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# Synthesis of (−)-xialenon A by enantioselective α-deprotonation-rearrangement of a *meso*-epoxide

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**Abstract**—The first total synthesis of (−)-xialenon A was achieved via enantioselective transannular desymmetrisation of a substituted cycloctene oxide using an organolithium/(−)-α-isosparteine combination. Oxidation of the resulting bicyclo[3.3.0]octanol gave an enone which underwent stereoselective conjugate allylation; subsequent α′-hydroxylation on the more hindered face of a derived enone using hypervalent iodine chemistry led to the natural product.


## 1. Introduction

Recently isolated by Thiericke and co-workers, (−)-xialenon A **1** and its congeners are naturally occurring secondary metabolites from culture broths of the *Streptomyces* genus (Fig. 1).[1] The xialenons possess a bicyclo[3.3.0]octane skeleton, which is rarely found without additional ring appendages in nature. The structural study by spectroscopy and derivatisation established that (−)-xialenon A (**1**) is (2*R*,3*R*,4*S*)-3-allyl-3,4,5,6-tetrahydro-2,4-dihydroxy-2*H*-pentalen-1-one.

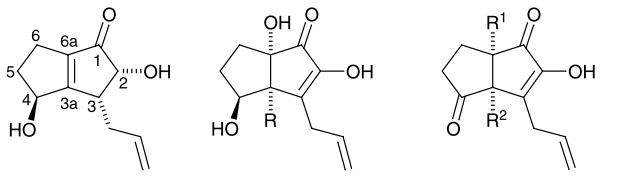
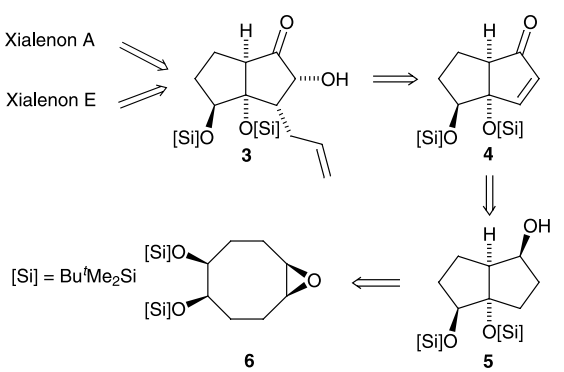



**Figure 1.** The family of xialenon natural products.

The principal issues confronting a total synthesis of xialenon A (**1**) are introduction, with the correct stereochemistry, of the lone hydroxyl group at C-4 and of the *cis* vicinal hydroxyl and allyl groups. Also, the presence of unsaturation at the ring fusion, aside from being part of a potentially sensitive enone, serves to flatten the bicycle and, when compared with the corresponding saturated bicycle, this removes the important facial biasing (concave, convex) effect typically relied on to control the introduction of stereocentres in such bicyclo[3.3.0]octane systems. Arising from our studies on enantioselective transannular desymmetrisation of substituted cycloctene oxide **6** ([Si]=Bu$^t$Me$_2$Si) using organolithium/(−)-sparteine [or (−)-α-isosparteine] combinations,[2,3] we considered that alcohol **5** could be used to address the above issues and, if successful, provide an attractive entry point to the xialenons, especially (−)-xialenon A (**1**), and potentially (−)-xialenon E (**2**) (Scheme 1). Thus, we planned to oxidise alcohol **5** to enone **4**. It was anticipated that the envelope shape of enone **4** should bias both allyl conjugate addition and, hopefully, oxidation of the intermediate enolate from the convex face to give hydroxyketone **3** with the desired stereochemistry; xialenon A would then be achieved via elimination of the tertiary silyloxy group. In the present paper we report full details of our studies culminating in the synthesis of xialenon A (**1**) by the above strategy,[4] together with attempts to use a common intermediate to synthesise xialenon E (**2**).




**Scheme 1.**

*Keywords*: desymmetrization; epoxide; lithiation; sparteine; total synthesis.
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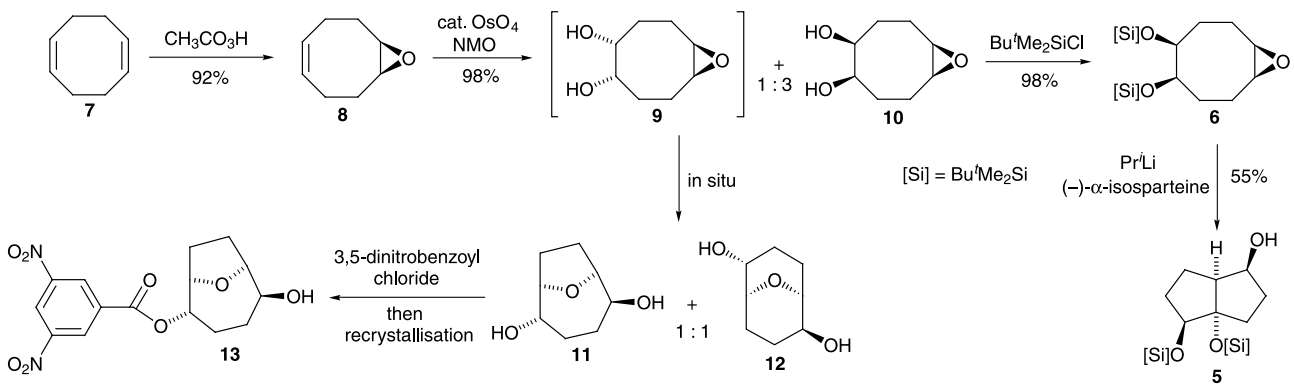
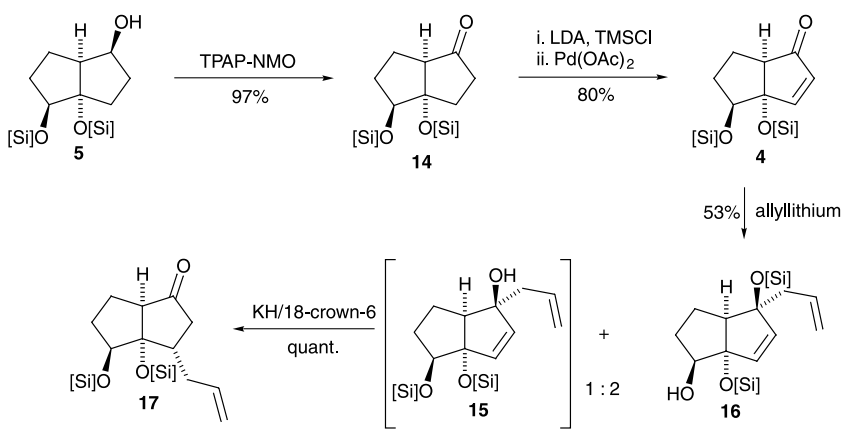



