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Palladium-mediated fragmentation reactions of *meta* photocycloadducts to afford arylated or oxidatively cyclised products

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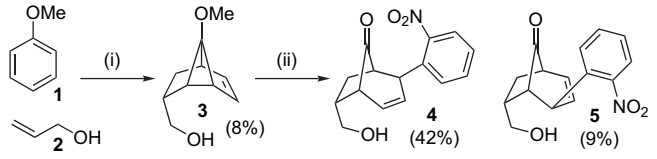
Abstract—Whilst seeking to improve the yield of a Heck-style arylation/fragmentation reaction using a silyloxy substituted *meta* photocycloadduct, an alternative reaction pathway was discovered that led to the formation of the unique oxidatively cyclised compound **8**. This tricyclic ether is believed to form as the result of the *meta* photocycloadduct structure fragmenting to give a π-allyl palladium species and then subsequently being displaced by a neighbouring hydroxyl group. An attempt to develop an enantioselective version of this reaction via the desymmetrisation of a *meso* π-allyl palladium intermediate was made using the *meta* photocycloadduct derived from anisole and *Z*-but-2-ene-1,4-diol, however no enantioenrichment of the products could be detected.

1. Introduction

The diverse reactivity of palladium and its associated compounds has led to the development of many remarkable chemical transformations.[1] We have recently shown[2] how palladium catalysis can be used to promote a fragmentation/arylation process involving a *meta* photocycloadduct and an aryl halide. Hence, when the anisole derived *meta* photocycloadduct **3** was subjected to Heck reaction[3] conditions in the presence of 1-iodo-2-nitrobenzene, compounds **4** and **5** were isolated (Scheme 1).



Scheme 1. Reagents and conditions: (i) hν, cyclohexane; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), NEt_3, DMF, 120 °C, 12 h.

The methoxy-substituted cyclopropylalkene moiety of the photoadduct underwent fragmentation to afford an arylated [3.2.1] bicyclic ketone structure, with the major isomer **4** being isolated in 42% yield. As it was our intention to use compound **4** in a potential synthesis of the alkaloid gelsemine,[4] we investigated the use of alternative substrates to improve the efficiency of its formation. When a similar arylation reaction was performed on the trimethylsilyloxy variant of **3**, an alternative reaction pathway was observed that involved an oxidation process. This publication reports this new mode of reactivity and its further exploitation.

2. Results and discussion

2.1. Arylation and oxidation studies of silyloxy substituted *meta* photoadducts

We wondered if, by replacing the methoxy group of compound **3** with a silyloxy group, the fragmentation and subsequent arylation of the *meta* photoadduct structure would be enhanced by the greater electron releasing power of the silicon group. To investigate this hypothesis the 7-*endo meta* photoadduct isomer **7** was prepared by irradiating a solution of trimethylphenoxysilane and allyl alcohol in cyclohexane with 254 nm UV light. The only photoadduct isomer that could be isolated as a single compound was fortuitously the desired compound **7**. This photoadduct was subjected to the same Heck-style arylation conditions as used on compound **3** in Scheme 1[2] and resulted in the formation of the three major products shown in Scheme 2.

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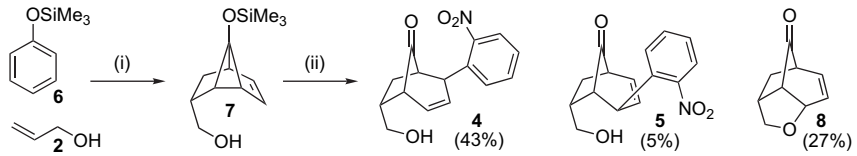


Scheme 2. Reagents and conditions: (i) hν, cyclohexane, 4.3%; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol %), $P(o\text{-Tol})_3$ (10 mol %), NEt_3, DMF, 120 °C, 12 h.

