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Towards aflatoxins: a formal synthesis of aflatoxin B2

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In memoriam J. Malcolm Bruce (5/10/32–15/5/2007). A true gentleman, chemist and selfless member of the University of Manchester

Abstract

The development of a formal synthesis of aflatoxin B2 is described, which utilizes a Dötz benzannulation reaction as a key step.

Keywords: Dötz; Benzannulation; Aflatoxin; Silatropic; Metallation

1. Introduction

A colleague once remarked[1] that the initiation of an independent research career may best be described as ‘‘the best and worst of times’’, which is a sentiment I can wholeheartedly attest to. As a fledgling academic I was intrigued by the work of Schrock[2] on the then emerging chemistry of nucleophilic, Tebbe-type, carbene complexes and decided to utilize these intermediates in an approach to the molecule of the moment—taxol[3]—unfortunately none of this work came to fruition and has never seen the light of day.

Having realized that taming such chemistry was just too much for a first year graduate student we decided to change the metal and investigate, for a couple of months at least, the chemistry of the better behaved, and more user friendly chromium–carbene complexes.[4] This paper describes the work leading to the formal synthesis of aflatoxin B2, which utilizes a Dötz benzannulation in the synthesis of the highly functionalized aromatic core of the natural product.

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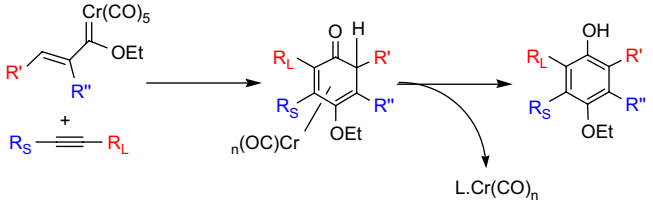
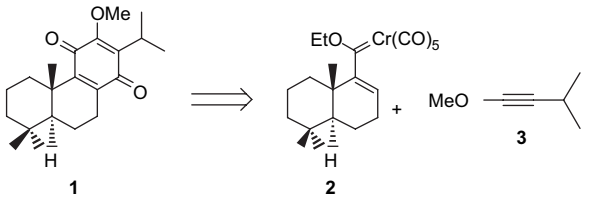
2. Results and discussion

Believing, at the time (1988), that the Dötz reaction,[5] Scheme 1, was ripe for exploitation our attention focused in gaining a footing in this area. Our initial synthetic target was to be 12-*O*-methyl royleanone, **1**, a member of the abietane family of diterpenes, which has a broad range of biological activity.



Scheme 1. The Dötz benzannulation reaction.[5]

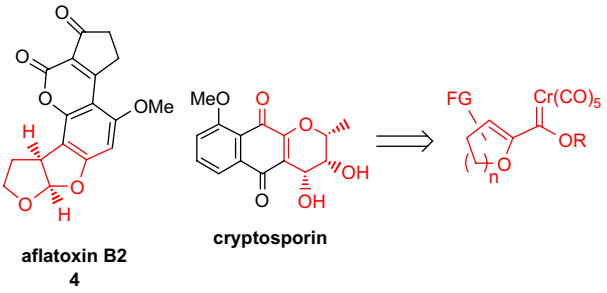
Gratifyingly the key reaction in our approach to **1**, the benzannulation reaction between the Fischer carbene complex **2** and the disubstituted alkyne **3**, proceeded without incident and afforded, after mild oxidative work-up, the target **1** in good overall yield, Scheme 2.[6] Crucially the regiochemical



Scheme 2. An approach to 12-*O*-methyl royleanone.[6]

outcome of this reaction appeared to be in accord with the paradigm enunciated by Dötz[7] and Wulff.[8] Previously these groups had clearly shown that the differing steric bulk of the substituents on the alkyne had a controlling effect on the regiochemistry of its incorporation into the benzannulated product (i.e., *i*-Pr [R_L]>OMe [R_S]), Scheme 1.

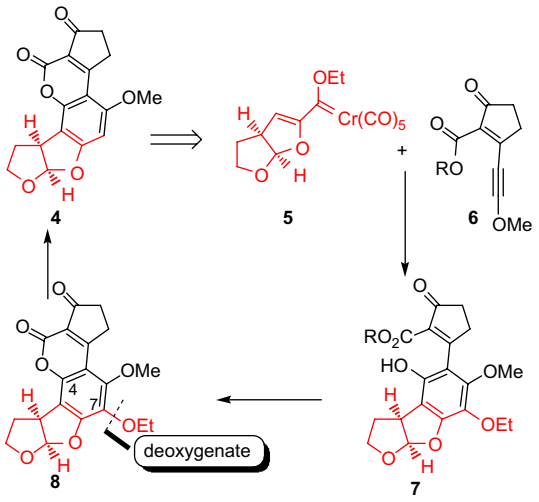
Encouraged by this early result we wished to apply the Dötz reaction to the synthesis of heterocyclic systems such as aflatoxin B2 (**4**) and cryptosporin, which, by necessity would utilize heterosubstituted α,β-unsaturated Fischer carbene complexes in the key benzannulation step, Scheme 3. Somewhat naively we proposed a convergent strategy to the synthesis of aflatoxin B2 (**4**), a representative member of the furo[2,3-*b*]benzofuran[9] family of mycotoxins, which was to involve a benzannulation reaction between the carbene complex **5** and the functionalized acetylene **6**.



Scheme 3. Dötz reaction—potential synthetic applications.

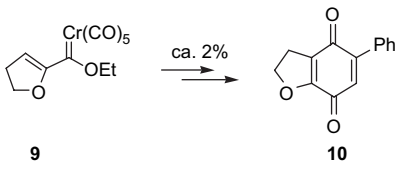
In keeping with our earlier work on royleanone[6] we presumed that the methoxy substituent of **6** would act as the 'small' group and be incorporated proximal to the alkoxy group of the carbene complex **5** during the pivotal benzannulation step. That said we were also confident[10,11] that ester **7**, the initial product of the benzannulation sequence, would cyclize to the lactone **8**, thereby providing a route to the desired target **4**, Scheme 4.

At the outset of this investigation we noted that although furan-derived Fischer carbene complexes had been utilized in Dötz reactions dihydropyranylcarbene complexes had only received limited scrutiny[11,12] and there were no reports of the application of dihydrofuranylcarbene complexes in such reactions. Similarly, the preparation and downstream chemistry of furo[2,3-*b*]furan-2-yl carbene complexes such as **5** was without literature precedent, a methodological challenge, which, in fact, provided the initial impetus for conducting this investigation. Due to the lack of literature precedent in this area we therefore set about the synthesis of the parent



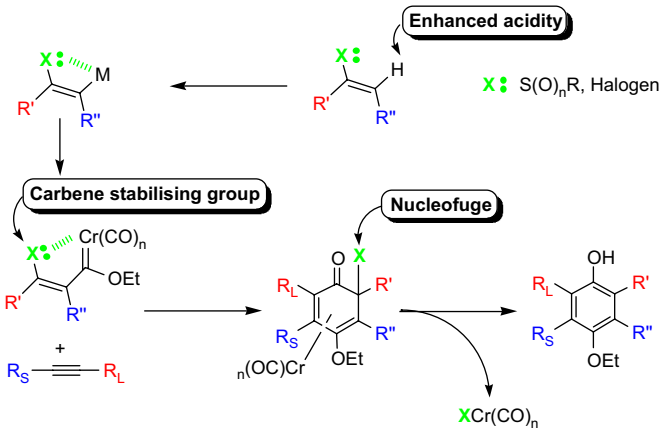
Scheme 4. Initial route to aflatoxin B2.

carbene complex **9** with a view to validating its utility in Dötz benzannulation sequences. Unfortunately lithiation of dihydrofuran using Boeckmans's[13a] procedure followed by the standard Fischer[13b] protocol afforded the carbene complex **9**, which rapidly decomposed on attempted isolation. As the instability of **9** precluded its purification we set about evaluating the use of the crude carbene complex in Dötz benzannulation reactions. Much to our dismay this particular complex proved to be an inefficient partner in such reactions, resulting in the isolation of only trace quantities of the desired benzannulated products even after extensive experimentation and variation of reaction conditions (DSA absorption techniques,[14] etc.), Scheme 5. This unfortunate set of observations was most disconcerting and led us conclude that, for some reason, the dihydrofuranyl complex **9** was innately unstable, a realization, which led us to consider the development of a surrogate for this particular system.



Scheme 5. Methodological limitation.

On considering the mechanism of the Dötz reaction,[5] we proposed that the introduction of a nucleofugal group onto the β-carbon of the carbene complex could have a number of potential (beneficial) effects such as: (i) increasing the acidity of the α-CH in the starting material thereby facilitating initial metallation prior to carbene synthesis; (ii) provide steric/electronic stabilization of the carbene complex once formed and (iii) act as a leaving group in the final aromatization step[15] of the benzannulation sequence, Scheme 6. In the intervening years we have investigated this hypothesis,[11,16] and have shown that a variety of β-substituents (Cl, SPh, SO_2Ph



Scheme 6. 'Second generation' Dötz reactions.

and F) could be introduced into a range of unsaturated carbene complexes (compounds **11**–**18**, Fig. 1).