**Scheme 2.**

## 2. Results and discussion

Alcohol **5** was prepared essentially following our previously described 4-step route from 1,5-cyclooctadiene (COD, **7**) (Scheme 2).[2] Some observations made during the scale-up of this sequence are worthy of note, however. First, mono-epoxidation of COD **7** was best affected using peracetic acid (92% yield, compared to 54% yield previously obtained with *m*-CPBA). Second, dihydroxylation of the resulting mono-epoxide **8** was found to give the corresponding epoxydiol **10** as previously reported. But, interestingly, the mass balance of this reaction has now been identified as an approximately equal mixture of 9-oxabicyclo[4.2.1]nonane-2,5-diol **11** and 9-oxabicyclo[3.3.1]nonane-2,6-diol **12**, for which the former isomer was unambiguously assigned by X-ray crystallographic analysis of the *exo*-mono-2,4-dinitrobenzoate derivative **13** (Section 4.1.3). This work indicates that the selectivity in the dihydroxylation of mono-epoxide **8** is 3:1, in favour of the desired epoxydiol **10**, and that the minor epoxydiol **9** isomer undergoes (non-regioselective)[5] transannular ring opening of the epoxide. Disilylation of epoxydiol **10** gave desymmetrisation substrate **6** in near quantitative yield; whilst we have also prepared the latter from COD via initial dihydroxylation, then disilylation and a completely stereoselective epoxidation,[2] the low yield in the initial dihydroxylation leads us to prefer the route via initial monoepoxidation of COD. Scale-up of the key transannular desymmetrisation step led to a slightly lower yield (and ee) of alcohol (+)-**5** than we had previously reported[2] (55% yield, 80% ee, vs 72% yield and 89% ee), but this provided sufficient material for us to begin to examine conversion of this intermediate to the xialenons. Formation of bicyclic alcohol **5** proceeds by enantioselective α-deprotonation of the epoxide **6** using the organolithium mediated by the chiral diamine;[3] in related work we have recently established that the resultant transient oxiranyl anion can be trapped with electrophiles to provide a conceptually new route to enantioenriched epoxides,[6] however in the present case warming allows transannular C–H insertion to occur generating the bicyclic alcohol **5**.

Recent reports by Nicolaou et al.[7] led us to consider that alcohol **5** could be directly oxidised to enone **4** in one step by treatment with *o*-iodoxydobenzoic acid (IBX).[8] Treatment of alcohol **5** with IBX (2.2 equiv.) in a 2:1 mixture of PhF/DMSO (0.1 M) at 55°C for 4 h gave ketone **14** in 90% yield. Extending the reaction time did produce some enone, but led to lower mass recovery overall (52% of a 1.5:1 mixture of enone **4**/ketone **14**). Raising the temperature gave progressively greater mass loss. Attempted reaction of ketone **14** with IBX (1.4 equiv.) in a 2:1 mixture of PhF/DMSO (0.1 M) at 55°C for 16 h returned the ketone unchanged, whereas addition of TsOH and 4 Å sieves (16 h, 55°C) gave an 89% yield of a 1:1 mixture of recovered ketone and enone **4**. We also examined the more recently reported IBX-4-methylpyridine-*N*-oxide complex[7c,d] with ketone **14**, but none of the desired enone **4** was obtained. We then decided to use a more robust oxidation sequence. Indeed, conversion of alcohol **5** to the enone **4** was best effected in a stepwise manner via TPAP-NMO oxidation[9] to the ketone **14** (97% yield, Scheme 3),

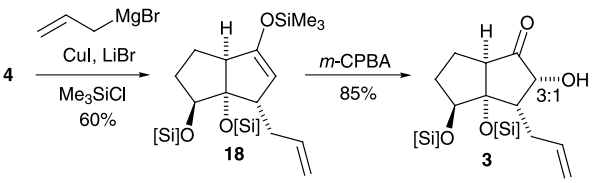



**Scheme 3.**

followed by further palladium-induced oxidation[10] of the derived silyl enol ether using $Pd(OAc)_2$ (80% yield from ketone **14**).

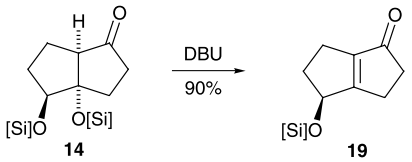
At this stage of the synthesis two strategies were investigated to introduce the allyl side-chain from the convex face of **4**. Consideration that the tertiary silyloxy substitutent might make conjugate addition difficult led us to first examine an oxy-Cope rearrangement following 1,2-addition of an allyl group to the enone functionality. In the event, addition of allyllithium[11] to enone **4** gave two products arising from *exo*-face addition of the allyl group directly to the ketone carbon (Scheme 3); these products were allylic alcohol **15** (17% yield) and allylic ether **16** (36% yield)—the later resulting from a $Bu^tMe_2Si$ migration. Pleasingly, allylic alcohol **15** underwent [3,3] sigmatropic rearrangement when treated with KH/18-crown-6, to give the desired allylated ketone **17** in quantitative yield. An analysis of the product's stereochemistry by $^1H$ NMR showed NOEs between C(6a)H*exo* and one of the allylic protons, thus supporting the intial *exo*-attack and pericyclic step. Unfortunately, allylic ether **16** could not be similarly coaxed to undergo silyloxy-Cope rearrangement even with heating up to 450°C (heating **16** to 450°C in a sand bath caused considerable decomposition; 20% recovered starting material **16** with detectable ($^1H$ NMR) expulsion of propene to return enone **4**). 1,2-Addition of allylmagnesium bromide to enone **4** was even less satisfactory, since it produced only compound **16** (80% yield).