In addition to compounds **4** and **5**, the unique tricyclic ether **8** was obtained, whose structure was confirmed by single crystal X-ray crystallography (Fig. 1).[5]

Compound **8** must have formed as a result of a formal oxidation process via an internal displacement reaction,[6] however as there was only 5 mol % of palladium diacetate present in the mixture and the reaction was performed in a sealed reaction vessel under an atmosphere of nitrogen, we concluded that the 1-iodo-2-nitrobenzene was acting as the reoxidation source for the palladium. If the reaction was repeated in the absence of any 1-iodo-2-nitrobenzene, none of the oxidised compound **8** was detected. We found that upon changing the palladium source from the diacetate to the dichloride, 91% of the compound **7** was converted to products and a highly creditable 63% yield of compound **4** was obtained. The yield of oxidation product **8** could be dramatically improved if copper(II) chloride (200 mol %) was used as the reoxidant[7] such that it was obtained in 69% yield from the silyloxy compound **7** and in 62% yield from the methoxy variant **3**. These results are summarised in Table 1.

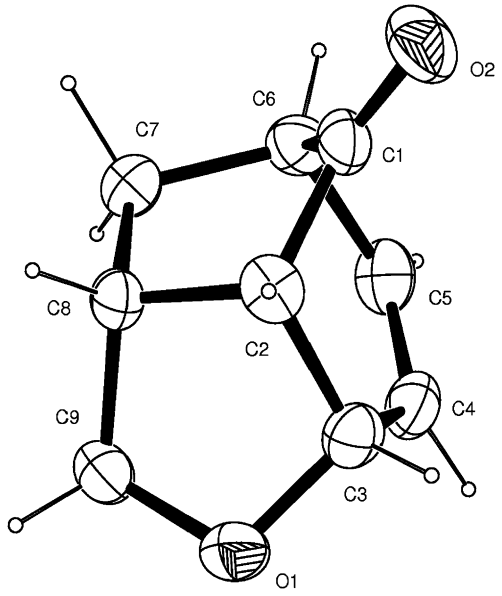


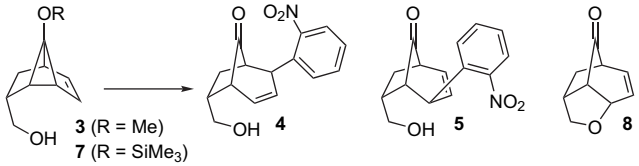
Figure 1. ORTEP drawing of compound **8**.

This unique transformation involving the formation of compound **8** led us to speculate on the nature of the reaction mechanism. Previous results[2] had hinted at the formation of a π-allyl palladium species following initial fragmentation of the *meta* photocycloadduct vinyl-cyclopropane moiety in the presence of a palladium(II) source. In this instance such an intermediate **9** would undergo an internal nucleophilic displacement by the hydroxyl group[6] and subsequently give rise to the heterocycle **8**. In order to maintain the catalytic cycle the reduced palladium[0] species would then need to be reoxidised (Scheme 3).

2.2. Oxidation of diol derived *meta* photoadducts and its implication for asymmetric synthesis

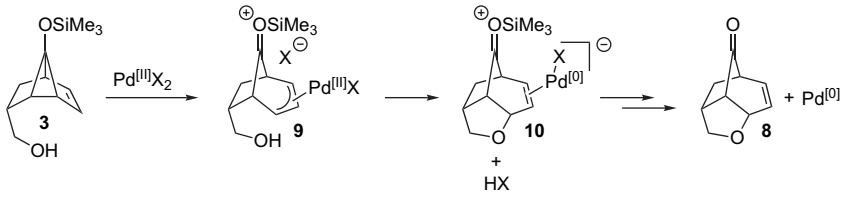
To further extend the application of this reaction, we wondered if an analogue of intermediate **9** that displayed *meso* symmetry could be generated. The attachment of a homochiral ligand to the palladium centre would cause the desymmetrisation of such an intermediate (**14** or **15**), which in turn would kinetically favour a stereoselective displacement process and result in the formation of an enantioenriched product **16**. We reasoned that such a transformation could be achieved starting from the *meta* photocycloadduct derived from *Z*-but-2-ene-1,4-diol **11** and either **1** or **6** (Scheme 4).