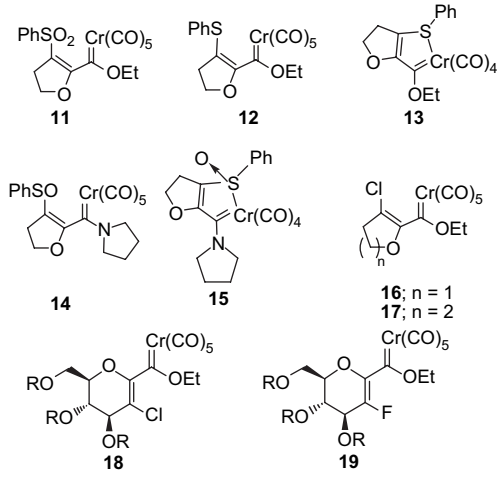
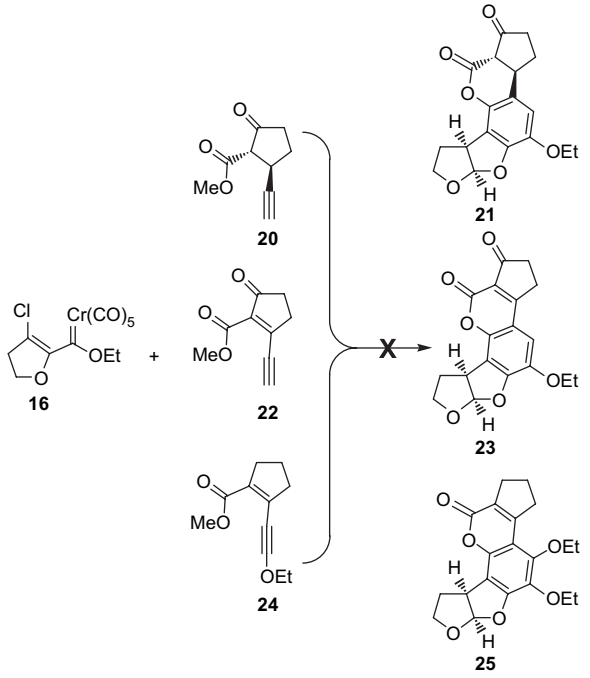


Figure 1. Heterofunctionalized Fischer carbene complexes.

By and large, the presence of these substituents had the desired effect both in terms of stabilization of the carbene complex yet facilitating our newly devised 'second generation' Dötz reaction. Although these studies proved interesting in terms of developing the co-ordination[16,17] chemistry of chromium and ultimately provided new methodology for the functionalization of carbohydrates[18] it was merely diversionary in terms of developing a strategy towards the synthesis of aflatoxins. Having lost sight of this objective for some time we decided therefore to re-investigate our synthetic strategy to this particular class of natural products. Once again, however, we were thwarted in our attempts to make headway towards this goal as we discovered that attempted benzannulation of the carbene complex **16** with either of the functionalized alkynes[19] **20**, **22** and **24** generated complex reaction mixtures, which were apparently devoid of the tetracyclic lactones **21**, **23** or **25**, respectively, Scheme 7.

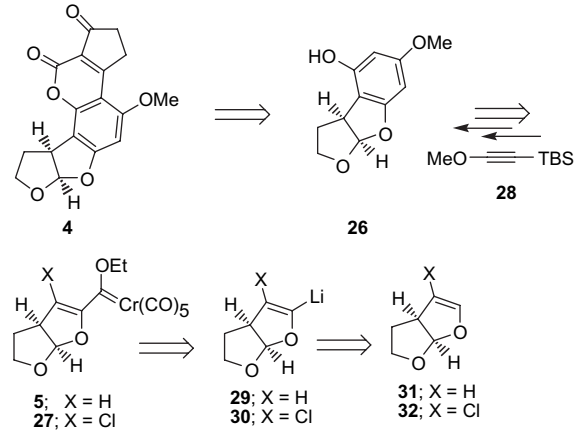
Not wholly dismayed by this setback we decided to modify our approach so that, in the first instance at least, we would



Scheme 7. Aflatoxin B2—initial model studies.

aim for the synthesis of the phenol **26**, which had previously been utilized[20] in the synthesis of **4**. We envisaged that **26** would be accessible from the Dötz reaction between the furo[2,3-*b*]furan-2-yl carbene complexes **5** (or **27**) and the functionalized alkyne **28**.

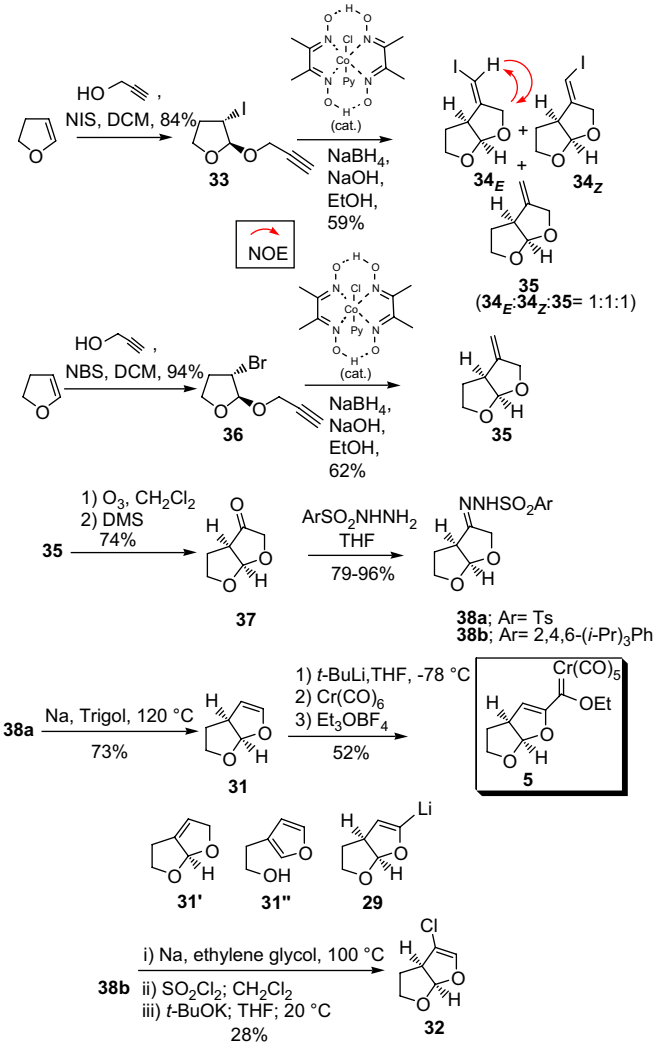
Again, while regiochemical issues arising from the use of oxygenated acetylenes in the Dötz reaction have not been extensively investigated we were confident, from the meager literature precedents[21] and from our own studies,[6,11] that this particular benzannulation reaction would result in the incorporation of the methoxy substituent at C6 in **26** (i.e., R_3Si [R_L]>OMe [R_S]). Given the much simpler structure of the alkyne **28** when compared to **20**, **22** and **24** we were confident that this analysis would provide a viable solution to the apparent limitations of the benzannulation methodology, Scheme 8. What was not so clear at this juncture was the manner in which



Scheme 8. Aflatoxin B2—revised strategy.

the two phenolic oxygens at C4 and C7 could be differentiated in order to permit selective deoxygenation at C7. The carbene complexes **5** and **27** were to be prepared from the furo[2,3-*b*]furans **31** and **32**, respectively, using standard Boeckman–Fischer methodology.[13] We proposed that the enol ether **31**[22] could be prepared in a five step sequence from dihydrofuran as outlined in Scheme 9. This sequence necessitated the use of a Bamford–Stevens reaction in the final step, a reaction, which surprisingly has little precedent for the synthesis of cyclic enol ethers.[23] Haloethetherification[24] of dihydrofuran with propargyl alcohol in the presence of NIS or NBS afforded the *trans*-haloethers **33** and **36** in near quantitative yield.

Unfortunately cyclization[25] (Bu_3SnH, AIBN, PhH) of the iodide **33** in our hands proved problematical as variable quantities (up to 40% isolated yield) of the vinyl iodides $\mathbf{34}_{E,Z}$ were also generated via a competing atom transfer cyclization reaction. Gratifyingly, however, radical cyclization of **36** using Okabe's[26] procedure afforded the exocyclic alkene[25] in reproducible yields of ca. 62% on a 260 mmol scale, Scheme 9. This cobalt catalyzed cyclization reaction proved to be very robust and proceeds without the generation of large quantities



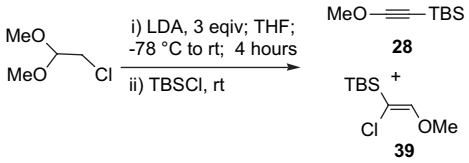
Scheme 9. Aflatoxin B2—synthesis of carbene complex.

of tin residues, which is an unfortunate feature of TBTH methodology when conducted on a preparative scale. Ozonolysis of **35** (O_3, CH_2Cl_2, −78 °C) followed by reductive work-up (Me_2S) was routinely carried out on a 100 mmol scale and afforded the ketone **37**,[22c] a low melting solid, in 74% isolated yield. Conversion of **37** to the hydrazones **38a** and **38b** (both as a 1:1 mixture of geometrical isomers) and hence to the enol ether **31** was next investigated. After careful optimization it was found that the Bamford–Stevens reactions of **38a**,**b** were best carried out by mild thermolysis of their respective sodium salts in either ethylene glycol or trigol under reduced pressure (20 mmHg). Under these conditions the enol ether **31** could simply be collected in a cardice trap on a preparative scale. The enol ether **31** generated in this way was isolated in an essentially pure state and was devoid of any trace of the alternate double bond isomer **31′** or furan **31″**. Although the Bamford–Stevens reaction of the hydrazone **38b** afforded enol ether **31** in higher yields (77%) on a small scale (8.9 mmol) this marginally greater efficiency was not translated to preparative-scale experiments where both substrates gave essentially the same yield. With a reliable route to the enol ether **31** in hand its conversion to the Fischer carbene complexes **5** and **27** was next pursued. As conversion of the enol ether **31** to the vinyl chloride **32**, the precursor to the chlorocarbene complex **27**, proved to be too low-yielding (28%) to be preparatively useful the synthesis of **27** was not pursued further and our efforts focused upon the synthesis of the complex **5**.

