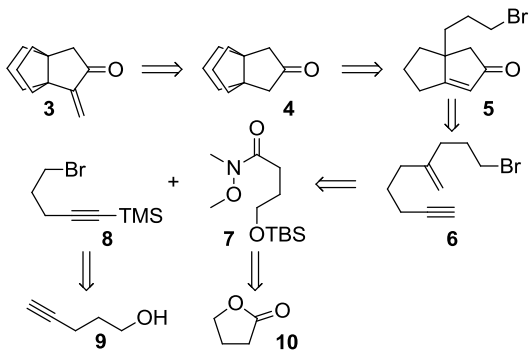


Fig. 1. Sarkomycin, methylenomycin B, and α-methylene propellanone.

As part of our continuing series of studies[4] to further develop the overall effectiveness and applicability of the Pauson–Khand annulation reaction in total synthesis,[5] we sought to utilise this cyclisation process as the central synthetic transformation underpinning a route towards α-methylene propellanone **3** and, in so doing, establish a more direct and efficient pathway for the synthesis of this structurally intriguing tricyclic skeleton. Our proposed pathway for gaining access to α-methylene propellanone centres on the strategic employment of metal-mediated cyclisation chemistry. Specifically, the key steps are (i) a cobalt-mediated intramolecular Pauson-Khand reaction (PKR), which constructs the 5,5-fused bicyclic moiety within the target, and (ii) a samarium-mediated intramolecular conjugate addition to complete the [3.3.3] propellanone carbon skeleton. Notably, the functional (bromo) handle for the samarium-induced cyclisation requires to be carried through both enyne complexation and Pauson-Khand cyclisation, in what would be a rare example of these latter processes tolerating a primary alkyl bromide. Our retrosynthetic approach, presented in **Scheme 1**, illustrates the initial removal of the methylene functionality present in **3** to furnish the key [3.3.3] cyclopentanone unit **4**. This intermediate could be derived from cyclopentenone **5**, via the samarium-mediated process described above. In turn, **5** could be constructed by Pauson-Khand annulation of precursor **6**. Enyne **6** may be formed from coupling of Weinreb amide **7** and the Grignard reagent derived from protected bromoalkyne **8**,



Scheme 1. Retrosynthetic approach to α-methylene propellanone **3**.

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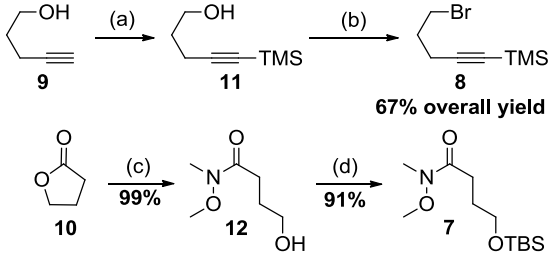
followed by carbonyl olefination and conversion of the protected alcohol to the primary alkyl bromide. Both **7** and **8** can be readily accessed from the commercially available starting materials pent-4-yn-1-ol **9** and γ-butyrolactone **10**, respectively.

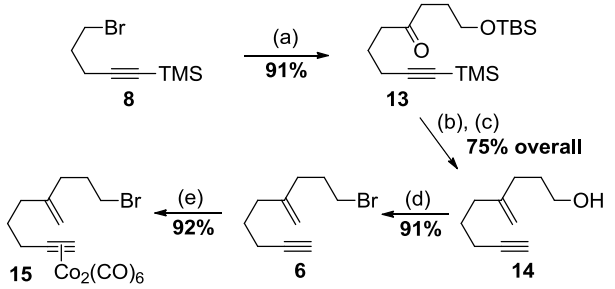
2. Results and Discussion

Our studies began with the synthesis of intermediates **7** and **8** (**Scheme 2**). As previously described by Trost,[6] commercially available pent-4-yn-1-ol **9** was transformed to protected alkyne **11** in a one-pot procedure, prior to conversion of the primary alcohol to the desired bromide derivative **8**. This short synthetic pathway delivered bromide **8** in an appreciable 67% overall yield. With respect to the second required fragment, compound **12** was prepared according to a procedure reported by Molander.[7] Treatment of γ-butyrolactone **10** with trimethylaluminium and *N*,*O*-dimethylhydroxylamine hydrochloride furnished Weinreb amide **12** in an excellent yield. Subsequent protection of **12** as its *t*-butyldimethylsilyl ether afforded **7** in excellent overall yield.



Scheme 2. Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) TMSCl, −78 °C - r.t., 14.5 h, (iii) 3M HCl, r.t., 7.5 h; (b) Ph_3P, Br_2, DCM, −5 °C - r.t., 4 h; (c) Me_3Al, $CH_3(CH_3O)NH{\cdot}HCl$, DCM, 5.5 h; (d) 2,6-lutidine, TBSOTf, DCM, 0 °C – r.t., 1 h.

