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Studies Toward the Synthesis of Natural and Unnatural Dienediynes 1. Approaches to a Functionalised Bicyclic Ring System

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Abstract

The synthesis of a functionalised bicyclic ring system related to the naturally occurring dienediynes, NCS and Kedarcidin Chromophores is presented. Key steps involve: conjugate addition of an enediyne to a functionalised enone and intramolecular boron mediated aldol reaction.

Keywords: Aldol Reactions; Cyclisation; Diynes

Introduction

The dienediyne chromoprotein antibiotics have been the subject of significant attention from synthetic, biological and medicinal chemists [1]. Interest in these molecules arises from their unusual synthetically challenging, molecular structure and their potent biological activity [2]. Members of this class include Neocarzinostatin (NCS), Kedarcidin, C-1027 and Maduropeptin which are all isolated from natural sources, and each comprise a 1:1 complex of an apoprotein and a chromophore [3]. The structures of the chromophores are depicted in scheme 1. The current opinion is that biological activity originates from the ability of the chromophore species to generate a biradical which can then mediate nucleic acid damage *via* H-atom abstraction from the 2-deoxyribose ring of DNA [4]. Much effort has been directed toward the chemical synthesis of natural and unnatural dienediyne chromophores and it is only recently that the first completed synthesis of a dienediyne chromoprotein natural product (NCS Chrom) has been reported [5]. This work provides opportunities for the evaluation of strained analogues of NCS which should further our

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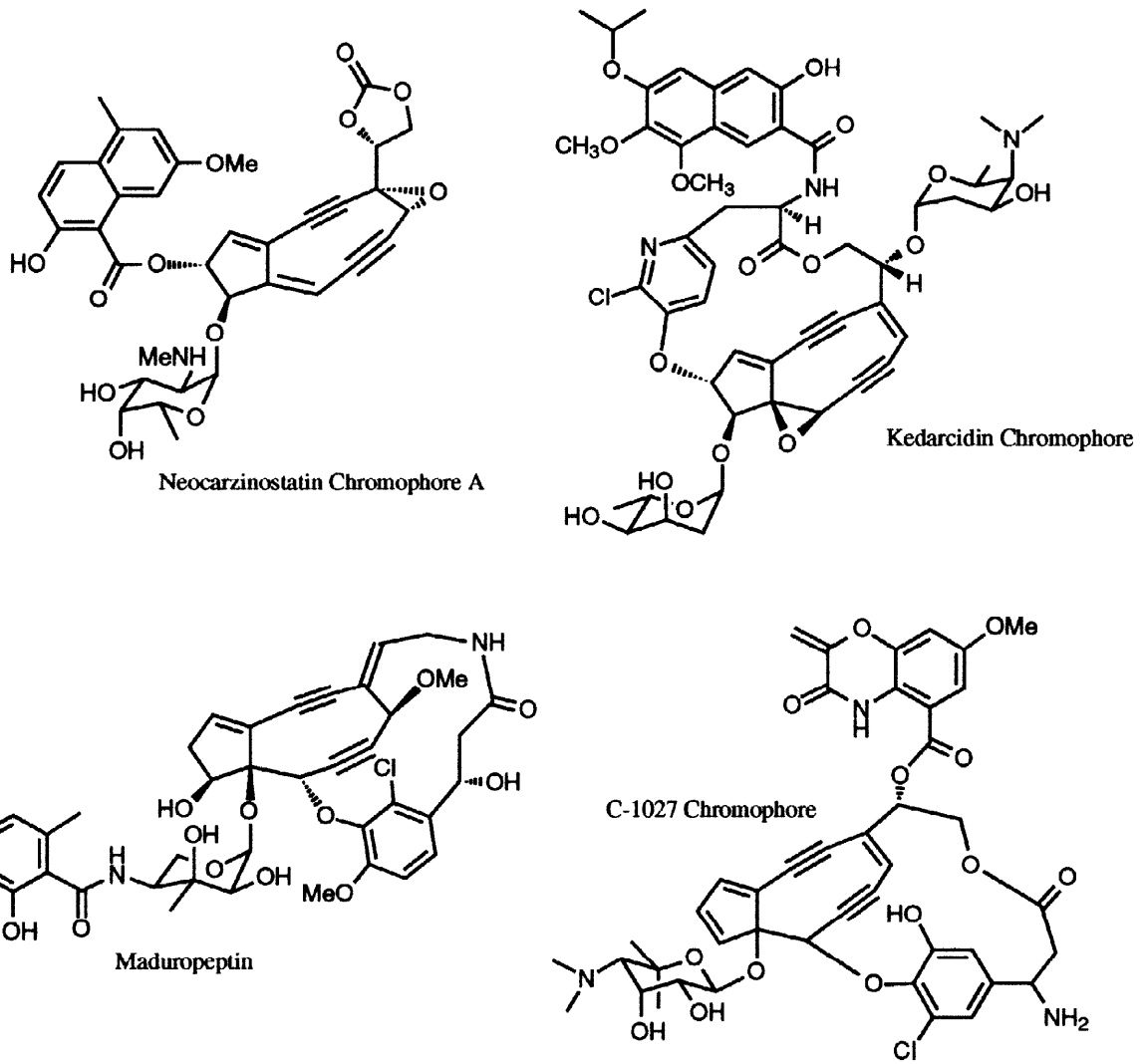
understanding of the interaction of this important natural product with biomolecules such as nucleic acids and proteins.

The purpose of this paper is to describe our recent efforts toward the synthesis of functionalised bicyclic ring systems related to naturally occurring dienediynes. This work details some problems encountered and demonstrates that an aldol strategy can be used for the practical construction of functionalised bicyclic ring systems related to dienediynes [6].

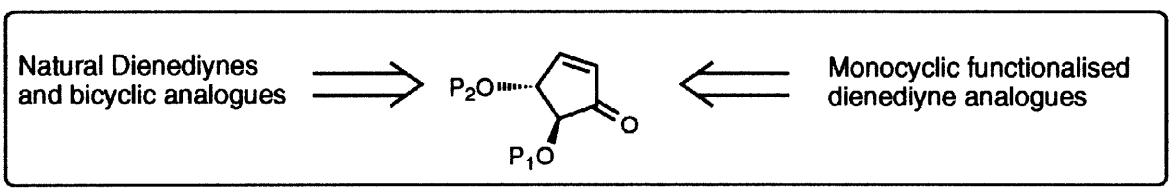
Scheme 1



Background

An important part of our research programme is to establish common methodologies for the synthesis of natural dienediynes NCS and Kedarcidin and functionalised analogues thereof. The key points of our total synthesis planning are the late introduction of the final elements of unsaturation, and, most importantly for all aspects of our work, the identification of a simple functionalised five-membered ring intermediate. From the outset we decided that all of our work should ideally utilise a fully dihydroxylated five-membered ring, primarily because it was likely that this would confer limitations on the type of methodology which could be used to effect the ring closure of the nine-membered ring. It is notable that, of the many elegant methods which have been published toward such strained ring systems [7], few have incorporated a dihydroxylated five-membered ring [8]. Moreover we felt that it was likely that a dihydroxylated cyclopentenone could be used to prepare both functionalised monocyclic NCS analogues [9] and the natural product chromophores. Thus, central to the philosophy of our programme is the preparation and utilisation of a functionalised five-membered ring in the construction of natural dienediynes and functionalised monocyclic analogues (scheme 2).