To our delight the direct metallation (^{t}BuLi, 1.1 equiv, THF, −78 °C, 15 min and then at 20 °C for 30 min) of enol **31** to the organolithium **29** proceeded smoothly as did its subsequent conversion to the carbene complex **5**, Scheme 8. Complex **5** was isolated as a deep red *stable solid*, in 52% yield *after* chromatography *and* recrystallization, an outcome, which was wholly unexpected when compared to our initial experience with the parent carbene complex **9**. We can only presume, at this stage, that the presence of the additional oxygen, which is embedded into the furo[2,3-*b*]furanyl ring system plays an important (electronic) role in stabilizing this particular carbene complex.

Given that we now had access to multigram quantities of carbene complex **5** its benzannulation reaction with the oxygenated acetylene **28** could be attempted. The alkyne **28** was conveniently prepared from chloroacetaldehyde dimethyl acetal using a modification of the method reported by Raucher.[27] Exposure of the acetal to LDA (3 equiv; −78 °C to rt, 4 h) followed by the addition of TBSCl (1 equiv) afforded the acetylene **28** in reproducible yields of 22% yield after Kügelrohr distillation. It should be pointed out that monitoring of this reaction is important as premature quenching the reaction too early with the TBSCl led to the isolation of the vinyl silane **39** as the sole product[28] (35% yield after Kügelrohr distillation), Scheme 10.

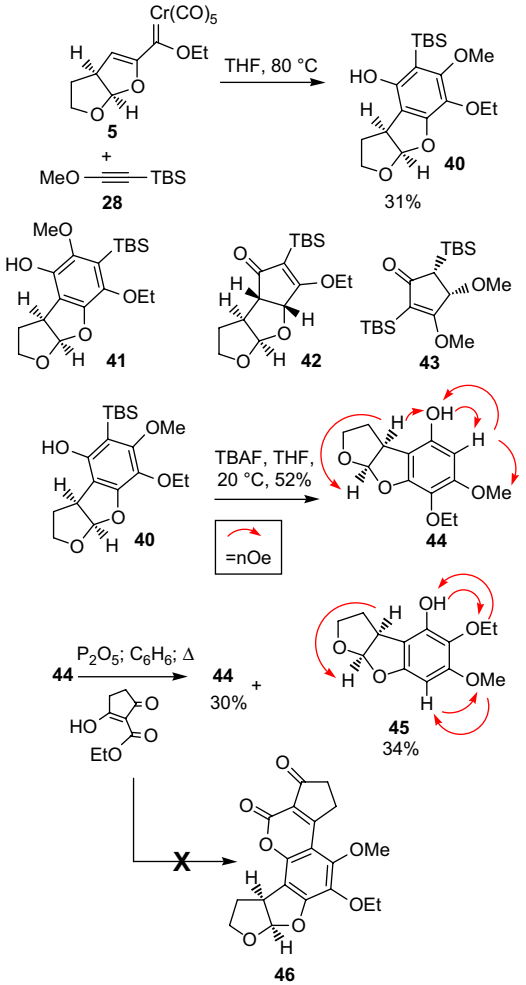
At this stage we were now ready to attempt the key Dötz reaction and were gratified to find that exposure of the complex **5** to the acetylene **28** (2.5 equiv) in THF at 80 °C for 2 h resulted in the complete consumption of the complex **5**



Scheme 10. Synthesis of alkyne **28**.

and afforded the phenol **33** in 31% yield after column chromatography. The regiochemical outcome of this benzannulation reaction is in keeping with previous methodological studies[6,11] and was substantiated by spectroscopic studies and further chemical manipulation. Hence desilylation of **40** (TBAF, THF, 20 °C) afforded the phenol **44** whose ^{1}H NMR spectrum was sufficiently dispersed to enable NOE experiments to be carried out, Scheme 11. Of note is the observation that we were unable to detect any of the alternate regioisomeric phenol **41** in the crude reaction mixture of this Dötz reaction but were able to isolate variable quantities[29] of the cyclopentenones **42** (ca. 1%) and **43** (<1%), Scheme 11.

The product distribution of this reaction was found to be quite sensitive to the reaction conditions employed[29] (solvent polarity, temperature and additives) but fortuitously those used in the first attempt proved to be optimal and reproducible in



Scheme 11. Aflatoxin B2—revised benzannulation sequence.

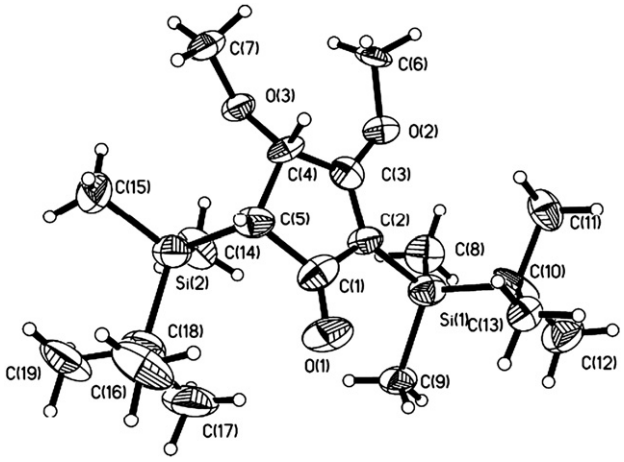
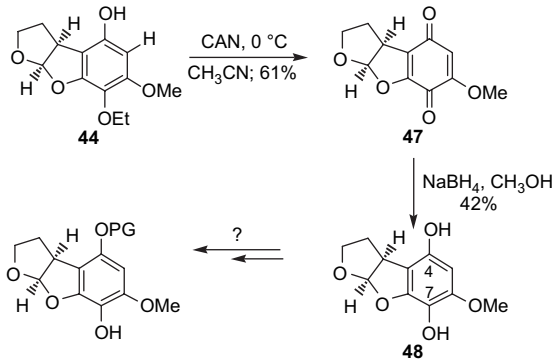


Figure 2. X-ray structure of cyclopentenone **43**.

terms of phenol **40**. Structural assignments in the case of **42** were based upon detailed spectroscopic analysis whilst the structure of **43** was unambiguously established by way of X-ray crystallography, Figure 2. At this juncture we decided, by way of a model study, to functionlize the free phenolic-OH group of **44**. Unfortunately attempted cyclization of the phenol **44** into lactone **46**, using a classical variant of the von Pechmann cyclization reaction,[30] resulted in the re-isolation of starting material **44** (30% yield) together with the rearranged phenol **45** (34% yield), Scheme 11. We suspect that this equilibration occurred via the reversible ring opening–trapping of the acetal moiety, a reaction, which was unforeseen but not without precedence in this system.[20h] Again NOE studies proved invaluable in providing corroborating evidence for this structural assignment as both the ^{1}H NMR and ^{13}C NMR spectra of **44** and **45** were almost identical.

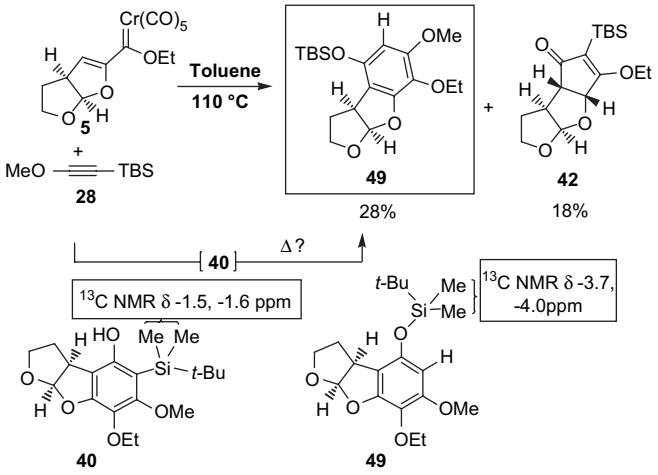
As we were unable to detect the formation of desired lactone **46**, Scheme 11, we obviously had to rethink our strategy for the selective deoxygenation of substrates such as **44**. We decided therefore to attempt regioselective protection hydroquinone **48** under less forcing conditions. However, although hydroquinone **48** could be prepared from phenol **44** in a simple two step oxidation–reduction sequence this route was hampered by the instability of hydroquinone **48** and failed to provide a practical solution to this problem, Scheme 12. At this stage, and quite fortuitously, we noted a marked solvent



Scheme 12. Planned protection of diol **48**.

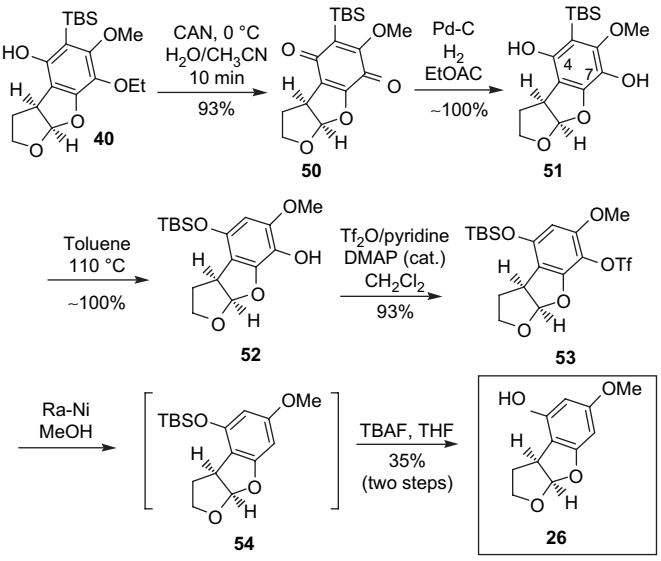
effect in the benzannulation reactions involving carbene complex **5** and alkyne **28**, an observation, which ultimately was to provide a practical solution for the regioselective deoxygenation of **40**.

In this study, Scheme 13, we found that conducting the Dötz reaction in toluene rather than in THF, which in our hands is usually the solvent of choice for such reactions, resulted in the isolation of the silyl ether **49** as the major product rather than the phenol **40**.