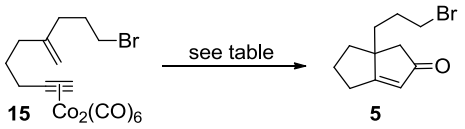
With intermediates **7** and **8** in hand, our attention was focused on the preparation of the desired Pauson-Khand annulation precursor, enyne **6** (**Scheme 3**). *In-situ* formation of the Grignard reagent from bromide **8**, followed by addition to Weinreb amide **7**, delivered ketone **13** in an excellent 91% yield. Olefination of the newly-formed ketone in **13** under standard Wittig conditions, followed by fluoride-mediated deprotection of the silyl ether furnished alcohol **14** in an excellent yield. Finally, alcohol **14** was converted to the Pauson-Khand precursor, bromoenyne **6**, by treatment with CBr_4 and Ph_3P. At this stage, with bromoenyne **6** in hand, the efficiency of the Pauson-Khand annulation in the assembly of the required cyclopentenone moiety could now be investigated. Prior to the evaluation of various cyclisation conditions, the requisite dicobalthexacarbonyl complex of alkyne **6** was prepared and isolated in an excellent 92% yield.



Scheme 3. Reagents and conditions: (a) Mg, THF, r.t., 1 h, then **7**, −5 °C - r.t, 96 h; (b) $MePh_3PBr$, *n*-BuLi, THF, 0 °C - r.t., 13 h; (c) TBAF, THF, r.t., 19 h; (d) Ph_3P, CBr_4, DCM, −78 °C - r.t., 18 h; (e) $Co_2(CO)_8$, pet. ether, r.t., 2.5 h.

With complex **15** in hand, a series of techniques for promoting this key cyclisation were probed, with a view to not only establishing the bicyclic system, but also to study the primary alkyl bromide in an intramolecular Pauson-Khand reaction.

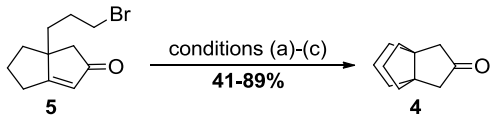
Table 1
Pauson-Khand reaction optimisation



Promoter	Solvent	T / °C	t / h	Conc. / M	Yield
brucine *N*-oxide	DCM/THF	−42	3	0.013	-
$NMO{\cdot}H_2O$	DCM	r.t.	15	0.012	28%
n-BuSMe	1,2-DCE	84	15	0.2	26%
n-BuSMe	1,2-DCE	84	4	0.02	70%

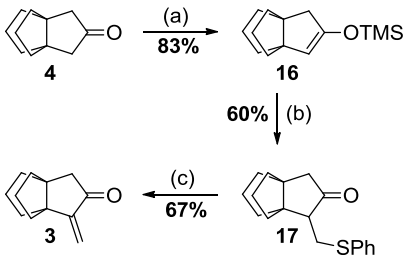
Initially, amine *N*-oxide conditions were examined for use within this cyclisation. More specifically, as described in **Table 1**, the use of brucine *N*-oxide (BNO) resulted in only decomposition of the reaction mixture. This result was somewhat surprising given that this particular promoter had been successfully employed during the synthesis of descarboxyquadrone analogues within our laboratories.[4g] Nevertheless, upon switching to *N*-methylmorpholine *N*-oxide monohydrate ($NMO{\cdot}H_2O$), we were pleased to obtain the desired cyclopentenone product **5**, albeit in a poor 28% yield. Encouraged by this result, attention was turned to the use of *n*-butyl methyl sulfide, a promoter for this annulation process which was first described by Sugihara and Yamaguchi.[8] Thus, treatment of cobalt alkyne complex **15** with 3.5 equivalents of *n*-butyl methyl sulfide followed by refluxing for 15 h in 1,2-dichloroethane resulted in the product being obtained in a 26% yield. Somewhat disappointed with this result, a concentration study was carried out and, to our pleasure, a much improved yield of the annulated product was achieved upon carrying out the reaction under more dilute conditions. Optimum efficiency for this challenging transformation was realised upon performing this transformation in a 0.02 M solution of 1,2-DCE, whereupon the desired cyclopentenone product **5** was obtained in a very good 70% yield.