Table 1. Arylation and oxidation studies carried out on compounds **3** and **7**

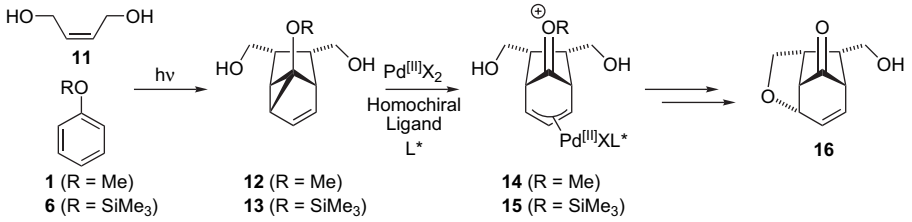


Entry	Starting substrate	Pd source	Aryl halide/oxidising agent	Base (equiv)	Time (h)	Temp (°C)	Yield of **4** (%)	Yield of **5** (%)	Yield of **8** (%)
1	**3**	$Pd(OAc)_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	12	120	42	9	—
2	**7**	$Pd(OAc)_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	4	120	43	5	27
3	**7**	$Pd(OAc)_2$	—	NEt_3 (1)	12	120	—	—	—
4	**7**	$PdCl_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	4	120	63	4	24
5	**7**	$PdCl_2$	$CuCl_2$	NEt_3 (2)	48	20	—	—	69
6	**3**	$PdCl_2$	$CuCl_2$	NEt_3 (2)	48	20	—	—	62

Reagents and conditions: Pd source (5 mol %), $P(o\text{-Tol})_3$ (10 mol %), NEt_3, aryl halide (100 mol %) or $CuCl_2$ (200 mol %), DMF.

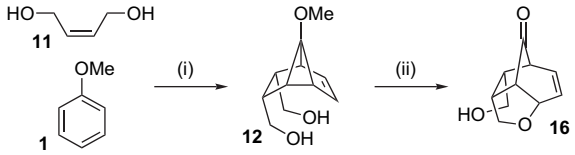


Scheme 3. Proposed reaction mechanism of oxidative cyclisation.



Scheme 4. Proposed reaction scheme for the palladium catalysed oxidative desymmetrisation of a diol photoadduct using a homochiral ligand.

Our initial investigations centred on the preparation of the silyloxy *meta* photocycloadduct **13** derived from **11** and trimethylphenoxysilane **6**, however this proved to be very unstable and rapidly degraded in the presence of silica gel. To get around this problem we reverted to using anisole **1** as the aromatic partner in the photoreaction, as **3** was known to undergo successful conversion to **8** (see Table 1, entry 6). A solution of anisole and *Z*-but-2-ene-1,4-diol in methanol was irradiated with UV light using a quartz immersion-well photoreactor to afford a 14% yield of the desired *endo* photoadduct **12**. When the previously effective conditions for converting **3** to **8** were used to oxidise **12**, only a disappointing 11% yield of **16** was obtained (Scheme 5).

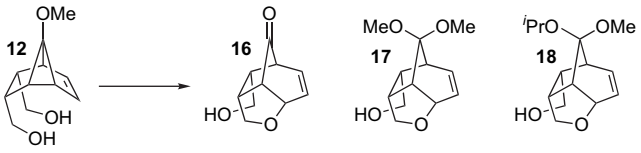


Scheme 5. Reagents and conditions: (i) hν, MeOH, 14%; (ii) $PdCl_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), $CuCl_2$, NEt_3, DMF, 20 °C, 48 h, 11%.

A number of other commonly used solvents were screened to improve the oxidation of **12**, however in each case the diol photoadduct was much less efficiently oxidised than either compounds **3** or **7** (Table 2). Acetonitrile gave a slight improvement in yield, but toluene afforded little and DMSO gave none of the desired ketone **16**. Methanol led to the formation of the oxidised product as its dimethyl acetal **17**[8] in an improved 36% yield, whilst isopropanol gave rise to the mixed acetal **18** in 19% yield. This final transformation for the formation of the mixed acetal **18** was very interesting as it was achieved in a highly stereoselective manner with only a single diastereoisomer being formed.[9]

For our preliminary studies into the formation of enantio-enriched oxidation products, we elected to use methanol as it was the most efficient solvent for oxidising **12** and carried out a series of experiments using the four ligands shown in Figure 2. The BINAP and Trost ligands were chosen as they