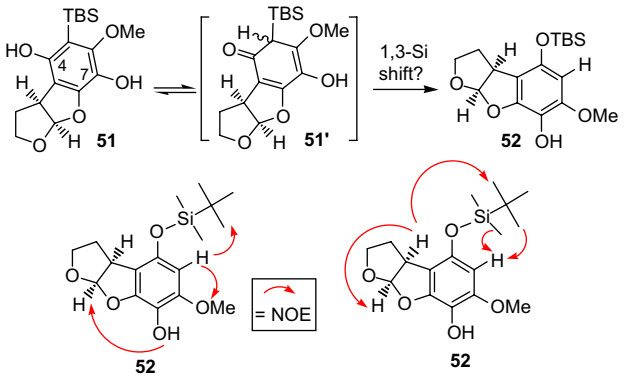
Scheme 13. A fortuitous result.

We presume that **42** arose via a formal 1,3-silatropic rearrangement[31] of the initial product **40** under these more forcing conditions. If this were the case, and was a reaction, which proved to be general,[32] then it could provide a deceptively simple solution to the selective protection of the C4 hydroxyl group in substrates such as **51**, Scheme 14. This hypothesis was readily tested and resulted in a simple three step sequence for the conversion of **40** into **52**, Scheme 14. In practise this entailed oxidation of the phenol **40** to the quinone **50** (CAN, CH_3CN/H_2O), reduction of **50** to the hydroquinone **51** (H_2–Pd/C) followed by rearrangement to **52**.



Scheme 14. Deoxygenation at C7—completion of route.

Rather pleasingly the 1,3-silatropic migration (**51** to **52**) occurs essentially quantitatively upon mild thermolysis in toluene (110 °C, 1 h) and is apparently wholly regioselective. The overall yield for three step sequence from **40** to **52** was pleasingly high (93%); regiochemical issues in the case of **52** were again addressed using NOE difference measurements, Scheme 15. Whilst there have been sporadic reports of similar silicon migrations in Dötz benzannulation reactions[31] its application to the in situ, regioselective, protection of hydroquinones (as opposed to monoalkyl derivatives[31]) has not to our knowledge been previously reported. Presumably, the rearrangement of **51** into **52** proceeds via the intermediacy of the tautomeric cyclohexadienone **51′**, followed by a formal 1,3-silatropic shift, the driving force for the reaction being the formation of a strong O–Si bond.[32]



Scheme 15. Mechanism for 1,3-Silatropic rearrangement.

Having developed a facile route to the preparation of the protected hydroquinone **52** its deoxygenation at C7 was next investigated. Most frustratingly deoxygenation of **52** proved to be less than straightforward. For example, whilst reduction of **53** using Sáa's[33] modification of Cacchi's procedure[34] ($PdCl_2$, dppp, HCO_2H, Bu_3N, DMF, 80 °C) did in fact effect deoxygenation with concomitant in situ deprotection to the desired intermediate **26**, the product was contaminated with *N*,*N*-dibutylformamide, which could only be removed by recrystallization resulting in a low overall isolated yield of pure material (11%). Fortunately Noland[20b] has described a modified procedure for this type of reduction involving the use of Raney nickel. Hence exposure of **53** to Raney nickel followed by desilylation (TBAF, THF, 20 °C) of the intermediate silylether **54** afforded the desired phenol **26** in 35% isolated yield over the two steps. The phenol **26** prepared in this manner was identical to that described by Rapoport[20c] and Noland[20b] and therefore constitutes a formal synthesis of the natural product.

In conclusion, we have demonstrated that the Dötz reaction between a furo[2,3-*b*]furanyl carbene complex and a silylated acetylene provides ready access to a pivotal intermediate for the synthesis of aflatoxin B2. Although this reaction proceeds in only moderate yield (31%) its convergent nature, leading to

the synthesis of a highly functionalized intermediate, is noteworthy. The silicon substituent fulfils two roles by controlling the regiochemistry of the initial Dötz reaction and providing a facile means by which the selective protection–deoxygenation of a hydroquinone intermediate can be achieved. This study also underscores the potential limitations of the Dötz reaction when applied to more sterically congested or electronically mismatched alkyne partners. α,β-Unsaturated Fischer carbene may be innately unstable and preclude their use in the Dötz reaction, a situation that can sometimes be remedied by the temporary introduction of a stabilizing substituent. The facile lithiation of the 2,3,3a,6a-tetrahydrofuro[2,3-*b*]furan may be of potential utility for the synthesis of other furo[2,3-*b*]furan-containing natural products.

3. Experimental

3.1. General

All reactions unless stated otherwise were carried out under a nitrogen atmosphere. Tetrahydrofuran and diethyl ether were dried by distillation from sodium–benzophenone; toluene, dichloromethane and acetonitrile were dried by distillation from calcium hydride; dimethylformamide was dried over 4 Å molecular sieves. All other chemicals were purified using standard procedures as required. Thin layer chromatography (TLC) was carried out on Merck silica gel F_{254} 0.255 mm plates, and spots were visualised, where appropriate, by UV fluorescence at 254 or 297 nm or by spraying with phosphomolybdic acid in ethanol, iodine or vanillin in ethanol/sulfuric acid. Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) silica. The purification of carbenes was carried out by flash column chromatography under a nitrogen atmosphere; solvent and silica was degassed prior to use. IR spectra were recorded on an AT1 Mattson Genesis series FTIR spectrometer and are given in cm^{-1}, points of maximum absorption (ν_{max}) are recorded with the strength of absorption being quoted as strong (s), medium (m), weak (w) and broad (br). ^1H NMR spectra were recorded on a Varian AC 300E NMR spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded on a Varian AC 300E NMR spectrometer operating at 75 MHz. All chemical shifts are reported in parts per million downfield from tetramethylsilane. Peak multiplicities are denoted by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) with coupling constants (*J*) given in hertz. Mass spectra were recorded on a Fisons VG Trio 2000 for (EI) electron impact and chemical ionization (CI) conditions. Electrospray (ES) spectra were recorded on a Micromass Platform. Accurate mass measurements were recorded on a Kratos Concept mass spectrometer. Melting points were recorded on a Reichert heated-stage microscope and are uncorrected. Microanalyses were performed in the Microanalytical Laboratory at the School of Chemistry, University of Manchester. X-ray data measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation. Dr J. Raftery should be consulted concerning the X-ray structure of compound **43**. On occasion the ^1H NMR spectra of carbene complex **5** proved to be quite broad, presumably due to the presence of trace amounts of paramagnetic material. However, addition[35] of a *very* small quantity of the mild reducing agent $Co(Cp)_2$ to the NMR sample generated sharp, well resolved, spectra.

*3.1.1. (2S*R*,3R*S*)-3-Bromo-2-(prop-2yn-1-yloxy)-tetrahydrofuran,* ***36****[22c]*

Dihydrofuran (16 mL, 211 mmol) and propargyl alcohol (24.5 mL, 421 mmol) were dissolved in dichloromethane (150 mL) and the solution cooled to −15 °C. Freshly recrystallized *N*-bromosuccinimide (45.0 g, 252.8 mmol) was added portionwise over 30 min to the solution, which was allowed to warm to room temperature and stirred for a further 5 h. The resulting solution was washed with brine (60 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude oil by column chromatography (flash silica, 7% EtOAc/petrol) afforded the *title compound* as a colourless oil (40.5 g, 94%). ν_{max} (film)/cm^{-1} 3292 (s), 2930 (m), 2900 (s), 1482 (s), 1440 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (1H, s, H-2), 4.20–4.00 (3H, m, H-3, 5), 4.10–4.00 (2H, m, $-OCH_2C{\equiv}H$), 2.63 (1H, m, H-4), 2.43 (1H, t, *J*=2.5 Hz, $-C{\equiv}CH$), 2.18 (1H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.8, 78.9, 74.6, 67.0, 53.9, 49.6, 33.6; *m/z* (CI) 222 (MNH_4^+, 55%) 204 (M^+, 5%); found MNH_4^+ 222.0133, $C_7H_9O_2^{79}Br$ requires MNH_4^+ 222.0130.

*3.1.2. (2S*R*,3R*S*)-3-Iodo-2-(prop-2-yn-1-yloxy)-tetrahydrofuran,* ***33****[25]*

Dihydrofuran (2.3 mL, 31.1 mmol) and propargyl alcohol (2.7 mL, 46.5 mmol) were dissolved in dichloromethane (50 mL) and cooled to 0 °C. Freshly recrystallized *N*-iodosuccinimide (7.0 g, 31.1 mmol) was then added portionwise over 30 min to the solution, which was allowed to warm to room temperature and stirred for a further 5 h. The resulting solution was washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude oil by column chromatography (flash silica, 10% EtOAc/petrol) afforded the *title compound* as a colourless oil (6.6 g, 84%). ν_{max} (film)/cm^{-1} 3291 (s), 2949 (m), 2897 (s), 1440 (s), 1024 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (1H, s, H-2), 4.02–4.34 (5H, m, H-3, H-5, $-CH_2C{\equiv}CH$), 2.70–2.55 (1H, m, H-4), 2.48 (1H, t, *J*=2.5 Hz, $C{\equiv}CH$), 2.25–2.15 (1H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8, 79.2, 74.7, 67.4, 53.6, 35.4, 24.3; *m/z* 252 (M^+, 18%), 270 (MNH_4^+, 18%), 214 (100%); found M^+ 251.9654, $C_7H_9O_2I$ requires M^+ 251.9649.

