1-1-2013

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Keywords

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

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Phutdhawong, W., Eksinitkun, G., Pyne, S. G., Willis, A. C. & Phutdhawong, W. S. (2013). Stereoselective synthesis of α-methylenecyclopentenones via a Diels-Alder/retro-Diels-Alder protocol. Tetrahedron, 69 (44), 9270-9276.

Stereoselective synthesis of α-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 α-methylenecyclopentenones bearing a γ-propyl or γ-octyl side chain, respectively, in moderate yields and as single geometric isomers.

Keywords: Stereoselective synthesis, α-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.[7-9] However, a drawback of this strategy remains the preparation of the chiral auxiliary via asymmetric synthesis.[10] Thus, we were interested in Thebtaranonth's anthracene template-Diels-Alder/reto-Diels-Alder protocol[6] to prepare α-methylenecyclopentenones in a diastereoselective fashion. Herein, we report a stereoselective synthesis of two α-methylenecyclopentenones **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).

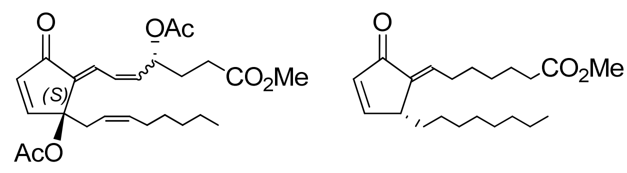
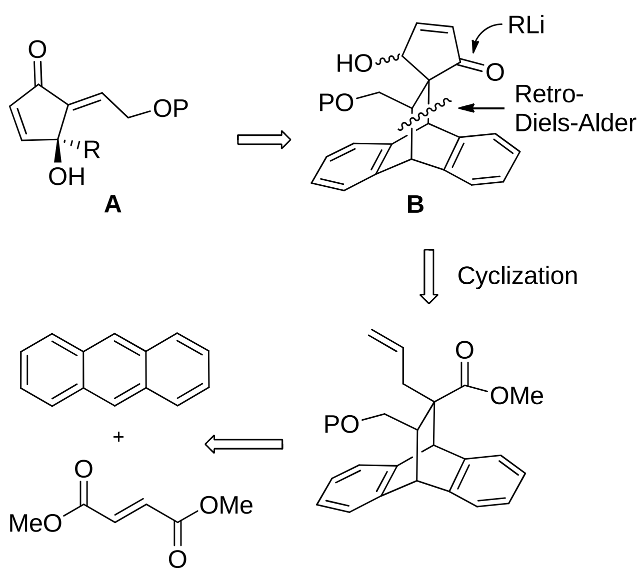