Table 2. Solvent optimisation studies for the oxidation of compound **12**



Entry	Solvent	Yield of **16** (%)	Yield of **17** (%)	Yield of **18** (%)
1	DMF	11	—	—
2	MeCN	15	—	—
3	Toluene	5	—	—
4	DMSO	—	—	—
5	MeOH	—	36	—
6	*i*-PrOH	—	—	19

Reagents and conditions: $PdCl_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), $CuCl_2$, NEt_3, solvent, 20 °C, 48 h.

both were good, standard, commercially available ligands for use in allylic alkylation reactions[10] to which this transformation has some similarity. The QUINAP ligand was chosen as it had two different ligating atoms (N and P),[11] whilst sparteine[12] was chosen as it was less prone to oxidation than the phosphine derived ligands.[13]

The palladium complexes were preformed prior to reaction with the photoadduct by stirring the red palladium chloride together with the ligand in methanol overnight under an atmosphere of nitrogen. The methanol was removed in vacuo to leave the various palladium complexes as yellow powders ready for reaction with **12**. In the first series of experiments

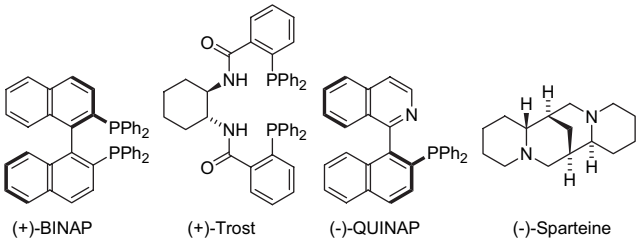
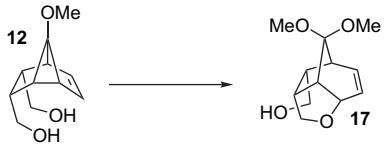


Figure 2. The four homochiral ligands used during the desymmetrisation studies.

Table 3. Oxidation studies involving the diol photoadduct **12** using various ligands and either copper(II) chloride or oxygen as the stoichiometric reoxidant



Entry	Ligand	Stoichiometric reoxidant	Base (mol %)	Time (h)	Yield of **17** (%)
1	(+)-BINAP	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	35
2	(+)-Trost	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	26
3	(−)-QUINAP	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	32
4	(−)-Sparteine	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	25
5	(+)-BINAP	O_2 (1 atm)	—	72	16
6	(+)-Trost	O_2 (1 atm)	—	72	16
7	(−)-QUINAP	O_2 (1 atm)	—	72	10
8	(−)-Sparteine	O_2 (1 atm)	—	48	35

Reagents and conditions: $PdCl_2$ (5 mol %), $CuCl_2$ (5 mol %), stoichiometric reoxidant, ligand, MeOH, 20 °C. Chiral HPLC analysis was carried out on the benzoate ester derivatives of each of the oxidised products and revealed no significant enantiomeric enrichment for any of the products.

(Table 3, entries 1–4) 2 equiv of copper(II) chloride were used as the reoxidant along with 2 equiv of triethylamine to neutralise the hydrogen chloride that was formed during the course of the reaction. Each reaction was carried out in a sealed reaction vessel under an atmosphere of nitrogen and left to stir for two days to allow complete consumption of starting material. In a second series of experiments (Table 3, entries 5–8) Wacker conditions were employed to achieve the desired oxidation reaction.[14] In these circumstances a catalytic quantity of copper(II) chloride was used to aid reoxidation of the palladium complex, but the stoichiometric oxidant was a balloon of oxygen gas. To establish if enantioselectivity had been achieved, the free hydroxyl group on each of the products was converted to a benzoate ester and each of these was submitted for chiral HPLC analysis.

Disappointingly no evidence of any enantioenrichment of the oxidised products could be detected for any of the entries in Table 3. In the best cases (entries 1 and 8) the oxidised product **17** was obtained in a similar yield to that observed when the tri-*ortho*-tolylphosphine ligand was used. On the whole the anaerobic conditions afforded a greater yield of **17**, whilst the Wacker conditions usually required longer reaction times for complete consumption of starting material and led to a reduced yield of product. The exception to this was when sparteine was used as the ligand and this may be related to the phosphine ligands being prone to oxidation under the aerobic conditions.[13] Stoltz et. al.[15] had shown how sparteine could be used very effectively to carry out asymmetric oxidative Wacker cyclisation reactions. The reaction involved heating a solution of the substrate in toluene at 80 °C under an oxygen atmosphere in the presence of 10 mol % palladium bis(trifluoroacetate), 40 mol % sparteine and molecular sieves. Unfortunately when analogous conditions were used to oxidise compound **12**, the reaction failed to afford any of the desired ketone **16**.

