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Studies of Stereo-selective Cyclo-additions and Transformations of Substituted 2-cyclopenten-1-one with Chiral Anthracene Templates

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ABSTRACT

The chiral (*S*)-9-(1-methoxyethyl), (*R*)-9-(1,2-dimethoxyethyl) and 9-(1*R*, 2*R*)-(1,2-dimethoxypropyl) anthracenes were synthesised and used for the thermal Diels-Alder reaction with cyclopentene-3,5-dione. Unlike the maleic anhydride and *N*-substituted malemides, the cyclo-adducts were obtained with high regio-selectivity as a single diastereomer. The X-ray structure of the cyclo-adduct showed an enol form but the ^{13}C NMR showed resonances for two cyclopentanone carbonyl groups suggesting the solution structure is in the diketone form. Stereo-controlled studies using organomagnesium additions to the carbonyl groups resulted in hydrolytic cleavage of the enol ether and elimination of water to give â-alkylketone anthracene adducts. These were unsuccessful in preparing chiral cyclopentenone core structures.

Keywords: Cyclopentenone, cyclopentene-3,5-dione, chiral anthracene, organomagnesium.

INTRODUCTION

The cyclopentenone skeleton has been reported in diverse biological active compounds. For example, prostanoids such as clavulone I and clavulone II[1] isolated from marine natural products and exhibiting strong cytotoxicity. Untenone A[2] isolated from the Okinawan marine sponge *Plakortis sp.* which inhibites cell proliferation of L1210 leukaemia (IC_{50} = 0.4 µg/mg) and mammalian DNA polymerases (pol. α and β), and human terminal deoxynucleotidyl transferase (TdT).[3] Recently, TEI-9826,[4] an antitumor agent in preclinical trials, has also been prepared.

Many strategies have been developed to synthesise cyclopentenones including the Nazarov cyclisation,[5] the Pauson-Khand reaction,[6] metal-catalysed cyclisation,[7] and Diels-Alder or retro Diels-Alder reactions using anthracene.[8] Thus, the

synthesis of the cyclopentenone ring system is highly desirable, particularly with control of relative and absolute stereo-chemistry. The Diels-Alder/retro Diels-Alder reactions between 9-substituted chiral anthracene and maleic anhydride and *N*-substituted maleimides, or *p*-benzoquinone has been described in previous reports as chiral anthracene could stereo-control the cyclo-addition and control asymmetric substitutions at the carbonyl groups.[9-11] In addition, regio- and diastereoselective additions has also been achieved in the Diels-Alder reaction of 2-cyclopentene-1-one and chiral anthracene templates.[12] The work of the authors in the preparation of (*S*)-9-(1-methoxyethyl)anthracene, (*R*)-9-(1,2-dimethoxyethyl)anthracene and 9-(1*R*, 2*R*)-(1,2-dimethoxypropyl)anthracene, and the availability of cyclopentene-3,5-dione prompted an investigation of the stereo-selective Diels-Alder reactions and transformation of cyclo-adducts *via* regio-selective and stereo-selective manipulations prior to the asymmetric synthesis of bioactive cyclopentenones.

The Diels-Alder reaction of cyclopentene-3,5-dione, a good dienophile, and anthracene has been reported to give a completely enolic anthracene adduct after refluxing in benzene for four days.[13] Thus, it was considered that the reaction of cyclopentene-3,5-dione with our synthetic chiral anthracenes might provide single diastereomers of corresponding enolic anthracene adducts. The single diastereomer could be obtained as the hydrogen bond interaction between the enol oxygen and the anthracene C-9 hydrogen similar to the previous discussion in the cyclo-addition of chiral anthracene and maleic anhydride or *N*-methyl maleimide.[9] The stereo-selective substitution from the less hindered face might provide asymmetric synthesis of cyclopentenone derivatives.

EXPERIMENTAL

General Methods

Melting points were determined with a Stuart Scientific SMP 2 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker Avance 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) using TMS as an internal standard. Mass spectra were recorded with a POLARIS Q or HEWLETT PACKARD 5973 mass spectrometer. Reactions were monitored by TLC using aluminium or plastic sheets pre-coated with silica gel 60 F_{254}. Column chromatography was performed with Kieselgel 60.

9-Vinylanthracene (1) was prepared as described previously[14], (*S*)-9-(1-methoxyethyl) anthracene (6) was synthesised as described previously using Snyder's method[15], and cyclopentene-3,5-dione (7) was commercially available.

Synthesis Method

(*R*)-9-(1,2-dihydroxyethyl)anthracene (2a)

A mixture of 9-vinylanthracene 0.1 g (1a) (0.49 mmol, 1.0 equiv), AD-mix β (0.69 g, ratio 1.414 g : 1.0 mmol) and methansulfonamide 0.1 g in *tert*-butanol (ratio 1:1 H_2O : *tert*-butanol) 7 mL was stirred at 0°C in a cool room for four days. Approximately half a teaspoon Na_2SO_3 was then added to the mixture with a further 30 min stirring, followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel) with Hexane/EtOAc (1 :1) as the mobile phase gave a light yellow solid (*2a*) 0.08 g (0.34 mmol, 70%); m.p. 130-132 °C (lit.[16] 133.5 °C), $[\alpha]_D^{25}$= -6.6 (lit.[16] = -6.4 (*c* 0.22, EtOH); R_f = 0.34); ^{1}H-NMR (300 Hz, $CDCl_3$) δ 8.61 (2H, d, *J* = 9.0 Hz, ArH), 8.38 (1H, s, ArH), 7.97 (2H, d, *J* = 9.0 Hz, ArH), 7.48-7.40 (4H, m, ArH), 6.32 (1H, dd, *J* = 4.0, 10.0 Hz, CH), 4.42 (1H, dd, *J* = 10.0, 12.0 Hz, CH), 3.86 (1H, dd, *J* = 4.0, 12.0 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.4, 66.2, 124.7, 124.9, 125.9, 128.7, 129.3, 129.9, 130.4, 131.9.