Scheme 2

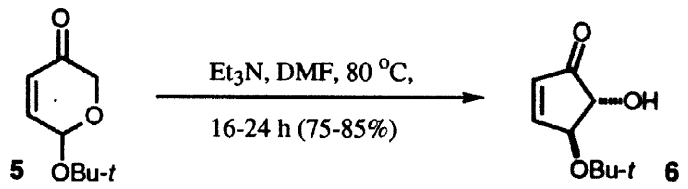


We herein present our work which describes our efforts towards the development of a synthetic approach to bicyclic dienediynes related to NCS and Kedarcidin Chromophores.

Results and Discussion

(i) Cyclopentenone Synthesis: After a considerable amount of investigation into methods for cyclopentannulation we found that we could promote an isomerisation of pyranone **5** (Scheme 3) [10]. This pyranone is readily prepared on large scale and such species have been widely used, most notably in recent years as precursors to oxopyriliums for cycloaddition reactions [11]. Thus treatment of **5** with Et_3N in DMF at 80 °C for 16-24 hours enables us to isolate the product **6** in 75-85% yield (scheme 3). We have found that these conditions offer the most effective method for this transformation and we have prepared 30-50 g batches of the desired material using this method [12].

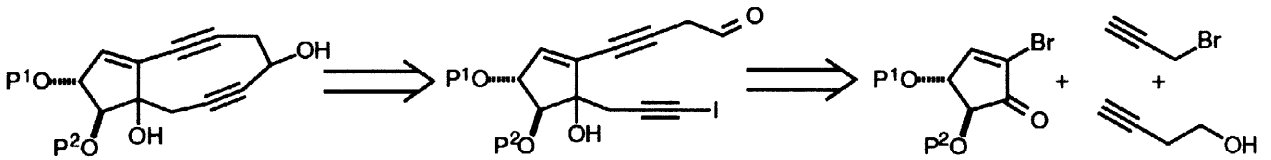
Scheme 3



(ii) Ring Closure: Studies Toward a Chromium Mediated Approach

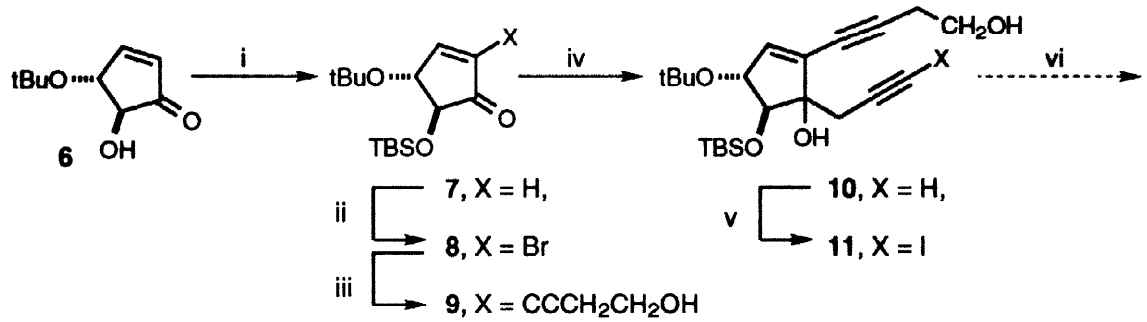
The use of chromium mediated coupling reactions in organic synthesis has been widely exploited in organic synthesis and is attractive because of the mildness of the reaction conditions and considerable functional group compatibility [13]. Work from the groups of Wender [14] and Buszek [15] demonstrated the applicability of such methods toward strained dienediyne ring systems, and we decided to evaluate the methods for the production of functionalised systems. The proposed approach is illustrated retrosynthetically in scheme 4.

Scheme 4



Protection of enone **6** using TBSCl followed by bromination gave **8** (Scheme 5). Cross coupling with 1-butynol and a sub-stoichiometric palladium (II) pre-catalyst led us to isolate the desired product **9** in excellent yield. It is noteworthy that this transformation is only successful with careful control of the reaction conditions. If, for example, slow addition techniques are not used, then we see none of the desired products and only traces of what we suspect to be enone dimer. In our experience, the application of these palladium "catalysed" protocols can be very effective in enyne and enediyne synthesis, but care must be taken in the preparation and storage of pre-catalysts and careful attention must be paid to experimental conditions. Addition of propargyl magnesium bromide to **9** followed by alkyne iodination gave the iodo-diol **11** in modest yield; these latter steps were not optimised. With the diol in place we attempted selective oxidation of the primary alcohol, but unfortunately treatment with the Dess-Martin periodinane reagent led to consumption of **11** and rapid decomposition of the derived products which may have included the desired aldehyde. Thus we were unable to evaluate the prospect of using the Cr/Ni coupling.

Scheme 5



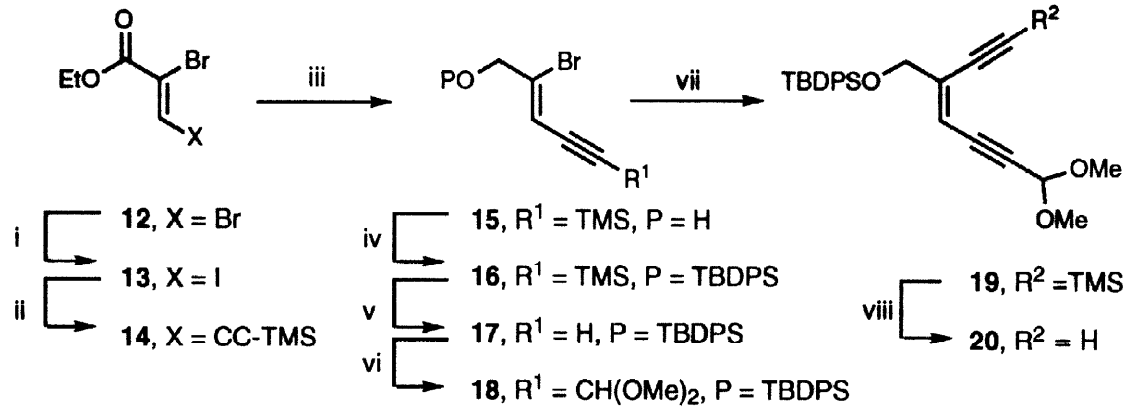
Reagents and conditions . i. TBSCl, Im, DMF, 0 °C, 92%. ii. Br_2, Et_3N, CH_2Cl_2, 81%. iii. $Pd(PPh_3)_2Cl_2$ (4%), CuI (9%), DIPA, 3-Butyn-1-ol (slow addn, 3h), THF, 50 °C, 98%. iv. $HCCCH_2MgBr$, Et_2O, -84 °C to r.t., 47%. v. I_2, morpholine, benzene, 50 °C, 44%. vi. DMP, CH_2Cl_2, r.t.