3. Conclusion

Whilst attempting to improve the yield of a palladium-mediated Heck-style arylation/fragmentation reaction of the 7-*endo meta* photocycloadduct compound **3** derived from anisole and allyl alcohol, the reaction was repeated with the equivalent photoadduct isomer **7** derived from trimethylphenoxysilane and allyl alcohol. In addition to isolating the expected arylated products **4** and **5**, an alternative mode of reactivity involving an oxidation process was observed, which resulted in the formation of the unique tricyclic ether **8**. The efficiency of the Heck reaction of photoadduct **7** to produce the arylated product **4** was significantly improved when palladium(II) chloride was used instead of palladium(II) acetate and the oxidation process to form **8** was also dramatically improved when palladium(II) chloride and copper(II) chloride were used as the oxidants. A similar oxidative cyclisation reaction could be induced using the *meta* photocycloadduct **12** derived from anisole and *Z*-but-2-ene-1,4-diol. The products from this process could be obtained either as a ketone (**16**) or an acetal (**17** or **18**) depending upon the nature of the solvent with methanol being the solvent of choice. Unfortunately attempts to induce the reaction asymmetrically via the desymmetrisation of a proposed π-allyl palladium intermediate **14** with the aid of various homochiral ligands failed to yield any enantioenriched products.

4. Experimental

4.1. General

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

IR spectra were recorded on Perkin–Elmer Spectrum One Fourier transform instruments and frequencies (ν_{max}) are quoted in wavenumbers (cm^{-1}).

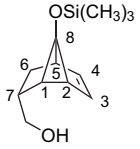
Low- and high-resolution electron impact (EI) and chemical impact (CI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionisation

(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 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. Analytical thin layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity).

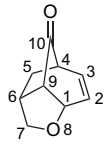
Irradiations were carried out in quartz immersion-well reactors fitted with 6 or 16 W low-pressure mercury vapour lamps or 125 or 400 W medium-pressure mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen-free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent at room temperature. 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. *rac*-(1*S*,2*R*,5*R*,7*R*,8*S*)-7-Hydroxymethyl-8-trimethylsilyloxytricyclo[3.2.1.0^{2,8}]oct-3-ene 7. A solution of trimethylphenoxysilane (33.4 g, 201 mmol) and allyl alcohol (23.3 g, 402 mmol) in cyclohexane (400 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O 2:1) to obtain the 7-*endo* isomer **7** (1.93 g, 4.3%) as a viscous, pale yellow oil.



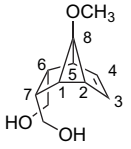
^{1}H NMR (500 MHz, C_6D_6) δ 0.12 (9H, s, $OSi(CH_3)_3$), 1.40 (1H, dd, J=1.4, 12.8 Hz, H-6a), 1.95 (1H, br d, J=8.4 Hz, H-2), 2.02 (1H, dd, J=6.3, 8.4 Hz, H-1), 2.08 (1H, br s, –OH), 2.37 (1H, ddd, J=6.6, 11.4, 12.8 Hz, H-6b), 2.70 (1H, m, H-7b), 2.96 (1H, ddd, J=1.2, 2.7, 6.4 Hz, H-5), 3.48 (1H, dd, J=7.5, 10.2 Hz, –C*H*HOH), 3.54 (1H, dd, J=8.0, 10.2 Hz, –CH*H*OH), 5.37 (1H, dddd, J=0.6, 1.3, 2.7, 5.6 Hz, H-4), 5.49 (1H, dd, J=2.3, 5.6 Hz, H-3); ^{13}C NMR (125 MHz, C_6D_6) δ 0.85, 38.3, 39.3, 39.9, 45.6, 56.2, 66.0, 86.4, 129.1, 136.5; IR 1646, 3370 cm^{-1}; HRMS (ESI) *m*/*z* calcd $C_{12}H_{20}NaO_2Si$ $[M+Na]^+$ 247.1130, found 247.1126.

