Intramolecular [2+2] photocycloadditions as an approach towards the right-hand side of solanoeclepin A

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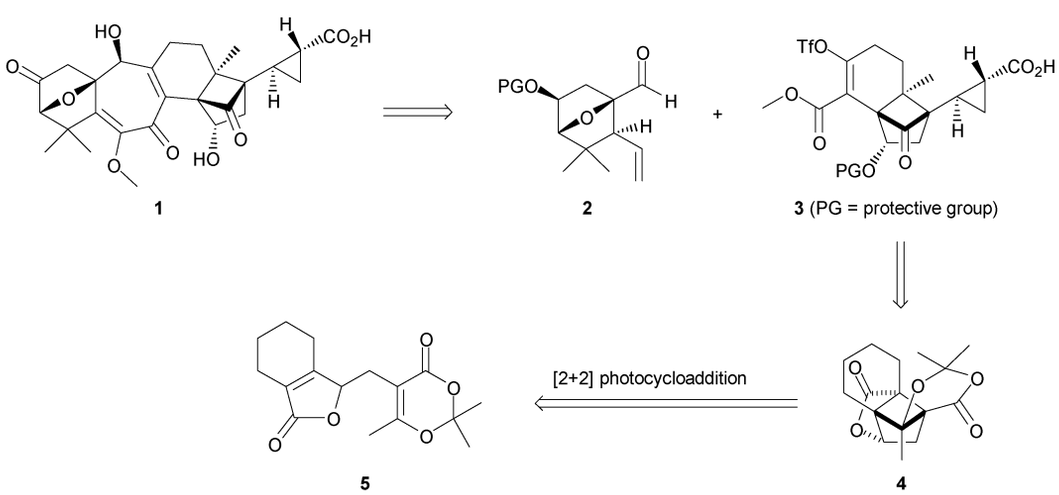
A racemic synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A (**1**), the most active natural hatching agent of potato cyst nematodes, was approached *via* an intramolecular [2+2] photocycloaddition of 6-unsubstituted dioxenones with variously substituted pendent alkenes. The synthesis of the cyclisation precursors involved a very efficient iodide–magnesium exchange reaction with iododioxenone **6**, which allowed facile allylation at C-5 of the dioxenone. Photochemistry with dioxenones **12** and **17** led to novel bicyclo[2.2.0]hexanes **24** and **26**. The use of the more rigid lactone precursor **14** led to bicyclo[2.1.1]hexane **25**, and allowed the stereoselective synthesis of the complex tricyclic core of solanoeclepin A. The structure of **25** was unequivocally proven by X-ray crystal structure determination.

Introduction

Solanoeclepin A (**1**, Scheme 1) is the most active natural hatching agent for potato cyst nematodes.[1] Its complex heptacyclic structure contains all ring sizes ranging from three to seven, including a highly strained bicyclo[2.1.1]hexanone moiety, which to the best of our knowledge is an unprecedented feature in natural products. Recently, we have described our efforts towards the synthesis of both the left- (**2**) and right-hand (**3**) fragments of this fascinating compound.[2] The key step in the model studies towards the right-hand side involved the intramolecular [2+2] photocycloaddition of dioxenone **5**, which afforded pentacyclic bislactone **4** in excellent yield. Although this structure contained the tricyclic core with appropriate stereochemistry for elaboration towards the target substructure, the presence of the methyl substituent on C-6 of the dioxenone, hampered the eventual formation of the necessary cyclobutanone. We now wish to report the application of 6-unsubstituted dioxenones in the construction of the right-hand side of solanoeclepin A. The 6-unsubstituted dioxenones have already found successful application in intermolecular [2+2] cycloadditions.[3] On the other hand, intramolecular examples are scarce.[4,5] Therefore, we set out to investigate the behaviour of these substrates in the photochemistry, in order to evaluate their potential in the synthesis of the target structure **3**. Please note that all compounds in the rest of this document correspond to racemic products.

Results and discussion

The synthesis of the cycloaddition precursors required the introduction of an allyl substituent at C-5 of the dioxenone. Although it is known that iododioxenone **6**[4,6] (Scheme 2) can be successfully applied in palladium catalyzed C–C bond forming reactions,[6] all attempts to introduce an allyl moiety *via* this method failed. Additionally, attempted lithium–iodide exchange with *tert*-butyllithium at −90 °C met with failure. However, Knochel recently reported the conversion of 5-iodouracil derivatives into the corresponding Grignard reagents by magnesium–iodide exchange with isopropylmagnesium bromide.[7] These polyfunctional organomagnesium compounds



Scheme 1

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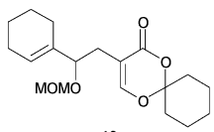
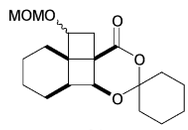
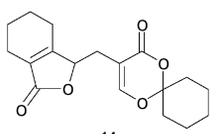
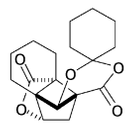
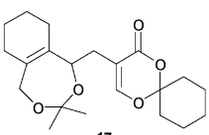
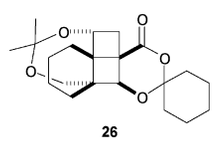
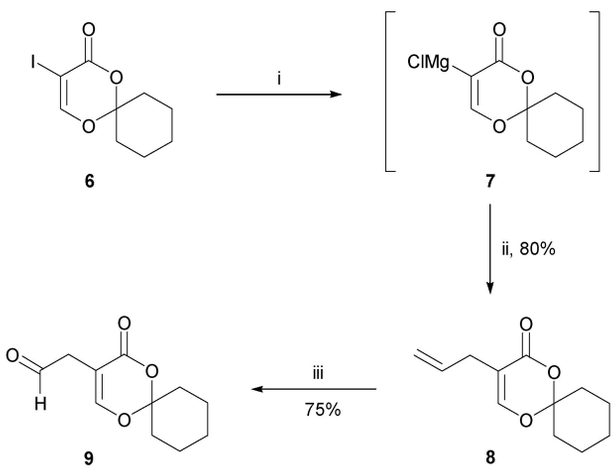
Table 1 Results of the photocycloaddition reactions

Entry	Precursor	Time	Cycloadduct	Yield (dr)
1	 **12**	30 min	 **24**	97% (50 : 50)
2	 **14**	1 h	 **25**	95%
3	 **17**	30 min	 **26**	88%



Scheme 2 *Reagents and conditions*: i, *i*-PrMgCl (1.05 equiv.), THF, −78 °C; ii, allyl bromide (1.2 equiv.), CuCN (10 mol%), −78 °C; iii, OsO_4 (0.5 mol%), $NaIO_4$ (2.2 equiv.), THF–water (1 : 1 v/v), rt, 7 h.

