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The use of temporary tethers in the *meta* photocycloaddition reaction

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Abstract—The use of temporary tethers in facilitating *meta* photocycloaddition reactions between phenol and allyl alcohol derivatives has been investigated. The merits of silicon, carbonate and methylene acetal tethers were assessed, whilst considering strategies for the preparation of the natural products gymnomitrol and gelsemine. The photoadducts were epoxidised, and then subjected to acid catalysed fragmentation with concomitant cleavage of the tether. Depending on whether water or methanol was used during the fragmentation stage of the methylene tethers, the methylene group was either removed altogether or transformed into a MOM group.

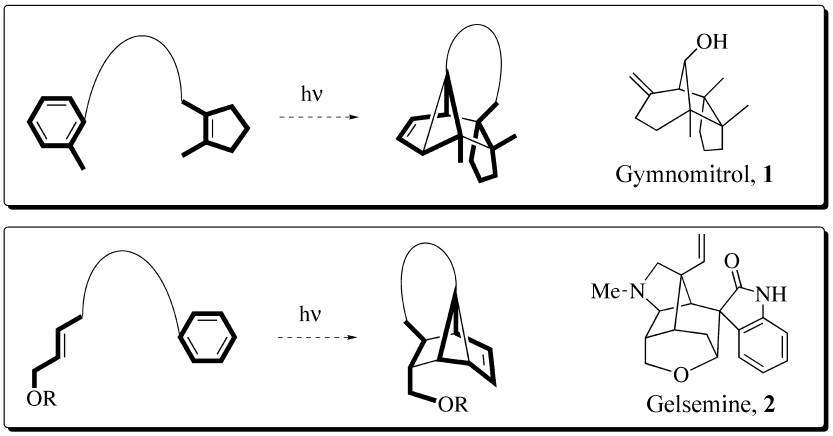
1. Introduction

The use of temporary tethers[1] to improve the efficiency of *meta* photocycloaddition reactions[2] has been investigated for the assembly of the core skeletons of the natural products gymnomitrol **1**[3] and gelsemine **2**[4] (Scheme 1).

1.1. Temporary tethers

Stork[5] originally introduced the concept of using a 'temporary tether' to convert an intermolecular reaction into an intramolecular one. The decreased entropic demands on such a system increased the likelihood of two reacting sites colliding with each other and thereby increased the rate of a particular reaction. The lower degrees of freedom of the unimolecular transition-state will also give rise to increased levels of regio- and stereoselectivity between the two reacting partners.

The three main considerations when selecting a suitable tether are that it is easily coupled to the two reacting partners via straightforward chemical transformation; that it is stable to a variety of chemical conditions; and, when it has served its purpose, that it be selectively cleaved from the final product, leaving no trace of its original existence.



Scheme 1.

Keywords: Temporary tethers; Photochemistry; Cycloaddition; Epoxidation; Fragmentation.
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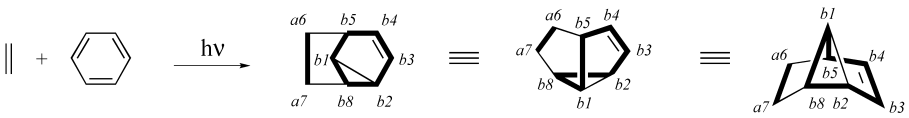


Figure 1. The *meta* photocycloaddition product between ethene and benzene is represented in three different forms. The numbering system of the basic *meta* photocycloadduct shown above is used throughout this publication, with the letters *a* and *b* signifying whether the atoms are derived from the former alkene and benzene portions, respectively.

Temporary tethers have found extensive use in radical and thermal cycloaddition reactions, because of the advantages these types of reaction have when carried out in an intramolecular sense.[1] They have also been applied in [2+2] photocycloaddition reactions,[6] although their usage has been somewhat limited.

1.2. The *meta* photocycloaddition reaction

The *meta* photocycloaddition reaction was initially reported in 1966[2a,b] and involves the 1,3-addition of an alkene across the excited state of a benzene derivative. The simplest version of this reaction between ethene and benzene is shown in Figure 1, with the former ethene and benzene ring portions being highlighted in bold.

The regiochemistry of the photocycloaddition reaction is strongly dependent on the electronic nature of the substituent on the aromatic ring of the photosubstrate. Electron-donating groups tend to favour position *b1* in the photoadduct, whilst electron-withdrawing groups favour positions *b2* or *b4* (Fig. 2).

The intramolecular variant of the *meta* photocycloaddition reaction was discovered almost by accident,[7] whilst investigating light induced *cis*/*trans* isomerism of 6-phenyl-hex-2-ene. So far the majority of such reactions have involved a three-atom chain linking the benzene and alkene portions, for which three modes of *meta* cycloaddition tend to occur. Two photoadducts are derived from alkene addition across the 1,3-positions of the aromatic ring, whilst the other is derived from alkene addition across the aromatic 2,6-positions (Fig. 3).

Most of the photoadducts reported in this publication have a four-atom tether between the benzene and alkene portions and, because the tethers were electron donating, only the 2,6-mode of cycloaddition across the aromatic ring was observed. The additional flexibility associated with this longer tether allowed it to link from the *b1* position of the photoadduct to either the *a6* or the *a7* positions (Fig. 4).

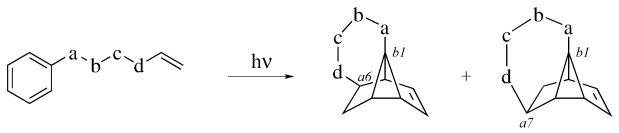


Figure 4. The two modes of intramolecular *meta* photocycloaddition for benzene linked to an alkene by a four-atom tether involving 2,6 addition of the olefin across the aromatic ring.

2. Results and discussion

2.1. Gymnomitrol studies

Whilst investigating the steric effects associated with the *meta* photocycloaddition reaction between cyclopentene and anisole derivatives, Hoye[8] attempted to assemble the

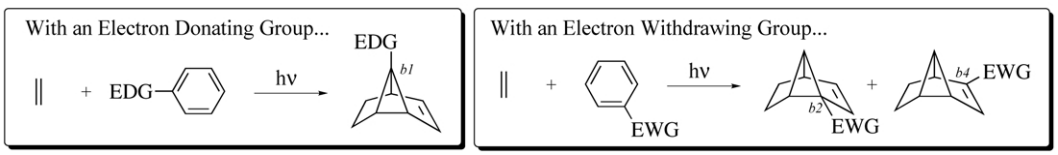


Figure 2. Regioselectivity of *meta* photocycloaddition reactions.

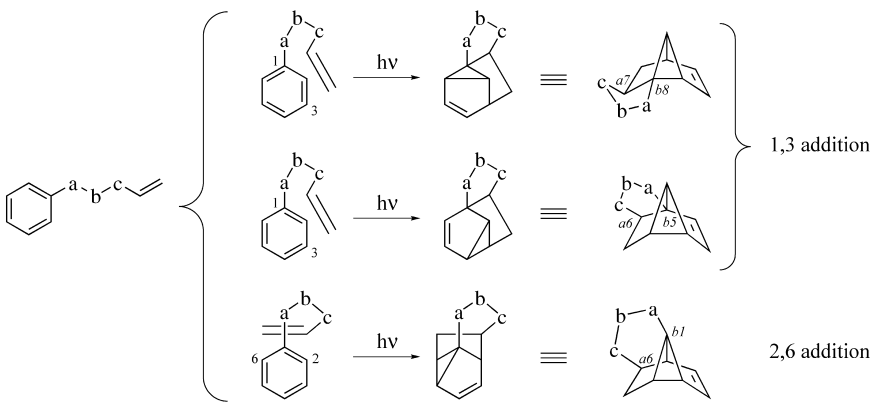
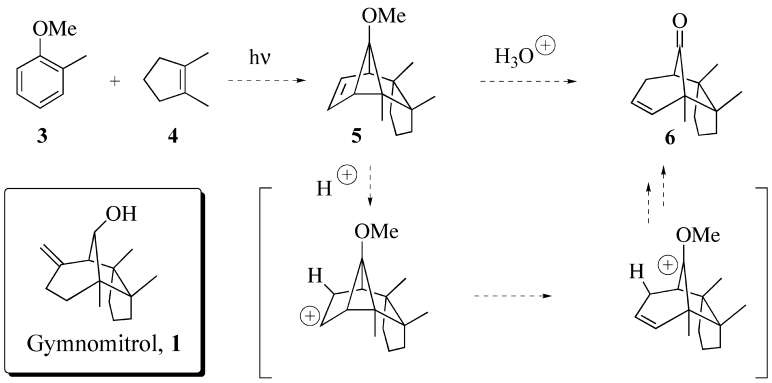


Figure 3. The three possible modes of intramolecular *meta* photocycloaddition for benzene linked to an alkene by a three-atom tether.



Scheme 2.

core structure of the sesquiterpene gymnomitrol **1** by irradiating 1-methoxy-2-methylbenzene **3** in the presence of 1,2-dimethylcyclopentene **4** and then fragmenting the *meta* photoadduct **5** using aqueous acid (Scheme 2). Unfortunately, the desired *meta* photocycloaddition between **3** and **4** failed to provide any of the desired photoadduct **5**, leading the authors to conclude that an intermolecular photoaddition reaction between a di-substituted aromatic and a tetra-substituted alkene was disfavoured on the grounds of steric hindrance.