Figure 1. Structure of cross-conjugated dienone prostanoids

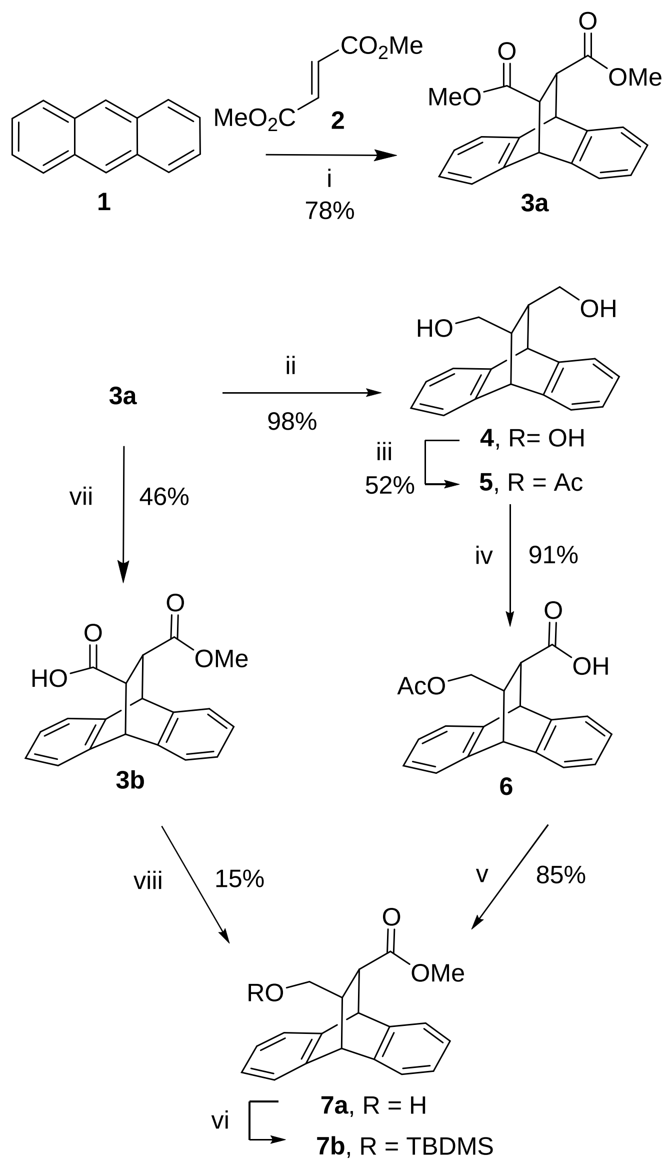


Scheme 1 Retrosynthetic analysis of α-methylenecyclopentenone **A**

2. Results and discussion

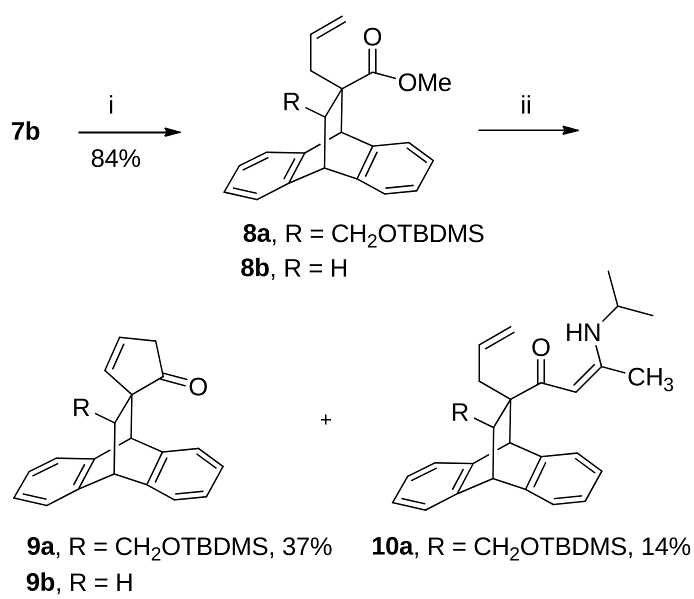
To investigate our proposed synthesis the known dimethyl fumarate-anthracene adduct **3**a was prepared by a Diels-Alder reaction of anthracene and dimethyl fumarate which gave racemic *trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethyl ester (**3a**) in 78% yield

(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.[11] Reduction of the adduct **3a** using $LiAlH_4$ 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 H_2SO_4 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.[12] Reduction of **3b** with $NaBH_4/I_2$[13] 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) $LiAlH_4$, THF, 0 °C (iii) Ac_2O, pyridine, rt (iv) CrO_3 in H_2O, H_2SO_4, 0 °C (v) H_2SO_4, MeOH, rt (vi) TBDMSCl, imidazole, rt, 81% from **6** or TBDMSOTf, 2,6-lutidine, rt, 96% from **3b** (vii) KOH, MeOH (viii) $NaBH_4$, I_2, 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,[6] afforded 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).[14] 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 δ 3.60. In addition, the ^{1}H NMR spectrum showed a 3H singlet at δ 1.89 for the vinyl methyl group and a 1H singlet resonance at δ 5.06 for the vinyl proton (COC*H*=C(Me)(NH^{i}Pr).