With an efficient route to key enone **5** established, our focus was directed to the final ring closure required to complete the [3.3.3] propellanone structure. In this respect, a samarium diiodide-promoted intramolecular conjugate addition was investigated (**Scheme 4**). Following a protocol reported by Curran,[9] treatment of bromide **5** with 2.2 equivalents of samarium diiodide and DMPU gave, after careful purification, a 41% yield of the requisite propellanone **4**. With regards isolation, it is important to note the relatively high volatility of this product. Based on this initial, encouraging result, our attention turned to the quantity of samarium diiodide used. Indeed, increasing the amount of samarium diiodide to 5 equivalents resulted in a much improved yield of 70%. Finally, using 5.5 equivalents of samarium diiodide within the reaction culminated in an excellent 89% yield of propellanone **4**.



Scheme 4. Reagents and conditions: (a) 2.5 eq. SmI_2, DMPU, THF, r.t., 3 h, 41%; (b) 5.0 eq. SmI_2, DMPU, THF, 0 °C, 3 h, 70%; (c) 5.5 eq. SmI_2, DMPU, THF, 0 °C, 6 h, 89%.

With the core of the target molecule established, the final requirement for completion of the synthesis was the installation of the α-methylene moiety. In this regard, **Scheme 5** illustrates the final steps towards completion of this synthetic programme. Firstly, silyl enol ether **16** was prepared in good yield, followed by alkylation with chloromethylphenyl sulfide to provide sulfide **17** in 60% yield. Finally, treatment of sulfide **17** with sodium metaperiodiate, which formed the sulfoxide derivative *in situ*, was followed by thermally-promoted elimination to deliver the target α-methylene propellanone **3** in 67% yield.



Scheme 5. Reagents and conditions: (a) LDA, TMSCl, THF, −78 °C - r.t., 2 h; (b) $TiCl_4$, $PhSCH_2Cl$, DCM, −25 °C - r.t., 4.5 h; (c) $NaIO_4$, MeOH, H_2O, r.t., 17 h, then $CHCl_3$, reflux, 4 h.

3. Conclusion

In conclusion, α-methylene propellanone, **3** was successfully synthesised with a longest linear sequence of 12 steps. The overall optimised yield of 11% represents a very good average yield of 82% per step. Amongst the salient features of this synthesis are a notable and effective intramolecular Pauson-Khand reaction on a bromide-containing enyne, and a high-yielding, samarium-induced, intramolecular conjugate addition. This sequence of Pauson-Khand reaction followed by samarium-mediated cyclisation represents a novel and rapid approach to the assembly of the challenging propellane carbon skeleton from a relatively simple acyclic starting material. Additionally, the cobalt-alkyne complexation and subsequent Pauson-Khand reaction of enyne **6** provides a rare example of a primary alkyl bromide featuring in this low-valent, metal-mediated process.

4. Experimental section

4.1. General information

All reactions were carried out using flame or oven dried glassware, which had been cooled under a positive pressure of nitrogen prior to use. Starting materials and solvents were used as obtained from commercial suppliers without further purification. For air sensitive reactions, standard protocols were employed using dry solvents and under a N_2 atmosphere. Solutions, solvents and liquid reagents were added *via* syringe. Light petrol refers to the fraction of b.p. 30-40 °C. Thin layer chromatography was carried out using Camlab silica plates coated with indicator UV254. These were analysed using a Mineralight UVGL-25 lamp or developed using vanillin or potassium permanganate solutions. Flash column chromatography was carried out using silica gel (230–400 mesh). IR spectra were obtained on a Nicolet Impact 400D machine. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants refer to $^3J_{H\text{-}H}$ couplings, unless otherwise stated, and are reported in Hz. High-resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at the University of Wales, Swansea.

4.2. 5-Trimethylsilylpent-4-yn-1-ol 11[6]

n-Butyllithium (50 mL, 125 mmol, 2.5 M in hexanes) was added over 1 h to a solution of 4-pentyn-1-ol **9** (5.0 g, 59.4 mmol) in THF (90 mL) at −78 °C. Trimethylsilyl chloride (20 mL, 158 mmol) was added over 30 min and the reaction mixture was warmed to room temperature and stirred for 14 h. To the reaction was added 3 M HCl (60 mL) and the solution was stirred for a further 7.5 h. The reaction mixture was poured into a separating funnel, the organic phase was separated and washed with saturated sodium bicarbonate solution (2 × 50 mL), brine (2 × 50 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to give **11** (10.0 g, 108% crude yield) as a yellow oil, which was used directly in the next step. IR (thin film): 3600-3000 (br s, OH), 2957, 2899, 2877, 2176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79—3.75 (m, 2H, OCH_2), 2.35 (t, J = 6.9 Hz, 2H, CH_2), 1.81—1.76 (m, 2H, CH_2), 1.63 (s, 1H, OH), 0.15 (s, 9H, $Si(CH_3)_3$).