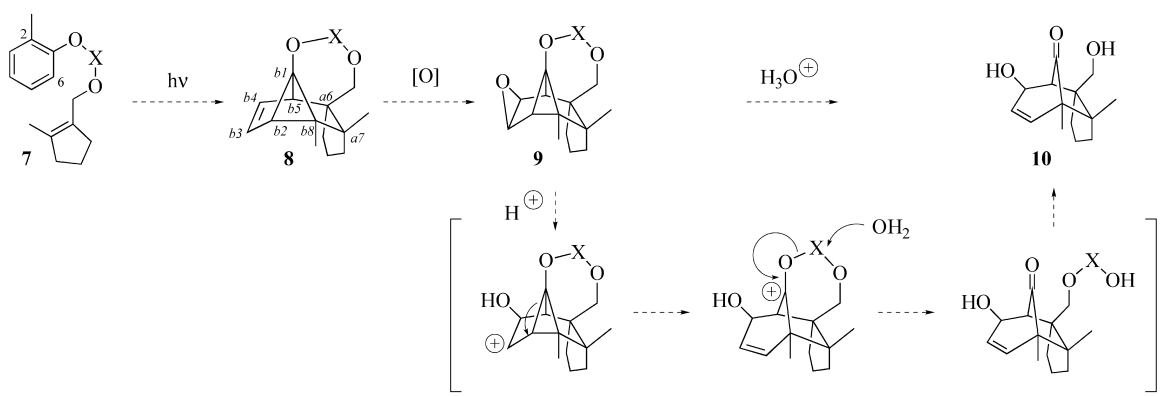
We considered that the inherent advantages of carrying out an intramolecular version of this reaction might overcome these steric obstacles and proposed using a temporary tether, X, to assemble the core skeleton of gymnomitrol. Our strategy was to couple appropriate aromatic and olefin groups together via a tether to provide the photosubstrate **7** and then initiate an intramolecular *meta* photocycloaddition reaction. The predicted photoadduct **8** would be epoxidised to **9** and hydrolysed under acidic conditions to afford the keto-diol **10**, which would subsequently be converted to gymnomitrol **1** (Scheme 3).

The electron-donating oxygen atom on the phenolic ring of **7** should direct the addition of the alkene across the 2,6 positions of the aromatic ring of the photosubstrate during the *meta* photocycloaddition reaction[2c] to give **8**. Other regioisomers could also be formed, which would be related by the ultimate position of the methyl group derived from the aromatic ring (at either position *b5* or *b8* in compound **8**) and the attachment points of the tether (between *b1* and either the *a6* or *a7* positions). The potential photoadduct **8** represented in Scheme 3 shows the methyl group at position *b8* and the tether attached between the *b1* and *a6* positions. Quite which regioisomer would be generated would be resolved as a result of experimentation. (Note that the same numbering system in Figure 1 is used, when referring to *meta* photocycloadducts).

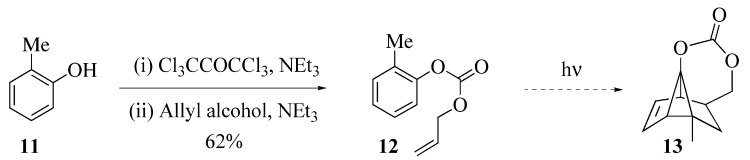
We prepared a series of simplified model substrates using 2-methylphenol **11** to determine what would be the most appropriate tether. One priority in considering a suitable tether was its stability towards silica-based chromatography since earlier work had shown some silicon-based tethers to be very labile under these conditions.

The first type of tether we chose was the carbonate. The mixed carbonate **12** was prepared using the procedure of Larock and Lee[9] by sequential reaction of triphosgene with 2-methylphenol and allyl alcohol in the presence of triethylamine. Unfortunately, irradiation of **12** failed to yield any of the desired photoadduct **13** (Scheme 4). This may have been due to internal quenching of the excited state in the aromatic ring by the adjacent carbonyl group. Alternatively, the restricted conformation of the various rotomeric forms associated with the ester-like carbonate may have prevented close association of the alkene with its aromatic partner.

Next, we turned our attention to the preparation of a methylene acetal tether. To achieve this we required a source of aryl chloromethyl ether, which could be

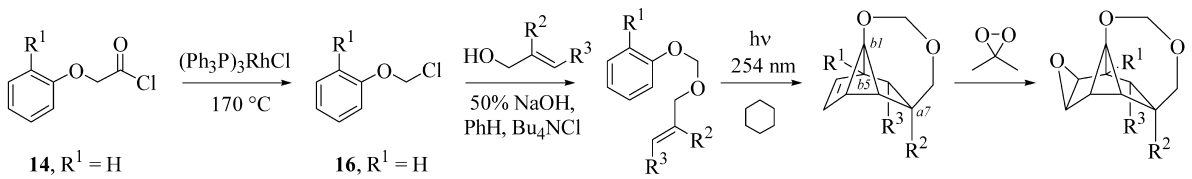


Scheme 3.



Scheme 4.

Table 1. The preparation, irradiation and oxidation of methylene acetal tethered *meta* photocycloadducts



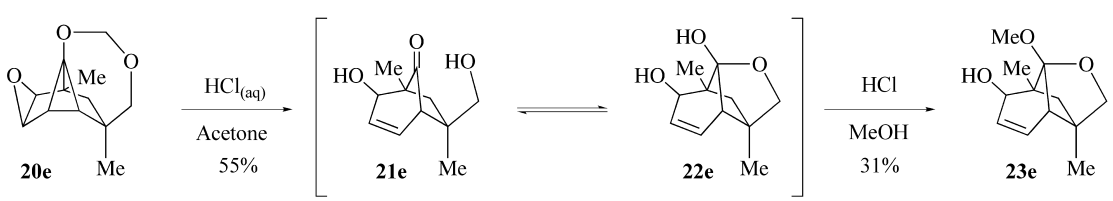
Entry	R^1	R^2	R^3	Yield of **18** (%)	Yield of **19** (%)	Yield of **20** (%)
a	H	H	H	77	0	—
b	H	Me	H	71	0	—
c	H	H	Me	72[a]	0	—
d	Me	H	H	79	13	100
e	Me	Me	H	86	17	100
f	Me	H	Me	78[a]	7[b]	100

[a] Obtained as a 4:1 mixture of *E*/*Z* isomers.
[b] Only *E* isomer underwent *meta* photocycloaddition.

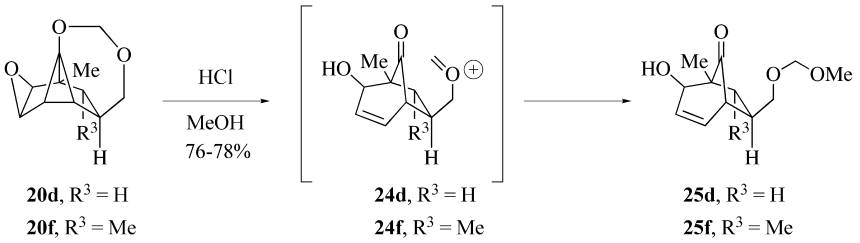
subsequently coupled to various allylic alcohols. The highly efficient procedure of Benneche and Undheim[10] was employed, which involved decarbonylation of a phenoxyacetyl chloride by heating with Wilkinson's catalyst at 170 °C. 2-Methylphenyl chloromethyl ether **17** was prepared as gymnomitrol required the aromatic ring to be substituted with a methyl group. We also prepared phenyl chloromethyl ether **16**, to assess the effect of removing the 2-methyl group on the photoreaction. Both aryl chloromethyl ethers were then coupled to three allylic alcohols to give six potential methylene acetal photosubstrates **18a–f**. Each were separately dissolved in cyclohexane (0.1 M) and irradiated in a quartz immersion-well photoreactor for 7 days using a 6 W low-pressure mercury vapour lamp. We found that only the photosubstrates **18d–f** derived from 2-methylphenol underwent *meta* photocycloaddition. Irradiation of the photosubstrates **18a–c** derived from phenol led to unreacted starting material and the formation of a complex polymeric mixture. At this point, we resolved the regiochemical issues spoken of earlier and found that the former aromatic methyl group was incorporated at the *b5* position of the photoadducts **19d–f** with the tether attached between the *b1* and *a7* positions (see Fig. 1 for photoadduct numbering system). In the case of **18f**, which was a 4:1 mixture of *E* and *Z* alkenes, only the *E* isomer underwent *meta* photocycloaddition. After chromatographic purification, the 1,3-cycloadducts **19d–f** were oxidised to their corresponding *exo*-epoxides using dimethyl dioxirane.[11] The results of these experiments are summarised in Table 1.

Alternative methods for fragmentating the epoxides **20d–f** was next investigated. Epoxide **20e** was fragmented using aqueous acid to produce the hydroxy-ketone **21e**, which existed in equilibrium with its hemi-acetal **22e**. This mixture was converted to the methoxyacetal **23e** by stirring in acidified methanol for a few days, which had the effect of protecting the primary hydroxyl group and the bridgehead ketone and leaving the allylic alcohol free for further chemical manipulation (Scheme 5).

Whilst trying to convert epoxides **20d** and **20f** directly to **23d** and **23f** using only acidified methanol, a different transformation was observed. The methylene oxonium ion **24**, which must have formed initially, was trapped with methanol rather than water. This had the effect of protecting the primary hydroxyl as a MOM group, whilst the bridgehead position remained as an unprotected ketone (Scheme 6). Extended exposure of either **25d** or **25f** to acidified methanol led only to significant decomposition.



Scheme 5.



Scheme 6.

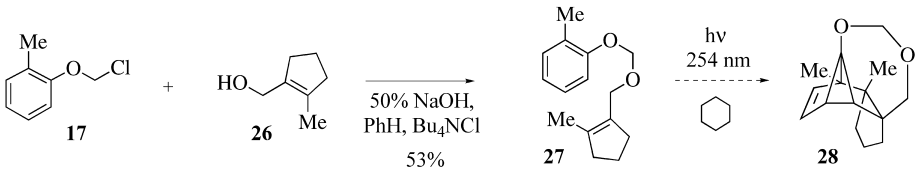
Having established these encouraging results with a methylene acetal tether, (2-methylcyclopent-1-enyl)methanol **26** was prepared according to the procedure of Inouye et al.[12] and reacted with 2-methylphenyl chloromethyl ether **17** using phase transfer conditions again. Unfortunately, irradiation of **27** led to none of the desired *meta* photocycloadduct **28** being isolated (Scheme 7). This indicated that even the inherent steric advantages of an intramolecular reaction were insufficient to overcome the steric encumbrance involved with a tetra-substituted olefin reacting with a di-substituted aromatic ring.