*3.1.3. (3aS*R*,6aR*S*)-3-Methylenehexahydrofuro[2,3-b]furan,* ***35****[22c]*

To a solution of bromoether **36** (54.50 g, 267 mmol) in ethanol (500 mL) was added sodium borohydride (8.8 g, 243 mmol) and sodium hydroxide (8.4 g, in water 20 mL, 225 mmol). The resulting mixture was stirred until it was homogenous. Cobaloxime (5.30 g, 13.3 mmol) was added slowly over a 10 min period, with gentle warming of the solution. The solution was stirred for a further 1 h after which time the ethanol was removed in vacuo. Water (15 mL) was added

and the mixture extracted with dichloromethane (3×25 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (flash silica 10% EtOAc/petrol) gave the *title compound* as an oil (17.4 g, 62%). ν_{max} (film)/cm^{-1} 2955 (s), 2871 (s), 1736 (s), 1655 (m), 1462 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, d, J=4.9 Hz, H-6a), 5.06 (1H, app. q, J=2.2 Hz, C=CH_2), 5.02 (1H, app. q, J=2.2 Hz, C=CH_2), 4.55–4.35 (2H, m, H-2), 3.97 (1H, td, J=8.0, 1.5 Hz, H-5), 3.85–3.75 (1H, m, H-5), 3.33–3.24 (1H, m, H-3a), 2.10–2.30 (1H, m, H-4), 1.95 (1H, dd, J=12.5, 5.5 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 109.6, 105.8, 72.0, 67.4, 47.2, 34.1; *m/z* (CI) 127 (MH^+, 80%) 144 (MNH_4^+, 100%); found MNH_4^+ 144.1028, $C_7H_{10}O_2$ requires MNH_4^+ 144.1024.

3.1.4. (*E*)-(3a*S**R*,6a*R**S*)-3-Iodomethylenehexahydrofuro[2,3-b]furan, **34$_E$**

Sodium borohydride (150 mg, 3.97 mmol) and cobaloxime (161 mg, 0.4 mmol) were added to ice cold ethanol (50 mL) containing 10 M sodium hydroxide solution (0.12 mL, 4.05 mmol) and pyridine (2.0 mL). To this solution was added iodo ether **33** (portionwise) (1.0 g, 3.97 mmol) in ether (3.75 mL). The solution was stirred for a further 1 h after which time the ethanol was removed in vacuo. Water (15 mL) was added and the mixture extracted with DCM (3×25 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a crude mixture of the bicyclic acetal **35** and a mixture of *E* and *Z*-iodo acetals ***E*,*Z*-34** in a 1:1:1 ratio (302 mg, 59%). Purification by column chromatography (flash silica 10% EtOAc/petrol) afforded the *title compound*, **34$_E$**, a straw-coloured oil, whose colour rapidly deepened on standing. ν_{max} (film)/cm^{-1} 3061 (s), 2953 (s), 2868 (s), 1639 (s), 1357 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (1H, app. q, J=2.1 Hz, H-C*H*I), 5.88 (1H, d, J=5.0 Hz, H-6a), 4.40–4.52 (2H, m, H-2), 4.05 (1H, app. td, J=8.7, 2.2 Hz, H-5), 3.86–3.78 (1H, m, H-5), 3.30–3.22 (1H, m, H-3a), 2.05–2.14 (1H, m, H-4), 2.22–2.31 (1H, m, H-4); *m/z* (CI) 253 (MH^+, 5%) 270 (MNH_4^+, 7%); found M^+ 251.9653, $C_7H_9O_2I$ requires M^+ 251.9649. Comparison of this data with the ^1H NMR spectrum of the partially separated mixture of isomers allowed us to deduce the following ^1H NMR for the *Z*-iodo acetal, **34$_Z$**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, q, J=2.5 Hz, H–C*H*I), 5.95 (1H, d, J=4.8 Hz, H-6a), 4.42–4.50 (2H, m, H-2), 3.96 (1H, td, J=9.8, 2.2 Hz, H-5), 3.80–3.72 (1H, m, H-5), 3.25–3.12 (1H, m, H-3a), 2.00–2.10 (1H, m, H-4), 2.20–2.30 (1H, m, H-4).

3.1.5. (2a*S**R*,3a*R**S*) Hexahydrofuro[2,3-b]furan-3-one, **37**[22c]

Alkene **35** (13.75 g, 109.1 mmol) was dissolved in dichloromethane (70 mL) and the solution cooled to −78 °C. Ozone was passed through the solution for 2 h after which time the solution turned blue. The system was purged with oxygen for 20 min. Dimethylsulfide (16 mL, 218.2 mmol) was added and the solution stirred overnight at room temperature. The resulting solution was washed with brine (100 mL), dried $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (flash silica 20% EtOAc/petrol) to afford the *title compound*, a white crystalline solid (3.50 g, 74%, mp 41.5–43.0 °C; no lit. mp). ν_{max} (film)/cm^{-1} 2957 (s), 2873 (m), 1760 (s), 1440 (m), 1246 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (1H, d, J=5.0 Hz, H-6a), 4.19 (2H, s, H-2), 4.15–4.05 (1H, m, H-5), 3.80 (1H, q, J=8.0 Hz, H-5), 3.10–3.00 (1H, m, H-3a), 2.32–2.22 (2H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 107.7, 71.4, 67.4, 49.4, 30.1; *m/z* (CI) 129 (MH^+, 18%) 128 (M^+, 37%); 146 (MNH_4^+, 10%), found M^+ 128.0471, $C_6H_8O_3$ requires M^+ 128.0473.

3.1.6. (*E*/*Z*)-(2a*S**R*,3a*R**S*) Hexahydrofuro[2,3-b]furan-3-one toluenesulfonylhydrazone, **38a**

Ketone **37** (6.46 g, 50 mmol) and *p*-toluenesulfonyl hydrazide (10.23 g, 55 mmol) were dissolved in THF (50 mL) and the solution stirred for 3 h. The solvent was removed in vacuo. Purification was carried out by recrystallization (MeOH/hexane) to afford the *title compound*, a yellow solid (*E*:*Z*=1:1) (11.79 g, 79%, mp 141–145.5 °C). ν_{max} (film)/cm^{-1} 3206 (br), 2959 (s), 2873 (s), 1597 (s), 1342 (s), 1165 (s), 1015 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, s, N*H*), 8.05 (1H, s, N*H*), 7.87 (2H, s, Ar*H*), 7.84 (2H, s, Ar*H*), 7.37 (2H, d, J=3.2 Hz, Ar*H*), 7.34 (2H, d, J=3.2 Hz, Ar*H*), 5.87 (1H, d, J=5 Hz, H-6a), 5.83 (1H, d, J=5 Hz, H-6a), 4.50–4.30 (4H, m, H-2), 4.04–3.97 (1H, m, H-5), 3.97–3.90 (1H, m, H-5), 3.83–3.73 (1H, m, H-5), 3.67–3.58 (1H, m, H-5), 3.38–3.30 (2H, m, H-3a), 2.46 (6H, s, Ar*CH*$_3$), 2.28–2.10 (2H, m, H-4), 2.08–1.98 (2H, br dd, J=12.5, 5.9 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 162.0, 145.0, 144.8, 135.1, 135.0, 130.2, 130.0, 128.2, 128.1, 109.7, 108.8, 70.5, 68.4, 67.8, 67.3, 47.1, 42.9, 33.2, 29.3, 21.9; *m/z* (CI) 297 (MH^+, 80%) found C 53.19%, H 5.61%, N 9.35%, MH^+ 297.0912, $C_{13}H_{16}N_2O_4S$ requires C 52.69%, H 5.44%, N 9.45%, MH^+ 297.09089.

3.1.7. (*E*/*Z*)-(2a*S**R*,3a*R**S*) Hexahydrofuro[2,3-b]furan-3-one 2,4,6-(tri-isopropyl)phenylsulfonylhyrazone, **38b**

To a solution of the ketone **37** (1.81 g, 14.1 mmol) in THF (15 mL) was added 2,4,6-tri-isopropylbenzenesulfonylhydrazide (4.20 g, 14.1 mmol) and the solution stirred for 3 h. The solvent was then removed in vacuo and the residue purified by column chromatography (flash silica 30% EtOAc/petrol with 5% Et_3N) to afford the *title compound* as a white solid (*E*:*Z*=1:1) (2.40 g, 42%, mp 101.0–103.0 °C). ν_{max} (film)/cm^{-1} 3196 (br), 2960 (s), 2931 (m), 2870 (m), 1599 (s), 1462 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (1H, s, N*H*), 8.32 (1H, s, N*H*), 7.22 (1H, s, Ar*H*), 7.21 (1H, s, Ar*H*), 5.85 (1H, d, J=4.9 Hz, H-6a), 5.82 (1H, d, J=4.9 Hz, H-6a), 4.50–4.35 (4H, m, H-2), 4.26 (4H, sep, J=7.0 Hz, ArC*H* H-2′,6′), 4.18–4.08 (1H, q, J=7.0 Hz, H-5), 4.18–4.08 (1H, q, J=7.0 Hz, H-5), 4.08–3.60 (4H, m, H-2,5), 3.42–3.36 (1H, m, H-3a), 3.35–3.28 (1H, m, H-3a), 2.92 (2H, sep, J=6.9 Hz, ArC*H* H-4′), 2.10–2.00 (4H, m, H-4), 1.35–1.25 (36H, m, 6×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 161.7, 159.6, 153.7, 153.6, 151.6, 151.5, 130.7, 130.6, 123.9, 123.8, 109.5, 108.6, 70.2, 68.2, 67.6, 67.1, 60.4, 46.8, 42.3, 34.2, 32.7, 29.9, 29.8, 29.1, 24.8, 24.7, 23.5, 21.0, 14.2; *m/z* (CI) 409 (MH^+, 3%) 189 (M^+, 45%);426 (MNH_4^+, 22%), found MH^+ 409.2171, $C_{21}H_{32}N_2SO_4$ requires MH^+ 409.2161.