4.3. (5-Bromopent-1-ynyl)trimethylsilane 8[6]

Bromine (3.35 mL, 65.4 mmol) was added over 10 min to a solution of Ph_3P (17.2 g, 65.5 mmol) in DCM (120 mL) to give a white precipitate. The reaction mixture was then cooled to −5 °C and 5-trimethylsilylpent-4-yn-1-ol **11** (10.0 g, 58.4 mmol) was added slowly, keeping the internal temperature below 0 °C. The resulting solution was allowed to warm to room temperature and stirred for a further 4 h. The reaction mixture was poured into a separating funnel and diluted with hexane (500 mL), washed with saturated solutions of sodium bicarbonate (2 × 100 mL) and brine (2 × 100 mL), dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. The precipitated triphenylphosphine oxide was filtered, washed with hexane, and the solvent removed *in vacuo* to leave a yellow oil. Purification *via* distillation under reduced pressure affored **8** (10.2 g, 67% over 2 steps) as a colourless oil. IR (thin film): 2960, 2900, 2177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.52 (t, J = 6.5 Hz, 2H, CH_2Br), 2.42 (t, J = 6.8 Hz, 2H, CH_2), 2.09—2.04 (m, 2H, CH_2), 0.16 (s, 9H, $Si(CH_3)_3$).

4.4. 4-Hydroxy-*N*-methoxy-*N*-methylbutanamide 12[10]

Following the procedure described by Molander,[7] trimethylaluminium (66 mL, 132 mmol, 2 M in toluene) was added over 1 h to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (13.6 g, 139.4 mmol) in DCM (50 mL) at −78 °C. The solution was warmed to room temperature and stirred for 4 h. The solution was then cooled to −5 °C, γ-butyrolactone **10** (4.4 ml, 57.2 mmol) was added and the resulting mixture stirred for a further 1.5 h. After this time, the solution was carefully quenched at 0 °C by addition of a solution of potassium sodium L-tartrate tetrahydrate (16 g) in water (20 mL) and stirred overnight. The resulting precipitate was filtered through a plug of celite and washed with DCM. The organic phase was dried over sodium

sulfate, filtered, and the solvent removed *in vacuo* to give **12** (8.31 g, 99%) as a light yellow oil. IR (thin film): 3666—3071 (br s, OH), 2940, 2877, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72—3.67 (m, 5H, CH_2 and OCH_3), 3.20 (s, 3H, NCH_3), 2.76 (br t, J = 4.8 Hz, 1H, OH), 2.62 (t, J = 6.8, 2H, CH_2), 1.95—1.87 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 62.9, 61.6, 32.7, 39.6, 27.6; HRMS (ES^+): $C_6H_{14}NO_3$ (M^++H^+) requires 148.0973; found 148.0972.

4.5. 4-((1,1-Dimethylethyl)dimethylsilyloxy)-*N*-methoxy-*N*-methylbutanamide 7

To a solution of 4-hydroxy-*N*-methoxy-*N*-methylbutanamide **12** (0.20 g, 1.37 mmol) in DCM (5 mL) at 0 °C was added and *tert*-butyldimethylsilyl triflate (0.34 mL, 1.5 mmol) followed by 2,6-lutidine (0.24 mL, 2.04 mmol) and the reaction stirred for 1 h whilst warming to room temparature. After this time, the solvent was removed *in vacuo* and the residue purified *via* flash column chromatography (eluent: 4:1 petrol/ether) to yield **7** (0.325 g, 91%) as a colourless oil. IR (thin film): 2956, 2930, 2889, 2864, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64—3.60 (m, 5H, CH_2 and OCH_3), 3.13 (s, 3H, NCH_3), 2.46 (br t, J = 7.4 Hz, 2H, CH_2), 1.83—1.76 (m, 2H CH_2), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 62.5, 61.3, 32.4, 28.4, 27.8, 26.1, 18.5, -5.2; HRMS (ES^+): $C_{12}H_{28}NO_3Si$ (M^++H^+) requires 262.1838; found 262.1842.

4.6. 4-((1,1-Dimethylethyl)dimethylsilyloxy)-9-trimethylsilylnon-8-yn-4-one 13[11]

