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Keywords
alder, diels, via, methylenecyclopentenones, stereoselective, synthesis, protocol, retro, CMMB

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Stereoselective synthesis of $\alpha$-methylenecyclopentenones via a Diels-Alder/retro-Diels-Alder Protocol

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Abstract

A new procedure for the stereoselective synthesis of cross-conjugated dienones is reported. This method makes use of the Diels-Alder adduct of anthracene and dimethyl fumarate, a precursor to a spirocyclopent-2-enone anthracene adduct as the key intermediate. The addition of propyllithium or octyllithium to the key intermediate followed by a retro-Diels-Alder reaction furnished $\alpha$-methylenecyclopentenones bearing a $\gamma$-propyl or $\gamma$-octyl side chain, respectively, in moderate yields and as single geometric isomers.

Keywords: Stereoselective synthesis, $\alpha$-methylenecyclopentenones, Diels-Alder/retro-Diels-Alder, anthracene

1. Introduction

Cyclopentenones are important precursors in the synthesis of a large number of bioactive natural products such as the prostanoids, including, clavulone I and clavulone II,$^1$ marine natural products exhibiting strong cytotoxicity, and TEI-9826,$^2$ an antitumour agent in preclinical trials. Many strategies have been developed to synthesise this class of compounds including the Nazarov cyclisation,$^3$ the Pauson-Khand reaction,$^4$ metal-catalysed cyclisations,$^5$ and Diels-Alder/retro-Diels-Alder reactions using anthracene.$^6$ Among these, the synthesis of the cyclopentenone ring system, particularly with control of relative and absolute stereochemistry, is highly desirable. There have been a number of reports on the use of 9-substituted chiral anthracene templates to generate enantiomerically pure building blocks.
with highly diastereo- and regioselective reactions.\textsuperscript{7-9} However, a drawback of this strategy remains the preparation of the chiral auxiliary via asymmetric synthesis.\textsuperscript{10} Thus, we were interested in Thebtaranonth’s anthracene template-Diels-Alder/reto-Diels-Alder protocol\textsuperscript{6} to prepare $\alpha$-methylene cyclopentenones in a diastereoselective fashion. Herein, we report a stereoselective synthesis of two $\alpha$-methylene cyclopentenones A ($R$ = propyl or octyl) via a spiro-cyclopent-2-enone anthracene template B using a retro-Diels-Alder reaction as the final step (Scheme 1).

![Figure 1. Structure of cross-conjugated dienone prostanooids](image)

**Figure 1.** Structure of cross-conjugated dienone prostanooids

![Scheme 1](image)

**Scheme 1** Retrosynthetic analysis of $\alpha$-methylene cyclopentenone A

### 2. Results and discussion

To investigate our proposed synthesis the known dimethyl fumarate-anthracene adduct 3a was prepared by a Diels-Alder reaction of anthracene and dimethyl fumarate which gave racemic trans-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethyl ester (3a) in 78% yield
(Scheme 2). The cis-isomer of 3a was also detected as a minor component in large scale reactions. The structure of the trans-isomer was confirmed based on a comparison of its spectroscopic data with those in the literature. Reduction of the adduct 3a using LiAlH₄ led to the diol 4 in quantitative yield. The diol 4 was converted to its monoacetate 5 and the unprotected hydroxyl group was oxidized to the carboxylic acid 6 in 91% yield (Scheme 2). Treatment of 6 under esterification conditions with methanol in the present of H₂SO₄ gave the hydroxy-methyl ester 7a. Re-protection the hydroxyl group of this compound by treatment with tert-butyldimethylsilylchloride/imidazole gave the silyl ether 7b in 89% from 6 (Scheme 2). An alternative route to 7b was alkaline hydrolysis of 3a with KOH/MeOH to afford the monoacid 3b in 46% yield. Reduction of 3b with NaBH₄/I₂ gave alcohol 7a, however, in low yield (15%) together with various unidentified products. This was probably due to reduction of both the carboxylic acid and ester groups. Protection of the hydroxyl group in 7a with tert-butyldimethylsilyltriflate/2,6-lutidine provided silyl ether 7b in 96% yield (Scheme 2).
Scheme 2. Synthetic route to methyl ester adduct 7b: (i) Xylene, 160 °C, overnight (ii) LiAlH₄, THF, 0 °C (iii) Ac₂O, pyridine, rt (iv) CrO₃ in H₂O, H₂SO₄, 0 °C (v) H₂SO₄, MeOH, rt (vi) TBDMSOTf, 2,6-lutidine, rt, 96% from 6 or TBDMSOTf, 2,6-lutidine, rt, 96% from 3b (vii) KOH, MeOH (viii) NaBH₄, I₂, rt.
To complete the cyclopentenone synthesis, allylation of the methyl ester 7b was undertaken by treatment with LDA/allyl bromide in THF at −78 °C which afforded the allyl-methyl ester 8a in 84% yield (dr 11:1). The annulation reaction of 8a, involving the intramolecular acylation of the allylic anion generated using LDA/TMEDA, affored the spiro-cyclopentenone anthracene adduct 9a in 37% yield together with the β-enaminone 10a in 14% yield (Scheme 3). Attempts to increase the yield of 9a by using an excess of LDA were unsuccessful, often resulting in formation of the β-enaminone 10a and starting material 8a.

The structure of spiro-ketone 9a was confirmed by NMR spectroscopic analysis and from a comparison of its spectroscopic data with those of the previously prepared 9b (Scheme 3). The structure of the β-enaminone 10a was supported by its NMR data which indicated the absence of methoxy protons and the presence of one N-isopropyl group, which was characterized by the nonequivalent methyl groups (1.17 and 1.18 ppm, each a doublet with $J = 6.3$ Hz) which showed vicinal coupling to the methine proton at $\delta$ 3.60. In addition, the $^1$H NMR spectrum showed a 3H singlet at $\delta$ 1.89 for the vinyl methyl group and a 1H singlet resonance at $\delta$ 5.06 for the vinyl proton (COCH=CH(NH$_2$)Pr).