*3.1.8. (2aS*R*,3aR*S*)-3a,4,5,6a-Tetrahydrofuro[2,3-b]furan, **31** (Method A)*[22]

Sodium (1.49 g, 67 mmol) was added to trigol (50 mL) and the suspension stirred until the metal had dissolved (2 h). Hydrazone **38a** (10.0 g, 34 mmol) was added and the solution heated to 120 °C for 2 h. Short path distillation under reduced pressure afforded the *title compound*, a colourless oil (2.70 g, 73%). ν_{max} (film)/cm^{-1} 2958 (s), 2870 (s), 1597 (s), 1462 (s), 1128 (m), 950 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (1H, app. t, J=2.5 Hz, H-2), 6.07 (1H, d, J=6 Hz, H-6a), 4.77 (1H, t, J=2.5 Hz, H-3), 4.00 (1H, app. t, J=7.7 Hz, H-5), 3.78–3.70 (1H, m, H-5), 3.55–3.45 (1H, m, H-3a), 2.12–1.88 (1H, m, H-4), 1.8 (1H, dd, J=12.4, 5.1 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 109.7, 102.0, 67.0, 46.5, 32.1; *m/z* (CI) 112 (M^+, 23%) 113 (MH^+, 60%), 130 (MNH_4^+, 100%); found MNH_4^+ 130.0865, $C_6H_8O_2$ requires MNH_4^+ 130.09066.

*3.1.9. (2aS*R*,3aR*S*)-3a,4,5,6a-Tetrahydrofuro[2,3-b]furan, **31** (Method B)*

Sodium (408 mg, 17.8 mmol) was added to ethylene glycol (30 mL) and the suspension stirred until the metal had dissolved (2 h). To this solution was added **38b** (3.63 g, 8.9 mmol) and the reaction mixture heated to 100 °C for 2 h. The cooled mixture was poured into water (50 mL) and extracted with ether (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford the *title compound* (768 mg, 77%) as a colourless oil.

*3.1.10. (3aS*R*,6aS*R*)-4-Chloro-2,3,3a,6a-tetrahydrofuro[2,3-b]furan, **32***

Sodium (303 mg, 13.2 mmol) was added to ethylene glycol (20 mL) and allowed to stir until all of the sodium had reacted (approximately 2 h). To this solution was added **38b** (2.70 g, 6.6 mmol) and the mixture heated at 100 °C for 2 h. The cooled mixture was poured into water (30 mL) and extracted with dichloromethane (3×15 mL), which was then dried ($MgSO_4$). Sulfurylchloride (530 μL, 6.6 mmol) was added to the dried organic phase, which was stirred for 30 min. Air was blown through the solution for 30 min, and the solvent was removed in vacuo. THF (50 mL) was added, followed by potassium *tert*-butoxide (738 mg, 6.6 mmol), and the solution was stirred for 5 h. The solvent was removed in vacuo, water (30 mL) added and the mixture extracted with dichloromethane (3×50 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (flash silica, 5% EtOAc/petrol) to afford the *title compound* (273 mg, 28%) as a colourless oil. ν_{max} (cm^{-1}) 2978 (s), 2884 (s), 1636 (m), 1123 (s), 1057 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (1H, d, J=2 Hz, H-5), 6.10 (1H, d, J=6 Hz, H-6a), 4.11 (1H, t, J=8 Hz, H-2), 3.70–3.85 (1H, m, H-3a), 3.55 (1H, m, H-2), 1.90–2.20 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 109.6, 107.5, 67.0, 50.0, 29.2; *m/z* (EI), 147 (M^++H, 32%), 146 (M^+, 69%); (CI, NH_3) *m/z* 164 (MNH_4^+, 100%), 147 (M^++1, 40%), 146 (M^+, 75%); found 146.0130, $C_6H_7O_2^{35}Cl$ requires 146.0134.

*3.1.11. (2aS*R*,3aR*S*)-Pentacarbonyl[ethoxy(3a,4,5,6a-tetrahydrofuro[2,3-b]furan-2-yl)carbene]chromium(0), **5***

To a degassed solution of enol ether **31** (1.71 g, 15.3 mmol) in THF (25 mL) at −78 °C was added *tert*-butyl lithium (9 mL, 1.7 M in pentane, 15.3 mmol) dropwise and the solution stirred for 15 min at −78 °C and then at 17 °C for 30 min to give a yellow solution. The solution was recooled to −78 °C and chromium hexacarbonyl (3.37 g, 15.3 mmol) was added and the mixture warmed to 17 °C and stirred for 2 h giving a deep red colour. The solvent was then removed in vacuo and degassed water (20 mL) added, followed by triethyloxonium tetrafluoroborate (4.36 g, 23 mmol) and immediately the products extracted with pentane (3×40 mL). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography under a nitrogen atmosphere (flash silica degassed 5% EtOAc/petrol) afforded a red amorphous solid. Recrystallization from hexane afforded the *title compound*, a deep red-coloured solid (2.88 g, 52%, mp 57–63 °C). ν_{max} (film)/cm^{-1} 2961 (m), 2876 (m), 2060 (m), 1993 (w), 1929 (s), 1725 (w), 1574 (w), 1214 (m), 1021 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (1H, d, J=5.6 Hz, H-6a), 5.40 (1H, d, J=3.6 Hz, H-3), 5.20–5.08 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.11 (1H, app. t, J=8.1 Hz, H-5), 3.85–3.75 (1H, m, H-5), 3.75–3.65 (1H, m, H-3a), 2.15–2.05 (1H, m, H-4), 1.96–1.88(1H, dd, J=11.7, 4.3 Hz, H-4), 1.68–1.60 (3H, t, J=7.0 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 324.2, 224.7, 216.4, 164.1, 109.4, 103.0, 76.3, 66.9, 60.4, 47.4, 31.2, 15.1, 14.2; found C 46.58%, H 3.48%, $C_{14}H_{12}O_8Cr$ requires C 46.68%, H 3.36%.

*3.1.12. tert-Butyl(2-methoxy-1-ethynyl)dimethylsilane, **28***

To a solution of di-isopropylamine (22.4 mL, 160 mmol) in THF (300 mL) at −78 °C was added dropwise *n*-BuLi (100 mL, 1.6 M in hexane, 160 mmol). The resulting solution was left to stir for 20 min at −78 °C, then at 0 °C for 1 h. Chloroacetalaldehyde dimethylacetal (6.0 mL, 53.3 mmol) was then added dropwise at −78 °C and brought to 17 °C to stir for 4 h. The reaction was recooled to −78 °C and TBDSCl (8.0 g, 53.3 mmol) was added and the solution stirred overnight at 17 °C. The mixture was concentrated in vacuo and the residue partitioned between diethyl ether (3×100 mL) and water (200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by Kügelrohr distillation (760 mmHg, 110 °C) to yield the *title compound*, a yellow oil (6.10 g, 22%). ν_{max} (film)/cm^{-1} 2953 (s), 2932 (s), 2892 (s), 2858 (s), 2187 (s), 1465 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s, OMe), 0.91 (9H, s, $-C(CH_3)_3$), 0.80 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.5, 66.1, 26.3, 25.9, 16.9, −3.7; *m/z* (CI) 188 (MNH_4^+, 100%), 171 (MH^+, 20%), found M^+ 170.1129, $C_9H_{18}OSi$ requires 170.11269.

*3.1.13. tert-Butyl-(1-chloro-2-methoxyethenyl)-dimethylsilane, **39***

To a solution of di-isopropylamine (35.0 mL, 250 mmol) in THF (400 mL) at −78 °C was added dropwise *n*-BuLi (100 mL, 2.5 M in hexane, 250 mmol). The resulting solution

was left to stir for 20 min at −78 °C, then at 0 °C for 1 h. Chloroacetalaldehyde dimethylacetal (9.4 mL, 83.3 mmol) was then added dropwise at −78 °C and brought to 17 °C and left to stir for 4 h. The reaction was recooled to −78 °C and TBDSCl (12.50 g, 83.3 mmol) was added and the solution stirred overnight at 17 °C. The mixture was concentrated in vacuo and the residue partitioned between diethyl ether (3×100 mL) and water (200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by Kügelrohr distillation (760 mmHg, 110 °C) to afford the *title compound*, a yellow oil (6.0 g, 35%). ν_{max} (film)/cm^{-1} 2955 (s), 2932 (s), 2891 (s), 2858 (s), 1723 (s), 1623 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, s, CH), 3.80 (3H, s, OMe), 0.98 (9H, s, $-C(CH_3)_3$), 0.18 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 107.1, 60.8, 26.9, 17.0, −6.1.

3.1.14. (3a*S*R*,8a*R*S*)-5-(tert-Butyl-dimethylsilanyl)-7-ethoxy-6-methoxy-2,3,3a,8a-tetrahydro-1.8-dioxa-cyclopenta[a]inden-4-ol, **40**

The carbene complex **5** (1.78 g, 4.9 mmol) and acetylene **28** (2.10 g, 12.3 mmol) were dissolved in THF (30 mL), degassed and brought to reflux for 2 h under an atmosphere of nitrogen. On cooling to ambient temperature the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (flash silica 15% EtOAc/petrol) affording the *title compound* as a brown oil (550 mg, 31%). Recrystallization of a sample from hexane at −78 °C afforded the *title compound*, a cream-coloured solid (mp 110−111 °C). ν_{max} (film)/cm^{-1} 3416, 2948, 2886, 2855, 1596; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (1H, d, *J*=5.9 Hz, H-8a), 5.02 (1H, s, OH), 4.18−4.08 (3H, m, H-2, OCH_2CH_3), 4.05−3.96 (1H, m, H-3a), 3.87 (3H, s, OCH_3), 3.80−3.70 (1H, m, H-2), 2.23−2.15 (2H, m, H-3), 1.35 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 0.92 (9H, s, $Si-(CH_3)_3$), 0.42 (3H, s, $Si-CH_3$), 0.40 (3H, s, $Si-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 154.9, 152.4, 129.5, 112.8, 109.8, 106.2, 68.7, 67.8, 60.9, 45.0, 31.6, 27.1, 27.0, 18.6, 15.7, −1.5, −1.6; *m/z* (CI) 367 (MH^+, 100%); found C 61.71%, H 8.15%, M^+ 366.1866, $C_{19}H_{30}O_5Si$ requires C 62.26%, H 8.25% M^+ 366.18624.