Magnesium turnings (8.83 g, 0.368 mmol) were charged to a round bottom flask and stirred under nitrogen for 2 days. To the resulting black powder was added THF (10 mL). A solution of (5-bromopent-1-ynyl)trimethylsilane **8** (8.16 g, 37.26 mmol) in THF (50 mL) was then added slowly over 1.5 h. After completion of the addition, the mixture was stirred for 1 h, then cooled to −5 °C. A solution of 4-((1,1-dimethylethyl)dimethylsilyloxy)-*N*-methoxy-*N*-methylbutanamide **7** (8.08 g, 30.96 mmol) in THF (50 mL) was then added over 1 h. The resulting reaction mixture was allowed to warm to room temperature and stirred for a further 96 h before being quenched with a saturated solution of ammonium chloride (10 mL). The remaining magnesium residues were removed by filtration through a plug of celite, then the residue was washed with ether and the solvent removed *in vacuo*. The resulting oil was dissolved in ether (175 mL), washed with solutions of saturated ammonium chloride (2 × 30 mL) and brine (30 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent: 5:1 petrol/ether) to afford **13** (9.66 g, 91%) as a colourless oil. IR (thin film): 2956, 2930, 2897, 2858, 2175, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, J = 6.1 Hz, 2H, OCH_2), 2.55 (t, J = 7.3 Hz, 2H, CH_2), 2.50 (t, J = 7.3 Hz, 2H, CH_2), 2.26 (t, J = 6.9 Hz, 2H, CH_2), 1.82—1.76 (m, 4H, 2 × CH_2), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.15 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 106.6, 85.5, 62.4, 41.4, 39.4, 27.1, 26.1, 22.7, 19.4, 18.5, 0.3, -5.2; HRMS (ES^+): $C_{18}H_{37}O_2Si_2$ (M^++H^+) requires 341.2332; found 341.2336.

4.7. 9-((1,1-Dimethylethyl)dimethylsilyloxy)-6-methylene-1-trimethylsilylnon-1-yne [11]

n-Butyllithium (3.6 mL, 0.9 mmol, 2.5 M in hexanes) was added to a suspension of methyltriphenylphosphonium bromide (3.22 g, 0.9 mmol) in THF (5 mL) at 0 °C and left to stir for 30 min. To the resulting yellow solution was added 4-((1,1-dimethylethyl)dimethylsilyloxy)-9-trimethylsilylnon-8-yn-4-one **13** (0.103 g, 0.303 mmol) in THF (5 mL) and the reaction mixture allowed to warm to room temperature and stirred for a further 13 h. The reaction was then quenched with a saturated solution of ammonium chloride (2 mL), placed in a separating funnel, and diluted with ether (30 mL). The organic phase was separated, washed with ammonium chloride (15 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. To the remaining oil was added petrol (50 mL), the precipitate was filtered through a plug of celite and the residues washed with petrol. The solvent was removed *in vacuo* and the remaining oil was purified *via* flash column chromatography (eluent: 19:1 petrol/ether) to give the desired product (0.075 g, 77%) as a colourless oil. IR (thin film): 2955, 2930, 2898, 2858, 2176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75—4.74 (m, 2H, olefinic CH_2), 3.62 (t, J = 6.4 Hz, 2H, OCH_2), 2.23 (t, J = 7.2 Hz, 2H, CH_2), 2.13 (t, J = 7.5 Hz, 2H, CH_2), 2.07 (t, J = 7.9 Hz, 2H, CH_2), 1.70—1.62 (m, 4H, 2 × CH_2), 0.90 s, (9H, $Si(CH_3)_3$), 0.15 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 109.7, 107.5, 84.9, 63.0, 35.3, 32.3, 31.2, 27.0, 26.2, 19.7, 18.5, 0.4, -5.0; HRMS (ES^+): $C_{19}H_{39}OSi_2$ (M^++H^+) requires 339.2539; found 339.2544.

4.8. 4-Methylenenon-8-yn-1-ol 14[11]

Tetra-*n*-butylammonium fluoride (0.6 mL, 0.6 mmol, 1 M in THF) was added over 10 min to a solution of 9-((1,1-dimethylethyl)dimethylsilyloxy)-6-methylene-1-trimethylsilylnon-1-yne (0.097 g, 0.285 mmol) in THF (5 mL) at 0 °C, the reaction mixture allowed to warm to room temperature and left to stir for 19 h. After this time, the reaction mixture was filtered through a plug of silica gel, the plug washed with ether, and the solvent removed *in vacuo*. The resulting oil was purified *via* column chromatography (eluent: 4:1 petrol/ether) to give **14** (0.042 g, 97%) as a colourless oil. IR (thin film): 3680—3000 (br s, OH), 3302, 2941, 2886 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77—4.72 (m, 2H, olefinic CH_2), 3.64 (t, J = 6.5 Hz, 2H, OCH_2), 2.20 (dt, J = 7.2 Hz, ^4J = 2.7 Hz, 2H, CH_2), 2.18—2.09 (m, 4H, 2 × CH_2), 2.10 (t, ^4J = 2.6 Hz, 1H, alkyne CH), 1.81 (s, 1H OH), 1.73—1.42 (m, 4H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 110.1, 84.5, 68.7, 62.7, 35.0, 32.4, 30.9, 26.7, 18.1; HRMS (ES^+): $C_{10}H_{17}O$ (M^++H^+) requires 153.1279; found 153.1281.