The second strategy studied was to introduce the allyl side-chain in a 1,4-fashion. We started by investigating the use of allyltrimethylsilane. Whilst Sakurai reaction using a standard protocol[12] or an allylbarium reagent[13] gave none of the desired product **17**, the recent allylation procedure developed by Robertson et al.[14] using allyltrimethylsilane and catalytic bistrifluoromethanesulfonimide gave the required allylated ketone **17** in 54% yield. Encouraged by this result, copper-mediated allylation was studied[15] with the best result being obtained using the procedure of Lipshutz and co-workers (Scheme 4).[15a] Furthermore, dependent on the work-up conditions (depending on whether the reaction was worked-up with a saturated solution of $NH_4Cl$, or with water first for 30 min then addition of a saturated solution of $NH_4Cl$) either silyl enol ether **18** or allylated ketone **17** were recovered (both in 60% yields) and with complete stereoselectivity once again. Having secured the allyl side-chain introduction, we then focused on α-hydroxylation via Rubottom oxidation[16] of silyl enol ether **18**. This procedure gave hydroxyketone **3** as an easily separable mixture of epimers (85% yield in total, 3:1 in favour of the desired diastereoisomer as determined by NOE experiments; for the major epimer *exo*-**3** NOEs were observed between C(2)H and C(5)H*endo*/C(6)H*endo*; for the minor epimer *endo*-**3** NOEs were observed between C(2)H and C(6a)H and no NOEs were detected between C(2)H and C(3)H). The modest *exo*-selectivity in the oxidation compared with the completely *exo*-selective cuprate allylation may originate from two factors: first, the α-carbon to the ketone is less subject to the concave shielding effect of the bicycle; and second the newly introduced allyl side-chain now reduces accessibility on the convex face.




**Scheme 4.**

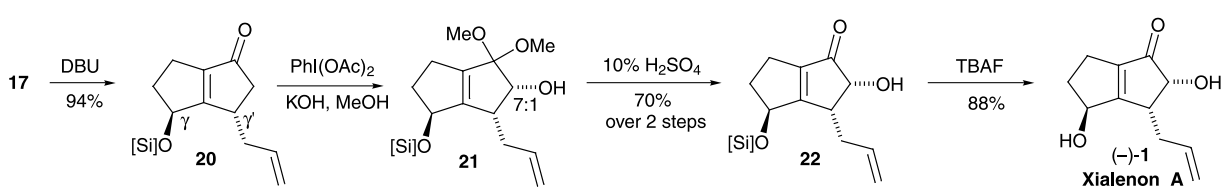
In model studies on the key elimination (c.f. **3** to **1**) using ketone **14** we found that basic conditions (e.g. 2 equiv. of DBU in MeCN at 25°C for 48 h) caused elimination of the tertiary silyloxy group yielding the corresponding fused enone **19** in 90% yield (Scheme 5). Unfortunately, application of this method to hydroxyketone **3** only resulted in its complete decomposition.




**Scheme 5.**

Suspecting that the presence of the hydroxyl group in hydroxyketone **3** was the origin of the problem, we investigated reversing the sequence of elimination and hydroxylation steps. In order to examine hydroxylation by this latter strategy, enone **20** was prepared in 94% yield from allylated ketone **17** via a smooth (E1cB) elimination using DBU in MeCN for 48 h (Scheme 6).

Many procedures are known for the oxidation of an α,β-unsaturated ketone to an α′-acetoxyenone or α′-hydroxyenone,[17] but most of them would likely oxidise enone **20** from the undesired, less-hindered face (*trans* to the allyl side-chain, with the convex facial bias also not now present). However, hypervalent iodine oxidation of cyclic, enolisable carbonyl compounds leading to α-hydroxydimethylacetals is known to proceed via an oxidation–inversion process, with the hydroxyl group being introduced on the same same face as bulky substituents present in β- or γ-positions.[18] In the event, when enone **20** was exposed to a solution of KOH in dry




**Scheme 6.**

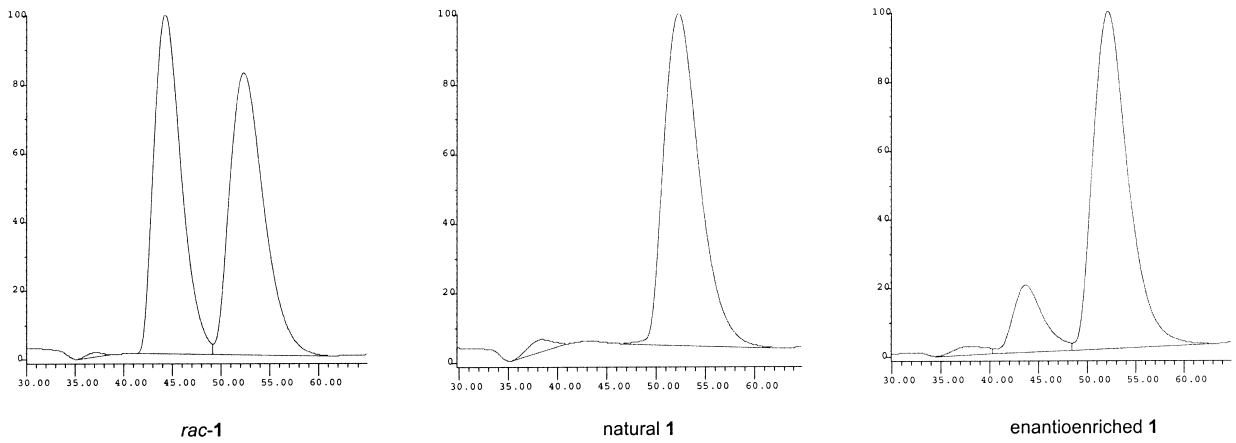
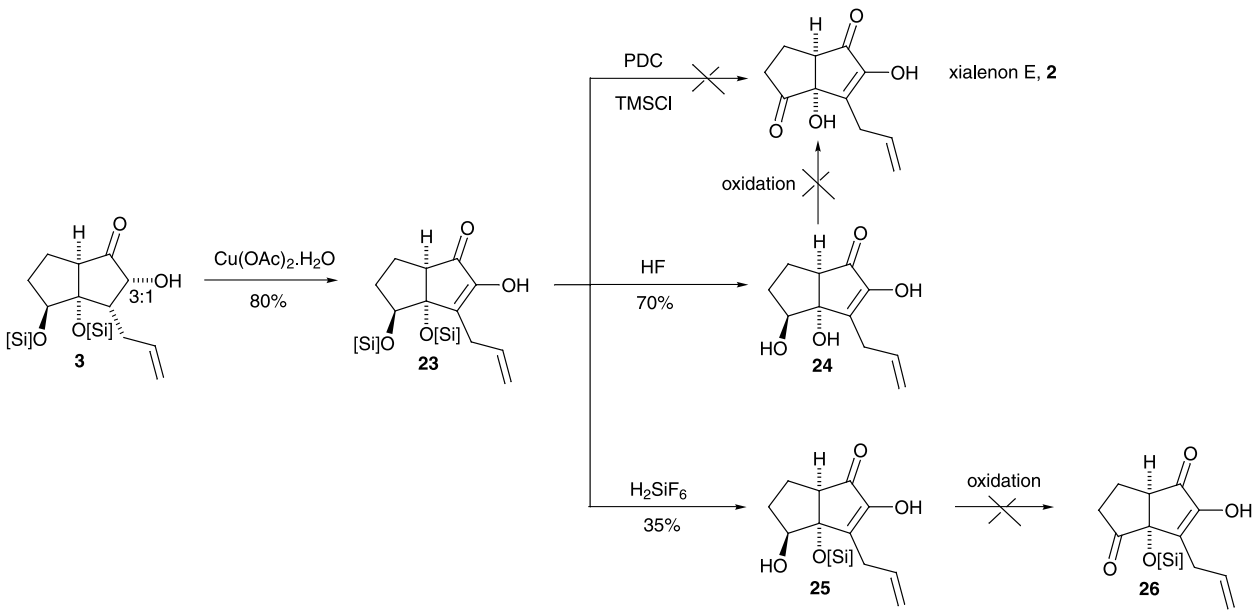