![Scheme 3](image_url)

**Scheme 3.** (i) Allyl bromide, LDA, THF, HMPA, −78 °C, 84% (ii) LDA, TMEDA, −78 °C.
Such enaminones have been previously observed as by-products upon treatment of esters with an excess amount of LDA at 0 °C.\textsuperscript{15-17} This has been shown to be a result of the formation of the corresponding \(N\)-isopropyl ketimine (\(\text{Me}_2\text{C}=\text{N}^\text{Pr}\)) from the \textit{in situ} oxidation of LDA. This ketimine is subsequently deprotonated by the excess of LDA to generate the corresponding aza-enolate which can attack the carbonyl group of the ester to provide an enaminone product. In contrast, treatment of the allyl-methyl ester 8\(b\) under similar conditions afforded the cyclopentenone 9\(b\) as a single product in good yield.\textsuperscript{14} These differences in yields of spiro-cyclopentenone products might be a result of the steric crowding caused by the \(\text{CH}_2\text{OTBS}\) group in 8\(a\) which may inhibit formation of 9\(a\), and thus enhance the formation of the \(N\)-isopropyl ketimine, by slowing down the rate of allylic deprotonation of 8\(a\) by the LDA.

Transformation of ketone 9\(a\) to the \(\gamma\)-hydroxyenone 11 was readily achieved by epoxidation followed by base-catalysed ring opening using \(\text{Et}_3\text{N}\) to afford 11 in 95% yield (dr 2.3:1) after purification by flash column chromatography (15:1 system of hexane/\(\text{EtOAc}\)). The diastereomers were separated by flash column chromatography (20:1 system of hexane/\(\text{EtOAc}\)) and the major diastereomer 11\(a\) was confirmed by an NOESY experiment which revealed the correlation between H-2\('\) and the \(\text{CH}_2\text{OSMDBT}\). This indicated that the major diastereomer arose from preferential epoxidation on the less hindered side of the alkene. The 1,2-addition reactions of the diastereomeric mixture 11 with propyllithium or octyllithium gave the corresponding diols 12\(a\) and 12\(b\) as the major diastereomers in yields of 34% and 30%, respectively together with several unidentified products. Unfortunately the relative configurations of these major diastereomers could not be established by NMR experiments. The structure of 13\(a\) was confirmed unequivocally by single-crystal X-ray crystallography (Figure 2) after oxidation of 12\(a\) with PDC (Scheme 4). The analysis of 13\(a\) by single crystal X-ray crystallographic data (Figure 2) are (\(\text{C}_{30}\text{H}_{38}\text{O}_3\text{Si}\cdot\text{H}_2\text{O}\)), \(M_r\) 492.73. Triclinic, \(P \bar{1}\), \(a = 9.3804\) (2) Å, \(b = 11.5664\) (3) Å, \(c = 13.9475\) (4) Å, \(\alpha = 82.5505\) (11)°, \(\beta = 84.4853\) (14)°, \(\gamma = 66.8558\) (14)°, \(V = 1378.04\) (6) Å\(^3\), \(Z = 2\), \(F(000) = 532\), \(D_c = 1.187\) Mg m\(^{-3}\), \(\mu = 0.12\) mm\(^{-1}\), \(T = 200\) K, specimen = 0.54×0.26×0.12 (colorless, block). 29223 reflections were measured. Final \(R\left(\sigma(F^2)>2\sigma(F^2)\right) = 0.042\), \(wR(F^2) = 0.108\), \(S = 0.97\). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 935128. The crystal structure revealed that the propyl group in 12\(a\) had been added from the more hindered face of the ketone carbonyl group of 11.
Upon heating of solutions of \( 13a \) and \( 13b \) in 1,2-dichlorobenzene at 180 °C they underwent a retro-Diels Alder reaction\(^9 \) to afford the highly functionalized cyclopentenones \( 14a \) and \( 14b \), respectively in poor yields (8-11%) and as single geometric isomers. While NMR experiments could not confirm the configuration of the exocyclic double bond in \( 14a \) or \( 14b \), the geometry shown for these compounds in Scheme 4 is that expected based on the established relative configuration of the starting compounds \( 13a \) and \( 13b \).

\[
\begin{align*}
9a \\
i-ii & \quad 95\%, \text{ in 2 steps} \\
\begin{array}{c}
\text{TBDMOSO} \\
\text{HO} \\
\text{11 (dr 2.3:1)} \\
\end{array}& \quad \begin{array}{c}
\text{TBDMOSO} \\
\text{OH} \\
\text{11a } \text{ as major diastereomer} \\
\text{11b } \text{ as minor diastereomer} \\
\end{array} \\
\begin{array}{c}
\text{H} \\
\text{2'} \\
\end{array}& \quad \begin{array}{c}
\text{HO} \\
\text{rac-12a, n = 1 (34\%)} \\
\text{rac-12b, n = 6 (30\%)} \\
\end{array} \\
\begin{array}{c}
\text{OTBDMS} \\
\text{OH} \\
\text{rac-14a, n = 1 (11\%)} \\
\text{rac-14b, n = 6 (8\%)} \\
\end{array} & \quad \begin{array}{c}
\text{TBDMOSO} \\
\text{OH} \\
\text{rac-13a, n = 1 (81\%)} \\
\text{rac-13b, n = 6 (75\%)} \\
\end{array}
\end{align*}
\]

\textbf{Scheme 4.} (i) mCPBA, CH\(_2\)Cl\(_2\) (ii) Et\(_3\)N, THF (iii) alkyl lithium, THF (iv) PDC, DMF, 0 °C (v) 1,2-dichlorobenzene, 180 °C in sealed tube.
3. Conclusions

In summary, we have developed a procedure which allows for the stereoselective synthesis of 4,4,5-trisubstituted cyclopent-2-enones bearing a α-methylene side chain via a Diels-Alder/retro-Diels-Alder process starting from anthracene. This methodology may in the future provide an efficient route for the synthesis of prostanoid natural products without having to overcome stereoselectivity issues.