2.2. Gelsemine studies

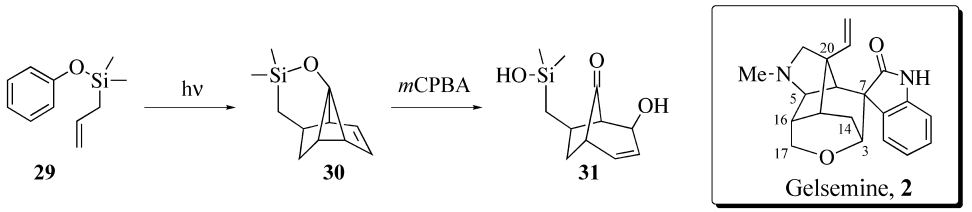
We have already shown how the core skeleton of gelsemine **2** might be assembled with a silicon tethered *meta* photocycloaddition protocol[13] (Scheme 8).

The hydroxyketone **31**, which formed as a result of an epoxidation-fragmentation reaction on photoadduct **30**, contained suitable functionality at all positions to complete a possible gelsemine synthesis, except at what would become C16 (gelsemine numbering, Scheme 8). The carbonyl group could be used to create the quarternary centre at C20, the allylic alcohol group could be used to introduce the oxindole unit at C7 and the silicon group could be oxidatively cleaved and replaced by nitrogen at C5 using a Curtius rearrangement. The shortcoming of this approach was that it would not allow the incorporation of the *endo* oxymethylene group at C17, as the appropriate *E* disubstituted olefin photosubstrate would be extremely unstable due to elimination (Scheme 9).

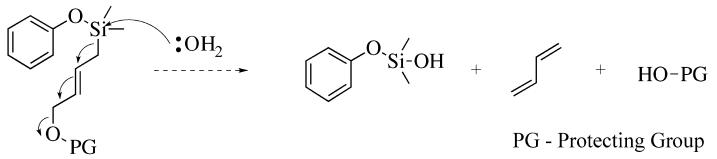
The obvious solution to this problem was to introduce an additional oxygen atom between the removable tether and the allyl group. We could not use a methylene acetal tether, as we had already discovered allyloxymethoxybenzene **18a** would not undergo the desired *meta* photocycloaddition reaction, so we chose the more labile silicon tether instead. Preliminary studies were performed with allyloxydimethylphenoxysilane **35**, which was prepared by the reaction of chlorodimethylphenoxysilane[14] **33** with the lithium salt of allyl alcohol **34**. A solution of the silicon-tethered photosubstrate **35** in cyclohexane was irradiated in a quartz immersion-well photoreactor using a 16 W low-pressure mercury vapour lamp. The silicon tether was very prone to hydrolysis during silica-based chromatography, although we managed to isolate both the *b1–a6* and *b1–a7* tethered



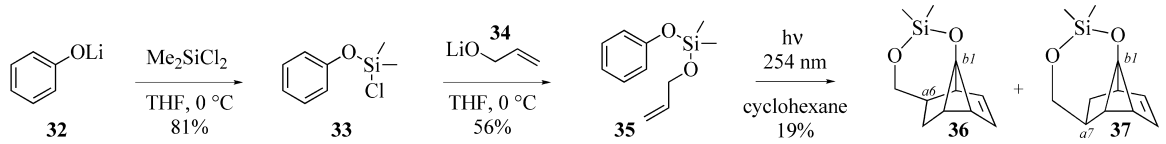
Scheme 7.



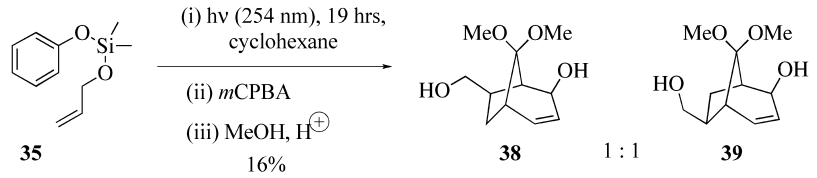
Scheme 8.



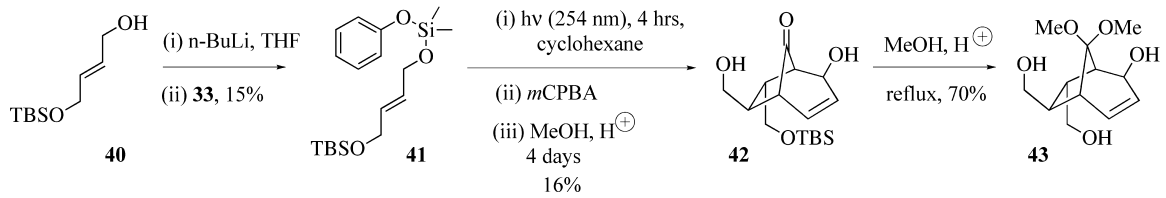
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

meta photocycloadducts **36** and **37** together as a 1:2 inseparable mixture (Scheme 10).

The losses we encountered whilst attempting to isolate **36** and **37**, caused us to irradiate **35**, oxidise and then fragment in one pot. A 1:1 mixture of the ketodiols **38** and **39** was obtained in 16% overall yield (Scheme 11) and the diastereomeric pair could be separated at this stage. In each case the primary hydroxyl group did not cyclise onto the bridgehead position, which was protected as a dimethyl acetal. Interestingly, the diols **38** and **39** were isolated as a 1:1 mixture in contrast to the 1:2 mixture of photoadducts **36** and **37** after irradiation.

Diol **38** provided strong encouragement for the preparation of the gelsemine skeleton, because if a *trans* oxymethylene group could be introduced onto the terminus of the olefin of **35**, the resulting *endo* oxymethylene group would be incorporated at what would become C16 of the gelsemine structure after the photochemical stage. *E*-4-(ᵗButyl-dimethylsilanyloxy)-but-2-en-1-ol **40**, prepared by mono-silylation[15] of the corresponding diol,[16] was chosen as the alkene partner to accomplish this, and was coupled to chlorodimethylphenoxysilane **33**. The resulting silicon tethered photosubstrate **41** was irradiated, epoxidised and hydrolysed to afford the single keto-diol **42** in 16% overall yield from **41** (Scheme 12).

There were significant differences between the preparation of **42** from **41** compared with the corresponding reaction using **35** (Scheme 11). Only one diol product **42** was formed, which indicated that one mode of photocyclo-addition had occurred. During the photoaddition step, the tether was attached at the *a7 exo* position (see Fig. 1) in a manner similar to **39** and none of the *a6 exo* regioisomer was formed. Unlike compounds **38** and **39**, the diol **42** was isolated with the bridgehead ketone intact and not protected as a dimethyl acetal. Further exposure to acidic methanol at elevated temperatures led to the formation of dimethyl acetal **43**, however, the silyl-protecting group was hydrolysed as a consequence.

3. Conclusion

This methodology allows the formation of unique tetra-cyclic compounds, which would otherwise be inaccessible through conventional means. We have shown that temporary tethers can play an important role in promoting certain *meta* photocycloaddition reactions, although they require an additional degree of complexity in their formation. It has also been demonstrated that methylene acetal tethers can act as alternatives to silicon tethers. Their increased stability has advantages in their purification and they can also be converted into useful protecting groups (e.g., a MOM group) after they have served their initial purpose.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Bruker DPX300, Varian unityINOVA-300, Varian unityINOVA-400 or Bruker AMX500 Fourier transform spectrometers at 300, 400 or 500 MHz, respectively. Chemical shifts (δ) are quoted in ppm using tetramethylsilane or residual chloroform as internal reference (δ=0.00 ppm), and coupling constants (J) are quoted in Hz. ^{13}C NMR spectra were recorded using the same instruments, and chemical shifts (δ) are quoted in ppm using $CDCl_3$ as internal reference ((δ)=77.0 ppm).

IR spectra were recorded on Perkin–Elmer Spectrum One Fourier transform instruments, either using a liquid film between sodium chloride plates (LF) or by the method of attenuated total reflectance (ATR). Frequencies (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Low- and high-resolution electron impact (EI) and chemical impact (CI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionisation (ESI) mass spectra were recorded using a Bruker Daltonics APEXIII instrument.

The starting materials for the synthesis of the compounds were obtained from the usual suppliers (Sigma-Aldrich-Fluka, Lancaster, Fisher etc.) unless otherwise stated. The anhydrous solvents, tetrahydrofuran and diethyl ether (ether), were obtained from Aldrich Chemicals in Sure/Seal™ bottles and were used without further purification. Petrol refers to petroleum ether with a boiling range of 40–60 °C. Flash column chromatography was performed using Fisher Matrex 60 (35–70 μm) silica, and the same silica was used for silver nitrate impregnation by the method of Li et al.[17] Analytical thin layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity) developed with UV light or an alkaline solution of potassium permanganate followed by heating to give yellow spots. Analytical silver nitrate impregnated plates were also prepared from these and developed simply by heating to give black spots.

Irradiations were carried out in 75 ml and 150 ml quartz immersion well reactors fitted with 6- or 125-watt mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent for 15 min at rt. Experiments were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

4.1.1. 2-Methylphenyl 2-propenyl carbonate 12. Following the procedure of Larock and Lee[9] a solution of triethylamine (6.44 ml, 46.2 mmol) in ether (20 ml) was added dropwise over 45 min to an ice-cold solution of 2-methylphenol **11** (5.00 g, 46.6 mmol) and triphosgene (4.59 g, 15.5 mmol) in ether (50 ml) to form a dense white suspension. More ether (50 ml) was added to aid stirring, followed by triethylamine (6.44 ml, 46.2 mmol) in one portion. A solution of 2-propen-1-ol (3.14 ml, 46.2 mmol) in ether (20 ml) was added dropwise over 20 min to the ice-cold suspension, which was then slowly allowed to warm to rt by stirring overnight. The dense suspension was filtered and the filtrate was concentrated in vacuo to afford an orange oil (8.17 g). Distillation afforded the pure product **12** (5.53 g, 62%) as a colourless liquid (bp 90–94 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.26 (4H, m, Ar-*H*), 5.94–6.07 (1H, m, $(CH_2)CH{=}C$), 5.32–5.46 (2H, m, $=CH_2$), 4.74 (2H, d, J=5.8 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 149.6, 131.2, 131.1, 130.0, 127.0, 126.3, 121.4, 119.4, 69.1, 15.9; IR (film) 3085, 3029, 2985, 2954, 1762, 1720, 1649, 1585, 1492, 1461 cm^{-1}; MS (EI) *m/z* 192 (2, M^+), 148 (23), 133 (29), 107 (25), 91 (20), 77 (23), 41 (100). Sample decomposed prior to accurate mass measurement.