(iii) Ring Closure: Aldol Approach

Our efforts were then directed toward an aldol based strategy, and we were attracted to the prospect of using a cobalt carbonyl assisted approach which has been widely used in enediyne synthesis [16]. Of particular note are the pioneering contributions of Magnus and co-workers who have made extensive use of this type of approach in synthesis [17]. However to our knowledge, application to appropriately functionalised nine-membered rings related to NCS and Kedarcidin had not been achieved. In order to evaluate this type of approach, we needed to prepare an appropriate enediyne and then establish methods for its union with an appropriate cyclopentenone. It became apparent that conjugate addition may offer a very convergent strategy to the desired intermediate.

Synthesis of the enediyne fragment **20** is presented in scheme 6. Addition of Br_2 to ethyl propiolate gave the dibromide **12**, which could, as reported, undergo regioselective palladium mediated coupling with trimethylsilyl acetylene (TMSA) [18]. However we found that coupling of the iodide was preferable, and that bromide-iodide displacement could be readily achieved by a vinylogous Finkelstein reaction employing sodium iodide in acetone. Reduction and protection using TBDPSCl proceeded without event and TMS deprotection gave enyne **17**. Functionalisation of the terminal alkyne using a zinc assisted acetalisation gave acetal **18**, which, under carefully optimised conditions, could be transformed into enediyne **19** using a Pd(II) pre-catalyst. Deprotection using potassium carbonate provided enediyne **20** in acceptable yield. It is noteworthy that this approach, whilst somewhat lengthy, can be used to deliver multi-gram quantities of the desired enediyne **20**.

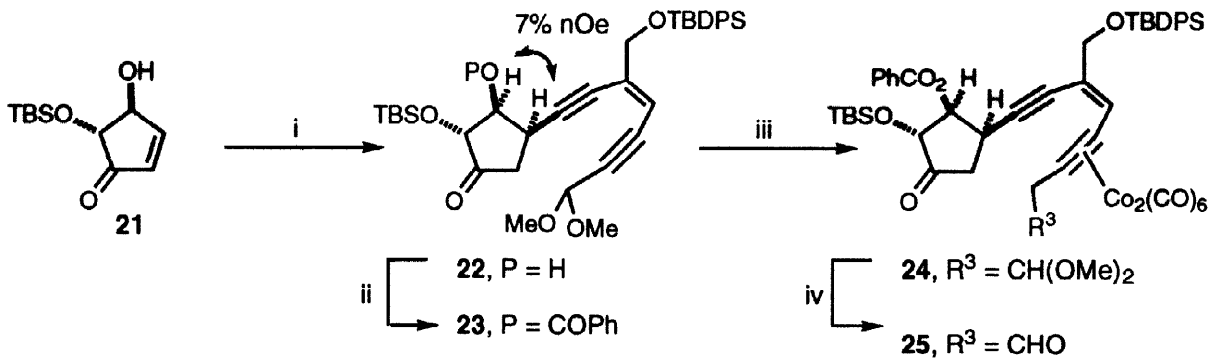
Scheme 6



Reagents and Conditions. i. NaI, acetone, 60°C, 94%. ii. $Pd(PPh_3)_4$, CuI, *i*-Pr_2NEt, TMSA, DMF, 0°C, 87%. iii. DIBALH, Et_2O, -78°C to 0°C, 97%. iv. TBDPSCl, DMAP, Im, DMF, 97%. v. K_2CO_3, MeOH, 75%. vi. $(MeO)_3CH$, $ZnCl_2$, 160°C, 96%. vii. $PdCl_2(PPh_3)_2$, CuI, *n*-$PrNH_2$, TMSA, THF, 60°C, 82%. viii. K_2CO_3, MeOH, 78%

In order to effect a conjugate addition of enediyne **20** with an enone, we needed to make use of a neighbouring hydroxyl group, and thus unmasking of the *tert*-butyl protecting group of **7** was effected using $TiCl_4$ to give enone **21**. Conjugate addition of alkynyl aluminium species to enones has been shown to be effective in the presence of a proximal hydroxyl group, presumably *via* some intramolecular delivery process [19]. These early reports specifically recommend the use of a non-polar solvent to effect such reactions. However our early attempts to use non-polar solvents were singularly unsuccessful, and it was only when we used THF as solvent that we were able to effect the clean conjugate addition. Under these conditions we were able to isolate the desired conjugate addition product **22** in reasonable yield (51%) with good recovery of unreacted enediyne **20** (yield based on recovered enediyne, 99%, scheme 7). The stereochemistry of the addition process is assigned on the basis of nOe difference experiments (protons at C-3 and C-4, 7%). Manipulation of adduct **22** required benzoate protection and thence cobalt carbonyl complexation (84%). Regioselectivity was assigned on the basis of chemical shift values by analogy with related systems [20]. Deprotection furnished the key aldehyde **25** (96%) required to assess the viability of the aldol ring closure.

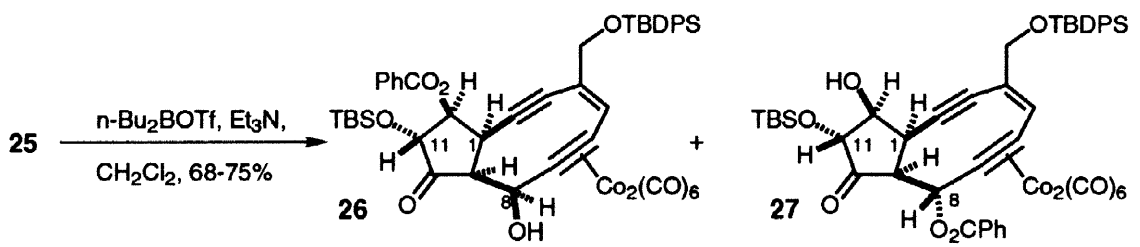
Scheme 7



Reagents and Conditions i. **20**, *n*-BuLi, THF, 0 °C, -78 °C, 30 min then Et_2AlCl, r.t. 1 h, then **21**, 51%. ii. PhCOCl, Pyr, DMAP, CH_2Cl_2, 89%. iii. $Co_2(CO)_8$, CH_2Cl_2, 0°C, 84%. iv. TFA, CH_2Cl_2, 96%.

Treatment of the aldehyde **25** with di-*n*-butylboron triflate and triethylamine effected the ring closure in good yield (75%) (scheme 8). Spectroscopic studies confirmed the structure of the major product (ratio 10:1) as the desired product **26** as a single diastereomer, assigned on the basis of extensive NMR spectroscopic experiments. In particular the observed nOe enhancements confirmed the syn relationship of protons at C-12, C-1, C-8 and C-9 (NCS-numbering). Careful analysis of the minor isomeric product using 2D COSY allowed us to carry out useful nOe experiments; a key enhancement between the protons at C-11 and C-8 (6.1%) established the stereochemistry at C-11, and a single observed enhancement of the proton at C-12 on irradiation of the OH corroborated the position of the benzoate group. From our data we propose the structure of the minor product to be consistent with **27** which is epimeric at C-8 and in which the benzoate group has migrated. The lack of nOe enhancement between the protons at C-8 and C-9 is also supportive of the proposed structure.

