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

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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 sarkomycin1 and methylenomycin B2, 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 studies4 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 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.
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, 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 alkene 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. 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.

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 CBr₄ and Ph₃P. 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.

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

<table>
<thead>
<tr>
<th>Promoter</th>
<th>Solvent</th>
<th>T / °C</th>
<th>t / h</th>
<th>Conc. / M</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>brucine N-oxide</td>
<td>DCM/THF</td>
<td>−42</td>
<td>3</td>
<td>0.013</td>
<td>-</td>
</tr>
<tr>
<td>NMO-H₂O</td>
<td>DCM</td>
<td>r.t.</td>
<td>15</td>
<td>0.012</td>
<td>28%</td>
</tr>
<tr>
<td>n-ButSMe</td>
<td>1,2-DCE</td>
<td>84</td>
<td>15</td>
<td>0.2</td>
<td>26%</td>
</tr>
<tr>
<td>n-ButSMe</td>
<td>1,2-DCE</td>
<td>84</td>
<td>4</td>
<td>0.02</td>
<td>70%</td>
</tr>
</tbody>
</table>

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. Nevertheless, upon switching to N-methylmorpholine N-oxide monohydrate (NMO-H₂O), 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. Thus, treatment of cobalt alkene 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, 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.
With the core of the target molecule established, the final requirement for completion of the synthesis was the installation of the \( \alpha \)-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 metaperiodate, which formed the sulfoxide derivative in situ, was followed by thermally-promoted elimination to deliver the target \( \alpha \)-methylene propellanone 3 in 67% yield.

### 3. Conclusion

In conclusion, \( \alpha \)-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 propellan 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 \( \mathrm{N}_2 \) 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 spectrometer. \( ^1 \mathrm{H} \) and \( ^{13} \mathrm{C} \) 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 \( ^1 \mathrm{J}_{\mathrm{HH}} \) couplings, unless otherwise stated, and are reported in Hz. High-resolution mass spectra were recorded on a Finnigan MAT 90XL instrument at the EPSRC Mass Spectrometry facility at the University of Wales, Swansea.

#### 4.2. 5-Trimethylsilylpent-4-yn-1-ol 11

\( \text{n-Butyllithium} \) (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 \(-78 \, ^\circ\mathrm{C} \). 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 \( \mathrm{M} \) 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 \( \times \) 50 mL), brine (2 \( \times \) 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, \( \mathrm{OH} \)), 2960, 2900, 2177 cm\(^{-1}\). \( ^1 \mathrm{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.79–3.75 (m, 2H, CH\(_2\)), 2.35 (t, J = 6.9 Hz, 2H, CH\(_3\)), 1.81–1.76 (m, 2H, CH\(_2\)).

#### 4.3. (5-Bromopent-1-ynyl)trimethylsilane 8

Bromine (3.35 mL, 65.4 mmol) was added over 10 min to a solution of Ph\(_3\)P (17.2 g, 65.5 mmol) in DCM (120 mL) to give a white precipitate. The reaction mixture was then cooled to \(-5 \, ^\circ\mathrm{C} \) 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 \( \times \) 100 mL) and brine (2 \( \times \) 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 afforded 8 (10.2 g, 67% over 2 steps) as a colourless oil. IR (thin film): 2960, 2900, 2177 cm\(^{-1}\); \( ^1 \mathrm{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.52 (t, J = 6.5 Hz, 2H, CH\(_3\)Br), 2.35 (t, J = 6.8 Hz, 2H, CH\(_2\)), 2.09–2.04 (m, 2H, CH\(_2\)).

#### 4.4. 4-Hydroxy-N-methoxy-N-methylbutanamide 12

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 \(-78 \, ^\circ\mathrm{C} \). The solution was warmed to room temperature and stirred for 4 h. The solution was then cooled to \(-5 \, ^\circ\mathrm{C} \) and \( N,\gamma \)-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
4. 4-((1,Dimethylthyl)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 4-((1,1-dimethylthyl)dimethylsilyl) 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 temperature. 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, 1762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.77—4.72 (m, 2H, olefinic CH), 3.64 (t, J = 6.5 Hz, 2H, OCH₂), 2.20 (dt, J = 7.2 Hz, 2H, CH₂), 1.81 (s, 1H, Si(CH₃)₂), 0.90 (s, 9H, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 147.4, 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⁺): C₁₀H₁₉O₂Si (M⁺H) requires 239.2539; found 239.2544.

4.8. 4-Methylenenon-8-yn-1-ol 14

Tetraethydron-butyrammonium fluoride (0.6 mL, 0.6 mmol, 1 M in THF) was added over 10 min to a solution of 9-((1,1-dimethylthyl)dimethylsilyloxy)-6-methylene-1-trimethylsilylvinyl-1-none (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 (br s, OH), 2940, 2877, 1653 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.81—4.80 (m, 2H, olefinic CH₂), 3.43 (t, J = 6.7 Hz, 2H, CH₂Br), 2.21 (dt, J = 7.1 Hz, 3J = 2.6 Hz, 2H, CH₂), 1.84—1.79 (m, 4H, 2 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 148.7, 109.7, 107.5, 84.9, 63.0, 35.3, 32.4, 30.9, 26.7, 18.1; HRMS (ES⁺): C₁₀H₁₇OBr (M⁺) requires 153.1279; found 153.1281.