4.9. 9-Bromo-6-methylenenon-1-yne 6

Carbon tetrabromide (2.72 g, 8.20 mmol) was added to a solution of 4-methylenenon-8-yn-1-ol **14** (0.995 g, 6.55 mmol) in DCM (40 mL) at −78 °C and the resulting reaction mixture stirred for 5 min. To this was added triphenylphosphine (2.57 g, 9.81 mmol) portion-wise over 5 min and the reaction mixture allowed to warm to room temperature over 3 h and then allowed to stir for a further 15 h. The solvent was removed *in vacuo* to leave a brown semi-solid, which was dissolved in petrol and filtered through a plug of silica. The silica was washed exhaustively with petrol and the solvent removed *in vacuo* to afford **6** (1.28 g, 91%) as a colourless oil. IR (thin film): 3301, 2943, 2855, 2123, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81—4.80 (m, 2H olefinic CH_2), 3.43 (t, J = 6.7 Hz, 2H, CH_2Br), 2.21 (dt, J = 7.1 Hz, ^4J = 2.6 Hz, 2H, CH_2), 2.18—2.09 (m, 4H, 2 × CH_2), 2.04—1.97 (m, 2H CH_2), 1.96 (t, ^4J = 2.7 Hz, 1H, alkyne CH), 1.74—1.62 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 110.8, 84.4, 68.8, 35.0, 34.4, 33.5, 30.9, 26.7, 18.2; HRMS (ES^+): $C_{10}H_{15}{}^{79}Br$ (M^+) requires 214.0357; found 214.0354.

4.10. **Hexacarbonyl[μ-[(1,2-η:1,2-η)-9-bromo-6-methylenenon-1-yne]]dicobalt 15**

A solution of 9-bromo-6-methylenenon-1-yne **6** (0.193 g, 0.9 mmol) in petrol (10 mL) was added over 10 min to a solution of octacarbonyldicobalt (0.338 g, 0.988 mmol) in petrol (10 mL) and stirred at room temperature for 2.5 h. After this time, the solution was directly purified *via* flash column chromatography (eluent: petrol) to yield complex **15** (0.416 g, 92%) as a red oil. IR (CH_2Cl_2): 2111, 2060, 2015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (t, ^4J = 1.1 Hz, 1H, alkyne CH), 4.85 (s, 2H, olefinic CH_2), 3.43 (t, J = 6.7 Hz, 2H, CH_2Br), 2.86 (dt, J = 7.9 Hz, ^4J = 1.0 Hz, 2H, CH_2), 2.21—2.00 (m, 4H, 2 × CH_2), 2.05—1.98 (m, 2H, CH_2), 1.82—1.75 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 147.0, 110.8, 97.3, 73.3, 35.7, 34.4, 33.6, 33.4, 31.0, 30.0.

4.11. **3a-(3-Bromopropyl)-3a,4,5,6-tetrahydro-2(3*H*)-pentalenone 5**

Using brucine N-oxide

Brucine *N*-oxide (0.320 g, 0.780 mmol) was added in one portion to a solution of hexacarbonyl[μ-[(1,2-η:1,2-η)-9-bromo-6-methylenenon-1-yne]]dicobalt **15** (0.065 g, 0.13 mmol) in THF (5 mL) and DCM (5 mL) at −42 °C. The resulting reaction mixture was allowed to warm to room temperature over 1 h and stirred for a further 2 h. TLC analysis indicated complete consumption of the starting material. However, no formation of the desired product was observed.

Using N-methylmorpholine N-oxide monohydrate

A solution of *N*-methylmorpholine *N*-oxide monohydrate (0.157 g, 1.16 mmol) in DCM (10 mL) was added, over 3 h, to a solution of hexacarbonyl[μ-[(1,2-η:1,2-η)-9-bromo-6-methylenenon-1-yne]]dicobalt **15** (0.058 g, 0.12 mmol) in DCM (10 mL) and the reaction was stirred for 15 h. The resultant purple solution was filtered through a plug of silica, the plug washed with ether, and the solvent removed *in vacuo*. The resulting oil was purified *via* flash column chromatography (eluent: 1:1 petrol/ether) to give **5** (0.008 g, 28%) as a colourless oil.

Using n-butyl methyl sulfide under normal dilution

n-Butyl methyl sulfide (0.92 mL, 7.5 mmol) was added to a solution of hexacarbonyl[μ-[(1,2-η:1,2-η)-9-bromo-6-methylenenon-1-yne]]dicobalt **15** (1.072 g, 2.14 mmol) in 1,2-DCE (10 mL) and the resulting reaction mixture was heated at reflux for 15 h. After this time, the reaction mixture was allowed to cool, filtered through a plug of silica, the plug washed with ether, and the solvent removed *in vacuo*. The resulting oil was purified *via* flash column chromatography (eluent: 1:1 petrol/ether) to give **5** (0.136 g, 26%) as a colourless oil.