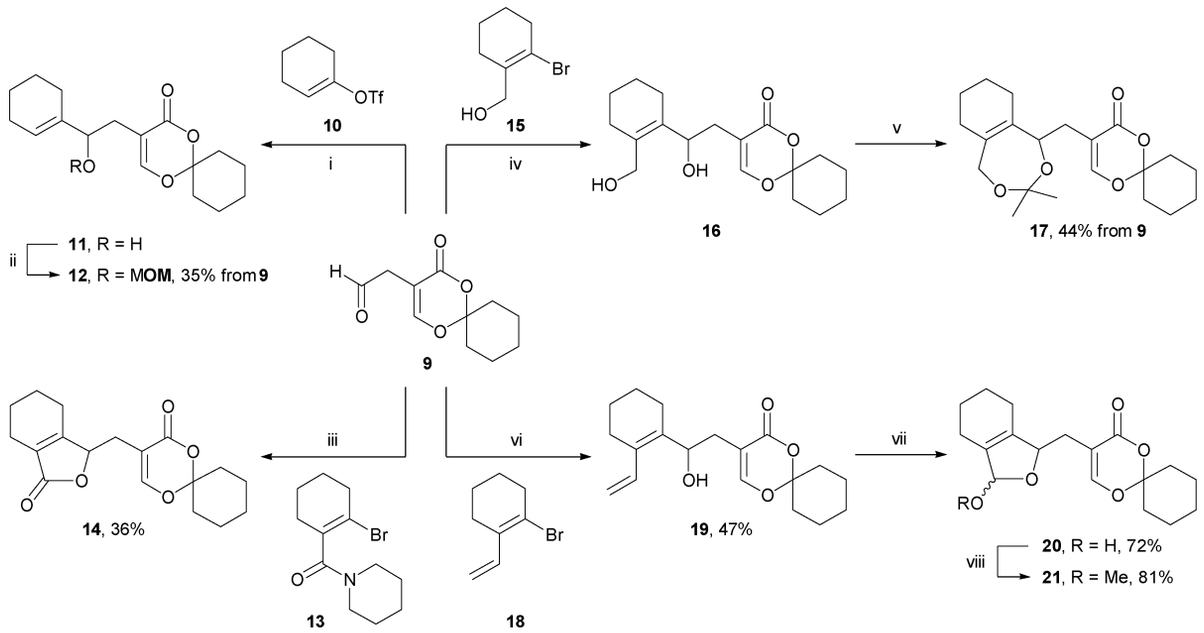
could then be reacted with various electrophiles in good yields. We were very pleased to find that the application of this method to iododioxenone **6** resulted in the quantitative formation of the magnesiated species **7**. The *in situ* formed Grignard reagent **7** was then reacted with allyl bromide and a catalytic amount of copper cyanide to afford allyldioxenone **8** in 80% yield. Subsequent oxidative cleavage of olefin **8** with OsO_4–$NaIO_4$ allowed formation of aldehyde **9**, which served as a key building block in the construction of the cyclisation precursors.

To study the photochemical behaviour of the 6-unsubstituted dioxenones, a number of precursors were synthesized (Scheme 3). Precursor **12** was prepared for the study of the influence of the lack of a substituent on C-6 of the dioxenone on the photochemistry, because the corresponding 6-methyl derivative was known to provide the cycloadduct.[2c] Cr(II)–Ni(II) mediated coupling[8] of cyclohexenyl triflate[9]† (**10**) with aldehyde **9** followed by protection with a methoxymethyl (MOM) group, afforded precursor **12**. Precursor **14** was anticipated to provide the appropriate skeleton for use in model studies towards the right-hand side of solanoeclepin A. Unfortunately, the coupling method used in the synthesis of **12** could not be applied in the synthesis of **14**, due to the instability of aldehyde **9** under the required reaction conditions. However, the organomagnesium species derived from bromo-amide **13**[10] could be coupled to **9**, affording lactone **14** after treatment of the intermediate adduct with acetic acid, albeit in a modest yield. The main reason for the low yield is enolisation of aldehyde **9** during the Grignard addition, rendering it unreactive towards the organometallic reagent and leading to substantial amounts of self-condensation product **22** (27%). In order to investigate whether the five-membered ring lactone of **14** was crucial for the regiochemical outcome of the cycloaddition, or that connecting the tether and the alkene *via* any other ring would also suffice, seven-membered ring acetonide **17** and five-membered ring acetal **21** were synthesized. Acetonide **17** was obtained from coupling of **9** with vinyl bromide **15**,[11] followed by acetalization of diol **16**. Finally, addition of lithiated **18**[12] to aldehyde **9** afforded alcohol **19**. Oxidation of the terminal olefin of **19** afforded the sensitive five-membered ring lactol **20**. The propensity of lactol **20** to eliminate the hydroxy group became apparent upon attempted silylation, which rapidly led to furan **23** in a virtually quantitative yield (96%). However, methylation of the hydroxy group at low temperature led to the desired cyclisation precursor **21**.