(1*R*,2*R*)-1-(anthracen-9-yl)propane-1,2-diol (2b)

A mixture of (*E*)-9-(prop-1-en-1-yl) anthracene (1b) 0.1 g (0.458 mmol, 1.0 equiv), AD-mix β (0.66 g, ratio 1.414 g : 1.0 mmol) and methansulfonamide 0.1 g (1.05 mmol, 1.0 equiv) in *tert*-butanol (ratio 1:1 H_2O : *tert*-butanol) 7 mL was stirred at 0°C in a cool room for four days. Approximately half a teaspoon Na_2SO_3 was then added to the mixture with a further 30 min stirring, followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel) with Hexane/EtOAc (1 :1) as the mobile phase gave a light yellow solid

(2b) 0.09 g (0.36 mmol, 45%); m.p. 130-132°C, = -129.3 (*c* 0.75, $CHCl_3$); ^{1}H-NMR (300 Hz, $CDCl_3$) δ 8.65 (2H, brs, ArH), 8.41 (1H, s, ArH), 8.01-7.97 (2H, m, ArH), 7.48-7.44 (4H, m, ArH), 5.95 (1H, d, *J* = 9.0 Hz, ArH), 4.83-4.73 (1H, m, CH), 0.84 (3H, d, *J* = 6.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 71.1, 75.6, 124.8, 125.8, 128.6, 129.3, 130.2, 131.4, 131.7; HR-ESI MS calculated for $C_{17}H_{16}NaO_2$ $(M+Na)^+$ 275.1048, found 275.1043.

Methylation of (*R*)-9-(1,2-dihydroxyethyl) anthracene (2a)

A mixture of (*R*)-9-(1,2-dihydroxyethyl) anthracene (2a) 0.1 g (0.42 mmol, 1.0 equiv) with sodium hydride 60% wt (0.07 g, 3.0 mmol) was stirred in 15 mL dry THF under argon at 0 °C for 10 min. methyl iodide (0.13 mL, 2.00 mmol) was added dropwise and the mixture was stirred at room temperature for 6 hours. The resulting mixture was quenched with an aqueous saturated NH_4Cl solution, extracted with Et_2O (3x20 mL) and washed with water (30 mL) and saturated NaCl (30 mL). The combined organic layer was dried (anh. Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by preparative layer chromatography using Hexane/EtOAc (10:1) as the mobile phase gave the first fraction at R_f= 0.45 as a yellow solid of (*R*)-9-(1,2-dimethoxyethyl) anthracene (*3a*) 0.06 g (0.21 mmol, 52%) and the second fraction at R_f= 0.15 as a yellow oil of (*R*)-1-(anthracen-9-yl)-2-methoxyethanol (4a) 0.04 g (0.16 mmol, 36%).

(*R*)-9-(1,2-dimethoxyethyl)anthracene (3a); m.p. 78.0-80.0 °C (lit.[17] 78.0-80.0 °C); = -134.6 (c 0.75, $CHCl_3$); ^{1}H-NMR (300Hz, $CDCl_3$) δ 8.70 (2H, brs, ArH), 8.44 (1H, s, ArH), 8.02 (2H, d, *J* = 12.0 Hz, ArH), 7.52-7.45 (4H, m, ArH), 6.05 (1H, dd, *J* = 3.0, 9.0 Hz, CH), 4.34 (1H, dd, *J* = 9.0, 12.0 Hz, CH), 3.65 (1H, dd, *J* = 3.0, 9.0 Hz, CH), 3.47 (3H, s, OCH_3), 3.29 (3H, s, OCH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 56.9, 59.3, 75.9, 80.0, 124.9, 125.9, 127.2, 128.6, 128.9, 129.3, 130.5, 131.5; HR-ESI MS calculated for $C_{18}H_{18}O_2$ $(M+Na)^+$ 289.1204, found 289.1199.

(*R*)-1-(anthracen-9-yl)-2-methoxyethanol (4a); = -18.95 (C 0.21, $CHCl_3$) (lit.[18] = -18.76 (*c* 0.22, $CHCl_3$)); ^{1}H-NMR (300Hz, $CDCl_3$) δ 8.70 (2H, d, *J* = 9.0 Hz, ArH), 8.43 (1H, s, ArH), 8.00 (2H, d, *J* = 9.0 Hz, ArH), 7.53-7.43 (4H, m, ArH), 6.49 (1H, dd, *J* = 3.0, 9.0 Hz, CH), 4.28 (1H, dd, *J* = 9.0, 9.0 Hz, CH_2), 3.68 (1H, dd, *J* = 3.0, 9.0 Hz, CH_2), 3.53 (3H, s, OCH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 48.9, 57.2, 68.6, 122.8, 123.8, 125.3, 126.7, 127.3, 127.9, 129.7, 132.2; HR-EI MS calculated for $C_{17}H_{16}O_2$ $(M)^+$ 252.1151, found 252.1150.

9-((1*R*,2*R*)-1,2-dimethoxypropyl)anthracene (3b)

A mixture of (1*R*,2*R*)-1-(anthracen-9-yl)propane-1,2-diol (2b) 0.1 g (0.396 mmol, 1.0 equiv) with sodium hydride 0.02 g (0.793 mmol, 2.0 equiv) was stirred in dry THF 15 mL under argon at 0 °C for 10 min. Methyl iodide (0.18 mL, 2.00 mmol) was added dropwise and the mixture was stirred at room temperature for 6 hours. The resulting mixture was quenched with an aqueous saturated NH_4Cl solution, extracted with Et_2O (3x20 mL) and washed with water (30 mL) and saturated NaCl (30 mL). The combined organic layer was dried (anh. Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by preparative layer chromatography using Hexane/EtOAc (4:1) as the mobile phase gave compound (3b) as a yellow solid 0.02 g (0.07 mmol, 18%); m.p. 110-112 °C; = -134.6 (c 0.75, $CHCl_3$); ^{1}H-NMR (300Hz, $CDCl_3$) δ 9.02 (1H, m, ArH), 8.44 (2H, s, ArH), 8.02 (2H, d, *J* = 6.0 Hz, ArH), 7.55-7.44 (4H, m, ArH), 5.75 (1H, d, *J* = 9.0 Hz, CH), 4.43-4.36 (1H, m, CH), 3.61 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 0.68 (3H, d, *J* = 6.0 Hz, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.3, 56.9, 57.6, 80.2, 84.3, 123.5, 124.7, 125.1, 125.4, 126.3, 126.6, 127.3, 128.5, 129.0, 129.5, 130.0, 131.8, 134.1; HR-ESI MS calculated for $C_{19}H_{20}NaO_2$ $(M+Na)^+$ 303.1361, found 303.1348.