4.1.2. [(2-Propenyloxy)methoxy]benzene 18a. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.834 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.29 g, 30 mmol) and 2-propen-1-ol (2.0 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 4 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a colourless liquid (4.94 g). Distillation afforded the pure product **18a** (3.72 g, 77%) as a colourless liquid (bp 52–54 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.32 (2H, m, Ar-*H*), 6.98–7.07 (3H, m, Ar-*H*), 5.85–5.98 (1H, m, $(CH_2)CH{=}$), 5.19–5.34 (2H, m, $=CH_2$), 5.25 (2H, s, OCH_2O), 4.21 (2H, d, J=5.5 Hz, OCH_2C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 133.8, 129.4, 121.8, 117.6, 116.2, 92.4, 69.1; IR (film) 3074, 3042, 3020, 2958, 2896, 1648, 1598, 1589 cm^{-1}; MS (EI) *m/z* 164 (30, M^+), 134 (69), 119 (25), 107 (25), 94 (33), 77 (43), 65 (21), 41 (100); HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NaO_2$ ($[M+Na]^+$) 187.0730, found 187.0733.

4.1.3. [[(2-Methyl-2-propenyl)oxy]methoxy]benzene 18b. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.840 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.30 g, 30 mmol) and 2-methyl-2-propen-1-ol (2.52 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a colourless liquid (6.11 g). Distillation afforded the pure product **18b** (3.79 g, 71%) as a colourless liquid (bp 65–67 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.32 (2H, m, Ar-*H*), 6.98–7.08 (3H, m, Ar-*H*), 5.24 (2H, s, OCH_2O), 5.00 (1H, s, $=C(H)H$), 4.91 (1H, s, $=C(H)H$), 4.10 (2H, s, OCH_2C), 1.73 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 141.3, 129.4, 121.8, 116.2, 112.7, 92.3, 72.0, 19.5; IR (film) 3075, 3042, 3041, 2973, 2946, 2909, 1659, 1599, 1589 cm^{-1}; MS (EI) *m/z* 178 (12, M^+), 148 (22), 133 (58), 94 (31), 77 (27), 55 (100); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}NaO_2$ ($[M+Na]^+$) 201.0886, found 210.0886.

4.1.4. [(2-Butenyloxy)methoxy]benzene 18c. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.830 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.32 g, 30 mmol) and 2-buten-1-ol (2.55 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 4 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.01 g). Distillation afforded **18c** (3.86 g, 72%) as a colourless liquid (bp 70–74 °C at 1 mm Hg), which was a 4:1 mixture of (*E*)/(*Z*) alkenes.

^{1}H NMR (300 MHz, $CDCl_3$) δ [(*E*)-major isomer] 7.25–7.32 (2H, m, Ar-*H*), 6.97–7.08 (3H, m, Ar-*H*), 5.66–5.81

(1H, m, =C*H*(Me)), 5.51–5.62 (1H, m, –(H_2C)*H*C=), 5.23 (2H, s, OCH_2O), 4.13 (2H, d, *J*=6.2 Hz, OCH_2C), 1.71 (3H, d, *J*=6.2 Hz, =C(H)*Me*); δ [(*Z*)-minor isomer] 7.25–7.32 (2H, m, Ar-*H*), 6.97–7.08 (3H, m, Ar-*H*), 5.66–5.81 (1H, m, =C*H*(Me)), 5.51–5.62 (1H, m, –(H_2C)*H*C=), 5.24 (2H, s, OCH_2O), 4.27 (2H, d, *J*=6.7 Hz, OCH_2C), 1.66 (3H, d, *J*=6.7 Hz, =C(H)*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) [(*E*)/(*Z*) mixture ~4:1] δ [(*E*)-major isomer] 157.3, 130.6, 129.4, 126.5, 121.7, 116.2, 92.1, 68.8, 17.8; δ [(*Z*)-minor isomer] 157.3, 129.4, 129.0, 125.7, 121.7, 116.2, 92.2, 63.3, 13.1; IR (film) 3064, 3027, 2963, 2943, 2916, 2859, 1674, 1599 cm^{-1}; MS (EI) *m/z* 178 (36, M^+), 148 (60), 107 (54), 94 (94); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}NaO_2$ ([M+Na]$^+$) 201.0886, found 210.0886.

4.1.5. 1-Methyl-2-[(2-propenyloxy)methoxy]benzene 18d. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.832 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-propen-1-ol (2.0 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 75 min and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.59 g). Distillation afforded the pure product **18d** (4.10 g, 79%) as a colourless liquid (bp 62–66 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.16 (3H, m, Ar-*H*), 6.89–6.93 (1H, m, Ar-*H*), 5.86–5.99 (1H, m, (CH_2)C*H*=), 5.27 (2H, s, OCH_2O), 5.26 (2H, m, =CH_2), 4.21 (2H, d, *J*=5.6 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.9, 130.7, 127.3, 126.8, 121.5, 117.5, 113.9, 92.4, 69.1, 16.3; IR (film) 3080, 3024, 2951, 2908, 1648, 1602, 1591, 1495, 1463 cm^{-1}; MS (EI) *m/z* 178 (41, M^+), 148 (57), 133 (32), 107 (42), 91 (35), 77 (27), 41 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2$ (M^+) 178.0993, found 178.1007.

4.1.6. 1-Methyl-2-[[(2-methyl-2-propenyl)oxy]methoxy]-benzene 18e. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.836 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-methyl-2-propen-1-ol (2.53 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (8.16 g). Distillation afforded the pure product **18e** (4.97 g, 86%) as a colourless liquid (bp 74–76 °C at 1 mm Hg).

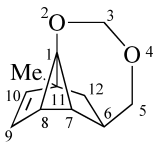
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.15 (3H, m, Ar-*H*), 6.89–6.92 (1H, m, Ar-*H*), 5.26 (2H, s, OCH_2O), 5.00 (1H, s, =C(H)*H*), 4.91 (1H, s, =C(*H*)H), 4.11 (2H, s, OCH_2C), 2.24 (3H, s, Ar-*Me*), 1.73 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 141.5, 130.7, 127.3, 126.8, 121.5, 113.9, 112.6, 92.5, 72.1, 19.5, 16.3; IR (film) 3077, 3026, 2973, 2948, 2915, 2862, 1656, 1603, 1591, 1495, 1461 cm^{-1}; MS (EI) *m/z* 192 (52, M^+), 162 (80), 147 (100), 121 (43), 107 (79), 91 (67), 79 (83), 55 (37), 41 (54); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1143.

4.1.7. 1-[(2-Butenyloxy)methoxy]-2-methylbenzene 18f. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.835 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-buten-1-ol (2.5 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a yellow liquid (6.42 g). Distillation afforded **18f** (4.37 g, 78%) as a colourless liquid (bp 64–74 °C at 1 mm Hg), which was a 4:1 mixture of (*E*)/(*Z*) alkenes.

^{1}H NMR (400 MHz, $CDCl_3$) δ [(*E*)-major isomer] 7.12–7.15 (2H, Ar-*H*), 7.05–7.09 (1H, m, Ar-*H*), 6.88–6.92 (1H, m, Ar-*H*), 5.67–5.79 (1H, m, =C*H*(Me)), 5.53–5.62 (1H, m, –(H_2C)*H*C=), 5.25 (2H, s, OCH_2O), 4.13 (2H, d, *J*=6.4 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*), 1.71 (3H, d, *J*=6.4 Hz, =C(H)*Me*); δ [(*Z*)-minor isomer] 7.12–7.15 (2H, m, Ar-*H*), 7.05–7.09 (1H, m, Ar-*H*), 6.88–6.92 (1H, m, Ar-*H*), 5.67–5.79 (1H, m, =C*H*(Me)), 5.53–5.62 (1H, m, –(H_2C)*H*C=), 5.26 (2H, s, OCH_2O), 4.27 (2H, d, *J*=6.9 Hz, =CH(Me)), 2.25 (3H, s, Ar-*Me*), 1.66 (3H, d, *J*=6.9 Hz, =C(H)*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ [(*E*)-major isomer] 155.4, 130.7, 130.4, 127.3, 126.8, 126.6, 121.4, 113.8, 92.1, 68.9, 17.8, 16.3; δ [(*Z*)-minor isomer] 155.4, 130.7, 129.0, 127.3, 126.8, 125.8, 121.4, 113.8, 92.1, 63.2, 16.3, 13.1; IR (film) 3024, 2946, 2917, 2859, 1602, 1591, 1495, 1463 cm^{-1}; MS (EI) *m/z* 192 (12, M^+), 162 (24), 108 (100), 55 (84), 39 (96); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1163.

4.1.8. 2,4-Dioxa-11-methyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]-dodec-9-ene 19d. Under an atmosphere of nitrogen, a solution of **18d** (1.34 g, 7.5 mmol) in oxygen free cyclohexane (75 ml) was irradiated with a 6-watt low-pressure mercury vapour lamp for 7 days using a 75 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (1.30 g). The oil was purified by flash chromatography on silica (65 g) eluted with increasing concentrations of dichloromethane in petrol (30, 50 and 100%). Five components were isolated: (in order of increasing polarity) unchanged starting material (0.78 g, 58%); possible intermolecular by-product (0.013 g, 1%); impure uncharacterised by-product (0.008 g, 0.6%); impure *meta*-addition product (0.324 g, 24%); and possible unstable *ortho*-addition product (0.069 g, 5%).