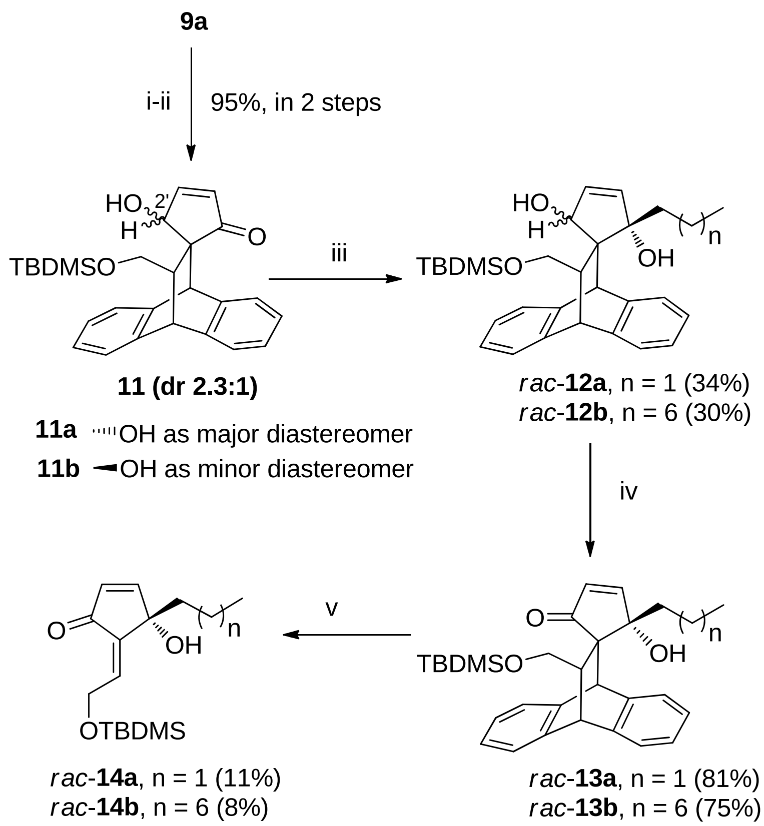


Scheme 3. (i) Allyl bromide, LDA, THF, HMPA, -78 °C, 84% (ii) LDA, TMEDA, -78 °C

Such enaminones have been previously observed as by-products upon treatment of esters with an excess amount of LDA at 0 ^{o}C.[15-17] This has been shown to be a result of the formation of the corresponding *N*-isopropyl ketimine ($Me_2C{=}N^{i}Pr$)) from the *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 **8b** under similar conditions afforded the cyclopentenone **9b** as a single product in good yield.[14] These differences in yields of spiro-cyclopentenone products might be a result of the steric crowding caused by the CH_2OTBS group in **8a** which may inhibit formation of **9a**, and thus enhance the formation of the *N*-isopropyl ketamine, by slowing down the rate of allylic deprotonation of **8a** by the LDA.

Transformation of ketone **9a** to the γ-hydroxyenone **11** was readily achieved by epoxidation followed by base-catalysed ring opening using Et_3N to afford **11** in 95% yield (dr 2.3:1) after purification by flash column chromatography (15:1 system of hexane/EtOAc). The diasteromers were separated by flash column chromatography (20:1 system of hexane/EtOAc) and the major diastereomer **11a** was confirmed by an NOESY experiment which revealed the correlation between H-2′ and the C$\underline{H}_2$-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 **12a** and **12b** 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 **13a** was confirmed unequivocally by single-crystal X-ray crystallography (Figure 2) after oxidation of **12a** with PDC (Scheme 4). The analysis of **13a** by single crystal X-ray crystallographic data (Figure 2) are ($C_{30}H_{38}O_3Si.H_2O$), M_r 492.73. Triclinic, $P\ \bar{1}$, a = 9.3804 (2) Å, b = 11.5664 (3) Å, c = 13.9475 (4) Å, α = 82.5505 (11)°, β = 84.4853 (14)°, γ = 66.8558 (14)°, V = 1378.04 (6) Å^3, Z = 2, F(000) = 532, D_x = 1.187 Mg m^{-3}, Mo $K\alpha$ radiation, λ= 0.71073Å, Cell parameters from 16794 reflections, θ = 2.6 - 27.5°, μ = 0.12 mm^{-1}, T = 200 K, specimen = 0.54× 0.26×0.12 (colorless, block). 29223 reflections were measured. Final R ($F^2 > 2\sigma(F^2)$) = 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 **12a** 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**.



Scheme 4. (i) mCPBA, CH_2Cl_2 (ii) Et_3N, THF (iii) alkyl lithium, THF (iv) PDC, DMF, 0 °C (v) 1,2-dichlorobenzene, 180 °C in sealed tube.

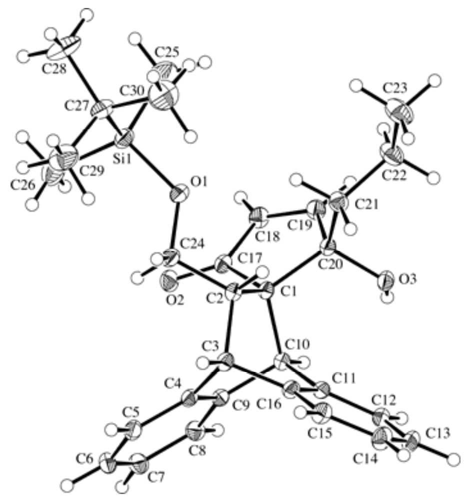


Figure 2. Single-crystal X-ray structure of *rac*-**13a** (n = 1)