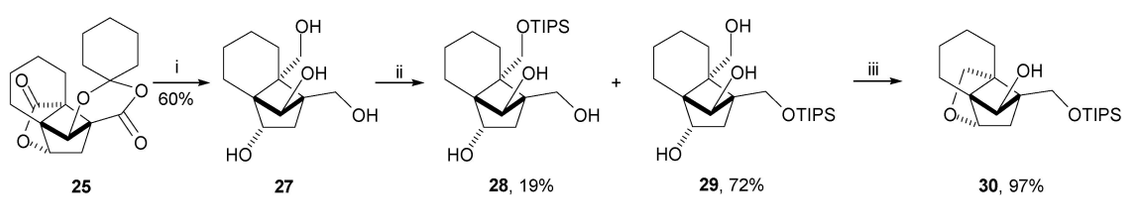
With the cyclisation precursors in hand, the stage was set for the photochemistry (Table 1). Irradiation of dioxenone **12** at 300 nm (acetonitrile–acetone 9 : 1 v/v, rt) for 30 min afforded cycloadduct **24** as a 50 : 50 mixture of diastereoisomers in excellent yield (Table 1 entry 1). This mode of closure indicated that the lack of a substituent on C-6 of the dioxenone had no influence on the regiochemistry of the cycloaddition. The more rigid lactone precursor **14** afforded the corresponding crossed adduct **25** as a single product (Table 1 entry 2). The structure of **25** was unequivocally proven by X-ray crystal structure determination (Fig. 1). Compound **25** contains the appropriate substitution pattern and stereochemistry for elaboration towards the right-hand side of solanoeclepin A. Acetonide **17** afforded exclusively the straight cycloadduct **26** as a single diastereomer in excellent yield, indicating that the 7-membered ring offers too much flexibility to direct the cycloaddition towards the crossed mode of closure (Table 1 entry 3).[2c] Unfortunately, acetal **21** exhibited very limited stability towards the irradiation conditions, leading to a complex mixture of products.

Cycloadduct **25** was exhaustively reduced with excess lithium aluminium hydride to afford tetraol **27** (Scheme 4). These rather harsh reduction conditions were necessary to prevent competitive retro-aldol fragmentation of the reduction intermediate.[2c] Unfortunately, all attempts to directly differentiate the hydroxy functions of **27** by acetalization resulted in complex mixtures of

† The IUPAC name for triflate is trifluoromethanesulfonate.



Scheme 3 *Reagents and conditions*: i, **10** (2 equiv.), $CrCl_2$ (4 equiv.), $NiCl_2$ (1 mol%), DMF, rt, 16 h; ii, MOMCl, *i*-$PrNEt_2$, CH_2Cl_2, rt, 16 h; iii, **13**, *t*-BuLi (2.1 equiv.), THF–pentane, −78 °C, 15 min then $MgBr_2{\cdot}OEt_2$ (1.1 equiv.), Et_2O, −78 °C, 30 min then **9**, −78 °C, 30 min then AcOH–water (1 : 1 v/v), −78 °C ⟶ rt, 1 h; iv, **15**, *t*-BuLi (3.3 equiv.), THF–pentane, −78 °C, 15 min then **9**, −78 °C, 30 min; v, 2,2-dimethoxypropane, PPTS, DMF, rt, 4 h; vi, **18**, *t*-BuLi (2.1 equiv.), THF–pentane, −78 °C, 15 min then **9**, −78 °C, 30 min; vii, OsO_4 (0.5 mol%), $NaIO_4$ (2.2 equiv.), THF–water (1 : 1 v/v), rt, 4 h; viii, KHMDS, THF, −78 °C, 30 min then MeI, −78 °C, 1 h.



Scheme 4 *Reagents and conditions*: i, lithium aluminium hydride (5 equiv.), THF, rt, 5 min; ii, TIPSCl (1.5 equiv.), imidazole (5 equiv.), DMF, 0 °C ⟶ rt, 16 h; iii, tosyl chloride (1.5 equiv.), pyridine, rt, 1 h.

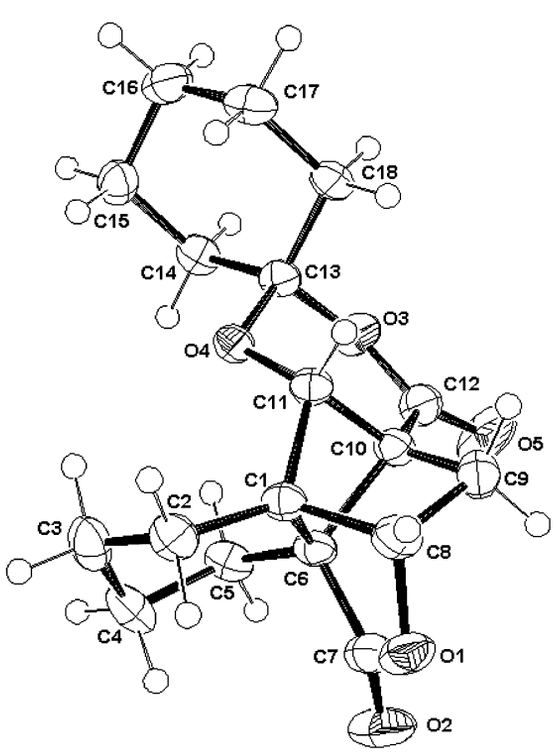
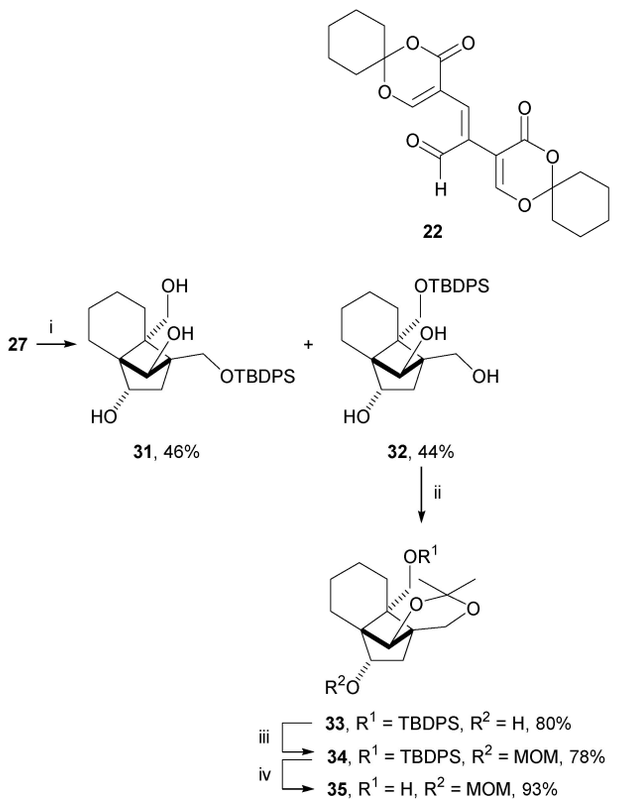