4. Experimental

4.1 General

Melting points were determined on a Stuart Scientific SMP 2 melting point apparatus and are uncorrected. Infrared spectra were recorded as CH₂Cl₂-films with a Perkin Elmer Spectrum GX FT-IR spectrophotometer. ¹H- and ¹³C-NMR spectra were recorded in (D) chloroform solutions at 300 MHz for ¹H and 75 MHz for ¹³C with a Bruker AVANCE 300 spectrometer. Tetramethylsilane was used as the internal standard. Mass spectra were recorded on a POLARIS Q or HEWLETT PACKARD 5973 mass spectrometer.

4.2. 9,10-Dihydro-9,10-ethanoanthracene-11,12-dimethyl ester (3a)

A mixture of anthracene (2.00 g, 11.2 mmol), dimethyl fumarate (2.05 g, 14.2 mmol) and xylene (15 mL) in a pressured tube with boiling chips was heated at 130 °C for 24 h. The reaction mixture was cooled to rt and the xylene was then removed under vacuo. The crude
product was purified using column chromatography (silica gel, 30:1 hexane/EtOAc) to afford the adduct 3 (2.82 g, 78%) as a white solid, m.p. 103-105 °C (lit.\textsuperscript{11} 107-108 °C); IR (CH\textsubscript{2}Cl\textsubscript{2}) \textit{\nu}_{max}: 1732, 1459, 1435, 1221, 1198, 1018, 760 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 7.28-7.31 (m, 2H), 7.22-7.25 (m, 2H), 7.07-7.14 (m, 4H), 4.73 (s, 2H), 3.62 (s, 6H), 3.42 (s, 2H); \textsuperscript{13}C NMR \delta 172.8, 142.0, 140.3, 126.4, 126.3, 124.6, 123.8, 52.2, 47.8, 46.7.

4.3 11-Carboxylic acid-9,10-dihydro-9,10-ethanoanthracene-12-methyl ester (3b)
Dimethyl ester 3a (0.10 g, 0.31 mmol) was added to a solution of THF (2.6 mL), MeOH (0.50 mL) and water (0.40 mL). 1 M KOH (0.37 mL, 0.37 mmol) was added and the mixture was stirred at rt for 50 min. The reaction was then cooled to 0 °C and quenched with 1M HCl (1 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The mixture was purified by flash column chromatography (silica gel, 4:1 hexane/EtOAc) to give monoacid 3b (88 mg, 46%) as a white solid; m.p. 199-201 °C (lit.\textsuperscript{3} 202 °C); IR (CH\textsubscript{2}Cl\textsubscript{2}) \textit{\nu}_{max}: 3444, 1737, 1704, 1434, 1267, 1208, 740 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 7.31 (m, 2H), 7.24 (m, 2H), 7.10 (m, 4H), 4.70 (d, \textit{J} = 2.0, 2H), 3.62 (s, 3H), 3.41 (dd, \textit{J} = 2.6, 5.0 Hz, 1H), 3.32 (dd, \textit{J} = 2.6, 5.0 Hz, 1H). \textsuperscript{13}C NMR \delta 176.8, 172.2, 142.0, 141.9, 140.1, 140.0, 126.5, 126.5, 126.4, 126.4, 125.0, 124.6, 123.7, 52.3, 47.8, 47.7, 46.6, 46.4.; HRESI-MS \textit{m/z} cald for [M+Na]\textsuperscript{+}C\textsubscript{19}H\textsubscript{16}NaO\textsubscript{4}: 331.0946, found: 331.0952.

4.4 9,10-Dihydro-9,10-ethanoanthracene-11,12-dimethyl alcohol (4)
To a solution of 3a (2.75 g, 8.54 mmol) in THF (60 mL) at 0 °C was slowly added lithium aluminium hydride (1.94 g, 51.2 mmol). The mixture was stirred at 0 °C under argon atmosphere for 30 min. The reaction mixture was quenched with sat. NaHCO\textsubscript{3} solution and extracted with Et\textsubscript{2}O (3 × 30 mL). The combined organic phase was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated under reduced pressure to give the diol 4 (2.15 g, 98%) as a white solid; m.p. 196-198 °C; IR (CH\textsubscript{2}Cl\textsubscript{2}) \textit{\nu}_{max}: 3442, 3054, 2987, 1422, 1022 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 7.38–7.35 (m, 4H), 7.18-7.15 (m, 4H), 4.44 (s, 2H), 3.22-3.17 (m, 1H), 2.89-2.81 (m, 1H), 1.38-1.33 (m, 2H); \textsuperscript{13}C NMR \delta 144.5, 141.7, 126.1, 125.8, 123.4, 64.5, 45.9, 45.3; HRESI-MS \textit{m/z} cald for [M+Na]\textsuperscript{+}C\textsubscript{18}H\textsubscript{18}NaO\textsubscript{2}: 289.1193, found: 289.1182.