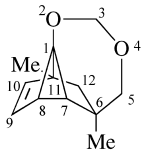
The impure *meta*-addition product was purified further by flash chromatography on silver nitrate impregnated silica[17] (30 g) and eluted with methanol/dichloromethane/petrol (5:20:75) to afford another uncharacterised by-product (0.049 g, 4%) and the pure *meta*-addition product **19d** as a pale yellow oil (0.178 g, 13%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, d, *J*=5.6 Hz, H-10), 5.46 (1H, dd, *J*=5.6, 2.6 Hz, H-9), 5.31 (1H, d,

J=6.1 Hz, H-3$_{endo}$), 4.68 (1H, d, J=6.1 Hz, H-3$_{exo}$), 3.80 (1H, dd, J=11.2, 1.9 Hz, H-5$_{endo}$), 3.42 (1H, d, J=11.2 Hz, H-5$_{exo}$), 2.87 (1H, d, J=7.0 Hz, H-6), 2.73 (1H, ddd, J=8.2, 2.6, 1.4 Hz, H-8), 1.87 (1H, dd, J=12.7, 7.0 Hz, H-12$_{endo}$), 1.59 (1H, d, J=2.7 Hz, H-12$_{exo}$), 1.47 (1H, d, J=8.2 Hz, H-7), 1.30 (3H, s, 11-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 121.3, 98.7, 85.3, 83.0, 57.9, 48.1, 46.9, 42.4, 37.8, 17.6; IR (film) 3059, 3039, 2949, 2927, 2869, 1604, 1456, 1449 cm^{-1}; MS (EI) m/z 178 (18, M$^+$), 97 (28), 81 (49), 69 (100), 57 (56), 41 (64). Sample decomposed prior to accurate mass measurement.

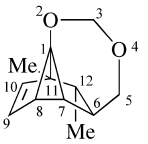
4.1.9. 2,4-Dioxa-6$_{endo}$,11-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 19e. Under an atmosphere of nitrogen, a solution of **18e** (1.45 g, 7.5 mmol) in oxygen free cyclohexane (75 ml) was irradiated with a 6-watt low-pressure mercury vapour lamp for 16 days using a 75 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (1.37 g). The oil was purified by flash chromatography (dichloromethane/petrol 1:1) then neat dichloromethane. Four components were isolated: (in order of increasing polarity) unchanged starting material (0.882 g, 61%); possible intermolecular by-product (0.013 g, 0.9%); possible *ortho*-addition product (0.012 g, 0.8%); and pure *meta*-addition product **19e** as a pale yellow oil (0.250 g, 17%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, d, J=5.6 Hz, H-10), 5.49 (1H, dd, J=5.6, 2.6 Hz, H-9), 5.29 (1H, d, J=5.9 Hz, H-3$_{endo}$), 4.69 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.53 (1H, d, J=11.0 Hz, H-5$_{endo}$), 3.23 (1H, d, J=11.0 Hz, H-5$_{exo}$), 2.66 (1H, ddd, J=8.2, 2.6, 1.3 Hz, H-8), 1.79 (1H, d, J=12.6 Hz, H-12$_{exo}$), 1.60 (1H, dd, J=12.6, 1.3 Hz, H-12$_{endo}$), 1.29 (3H, s, 11-Me), 1.28 (1H, m, H-7), 1.18 (3H, s, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 121.4, 98.1, 88.7, 85.2, 58.3, 53.7, 49.5, 47.7, 40.6, 19.0, 17.9; IR (ATR) 2927, 2866, 1605 cm^{-1}; MS (EI) m/z 192 (1, M$^+$), 132 (100), 117 (84), 91 (31). Sample decomposed prior to accurate mass measurement.

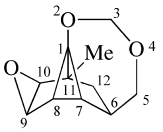
4.1.10. 2,4-Dioxa-11,12$_{endo}$-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 19f. Under an atmosphere of nitrogen, a solution of **18f** (2.88 g, 15.0 mmol) in oxygen free cyclohexane (150 ml) was irradiated with a 125-watt low-pressure mercury vapour lamp for 13 days using a 150 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (2.72 g). The oil was purified by flash chromatography using increasing concentrations of dichloromethane with petrol (30, 50 and 100%). Four components were isolated: (in order of increasing polarity) unchanged starting material (1.31 g, 45%); impure uncharacterised by-product (0.014 g, 0.5%); impure *meta*-addition product (0.422 g, 15%); and possible unstable *ortho*-addition product (0.104 g, 4%).

The impure *meta*-addition product was purified further by flash chromatography on silver nitrate impregnated silica[17] (42 g) eluted with methanol/dichloromethane/petrol (5:20:175) to afford the still impure *meta*-addition product (0.343 g, 12%). Another purification by flash chromatography on silica (100 g) eluted with 7.5% 2-methoxy-2-methylpropane in petrol gave an uncharacterised by-product (0.063 g, 2%) and the pure *meta*-addition product **19f** (0.194 g, 7%) as a pale yellow low-melting solid mp <20 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, dd, J=5.5, 2.4 Hz, H-9), 5.52 (1H, d, J=5.5 Hz, H-10), 5.28 (1H, d, J=6.0 Hz, H-3$_{endo}$), 4.65 (1H, d, J=6.0 Hz, H-3$_{exo}$), 3.89 (1H, dd, J=11.3, 1.8 Hz, H-5$_{endo}$), 3.42 (1H, d, J=11.3 Hz, H-5$_{exo}$), 2.73 (1H, ddd, J=8.2, 2.4, 1.5 Hz, H-8), 2.43 (1H, m, H-6), 2.06 (1H, q, J=7.4 Hz, H-12), 1.34 (1H, d, J=8.2 Hz, H-7), 1.21 (3H, s, 11-Me), 0.85 (3H, d, J=7.4 Hz, 12-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 122.6, 98.1, 87.5, 82.2, 60.6, 54.7, 48.9, 47.5, 35.2, 17.4, 17.1; IR (ATR) 3062, 2957, 2915, 2861, 1609 cm^{-1}; MS (EI) m/z 192 (1, M$^+$), 162 (27), 147 (21), 119 (44), 108 (100), 91 (47), 77 (23), 55 (47); HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_2$ ([M+Na]$^+$) 215.1043, found 215.1035.

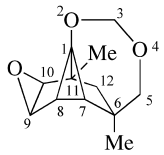
4.1.11. 2,4-Dioxa-11-methyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]-dodec-9-ene oxide 20d. A 0.1 M solution of ice cold dimethyldioxirane[9] in acetone (27 ml, 2.7 mmol) was added to the *meta* photoadduct **19d** (53 mg, 0.30 mmol) and allowed to warm to rt overnight. The remaining solvent was removed in vacuo and any residual water was removed by addition of ethyl acetate (20 ml), drying ($MgSO_4$), filtering and concentrating in vacuo to give the product **20d** (57 mg, 100%) as a pale yellow crystalline solid mp 79–80 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (1H, dd, J=5.9, 0.5 Hz, H-3$_{endo}$), 4.47 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.92 (1H, dd, J=11.4, 1.8 Hz, H-5$_{endo}$), 3.45 (1H, br d, J=11.3 Hz, H-5$_{exo}$), 3.35 (1H, dd, J=3.3, 1.3 Hz, H-9), 2.95 (1H, dd, J=3.3, 1.3 Hz, H-10), 2.88 (1H, ddd, J=8.9, 1.3, 1.2 Hz, H-8), 2.65 (1H, br d, J=6.7 Hz, H-6), 1.65 (1H, ddd, J=13.4, 6.7, 1.2 Hz, H-12$_{endo}$), 1.57 (1H, br d, J=13.4 Hz, H-12$_{exo}$), 1.33 (3H, s, 11-Me), 1.31 (1H, dd, J=8.9, 1.8 Hz, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.1, 81.6, 74.3, 62.5, 53.7, 52.2, 49.3, 42.0, 40.2, 35.2, 16.0; IR (ATR) 2981, 2928, 2869, 1485, 1457, 1383 cm^{-1}; MS (EI) m/z 194 (25, M$^+$), 169 (35); HRMS (ESI) m/z calcd $C_{22}H_{28}Na\ O_6$ ([2M+Na]$^+$) 411.1778, found 411.1774.

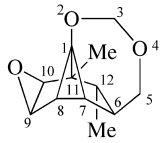
4.1.12. 2,4-Dioxa-6$_{endo}$,11-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene oxide 20e. An ice-cold solution of the *meta* photoadduct **19e** (0.100 g, 0.52 mmol) in dichloromethane (10 ml) was treated with small aliquots of a ~0.1 M solution of dimethyldioxirane[9] in acetone, over 1 h,

until TLC indicated that all of the starting material had been consumed (total volume added: 9.3 ml, ~0.93 mmol). After stirring at ice temperature for 1 h, the solution was concentrated in vacuo to give the product **20e** (0.108 g, 100%) as a colourless waxy solid mp 79–80 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, d, J=5.9 Hz, H-3$_{endo}$), 4.49 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.68 (1H, d, J=11.2 Hz, H-5$_{endo}$), 3.37 (1H, dd, J=3.3, 1.3 Hz, H-9), 3.28 (1H, dd, J=11.2, 1.1 Hz, H-5$_{exo}$), 2.96 (1H, dd, J=3.3, 1.2 Hz, H-10), 2.80 (1H, ddd, J=8.8, 1.3, 1.2 Hz, H-8), 1.73 (1H, dd, J=13.3, 1.2 Hz, H-12$_{exo}$), 1.37 (1H, dd, J=13.3, 1.1 Hz, H-12$_{endo}$), 1.31 (3H, s, 11-Me), 1.13 (1H, dd, J=8.8, 1.2 Hz, H-7), 1.06 (3H, s, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.5, 87.2, 74.5, 62.7, 54.0, 52.2, 49.0, 48.4, 47.4, 38.7, 18.6, 16.3; IR (ATR) 2999, 2956, 2932, 2861 cm^{-1}; MS (EI) m/z 208 (5, M$^+$), 178 (17), 133 (22), 119 (72), 105 (100), 97 (24), 91 (89), 83 (38), 65 (20), 55 (25), 41 (36). Sample decomposed prior to accurate mass measurement.