Fig. 1 ORTEP plot of the crystal structure of **25**.

products. However, TIPS protection of the primary alcohols, resulted in the preferential formation of one of both possible mono-silyl ethers. The major isomer from this reaction, silyl ether **29**, seemed a good starting point for further functionalisation. In order to minimise the amount of protection steps, it was deemed necessary to remove the remaining primary alcohol of **29** as soon as possible. Therefore, a reductive removal of the alcohol *via* the corresponding tosylate was envisaged. Unfortunately, treatment of **29** with toluene-*p*-sulfonyl chloride and pyridine resulted in the nearly quantitative formation of tetrahydrofuran **30**. A plausible explanation for the formation of **30** is the displacement of the intermediate tosylate by the proximate secondary hydroxy group. Therefore, an alternative strategy towards a suitably functionalised intermediate for our model studies had to be explored. It was found that treatment of tetraol **27** with TBDPSCl resulted in a nearly 50 : 50 distribution of mono-silyl ethers **31** and **32** (Scheme 5). Silyl ether **32** was chosen as the best candidate for further elaboration, and converted to acetonide **33** in good yield. This left only one secondary alcohol unprotected, and after treatment of **33** with MOMCl, the fully protected intermediate **34** was obtained. Deprotection with TBAF allowed the release of one primary alcohol, leading to **35**. This compound constitutes a useful intermediate in studies towards the right-hand side of solanoeclepin A.

Conclusions

In conclusion, a number of 6-unsubstituted dioxenones have been prepared and subjected to intramolecular [2+2] photocycloadditions. The conversion of iododioxenone **6** to the corresponding Grignard reagent **7** allowed facile allylation at C-5 of the dioxenone. Photochemistry with 6-unsubstituted dioxenones **12** and **17** led to novel bicyclo[2.2.0]hexanes **24**



Scheme 5 *Reagents and conditions*: i, TBDPSCl (1.5 equiv.), imidazole (5 equiv.), DMF, 0 °C ⟶ rt, 16 h; ii, 2,2-dimethoxypropane (5 equiv.), PPTS (cat.), DMF, rt, 4 h; iii, MOMCl (2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, rt, 16 h; iv, TBAF (2 equiv.), THF, 0 °C, 1 h.

and **26**. The use of the more rigid lactone precursor **14** allowed the stereoselective synthesis of the complex tricyclic core of the right-hand side of solanoeclepin A. The application of this methodology in the total synthesis of solanoeclepin A is currently under investigation and will be reported in due course.

Experimental

All reactions were carried out under an inert atmosphere of dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for transfer of air sensitive reagents and dry solvents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions, using a Bruker IFS 28 FT-spectrophotometer and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ using a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HRMS measurements were carried out using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and Acros silica gel (0.030–0.075 mm). R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F_{254}) with the aforementioned solvent (mixture) unless noted otherwise. Melting points are uncorrected. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over MS 4 Å under a dry nitrogen atmosphere. Triethylamine was dried and distilled from KOH pellets. All commercially available reagents were used as received, unless indicated otherwise. PE refers to petroleum ether fraction boiling at 60–80 °C.

3-Allyl-1,5-dioxaspiro[5.5]undec-3-en-2-one (8)

To a solution of isopropylmagnesium chloride (2 M in Et_2O, 2.8 mL, 5.6 mmol) was added *via* syringe pump at −78 °C, a solution of **6**[4,6] (1.47 g, 5 mmol) in THF (10 mL). After the addition was complete, CuCN (45 mg, 0.5 mmol) and allyl bromide (0.65 mL, 7.5 mmol) were added sequentially. After being stirred for 30 min at −78 °C the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 5) afforded **8** (833 mg, 80%) as a colorless oil. $R_f = 0.29$. ^1H NMR: 6.89 (s, 1H), 5.81 (ddt, $J = 16.8$, 10.1, 6.6 Hz, 1H), 5.12–5.04 (m, 2H), 2.91 (dd, $J = 6.6$, 1.2 Hz, 2H), 2.02–1.88 (m, 4H), 1.71–1.39 (m, 6H). ^{13}C NMR: 161.2, 153.4, 134.6, 116.8, 108.0, 107.2, 33.7, 29.8, 24.5, 22.0.

(4-Oxo-1,5-dioxaspiro[5.5]undec-2-en-3-yl)acetaldehyde (9)

To a solution of **8** (890 mg, 4.27 mmol) in THF–water (60 mL, 1 : 1 v/v) were added at 0 °C, osmium tetraoxide (0.4 mL, 1 wt.% solution in water, 0.03 mmol) and $NaIO_4$ (2.0 g, 9.4 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 7 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (50 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (25 mL), water (25 mL), 2 M $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 1) afforded **9** (673 mg, 75%) as white waxy solid. $R_f = 0.28$. ^1H NMR: 9.72 (s, 1H), 7.04 (s, 1H), 3.30 (s, 2H), 2.11–1.97 (m, 4H), 1.74–1.43 (m, 6H). ^{13}C NMR: 197.9, 161.1, 155.4, 108.2, 102.1, 40.1, 33.6, 24.5, 22.1. IR: 1725, 1644. HRMS (FAB) calculated for $C_{11}H_{15}O_4$ (MH^+) 211.0970, found 211.0987.