Using n-butyl methyl sulfide under high dilution

n-Butyl methyl sulfide (0.5 mL, 3.9 mmol) was added to a solution of hexacarbonyl[μ-[(1,2-η:1,2-η)-9-bromo-6-methylenenon-1-yne]]dicobalt **15** (0.554 g, 1.106 mmol) in 1,2-DCE (60 mL) and the resulting reaction mixture was heated at reflux for 4 h. After this time, the reaction mixture was allowed to cool, filtered through a plug of silica, the plug washed with ether, and the solvent removed *in vacuo*. The resulting oil was purified *via* flash column chromatography (eluent: 1:1 petrol/ether) to give **5** (0.187 g, 70%) as a colourless oil. IR (thin film): 2960, 2857, 1702, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (t, ^4J = 1.6 Hz, 1H, olefinic CH), 3.41—3.32 (m, 2H, CH_2Br), 2.65—2.55 (m, 2H, CH_2), 2.41 (d, ^2J = 17.6 Hz, 1H, CH), 2.18 (d, ^2J = 17.7 Hz, 1H, CH), 2.19—2.09 (m, 1H, CH), 2.04—1.92 (m, 2H, 2 × CH), 1.84—1.70 (m, 1H, CH_2), 1.70—1.60 (m, 2H, 2 × CH), 1.50—1.35 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 192.7, 125.1, 53.36, 48.8, 35.2, 34.9, 33.8, 28.6, 25.2, 23.3; HRMS (ES^+): $C_{11}H_{16}{}^{79}BrO$ (M^++H^+) requires 243.0384; found 243.0390.

4.12. **Tricyclo[3.3.3.0^{1,5}]undecan-3-one 4**[12]

(a) Using 2.5 eq. of SmI_2

N,*N*'-Dimethylpropyleneurea (0.25 mL, 2.07 mmol) was added to a solution of samarium diiodide (5.2 mL, 0.52 mmol, 0.1 M in THF) and the reaction mixture stirred for 5 min. To the resultant purple solution was slowly added 3a-(3-bromopropyl)-3a,4,5,6-tetrahydro-2(3*H*)-pentalenone **5** (0.050 g, 0.207 mmol) in THF (10 mL) over a period of 2 h. On completion of the addition, the reaction mixture was stirred for a further 1 h. The reaction was then quenched by the addition of water (1 mL) followed by 2 M HCl (0.5 mL), and the THF removed *in vacuo*. The remaining aqueous solution was transferred into a separating funnel and extracted with ether (3 × 25 mL). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo* with cooling. The residue was purified *via* flash column chromatography (eluent: 4:1 petrol/ether to 1:1 petrol/ether) to afford cyclopentanone **4** (0.014 g, 41%) as a white solid. Starting ketone **5** was also recovered (24.5 mg).

(b) Using 5 eq. SmI_2

N,*N*'-Dimethylpropyleneurea (0.25 mL, 2.07 mmol) was added to a solution of samarium diiodide (5.5 mL, 0.55 mmol, 0.1 M in THF) and the reaction mixture stirred for 5 min then cooled to 0 °C. To the resultant purple solution was slowly added 3a-(3-bromopropyl)-3a,4,5,6-tetrahydro-2(3*H*)-pentalenone **5** (0.026 g, 0.105 mmol) in THF (6 mL) over a period of 1 h. On completion of the addition, the reaction mixture was stirred for a further 2 h. The reaction was then quenched by the addition of water (0.5 mL) followed by 2 M HCl (0.5 mL), and the THF removed *in vacuo*. The remaining aqueous solution was transferred into a separating funnel, diluted with water (4 mL) and extracted with ether (3 × 15 mL). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo* with cooling. The residue was purified *via* flash column chromatography (eluent: 10:1 petrol/) to afford cyclopentanone **4** (0.012 g, 70%) as a white solid.