4.1.2. *rac*-(1*S*,4*R*,6*R*,9*S*)-8-Oxatricyclo[4.2.1.1^{4,9}]dec-2-ene-10-one 8. A mixture of the 7-*endo* photoadduct **7** (130 mg, 0.58 mmol), palladium(II) chloride (10 mg, 0.06 mmol), copper(II) chloride (156 mg, 1.16 mmol), triethylamine (118 mg, 1.16 mmol), tri-*ortho*-tolylphosphine (36 mg, 0.06 mmol) and dry DMF (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into 2 M hydrochloric acid (50 ml) and diethyl ether (50 ml). The resulting heavy emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×50 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O 2:1) to afford **8** (60 mg, 69%) as a colourless solid of prism crystals (for crystallographic details see Ref. 5) mp 87.8–89.5 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (1H, dd, J=1.6, 13.0 Hz, H-5a), 2.33 (1H, ddd, J=6.0, 9.4, 13.0 Hz, H-5b), 2.68 (1H, ddd, J=2.0, 6.0, 7.7 Hz, H-4), 2.88 (1H, ddd, J=2.0, 6.8, 7.6 Hz, H-9), 2.97–3.03 (1H, m, H-6b), 3.68 (1H, dd, J=4.0, 8.7 Hz, H-7a), 4.36 (1H, t, J=8.5 Hz, H-7b), 5.12 (1H, dd, J=3.8, 7.0 Hz, H-1), 5.64 (1H, dddd, J=0.5, 0.9, 3.6, 9.0 Hz, H-2), 6.22 (1H, dd, J=7.5, 9.0 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.4, 37.2, 44.2, 53.3, 75.9, 85.8, 125.5, 134.6, 209.9; IR 1626, 1764 cm^{-1}; HRMS (EI) *m*/*z* calcd $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0688.

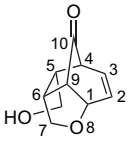
4.1.3. *rac*-(1*S*,2*R*,5*S*,6*S*,7*R*,8*S*)-6,7-Dihydroxymethyl-8-methoxytricyclo[3.2.1.0^{2,8}]oct-3-ene 12. A solution of anisole (43.2 g, 400 mmol) and *Z*-but-2-ene-1,4-diol (70.4 g, 800 mmol) in methanol (350 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed by distillation and the residue was subjected to column chromatography (silica, eluting with Et_2O/MeOH 100:1, then CH_2Cl_2/MeOH 20:1) to obtain the *endo* isomer **12** (11.3 g, 14%) as a viscous, pale green oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (1H, ddd, J=1.2, 2.4, 8.4 Hz, H-2), 2.26 (1H, dd, J=6.7, 8.4 Hz, H-1), 2.80–2.88 (1H, br s, –OH), 2.87–2.94 (1H, m, H-7b), 3.03–3.09 (1H, m, H-6b), 3.14 (1H, ddd, J=1.3, 2.6, 5.7 Hz, H-5), 3.38 (3H, s, $-OCH_3$), 3.48–3.60 (1H, br s, –OH), 3.50 (1H, dd, J=3.7, 10.7 Hz, –C*H*HOH), 3.57 (1H, dd, J=4.5, 11.4 Hz, –C*H*HOH), 3.67 (1H, t, J=11.2 Hz, –CH*H*OH), 3.98 (1H, t, J=10.3 Hz, –CH*H*OH), 5.63 (1H, ddd, J=1.2, 2.6, 5.8 Hz, H-4), 5.73 (1H, dd, J=2.4, 5.8 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.2, 39.0, 44.7, 53.4, 55.4, 56.4, 60.9, 62.8, 90.6, 131.3, 133.0; IR 1592, 1656, 3306 cm^{-1};

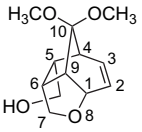
HRMS (ESI) *m/z* calcd $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0997, found 219.0998.