**Figure 2.** Comparison of chiral HPLC data for xialenon A (**1**) samples.

MeOH at −15°C for 15 min, followed by addition of iodobenzene diacetate (IBD), a mixture of α′-hydroxydimethylacetals **21** was obtained (7:1, as determined by $^1$H NMR analysis of the C(2)H signals). The crude mixture of α′-hydroxydimethylacetals **21**, diluted in $CH_2Cl_2$, was briefly treated with 10% sulfuric acid at 25°C to yield, after column chromatography, 70% of the desired hydroxyenone **22** and 10% of the isomer epimeric at the hydroxyl group, *epi*-**22** (the *cis* relative stereochemistry between C(2)H and C(3)H in hydroxyenone **22** was provisionally assigned from the larger $^3J$ value between C(2)H and C(3)H (6.1 Hz) relative to that observed for *epi*-**22** (2.5 Hz), and comparison with $^3J$ between C(2)H and C(3)H (6.1 Hz) reported for natural xialenon A (**1**)[1] and, ultimately, by conversion of **22** to **1**). This transformation is a rare, efficient α′-hydroxylation of an α,β-unsaturated ketone using hypervalent iodine chemistry; usually such a reaction is complicated by partial γ-oxidation (or double bond dioxygenation).[18,19] In the present case, the presence of both the γ-silyloxy group and the γ′-allyl side-chain on opposite faces of enone **20** may be shielding[19] the enone system from such unwanted side reactions.

Desilylation of hydroxyenone **22** using TBAF in THF gave (−)-xialenon A (**1**) {88% yield, $[\alpha]_D^{25}=-83.3$ (*c* 0.54, MeOH) [lit.[1] $[\alpha]_D^{25}=-108.0$ (*c* 0.66, MeOH)]}, with data ($^1$H, $^{13}$C, IR, MS, TLC) consistent with the natural material.[1] As the absolute configuration of alcohol (+)-**5** is known,[2] the consistency in the sign of the specific rotation values of synthetic and natural xialenon A (**1**) confirm the 2*R*,3*R*,4*S* absolute stereochemistry of xialenon A (**1**) originally determined by Thiericke et al.[1] by bis-esterification of xialenon A (**1**) with the individual enantiomers of 2-phenylbutyric acid and $^1$H NMR analysis using the rules of Helmchen.[20] Comparison by chiral HPLC of racemic xialenon A (prepared via desymmetrisation of **6** using *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine as ligand with Bu$^s$Li in 70% yield)[2] with an authentic sample of the natural product, and our enantioenriched material indicated that the latter was of 80% ee (Fig. 2), indicating that no loss of enantiointegrity had occurred in the transformations from enantioenriched **5** to **1**.

In order to probe the generality of our strategy to other xialenons we also examined the potential of both epimeric




**Scheme 7.**

alcohols **3** in an approach towards xialenon E (**2**). Introduction of the characteristic 2-hydroxyenone unit of xialenon E was achieved using $Cu(OAc)_2 \cdot H_2O$[21] in methanol for 24 h to give hydroxyenone **23** in 80% yield (Scheme 7). Hydroxyenone **23** was then examined in three different strategies to try to access xialenon E (**2**). The first method consisted in applying the conditions of Cossio et al. (pyridinium dichromate in combination with chlorotrimethylsilane)[22] for (double) desilylation followed by in situ oxidation of the liberated secondary alcohol to hopefully give xialenon E (**2**) in one-pot. Unfortunately, these conditions appeared too drastic and gave complete decomposition of **23**. The second approach consisted of two separate steps. Deprotection was best accomplished using HF in MeCN to give diol **24** in 70% yield. Unfortunately, oxidation once again gave complete decomposition of the starting diol after only 5 min reaction time, even using the mild oxidants Dess–Martin periodinane or TPAP-NMO. Thinking that the free tertiary alcohol could be a problem in the stability of the substrate, we decided to attempt selective deprotection to the secondary alcohol of **23** and perform its oxidation. Fluorosilicic acid is probably the best reagent when combined with appropriate solvent to selectively deprotect the secondary $Bu^tMe_2Si$ group.[23] Using an improved protocol (cat. fluorosilicic acid in MeCN/$Bu^tOH$ 9:1)[23b] no reaction took place. However, by using 1 equiv. of fluorosilicic acid, a mixture of starting material, monoprotected alcohol **25** (35% yield) and diol **24** were recovered in a 3:3:1 ratio ($^1H$ NMR ratio). This low selectivity could be due to the comparatively accessible *exo*-tertiary $Bu^tMe_2Si$ group compared with the more hindered *endo*-secondary $Bu^tMe_2Si$ group. Unfortunately, further attempts to oxidise **25** into **26** resulted in complete decomposition of this material. It is likely that xialenon E (**2**) and related structure such as **26** are not stable under the above conditions. Indeed, it has been observed that, unlike xialenon A (**1**), xialenons B, C, D, and E are 'rapidly decomposed by the addition of bases or acid'.[1]