(*R*)-1-(Anthracen-9-yl)-2-methoxyethyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (5a)

To a solution of (*R*)-1-(anthracen-9-yl)-2-methoxyethanol (4a) 60 mg (0.237 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL), (*S*)-(-)-α-methoxy-α (trifluoromethyl)phenylacetic acid (*S*-Mosher) 110 mg (0.470 methyl mmol, 2 equiv.), *N,N*-dicyclohexylcarbodiimide (DCC) 97.8 mg (0.474 mmol, 2 equiv) and 4-dimethylamino pyridine (DMAP) 3.5 mg (0.0286 mmol, 0.12 equiv) were added and stirred at room temperature overnight. The reaction mixture was filtered and concentrated. Purification by preparative layer chromatography using Hexane/EtOAc (10:1) as the mobile phase gave a light yellow solid (5a) 0.32 g (0.68 mmol, 29%); ^{1}H-NMR (300 Hz, $CDCl_3$) δ 8.70 (2H, brs, ArH), 8.48 (1H, s, ArH), 8.04 (2H, d, *J* = 9.0 Hz, ArH), 7.61-7.38 (9H, m,

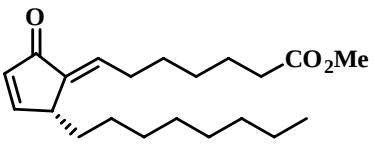
ArH), 6.10 (1H, dd, *J* = 6.0, 9.0 Hz, CH), 5.23 (1H, dd, *J* = 12.0, 12.0 Hz, CH), 4.62 (1H, dd, *J* = 3.0, 12.0 Hz, CH), 3.57 (3H, s, CH_3), 3.22 (3H, s, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 45.3, 55.1, 63.7, 100.0, 122.8, 123.8, 124.1, 125.3, 126.7, 127.3, 127.5, 127.9, 128.1, 128.5, 129.1, 129.7, 131.9, 132.2, 165.7; HR-ESI MS calculated for $C_{27}H_{23}F_3NaO_4$ $(M+Na)^+$ 491.1446, found 491.1452.

(9*R*,10*S*,11*S*,12*S*)-10-((*R*)-1,2-dimethoxyethyl)-15-hydroxy-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (8a)

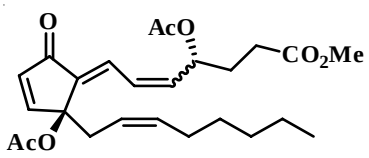
A mixture of (*R*)-9-(1,2-dimethoxyethyl) anthracene (3a) 0.03 g (0.114 mmol, 1.0 equiv) and 4-cyclopentene-1,3-dione 0.012 g (0.125 mmol, 1.2 equiv) in dry benzene 1 mL under argon was refluxed at 110°C overnight. The reaction mixture was cooled to room temperature and purification of the residue by preparative-layer chromatography (PLC) (silica gel) using Hexane/EtOAc (1:1) as the mobile phase gave (9*R*,10*S*,11*S*,12*S*)-10-((R)-1,2-dimethoxyethyl)-15-hydroxy-10,11-dihy-dro-9H-9,10-[1,2]epicyclepentaanthracen-13(12H)-one (8a) as a yellow oil 0.03 g (10% yield); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.92 (1H, s, OH), 7.45-7.12 (8H, m, ArH), 5.72 (1H, d, *J* = 6.0 Hz, CH), 4.88 (1H, s, CH), 4.62 (1H, d, *J* = 6.0 Hz, CH), 3.56 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.47 (1H, d, *J* = 6.0 Hz, CH), 3.28 (1H, dd, *J* = 9.0 Hz, CH), 2.98 (2H, m, CH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 50.6, 53.5, 55.4, 58.8, 60.6, 75.0, 76.6, 100.0, 127.4, 127.6, 128.9, 129.3, 129.7, 129.8, 130.5, 142.6, 143.4, 144.3, 147.4, 203.0, 211.9; HR-ESI MS calculated for $C_{23}H_{22}NaO_4$ $(M+Na)^+$ 385.1416, found 385.1441.

(9*R*,10*S*,11*S*,12*S*)-10-((1*R*,2*R*)-1,2 dimethoxypropyl)-15-hydroxy-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (8b)

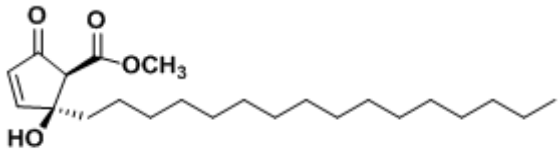
A mixture of 9-((*1R*,*2R*)-1,2 dimethoxypropyl)anthracene (3b) 0.02 g (0.713 μmol), propyl 4-cyclopentene-1,3-dione 0.01 g (1.5 eq.) and dry benzene 1 ml were added in a pressure tube and heated at 110°C overnight. After cooling to room temperature, the solvent was evaporated to dryness and the crude product was purified by column chromatography (silica gel, Hexane:EtOAc (1:1)). The product of (9*R*,10*S*,11*S*,12*S*)-10-((1*R*,2*R*)-1,2-dimethoxypropyl)-15-hydroxy-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (8b) was obtained as a yellow viscous oil 0.002 g (11% yield); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.46 (1H, s, OH), 7.35 (2H, d, *J* = 6.0 Hz, ArH), 7.25 (1H,s, ArH), 7.14-7.03 (4H, m, ArH), 6.85 (2H, d, *J* = 6.0 d Hz, ArH), 5.12 (1H, s, CH), 4.70 (1H, s, CH), 4.59 (1H, d, *J* = 3.0 Hz, CH), 4.13 (1H, q, *J* = 6.0 Hz, CH), 3.93 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 3.18 (1H, d, *J* = 6.0 Hz, CH), 3.06 (1H, dd, *J* = 6.0, 6.0 Hz, CH), 1.85 (3H, d, *J* = 6.0 Hz, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.4, 46.0, 46.3, 50.6, 53.4, 55.8, 60.3, 75.2, 83.5, 111.4, 122.6, 124.2, 124.6, 125.3, 125.6, 126.1, 126.3, 126.5, 141.7, 142.3, 147.3, 144.2, 203.8, 211.9; HR-ESI MS calculated for $C_{24}H_{24}NaO_4$ $(M+Na)^+$ 399.1572, found 399.1600.