3-(2-Cyclohex-1-enyl-2-methoxymethoxyethyl)-1,5-dioxaspiro-[5.5]undec-3-en-2-one (12)

To a solution of aldehyde **9** (210 mg, 1 mmol) in DMF (3 mL) at 0 °C were added $CrCl_2$ (492 mg, 4 mmol), $NiCl_2$ (1 mg, 0.008 mmol) and cyclohexenyl triflate[9] (506 mg, 2.2 mmol). The mixture was allowed to warm to room temperature and stirred at room temperature for 16 h. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (2 mL) and treated with *N*,*N*-diisopropylethylamine (DIPEA) (0.5 mL, 2.9 mmol) and MOMCl (150 μL, 2 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 3) afforded **12** (118 mg, 35%) as a colorless oil. $R_f = 0.29$. ^1H NMR: 6.91 (s, 1H), 5.60 (br s, 1H), 4.55 (d, $J = 6.5$ Hz, 1H), 4.42 (d, $J = 6.5$ Hz, 1H), 4.05 (t, $J = 7.0$ Hz, 1H), 3.29 (s, 3H), 2.42 (dd, $J = 14.2$, 7.3 Hz, 1H), 2.34 (dd, $J = 14.2$, 6.9 Hz, 1H), 2.01–1.84 (m, 8H), 1.65–1.37 (m, 10H). ^{13}C NMR: 161.4, 154.2, 135.7, 127.2, 107.1, 106.4, 93.6, 79.0, 55.6, 33.9, 33.2, 30.1, 25.0, 24.6,

22.7, 22.4, 22.1. IR: 1722, 1640. HRMS (FAB) calculated for $C_{19}H_{29}O_5$ (MH^+) 337.2015, found 337.2019.

3-(3-Oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (14)

To a solution of **13**[10] (272 mg, 1.0 mmol) in THF (2 mL) was added dropwise at −78 °C, *tert*-butyllithium (1.7 M in pentane, 1.3 mL, 2.2 mmol). The resulting mixture was stirred for 15 min. Then, freshly prepared $MgBr_2$ (1 M in Et_2O–benzene 3 : 1 v/v, 1.1 mL, 1.1 mmol) was added dropwise at −78 °C and the resulting mixture was stirred for 30 min. Next, a solution of **9** (210 mg, 1.0 mmol) in THF (1 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched by addition of a mixture of AcOH–H_2O–THF (5 mL, 1 : 4 : 4 v/v), allowed to warm to room temperature and stirred for 1 h. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 3) afforded **14** (115 mg, 36%) as a colourless oil. ^{1}H NMR: 7.06 (s, 1H), 4.95 (br s, 1H), 2.77 (dd, J = 14.9, 3.1 Hz, 1H), 2.52–2.46 (m, 1H), 2.48 (dd, J = 14.9, 6.3 Hz, 1H), 2.26–1.84 (m, 7H), 1.72–1.42 (m, 10H). ^{13}C NMR: 173.2, 163.5, 161.4, 156.4, 127.7, 107.7, 102.7, 80.6, 34.3, 32.6, 28.4, 24.5, 23.2, 22.1, 21.5, 20.0. IR: 1745, 1721, 1676, 1635. HRMS (FAB) calculated for $C_{18}H_{23}O_5$ (MH^+) 319.1545, found 319.1548.

3-(3,3-Dimethyloctahydro-2,4-benzodioxepin-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (17)

To a solution of **15**[11] (80 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at −78 °C, *tert*-butyllithium (1.7 M in pentane, 0.74 mL, 1.26 mmol). The resulting mixture was stirred for 15 min. Then, a solution of **9** (88 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at −78 °C. After stirring for 1 h at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was dissolved in DMF (2 mL) and treated with 2,2-dimethoxypropane (0.25 mL, 2.0 mmol) and a catalytic amount of PPTS. The resulting mixture was stirred for 4 h and quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with water (2 mL), brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 5) afforded **17** (67 mg, 44%) as a colorless oil. R_f = 0.28. ^{1}H NMR: 7.02 (s, 1H), 4.62 (br d, J = 10.0 Hz, 1H), 4.48 (d, J = 15.7 Hz, 1H), 3.61 (d, J = 15.8 Hz, 1H), 2.85 (ddd, J = 14.4, 2.9, 1.1 Hz, 1H), 2.07 (dd, J = 14.4, 10.0 Hz, 1H), 2.04–1.85 (m, 8H), 1.80–1.42 (m, 8H), 1.37 (s, 3H), 1.33–1.27 (m, 2H), 1.30 (s, 3H).

3-[2-Hydroxy-2-(2-vinylcyclohex-1-enyl)ethyl]-1,5-dioxaspiro-[5.5]undec-3-en-2-one (19)

To a solution of **18**[12] (79 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at −78 °C, *tert*-butyllithium (1.7 M in pentane, 0.50 mL, 0.85 mmol). The resulting mixture was stirred for 15 min. Then, a solution of **9** (88 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 2) afforded **19** (63 mg, 47%) as a colorless oil. R_f = 0.27. ^{1}H NMR: 6.94 (s, 1H), 6.85 (dd, J = 17.1, 11.0 Hz, 1H), 5.16 (d, J = 17.1 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 5.01 (d, J = 11.0 Hz, 1H), 2.48 (dd, J = 14.2, 8.0 Hz, 1H), 2.36– 2.31 (m, 1H), 2.33 (dd, J = 14.2, 5.8 Hz, 1H), 2.18–2.16 (m, 2H), 2.05–1.87 (m, 6H), 1.70–1.41 (m, 10H). ^{13}C NMR: 162.2, 154.3, 137.4, 133.5, 130.7, 112.6, 107.5, 106.5, 68.5, 34.0, 33.2, 32.3, 25.3, 24.5, 23.5, 22.7, 22.2.