## 3. Conclusion

We have accomplished the first total synthesis of xialenon A (**1**) in 12 steps from 1,5-cyclooctadiene via the previously known alcohol **5**. The allyl side-chain has been introduced with complete stereoselectivity, and a highly stereoselective $\alpha'$-hydroxylation of the hindered face of an enone using hypervalent iodine chemistry has been achieved. This chemistry reported herein constitutes the first application of our recently reported enantioselective α-deprotonation transannular C–H insertion of epoxides in natural product synthesis.

## 4. Experimental

### 4.1. General

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were oven-dried and allowed to cool in a desiccator over $P_2O_5$ before use. Ethers were distilled from benzophenone ketyl radical, hydrocarbons from $CaH_2$, and alcohols from their magnesium alkoxides. All reactions were monitored by TLC using commercially available (Merck or Camlab) plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualisation of reaction components was achieved with 254 nm light, and $KMnO_4$ dip. Organic layers were dried ($MgSO_4$), evaporated with a Buchi rotary evaporator, followed by drying on a high vacuum oil pump (~1 mm Hg). Column chromatography was carried out on Kieselgel 60 (40–63 μm). IR spectra were recorded as either KBr discs or thin films, using a Perkin–Elmer 1750 FTIR spectrophotometer. Peak intensities are specified as strong (s), medium (m) or weak (w). Only selected absorbancies are reported. $[\alpha]_D$ values are given in $10^{-1}$ deg $cm^2$ $g^{-1}$. $^1H$ NMR spectra of compounds were recorded in $CDCl_3$ unless otherwise stated, using a Varian Gemini 200 (200 MHz) or Bruker DPX400 (400 MHz). Chemical shifts ($\delta$) are reported relative to $CHCl_3$ ($\delta$ 7.27). Coupling constants ($J$) are given in Hz, multiplicities are given as multiplet (m), doublet (d), triplet (t) and quartet (q). $^{13}C$ NMR spectra were recorded on the Bruker DPX400 (100 MHz) or a DPX200 (50 MHz). Chemical shifts are reported relative to $CDCl_3$ (central line of triplet $\delta$ 77.0) unless stated otherwise. Mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea with a Micromass, ZAB-E instrument or 900 XLT high resolution double focusing mass spectrometer with tandem ion trap. Alternatively they were recorded in-house using a VG mass Lab. TRIO1 (GCMS) or Micromass platform APCI spectrometer. All organolithiums were titrated against *N*-(2-methylphenyl)dimethylethyl amide before use. A known amount of the amide was dissolved in THF (2 mL) and the organolithium was then added to this stirring solution until a colour change is observed (clear colourless to bright orange).'Petroleum ether' refers to the fraction boiling in the range 30–40°C. Chiral stationary phase HPLC was performed using a Daicel Chiralpak AD column (4.6 mm×250 mm) on a Gilson system with 712 Controller Software and a 118 UV–VIS dectector set at 254 nm. Chiral gas chromatography was carried out using a Ce instruments Trace GC (thermoquest) machine with a CP Chirasil Dex-CD column. Retention times for major ($t_R$mj) and minor ($t_R$mn) enantiomers are given in minutes.

**4.1.1. 5,6-Epoxycyclooctene 8.** A solution of peracetic acid (40% in acetic acid; 21.1 g, 111 mmol) in $CH_2Cl_2$ (250 mL) was added dropwise to a stirred mixture of 1,5-cyclooctadiene **7** (10.0 g, 92.6 mmol) and $Na_2CO_3$ (58.8 g, 555 mmol) in $CH_2Cl_2$ (280 mL) at 0°C. The mixture was stirred at 0°C for 6 h. Water (100 mL) was then added and the mixture filtered. The filtrate was extracted with $CH_2Cl_2$ (3×100 mL), washed with brine (100 mL), dried and the solvent removed at reduced pressure. Rapid filtration through a plug of silica gave monoepoxide **8** (10.5 g, 92%) as a colourless oil; data as previously reported.[2]

**4.1.2. (1*R**,4*S**,5*R**,8*S**)-9-Oxabicyclo[6.1.0]nonane-4,5-diol 10, (1*R**,2*S**,5*S**,6*S**)-9-oxabicyclo[4.2.1]nonane-2,5-diol 11 and (1*R**,2*R**,5*R**,6*S**)-9-oxabicyclo[3.3.1]-nonane-2,6-diol 12.** $OsO_4$ (4% w/w in $H_2O$; 2 mL, 0.3 mmol) was added to a stirred solution of monoepoxide **8** (10.0 g, 80.6 mmol) and NMO (24.0 g, 205 mmol) in 1:1