4.9. 9-Bromo-6-methylene-1-yn-6-one 6

Carbon tetrabromide (2.72 g, 8.20 mmol) was added to a solution of 4-methylene-8-yn-1-ol 14 (0.099 g, 0.65 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, CDCl₃) δ 4.81—4.80 (m, 2H, olefinic CH₂), 3.43 (t, J = 6.7 Hz, 2H, CH₂Br), 2.21 (dt, J = 7.1 Hz, 3J = 2.6 Hz, 2H, CH₂), 1.84—1.79 (m, 4H, 2 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 148.4, 110.1, 84.5, 68.7, 62.7, 35.0, 32.4, 30.9, 26.7, 18.1; HRMS (ES⁺): C₁₀H₁₇OBr (M⁺) requires 153.1279; found 153.1281.
4.10. Hexacarbonyl[μ-(1,2-η,1,2-η)-9-bromo-6-methylene-1-ynyl]dicobalt 15

A solution of 9-bromo-6-methylene-1-ynol 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 (CHCl₃): 2111, 2060, 2015 cm⁻¹; H NMR (400 MHz, CDCl₃) δ 6.0 (t, J = 1.1 Hz, 1H, alkyn CH), 4.85 (s, 2H, olefinic CH₂), 3.43 (t, J = 6.7 Hz, 2H, CH₂Br), 2.78 (dt, J = 17.9 Hz, J = 1.0 Hz, 2H, CH₂), 2.21—2.00 (m, 4H, 2 × CH₂), 2.05—1.98 (m, 2H, CH₂), 1.82—1.75 (m, 2H, CH₂); ¹³C NMR (100 MHz, CDCl₃) 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(3H)-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-methylene-1-ynyl]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-methylene-1-ynyl]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-methylene-1-ynyl]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-methylene-1-ynyl]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; H NMR (400 MHz, CDCl₃) δ 5.85 (t, J = 1.1 Hz, 1H, olefinic CH), 3.41—3.32 (m, 2H, CH₂Br), 2.65—2.55 (m, 2H, CH₂), 2.41 (d, J = 17.6 Hz, 1H, CH), 2.18 (d, J = 17.6 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), 1.70—1.60 (m, 2H, 2 × CH), 1.50—1.35 (m, 2H, 2 × CH); ¹³C NMR (100 MHz, CDCl₃) 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⁺): C₁₇H₁₆BrO (M⁺+H⁺) requires 243.0384; found 243.0390.

4.12. Tricyclo[3.3.3.0¹5]dodecan-3-one 4₁²

(a) Using 2.5 eq. of Sm₂

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(3H)-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. Sm₂

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(3H)-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/ether) to afford cyclopentanone 4 (0.012 g, 70%) as a white solid.

(c) Using 5.5 eq. Sm₂

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(3H)-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 (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/ether) 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; H NMR (400 MHz, CDCl₃) δ 2.29 (s, 4H), 1.69—1.58 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 219.6, 56.1, 53.1, 41.9, 25.2.
4.13. 3-(Trimethylsilyloxy)tricyclo[3.3.3.0²⁸]jundec-2-ene 16

Following the procedure of Kakiuchi et al., 3\textsuperscript{a} n-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexanes) was added to a solution of i-Pr₂NH (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\(_3\)) \(\delta\) 4.14 (t, \(J = 1.8\) Hz, 1H, olefinic CH), 2.29 (d, \(J = 1.9\) Hz, 2H, CH\(_2\)), 1.56—1.49 (m, 12H), 0.20 (s, 9H, Si(CH\(_3\))\(_3\)) \(\delta\) 151.7, 112.6, 64.7, 57.3, 50.1, 42.4, 40.9, 26.1, 0.6.

4.14. 2-(Phenylthiomethyl)tricyclo[3.3.3.0²⁸]jundecan-3-one 17

Following the procedure of Kakiuchi et al., 3\textsuperscript{a} 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, 0.166 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 afford 2-(phenylthiomethyl)tricyclo[3.3.3.0²⁸]jundecan-3-one 17 (0.025 g, 83%) as a colourless oil, which was used immediately in the next step. IR (thin film): 2946, 2857, 1740 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.00 (m, 2H, ArH), 6.93—2.25 (m, 1H, CHSPh), 2.78 (dd, \(J = 13.1\) Hz, \(J = 9.7\) Hz, 1H, CHSPh), 1.97 (d, \(J = 17.0\) Hz, 1H, CH), 1.80 (d, \(J = 17.0\) Hz, 1H, CH), 1.45—0.9 (m, 12H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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\(^{±}\)): \(C_{20}H_{22}O\) (M\(^{+}\)+H\(^{+}\)) requires 287.1469; found 287.1471.

4.15. 2-Methylenetricyclo[3.3.3.0²⁸]jundecan-3-one 3\textsuperscript{b}

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 \(\times\) 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 \(\alpha\)-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\(_3\)) \(\delta\) 5.96 (s, \(J = 0.6\) Hz, 1H, olefinic CH), 5.28 (d, \(J = 0.7\) Hz, 1H, olefinic CH), 2.44 (s, 2H, CH\(_2\)), 1.86—1.51 (m, 12H).

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References and notes