2' Z = Clavulone I
2' E = Clavulone II



TEI-9826



Untenone A

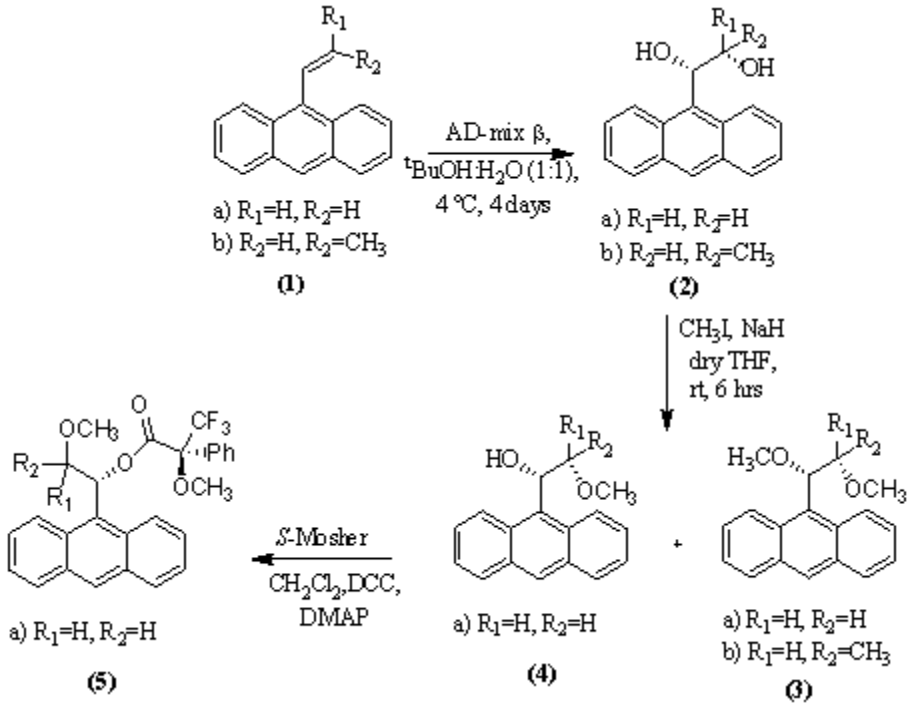
Fig. 1. Structure of Clavulone I, II, TEI-9826 and Untenone A

15-Hydroxy-10-((*S*)-1-methoxymethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-13-one (8c)

A mixture of (*S*)-9-(1-Mehtoxyethyl) anthracene (6) 3.55 g (15.0 mmol, 1 equiv) and cyclopentene-1,3-dione (7) 1.75 g (18.4 mmol, 1.2 equiv) in anhydrous benzene (25 mL) under argon was refluxed at 120 °C for 6 h. After cooling to room temperature, the precipitated adduct was filtered and purified by flash column chromatography on silica gel (diethyl acetate) to give 15-Hydroxy-10-((*S*)-1-methoxymethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-13-one (8c) 4.40 g (88%); m.p. 265-267 °C; ^{1}H-NMR (300Hz, $CDCl_3$: MeOD, 9:1) δ 7.86 (1H, m, ArH), 7.35-7.32 (1H, m, ArH), 7.15-7.05 (6H, m, ArH), 5.04 (1H, q, *J* = 2.1 Hz, CH), 4.54 (1H, d, *J* = 7.8 Hz, CH), 3.89 (3H, s, OCH_3), 3.72 (1H, s, CH), 3.51 (1H, d, *J* = 6.4 Hz, OH), 3.03 (1H, d, *J* = 6.2, ArH), 1.94 (3H, d, *J* = 5.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl^3$) δ 20.8, 34.7, 50.6, 53.5, 55.4, 60.6, 78.0, 127.4, 127.6, 128.9,129.3, 129.7, 129.8, 130.5, 142.6, 143.4, 144.3, 147.4, 203.8, 211.9; HR-ESI MS calculated for $C_{22}H_{20}O_3$ $(M+H)^+$ 332.1459, found 332.1412.

Methylation of 15-Hydroxy-10-((*S*)-1-methoxy methyl)-11,12-dihydro-9H-9,10-[1,2]epicy clopenta-anthracen-13-one (8c)

To a solution of 15-Hydroxy-10-((*S*)-1-methoxymethyl)-11,12-dihydro-9H-9,10-[1,2]epi cyclopenta-anthracen-13-one (8c) 0.23 g (0.69 mmol) and sodium hydride 60 mg (1.50 mmol) in DMF 4 mL at 0 °C under argon, methyl iodide 0.1 mL (1.40 mmol, 2 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred for 9 h before being quenched by the addition of saturated ammonium chloride solution (10 mL). After stirring for 15 min. at room temperature, the mixture was extracted with diethyl ether (3×10 mL), and the combined organic layers were dried over anh. Na_2SO_4. After filtration and evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (Hexane/EtOAc, (2:1)) to give 15-methoxy-10-((*S*)-1-methoxyethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-13-one (9a) 0.072 g (30%) and 13-methoxy-10-((*S*)-1-methoxyethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-15-one (10a) 0.12 g (50%) as a yellow solid.