4.1.4. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*)-8-Oxa-5-hydroxymethyltricyclo[4.2.1.1^{4,9}]dec-2-ene-10-one 16. A mixture of the diol photoadduct **12** (210 mg, 1.07 mmol), palladium(II) chloride (10 mg, 0.054 mmol), copper(II) chloride (317 mg, 2.36 mmol), triethylamine (238 mg, 2.36 mmol), tri-*ortho*-tolylphosphine (35 mg, 0.12 mmol) and isopropanol (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with CH_2Cl_2/EtOAc 1:1) to afford **16** (29 mg, 15%) as a pale amber, viscous oil.



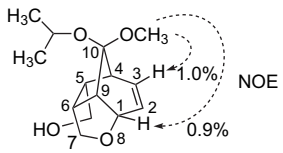
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (1H, br s, –OH), 2.72 (1H, dddd, *J*=5.2, 7.9, 7.9, 9.4 Hz, H-5b), 2.80 (1H, ddd, *J*=1.9, 5.2, 7.2 Hz, H-4), 2.97 (1H, dddd, *J*=0.7, 1.9, 6.9, 7.8 Hz, H-9), 3.11–3.17 (1H, m, H-6b), 3.77 (1H, dd, *J*=7.9, 10.4 Hz, –C*H*HOH), 3.82 (1H, dd, *J*=4.1, 9.5 Hz, H-7), 3.87 (1H, dd, *J*=7.9, 10.4 Hz, –CH*H*OH), 4.07 (1H, dd, *J*=8.5, 9.5 Hz, H-7), 5.04 (1H, dd, *J*=3.7, 6.7 Hz, H-1), 5.77 (1H, ddd, *J*=0.8, 3.7, 9.1 Hz, H-2), 6.06 (1H, dd, *J*=7.3, 9.1 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 44.5, 46.9, 54.6, 60.0, 67.8, 85.2, 128.1, 131.5, 208.3; IR 1626, 1755, 3436 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{10}H_{12}NaO_3$ $[M+Na]^+$ 203.0684, found 203.0682.

4.1.5. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*)-8-Oxa-5-hydroxymethyltricyclo-10,10-dimethoxy[4.2.1.1^{4,9}]dec-2-ene 17. A mixture of the diol photoadduct **12** (435 mg, 2.22 mmol), palladium(II) chloride (20 mg, 0.11 mmol), copper(II) chloride (657 mg, 4.88 mmol), triethylamine (493 mg, 4.88 mmol) and tri-*ortho*-tolylphosphine (74 mg, 2.44 mmol) and MeOH (8 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 4:1) to afford **17** (182 mg, 36%) as a colourless solid of plate crystals (for crystallographic details see Ref. 15) mp 90.4–91.8 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (1H, br s, –OH), 2.63 (1H, ddd, *J*=2.1, 5.1, 7.0 Hz, H-4), 2.76 (1H, dddd, *J*=5.1, 7.9, 7.9, 9.0 Hz, H-5b), 2.82–2.88 (1H, m, H-6b), 2.89–2.92 (1H, m, H-9), 3.18 (3H, s, –OCH_3), 3.27 (3H, s, –OCH_3), 3.66 (1H, dd, *J*=3.8, 9.3 Hz, H-7), 3.67 (1H, dd, *J*=8.0, 10.4 Hz, –C*H*HOH), 3.74 (1H, dd, *J*=8.0, 10.4 Hz, –CH*H*OH), 3.91 (1H, dd, *J*=8.0, 9.4 Hz, H-7), 4.70 (1H, dd, *J*=3.6, 6.2 Hz, H-1), 5.73 (1H, ddd, *J*=1.0, 3.6, 9.4 Hz, H-2), 5.89 (1H, dd, *J*=7.0, 9.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.3, 41.3, 47.0, 48.3, 49.2, 51.0, 61.2, 67.0, 79.1, 110.0, 128.5, 129.3; IR 1641, 3400 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{12}H_{18}NaO_4$ $[M+Na]^+$ 249.1103, found 249.1101.