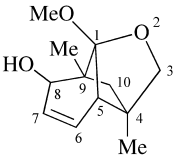
4.1.13. 2,4-Dioxa-11,12$_{endo}$-dimethyl-tetracyclo-[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene oxide 20f. A 0.1 M solution of ice cold dimethyldioxirane[9] in acetone (27 ml, 2.7 mmol) was added to the *meta* photoadduct **19f** (62 mg, 0.32 mmol) and allowed to warm to rt overnight. The remaining solvent was removed in vacuo and any residual water was removed by addition of ethyl acetate (20 ml), drying ($MgSO_4$), filtering and concentrating in vacuo to give the product **20f** (67 mg, 100%) as a pale yellow crystalline solid mp 81–82 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (1H, dd, J=6.0, 0.5 Hz, H-3$_{endo}$), 4.47 (1H, d, J=6.0 Hz, H-3$_{exo}$), 3.98 (1H, dd, J=11.3, 1.9 Hz, H-5$_{endo}$), 3.43 (1H, dd, J=3.2, 1.4 Hz, H-9), 3.39 (1H, ddd, J=11.3, 0.8, 0.8 Hz, H-5$_{exo}$), 3.14 (1H, dd, J=3.2, 1.3 Hz, H-10), 2.84 (1H, ddd, J=8.8, 1.4, 1.4 Hz, H-8), 2.33 (1H, m, H-6), 2.10 (1H, br q, J=7.7 Hz, H-12$_{exo}$), 1.27 (3H, s, 11-Me), 1.22 (1H, br d, J=8.9 Hz, H-7), 1.02 (1H, d, J=7.7 Hz, 12$_{endo}$-Me); ^{13}C NMR (125 MHz) δ 98.7, 81.2, 76.0, 59.7, 55.0, 53.2, 52.0, 50.4, 46.9, 34.9, 15.3, 15.0; HRMS (ESI) m/z calcd $C_{12}H_{16}NaO_3$ ([M+Na]$^+$) 231.0992, found 231.0983. Structure also confirmed by single crystal X-ray analysis.[18]

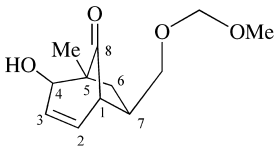
4.1.14. 2-Oxa-8$_{exo}$-hydroxy-1-methoxy-4,9-dimethyl-tricyclo[4.4.0.0^{4,5}.0.^{9,10}]dec-6-ene 23e. A single drop of 2.0 M aqueous hydrochloric acid was added to an ice-cold solution of epoxide **20e** (60 mg, 0.29 mmol) in acetone (12 ml). The solution was stirred for 1 h and allowed to warm to rt, after which flash silica (0.75 g) was added and the resulting mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica (6 g) eluted with 3% methanol in dichloromethane to afford the major product as a pale yellow oil (31 mg, 55%). ^{1}H NMR spectrum indicated that this was a mixture of ketone **21e** and hemiacetal **22e**.

This mixture (31 mg, 0.16 mmol) was dissolved in a 0.01 M solution of HCl in anhydrous methanol (2 ml) and stirred at rt for 4 days. Flash silica (0.25 g) was then added and the mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica (3 g) eluted with 2% methanol in dichloromethane to afford the product **23e** (10 mg, 30%) as a white crystalline solid mp 71.5–73.5 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, dd, J=9.5, 4.3 Hz, H-7), 5.72 (1H, dd, J=9.5, 6.3 Hz, H-6), 3.66 (2H, m, H-3), 3.53 (1H, dd, J=11.5, 4.3 Hz, H-8), 3.37 (3H, s, 1-OMe), 2.88 (1H, d, J=11.5 Hz, 8-OH), 2.42 (1H, dd, J=6.3, 0.9 Hz, H-5), 1.35 (1H, dd, J=12.7, 0.9 Hz, H-10$_{exo}$), 1.28 (1H, dd, J=12.7, 2.7 Hz, H-10$_{endo}$), 1.20 (3H, s, 9-Me), 0.98 (3H, s, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 124.3, 111.6, 77.9, 76.6, 52.3, 47.7, 46.5, 45.8, 45.5, 16.0, 15.5; IR (ATR) 3536, 3034, 2971, 2960, 2932, 2871, 1645 cm^{-1}; MS (EI) m/z 210 (2, M$^+$), 121 (25), 110 (26), 105 (29), 95 (100); HRMS (ESI) m/z calcd $C_{12}H_{18}NaO_3$ ([M+Na]$^+$) 233.1148, found 233.1156.

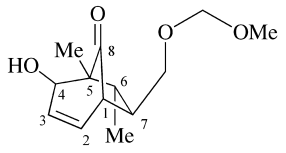
4.1.15. 4$_{exo}$-Hydroxy-7$_{exo}$-methoxymethoxymethyl-5-methyl-bicyclo[3.2.1]oct-2-en-8 one 25d. Epoxide **20d** (17 mg, 0.087 mmol) was stirred in a 0.01 M solution of HCl in methanol (5 ml) for 1 h. The residue was isolated by concentration in vacuo and then passed through a small plug of silica eluting with petrol/ethyl acetate (1:2) to yield the product **25d** as a yellow oil (15 mg, 76%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (1H, dd, J=8.9, 7.1 Hz, H-2), 5.76 (1H, dd, J=9.0, 3.8 Hz, H-3), 4.57 (2H, s, OCH_2OMe), 4.30 (1H, m, H-4), 3.42 (1H, dd, J=9.6, 5.0 Hz, 7-CH(H)O), 3.34 (3H, s, OMe), 3.32 (1H, dd, J=9.6, 6.8 Hz, 7-CH(H)O), 2.70 (1H, dd, J=11.0, 7.0 Hz, H-1), 2.35 (1H, m, H-7), 2.08 (1H, dd, J=14.0, 9.5 Hz, H-6$_{endo}$), 1.63 (1H, dd, J=14.0, 2.0 Hz, H-6$_{exo}$), 1.56 (1H, br s, 4-OH), 1.19 (3H, s, 5-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 135.0, 128.4, 96.5, 85.0, 70.4, 55.4, 50.6, 39.3, 34.4, 30.9, 15.8; IR (film) 3430, 2930, 1749, 1635 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{18}O_4$ (M$^+$) 226.1205, found 226.1223.

4.1.16. 4$_{exo}$-Hydroxy-7$_{exo}$-methoxymethoxymethyl-5,6$_{endo}$-dimethyl-bicyclo[3.2.1]oct-2-en-8-one 25f. Epoxide

20f (11 mg, 0.053 mmol) was stirred in a 0.01 M solution of HCl in methanol (5 ml) for 1 h. The residue was isolated by concentration in vacuo and then passed through a small plug of silica eluting with petrol/ethyl acetate (1:2) to yield the product **25f** as a yellow oil (10 mg, 78%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (1H, dd, J=9.0, 7.2 Hz, H-2), 5.78 (1H, dd, J=9.0, 3.9 Hz, H-3), 4.57 (2H, s, OCH_2OMe), 4.47 (1H, m, H-4), 3.41 (1H, dd, J=9.6, 5.0 Hz, 7-CH(H)O), 3.35 (3H, s, OMe), 3.27 (1H, dd, J=9.6, 7.0 Hz, 7-CH(H)O), 2.63 (1H, d, J=7.2 Hz, H-1), 1.91 (1H, ddd, J=7.0, 5.1, 4.2 Hz, H-7), 1.82 (1H, m, H-6$_{exo}$), 1.38 (1H, br d, J=10 Hz, 4-OH), 1.20 (3H, s, 5-Me), 1.82 (1H, d, J=11.0 Hz, 6$_{exo}$-Me); ^{13}C NMR (1 MHz, $CDCl_3$) δ 216.3, 136.2, 128.7, 96.5, 87.2, 70.1, 55.4, 54.0, 50.1, 47.6, 40.0, 16.1, 15.2; IR (film) 3418, 2962, 2929, 1747, 1640 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1379.

4.1.17. 1-Methyl-2-[[(2-methyl-1-cyclopenten-1-yl)methoxy]methoxy]benzene 27. Fifty percent aqueous sodium hydroxide (33 ml) and tetrabutylammonium chloride (0.460 g, 1.7 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (2.58 g, 16 mmol) and 2-methyl-1-cyclopentene-1-methanol[10] **26** (1.85 g, 16 mmol) in benzene (33 ml). The resulting two-phase mixture was stirred vigorously at rt for 5 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.10 g). Distillation afforded a colourless liquid (bp 94–96 °C at 1 mm Hg) (2.62 g), which was still impure. Further purification by flash chromatography on silica (130 g) eluted with 10% dichloromethane in petrol afforded the product **27** as a colourless liquid (2.04 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.15 (2H, m, Ar-H), 7.07–7.09 (1H, m, Ar-H), 6.88–6.92 (1H, m, Ar-H), 5.22 (2H, s, OCH_2O), 4.23 (2H, s, OCH_2C), 2.31–2.39 (4H, m), 2.25 (3H, s, Ar-Me), 1.75–1.83 (2H, m), 1.69 (3H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 138.3, 130.9, 130.7, 127.2, 126.8, 121.3, 113.9, 92.0, 64.0, 38.8, 34.7, 21.6, 16.3, 13.9; IR (ATR) 2949, 2843, 1603, 1591, 1494 cm^{-1}; MS (EI) m/z 232 (10, M^+), 202 (18), 163 (7), 141 (55), 121 (70); HRMS (EI) m/z calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1478.

