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

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Received (in Cambridge, UK) 7th May 2001, Accepted 24th July 2001 First published as an Advance Article on the web 29th August 2001 PERKIN

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.<sup>1</sup> 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.<sup>2</sup> 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 6unsubstituted 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.<sup>3</sup> On the other hand, intramolecular examples are scarce.<sup>4,5</sup> 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,<sup>6</sup> 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.<sup>7</sup> These polyfunctional organomagnesium compounds



Scheme 1

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DOI: 10.1039/b104165g

 Table 1
 Results of the photocycloaddition reactions





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<sub>4</sub> (0.5 mol%), NaIO<sub>4</sub> (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<sub>4</sub>–NaIO<sub>4</sub> 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.<sup>2c</sup> Cr(II)–Ni(II) mediated coupling<sup>8</sup> of cyclohexenyl triflate<sup>9</sup>† (**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<sup>10</sup> 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,<sup>11</sup> followed by acetalization of diol 16. Finally, addition of lithiated 18<sup>12</sup> 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 silvlation, 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).<sup>2c</sup> 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.<sup>2c</sup> Unfortunately, all attempts to directly differentiate the hydroxy functions of **27** by acetalization resulted in complex mixtures of

<sup>†</sup> 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<sub>2</sub>,  $CH_2Cl_2$ , rt, 16 h; iii, 13, *t*-BuLi (2.1 equiv.), THF–pentane, -78 °C, 15 min then MgBr<sub>2</sub>·OEt<sub>2</sub> (1.1 equiv.), Et<sub>2</sub>O, -78 °C, 30 min then 9, -78 °C, 30 min then AcOH–water (1 : 1 v/v), -78 °C  $\rightarrow$  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; vii, 18, *t*-BuLi (2.1 equiv.), THF–pentane, -78 °C, 15 min then 9, -78 °C, 30 min; vii, OsO<sub>4</sub> (0.5 mol%), NaIO<sub>4</sub> (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,  $0 \degree C \rightarrow rt$ , 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

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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  $\rightarrow$  rt, 16 h; ii, 2,2-dimethoxypropane (5 equiv.), PPTS (cat.), DMF, rt, 4 h; iii, MOMCl (2 equiv.), Et<sub>3</sub>N (5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>3</sub> solutions, using a Bruker IFS 28 FT-spectrophotometer and wavelengths (v) are reported in cm<sup>-1</sup>. <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) spectra were determined in CDCl<sub>3</sub> using a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Chemical shifts ( $\delta$ ) 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).  $R_{\rm f}$  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 Et2O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH<sub>2</sub>Cl<sub>2</sub> and MeCN were distilled from CaH<sub>2</sub> 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<sub>2</sub>O, 2.8 mL, 5.6 mmol) was added *via* syringe pump at -78 °C, a



solution of **6**<sup>4,6</sup> (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<sub>4</sub>Cl (10 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 5) afforded **8** (833 mg, 80%) as a colorless oil.  $R_f = 0.29$ . <sup>1</sup>H 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). <sup>13</sup>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<sub>4</sub> (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 ( $4 \times 25$  mL). The combined organic layers were washed with 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL), water (25 mL), 2 M NaHCO<sub>3</sub> (25 mL) and brine (25 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 1:1) afforded 9 (673 mg, 75%) as white waxy solid.  $R_f = 0.28$ . <sup>1</sup>H 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). <sup>13</sup>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<sub>11</sub>H<sub>15</sub>O<sub>4</sub> (MH<sup>+</sup>) 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<sub>2</sub> (492 mg, 4 mmol), NiCl<sub>2</sub> (1 mg, 0.008 mmol) and cyclohexenyl triflate<sup>9</sup> (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<sub>4</sub>Cl (2 mL) was added and the aqueous phase was extracted with EtOAc  $(3 \times 5 \text{ mL})$ . The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO4 and concentrated in vacuo. The crude mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (2 mL) was added and the aqueous phase was extracted with EtOAc (3  $\times$ 2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO4 and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 1 : 3) afforded 12 (118 mg, 35%) as a colorless oil.  $R_f = 0.29$ . <sup>1</sup>H 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). <sup>13</sup>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<sup>+</sup>) 337.2015, found 337.2019.

#### 3-(3-Oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-ylmethyl)-1,5dioxaspiro[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<sub>2</sub> (1 M in Et<sub>2</sub>O-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-H2O-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 ( $3 \times 5$  mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (5 mL), water (5 mL) and brine (5 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 2:3) afforded 14 (115 mg, 36%) as a colourless oil. <sup>1</sup>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). <sup>13</sup>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<sup>+</sup>) 319.1545, found 319.1548.