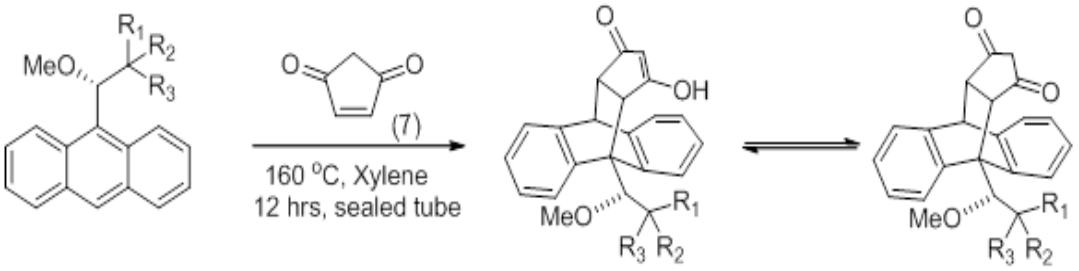
Scheme 1: Reagents and conditions for the synthesis of chiral anthracene auxiliary

(9a); m.p. 193-195°C, ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.79 (1H, m, ArH), 7.24 (1H, m, ArH), 7.11-7.00 (5H, m, ArH), 5.06 (1H, q, *J* = 2.1 Hz, ArH), 4.76 (1H, s, ArH), 4.40 (1H, d, *J* = 1.0 Hz, ArH), 3.63 (3H, s, ArH), 3.51 (3H, s, OCH_3), 3.17 (1H, d, *J* = 2.2 Hz, ArH), 3.02 (1H, dd, *J* = 1.0, 0.9 Hz, ArH), 1.80 (3H, d, *J* = 2.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 45.8, 48.1, 50.2, 54.1, 56.0, 57.4, 72.6, 106.3, 122.8,123.0, 123.4, 124.4, 124.5, 124.7, 124.9, 125.1, 125.6, 137.7, 138.5, 139.4, 142.1, 188.0, 202.7; HR-ESI MS calculated for $C_{23}H_{22}O_3$ $(M+H)^+$ 346.1641, found 346.1569.

(10a); m.p. 275-277°C, ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.88-7.85 (1H, m, ArH), 7.37-7.34 (1H, m, ArH), 7.32-7.28 (1H, m, ArH), 7.17-7.12 (5H, m, ArH), 4.87 (1H, s, ArH), 4.61 (1H, d, *J* = 3.1 Hz, ArH), 3.65 (1H, d, *J* = 8.6 Hz, ArH), 3.64 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 2.82 (1H, dd, *J* = 6.8, 3.2 Hz, ArH), 1.85 (3H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 46.9, 47.8, 54.4, 55.8, 56.7, 58.7, 74.9, 107.6, 123.0, 123.7, 125.3, 125.6, 125.9, 126.1, 126.4, 126.8, 138.6, 139.5, 140.2, 143.6, 190.7, 204.2; HR-ESI MS calculated for $C_{23}H_{22}O_3$ $(M+H)^+$ 346.1641, found 346.1569.

13-Acetoxy-10-((*S*)-1-methoxyethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-15-one (10b)

To a solution of 15-Hydroxy-10-((*S*)-1-methoxymethyl)-11,12-dihydro-9H-9,10-[1,2]epi



(3a); $R_1 = R_2 = H$, $R_3 = OMe$
(3b); R_1 =H, $R_2 = CH_3$, $R_3 = OMe$
(6); $R_1 = R_2 = R_3 = H$

(8a); $R_1 = R_2 = H$, $R_3 = OMe$
(8b); R_1 =H, $R_2 = CH_3$, $R_3 = OMe$
(8c); $R_1 = R_2 = R_3 = H$

Scheme 2: Enolic anthracene adducts via Diels-Alder reactions

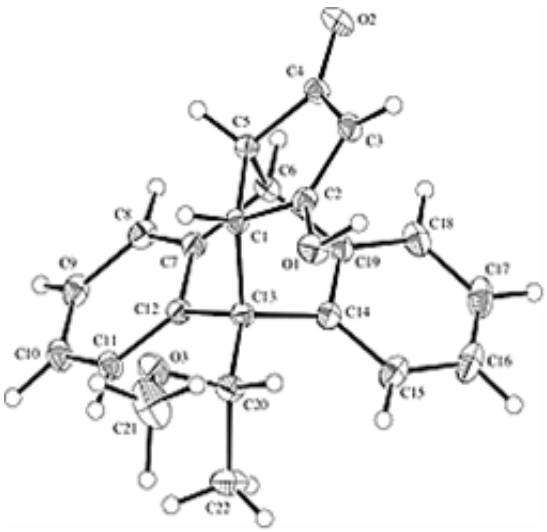


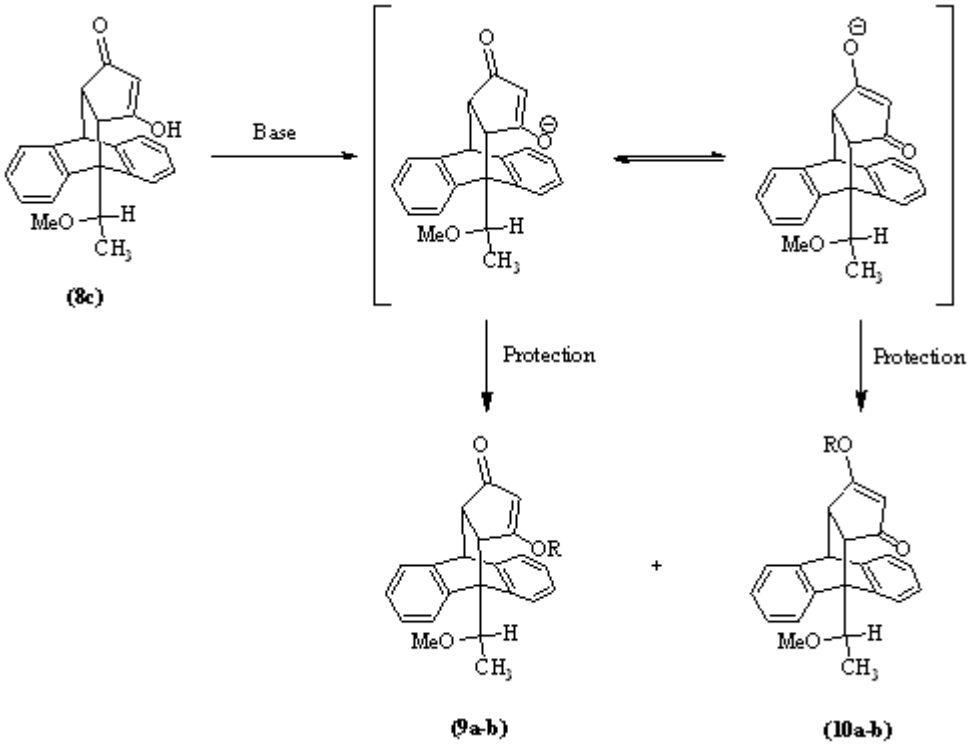
Fig. 2. X-ray crystallography of enolic anthracene adduct (8c)