(c) Using 5.5 eq. SmI_2

N,*N*'-Dimethylpropyleneurea (1.0 mL, 8.24 mmol) was added to a solution of samarium diiodide (21 mL, 2.10 mmol, 0.1 M in THF) and the reaction mixture stirred for 5 min then cooled to 0 °C. To the resultant purple solution was slowly added 3a-(3-bromopropyl)-3a,4,5,6-tetrahydro-2(3*H*)-pentalenone **5** (0.101 g, 0.416 mmol) in THF (10 mL) over a period of 2 h. On completion of the addition, the reaction mixture was stirred for a further 3.5 h. A further portion of samarium iodide (2 mL, 0.20 mmol) was added and the reaction mixture stirred for 30 min. The reaction was then quenched by the addition of water (1 mL) followed by 2 M HCl (1 mL), and the THF removed *in vacuo*. The remaining aqueous solution was transferred into a separating funnel, diluted with water (4 mL) and extracted with ether (3 × 25 mL). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo* with cooling. The residue was purified *via* flash column chromatography (eluent: 10:1 petrol/) to afford cyclopentanone **4** (0.060 g, 89%) as a white solid, m.p. 63—65 °C. IR (thin film): 2933, 2854, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 4H), 1.69—1.58 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.6, 56.1, 53.1, 41.9, 25.2.

4.13. 3-(Trimethylsilyloxy)tricyclo[3.3.3.0^{1,5}]undec-2-ene 16

Following the procedure of Kakiuchi *et al.*,[3a] *n*-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexanes) was added to a solution of *i*-Pr_2NH (0.036 mL, 0.256 mmol) in THF (5 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature and then re-cooled to −78 °C. To the reaction was added trimethylsilyl chloride (0.23 mL, 1.83 mmol), followed by a solution of ketone **4** (0.021 g, 0.128 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C for 30 min, warmed to r.t. and stirred for a further 1.5 h . The solvent and excess reagents were removed *in vacuo* and the residue was purified by flash column chromatography (eluent: petrol) to furnish silyl enol ether **16** (0.025 g, 83%) as a colourless oil, which was used immediately in the next step. IR (thin film): 2946, 2858, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (t, ^4J = 1.8 Hz, 1H, olefinic CH), 2.29 (d, ^4J = 1.9 Hz, 2H, CH_2), 1.56—1.49 (m, 12H), 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 112.6, 64.7, 57.3, 50.1, 42.4, 40.9, 26.1, 0.6.

4.14. 2-(Phenylthiomethyl)tricyclo[3.3.3.0^{1,5}]undecan-3-one 17

Following the procedure of Kakiuchi *et al.*,[3a] titanium tetrachloride (0.12 mL, 0.12 mmol, 1 M in DCM) was added to a solution of silyl enol ether **16** (0.025 g, 0.106 mmol) and chloromethyl phenyl sulfide (0.02 mL, 0.148 mmol) in DCM (5 mL) at −25 °C. The resulting reaction mixture was stirred at this temperature for 3 h. The resultant red solution was warmed to room temperature and stirred for a further 1.5 h before being poured into a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous layer was extracted exhaustively with ether, and the combined organic layers dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The resulting oil was purified *via* flash column chromatography (eluent: petrol to 25:1 petrol/ether) to give **17** (0.018 g, 60%) as a colourless oil. IR (thin film): 2953, 2870, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32—7.30 (m, 2H, ArH), 7.04—7.00 (m, 2H, ArH), 6.93—6.89 (m, 1H, ArH), 3.61 (dd, ^2J = 13.1 Hz, J = 4.6 Hz, 1H, CHSPh), 2.78 (dd, ^2J = 13.1 Hz, J = 9.7 Hz, 1H, CHSPh), 2.25—2.22 (m, 1H, CH_2), 1.97 (d, ^2J = 17.0 Hz, 1H, CH), 1.80 (d, ^2J = 17.0 Hz, 1H, CH), 1.45—0.9 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 138.1, 129.6, 129.2, 126.0, 59.2, 56.4, 53.7, 51.2, 42.2, 41.8, 41.75, 35.0, 30.6, 25.8, 24.5; HRMS (ES^+): $C_{18}H_{23}OS$ (M^++H^+) requires 287.1469; found 287.1471.

4.15. 2-Methylenetricyclo[3.3.3.0^{1,5}]undecan-3-one 3[3a]

Sulfide **17** (0.031 g, 0.109 mmol), sodium metaperiodate (0.024 g, 0.111 mmol), MeOH (0.9 mL), and water (0.1 mL) were charged to a flask, protected from light, and stirred for 17 h. After this time, the reaction mixture was diluted with DCM (20 mL) and water (15 mL). The organic layer was separated and the aqueous layer was washed with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in chloroform (5 mL) and heated to reflux for 4 h. The solvent was removed *in vacuo* and the resulting oil was purified by flash column chromatography (eluent: 10:1 petrol/ether) to afford α-methylene propellanone **3** (0.013 g, 67%) as a pale yellow oil. IR (thin film): 2946, 2857, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, ^2J = 0.6 Hz, 1H, olefinic CH), 5.28 (d, ^2J = 0.7 Hz, 1H, olefinic CH), 2.44 (s, 2H, CH_2), 1.86—1.51 (m, 12H).

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