3-(3-Hydroxy-1,3,4,5,6,7-hexahydroisobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (20)

To a solution of **19** (40 mg, 0.13 mmol) in THF–water (2 mL, 1 : 1 v/v) were added at 0 °C, osmium tetraoxide (0.1 mL, 1 wt.% solution in water, 0.008 mmol) and $NaIO_4$ (65 mg, 0.3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 4 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (2 mL) and extracted with EtOAc (4 × 2 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 mL), water (2 mL), 2 M $NaHCO_3$ (2 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*, to afford **20** (30 mg, 72%), which was used without further purification. ^{1}H NMR: 7.10 (s, 1H), 7.05 (s, 1H), 5.77 (s, 1H), 5.71 (d, J = 2.8 Hz, 1H), 4.88 (br s, 1H), 4.63 (d, J = 3.7 Hz, 1H), 3.00–2.60 (br s, 2H), 2.59 (dd, J = 14.8, 3.1 Hz, 1H), 2.51 (dd, J = 14.8, 3.6 Hz, 1H), 2.42 (dd, J = 14.8, 5.2 Hz, 1H), 2.32 (dd, J = 14.8, 7.2 Hz, 1H), 2.11–1.90 (m, 16H), 1.68–1.41 (m, 20H). ^{13}C NMR: 162.0, 161.6, 155.6, 155.3, 138.8, 138.3, 133.8, 133.4, 107.2, 107.0, 104.9, 104.5, 103.7, 103.6, 84.6, 84.2, 34.6, 34.2, 33.0, 32.2, 30.9, 29.2, 24.6, 24.5, 22.1, 22.1, 22.1, 22.0, 21.6, 21.4, 21.1.

3-(3-Methoxy-1,3,4,5,6,7-hexahydroisobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (21)

To a solution of KHMDS (0.5 M in toluene, 0.2 mL, 0.1 mmol) was added dropwise at −78 °C, a solution of **20** (30 mg, 0.094 mmol) in THF (1 mL). The resulting mixture was stirred at −78 °C for 30 min. Then, methyl iodide (30 μL, 0.47 mmol) was added dropwise at −78 °C, and the resulting mixture was stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 4) afforded **21** (25 mg, 81%) as an inseparable 60 : 40 mixture of diastereomers as a colorless oil. R_f = 0.27. ^{1}H NMR: 7.07 (s, 1H), 7.02 (s, 1H), 5.47 (d, J = 2.3 Hz, 1H), 5.39 (s, 1H), 4.86 (br s, 1H), 4.68 (s, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 2.62–2.44 (m, 3H), 2.33–2.28 (m, 1H), 2.11–1.82 (m, 16H), 1.76–1.39 (m, 20H). ^{13}C NMR: 162.3, 162.1, 155.8, 155.6, 139.7, 138.7, 131.9, 131.8, 110.2, 109.6, 107.2, 107.0, 105.0, 104.7, 84.9, 84.6, 54.9, 52.9, 34.6, 34.3, 34.2, 33.8, 33.0, 32.2, 30.6, 29.2, 26.2, 24.6, 22.5, 22.1, 21.7, 21.3, 20.9. IR: 1721, 1644. HRMS (FAB) calculated for $C_{19}H_{27}O_5$ (MH^+) 335.1858, found 355.1861.

General procedure A for the intramolecular [2+2] cycloadditions

The photoreaction was carried out in a pyrex glass vessel with a Rayonet RPR 3000 Å at room temperature. A solution of precursor in acetonitrile–acetone (25 mM, 9 : 1 v/v) was degassed by bubbling argon through for 30 min. The solution was kept under argon and irradiated for the time indicated. The reaction was followed by monitoring the UV absorption of the starting material on TLC. When complete conversion was observed, the solvent was removed *in vacuo*.

Cycloadduct 24. According to general procedure **A**, irradiation of **12** (50 mg, 0.15 mmol) for 30 min afforded **24** (43 mg, 86%) as an inseparable 56 : 44 mixture of diastereomers as

colorless oil after purification (EtOAc–PE = 1 : 2). R_f = 0.26. ^{1}H NMR: 4.59–4.51 (m, 5H), 4.33 (d, J = 5.6 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 4.01 (dd, J = 9.6, 6.9 Hz, 1H), 3.30 (s, 6H), 3.14–3.09 (m, 1H), 2.86 (dd, J = 13.0, 9.6 Hz, 1H), 2.59 (dd, J = 12.2, 6.6 Hz, 1H), 2.42–2.38 (m, 2H), 2.04–1.87 (m, 3H), 1.98 (dd, J = 13.0, 6.9 Hz, 1H), 1.81–0.99 (m). IR: 1717. HRMS (FAB) calculated for $C_{19}H_{29}O_5$ (MH^+) 337.2015, found 337.2021.

Cycloadduct 25. According to general procedure **A**, irradiation of alkene **14** (120 mg, 0.38 mmol) for 1 h afforded **25** (114 mg, 95%), as a crystalline solid after purification by recrystallisation from acetone–*n*-hexane. Colourless crystals, mp 186–187 °C. ^{1}H NMR: 4.67 (d, J = 3.9 Hz, 1H), 4.02 (s, 1H), 2.34 (dt, J = 13.3, 4.5 Hz, 1H), 2.23 (br d, J = 13.0 Hz, 1H), 2.17–2.07 (m, 2H), 1.97–1.90 (m, 3H), 1.81–1.42 (m, 12H), 1.07–0.95 (m, 1H). ^{13}C NMR: 174.5, 165.2, 110.5, 78.4, 78.0, 60.5, 57.8, 46.8, 36.9, 34.8, 34.6, 24.5, 22.2, 22.1, 21.7, 21.6, 21.3, 20.6. IR: 1783, 1740. HRMS (FAB) calculated for $C_{18}H_{23}O_5$ (MH^+) 319.1545, found 319.1553.