4.5 11-Acetoxy-9,10-dihydro-9,10-ethanoanthracene-12-methanol (5)
To a solution of the diol 4 (5.80 g, 21.8 mmol) in pyridine (2.11 mL, 26.2 mmol) at rt was added acetic anhydride (2.06 mL, 21.8 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was quenched with water and extracted with CH₂Cl₂ (2 × 20 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 3:1 hexane/EtOAc) to give the mono-acetate 5 (3.48 g, 52%) as a white solid; m.p. 89-91 °C; IR (CH₂Cl₂) νmax: 3451, 3054, 2987, 1736, 1422, 1025 cm⁻¹; ¹H NMR δ 7.27-7.23 (m, 4H), 7.11-7.07 (m, 4H), 4.32 (d, J = 1.8 Hz, 1H), 4.21 (d, J = 1.8 Hz, 1H), 3.81 (dd, J = 10.6, 5.8 Hz, 1H), 3.51 (dd, J = 10.4, 8.7 Hz, 1H), 3.27 (dd, J = 10.6, 5.8 Hz, 1H), 3.06 (dd, J = 10.4, 8.7 Hz, 1H), 2.48 (br. s, 1H), 2.03 (s, 3H), 1.66-1.52 (m, 2H); ¹³C NMR δ 171.2, 143.5, 143.1, 140.7, 140.4, 126.3, 126.2, 125.9, 125.8, 125.5, 125.4, 123.5 (2×C), 67.1, 65.5, 45.9, 45.7, 45.5, 42.2, 21.0; HRESI-MS m/z cald for [M+Na]⁺ C₂₀H₂₀NaO₃: 331.1310, found: 331.1306.

4.6 11-Acetoxy-9,10-dihydro-9,10-ethanoanthracene-12-acetic acid (6)

A solution of the alcohol 5 (0.22 g, 0.71 mmol) in acetone (6 mL) was treated with Jones reagent(18)(4 mL) at 0 °C until TLC analysis showed the reaction was complete (ca. 1h). Isopropanol (0.6 mL) was added slowly dropwise to destroy excess reagent and the mixture was stirred for another 5-10 min until the colour of the solution changed from red to green. CH₂Cl₂ (20 mL) and water (20 mL) were added. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL) and then dried (Na₂SO₄), filtered and evaporated in vacuo to give compound 6 (0.21g, 91%) as a yellow oil; IR (CH₂Cl₂) νmax: 3436, 2987, 1737, 1708, 1036 cm⁻¹; ¹H NMR δ 7.35-7.28 (m, 4H), 7.18-7.12 (m, 4H), 4.68 (d, J = 2.1 Hz, 1H), 4.33 (d, J = 2.1 Hz, 1H), 3.89-3.84 (m, 1H), 3.77-3.70 (m, 1H), 2.73-2.65 (m, 1H), 2.42 (dd, J = 5.6, 2.3 Hz, 1H), 2.60 (s, 3H); ¹³C NMR δ 178.1, 171.0, 143.3, 141.9, 140.2, 139.9, 126.4 (3×C), 126.1, 125.5, 125.3, 123.6, 123.5, 66.7, 48.2, 46.3, 45.9, 41.7, 20.9; HRESI-MS m/z cald for [M+Na]⁺ C₂₀H₁₈NaO₄: 345.1103, found: 345.1089.

4.7 9,10-Dihydro-9,10-ethanoanthracene-11-methanol-12-methyl ester (7a)

Method A

To a suspension of NaBH₄ (0.12 g, 3.24 mmol) in THF (3.5 mL) was slowly added a solution of the monoacid 3b (0.50 g, 1.62 mmol) in THF (5 mL) at rt. The mixture was stirred until the evolution of gas ceased. A solution of iodine (0.36 g, 1.41 mmol) in THF (3 mL) was then
added slowly (5 min) at rt and the mixture was stirred for a further 1 h. 3 M HCl (5 mL) was then added carefully and the mixture was extracted with ether. The organic extract was washed with 3 M NaOH (3 × 10 mL) and brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure to give alcohol 7a (69 mg, 15%) as a yellow oil.

Method B
To a solution of 6 (2.34 g, 7.27 mmol) in methanol (14 mL) was added dropwise conc. H₂SO₄ (1 mL). The mixture was stirred at rt for 12 h. The reaction mixture was quenched with water and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated to give 7a (1.82 g, 85%) as a yellow oil.

7a; IR (CH₂Cl₂) ν max: 3443, 2987, 1733, 1422, 1023 cm⁻¹; ¹H NMR δ 9.20 (br. s, 1H), 7.32-7.23 (m, 4H), 7.11-7.05 (m, 4H), 4.62 (d, J = 2.1 Hz, 1H), 4.31 (d, J = 2.1 Hz, 1H), 3.27 (s, 3H) 3.09-2.96 (m, 2H), 2.58-2.50 (m, 1H), 2.22 (dd, J = 5.7, 2.1 Hz, 1H); ¹³C NMR δ 177.2, 143.6, 142.4, 140.7, 140.2, 126.3, 126.28, 126.25, 126.0, 125.6, 125.5, 123.5, 123.4, 75.8, 58.9, 48.7, 46.1, 45.6, 42.7; HRESI-MS m/z cald for [M+Na]⁺ C₁₉H₁₈NaO₃: 317.1154, found: 317.1148.

4.8 11-((tert-Butyl-dimethyl-silanyloxy)methyl)-9,10-dihydro-9,10-ethanoanthracene-12-methyl ester (7b)

Method A
To a solution of alcohol 7a (1.23 g, 4.18 mmol) in dry CH₂Cl₂ (20 mL) under an argon atmosphere was added 2,6-lutidine (0.62 mL, 5.44 mmol) followed by TBDMSOTf (1.15 mL, 5.02 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was quenched with sat. NaHCO₃ solution and then extracted with CH₂Cl₂ (2 × 30 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated. Purification by flash column chromatography (silica gel, 30:1 hexane/ EtOAc) gave TBDMS ether 7b (1.64 g, 96%) as a white solid.