cyclopenta-anthracen-13-one (8c) 1.0 g (3.00 mmol, 1.0 equiv) in acetic anhydride 5 mL, iodide was added with stirring and then refluxed at 120 °C for 2 h, The mixture was cooled to room temperature and quenched with water (10 mL) and stirred for a further 20 min. followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel) with Hexane:EtOAc, (10:1) as the mobile phase gave 13-acetoxy-10-((*S*)-1-methoxyethyl)-11,12-dihydro-9H-9,10-[1,2]epicyclopenta-anthracen-15-one (10b) 1.0 g (90%); m.p. 215-217 °C; ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.90 (1H, m, ArH), 7.37 (1H, m, ArH), 7.15 (6H, m, ArH), 5.75 (1H, s, ArH), 5.13 (1H, q, *J* = 6.3 Hz, ArH), 4.50 (1H, s, ArH), 3.73 (3H, s, ArH), 3.24 (2H, s, ArH), 2.32 (3H, s, OCH_3), 1.85 (3H, d, *J* = 6.3 Hz,

Table. 1: Condition and reagent of the synthetic adducts (9) and (10)

Entry	Conditions	R	% Yield
1	NaH, CH_3I, DMF	Me	9a: 10a = 30: 50
2	Ac_2O, I_2	Ac	9b: 10b = 0: 90

CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 21.4, 46.8, 49.8, 50.1, 55.1, 57.0, 73.5, 119.0, 123.8, 124.0, 124.5, 125.7, 125.9, 126.3, 126.5, 126.7, 138.4, 139.1, 140.3, 143.0, 165.8, 177.2, 204.9; HR-ESI MS calculated for $C_{23}H_{22}O_3$ $(M+H)^+$ 455.2018, found 455.1974.



Scheme 3: Transformation into enolate anion and protection of the hydroxy group of adduct (8c)

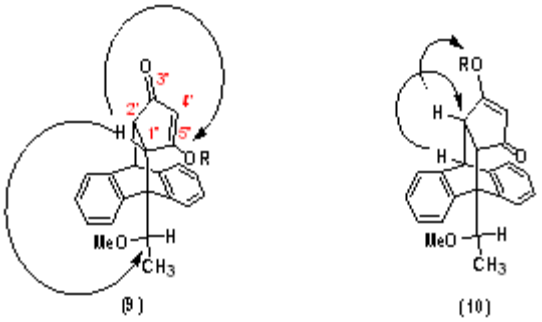


Fig. 3. HMBC correlations of adducts (9) and (10)

General Procedure for the Grignard Addition to Cyclo-adduct 9,10

To a mixture of magnesium (5.0 equiv) in diethyl ether (5 mL) at 0°C, alkyl/allyl bromide solution (1.0 equiv) was added and stirred for 30 min. to give alkyl/allyl magnesium bromide solution as a turbid grey solution. To the cyclo-adduct 9, 10 (0.20 mmol) in CH_2Cl_2 2 mL in a 50 ml round bottom flask at -78°C in an acetone/dry ice cooling bath, the solution of the Grignard reagent (0.40 mmol) was slowly added dropwise over

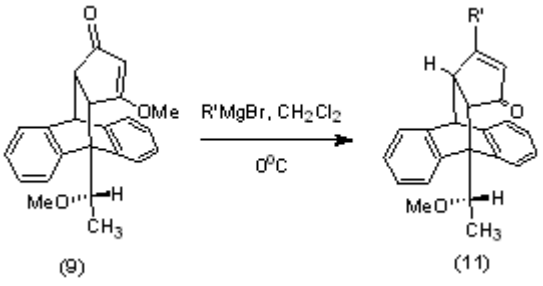
2 h under argon. The resulting mixture was quenched with an aqueous saturated 20 mL NH_4Cl solution and extracted with CH_2Cl_2 (3x20 mL). The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel) with Hexane:EtOAc, (10:1) as the mobile phase gave the desired Grignard addition products.

(9*S*,10*S*,11*S*,12*S*)-9-((*S*)-1-methoxyethyl)-15-methyl-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (11a)

Using the general procedure with the addition of MeMgBr (0.05 mL,0.40 mmol) to the cyclo-adduct 9 (0.07 g, 0.20 mmol), the title compound was obtained after column chromatography (0.055 g, 83%); m.p. 224-226°C; ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.86 (1H, m, ArH), 7.34 (1H, m, ArH), 7.18-7.05 (6H, m, ArH), 5.43 (1H, t, *J* = 1.2 Hz, ArH), 5.03 (1H, q, *J* = 6.3 Hz, ArH), 4.39 (1H, d, *J* = 3.0 Hz, ArH), 3.72 (3H, s, OCH_3), 3.16 (1H, d, *J* = 6.3 Hz, ArH), 3.07 (1H, dd, *J* = 0.9, 4.8 Hz, ArH), 2.04 (3H, s, CH_3), 1.82 (3H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 17.1, 47.3, 51.4, 53.8, 55.3, 57.0, 73.4, 123.7, 124.0, 124.3, 125.6, 125.8, 126.0, 126.2, 126.6, 134.1, 138.5, 139.4, 140.5, 143.7, 176.7, 207.4; HR-EI MS calculated for $C_{23}H_{22}O_2$ $(M)^+$ 330.1630, found 330.1673.