A second component (3a*S*R*,7a*R*S*,3b*R*S*,6a*S*R*)-5-(*tert*-butyldimethylsilanyl)-6-ethoxy-2,3,3a,3b,6a,7a-hexahydo-cyclopenta[*b*]furo[3,2-*d*]furan-4-one, **42**, was also isolated from the above reaction as a white solid, which was recrystallized from hexane (21 mg, 1%, mp 99−101 °C). ν_{max} (film)/cm^{-1} 2952 (s), 2931 (s), 2888 (s), 2856 (s), 1685 (s), 1571 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, d, *J*=4.7 Hz, H-7a), 5.35 (1H, d, *J*=6.3 Hz, H-6a), 4.64−4.52 (1H, dq, *J*=9.8, 7.2 Hz, $-OCH_2CH_3$), 4.44−4.32 (1H, dq, *J*=9.8, 7.2 Hz, $-OCH_2CH_3$), 4.08−3.94 (2H, m, H-2), 3.10−3.02 (1H, m, H-3a), 2.98−2.92 (1H, dd, *J*=6.3, 2.9 Hz, H-3b), 2.28−2.14 (1H, m, H-3), 2.00−1.90 (1H, m, H-3), 1.44−1.38 (3H, t, *J*=7.2 Hz, $-OCH_2CH_3$), 0.90 (9H, s, Si^tBuMe_2), 0.22 (3H, s, Si^tBuMe_2), 0.21 (3H, s, Si^tBuMe_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 192.4, 114.6, 111.2, 79.7, 67.9, 66.9, 57.3, 46.1, 33.3, 26.8, 17.9, 15.4, −5.3, −5.5; *m/z* (CI) 325 (MH^+, 28%), found C 62.84%, H 8.64%, MH^+ 325.1835, $C_{17}H_{28}O_4Si_2$ requires C 62.92%, H 8.70%, MH^+ 325.1828.

Also isolated was a trace amount of (4*R*S*,5*S*R*)-2,5-bis-(*tert*-butyldimethylsilanyl)-3,4-dimethoxycyclopent-2-enone, **43** (mp 72−73 °C). ν_{max} (film)/cm^{-1} 2951 (s), 2890 (s), 2855 (s), 1669 (s), 1582 (s), 1465 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (1H, d, *J*=6.7 Hz, H-4), 3.89 (3H, s, C=C−OMe), 3.42 (3H, s, CH−O*Me*), 2.74 (1H, d, *J*=6.7 Hz, H-5), 0.98 (9H, s, C=CSi−$C(CH_3)_3$), 0.86 (9H, s, Si−$C(CH_3)_3$), 0.18 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 190.5, 118.6, 81.2, 76.9, 58.5, 57.9, 47.6, 44.3, 30.0, 27.7, 27.0, 26.9, 18.2, 17.8, −4.0, −4.2, −4.9, −5.2; *m/z* (CI) 371 (MH^+, 100%) found MH^+ 371.2447, $C_{19}H_{38}O_3Si$ requires MH^+ 371.24388.

3.1.15. (3a*S*R*,8a*R*S*)-tert-Butyl-(7-ethoxy-6-methoxy-2,3,3a,8a-terahydro-1,8-dioxa-cyclopenta[a]inden-4-yloxy)dimethylsilane, **49**

A solution of the carbene complex **5** (500 mg, 1.4 mmol) and acetylene **28** (950 mg, 5.6 mmol) in degassed toluene (20 mL) was brought to reflux for 4 h, passed through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (flash silica 15% EtOAc/petrol) to afford the cyclopenteneone **42** (80 mg, 18%) and the *title compound*, a colourless oil (100 mg, 28%). ν_{max} (film)/cm^{-1} 2954 (s), 2934 (s), 2888 (s), 2859 (s), 1723 (w), 1617 (s), 1503 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (1H, d, *J*=5.6 Hz, H-8a), 5.97 (1H, s, H-5), 4.16−4.08 (3H, m, H-2, OCH_2CH_3), 3.95−3.92 (1H, m, H-3a), 3.82 (3H, s, OMe), 3.73−3.64 (1H, m, H-2), 2.28−2.09 (2H, m, H-3), 1.38 (3H, t, *J*=7 Hz, OCH_2CH_3), 1.02 (9H, s, $-C(CH_3)_3$), 0.30 (3H, s, $SiCH_3$), 0.25 (3H, s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 153.0, 147.3, 126.6, 112.3, 111.2, 97.2, 68.9, 67.6, 56.6, 45.8, 45.4, 31.9, 26.5, 25.9, 18.3, 15.7, −3.7, −4.0; *m/z* (CI) 366 (M^+, 20%), 367 (MH^+, 100%), 384 (MNH_4^+, 80%), found M^+ 366.1866, $C_{19}H_{30}O_5Si$ requires M^+ 366.18624.

3.1.16. (3a*S*R*,8a*R*S*)-7-Ethoxy-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-4-ol, **44**

To a solution of phenol (737 mg, 2.0 mmol) in THF (30 mL) at 0 °C was added TBAF (2.0 mL, 1 M in THF, 2.0 mmol), and the mixture stirred at 17 °C for 1 h. The solution was diluted with diethyl ether (30 mL), washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow solid. Recrystallization from EtOAc and hexane afforded the *title compound* as colourless crystals (257 mg, 52%, mp 119−120 °C). ν_{max} (film)/cm^{-1} 3366, 2979, 1636; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38−6.36 (1H, d, *J*=5.6 Hz, H-8a), 6.34 (1H, br s, OH), 6.20 (1H, s, H-5), 4.14−4.01 (4H, m, H-2, OCH_2CH_3, H-3a), 3.74 (3H, s, OMe), 3.72−3.64 (1H, m, H-2), 2.28−2.08 (2H, m, H-3), 1.35 (3H, t, *J*=7.0 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.1, 148.3, 125.1, 112.6, 106.8, 93.9, 69.3, 67.8, 56.4, 44.8, 31.7, 15.6; *m/z* (CI) 253 (MH^+, 100%) found C 61.45%, H 6.42%, M^+ 252.0995, $C_{13}H_{16}O_5$ requires C 61.90%, H 6.39%, M^+ 252.09976.

*3.1.17. (3aS*R*,8aR*S*)-5-Ethoxy-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-4-ol,* ***45***

P_2O_5 (1.98 g, 14 mmol) was added to a solution of phenol **44** (50 mg, 0.2 mmol) and ethyl 2-hydroxy-5-oxo-1-cyclopentene-1-carboxylate[36] (34 mg, 0.2 mmol) in dry benzene (10 mL) and stirred at 17 °C for 2 h. The mixture was cooled to 0 °C and stirred for a further 2 h. The mixture was warmed to 17 °C and diluted with EtOAc (10 mL) and 10% aqueous HCl (5 mL). The organic layer was separated and washed with saturated sodium bicarbonate (5 mL), dried ($MgSO_4$) and concentrated in vacuo. Initial crude ^{1}H NMR showed the phenol **44** and the *title compound* in a 2:3 ratio. Separation by column chromatography (flash silica 50% EtOAc/petrol) afforded the phenol **44** (15 mg, 30%) and the *title compound* **45**, a microcrystalline solid (17 mg, 34%, mp 117–120 °C). ν_{max} (film)/cm^{-1} 3429 (br), 2966 (s), 2924 (s), 2852 (s), 1629 (s), 1498 (s), 1462 (s), 1126 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (1H, d, J=5.4 Hz, H-8a), 6.10 (1H, s, Ar*H*), 5.90 (1H, s, OH), 4.16–4.02 (4H, m, O*CH*$_2$CH$_3$, H-2, H-3a), 3.84 (3H, s, OMe), 3.74–3.64 (1H, m, H-2), 2.30–2.12 (2H, m, H-3), 1.40 (3H, t, J=6.7 Hz, OCH$_2$*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 153.2, 146.2, 129.0, 112.2, 104.7, 86.8, 69.6, 67.8, 56.2, 45.2, 31.7, 15.9; *m/z* (CI) 253 (MH^+, 100%), found MH^+ 252.09929, $C_{13}H_{16}O_5$ requires MH^+ 253.1071.

*3.1.18. (3aS*R*,8aR*S*)-6-Methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]indene-4,7-dione,* ***47***

To a solution of phenol **44** (161 mg, 0.64 mmol) in CH_3CN (7 mL) at 0 °C was added CAN (771 mg dissolved in water 4 mL, 1.4 mmol). The reaction mixture was stirred for 10 min, followed by extraction with EtOAc (2×10 mL) and water (20 mL). Purification of the residue by column chromatography (flash silica 50% EtOAc/petrol) afforded a brown solid, which on recrystallization from EtOAc/hexane gave the *title compound*, an orange-coloured solid (86 mg, 61%, mp 137–138 °C). ν_{max} (film)/cm^{-1} 2988 (s), 2947 (s), 2891 (s), 1695 (s), 1648 (s), 1589 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (1H, d, J=6.0 Hz, H-8a), 5.72 (1H, s, H-5), 4.20–4.13 (1H, m, H-2), 3.95–3.93 (1H, m, H-3a), 3.80 (3H, s, OMe), 3.76–3.66 (1H, m, H-2), 2.24–2.12 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 173.7, 157.8, 156.7, 121.6, 114.1, 107.3, 68.4, 57.0, 45.4, 30.5; *m/z* (CI) 222 (M^+, 40%), found C 59.84%, H 4.47%, $C_{11}H_{10}O_5$ requires C 59.46%, H 4.54%.

*3.1.19. (3aS*R*,8aR*S*)-6-Methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]indene-4,7-diol,* ***48***

To a solution of quinone **47** (43 mg, 0.2 mmol) in methanol (5 mL) was added $NaBH_4$ (30 mg, 0.8 mmol). The resulting solution was stirred at 17 °C for 30 min. Water (15 mL) was added and the organic layers extracted with EtOAc (2×20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (flash silica 50% EtOAc/petrol) afforded the *title compound*, a colourless oil (19.1 mg, 42%). ν_{max} (film)/cm^{-1} 3388 (br), 2963 (s), 2885 (s), 1640 (s), 1592 (s), 1492 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (1H, d, J=6.0 Hz, H-8a), 6.07 (1H, s, H-5), 5.43 (1H, br s, OH), 4.92 (1H, br s, OH), 4.18–4.00 (2H, m, H-2), 3.80 (3H, s, OMe), 3.78–3.60 (1H, m, H-3a), 2.30–2.12 (2H, m, H-3); *m/z* (CI) 224 (M^+, 20%) 225 (MH^+, 100%), found M^+ 224.0691, $C_{11}H_{12}O_5$ requires 224.06847.