4.1.18. Chlorodimethylphenoxysilane 33. To a stirred solution of phenol (11.75 g, 125 mmol) in dry tetrahydrofuran (90 ml) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of n-butyllithium (50 ml, 2.5 M in hexanes). After addition, the phenoxide solution was allowed to warm to rt and added dropwise to a stirred solution of freshly distilled dichlorodimethylsilane (113.7 ml, 938 mmol) in dry tetrahydrofuran (100 ml) at −78 °C. The reaction mixture was left to stir overnight allowing it to warm to rt whereby it was concentrated in vacuo, washed with petrol and filtered to remove the white salts. The orange solution was then concentrated in vacuo and distilled under high vacuum to yield **33** a colourless oil (18.85 g, 81%)

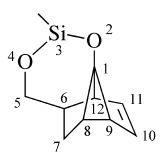
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, dd, J=7.5, 8.5 Hz, Ar-H), 7.07 (1H, t, J=7.4 Hz, Ar-H), 7.00 (2H, d, J=8.5 Hz, Ar-H), 0.63 (6H, s, Si–Me$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 129.6, 122.7, 120.0, 2.4; IR (film) 3065, 3041, 2970, 1596 cm^{-1}; MS (EI) m/z 186 (70%, $[M]^+$), 171 (78), 151 (50), 93 (98), 77 (100); HRMS (EI) m/z calcd for $C_8H_{11}OSiCl$ (M^+) 186.0268, found 186.0284.

4.1.19. Allyloxydimethylphenoxysilane 35. To a stirred solution of allyl alcohol (2.2 ml, 32.2 mmol) in dry tetrahydrofuran (60 ml) at 0 °C was added a solution of n-butyllithium (12.9 ml, 2.5 M, 32.2 mmol) dropwise. This was then added dropwise to a solution of chlorodimethylphenoxysilane **33** (6.00 g, 32.2 mmol) in dry tetrahydrofuran (125 ml) and allowed to stir at rt for 2 days. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (50 ml), filtered and concentrated in vacuo leaving a yellow liquid, which was distilled under high vacuum to give **35** as a colourless oil (3.75 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, m, Ar-H), 6.99 (3H, m, Ar-H), 5.97 (1H, ddt, J=17.1, 10.4, 4.9 Hz, (H_2C)HC=), 5.31 (1H, dt, J=17.1, 1.7 Hz, =C(H)H), 5.14 (1H, dt, J=10.4, 1.5 Hz, =C(H)H), 4.34 (2H, dd, J=4.9, 1.6 Hz, OCH_2), 0.30 (6H, s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 136.3, 129.4, 121.7, 119.7, 114.9, 63.6, −2.8; IR (film) 2965, 1597 cm^{-1}; MS (EI) m/z 208 (100, $[M^+]$), 193 (60), 175 (61), 151 (94); HRMS (EI) m/z calcd for $C_{11}H_{16}O_2Si$ (M^+) 208.0919, found 208.0899.

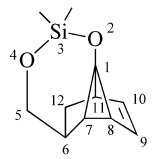
4.1.20. 2,4-dioxa-3-(dimethylsilyl)tetracyclo-[6.4.0.0^{1,9}.0^{6,12}]dodec-10-ene 36 and 2,4-dioxa-3-(dimethylsilyl)tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 37. A stirred solution of allyloxydimethylphenoxysilane **35** (650 mg) in cyclohexane (180 ml) was irradiated for 19 h with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solvent was removed in vacuo and the residue was subjected to column chromatography (silica gel, petrol/ethyl acetate 20:1) to yield a mixture of **36** and **37** in a 1:2 ratio as a colourless oil (123 mg, 19%).

Minor isomer **36**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (1H, dd, J=5.8, 2.5 Hz, H-11), 5.51 (1H, dddd, J=5.8, 2.7, 1.5, 0.9 Hz, H-10), 4.03 (1H, ddd, J=11.5, 1.7, 0.9 Hz, H-5), 3.96 (1H, dd, J=11.5, 2.3 Hz, H-5), 2.97 (1H, dd, J=2.5, 2.5 Hz, H-12), 2.37 (1H, ddddd, J=8.0, 1.1, 1.1, 1.1, 1.1 Hz, H-9), 1.97 (1H, ddd, J=13.6, 6.5, 2.3 Hz, H-7), 2.11 (1H, m, H-6), 1.74 (1H, ddd, J=8.1, 6.5, 1.7 Hz, H-8), 1.69 (1H, dddd, J=13.7, 5.9, 1.9, 0.9 Hz, H-7), 0.27 (3H, s, Si–Me), 0.18 (3H, s, Si–Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.4, 127.5, 83.8, 70.5, 59.7, 52.3, 38.8, 33.4, 27.3, −1.5.

Major isomer **37**

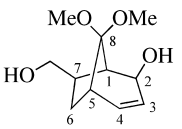


^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (1H, dddd, J=5.8, 2.8, 0.8, 0.8 Hz, H-10), 5.53 (1H, dd, J=5.8, 2.5 Hz, H-9), 3.82 (1H, dd, J=10.4, 1.1 Hz, H-5), 3.72 (1H, dd, J=10.4, 2.1 Hz, H-5), 3.18 (1H, dddd, J=8.3, 2.8, 1.5, 0.9 Hz, H-11), 2.79 (1H, dddd, J=7.7, 2.1, 2.1, 1.1 Hz, H-6), 2.44 (1H, dd, J=8.4, 2.5 Hz, H-8), 2.22 (1H, ddd, J=12.9, 8.3, 2.1 Hz, H-12$_{exo}$), 1.56 (1H, ddd, J=12.9, 7.7, 1.5 Hz, H-12$_{endo}$), 1.44 (1H, br d, J=8.4 Hz, H-7), 0.26 (3H, s, Si–Me), 0.17 (3H, s, Si–Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 123.9, 83.6, 73.9, 56.6, 46.4, 41.7, 40.7, 35.5, −0.5.

For the mixture: MS (EI) m/z 208 (98, [M$^+$]), 193 (71), 176 (76), 151 (89), 75 (100); HRMS (EI) m/z calcd for $C_{11}H_{16}O_2Si$ (M$^+$) 208.0919, found 208.0901.

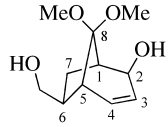
4.1.21. 7-Hydroxymethyl-8,8-dimethoxy-bicyclo-[3.2.1]oct-3-en-2-ol 38 and 6-hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol 39. A stirred solution of allyloxydimethylphenoxysilane 35 (1.00 g, 4.8 mmol) in cyclohexane (180 ml) was irradiated for 19 h with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solution was filtered and concentrated in vacuo, whereby the resultant oil was dissolved in CH_2Cl_2 (20 ml). With stirring, a solution of basewashed m-CPBA (4.8 mmol) in CH_2Cl_2 (10 ml) was added slowly at rt. After 2 h 2-methyl-2-butene (1.5 ml) was added and the solution was allowed to stir for a further 0.5 h, before adding a saturated solution of $NaHCO_3$.The organic phase was separated and washed with saturated brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The resultant oil was dissolved in a solution of PTSA (0.100 g) in methanol (20 ml) and stirred under an atmosphere of nitrogen for 3 days at rt. Ethyl acetate (20 ml) was added and the solution was concentrated in vacuo until approximately 5 ml remained, this process was repeated a further 3 times. After a further addition of ethyl acetate (20 ml) the organic material was washed with saturated $NaHCO_3$ solution, then saturated brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica chromatography (Et_2O/acetone 9:1) to yield 38 (80 mg, 8%) and 39 (80 mg, 8%) as colourless oils.

7-Hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol **38**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, dd, J=9.4, 6.8 Hz, H-4), 5.65 (1H, ddd, J=9.4, 3.9, 1.5 Hz, H-3), 3.92 (1H, m, H-2), 3.62 (1H, br d, J=11.5 Hz, 2-O*H*), 3.54 (1H, dd, J=10.3, 6.6 Hz, 7-C(*H*)H), 3.48 (1H, dd, J=10.3, 7.7 Hz, 7-C(H)*H*), 3.17 (3H, s, 8-OMe), 3.13 (3H, s, 8-OMe), 2.48 (1H, ddd, J=6.8, 2.0, 6.0 Hz, H-5), 2.38 (1H, m, H-1), 1.86 (1H, br s, CH_2O*H*), 1.73 (1H, m, H-7$_{endo}$), 1.64 (1H, dd, J=12.1, 9.0 Hz, H-6$_{exo}$), 1.47 (1H, ddd, J=12.1, 6.2, 6.0 Hz, H-6$_{endo}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 128.4, 109.2, 75.0, 65.9, 50.1, 48.0, 43.7, 40.9, 40.5, 32.0; IR (film) 3433, 2952 cm^{-1}; MS (EI) m/z 213 (1, [M−H]$^+$), 197 (4, [M−OH]$^+$), 183 (5), 101 (100); HRMS (EI) m/z calcd for $C_{11}H_{17}O_3$ ([M−OH]$^+$) 197.1178, found 197.1182.

6-Hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol **39**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (1H, ddd, J=9.4, 7.1, 0.5 Hz, H-4), 5.65 (1H, ddd, J=9.4, 3.6, 1.4 Hz, H-3), 3.92 (1H, br d, J=9.9 Hz, H-2), 3.54 (2H, d, J=6.2 Hz, 7-CH_2O), 3.39 (1H, br d, J=10.6 Hz, 2-O*H*), 3.20 (3H, s, 8-OMe), 3.13 (3H, s, 8-OMe), 2.51 (1H, br s, O*H*), 2.50 (1H, dd, J=7.5, 1.6 Hz, H-1), 2.39 (1H, dd, J=7.1, 2.0 Hz, H-5), 2.08 (1H, m, H-6$_{endo}$), 1.58 (1H, ddd, J=13.8, 7.5, 5.3 Hz, H-7$_{exo}$), 1.45 (1H, dd, J=13.8, 9.7 Hz, H-7$_{endo}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 128.7, 109.7, 74.5, 65.9, 50.3, 47.5, 47.0, 43.2, 42.7, 26.1; IR (film) 3412, 2948 cm^{-1}; MS (EI) m/z 197 (9, [M−OH]$^+$), 183 (22), 149 (16), 131 (100); HRMS (EI) m/z calcd for ([M−OH]$^+$) 197.1178, found 197.1187.