Scheme 8



In conclusion, we have established a boron-mediated aldol approach to functionalised bicyclic dienediynes, using a convergent and highly stereocontrolled synthetic approach. The control of relative stereochemistry is an important feature of the work and the following steps all proceed with very high levels of control: diastereoselective isomerisation of **5** to **6**; synthesis of enediyne **13**; conjugate addition to give **15**; alkyne complexation to give **16**;

intramolecular aldol reaction to give **17**. This work highlights the potential for using boron-mediated aldol reactions of cobalt hexacarbonyl complexed alkynyl aldehydes in the preparation of highly functionalised dienediynes. Our future work will concentrate on extending this strategy to further elaborated natural and unatural dienediynes.

Acknowledgements

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Experimental Section

General: All glassware was oven or flame dried prior to use. All reagents and solvents were purchased from commercial sources and used as supplied or purified using standard methods. ^{1}H NMR spectra were recorded on Bruker spectrometers at 500, 360 or 300 MHz. ^{13}C NMR spectra were recorded at 125.6 or 75 MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference. IR spectra were obtained on a Perkin Elmer 1710 FTIR spectrometer as thin films, solutions or KBr discs. Tlc was carried out on pre-coated silica-gel plates and visualised using standard procedures. Melting points are uncorrected.

***trans*-[4-(1,1-Dimethylethoxy)-5-(hydroxy)-2-cyclopenten-1-one 6**

A stirred solution of **5** (42 g, 0.25 mol) in DMF (800 ml) and Et_3N (16 ml, 1.24 mol) was heated at 80 °C for 24 h. The black reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* and purified by flash column chromatography on silica eluting with 2:1 petrol/ether to give **6** as a white solid (32.8 g, 78 %) m.p. 61 - 63 °C. νmax (cm^{-1}) 3430, 2979, 1719, 1615, 1393, 1266, 922; δ_H 7.28 (1H, dd, J 6.1, 1.8 Hz), 6.18 (1H, d, J 6.1 Hz), 4.53 - 4.56 (1H, m), 4.03 (1H, d, J 2.2 Hz), 3.42 (1H, bs), 1.25 (9H, s); δ_C 205.0, 161.5, 131.3, 80.7, 76.4, 75.1, 28.2; HRMS (EI) calcd. for $C_8H_{11}O_3$ $(M-CH_3)^+$ 155.0708, found *m/e* 155.0703.

***trans*-[4-(1,1-Dimethylethoxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]]-2-cyclopenten-1-one 7**

To a solution of **6** (10.3 g, 60.6 mmol) in dry DMF (94 ml) at 0 °C was added *tert*-butyldimethylsilyl chloride (11.1 g, 73.3 mmol) and the mixture stirred for 15 min. Imidazole (4.8 g, 73.3 mmol) was then added to the mixture in 4 portions over 10 min, after 4 h the reaction was quenched with saturated $NaHCO_3$ solution and extracted with ether. The extracts were washed with water, brine and dried using $MgSO_4$. The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica eluting with 15:1 petrol/ether to give **7** as a pale yellow oil (15.9 g, 92 %). νmax (cm^{-1}) 2931, 2887, 2858, 1729, 1619, 1587, 1473, 1391, 1366, 1342, 1191, 1142, 1079, 1044, 917, 840, 782, 681; δ_H 7.19 (1H, dd, J 6.3, 1.6 Hz), 6.07 (1H, d, J 6.3 Hz), 4.5 (1H, d, J 1.2 Hz), 4.07 (1H, d, J 2.9 Hz), 1.24 (9H, s), 0.88 (9H, s), 0.14 (3H, s), 0.09 (3H, s); δ_C 203.3, 160, 132.3, 81.7, 77.6, 75.3, 28.8, 26.2, 18.8, -3.8, -4.7; HRMS (FAB) calcd. for $C_{15}H_{29}O_3Si$ $(M+H)^+$ 285.1886, found 285.1886.

***trans*-[4-(1,1-Dimethylethoxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]]-2-bromo-2-cyclopenten-1-one 8**

A solution of **7** (1.13 g, 3.9 mmol) in dry distilled CH_2Cl_2 (3.5 ml) was stirred at 0 °C under N_2. Br_2 (0.3 ml, 5.6 mmol) in CH_2Cl_2 (3.5 ml) was added dropwise over 15 min and thereaction mixture was allowed to stir at 0 °C under N_2 for 30 min. Et_3N (0.65 ml, 4.7 mmol) in CH_2Cl_2 (3.5 ml) was added dropwise over 20 min and the reaction mixture was stirred at 0 °C under N_2 for a further 60 min. The reaction mixture was then stirred at room temperature overnight, diluted with CH_2Cl_2 (50 ml), washed with H_2O (15 ml), and brine (15 ml). The resultant organic solution was dried (Na_2SO_4, 30 min) and reduced *in vacuo* to yield the crude product as an orange oil (1.84g). The crude material was purified by flash column chromatography on silica using a gradient elution of petrol/ether 10:1 to 1:1 to give **8** as a yellow oil (1.15 g, 81 %). νmax (film) cm^{-1} 2931, 2858, 1743, 1586, 1392, 1366, 1071, 1257, 841, 782, 701, 632. δ_H 7.38 (1H, s), 4.51 (1H, s), 4.18 (1H, d, J 2.0), 1.28 (9H, s), 0.92 (9H, s), 0.20 (3H, s), 0.15 (3H, s). δ_C 196.7, 158.2, 124.5, 80.5, 77.0, 75.8, 28.7, 26.1, 18.7, -3.9, -4.7. HRMS calcd for $C_{15}H_{27}O_3Si^{79}Br$ $(M)^+$: 362.09128, found: 362.0913.

***trans*-[4-(1,1-Dimethylethoxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]]-2-(4-hydroxy-1-butynyl)-2-cyclopenten-1-one 9**

A solution of **8** (0.075 g, 0.21 mmol), *N,N*-diisopropylamine (0.15 ml, 1.1 mmol), CuI (0.032 g, 0.16 mmol) and $(PPh_3)_2PdCl_2$ (0.0052 g, 0.0075 mmol) stirred in dry distilled THF (5 ml) was heated to 50 °C. A solution of 3-butyn-1-ol (0.016 ml, 0.21 mmol) in dry distilled THF (2 ml) was added dropwise over 2 hours and the resultant mixture was stirred at 50 °C for a further 2 hours. The mixture was allowed to cool to room temperature, quenched with saturated aqueous NH_4Cl solution (2 ml) and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$, 30 mins) and reduced *in vacuo* to yield the crude product as a brown oil. The crude material was purified by flash column chromatography (gradient petrol/ether 3:1 to 1:1) to give **9** as a yellow oil (0.070 g, 98 %). νmax (cm^{-1}) 3426, 2958, 2930, 2853, 2362, 1372, 1392, 1367, 1257, 1084, 839, 781. δ_H 7.23 (1H, s), 4.54 (1H, s), 4.16 (1H, d, J 2.9), 3.79 (2H, t, J 6.2), 2.68 (2H, t, J 6.2), 2.10 (1H, s), 1.29 (9H, s), 0.93 (9H, s), 0.19 (3H, s), 0.14 (3H, s); δ_C 199.0, 159.5, 128.5, 95.7, 81.6, 76.2, 75.6, 61.2, 28.8, 26.2, 24.5, 18.8 -3, -4.7. HRMS calcd for $C_{19}H_{33}O_4Si$ $(M+H)^+$: 353.21481, found: 353.2148.