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 CH_2Cl_2-films with a Perkin Elmer Spectrum GX FT-IR spectrophotometer. ^1H- and ^{13}C-NMR spectra were recorded in (D) chloroform solutions at 300 MHz for ^1H and 75 MHz for ^{13}C 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 ^oC 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.[11] 107-108 °C); IR (CH_2Cl_2) ν_{max}: 1732, 1459, 1435, 1221, 1198, 1018, 760 cm^{-1}; ^1H NMR δ 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); ^{13}C NMR δ 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_2SO_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.[3] 202 °C); IR (CH_2Cl_2) ν_{max}: 3444, 1737,1704, 1434, 1267, 1208, 740 cm^{-1}; ^1H NMR δ 7.31 (m, 2H), 7.24 (m, 2H), 7.10 (m, 4H), 4.70 (d, *J* = 2.0, 2H), 3.62 (s, 3H), 3.41 (dd, *J* = 2.6, 5.0 Hz, 1H), 3.32 (dd, *J* = 2.6, 5.0 Hz, 1H). ^{13}C NMR δ 176.8, 172.2, 142.0, 141.9, 140.1, 140.0, 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 *m/z* cald for $[M+Na]^+ C_{19}H_{16}NaO_4$: 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. $NaHCO_3$ solution and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried (Na_2SO_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_2Cl_2) ν_{max}: 3442, 3054, 2987, 1422, 1022 cm^{-1}; ^1H NMR δ 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); ^{13}C NMR δ 144.5, 141.7, 126.1, 125.8, 123.4, 64.5, 45.9, 45.3; HRESI-MS m/z cald for $[M+Na]^+$ $C_{18}H_{18}NaO_2$: 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 CH_2Cl_2 (2 × 20 mL). The combined extracts were dried (Na_2SO_4), 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 ^{o}C; IR (CH_2Cl_2) ν_{max}: 3451, 3054, 2987, 1736, 1422, 1025 cm^{-1}; ^{1}H 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); ^{13}C 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]$^+$ $C_{20}H_{20}NaO_3$: 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. CH_2Cl_2 (20 mL) and water (20 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL) and then died (Na_2SO_4), filtered and evaporated in *vacuo* to give compound **6** (0.21g, 91%) as a yellow oil; IR (CH_2Cl_2) ν_{max}: 3436, 2987, 1737, 1708, 1422, 1036 cm^{-1}; ^{1}H 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); ^{13}C 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]$^+$ $C_{20}H_{18}NaO_4$: 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 $NaBH_4$ (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 (Na_2SO_4), 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. H_2SO_4 (1 mL). The mixture was stirred at rt for 12 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated to give **7a** (1.82 g, 85%) as a yellow oil.

7a; IR (CH_2Cl_2) 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); ^{13}C 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 $[M+Na]^+$ $C_{19}H_{18}NaO_3$: 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 CH_2Cl_2 (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. $NaHCO_3$ solution and then extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried (Na_2SO_4), 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 CH_2Cl_2 (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. $NaHCO_3$ solution and then extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried (Na_2SO_4), 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 ^oC; IR (CH_2Cl_2) 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); ^{13}C 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 $[M+Na]^+$ $C_{25}H_{32}NaO_3Si$: 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 NH_4Cl solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with water (30 mL) and saturated NaCl solution (30 mL). The combined organic layer was dried (Na_2SO_4), 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 ^oC; IR (CH_2Cl_2) 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); ^{13}C 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 $[M+H]^+$ $C_{28}H_{37}NaO_3Si$: 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 NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with water (20 mL) and saturated NaCl solution (20 mL) and then dried (Na_2SO_4), 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-dihydrospiro[9,10-ethanoanthracene-12,1'-cyclopent[2']en]-5'-one **9a** (0.10 g, 37%) as a white solid and 12-allyl-11-(*ter*t-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 ^{o}C; IR (CH_2Cl_2) ν_{max}: 2952, 1746, 1468, 1256, 1103, 1094, 837, 758 cm^{-1}; ^{1}H NMR δ 7.34 (d, *J* = 6.3 Hz, 2H), 7.19-7.11 (m, 6H), 6.08 (d, *J* = 7.2 Hz, 1H), 5.23 (d, *J* = 7.2 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 δ 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; HRCI-MS *m/z* cald for $[M+H]^+$ $C_{27}H_{33}O_2Si$: 417.2250, found: 417.2240.