Table 2: Results of the synthesis adducts 11a-d

Entry	Product	R	Yields (%)
1	11a	CH_3	83
2	11b	$CH_2CH{=}CH_2$	70
3	11c	C_5H_{11}	78
4	11d	$C_{16}H_{33}$	75



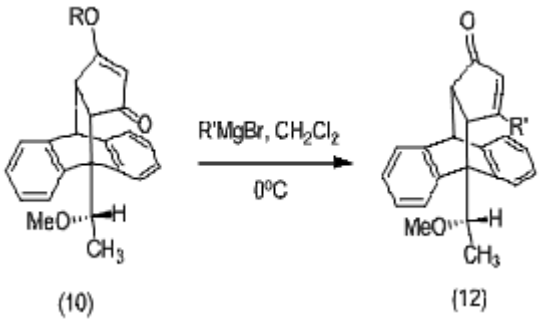
Scheme 4: Preparation of adducts 9 via Grignard reagents and hydrolysis

(9*S*,10*S*,11*S*,12*S*)-15-allyl-9-((*S*)-1-methoxyethyl)-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (11b)

Using the general procedure with the addition of allylmagnesium bromide (0.07 mL, 0.60 mmol) to the cyclo-adduct 9 (0.07 g, 0.20 mmol), the title compound was obtained after column chromatography (0.053 g, 70%); m.p. 188-190°C; ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.85 (1H, m, ArH), 7.32 (1H, m, ArH), 7.12 (6H, m, ArH), 5.72 (1H, m, ArH), 5.45 (1H, d, *J* = 0.9 Hz, ArH), 5.15 (3H, m, ArH), 4.41 (1H, d, *J* = 2.1 Hz, ArH), 3.71 (3H, s, OCH_3), 3.15 (3H, m, ArH, CH_2), 3.07 (1H, d, *J* = 7.5 Hz, ArH), 1.81 (3H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 29.7, 35.4, 47.4, 51.7, 52.4, 55.3, 57.0, 73.4, 123.4, 124.0, 124.4, 125.6, 125.8, 126.0, 126.2, 126.6, 132.5, 133.3, 138.6, 139.4, 140.5, 143.6, 178.4, 207.0; HR-EI MS calculated for $C_{25}H_{24}O_2$ $(M)^+$ 356.1776, found 356.1806.

(9*S*,10*S*,11*S*,12*S*)-9-((*S*)-1-methoxyethyl)-15-pentyl-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (11c)

Using the general procedure with the addition of pentanylmagnesium bromide (0.75 mL, 0.30 mmol) to the cyclo-adduct 9 (0.05 g, 0.15 mmol), the title compound was obtained after column chromatography (0.045 g, 78%); ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.91 (1H, m, ArH), 7.38 (1H, m, ArH), 7.18 (6H, m, ArH), 5.48 (1H, d, *J* = 1.2 Hz, ArH), 5.19 (1H, q, *J* = 6.3 Hz, ArH), 4.42 (1H, d, *J* = 2.7 Hz, ArH), 3.76 (3H, s, OCH_3), 3.18 (2H, m, ArH), 2.36 (2H, m, CH_2), 1.85 (3H, d, *J* = 6.3 Hz, CH_3), 1.53 (2H, m, CH_2), 1.30 (4H, s, CH_2), 0.93 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 16.7, 22.4, 26.2, 29.7, 31.0, 31.5, 47.6, 51.4, 52.7, 57.0, 73.4, 123.6, 123.9, 124.4, 125.5, 125.7, 125.9, 126.1, 126.6, 132.5, 138.6, 139.5, 140.6, 143.8, 181.1, 207.3; HR-



Scheme 5: Preparation of adducts 10 via Grignard reagents and hydrolysis

EI MS calculated for $C_{27}H_{30}O_2$ $(M)^+$ 386.2246, found 386.2275.

(9*S*,10*S*,11*S*,12*S*)-15-hexadecyl-9-((*S*)-1-methoxyethyl)-10,11-dihydro-9H-9,10-[1,2]epicyclopentaanthracen-13(12H)-one (11d)

Using the general procedure with the addition of hexadecylmagnesium bromide (2.00 mL, 6.40 mmol) to the cyclo-adduct 9 (1.00 g, 0.30 mmol), the title compound was obtained after column chromatography (0.12 g, 75%); m.p. 201-203 °C; ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.86 (1H, m, ArH), 7.33 (1H, m, ArH), 7.11 (6H, m, ArH), 5.43 (1H, s, ArH), 5.15 (1H, q, *J* = 6.3 Hz, ArH), 4.38 (1H, d, *J* = 6.3 Hz, ArH), 3.72 (3H, s, OCH_3), 3.15 (1H, d, *J* = 6.3 Hz, ArH), 3.13 (1H, d, *J* = 6.6 Hz, CH_2), 2.35 (2H, m, CH_2), 1.82 (3H, d, *J* = 6.3 Hz, CH_3), 1.44 (2H, m, CH_2), 1.26 (26H, s, CH_2), 0.88 (3H, t, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 15.6, 21.7, 22.9, 25.5, 25.9, 28.4, 28.5, 28.7, 29.3, 30.0, 30.9, 40.9, 46.6, 50.4, 51.6, 54.3, 56.0, 72.4, 122.6, 122.9, 123.4, 124.5, 124.7, 124.9, 125.1, 125.6, 131.4, 137.6, 138.4, 139.6, 142.7, 180.0, 206.3; HR-EI MS calculated for $C_{38}H_{52}O_2$ $(M)^+$ 540.3967, found 540.4010.

(9S,10S,11S,12R)-9-((S)-1-methoxyethyl)-13-methyl 10,11-dihydro-9H-9,10-[1,2]epicyclopentaanth racen-15(12H)-one (12a)

Using the general procedure with the addition of methylmagnesium bromide (0.07 mL, 0.60 mmol) to the cyclo-adduct 10 (1.00 g, 0.30 mmol), the title compound was obtained after column chromatography (0.07, 70%); m.p. 232-234 °C; ^{1}H-NMR (300Hz, $CDCl_3$) δ 7.85 (1H, m, ArH), 7.21 (7H, m, ArH), 5.59 (1H, s, ArH), 4.79 (1H, q, *J* = 6.0 Hz, ArH), 4.58 (1H, d, *J* = 3.0 Hz, ArH), 3.68 (3H, s, OCH_3), 3.65 (1H, d, *J* = 6.9 Hz, ArH), 2.76 (1H, dd, *J* = 3.0, 6.0 Hz, ArH), 2.15 (3H, s, CH^3), 1.86 (3H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl^3$) δ 17.1, 19.9, 47.0, 52.5, 55.5, 55.7, 74.9, 123.0, 123.6, 125.1, 125.5, 126.0, 126.1, 126.4, 126.6, 135.7, 136.8, 138.4, 139.5, 140.9, 143.7, 178.5, 207.8; HR-EI MS calculated for $C_{23}H_{22}O_2$ $(M)^+$ 330.1630, found 330.1673.