THF/$H_2O$ (200 mL) at 0°C. The solution was allowed to warm to 25°C and stirred for 15 h before being cooled to 0°C. Excess $Na_2S_2O_4$ was added. After filtration the solution was concentrated under reduced pressure and transferred to a liquid–liquid extractor and continuously extracted with EtOAc for 24 h, then with $CH_2Cl_2$ for 72 h. The combined organic phases were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (5% MeOH in $CH_2Cl_2$) gave the epoxydiol **10** (9.2 g, 73%) as a white solid (data as previously reported)[2] and an inseparable mixture of 9-oxabicyclo[4.2.1]nonane-2,5-diol **11** and 9-oxabicyclo[3.3.1]nonane-2,6-diol **12** (3.2 g, 25%) as a colourless oil; data for **11** and **12**: $R_f$ 0.27 (10% MeOH in $CH_2Cl_2$); $\nu_{max}$(KBr)/cm$^{-1}$ 3337s, 2936s, 1037m, 1000m; $\delta_H$ (400 MHz, $CD_3OD$) 4.32–4.26 (2H, m), 3.92–3.87 (1H, m), 3.80–3.72 (3H, m), 3.64–3.57 (2H, m), 2.25–2.15 (1H, m), 2.07–1.94 (4H, m), 1.92–1.66 (8H, m), 1.58–1.13 (3H, m); $\delta_C$ (100 MHz, $CD_3OD$) 85.0 (CH **11**), 81.7 (CH **11**), 77.2 (CH **11**), 72.6 (CH **11**), 72.5 (CH), 70.5 (CH), 68.4 (CH), 68.2 (CH), 30.3 ($CH_2$ **11**), 28.5 ($CH_2$ **11**), 27.4 ($CH_2$ **11**), 26.6 ($CH_2$), 26.5 ($CH_2$), 25.8 ($CH_2$), 22.8 ($CH_2$ **11**), 17.7 ($CH_2$); *m/z* (ES+), 181 (M+Na$^+$, 100%), (Found M+Na$^+$ 181.0841, $C_8H_{14}O_3Na$ requires 181.0841).

**4.1.3. (1*R**,2*S**,5*S**,6*S**)-5-Hydroxy-9-oxabicyclo[4.2.1]-non-2-yl 3,5-dinitrobenzoate 13.**[24] 3,5-Dinitrobenzoyl chloride (6.4 g, 27.8 mmol) was added to a stirred solution of **11** and **12** (2.0 g, 12.7 mmol), $Et_3N$ (8.8 mL, 63.3 mmol) and imidazole (185 mg, 2.7 mmol) in $CH_2Cl_2$ (50 mL) at 25°C. After 24 h the reaction mixture was washed with water (50 mL) and extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated aq. $Na_2CO_3$ (50 mL) and brine (30 mL). The organic layer was dried and evaporated to leave a yellow residue. Purification of the residue by column chromatography (1% MeOH in $CH_2Cl_2$) gave mixture of mono-benzylated alcohols (2.45 g, 55%) as a yellow solid which was recrystallised (DCM:hexane) to give **13** as white crystals; mp 148–150°C; $R_f$ 0.57 (10% MeOH:$CH_2Cl_2$); $\nu_{max}$(KBr)/cm$^{-1}$ 3247w, 2938w, 1725m, 1544s, 1345s, 1280s; $\delta_H$ (400 MHz,) 9.23 (1H, t, *J*=2 Hz), 9.17 (2H, d, *J*=2 Hz), 5.06 (1H, dd, *J*=10, 6 Hz, C(2)H,), 4.57–450 (1H, m), 4.10–4.00 (3H, m), 2.45–2.35 (1H, m), 2.33–2.21 (1H, m), 2.19–2.05. (2H, m), 2.00–1.85 (2H, m), 1.75–1.47 (2H, m), $\delta_C$ (100 MHz) 162.0 (C=O), 148.6 (Ar), 134.0 (Ar), 129.5 (Ar), 122.4 (Ar), 82.4 (*C*HO), 81.8 (*C*HO), 81.4 (*C*HO), 72.2 (*C*HO), 30.6 ($CH_2$), 27.5 ($CH_2$), 24.8 ($CH_2$), 22.7 ($CH_2$); *m/z* (CI$^+$), 370 (M+NH$_4^+$, 100%), 356 (60) (Found M+NH$_4^+$ 370.1245, $C_{15}H_{20}O_8N_3$ requires 370.1235).

**4.1.4. (1*R**,4*S**,5*R**,8*S**)-4,5-Bis(*tert*-butyldimethylsilyl-oxy)-9-oxabicyclo[6.1.0]nonane 6.**[24] Epoxydiol **10** (4.1 g, 26 mmol), Bu$^t$Me$_2$SiCl (9.9 g, 65 mmol) and imidazole (33.5 g, 492 mmol) were stirred at 25°C in DMF (15 mL) for 18 h. The solution was diluted with water (200 mL) and $CH_2Cl_2$ (200 mL). The aqueous layer was extracted with $CH_2Cl_2$ (4×$CH_2Cl_2$), dried, and evaporated under reduced pressure to give a clear oil. Purification of the residue by column chromatography (10% $Et_2O$ in light petroleum) gave the epoxide **6** (10 g, 98%) as a clear oil which solidified on standing in the refrigerator over several days; data as previously reported.[2]

**4.1.5. (1*S*,3a*S*,4*S*,6a*S*)-3a,4-Bis(*tert*-butyldimethylsilyl-oxy)octahydropentalen-1-ol 5.** Pr$^i$Li[25] (2.2 M in petroleum ether, 11.6 mL, 25.5 mmol) was added over 15 min to a stirred solution of (−)-α-isosparteine·$H_2O$ (3.28 g, 13.0 mmol) in 30 mL of ether at −90°C. After stirring for 1 h at this temperature a solution of epoxide **6** (2.0 g, 5.2 mmol) in ether (10 mL) was added over 20 min. The solution was then stirred at −90°C for a further 6 h, before being allowed to slowly warm to 25°C overnight. The reaction was cooled to 0°C and $H_3PO_4$ (0.5 mol dm$^{-3}$, 50 mL) was added dropwise. The organic layers were washed with saturated aq. $NaHCO_3$ (2×20 mL) and brine, dried and the solvent evaporated under reduced pressure. Column chromatography of the residue (10% $Et_2O$ in light petroleum) gave **5** (1.10 g, 55, 80% ee); $[\alpha]_D^{25}$=+28.2 (*c* 1.0, $CHCl_3$), data as previously reported.[2]