Method B
To a solution of alcohol 7a (1.50 g, 5.09 mmol) in dry CH₂Cl₂ (43 mL) under an argon atmosphere was added imidazole (0.66 g, 10.2 mmol) followed by TBDMSCl (0.88 g, 5.61 mmol). The mixture was stirred at rt for 15 h. The reaction mixture was quenched with sat. NaHCO₃ solution and then extracted with CH₂Cl₂ (2 × 30 mL). The combined extracts were
dried (Na₂SO₄), filtered and concentrated. Purification by flash column chromatography (silica gel, 30:1 hexane/ EtOAc) gave TBDMS ether 7b (1.68 g, 81%) as a white solid, m.p. 81.7-84.8 °C; IR (CH₂Cl₂) ν_max: 3445, 2953, 1737, 1470, 1253, 1213, 1094, 837, 746 cm⁻¹, ¹H NMR δ 7.29-7.25 (m, 4H), 7.12-7.06 (m, 4H), 4.59 (d, J = 2.2 Hz, 1H), 4.43 (d, J = 2.2 Hz, 1H), 3.60 (s, 3H), 3.45 (d, J = 9.7, 5.6 Hz, 1H), 2.95 (t, J = 9.7 Hz, 1H), 2.51-2.47 (m, 1H), 2.14 (dd, J = 5.6, 2.2 Hz, 1H), 0.91 (s, 9H), 0.0033 (s, 6H); ¹³C NMR δ 173.5, 144.1, 142.6, 141.1, 140.8, 126.4, 126.2 (2×C), 125.9, 125.8, 125.1, 123.6, 123.5, 65.7, 61.9, 48.0, 46.9, 45.7, 45.6, 26.1; HRESI-MS m/z cald for [M+Na]+ C₂₅H₃₂NaO₃Si: 431.2018, found: 431.2049.

4.9 11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydro-9,10-ethanoanthracene-12-(2-propenyl)-12-methyl ester (8a)

Butyllithium (2.79 mL, 2.79 mmol, 1.0 M in hexane) was added dropwise to a stirred solution of diisopropylamine (0.47 mL, 3.35 mmol) in THF (4 mL) at −78 °C, and the mixture was then stirred at 0 °C for 1 h. HMPA (0.61 mL) was then added at −78 °C, followed by a solution of 7b (0.95 g, 2.33 mmol) in THF (4 mL) and stirring was continued for 3 h at 0 °C. The solution was cooled to −78 °C and allylbromide (0.303 ml, 3.50 mmol) was added to the reaction mixture which was left stirring at 0 °C for 30 min. The mixture was stirred at rt for 15 h. The resulting mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with CH₂Cl₂ (3 × 15 mL). The combined extracts were washed with water (30 mL) and saturated NaCl solution (30 mL). The combined organic layer was washed (Na₂SO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 40:1 hexane/ EtOAc) gave allyl adduct 8a (0.88 g, 84%) as a white solid, m.p. 85.1-88.5 °C; IR (CH₂Cl₂) ν_max: 2952, 1737, 1470, 1211, 1213, 1094, 837, 746 cm⁻¹, ¹H NMR δ 7.32-7.29 (m, 2H), 7.26-7.25 (m, 1H), 7.22-7.20 (m, 1H), 7.12-7.09 (m, 2H), 7.06-7.04 (m, 2H), 5.80-5.72 (m, 1H), 5.10 (d, J = 10.1 Hz, 1H), 4.94 (d, J = 16.9 Hz, 1H), 4.56 (s, 1H), 4.51 (d, J = 1.9 Hz, 1H), 3.70 (dd, J = 9.6, 4.6 Hz 1H), 3.54 (s, 3H), 3.02 (t, J = 9.6 Hz, 1H), 2.51-2.48 (m, 1H), 2.09 (dd, J = 13.9, 6.7 Hz, 1H), 1.65 (dd, J = 13.9, 6.7 Hz, 1H), 0.96 (s, 9H), 0.074 (s, 3H), 0.057 (s, 3H); ¹³C NMR δ 180.8, 149.9, 146.6 (2×C), 146.3, 138.9, 131.2 (2×C), 131.1 (2×C), 130.7, 128.3, 123.5, 67.6, 59.1, 56.9, 55.2, 53.3, 50.8, 42.7, 31.2, -5.31; HRCI-MS m/z cald for [M+H]+ C₂₈H₃₇NaO₃Si: 449.2512, found: 449.2532.
4.10 Cyclization of 8a

Butyllithium (1.55 mL, 1.55 mmol, 1.0 M in hexane) was added dropwise to a stirred solution of diisopropylamine (0.25 mL, 1.76 mmol) in THF (2 mL) at \(-78\) °C, and stirring was continued at 0 °C for 1 h. TMEDA (0.86 mL) was added at \(-78\) °C, followed by allyl adduct 8a (0.23 g, 0.52 mmol) in THF (1.5 mL) and the mixture stirred at 0 °C for 30 min and then at rt for 18 h. The resulting mixture was quenched with an aqueous saturated NH₄Cl (20 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The combined extracts were washed with water (20 mL) and saturated NaCl solution (20 mL) and then dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 25:1 hexane/ EtOAc) gave 11-(tert-butyl-dimethyl-silanyloxy)methyl-9,10-dihydropyrido[9,10-ethanoanthracene-12,1'-cyclopent[2']ene]-5'-one 9a (0.10 g, 37%) as a white solid and 12-allyl-11-(tert-butyl-dimethyl-silanyloxy)methyl-9,10-dihydro-9,10-ethanoanthracen-12-yl)-3-isopropylamino)but-2-en-1-one 10a (15 mg, 14%) as a colorless oil.