RESULTS AND DISCUSSION

The synthesis of the chiral anthracene auxiliary started with vinyl anthracenes (1a-b) which was prepared according to the literature.[14] Asymmetric dihydroxylation with AD-mix β was prepared using literature procedure[16] to afford compounds 2a-b in fair yields. Then methylation of 2a with CH_3I and NaH in THF for 6 hours at room temperature gave the dimethoxy compound 3a in 52% yield and the mono-methylated product 4a in 36% yield. Methylation of 2b using the same conditions gave only the dimethylated product 3b in 18% yield. This low yield might be due to the steric strain of the methyl side chain of the propyl group. However, the methylated product yield was improved when the reaction time was increased.

The absolute stereochemistry of 2a was confirmed by comparing the spectroscopic data and optical rotation of the previous report.[17] To determine enantiomeric purity of 2a, (*R*)-9-(1,2-dimethoxyethyl)anthracene 4a was treated wtih (-)-(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid [(-)-(*S*)-MTPA] in the presence of DCC and DMAP. These reaction afforded (-)-(*S*)-MTPA ester 5a as a single diastereomer (dr ≥ 20:1) after structural elucidation. The low yield of 5a might be

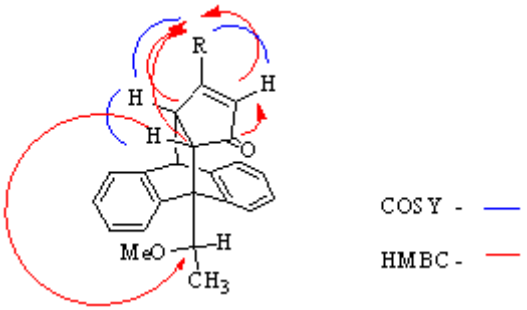


Fig. 4. COSY and HMBC correlations of adducts (11)

Table. 3: Results of the synthesis adducts 12a-d

Entry	10	Product	R	Yields (%)
1	R= CH_3	12a	CH_3	70
2		12b	$CH_2CH{=}CH_2$	-
3		12c	C_5H_{11}	-
4		12d	$C_{16}H_{33}$	-
5	R= Ac	12a	CH_3	-

due to the use of (-)-(*S*)-MTPA-acid reacted with steric alcohol 4a. The anthracene 6 was synthesised according to Snyder's method and the structure confirmation was compared to the literature.[15]

The Diels-Alder reactions of the chiral anthracene 3a-b and 6 with cyclopentene-3,5-dione (7) refluxing in xylenes for 12 h resulted in the ketone forms of 8a-c as single diastereomers (Scheme 2). The structures of the addition adducts were confirmed by NMR spectroscopy. The ^{13}C NMR spectra appeared to have peaks around 203 and 211 ppm which suggested the solution structures to be diketone carbonyl groups of 8a-c. However, the single crystal X-ray crystallography of adduct 8c were showed to be an enolic anthracene adduct (Fig. 2). These were supported the previous study[19] that cyclopentene-3,5-dione itself in refluxing benzene was present exclusively as the keto tautomer. The X-ray crystallography also showed the orientation of the methoxy group away from the approaching dienophile. These observations led to a proposition that in the transition state, the facial selectivity is controlled by minimisation of electrostatic repulsion between the methoxyl oxygen and the approaching dienophile. While the cyclo-addition completed, hydrogen bonding helped to stabilise the alternative product, giving rise to a single diastereomer as depicted in Scheme 2.

Prior to transformation of the carboxyl group of 8c, the hydroxyl group was converted to either an ether or ester derivative with good to poor regio-selectivity depending on the nature of the protection employed (Table 1). Transformation of 8c into enolate anions led to the breaking of the hydrogen bond, and consequently delocalisation of the enolate anion gave two regio-isomers (Scheme 3). The regio-selectivity obtained was due to the steric hindrance of substituents. The small steric group of the $-CH_3$ gave the methyl ether low selectivity and about a 2:3 ratio of adducts (9) and (10), respectively. Meanwhile, the -Ac group had high selectivity and gave exclusively adduct (10) (Table 1, entry 2). The HMBC analyses were used in assigning the regio-chemistry of the ether/ester adduct. In the regio-isomers (10), the HMBC spectra showed correlations between ether/ester carbons and proton at $C_2$2.

Treatment of enol ethers (9) and (10) with Grignard reagents gave 1,2-addition and then hydrolysis of the resulted products gave the corresponding β-alkylketone anthracene adducts (11) and (12), respectively (Scheme 4 and 5). The organomagnesium compounds added to the carbonyl group subsequently caused hydrolytic cleavage of the enol ether and elimination of water[16] to give 11 and 12. In this approach, steric hindrance plays an important role as using bulky Grignard reagents gave only product (11) from the addition to the less hindered carbonyl ketone (9). While the hindered carbonyl ketone 10 was not attacked by the bulky Grignard reagents (Table 2). The ^1H NMR spectra of (11) indicated the absence of the methoxy protons and the presence of the alkyl protons in high fields and the ^{13}C NMR spectra showed the present of carbonyl group at around δ 207.4 ppm. The HMBC spectra showed the correlations between C-H proton of the alkyl groups and the C1′′, C2′′ and C4′′, correlations between H4′′ proton and the C_5 carbonyl group, and correlations between H1′′ proton and C_9 anthracene substituent. The COSY spectra showed the correlations between H1′′ and H2′′ and the long length coupling between C-H proton of the alkyl groups and H2′′ and H4′′ protons. Thus, these NMR experiments assigned the carbonyl group to be on the same side as the C_9 anthracene substituent. The COSY spectra of 12 showed the long length coupling between H1′′ and C-H proton of the alkyl group, but correlation between H2′′ and C-H proton of the alkyl group was not observed.

CONCLUSIONS

Chiral anthracene templates were synthesised prior to use in Diels-Alder reactions with cyclopentene-3,5-dione. The results showed that the cyclo-adducts were obtained with good regio-selectivity as a single diastereomer from completely enolic forms in crystal structure and diketone forms in the solution structures. However, the studies on the stereo-selectivity using organomagnesium addition to the methoxyenones resulted in the cleavage of enol ether and elimination of water. These could undergo hydrogenation of the enone double bond to give a chiral cyclopentenones . On the other hand, studies with other nucleophilic additions to the carbonyl group without loss of stereo-centre should be investigated.

ACKNOWLEDGEMENT

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