**4.1.6. (3a*S*,4*S*,6a*R*)-3a,4-Bis(*tert*-butyldimethylsilyloxy)-hexahydro-2*H*-pentalen-1-one 14.** Tetrapropylammonium perruthenate (5 mol%, 55 mg, 0.15 mmol) was added in one portion to a stirred mixture of alcohol **5** (1.2 g, 3.1 mmol), 4-methylmorpholine *N*-oxide (546 mg, 4.67 mmol) and powdered 4 Å molecular sieves (1.6 g) in $CH_2Cl_2$ (15 mL) at 25°C. After 2 h the reaction mixture was filtered through a short pad of silica gel, eluting with $CH_2Cl_2$. The filtrate was evaporated and the residue was purified by column chromatography (98:2 petroleum ether/$Et_2O$) to afford **14** (1.17 g, 97%); $[\alpha]_D^{25}$=−20.6 (*c* 1.0, $CHCl_3$); $R_f$ (10% $Et_2O$/petroleum ether) 0.35; $\nu_{max}$(thin film)/cm$^{-1}$ 2955s, 2930s, 1754s, 1472m, 1258s, 1166s, 1107m, 1061s, 835s, 776s; $\delta_H$ (400 MHz) 3.93–3.91 (1H, m, C(4)H), 2.53–2.34 (4H, m), 2.02–1.92 (4H, m), 1.60–1.57 (1H, m), 0.86 (9H, s, C*Me*$_3$), 0.84 (9H, s, C*Me*$_3$), 0.11 (6H, s, Si*Me*), 0.07 (3H, s, Si*Me*), 0.05 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 218.8 (C=O), 91.4 (*C*OSi), 81.8 (*C*HOSi), 58.7 (*C*HCO), 39.6, 34.0, 29.9, 25.7 (C*Me*$_3$), 25.6 (C*Me*$_3$), 23.8, 17.8 (*C*Me$_3$), −2.5 (Si*Me*), −2.6 (Si*Me*), −4.6 (Si*Me*), −4.7 (Si*Me*); *m/z* (CI+), 402 (M+NH$_4^+$, 100%), 327 (10), 270 (20), 253 (25), 138 (65), and 121 (30) (Found M+NH$_4^+$ 402.2855, $C_{20}H_{44}NO_3Si_2$ requires 402.2860).

**4.1.7. (3a*S*,4*S*,6a*R*)-3a,4-Bis(*tert*-butyldimethylsilyloxy)-4,5,6,6a-tetrahydro-3a*H*-pentalen-1-one 4.** Bu$^n$Li (1.5 M in hexanes, 2.10 mL, 3.15 mmol) was added dropwise to a solution of *N*,*N*-diisopropylamine (0.45 mL, 3.12 mmol) in THF (10 mL) at 0°C. After 30 min, the solution was cooled to −78°C and a solution of ketone **14** (600 mg, 1.56 mmol) in THF (3 mL) was added dropwise. After 30 min $Me_3SiCl$ (0.39 mL, 3.12 mmol) was added dropwise. After 1 h at −78°C, the reaction was allowed to warm to −25°C, then diluted with $Et_2O$ before addition of water and extraction with $Et_2O$ (3×50 mL). The combined organic phases were dried and concentrated to leave a residue, which was passed through a short pad of Florisil (eluting with petroleum ether). The resulting crude silyl enol ether was rapidly used in the next step. $Pd(OAc)_2$ (330 mg, 1.56 mmol) was added to a solution of the crude silyl enol ether in dry MeCN (6 mL) and the mixture was stirred overnight at room temperature. The solvent was evaporated and the black residue was filtered through a pad of silica gel (eluting with $CH_2Cl_2$). The filtrate was washed with saturated aq. $NaHCO_3$ to remove traces of acetic acid. The organic phase was washed with brine, dried and evaporated under

reduced pressure. The residue was purified by column chromatography (98:2 petroleum ether/$Et_2O$) to afford **4** (480 mg, 80%) as a colourless oil; $[\alpha]_D^{25}=-27.8$ (*c* 1.0, $CHCl_3$); $R_f$ (10% $Et_2O$/petroleum ether) 0.35; $\nu_{max}$(thin film)/$cm^{-1}$ 2955s, 2930s, 1706s, 1471w, 1245s, 912w, 738w; $\delta_H$ (400 MHz) 7.48 (1H, d, *J*=6 Hz, C*H*=CHCO), 6.24 (1H, d, *J*=6 Hz, CH=C*H*CO), 4.17 (1H, dd, *J*=10, 6 Hz, C(4)H), 2.44 (1H, dd, *J*=19, 9 Hz, C(6a)H), 1.90–1.70 (3H, m), 1.28–1.18 (1H, m), 0.86 (9H, s, C$Me_3$), 0.87 (9H, s, C$Me_3$), 0.10 (3H, s, Si*Me*), 0.04 (3H, s, Si*Me*), 0.04 (3H, s, Si*Me*) and −0.01 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 210.1 (C=O), 164.0, (*C*H=CHCO), 134.8 (CH=C*H*CO), 90.8 (*C*OSi), 81.9 (*C*HOSi), 55.1 (*C*HCO), 31.7, 25.7 (C$Me_3$), 25.6 (C$Me_3$), 22.8, 18.0 (*C*$Me_3$), 17.8 (*C*$Me_3$), −2.4 (Si*Me*), −3.0 (Si*Me*), −4.7 (Si*Me*) and −4.8 (Si*Me*); *m*/*z* (CI+) 400.3 (40%, M+$NH_4^+$), 383 (60, $MH^+$), 270 (20, M+$NH_4^+$–TBSO) and 121 (100) (Found (ES+) M+$H^+$ 383.2443, $C_{20}H_{39}O_3Si_2$ requires 383.2438).