***trans* [4-(*t*-butoxy)-5-(*t*-butyldimethylsilyloxy)]-2-(4-hydroxy-1-butynyl)-1-(2-propynyl) cyclopent-2-ene-1-ol 10**

Propargylmagnesium bromide (1.5 ml of 1.03 M solution, 1.5 mmol) was added to a solution of **9** (0.299 g, 0.84 mmol) stirred in dry/distilled ether (12 ml) at -84 °C under N_2. The mixture was stirred at -84 °C for 15 mins, allowed to warm to room temperature, stirred for a further hour and then quenched with saturated aqueous NH_4Cl solution (8 ml). The aqueous layer was extracted with ether. The combined organic layers were dried with $MgSO_4$ and reduced *in vacuo* to give the crude product as a brown oil. The crude material was purified by flash column chromatography (gradient, petrol/ether 20:1 to 5:1) to give **10** as a pale yellow solid (0.154 g, 47 %). mpt. 117 - 120 °C. νmax (cm^{-1}) 3600, 3312, 2959, 2929, 2896, 2857, 1618, 1473, 1463, 1390, 1365, 1257, 1047, 839, 779. δ_H 5.98 (1H, s), 4.31 (1H, d, J 5.6), 3.96 (1H, d, J 5.6), 3.76 (2H, t, J 6.0), 2.70 - 2.60 (4H, m), 2.05 (1H, t, J 6.0), 1.21 (9H, s), 0.94 (9H, s), 0.15 (3H, s), 0.13 (3H, s). δ_C 136.9, 128.6, 91.1, 85.3, 80.1, 79.3, 76.6, 76.2, 73.1, 70.0, 59.8, 27.4, 24.9, 24.5, 22.9, 16.9, -3.9, -4.0. HRMS calcd for $C_{22}H_{44}NO_4Si$ $(M+NH_4)^+$: 410.27266, found: 410.2727.

trans[4-(_t_-butoxy)-5-(_t_-butyldimethylsilyloxy)]-2-(4-hydroxy-1-butynyl)-1-(3-iodo-2-propynyl) cyclopent-2-ene-1-ol 11

Morpholine (1.12 ml, 12.9 mmol) was added to a suspension of I_2 (1.0 g, 4 mmol) stirred in dry/distilled benzene (1 ml) at room temperature. The mixture was stirred until all the iodine had dissipated and an orange solid was formed. A solution of **10** (0.7 g, 1.8 mmol) in dry/distilled benzene (1 ml) was added to the orange solid and the resultant mixture was stirred at 50 °C for 48 hours. The mixture was diluted with ether (30 ml), washed with saturated aqueous sodium thiosulfate solution (10 ml), dried ($MgSO_4$, 30 mins) and reduced *in vacuo* to give the crude product as a brown oil. The crude material was purified by flash column chromatography on silica (gradient petrol/ether 10:1 to 5:1) to give **11** as a brown solid (0.41 g, 44 %). mpt. 62 - 64 °C. νmax (cm^{-1}) 3608, 3354, 2959, 2930, 2898, 2857, 2343, 2222, 1620, 1473, 1463, 1391, 1365, 1342, 1259, 1134, 1087, 1048, 861, 839, 469. δ_H 5.98, (1H, d, J 1.4), 4.29 (1H, d, J 5.8), 3.95 (1H, d, J 5.8), 3.80 (2H, t, J 6.1), 2.83 - 2.59 (4H, m), 1.94 (1H, s), 1.21 (9H, s), 0.94 (9H, s), 0.14 (3H, s), 0.13 (3H, s). δ_C 138.6, 129.8, 92.7, 92.7, 90.7, 86.8, 81.8, 78.1, 76.4, 74.6, 61.4, 28.8, 28.3, 26.3, 24.5, 18.4, -3.8, -4.0. HRMS calcd for $C_{18}H_{26}O_4SiI$ $(M\text{-}t\text{-}Bu)^+$: 461.06452, found: 461.0645.

(Z)- Ethyl 2-bromo-3-iodopropenoate 13

To a stirred solution of the dibromide **12** (21.0 g, 81.0 mmol) was added a solution of sodium iodide (28.5 g, 190 mmol) in dry acetone (70 ml) and the resulting orange suspension was heated at reflux for 3 days (reaction monitored by ^1H NMR). The reaction was cooled to room temperature and concentrated *in vacuo*. The crude mixture was filtered through silica (10:1 petrol/CH_2Cl_2) to give **13** as a colourless oil (23.1 g, 94 %) νmax (cm^{-1}) 2936, 2904, 1730, 1559, 1464, 1298, 1246, 1192, 1033, 733 cm^{-1}; δ_H, 8.71 (1H, s), 4.28 - 4.21 (2H, q, J 7.1 Hz), 1.3 (3H, t, J 7.1 Hz); δ_C 160.1, 129.1, 102.8, 63.2, 14.8; HRMS calcd. for $C_5H_6O_2{}^{79}BrI$ $(M)^+$ 303.8596, found 303.8596.

(Z)-Ethyl 2-bromo-3-ethynyl-(trimethylsilyl)propenoate 15

To a deoxygenated solution of **13** (7.47 g, 240 mmol) in DMF (46 ml) under nitrogen was added diisopropylethylamine (7.70 ml, 44.2 mmol). The mixture was then degassed and cooled in an ice bath and trimethylsilylacetylene (6.0 ml, 42.5 mmol) added. Cuprous iodide (950 mg, 5 mmol) and *tetrakis*-(triphenylphosphine) palladium (1.4 g, 11.2 mmol) were added to the reaction mixture. After 10 h at 0 °C the reaction was quenched with saturated ammonium chloride solution and extracted with ether. The organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue was

carried out by flash column chromatography on silica (45:1 petrol/ ether) to give **14** as a pale orange oil (5.90 g, 87 %) which was used immediately in the following reaction. To a solution of **14** (7.40 g, 27 mmol) in ether (80 ml) at -78 °C was added dropwise *diisobutylaluminium hydride* (10.5 ml, 59 mmol). After 15 min the reaction flask was placed in an ice bath and stirred for a further 3 hours then quenched carefully with saturated Rochelle salt and the slurry stirred for 45 mins and then extracted with ether. The organic layers were washed with H_2O, brine and dried with $MgSO_4$.and concentrated *in vacuo*. Purification was carried out by flash column chromatography (10:1 petrol/ether) to give **15** as a colourless oil which solidified in the fridge (6.1 g, 97 %). Mpt 29-30 °C; vmax (cm^{-1}) 3583, 3339, 2960, 2859, 2140, 1613, 1250, 1101, 1082, 1012, 844; δ_H 6.36 (1H, s), 4.37 - 4.35 (2H, m), 2.11 (1H, br s), 0.27 (9H, s); δ_C137.6, 110.9, 102.3, 100.8, 67.8, 0.0; HRMS (EI) calcd. $C_8H_{13}BrOSi$ $(M)^+$ 231.9919, found 231.9919.