*3.1.20. (3aS*R*,8aR*S*)-5-(tert-Butyl-dimethylsilanyl)-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]indene-4,7-dione,* ***50***

To a solution of phenol **40** (123 mg, 0.3 mmol) in CH_3CN (5 mL) at 0 °C was added CAN (362 mg dissolved in water 3 mL, 0.7 mmol). The reaction was stirred for 10 min, followed by extraction with EtOAc (2×10 mL) and water (20 mL). Purification by column chromatography (flash silica 20% EtOAc/petrol) afforded the *title compound* as a brown solid (102 mg, 93%, mp 99–100 °C). ν_{max} (film)/cm^{-1} 2949 (s), 2927 (s), 2895 (s), 2854 (s), 1687 (s), 1656 (s), 1613 (s), 1548 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (1H, d, J=6.0 Hz, H-8a), 4.24–4.15 (1H, m, H-2), 3.98 (3H, s, OMe), 3.96–3.88 (1H, m, H-3a), 3.78 (1H, m, H-2), 2.25–2.15 (2H, m, H-3), 0.90 (9H, s, Si–C(CH$_3$)$_3$), 0.28 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 175.0, 164.7, 156.5, 129.4, 122.6, 114.0, 68.4, 68.2, 61.2, 45.9, 30.5, 30.0, 27.3, 27.0, 25.9, 18.0, 14.4, −2.4; *m/z* (CI) 337 (MH^+, 40%), 354 (MNH_4^+, 10%), found C 61.40%, H 7.77%, $C_{17}H_{24}O_5Si$ requires C 60.69%, H 7.19%.

*3.1.21. (3aS*R*,8aR*S*)-5-(tert-Butyl-dimethyl-silanyl)-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]indene-4,7-diol,* ***51***

Quinone **50** (175 mg, 0.48 mmol) was dissolved in EtOAc (8 mL). To the reaction vessel was added Pd/C (17.5 mg, 10% w/w), the vessel was evacuated and refilled with an atmosphere of hydrogen. The flask was kept under a slight positive pressure of hydrogen (balloon) for a further period of 1.5 h at 17 °C and then filtered through a pad of Celite (EtOAc)—*CARE!* The excess solvent was removed in vacuo to afford the *title compound* as an amorphous white solid (175 mg, essentially quantitative yield). ν_{max} (film)/cm^{-1} 3407 (br), 2952 (s), 2930 (s), 2890 (s), 2855 (s), 1607 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (1H, d, J=5.7 Hz, H-8a), 5.02 (1H, br s, OH), 4.78 (1H, br s, OH), 4.20–4.12 (1H, m, H-2), 4.10–4.00 (1H, m, H-3a), 3.83 (3H, s, OMe), 3.80–3.70 (1H, m, H-2), 2.26–2.16 (2H, m, H-3), 0.94 (9H, s, Si–C(CH$_3$)$_3$), 0.44 (3H, s, SiCH$_3$), 0.42 (3H, s, SiCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 150.2, 150.1, 126.9, 113.2, 109.6, 106.5, 68.1, 60.9, 45.6, 31.5, 27.1, 18.6, −1.56, −1.61; *m/z* (CI) 338 (M^+, 20%), 339 (MH^+, 70%), found M^+ 338.15433, $C_{17}H_{26}O_5Si$ requires M^+ 338.1544.

*3.1.22. (3aS*R*,8aR*S*)-4-(tert-Butyl-dimethyl-silanyl-oxy)-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-7-ol,* ***52***

A solution of the hydroquinone **51** (175 mg, 0.54 mmol) in degassed toluene (20 mL) was brought to reflux under nitrogen. After 1 h the reaction was cooled to ambient temperature and the solvent removed in vacuo to afford the *title compound*

as an oil (175 mg, essentially quantitative yield). ν_{max} (film)/cm^{-1} 3544 (br), 2958 (s), 2931 (s), 2859 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (1H, d, J=5.7 Hz, H-8a), 5.98 (1H, s, H-5), 5.02 (1H, br s, OH), 4.08 (1H, br t, J=7.8 Hz, H-2), 4.00–3.94 (1H, m, H-3a), 3.84 (3H, s, OMe), 3.76–3.66 (1H, m, H-2), 2.30–2.08 (2H, m, H-3), 1.04 (9H, s, Si–C$(CH_3)_3$), 0.28 (3H, s, $SiCH_3$), 0.22 (3H, s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 147.2, 144.5, 124.5, 112.6, 111.4, 96.7, 67.8, 56.7, 45.7, 31.9, 25.9, 18.3, −3.7, −4.1; *m/z* (CI) 338 (M^+, 10%), 339 (MH^+, 100%), found M^+ 338.15415, $C_{17}H_{26}O_5Si$ requires M^+ 338.1544.

3.1.23. (3aS*R*,8aR*S*)-4-(tert-Butyldimethylsilanyloxy)-6-methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-7-yl trifluoromethanesulfonate, 53

To a solution of the phenol **52** (75 mg, 0.2 mmol) in dry DCM (1 mL) at 0 °C was added DMAP (1.3 mg, 0.01 mmol, 5%), pyridine (1 mL) followed by triflic anhydride (70 μL, 0.4 mmol). The resultant solution was stirred at 0 °C for 1 h and then quenched by the addition of water (5 mL). The aqueous layer was extracted with ether (3×5 mL) and the combined organic fractions were washed with 1 M HCl (20 mL) and brine (2×20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (flash silica 20% EtOAc/petrol) afforded the *title compound* as an amorphous white solid (87 mg, 93%). ν_{max} (film)/cm^{-1} 2956 (s), 2934 (s), 2889 (s), 2859 (s), 1632 (s), 1605 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, d, J=5.7 Hz, H-8a), 6.00 (1H, s, H-5), 4.18–4.10 (1H, m, H-2), 4.02–3.94 (1H, m, H-3a), 3.86 (3H, s, OMe), 3.74–3.64 (1H, m, H-2), 2.25–2.15 (2H, m, H-3), 1.05 (9H, s, Si–C$(CH_3)_3$), 0.33 (3H, s, $SiCH_3$), 0.29 (3H, s, $SiCH_3$); ^{19}F NMR (TFA=0) δ −74 (s, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 152.5, 151.3, 119 (q, J=284 Hz, CF_3), 113.4, 111.3, 96.3, 67.6, 56.4, 45.2, 31.5, 25.5, 18.0, −4.0, −4.2; *m/z* (CI) 470 (M^+, 3%), 471 (MH^+, 5%), 489 (MNH_4^+, 10%), found M^+ 470.10496, $C_{18}H_{25}O_7F_3SSi$ requires M^+ 470.1037.

3.1.24. (3aS*R*,8aR*S*)-6-Methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-4-ol, 26[20] (Method A)

To a solution of triflate **53** (96 mg, 0.2 mmol) in DMF (2 mL) was added tributylamine (0.19 mL, 0.8 mmol), 1,3-bis(di-phenylphosphino)propane (14 mg, 0.03 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.02 mmol) and formic acid (100 μL). The resulting mixture was heated to 80–90 °C and stirred for 18 h. The solution was cooled and water and ether (15 mL) were added. The organic layer was washed with 1.0 M HCl (20 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the *title compound* contaminated with *N*,*N*-dibutylformamide. Recrystallization from CCl_4 afforded the *title compound* as a white solid (5 mg, 12%, mp 148–150 °C, lit.[20b,c] 152–153 °C). ν_{max} (film)/cm^{-1} 3353 (br), 2954 (s), 2917 (s), 2848 (s), 2848 (s), 1625 (s), 1443 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (1H, d, J=5.7 Hz, H-8a), 6.03 (1H, d, J=1.8 Hz, Ar–H), 5.90 (1H, d, J=1.8 Hz, Ar–H), 4.80 (1H, br s, OH), 4.11–4.04 (1H, m, H-2), 4.01–3.94 (1H, m, H-3a), 3.70 (3H, s, OMe), 3.68–3.60 (1H, m, H-2), 2.20–2.07 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 160.2, 150.9, 110.4, 103.8, 93.3, 87.0, 65.9, 54.0, 42.5, 29.9; *m/z* (CI) 208 (M^+, 20%), 209 (MH^+, 100%), found M^+ 208.07345, $C_{11}H_{12}O_4$ requires M^+ 208.0736.

3.1.25. (3aS*R*,8aR*S*)-6-Methoxy-2,3,3a,8a-tetrahydro-1,8-dioxa-cyclopenta[a]inden-4-ol, 26[20] (Method B)

To solution of triflate **53** (19 mg, 0.04 mmol) in methanol (1 mL) was added Raney nickel (50% slurry in water (0.4 mL, settled volume)) that had been previously rinsed with methanol (*CARE*) and the mixture stirred for 12 h under nitrogen at ambient temperature. The mixture was passed through a pad of Celite to remove the Raney nickel (*CARE*) and the solution concentrated in vacuo to give an inseparable mixture of the triflate **53** and silyl ether **54** in a 4:3 ratio (9 mg, yield for mixture). TBAF (30 μL, 1 M in THF, 0.03 mmol) was added to the mixture (9 mg, 0.03 mmol) in THF (2 mL) and the solution stirred for 20 min at 17 °C. Water was added and the organic layers extracted with ether (2×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (flash silica 20% EtOAc/petrol) afforded the phenol **26** (3 mg, 38% over 2 steps), whose spectral data were identical with that reported above.

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