9a: m.p. 117-119 °C; IR (CH₂Cl₂) \(\nu \text{max}: 2952, 1746, 1468, 1256, 1103, 1094, 837, 758 \text{ cm}^{-1}\); \(^1\)H NMR \(\delta 7.34 (d, J = 6.3 \text{ Hz, 2H}), 7.19-7.11 (m, 6H), 6.08 (d, J = 7.2 \text{ Hz, 1H}), 5.23 (d, J = 7.2 \text{ Hz, 1H}), 4.49 (s, 1H), 3.89 (s, 1H), 3.14 (q, J = 9.9, 6.0 Hz, 1H), 3.10 (d, J = 20.4 Hz, 1H), 2.98 (dd, J = 9.9, 9.6 Hz, 1H) , 2.80 (d, J = 22.8 Hz, 1H), 2.27 (td, J = 9.6, 6 Hz, 1H), 0.88 (s, 9H), -0.04 (s, 6H); \(^13\)C NMR \(\delta 199.0, 161.5, 142.4, 141.9, 134.9, 126.7, 125.6, 125.3, 125.2, 125.1, 125.0, 124.9, 122.5, 117.0, 63.8, 49.1, 48.5, 46.6, 44.6, 38.5, 25.9, -5.3; HRCl-MS m/z cald for [M+H]^+ C_{27}H_{33}O_2Si: 417.2250, found: 417.2240.

10a: \(^1\)H NMR \(\delta 10.41 (d, J = 8.4 \text{ Hz, 1H}), 7.37 (d, J = 7.2 \text{ Hz, 1H}), 7.27-7.22 (m, 2H), 7.16 (d, J = 8.1 \text{ Hz, 1H}), 7.08-7.05 (m, 2H), 7.02-6.98 (m, 2H), 5.85-5.71 (m, 1H), 5.06 (d, J = 5.6 Hz, 2H), 4.87 (d, J =16.8 Hz, 1H), 4.63 (s, 1H), 4.39 (s, 1H), 3.71 (dd, J = 9.8, 6.0 Hz, 1H), 3.60 (q, J = 6.3 Hz, 1H), 3.23 (t, J = 9.8 Hz, 1H), 2.48 (td, J = 7.2, 6.0 Hz, 1H), 2.17 (dd, J = 13.7, 5.4 Hz, 1H), 1.89 (s, 3H), 1.50 (dd, J = 13.7, 8.7 Hz, 1H), 1.18 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 0.96 (s, 9H), 0.093 (s, 3H), 0.064 (s, 3H); \(^13\)C NMR \(\delta 199.0, 161.6, 145.0, 142.7, 142.6, 142.0, 134.9, 126.7, 125.7, 125.4, 125.3, 125.1, 125.0, 124.9, 122.5, 117.0, 93.2, 63.8, 56.2, 49.1, 48.5, 48.2, 46.6, 44.6, 38.6, 26.0, 23.9, 23.7, 19.1, -5.57; HRCl-MS m/z cald for [M+H]^+ C_{33}H_{46}NO_2Si: 516.3298, found: 516.3328.

4.11 11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydropyrido[9,10-ethanoanthracene-12, 1'-cyclopent[3']ene]-2'-hydroxy-5'-one (11)
To a solution of the spiro ketone 9 (82 mg, 0.19 mmol) in dry CH₂Cl₂ (0.72 mL) was added a solution of m-chloroperoxybenzoic acid (74 mg, 0.43 mmol) in dry CH₂Cl₂ (1.1 mL) at 0 °C and the mixture stirred at rt for 10 h. The mixture was then washed with sat. NaHCO₃ solution at 0 °C and then water and dried (Na₂SO₄), filtered and concentrated to dryness to give the crude epoxide which was used in the next step without any further purification. To a solution of the crude epoxide (90 mg, 0.21 mmol) in dry THF (1.2 mL) was added triethylamine (0.0058 mL, 0.42 mmol) at 0 °C and the mixture was left to stir at rt overnight. The solution was washed with water at 0 °C, and brine then dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (15:1 system of hexane/EtOAc) gave the alcohol 11 (87 mg, 95%) as a mixture of 2 diastereomers (dr 2.3:1) as a white solid. The diastereomers were separated by flash column chromatography (20:1 system of hexane/EtOAc) to afford (1'S,2'R,11'S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12,1'-cyclopent[3']ene]-2'-hydroxy-5'-one (11a) as a major diastereomer; m.p. 115.2-118.5 °C; IR (CH₂Cl₂) νmax: 3417, 2953, 2929, 1711, 1469, 1256, 1173, 1094, 837, 760 cm⁻¹; ¹H NMR δ 7.58 (dd, J = 6.0, 2.1 Hz, 1H), 7.39-7.31 (m, 4H), 7.20-7.09 (m, 4H), 6.25 (d, J = 6.0 Hz, 1H), 4.93 (s, 1H), 4.35 (d, J = 2.7 Hz, 2H), 3.6-3.57 (m, 2H), 2.54 (td, J = 6.0, 2.4 Hz, 1H), 0.82 (s, 9H), 0.016 (s, 3H), -0.07 (s, 3H); ¹³C NMR δ 206.3, 160.8, 144.3, 143.5, 141.9, 141.7, 132.5, 126.15, 126.1, 125.9, 125.6, 125.5, 125.2, 125.1, 122.9, 81.3, 75.2, 65.2, 50.7, 48.5, 48.0, 25.8, -5.5, -5.7; HRESI-MS m/z cald for [M+Na⁺] C₂₇H₃₂NaO₃Si: 455.2018, found: 455.1974. (1'S,2'S,11'S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12, l'-cyclopent[3']ene]-2'-hydroxy-5'-one (11b) was obtained as a minor diastereomer; ¹H NMR δ 7.39-7.17 (m, 9H), 6.18 (d, J = 6.0 Hz, 1H), 4.63 (s, 1H), 4.27-4.24 (m, 2H), 3.83-3.73 (m, 2H), 2.59-2.56 (m, 2H), 0.96 (s, 9H), 0.023 (s, 6H).