(1,1-Dimethylethyl)[(2-bromo-2-pentene-5-trimethylsilyl-4-ynyl)oxy]diphenylsilane 16

Imidazole (4.50 g, 66 mmol), and t-butyldiphenylsilylchloride (15.0 ml, 58 mmol) was added successively to a cold solution of **15** (12.30 g, 52.7 mmol) in DMF (60 ml) at 0 °C. After 3 hours the reaction was quenched with saturated sodium bicarbonate solution and extracted with ether. The extracts were washed with water, brine and dried with $MgSO_4$. The crude reaction mixture was purified by flash column chromatography eluting with 20:1 petrol/ether to give **16** as a clear oil (24.1 g, 97 %). vmax (cm^{-1}) 3072,2959, 2931, 2896, 2858, 2144, 1959, 1889, 1825, 1488, 1472, 1463, 1250, 1114, 1091, 844, 825, 701cm^{-1}; δ_H 7.65 - 7.63 (4H, m), 7.47 - 7.37 (6H, m), 6.57 (1H, s), 4.31 (2H, s), 1.26 (9H, s), 0.19 (9H, s); δ_C136.8, 136.4, 132.6, 130.2, 128.0, 109.1, 101.4, 101.3, 68.0, 26.8, 19.4, 0.00; HRMS (EI) calcd. for $C_{24}H_{32}BrOSi_2$ $(M+H)^+$ 471.1175, found 471.1175.

(1,1-Dimethylethyl)[(2-bromo-2-penten-4-ynyl)oxy]diphenylsilane 17

To a solution of **16** (10.8 g, 23 mmol) in methanol (140 ml) was added potassium carbonate (0.32 g, 2.3 mmol) and the mixture stirred for 2 hours. The reaction mixture was then concentrated *in vacuo*, and the residue diluted with ether, washed with water, brine and dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by chromatography on silica (25:1 petrol/ether) to give **17** as a white solid (6.88 g, 75 %). Mpt 72-73 °C; vmax (cm^{-1}) 3266, 2956, 2931, 2881, 2857, 1624, 1587, 1469, 1427, 1282, 1254, 1130, 1113, 1106, 832, 806, 747, 702, 609, 451; δ_H 7.58 - 7.56 (4H, m), 7.41 - 7.30 (6H, m), 6.46 - 6.44 (1H, m), 4.25 - 4.24 (2H, m), 3.23 (1H, d, J 2.2 Hz), 1.00 (9H, s); δ_C 137.7, 135.8, 133.0,

130.5, 128.4, 108.5, 83.7, 80.4, 68.3, 27.1, 19.7; HRMS (CI) calcd. for $C_{21}H_{27}BrONSi$ $(M+NH_4)^+$ 416.1045, found 416.1045.

(1,1-Dimethylethyl)[(2-bromo-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane 18

A mixture of **17** (4.91 g, 14.5 mmol) and zinc (II) chloride (2.0 g, 14.5 mmol) in trimethylorthoformate (90 ml) in a Dean-Stark apparatus was heated in an oil bath at 160 °C for 9 hours. The mixture was cooled to room temperature and filtered through celite with ether. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (10:1 petrol/ether) to give **18** (5.62 g, 96 %) as a pale brown oil. νmax (cm^{-1}) 3071, 2958, 2932, 2892, 2857, 2829, 2225, 1737, 1629, 1590, 1568, 1487, 1472, 1463, 1449, 1428, 1358, 1341, 1252, 1114, 1057, 963, 824, 702; δ_H 7.58 - 7.55 (4H, m), 7.38 - 7.30 (6H, m), 6.52 - 6.51 (1H, m), 5.26 (1H, d, J 1.5 Hz), 4.25 (2H, d, J 1.5 Hz), 3.37 (6H, s), 0.99 (9H, s); δ_C 137.9, 135.8, 132.9, 130.5, 128.3, 108.2, 93.9, 89.7, 82.7, 68.3, 53.1, 27.1, 19.7; HRMS (EI) calcd. for $C_{23}H_{26}{}^{81}BrO_2Si$ $(M\text{-}OMe)^+$ 443.0866, found 443.0866.

(1,1-Dimethylethyl)[(2-(2-(1,1,1-trimethylsilyl)ethynyl)-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane 19

To a suspension of **18** (7.50 g, 16.0 mmol) and $(PPh_3)_2PdCl_2$ (460 mg, 0.64 mmol) in dry THF (120 ml) was added *n*-propylamine (21 ml, 160 mmol) and the resulting clear solution stirred for 15 mins. Cuprous (I) iodide (160 mg, 1.44 mmol) was then added and the green solution stirred for a further 15 mins, followed by the addition of trimethylsilylacetylene (3.4 ml, 240 mmol). The reaction mixture was then placed in an oil bath at 60 °C and stirred for 6 hours. The reaction mixture was cooled to room temperature and quenched with saturated ammonium chloride solution and extracted with ether. The combined organic layers was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20:1 petrol/ether) to give **19** as a pale yellow oil (6.50 g, 82 %). νmax (cm^{-1}) 3072, 2998, 2958, 2829, 2218, 2145, 1590, 1472, 1428, 1357, 1251, 1161, 1096, 1058, 963, 879, 702, 638, 610; δ_H 7.65 - 7.62 (4H, m), 7.45 - 7.35 (6H, m), 6.28 - 6.27 (1H, m), 5.34 (1H, d, J 1.5 Hz), 4.22 (2H, d, J 1.5 Hz), 3.42 (6H, s), 1.04 (9H, s), 0.15 (9H, s); δ_C 136.2, 135.7, 133.1, 130.2, 128.2, 128.1, 112.7, 103.9, 100.8, 93.9, 90.1, 83.8, 65.3, 52.9, 27.0, 19.5, 0.00; HRMS (EI) calcd. for $C_{29}H_{38}O_3Si_2$ $(M)^+$ 490.2360, found 490.2360.

(1,1-Dimethylethyl)[(2-ethynyl-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane 20

To a solution of **19** (452 mg, 0.92 mmol) in dry methanol (15 ml) was added potassium carbonate (13 mg, 0.09 mmol) and stirred for 3 hours. The reaction mixture was then concentrated *in vacuo* and the residue was then diluted with ether, washed with water, brine and dried with $MgSO_4$. After concentrated the residue was chromatographed on silica (25:1 petrol/ ether) to give **20** as a pale green oil (301 mg, 78 %). vmax (cm^{-1}) 3284, 2958, 2932, 2892, 2858, 2830, 2219, 1963, 1892, 1826, 1589, 1472, 1428, 1358, 1342, 1190, 1175, 1155, 1095, 1056, 962, 824, 702, 488; δ_H 7.58 - 7.55 (4H, m), 7.37 - 7.18 (6H, m), 6.28 - 6.29 (1H, m), 5.29 - 5.28 (1H, m), 4.18 - 4.17 (2H,m), 3.36 (6H, s), 3.23 (1H, s), 0.99 (9H, s); δ_C 137.3, 136.7, 134.6, 131.8, 129.8, 115.1, 95.4, 91.9, 87.4, 84.9, 81.4, 66.9, 54.5, 28.6, 21.2; *m/e* (EI) 418, 417 , 387, 361, 331, 239, 199, 135.