Crystal data ***25***.‡ $C_{18}H_{22}O_5$, M_r = 318.36, monoclinic, $P2_1/c$, a = 6.6011(5), b = 16.1185(1), c = 14.513(1) Å, β = 91.431(7)°, V = 1543.7(2) Å^3, Z = 4, D_x = 1.37 g cm^{-3}, λ(Cu-Kα) = 1.5418 Å, μ(Cu-Kα) = 8.2 cm^{-1}, F(000) = 680, 243 K, crystal size 0.25 × 0.30 × 0.35 mm^3. 3172 reflections measured, 2586 unique (R_{int} = 0.050) which were used in all calculations. The final $wR(F^2)$ was 0.053 (all data).

Cycloadduct 26. According to general procedure **A**, irradiation of alkene **17** (32 mg, 0.088 mmol) for 30 min afforded **26** (28 mg, 88%), as a colorless oil after purification by chromatography (EtOAc–PE = 1 : 5). R_f = 0.24. ^{1}H NMR: 4.86 (s, 1H), 4.19 (d, J = 13.0 Hz, 1H), 4.10 (dd, J = 8.7, 1.6 Hz, 1H), 3.44 (d, J = 13.0 Hz, 1H), 2.91 (dd, J = 12.7, 8.7 Hz, 1H), 2.20–2.16 (m, 1H), 1.98 (dd, J = 12.7, 1.6 Hz, 1H), 1.80–1.35 (m, 16H), 1.39 (s, 3H), 1.37 (s, 3H), 1.21–1.15 (m, 1H). ^{13}C NMR: 171.1, 106.0, 102.3, 78.5, 73.1, 69.9, 54.0, 47.4, 39.6, 36.4, 35.7, 33.4, 30.4, 27.3, 24.8, 24.7, 23.8, 22.8, 22.6, 22.1, 19.5. IR: 1721. HRMS (FAB) calculated for $C_{21}H_{31}O_5$ (MH^+) 363.2171, found 363.2176.

1,7a-Bis(hydroxymethyl)octahydro-1,3a-methanoindene-3,8-diol (27)

To a solution of $LiAlH_4$ (1 M in THF, 2.0 mL, 2.0 mmol) was added in small portions, cycloadduct **25** (120 mg, 0.38 mmol). The reaction mixture was stirred for 5 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc : acetone = 1 : 1) afforded **27** (52 mg, 60%) as a white powder. Mp 173 °C. ^{1}H NMR (CD_3OD): 4.21 (dd, J = 11.4, 2.2 Hz, 1H), 3.83 (dd, J = 7.9, 2.9 Hz, 1H), 3.76 (d, J = 11.2 Hz, 1H), 3.47 (s, 1H), 3.41 (d, J = 11.2 Hz, 1H), 3.32 (d, J = 11.4 Hz, 1H), 2.77–2.70 (m, 1H), 1.98–1.88 (m, 3H), 1.78 (dd, J = 12.1, 8.0 Hz, 1H), 1.65–1.51 (m, 4H), 1.41–1.34 (m, 1H). ^{13}C NMR (CD_3OD): 83.6, 72.8, 61.5, 58.9, 57.5, 57.2, 50.2, 38.0, 25.1, 23.8, 22.7. HRMS (FAB) calculated for $C_{12}H_{21}O_4$ (MH^+) 229.1440, found 229.1437.

7a-Hydroxymethyl-1-triisopropylsilyloxymethyloctahydro-1,3a-methanoindene-3,8-diol (29)

To a solution of **27** (20 mg, 0.088 mmol) in DMF (1 mL) were added at 0 °C, imidazole (30 mg, 0.44 mmol) and TIPSCl (28 μL, 0.13 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 1) afforded **29** (24 mg, 72%) as a colorless oil. R_f = 0.28. ^{1}H NMR (CD_3OD): 4.22 (dd, J = 11.8, 2.2 Hz, 1H), 3.96 (d, J = 10.4 Hz, 1H), 3.83 (dd, J = 8.0, 2.9 Hz, 1H), 3.65 (d, J = 10.4 Hz, 1H), 3.48 (s, 1H), 3.28 (d, J = 11.8 Hz, 1H), 2.77–2.70 (m, 1H), 2.01–1.90 (m, 2H), 1.94 (dd, J = 12.1, 2.8 Hz, 1H), 1.79 (dd, J = 12.1, 8.0 Hz, 1H), 1.66–1.51 (m, 4H), 1.45–1.34 (m, 1H), 1.19–1.01 (m, 21H).

Tetrahydrofuran 30

To a solution of **29** (24 mg, 0.062 mmol) in pyridine (1 mL) was added, tosyl chloride (24 mg, 0.12 mmol). The resulting mixture was stirred for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 3) afforded **30** (23 mg, 97%) as a colorless oil. R_f = 0.26. ^{1}H NMR: 3.99 (d, J = 4.5 Hz, 1H), 3.95 (d, J = 2.2 Hz, 2H), 3.69 (d, J = 8.9 Hz, 1H), 3.55 (d, J = 8.9 Hz, 1H), 2.85 (d, J = 2.3 Hz, 1H), 2.55 (dt, J = 14.1, 4.7 Hz, 1H), 1.92–1.81 (m, 2H), 1.67–1.42 (m, 6H), 1.33–1.19 (m, 1H), 1.17–0.98 (m, 21H). ^{13}C NMR: 82.9, 80.9, 69.0, 61.7, 54.7, 53.1, 52.8, 33.9, 23.6, 22.1, 21.6, 20.7, 18.0, 11.9. HRMS (FAB) calculated for $C_{21}H_{39}O_3Si$ (MH^+) 367.2668, found 367.2672.