4.1.22. 4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-en-1-ol 40. This preparation followed the procedure of McDougal et al.[15] for the monosilylation of symmetrical diols. To a stirred solution of NaH (4.54 g, 114 mmol, 60% dispersion in oil) in dry tetrahydrofuran (100 ml) was added dropwise *E*-but-2-ene-1,4-diol[16] (10.0 g, 114 mmol) in dry tetrahydrofuran (60 ml) at rt. This was stirred for 45 min after which *tert*butyldimethylsilylchloride (17.1 g, 114 mmol) in tetrahydrofuran (15 ml) was added in one portion and allowed to stir for a further 45 min. Ether (450 ml) was added and the solution washed with 10% K_2CO_3 (300 ml) and then brine. The aqueous layers were washed with Et_2O and the organic layers combined, dried ($MgSO_4$), filtered and concentrated in vacuo to leave a yellow liquid, which was subjected to silica chromatography (petrol/ethyl acetate 4:1) to yield **40** (20.4 g, 89%)

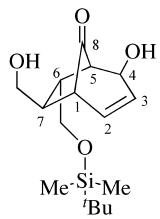
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (2H, m), 4.13 (4H, m), 1.62 (1H, brs, O*H*), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 128.9, 63.2, 63.1, 25.9, 18.4, −5.3; IR (film) 3367, 2955, 2930, 2857 cm^{-1}; MS (EI) m/z 171 (5, [M−CH_2OH]$^+$), 145 (63), 127 (41), 75 (100); HRMS (EI) m/z calcd for $C_9H_{19}OSi$ ([M−CH_2OH]$^+$) 171.1205, found 171.1206

4.1.23. {[4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-enyl-oxy]-dimethyl-silanyloxy}-benzene 41. To a stirred solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-but-2-en-1-ol **40** (7.44 g, 36.8 mmol) in dry tetrahydrofuran (60 ml) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of *n*-butyllithium (14.7 ml, 2.5 M in hexanes). The solution had turned yellow and after stirring for a

further 1 h the solution was allowed to reach rt before it was added dropwise to a solution of chlorodimethylphenoxysilane **33** (6.87 g, 36.82 mmol) in dry tetrahydrofuran (90 ml) at −78 °C under an atmosphere of nitrogen. After addition the solution was allowed to warm to rt over a period of 14 h and then concentrated in vacuo, washed with petrol, filtered and again concentrated in vacuo. The brown oil was then distilled under high vacuum and the highest boiling fraction was further subjected to silica chromatography (petrol/CH_2Cl_2 1:1) to yield **41** (1.99 g, 15%).

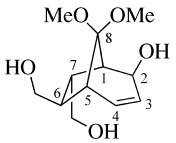
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (5H, m, Ar-H), 5.82 (2H, s, HC═CH), 4.33 (2H, s, OCH_2), 4.18 (2H, s, OCH_2), 0.93 (9H, s, SiC(*Me*)$_3$), 0.29 (6H, s, Si*Me*$_2$), 0.08 (6H, s, Si*Me*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 130.5, 129.5, 128.0, 121.7, 119.8, 63.1, 62.9, 25.9, 18.4, −2.6, −5.3; IR (film) 2956, 2929, 2857, 1597 cm^{-1}; MS (CI) *m*/*z* 370 (100, $[M+NH_4]^+$), 308 (22), 242 (16), 221 (16), 185 (11); HRMS (CI) *m*/*z* calcd for $C_{18}H_{36}NO_3Si_2$ ($[M+NH_4]^+$) 370.2234, found 370.2231.

4.1.24. 6-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-7-hydroxymethyl-bicyclo[3.2.1]oct-en-8-one 42. A stirred solution of **41** (520 mg, 1.48 mmol) in cyclohexane (180 ml) was irradiated for 4hrs with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solvent was removed in vacuo, the crude material taken up in CH_2Cl_2 (5 ml) and then a solution of base-washed *m*-CPBA (2.5 mmol, 7.5 ml, 0.33 M) in CH_2Cl_2 was added. After 1 h 2-methyl-2-butene (0.3 ml, 2.83 mmol) was added to ensure removal of excess *m*-CPBA and the resultant solution was washed and extracted from $NaHCO_3$ solution, then brine and the organic phase dried ($MgSO_4$), filtered and concentrated in vacuo. The yellow oil was then dissolved in methanol (10 ml) and PPTS (0.05 g) added. This was allowed to stir for 4 days before ethyl acetate (30 ml) was added and the solution was partially concentrated in vacuo until 10 ml remained. Ethyl acetate (30 ml) was again added and the process repeated 2 more times. The solution was then washed with $NaHCO_3$, then brine and dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then subjected to silica chromatography (petrol/ethyl acetate 1:2) to provide **42** as a colourless oil (49 mg, 11%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, dd, *J* 8.9, 0.4 Hz, H-2), 5.81 (1H, ddd, *J* 9.0, 3.7, 1.0 Hz, H-3), 4.85 (1H, dd, *J* 3.4, 3.2 Hz, H-4), 3.82 (1H, dd, *J*=9.6, 7.6 Hz, 6$_{endo}$-C*H*(H)), 3.63 (1H, dd, *J*=9.4, 8.3 Hz, 6$_{endo}$-CH(*H*)), 3.48 (1H, dd, *J*=10.3, 6.3 Hz, 7$_{exo}$-C*H*(H)), 3.44 (1H, dd, *J*=10.6, 7.0 Hz, 7$_{exo}$-CH(*H*)), 2.73 (1H, br d, *J*=7.6 Hz, H-5), 2.55 (1H, dd, *J*=7.2, 1.2 Hz, H-1), 2.28 (1H, dddd, *J*=7.8, 7.8, 7.7, 4.3 Hz, H-6$_{exo}$), 1.96 (1H, ddd, *J*=6.6, 6.6, 4.5 Hz, H-7$_{endo}$), 0.90 (9H, s, H-11), 0.83 (6H, s, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 135.9, 128.6, 75.1, 65.2, 64.0, 54.0, 48.7, 45.4, 39.4, 25.6, 18.0, −5.2; IR (film) 3400, 2954, 2929, 2857, 1754, 1471 cm^{-1}; MS (CI) *m*/*z* 330 (4, $[M+NH_4]^+$), 298 (100); HRMS (CI) *m*/*z* calcd for $C_{16}H_{32}NSiO_4$ ($[M+NH_4]^+$) 330.2101, found 330.2101.

4.1.25. 6,7-Bis-hydroxymethyl-8,8-dimethoxy-bicyclo-[3.2.1]-oct-3-en-2-ol 43. A stirred solution of **42** (11 mg, 35 mmol) and PPTS (48 mg) in methanol (5 ml) was heated to reflux for 4 h. After cooling to rt, ethyl acetate (25 ml) was added and the solution was partially concentrated in vacuo until ca. 5 ml remained and a white solid formed. Ethyl acetate (10 ml) was added and the solution was washed with $NaHCO_3$ then brine and the organic layer was separated and dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then subjected to silica chromatography (petrol/ethyl acetate 1:4) to yield **43** as a colourless oil (6 mg, 70% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J*=7.3, 9.2 Hz, H-4), 5.62 (1H, dd, *J*=3.7, 9.2 Hz, H-3), 4.73 (1H, dd, *J*=3.8, 6.6 Hz, H-2), 4.14 (1H, dd, *J*=7.6, 8.5 Hz, −CH_2O), 3.65 (2H, m, −CH_2O), 3.62 (1H, dd, *J*=2.6, 8.7 Hz, −CH_2O), 3.26 (3H, s, 8-OMe), 3.14 (3H, s, 8-OMe), 2.91 (1H, ddd, *J*=1.5, 6.6, 7.1 Hz, H-1), 2.50 (2H, m), 2.35 (1H, brs, O*H*, absent with CD_3OD), 1.93 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 126.9, 79.5, 74.9, 65.8, 58.3, 53.4, 51.1, 49.4, 48.1, 42.4, 41.8; IR (film) 3402, 2952 cm^{-1}; MS (CI) *m*/*z* 262 (3, $[M+NH_4]^+$), 231 (100); HRMS (CI) *m*/*z* calcd for $C_{12}H_{24}NO_5$ ($[M+NH_4]^+$) 262.1654, found 262.1654.

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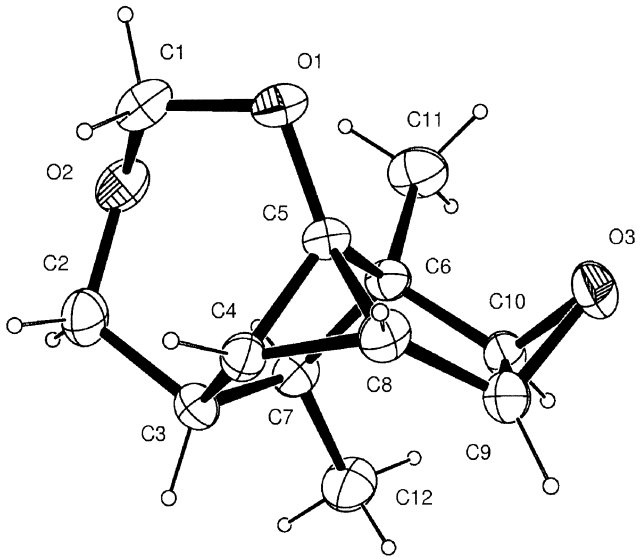
18. The crystallographic data for compound **20f** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 223831. Formula: C12 H16 O3 unit cell parameters: *a* 7.4462(2), *b* 12.6823(3), *c* 10.8486(3), beta 95.180(1), space group *P*21/*n*.



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