***trans*-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]]-4-hydroxy]-2-cyclopenten-1-one 21**

To a stirred solution of **7** (2.38 g, 8.36 mmol) in CH_2Cl_2 (33 ml) at 0 °C was added titanium (IV) tetrachloride (1.0 ml, 9.2 mmol) and the resulting dark red solution stirred for 15 mins. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers was washed with brine, dried using $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 petrol/ethyl acetate) to give **21** (1.10 g, 57 %) as a white solid. Mpt 60-61 °C; vmax (cm^{-1}) 3358, 2953, 2927, 2855, 1706, 1593, 1470, 1361, 1283, 1260, 1141, 1117, 1063, 1038, 871, 839, 774, 725; δ_H 7.33 (1H, dd, J 6.3 1.9 Hz), 6.16 (1H, dd, J 6.3 1.2 Hz), 4.70 - 4.72 (1H, m), 4.11 (1H, d, J 2.7 Hz), 2.31 (1H, br s), 0.91 (9H, s), 0.16 (3H, s), 0.13 (3H, s); δ_C 203.0, 158.9, 133.0, 82.7, 78.0, 26.2, 18.8, -4.1, -4.7; HRMS (EI) calcd. for $C_{11}H_{21}O_3Si$ $(M+H)^+$ 229.1260, found 229.1260.

[2α,3α,4β(E)]-2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-4-[3-[[[(1,1-dimethylethyl)diphenylsilyl]-oxy]methyl]-7,7-dimethoxy-3-heptene-1,5-diynyl]-3-hydroxy-cyclopentanone 22

To a stirred solution of **20** (1.22 g, 2.9 mmol) in THF (11 ml) at -78 °C was added dropwise *n*-BuLi (2.0 ml, 1.6 M in hexanes, 3.2 mmol) and the resulting red solution stirred for 40 mins while maintaining the temperature (-78 °C). A solution of diethylaluminium chloride (3.8 ml, 1 M in hexanes, 3.80 mmol) was addded dropwise and the mixture was then allowed to warm to room temperature and stirred for 1 hour. The aluminate reagent was then added *via* canula to a solution of **21** (0.31 g, 1.36 mmol) in THF (11 ml) at 0 °C. The reaction mixture was then warm to room temperature and stirred for 6 h, after which point saturated

NH_4Cl was added and the aqueous layer extracted with ethyl acetate. The combined extracts were washed with brine, dried using $MgSO_4$ and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (3:1 petrol/ether) to give **22** as a pale yellow oil (0.45 g, 51 %; 99 % based on recovered enediyne 0.93 g). νmax (cm^{-1}) 3050, 2930, 2857, 2218, 1761, 1590, 1472, 1463, 1428, 1360, 1254, 1191, 1173, 1113, 1057, 839, 782, 703, 610; δ_H 7.64 - 7.61(4H, m), 7.46 - 7.36 (6H, m), 6.26 (1H, s), 5.32 (1H, s), 4.22 - 4.21 (2H, m), 4.0 (1H, app.q, J 4.1 Hz), 3.9 (1H, d, J 4.0 Hz), 3.52 - 3.44 (1H, m), 3.4 (6H, s), 2.72 (1H, d, J 4.4 Hz), 2.52 - 2.47 (2H, m), 1.05 (9H, s), 0.86 (9H, s), 0.11 (3H, s), 0.09 (3H, s); δ_C 214.0, 138.5, 138.0, 135.3, 132.6, 114.7, 98.4, 96.0, 92.5, 86.3, 83.8, 80.5, 77.8, 67.6, 55.2, 41.7, 34.9, 29.3, 28.2, 21.8, 20.8, -2.1, -2.5; HRMS (CI, NH_3) calcd. for $C_{37}H_{54}NO_6Si_2$ $(M+NH_4)^+$ 664.3490, found 664.3490. n.O.e enhancement between protons at: C-3, C-4, 7%.

3-(Benzyloxy)-2α-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-4β-[3-[[[(1,1-dimethylethyl)diphenylsilyl]-oxy]methyl]-7,7-dimethoxy-3(E)-heptene-1,5-diynyl]-3α-hydroxy-cyclopentanone 23

To a solution of **22** (1.26 g, 1.95 mmol), in CH_2Cl_2 (25 ml) at 0 °C was added pyridine (1.7 ml, 21.2 mmol), 4-dimethylaminopyridine (25 mg, 0.20 mmol) and benzoyl chloride (1.7 ml, 14.7 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was then quenched with saturated $NaHCO_3$ solution and extracted with ether. The organic layer was then washed with HCl (10 %), brine, dried $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica (18:1 petrol/ether) to give **23** (1.30 g, 89 %) as a colourless oil. νmax (cm^{-1}) 3072, 2955, 2931, 2892, 2857, 2216, 1766, 1728, 1602, 1589, 1472, 1463, 1428, 1360,1269, 1175, 1113, 1057, 962, 839, 703, 610 δ_H 7.80 (2H, d, J 7.7 Hz), 7.45 - 7.40 (4H, m), 7.33 - 7.18 (7H, m), 7.11 - 7.06 (2H, m), 6.12 (1H, s), 5.12 (1H, d, J 7.0 Hz), 5.09 (1H, s), 4.26 (1H, d, J 7.5 Hz), 3.91 - 3.90 (2H, m), 3.74 - 3.67 (1H, q, J 6.5 Hz), 3.23 (6H, s), 2.57 (2H, d, J 7.0 Hz), 0.88 (9H, s), 0.72 (9H, s), 0.00 (3H, s), -0.05 (3H, s); δ_C 209.7, 166.1, 135.8, 133.8, 133.1, 130.4, 130.0, 129.6, 128.8, 128.3, 112.1, 95.8, 93.9, 90.2, 83.7, 80.6, 77.4, 77.0, 65.3, 52.9, 41.3, 29.0, 27.1, 26.0, 19.6, 18.6, -4.2, -4.6; HRMS (CI, NH_3) calcd. for $C_{44}H_{58}NO_7Si_2$ $(M+NH_4)^+$ 768.3750, found 768.3750.

[μ–[3α–(Benzyloxy)–2α-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-4β-[(5,6-η:5,6-η)-3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-7,7-dimethoxy-3(E)-heptene-1,5-diynyl]cyclopentanone]]]hexacarbonyldicobalt 24

Dicobalt octacarbonyl (0.90 g, 2.63 mmol) was added to a solution of **23** (1.30 g, 1.73 mmol) in CH_2Cl_2 (30 ml) at 0 °C. After 3 hours the dark red solution was then concentrated *in vacuo* and the residue was purified by flash column chromatography (15:1 petrol/ether) to give **24** (1.51 g, 84 %) as a red oil. νmax (cm^{-1}) 2956, 2932, 2858, 2830, 2093, 2055, 2027, 1767, 1729, 1473, 1317, 1268, 1113, 840, 710, 613; δ_H 7.86 - 7.83 (2H, m), 7.59 - 7.53 (4H, m), 7.44 - 7.23 (7H, m), 7.17 - 7.12 (3H, m), 5.38 (1H, s), 5.25 (1H, t, J 6.1 Hz), 4.24 (1H, d, J 6.5 Hz), 4.04 (2H, s), 3.82 (1H, q, J 6.1 Hz), 3.42 (3H, s), 3.40 (3H, s), 2.66 - 2.62 (2H, m), 1.01 (9H, s), 0.82 (9H, s), 0.07 (3H, s), 0.04 (3H, s); δ_C 209.3, 199.3, 165.5, 147.3, 135.2, 135.2, 133.3, 132.9, 132.9, 129.8, 129.8, 129.4, 129.2, 129.0, 128.3, 127.7, 127.3, 104.2, 99.4, 93.9, 83.0, 81.2, 76.9, 76.2, 66.3, 54.6, 40.1, 31.7, 29.5, 26.6, 25.5, 19.2, 18.1, -4.8, -5.2; HRMS (FAB) calcd. for $C_{44}H_{54}O_7Si_2CO_2$ $[M-(CO)_6]^+$ 868.2072, found 868.2083.