7a-(*tert*-Butyldiphenylsilyloxymethyl)-1-hydroxymethyl-octahydro-1,3a-methanoindene-3,8-diol (32)

To a solution of **27** (20 mg, 0.088 mmol) in DMF (1 mL) were added at 0 °C, imidazole (30 mg, 0.44 mmol) and TBDPSCl (34 μL, 0.13 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 5 : 1) afforded **32** (18 mg, 44%) as a white solid. R_f = 0.25. ^{1}H NMR (CD_3OD): 7.68–7.65 (m, 4H), 7.47–7.37 (m, 6H), 4.42 (dd, J = 11.0, 1.8 Hz, 1H), 3.93 (d, J = 11.5 Hz, 1H), 3.76 (dd, J = 7.8, 2.8 Hz, 1H), 3.61 (d, J = 11.5 Hz, 1H), 3.48 (s, 1H), 3.38 (d, J = 11.0 Hz, 1H), 2.80–2.74 (m, 1H), 2.09–2.05 (m, 1H), 1.97–1.38 (m, 3H), 1.50–1.30 (m, 4H), 1.06 (s, 9H), 0.96–0.90 (m, 1H). ^{13}C NMR (CD_3OD): 137.2, 136.9, 134.7, 134.4, 131.1, 131.0, 129.0, 83.5, 72.8, 63.8, 59.9, 57.6, 50.6, 37.9, 27.7, 24.7, 23.7, 22.8, 22.5, 20.3.

TBDPS acetonide (33)

To a solution of **32** (18 mg, 0.039 mmol) in DMF (1 mL) were added, 2,2-dimethoxypropane (24 μL, 0.20 mmol) and a catalytic amount of PPTS. The resulting mixture was stirred for 4 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 3) afforded **33** (16 mg, 80%) as a colorless oil. R_f = 0.33. ^{1}H NMR: 7.68–7.64 (m, 4H), 7.44–7.35 (m, 6H), 4.24 (dd, J = 10.8, 1.7 Hz, 1H), 4.22 (d, J = 11.9 Hz, 1H), 3.96 (d, J = 11.9 Hz, 1H), 3.95–3.90 (m, 1H), 3.53 (d, J = 10.8 Hz, 1H), 3.43 (s, 1H), 3.25–3.18 (m, 1H), 2.17 (br d, J = 13.9 Hz, 1H), 1.90 (d, J = 4.4 Hz, 1H), 1.75–1.50 (m, 5H), 1.44 (s, 3H), 1.43–1.36 (m, 1H), 1.36 (s, 3H), 1.25–1.07 (m, 1H), 1.07 (s, 9H). ^{13}C NMR: 135.9, 135.8,

‡ CCDC reference number 163621. See http://www.rsc.org/suppdata/p1/b1/b104165g/ for crystallographic files in .cif or other electronic format.

133.9, 133.6, 129.5, 129.5, 127.6, 97.3, 78.9, 73.3, 64.9, 62.5, 56.9, 48.4, 45.1, 36.7, 29.2, 27.1, 26.4, 23.0, 22.3, 22.2, 19.3, 19.0.

MOM TBDPS acetonide (34)

To a solution of **33** (16 mg, 0.032 mmol) in CH_2Cl_2 (1 mL) were added at 0 °C, triethylamine (22 μL, 0.16 mmol) and MOMCl (5 μL, 0.064 mmol). The resulting mixture was stirred for 16 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 3) afforded **34** (14 mg, 78%) as a colorless oil. $R_f = 0.40$. ^{1}H NMR: 7.68–7.63 (m, 4H), 7.43–7.32 (m, 6H), 4.35 (d, $J = 6.7$ Hz, 1H), 4.32 (d, $J = 11.9$ Hz, 1H), 4.31 (d, $J = 6.7$ Hz, 1H), 4.14 (dd, $J = 10.8$, 2.1 Hz, 1H), 3.98 (d, $J = 11.9$ Hz, 1H), 3.70 (dd, $J = 7.5$, 3.0 Hz, 1H), 3.49 (d, $J = 10.8$ Hz, 1H), 3.44 (s, 1H), 3.24–3.17 (m, 1H), 3.10 (s, 3H), 2.33 (br d, $J = 14.0$ Hz, 1H), 1.74–1.46 (m, 6H), 1.46 (s, 3H), 1.41–1.33 (m, 1H), 1.36 (s, 3H), 1.13–1.06 (m, 1H), 1.06 (s, 9H). ^{13}C NMR: 135.9, 135.8, 134.2, 133.8, 129.4, 127.5, 97.3, 95.5, 78.7, 78.0, 64.0, 62.7, 56.1, 55.1, 48.7, 44.9, 34.9, 29.2, 27.1, 25.7, 23.1, 22.4, 22.0, 19.2, 18.9.

MOM acetonide (35)

To a solution of **34** (14 mg, 0.025 mmol) in THF (1 mL) was added at 0 °C, a solution of TBAF (1 M in THF, 50 μL, 0.05 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 1) afforded **35** (8 mg, 93%) as a colorless oil. $R_f = 0.28$. ^{1}H NMR: 4.67 (d, $J = 6.7$ Hz, 1H), 4.60 (d, $J = 6.7$ Hz, 1H), 4.12 (br d, $J = 10.5$ Hz, 1H), 4.08 (d, $J = 12.3$ Hz, 1H), 3.96 (d, $J = 12.3$ Hz, 1H), 3.87 (dd, $J = 7.7$, 2.8 Hz, 1H), 3.62 (d, $J = 11.6$ Hz, 1H), 3.48 (s, 1H), 3.36 (s, 3H), 3.36–3.28 (m, 1H), 1.97–1.88 (m, 2H), 1.81–1.36 (m, 7H), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C NMR: 97.5, 96.1, 78.5, 78.2, 65.8, 62.5, 56.6, 55.5, 48.3, 45.0, 35.3, 29.1, 27.6, 23.5, 22.4, 22.1, 18.9. HRMS (FAB) calculated for $C_{17}H_{29}O_5$ (MH^+) 313.2015, found 313.2021.

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