10a: ^{1}H NMR δ 10.41 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.27-7.22 (m, 2H), 7.16 (d, *J* = 8.1 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 δ 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; HRCI-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-dihydrospiro[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 CH_2Cl_2 (0.72 mL) was added a solution of *m*-chloroperoxybenzoic acid (74 mg, 0.43 mmol) in dry CH_2Cl_2 (1.1 mL) at 0 °C and the mixture stirred at rt for 10 h. The mixture was then washed with sat. $NaHCO_3$ solution at 0 °C and then water and dried (Na_2SO_4), 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 (Na_2SO_4), 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 hexame/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 (CH_2Cl_2) ν_{max}: 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); ^{13}C 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 $[M+Na]^+$ $C_{27}H_{32}NaO_3Si$: 455.2018, found: 455.1974. (1'*S*,2'*S*,11'*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethano anthracene-12, 1'-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 NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with water (20 mL) and brine (20 mL) then dried (Na_2SO_4), 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 (CH_2Cl_2) ν_{max}: 3552, 3410, 2956, 1469, 1256, 1188, 837, 768 cm^{-1}; ^{1}H 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); ^{13}C NMR δ 144.7, 142.6, 142.1, 141.7, 135.8, 126.0, 125.7, 125.6, 125.56, 125.46, 125.3, 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 $[M+Na]^+$ $C_{30}H_{40}NaO_3Si$: 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 NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL) then dried (Na_2SO_4), 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 (CH_2Cl_2) ν_{max} : 3423, 2927, 1469, 1254, 1088, 837, 759 cm^{-1}; ^{1}H 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); ^{13}C NMR δ 144.7, 142.6, 142.1, 141.7, 135.8, 126.0, 125.7, 125.6, 125.56, 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 $[M+Na]^+$ $C_{35}H_{50}NaO_3Si$: 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_2Cl_2 and water. The layers were separated and the organic layer washed with water (3 × 10 mL), dried (Na_2SO_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_2Cl_2) ν_{max}: 3570, 3423, 2956, 2930, 1708, 1468, 1256, 1190, 836, 776, 735 cm^{-1}; ^{1}H NMR δ 7.43 (d, *J* = 6.0 Hz, 1H), 7.33-7.24 (m, 4H), 7.12-7.07 (m, 4H), 6.06 (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 δ 204.8, 162.0, 146.4, 141.9, 141.7, 141.4, 132.5, 126.0, 125.9, 125.8, 125.7, 125.6, 125.5, 124.7, 123.5, 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 $[M+Na]^+$ $C_{30}H_{38}NaO_3Si$: 497.2488, found: 497.2467.

4.15 (1'*R*,2'*S*,11*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)methyl-9,10-dihydrospiro[9,10-ethanoanthra cene-12,1'cyclopent[3']ene]-2'-hydroxy-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 °C and the mixture was stirred at 0 °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_2Cl_2) ν_{max}: 3425, 2927, 1710, 1467, 1255, 1090, 836, 776 cm^{-1}; ^{1}H NMR δ 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, 123.5, 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 $[M+Na]^+$ $C_{35}H_{48}NaO_3Si$: 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 °C for 4 h. The crude product was purified by column chromatography (silica gel, hexane) and then thin layer chromatrography (6:1 hexane/EtOAc) to give cyclopentenone **14a** (2 mg, 11%) as a clear oil; IR (CH_2Cl_2) ν_{max}: 3417, 2930, 1703, 1656, 1255, 1099, 838, 777 cm^{-1}; ^{1}H NMR δ 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 δ 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 $[M+Na]^+$ $C_{16}H_{28}NaO_3Si$: 319.1705, found: 319.1707.

4.17 (*S,Z*)-5-((*tert*-Butyl-dimethyl-silanyloxy)ethylidene)-4-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 chromatrography (8:1 hexane/EtOAc) to give cyclopentenone **14b** (5.4 mg, 8.1%) as a clear oil; IR (CH_2Cl_2) ν_{max}: 3444, 2928, 1704, 1658, 1464, 1256, 1100, 838, 778 cm^{-1}; ^{1}H NMR δ 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 δ 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 $[M+Na]^+$ $C_{21}H_{38}NaO_3Si$: 389.2488, found: 389.2484.

Acknowledgments

We gratefully acknowledge support from The Thailand Research Fund (Research grant No. RMU5080006), Silpakorn University and the University of Wollongong and the Department of Chemistry, Faculty of Science, Silpakorn University for a scholarship (to K.E.).

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Graphic Abstract

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

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