[μ-[(2,3-η:2,3-η)-7α-[2α–(benzyloxy)-3β-[((1,1-dimethylethyl)dimethylsilyl)oxy]-4-oxocyclopentyl]-5-[[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-4-heptene-2,6-diynal]]-hexacarbonyldicobalt 25

To a solution of **24** (1.50 g, 1.45 mmol) in CH_2Cl_2 (140 ml) at room temperature was added aqueous trifluoroacetic acid (14 ml, 30 %v/v). After 30 min the reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with brine, dried $MgSO_4$, concentrated *in vacuo* and the residue was purified by flash column chromatography (4:1 petrol/ether) to give **25** (1.37g, 96%) as a red oil. νmax (cm^{-1}) 3071, 2931, 2890, 2858, 2100, 2064, 2035, 1766, 1728, 1628, 1473, 1464, 1429, 1268, 1113, 738, 710, 702, 613; δ_H 10.28 (1H, s), 7.85 (2H, d, J 7.3 Hz), 7.57 - 7.52 (4H, m), 7.45 - 7.29 (7H, m), 7.20 - 7.14 (2H, m), 7.03 (1H, s), 5.24 (1H, t, J 6.0 Hz), 4.20 (1H, d, J 6.2 Hz), 4.00 (2H, s), 3.81 - 3.75 (1H, m), 2.65 (2H, AB), 1.03 (9H, s), 0.84 (9H, s), -0.10 (3H, s), -0.13 (3H, s); δ_C 209.6, 198.2, 190.6, 165.9, 135.7, 133.8, 133.3, 133.2, 130.4, 129.9, 129.5, 129.1, 128.8, 128.3, 126.7, 100.4, 88.0, 85.7, 81.6, 77.3, 76.7, 66.1, 40.3, 29.9, 27.1, 26.0, 19.7, 18.6, -4.3, -4.7; HRMS (FAB) calcd. for $C_{42}H_{48}O_6Si_2CO_2$ $[M-(CO)_6]^+$ 822.1653, found 822.1654.

(2R*, 3S*, 3aR*, 6E, 10S*, 10aS*)-[μ-[(8,9-η:8,9-η)-3-(benzyloxy)-4,5,8,9-tetra-dehydro-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-3,3a,10,10a-tetrahydro-10-hydroxy-1-2(H)-cyclopentacyclononenone]]-hexacarbonyldicobalt 26 & (2R*, 3S*, 3aR*, 6E, 10R*, 10aS*)-[μ-[(8,9-η:8,9-η)-10-(benzyloxy)-4,5,8,9-tetra-dehydro-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-3,3a,10,10a-tetrahydro-3-hydroxy-1-2(H)-cyclopentacyclononenone]]-hexacarbonyldicobalt 27

To a solution of freshly distilled di-*n*-butylboron triflate (70.0 μl, 0.34 mmol) in CH_2Cl_2 (5 ml) at -78 °C was added dropwise triethylamine (90 mml, 0.67 mmol) and the solution stirred for 30 mins. The reaction mixture was then placed in an ice bath and a solution of **25** (66.3 mg, 0.067 mmol) in CH_2Cl_2 (5 ml) was added over 1 hour by syringe pump. After completion of addition, the reaction was warmed to room temperature and stirred for a further 6 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted with ether. The combined extracts was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (7:1 and 3:1 petrol/ether) to give both **26** and **27** (45.4 mg) and (4.4 mg); overall yield 75% as a red oil. **27** (less polar) vmax (cm^{-1}) 3500, 3072, 2956, 2931, 2859, 2091, 2052, 2029, 1731, 1590, 1472, 1374, 1293, 1261, 1113, 1069, 909, 841, 737, 702; δ_H 7.96 - 7.79 (2H, m), 7.4 - 7.13 (13H, m), 6.97 (1H, s, H_5), 5.40 (1H, d, J 10.7 Hz, H_8) 5.36 (1H, dd, J 7.7 3.5 Hz, H_{12}), 4.47 (1H, s, OH), 4.27 (1H, d, J 3.6 Hz, H_{11}), 3.94 (1H, m, H_1), 3.89 - 3.58 (2H, m, CH_2), 2.53 (1H, dd, J 10.5, 6.9 Hz, H_9), 0.97 (9H, s), 0.91 (9H, s), 0.13 (3H, s), 0.09 (3H, s); δ_C 198.3, 164.3, 134.6, 134.3, 132.2, 132.0, 131.8, 128.8, 128.7, 128.5, 126.7, 126.6, 124.0, 101.8, 97.5, 97.2, 88.2, 83.8, 82.5, 70.4, 62.1, 51.6, 34.8, 25.6, 24.9, 24.6, 24.4, 18.2, 17.1, 12.9, -5.8, -6.0; *m/e* (FAB) 991, 909, n.O.e enhancement between protons at: C-8, C-11, 6.1%; C-9, C-1, 6.8%; O-H, C-12, 2.3%. **26** (more polar) : vmax (cm^{-1}) 3479, 3073, 2957, 2858, 2092, 2054, 2028, 1762, 1729, 1603, 1363, 1429, 1316, 1268, 1113, 840, 738, 709; δ_H 7.9 (2H, d, J 7.3 Hz), 7.48 - 7.12 (13H, m), 6.99 (1H, s, H_5), 5.5 (1H, dd, J 8.4, 5.6 Hz, H_8), 5.3 (1H, app.t, J 5.4 Hz, H_{12}), 4.4 (1H, d, J 5.2 Hz, H_{11}), 4.2 (1H, dd, J 8.8 5.8 Hz, H_1), 4.1 (2H, s, CH_2), 3.65 (1H, d, J 5.6 Hz, OH), 3.2 (1H, app. t, J 8.7 Hz, H_9), 1.0 (9H, s), 0.87 (9H, s), 0.15 (3H, s), 0.12 (3H, s); δ_C 211.7, 199.8, 166.0, 137.2, 135.8, 134.0, 133.4, 133.3, 130.3, 130.2, 129.5, 129.0, 128.2, 125.3, 101.1, 98.6, 89.7, 85.3, 77.9, 72.3, 63.9, 55.3, 33.2, 30.1, 29.5, 27.1, 26.0, 23.0, 19.6, 18.6, 11.9, -4.3, -4.6; *m/e* (FAB) 991 850, 881, 822, n.O.e

enhancement between protons at: C-8, O-H, 2.7%; C-8, C-9, 2.4%; C-1, C-12, 6.4%; C-1, C-9, 6.0%.

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