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

To a solution of 15<sup>11</sup> (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<sub>4</sub>Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc  $(3 \times 2 \text{ mL})$ . The combined organic layers were washed with brine (2 mL), dried over MgSO4 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<sub>3</sub> (2 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O  $(3 \times 2 \text{ mL})$ . The combined organic layers were washed with water (2 mL), brine (2 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 1 : 5) afforded 17 (67 mg, 44%) as a colorless oil.  $R_f = 0.28$ . <sup>1</sup>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<sub>4</sub>Cl (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<sub>4</sub> and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 2) afforded **19** (63 mg, 47%) as a colorless oil.  $R_{\rm f}$  = 0.27. <sup>1</sup>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). <sup>13</sup>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<sub>4</sub> (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 ( $4 \times 2$  mL). The combined organic layers were washed with 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 mL), water (2 mL), 2 M NaHCO<sub>3</sub> (2 mL) and brine (2 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo, to afford 20 (30 mg, 72%), which was used without further purification. <sup>1</sup>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). <sup>13</sup>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<sub>4</sub>Cl (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc  $(3 \times 2 \text{ mL})$ . The combined organic layers were washed with brine (2 mL), dried over MgSO4 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.  $R_f = 0.27$ . <sup>1</sup>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). <sup>13</sup>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<sub>19</sub>H<sub>27</sub>O<sub>5</sub> (MH<sup>+</sup>) 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).  $R_f = 0.26$ . <sup>1</sup>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<sub>19</sub>H<sub>29</sub>O<sub>5</sub> (MH<sup>+</sup>) 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. <sup>1</sup>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). <sup>13</sup>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<sub>18</sub>H<sub>23</sub>O<sub>5</sub> (MH<sup>+</sup>) 319.1545, found 319.1553.

Crystal data **25**.‡ C<sub>18</sub>H<sub>22</sub>O<sub>5</sub>,  $M_r = 318.36$ , monoclinic,  $P2_1/c$ , a = 6.6011(5), b = 16.1185(1), c = 14.513(1) Å,  $\beta = 91.431(7)^\circ$ , V = 1543.7(2) Å<sup>3</sup>, Z = 4,  $D_x = 1.37$  g cm<sup>-3</sup>,  $\lambda$ (Cu-K $\alpha$ ) = 1.5418 Å,  $\mu$ (Cu-K $\alpha$ ) = 8.2 cm<sup>-1</sup>, F(000) = 680, 243 K, crystal size  $0.25 \times 0.30 \times 0.35$  mm<sup>3</sup>. 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).  $R_f = 0.24$ . <sup>1</sup>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). <sup>13</sup>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<sub>21</sub>H<sub>31</sub>O<sub>5</sub> (MH<sup>+</sup>) 363.2171, found 363.2176.

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

To a solution of LiAlH<sub>4</sub> (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<sub>2</sub>SO<sub>4</sub> (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na<sub>2</sub>SO<sub>4</sub> 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. <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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). <sup>13</sup>C NMR (CD<sub>3</sub>OD): 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<sub>12</sub>H<sub>21</sub>O<sub>4</sub> (MH<sup>+</sup>) 229.1440, found 229.1437.

#### 7a-Hydroxymethyl-1-triisopropylsilyloxymethyloctahydro-1,3amethanoindene-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 TIPSCI ( $28 \mu$ L, 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<sub>3</sub> (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<sub>4</sub> and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 1) afforded **29** (24 mg, 72%) as a colorless oil.  $R_f = 0.28$ . <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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<sub>3</sub> (1 mL). The aqueous phase was extracted with EtOAc ( $3 \times 2$  mL). The combined organic layers were washed with brine (2 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 1 : 3) afforded **30** (23 mg, 97%) as a colorless oil.  $R_f$  = 0.26. <sup>1</sup>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). <sup>13</sup>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<sub>21</sub>H<sub>39</sub>O<sub>3</sub>Si (MH<sup>+</sup>) 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<sub>3</sub> (1 mL). The aqueous phase was extracted with EtOAc ( $3 \times$ 2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO4 and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 5:1) afforded 32 (18) mg, 44%) as a white solid.  $R_{\rm f} = 0.25$ . <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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). <sup>13</sup>C NMR (CD<sub>3</sub>OD): 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  $\mu$ L, 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<sub>3</sub> (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<sub>4</sub> and concentrated *in vacuo*. Purification by chromatography (EtOAc–PE = 2 : 3) afforded **33** (16 mg, 80%) as a colorless oil.  $R_f$  = 0.33. <sup>1</sup>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), 1.43 (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). <sup>13</sup>C NMR: 135.9, 135.8,

<sup>‡</sup> 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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc  $(3 \times 2 \text{ mL})$ . The combined organic layers were washed with brine (2 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 1:3) afforded 34 (14 mg, 78%) as a colorless oil.  $R_f = 0.40$ . <sup>1</sup>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).  $^{13}\mathrm{C}$ 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<sub>3</sub> (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc  $(3 \times 2 \text{ mL})$ . The combined organic layers were washed with brine (2 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by chromatography (EtOAc-PE = 2:1) afforded 35 (8 mg, 93%) as a colorless oil.  $R_f = 0.28$ . <sup>1</sup>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). <sup>13</sup>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<sup>+</sup>) 313.2015, found 313.2021.

# Acknowledgements

Jan Fraanje and Kees Goubitz (Laboratory of Crystallography, University of Amsterdam) are kindly acknowledged for the crystal structure determination of cycloadduct **25**. These investigations are supported (in part) by The Netherlands Research Council for Chemical Sciences (CW) with financial aid from The Netherlands Technology Foundation (STW).

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