4.12 (1'S,2'S,11'S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12,1'-cyclopent[3']ene]-2'-propyl-2',5'-diol (12a)

Propyllithium (1.59 mL, 0.64 mmol, 0.81 M in hexane) was added dropwise to a stirred solution of alcohol 11 (0.28 g, 0.64 mmol) in THF (8.3 mL) at −78 °C, then the mixture stirred at 0 °C for 2 h. The resulting reaction mixture was quenched with aqueous saturated NH₄Cl solution and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were washed with water (20 mL) and brine (20 mL) then dried (Na₂SO₄), filtered and concentrated in vacuo to give the crude mixture as a yellow solid. Purification of the mixture by flash column
chromatography (silica gel, 6:1 hexane/EtOAc) gave the major product **12a** (0.105 g, 34%) as a white solid, m.p. 143.3-146.0 °C; IR (CH₂Cl₂) νₘₐₓ: 3552, 3410, 2956, 1469, 1256, 1188, 837, 768 cm⁻¹; ¹H NMR δ 7.42-7.39 (m, 1H), 7.36-7.30 (m, 3H), 7.15-7.11 (m, 4H), 6.19 (d, J = 5.8 Hz, 1H), 6.07 (dd, J = 5.8, 2.8 Hz, 1H), 4.87 (s, 1H), 4.55 (d, J = 2.1 Hz, 1H), 3.33 (s, 1H), 3.22 (dd, J = 9.1, 3.2 Hz, 1H), 2.88 (t, J = 9.5 Hz, 1H), 1.95 (dd, J = 9.5, 2.5 Hz, 1H), 1.31-1.13 (m, 2H), 0.93-0.92 (m, 11H), 0.63 (t, J = 7.3 Hz, 3H), 0.02 (s, 3H), -0.03 (s, 3H); ¹³C NMR δ 144.7, 142.6, 142.1, 141.7, 135.8, 126.0, 125.7, 125.6, 125.56, 124.8, 123.5, 86.7, 77.4, 63.7, 58.9, 46.7, 46.4, 46.3, 35.5, 25.9, 17.5, 14.5, -5.19, -5.2; HRESI-MS m/z cald for [M+Na]⁺ C₃₀H₄₀NaO₃Si: 499.2644, found: 499.2632.

4.13 (1'S,2'S,11'S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12,1'-cyclopent[3']ene]-2'-octyl-2',5'-diol (12b)
Octyllithium (0.62 mL, 0.11 mmol, 0.1 M in hexane) was added dropwise to a stirred solution of alcohol **11** (40 mg, 0.090 mmol) in THF (0.5 mL) at −78 °C, and the mixture was stirred at 0 °C for 2 h. The resulting reaction mixture was quenched with aqueous saturated NH₄Cl and extracted with CH₂Cl₂ (3 × 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL) then dried (Na₂SO₄), filtered and concentrated in vacuo to give the crude mixture as a yellow solid. Purification of the mixture by flash column chromatography (silica gel, 20:1 hexane/EtOAc) gave the major product **12b** (15 mg, 30%) as a solid, m.p. 91.7-94.5 °C; IR (CH₂Cl₂) νₘₐₓ: 3423, 2927, 1469, 1254, 1088, 837, 759 cm⁻¹; ¹H NMR δ 7.44-7.28 (m, 4H), 7.17-7.11 (m, 4H), 6.20 (d, J = 5.8 Hz, 1H), 6.10 (dd, J = 5.8, 2.7 Hz, 1H), 4.88 (s, 1H), 4.57 (s, 1H), 3.35 (s, 1H), 3.25 (dd, J = 9.1, 3.0 Hz, 1H), 2.89 (t, J = 10 Hz, 1H), 1.99-1.95 (m, 1H), 1.33-1.13 (m, 10H), 0.95 (s, 13H), 0.92 (t, J = 6.6 Hz, 3H), 0.04 (s, 3H), -0.004 (s, 3H); ¹³C NMR δ 144.7, 142.6, 142.1, 141.7, 135.8, 126.0, 125.7, 125.6, 125.5, 125.2, 124.8, 123.5, 86.7, 77.5, 63.7, 58.9, 46.7, 46.32, 46.25, 33.0, 31.8, 29.9, 29.2, 25.9 (2×C), 24.0, 22.6, 14.1, -5.17, -5.2; HRESI-MS m/z cald for [M+Na]⁺ C₃₅H₄₀NaO₃Si: 569.3427, found: 569.3465.

4.14 (1'R,2'S,11'S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12,1'cyclopent[3']ene]-2'-hydroxy-2'-propyl-5'-one (13a)
To a solution of alcohol **12a** (0.11 mg, 0.22 mmol) in dry DMF (0.63 mL) was added a solution of pyridinium dichromate (0.16 g, 0.44 mmol) in dry DMF (0.64 mL) at 0 °C and the mixture was stirred at 0 °C for 10 h. The DMF was evaporated in vacuo and the residue was
partitioned between CH$_2$Cl$_2$ and water. The layers were separated and the organic layer washed with water (3 × 10 mL), dried (Na$_2$SO$_4$) and evaporated to dryness. The crude product was purified by column chromatography (silica gel; 6:1 hexane/ EtOAc) to give ketone 13a (85 mg, 81%) as a solid; m.p. 99.5-102.3; IR (CH$_2$Cl$_2$) $\tilde{\nu}$max: 3570, 3423, 2956, 2930, 1708, 1468, 1256, 1190, 836, 776, 735 cm$^{-1}$; $^1$H NMR $\delta$ 7.43 (d, $J = 6.0$ Hz, 1H), 7.33-7.24 (m, 4H), 7.06 (d, $J = 6.0$ Hz, 1H), 4.32 (d, $J = 3.5$ Hz, 2H), 3.56 (t, $J = 9.7$ Hz, 1H), 3.24 (dd, $J = 9.7$, 6.5 Hz, 1H), 2.42 (t, $J = 6.4$ Hz, 1H), 1.51-1.44 (m, 2H), 1.25-1.13 (m, 2H), 0.84 (s, 9H), 0.79 (t, $J = 7.0$ Hz, 3H), -0.08 (s, 6H); $^{13}$C NMR $\delta$ 204.8, 162.0, 146.4, 141.7, 141.4, 132.5, 126.0, 125.7, 125.9, 125.5, 125.6, 124.7, 84.3, 64.2, 63.1, 52.1, 48.3, 46.8, 44.1, 25.8, 17.2, 14.5, -5.4, -5.5; HRESI-MS m/z cald for [M+Na]$^+$ C$_{30}$H$_{38}$NaO$_3$Si: 497.2488, found: 497.2467.