4.1.6. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*,10*R*)-8-Oxa-5-hydroxymethyltricyclo-10-isopropoxy-10-methoxy[4.2.1.1^{4,9}]dec-2-ene 18. A mixture of the diol photoadduct **12** (200 mg, 1.02 mmol), palladium(II) chloride (9 mg, 0.05 mmol), copper(II) chloride (275 mg, 2.04 mmol), triethylamine (206 mg, 2.04 mmol) and tri-*ortho*-tolylphosphine (31 mg, 0.10 mmol) and isopropanol (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 4:1) to afford **18** (49 mg, 19%) as a pale green, viscous oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, d, *J*=6.2 Hz, –OCH(CH_3)CH_3), 1.21 (3H, d, *J*=6.2 Hz, –OCH(CH_3)CH_3), 1.36 (1H, br s, –OH), 2.54–2.57 (1H, m, H-4), 2.83–2.88 (2H, m, H-5b, H-6b), 2.91 (1H, m, H-9), 3.17 (3H, s, –OCH_3), 3.66 (1H, dd, *J*=3.3, 9.3 Hz, H-7), 3.69 (1H, dd, *J*=7.7, 10.3 Hz, –C*H*HOH), 3.76 (1H, dd, *J*=7.4, 10.4 Hz, –CH*H*OH), 3.92 (1H, dd, *J*=8.5, 9.5 Hz, H-7), 4.17 (1H, sept, *J*=6.2 Hz, –OC*H*(CH_3)CH_3), 4.71 (1H, dd, *J*=3.6, 6.4 Hz, H-1), 5.73 (1H, ddd, *J*=1.0, 3.6, 9.3 Hz, H-2), 5.88 (1H, dd, *J*=6.9, 9.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 40.4, 42.6, 47.4, 50.9, 51.5, 61.3, 64.3, 67.0, 79.5, 110.4, 128.6, 128.9; IR 1641, 3434 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{14}H_{22}NaO_4$ $[M+Na]^+$ 277.1416, found 277.1413.

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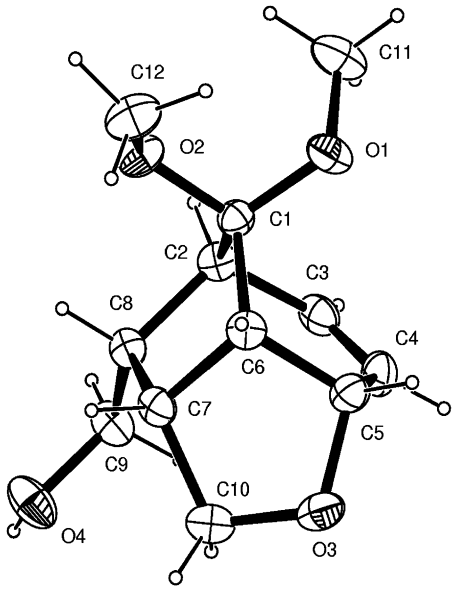
References and notes

1. Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: Chichester, UK, 2004.
2. (a) Penkett, C. S.; Sims, R. O.; French, R.; Dray, L.; Roome, S. J.; Hitchcock, P. B. *Chem. Commun.* **2004**, 1932; (b) Penkett, C. S.; Sims, R. O.; Byrne, P. W.; Kingston, L.; French, R.; Dray, L.; Berritt, S.; Lai, J.; Avent, A. G.; Hitchcock, P. B. *Tetrahedron* **2006**, *62*, 3423.
3. (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379; (b) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447; (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427; (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (e) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959; (f) Link, J. T. *Organic Reactions*; Wiley: Hoboken, NJ, 2002; Vol. 60, Chapter 2; (g) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
4. Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36.
5. The crystallographic data for compound **8** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 607017. Formula: $C_9H_{10}O_2$ Unit cell parameters: *a* 6.5756(3) *b* 9.3484(4) *c* 11.7491(3) space group P212121.
6. Muzart, J. *Tetrahedron* **2005**, *61*, 5955.
7. Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925.
8. The crystallographic data for compound **17** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 607018. Formula: $C_{12}H_{18}O_4$ Unit cell parameters: *a* 8.5840(5) *b* 11.6522(8) *c* 11.9274(6) β 108.976(4) space group P21/n.



9. Penkett, C. S.; Simpson, I. D. *Tetrahedron* **1999**, *55*, 6183.
10. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
11. Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.
12. (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475; (b) Ferreira, E. M.; Stolz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.
13. Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.
14. Hosokawa, T.; Murahashi, S. I. *Acc. Chem. Res.* **1990**, *23*, 49.
15. Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.