4.15 (1'R,2'S,11S)-11-(tert-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthracene-12,1'-cyclopent[3']ene]-2'-octyl-5'-one (13b)

To a solution of the alcohol 12b (0.13 g, 0.12 mmol) in dry DMF (0.69 mL) was added a solution of pyridinium dichromate (0.18 g, 0.48 mmol) in dry DMF (0.7 mL) at 0 $^\circ$C and the mixture was stirred at 0 $^\circ$C for 10 h. The crude reaction mixture was worked up as described above for 13a. The crude product was purified by column chromatography (silica gel; 6:1 hexane/EtOAc) to give ketone 13b (99 mg, 75%) as a clear oil; IR (CH$_2$Cl$_2$) $\tilde{\nu}$max: 3425, 2927, 1710, 1467, 1255, 1090, 836, 776 cm$^{-1}$; $^1$H NMR $\delta$ 7.45 (d, $J = 5.9$ Hz, 1H), 7.36-7.28 (m, 4H), 7.16-7.12 (m, 4H), 6.10 (d, $J = 5.9$ Hz, 1H), 4.35 (d, $J = 4.9$ Hz, 2H), 3.57 (t, $J = 9.2$ Hz, 1H), 3.25 (dd, $J = 9.8$, 6.4 Hz, 1H), 2.45 (dd, $J = 7.4$, 6.2 Hz, 1H), 1.29-1.18 (m, 14H), 0.91-0.84 (m, 12H), 0.033 (s, 3H), 0.024 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 204.9, 162.2, 146.3, 141.9, 141.7, 141.4, 132.5, 126.1, 125.9, 125.8, 125.7, 125.6, 125.5, 124.7, 84.3, 64.2, 63.0, 51.9, 48.3, 46.7, 41.7, 31.8, 30.0, 29.4, 29.1, 25.9, 23.7, 22.6, 14.1, -5.39, -5.45; HRESI-MS m/z cald for [M+Na]$^+$ C$_{35}$H$_{48}$NaO$_3$Si: 567.3270, found: 567.3293.

4.16 (S,Z)-5-(tert-Butyl-dimethyl-silanyloxy)ethylidene)-4-hydroxy-4-propylcyclopent-2-enone (14a)

A solution of 13a (50 mg, 0.092 mmol) in dry 1,2-dichlorobenzene (1 mL) was stirred in a sealed tube at 180 $^\circ$C for 4 h. The crude product was purified by column chromatography (silica gel, hexane) and then thin layer chromatography (6:1 hexane/EtOAc) to give cyclopentenone 14a (2 mg, 11%) as a clear oil; IR (CH$_2$Cl$_2$) $\tilde{\nu}$max: 3417, 2930, 1703, 1656,
1255, 1099, 838, 777 cm\(^{-1}\); \(^{1}\)H NMR \(\delta\) 7.31 (d, \(J = 6.0\) Hz, 1H), 6.33-6.27 (m, 2H), 4.87 (qd, \(J = 17.3, 4.7\) Hz, 2H), 1.85-1.78 (m, 2H), 1.32-1.26 (m, 2H), 0.94-0.89 (m, 12H), 0.09 (s, 6H); \(^{13}\)C NMR \(\delta\) 195.9, 160.8, 140.4, 138.8, 135.5, 78.7, 60.3, 41.6, 25.9, 17.8, 14.3, -5.2, -5.3; HRESI-MS \(m/z\) cald for [M+Na\(^{+}\)] C\(_{16}\)H\(_{28}\)NaO\(_{3}\)Si: 319.1705, found: 319.1707.

4.17 \((S,Z)-5-((\text{tert-Butyl-dimethyl-silanyloxy})\text{ethylidene})-4\text{-hydroxy-4-octylcyclopent-2-enone}\) (14b)

A solution of 13b (0.10 g, 0.18 mmol) in dry 1,2-dichlorobenzene (1.2 mL) was stirred in sealed tube at 180 °C for 4 h. The crude product was purified by column chromatography (silica gel, hexane) and then thin layer chromatography (8:1 hexane/EtOAc) to give cyclopentenone 14b (5.4 mg, 8.1%) as a clear oil; IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\): 3444, 2928, 1704, 1658, 1464, 1256, 1100, 838, 778 cm\(^{-1}\); \(^{1}\)H NMR \(\delta\) 7.33 (d, \(J = 6.3\) Hz, 1H), 6.34-6.29 (m, 2H), 4.89 (qd, \(J = 16.7, 4.3\) Hz, 2H), 1.87-1.84 (m, 2H), 1.28 (s, 12H), 0.93-0.89 (m, 12H), 0.11 (s, 6H); \(^{13}\)C NMR \(\delta\) 195.8, 160.8, 140.5, 138.8, 135.6, 78.7, 60.3, 39.4, 31.8, 29.8, 29.7, 29.4, 29.2, 25.9, 24.4, 14.0, -5.2 (2×C); HRESI-MS \(m/z\) cald for [M+Na\(^{+}\)] C\(_{21}\)H\(_{38}\)NaO\(_{3}\)Si: 389.2488, found: 389.2484.

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References


Graphic Abstract

**Stereoselective synthesis of α-methylenecyclopentenones via a Diels-Alder/retro-Diels-Alder Protocol**

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