**4.1.8. (1*S*,3a*S*,4*S*,6a*S*)-4-Allyl-4,6a-bis(*tert*-butyldimethylsilyloxy)-1,2,3,3a,4,6a-hexahydropentalen-1-ol 16 and (3*S*,3a*S*,4*S*,6a*R*)-3-allyl-3a,4-bis(*tert*-butyldimethylsilyloxy)hexahydro-2*H*-pentalen-1-one 17.** Bu$^n$Li (1.3 M solution in hexanes, 261 μL, 0.34 mmol) was added to a solution of allyltributyltin (113 mg, 0.34 mmol) in THF (2 mL) at −78°C. The mixture was stirred at −78°C for 1 h before addition of enone **4** (108 mg, 0.28 mmol) in THF (1 mL). After a further 3 h saturated aq. $NH_4Cl$ (5 mL) was added. The mixture was diluted with water (5 mL) and ether (10 mL) and the layers separated. The aqueous layer was extracted with $Et_2O$ (5 mL) and the combined organic fractions were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (39:1 petroleum ether/$Et_2O$) gave allylic alcohol **15** (19 mg, 17%) and allylic ether **16** (41 mg, 36%) as colourless oils. Allylic alcohol **15** (19 mg, 0.045 mmol) was then added to a solution of KH (20 mg, 0.50 mmol) and 18-crown-6 (150 mg, 0.50 mmol) in THF (5 mL). After 16 h at 25°C the reaction mixture was hydrolysed with water (15 mL) and extracted with ether (3×15 mL). The combined organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (39:1 petroleum ether/$Et_2O$) gave allylated ketone **17** (19 mg, 100%); data for allylic ether **16**: $R_f$ (3% $Et_2O$/petroleum ether) 0.29; $\nu_{max}$(thin film)/$cm^{-1}$ 3464w, 2956s, 2930s, 1641s, 1258s, 1086w, 837s, 776s; $\delta_H$ (200 MHz) 5.90–5.80 (1H, m, C*H*=$CH_2$), 5.85 (1H, d, *J*=6 Hz, C*H*=CH), 5.69 (1H, d, *J*=6 Hz, CH=C*H*), 5.18–5.08 (2H, m, CH=C$H_2$), 3.75 (1H, d, *J*=3 Hz, C(1)H), 3.35 (1H, brs, OH), 2.50–2.15 (4H, m), 2.05–1.95 (1H, m), 1.80 (1H, m), 1.75–1.65 (1H, m), 0.89 (9H, s, C$Me_3$), 0.87 (9H, s, C$Me_3$), 0.09 (3H, s, Si*Me*), 0.07 (9H, s, 3×Si*Me*); $\delta_C$ (50 MHz) 139.9 (C=C), 134.4 (C=C), 133.7 (C=C), 117.4 (C=C), 99.4 (CO), 80.9 (CO), 79.1 (CO), 57.7, 44.3, 36.8, 25.8 (C$Me_3$), 25.6 (C$Me_3$), 20.0, 18.1 (*C*$Me_3$), 17.9 (*C*$Me_3$), −2.5 (Si*Me*), −2.8 (Si*Me*) and −4.8 (2×Si*Me*), *m*/*z* (CI+) *m*/*z* 425 (100%, $MH^+$) and 407 ($MH^+-18$); (Found M+$H^+$ 425.2906, $C_{23}H_{45}O_3Si_2$ requires 425.2907); data for allylated ketone **17**: $[\alpha]_D^{25}=+22.0$ (*c* 1.0, $CHCl_3$), $R_f$ (10% $Et_2O$/petroleum ether) 0.35; $\nu_{max}$(thin film)/$cm^{-1}$ 2957m, 2254m, 1734m, 1472m, 911s; 742s; $\delta_H$ (400 MHz) 5.79 (1H, dddd, *J*=17, 10, 8, 7 Hz, C*H*=$CH_2$), 5.03 (1H, dm, *J*=17 Hz, CH=C$H_2$), 4.97 (1H, dm, *J*=10 Hz, CH=C$H_2$), 4.16 (1H, dd, *J*=9, 6 Hz, C(4)H), 2.77 (1H, dm, *J*=14 Hz, allylic $CH_2$), 2.57 (1H, dd, *J*=11, 3 Hz, C(6a)H), 2.46 (1H, dd, *J*=16, 7 Hz, C(2)H*endo*), 2.32 (1H, m, C(3)H), 2.22 (1H, ddd, *J*=16, 11, 1 Hz, C(2)H*exo*), 2.06 (1H, dm, *J*=14 Hz, allylic $CH_2$), 1.84 (3H, m), 1.44 (1H, m), 0.91 (9H, s, C$Me_3$), 0.90 (9H, s, C$Me_3$), 0.14 (3H, s, Si*Me*), 0.10 (6H, s, 2×Si*Me*) and 0.06 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 218.9 (C=O), 138.0 (C=C), 115.3 (C=C), 90.3 (*C*OSi), 82.3 (*C*HOSi), 57.9 (*C*HCO), 44.4 (homoallylic *C*H), 40.0, 35.8, 33.0, 25.9 (C$Me_3$), 25.8 (C$Me_3$), 22.4, 18.4 (*C*$Me_3$), 17.9 (*C*$Me_3$), −2.5 (Si*Me*), −2.5 (Si*Me*), −4.2 (Si*Me*) and −4.8 (Si*Me*); *m*/*z* (CI+) 442 (100%, $MNH_4^+$), 293 (80) (Found (ES+) M+$NH_4^+$ 442.3177, $C_{23}H_{48}NO_3Si_2$ requires 442.3172).

**4.1.9. (3*S*,3a*S*,4*S*,6a*R*)-3-Allyl-3a,4-bis(*tert*-butyldimethylsilyloxy)hexahydro-2*H*-pentalen-1-one 17.** CuI (776 mg, 4.10 mmol) and anhydrous LiBr (358 mg, 4.10 mmol) were placed in a 3-neck 25 mL round-bottom flask. While stirring the inorganic reagents, the flask was evacuated and heated for five minutes then flushed with argon (3 times). THF (10 mL) was injected, and the mixture was stirred for 5 min to yield a yellow homogeneous solution, which was cooled to −78°C. Allylmagnesium bromide (1.0 M in $Et_2O$, 3.58 mL, 3.58 mmol) was added dropwise to the yellow solution at −78°C to yield a tan solution. TMSCl (500 μL, 3.96 mmol) was added followed immediately by the addition of enone **4** (500 mg, 1.27 mmol) in THF (3 mL). After 30 min at −78°C the reaction mixture was hydrolysed with water (15 mL) then allowed to quickly warm to 25°C over 30 min, followed by the addition of saturated aq. $NH_4Cl$ solution (30 mL). Extraction with ether was followed by combining the organic layers and drying. The solvent was removed in vacuo, and the resulting residue was subjected to flash chromatography (96:4 petroleum ether/$Et_2O$) to yield allylated ketone **17** (333 mg, 60%); data as above.

**4.1.10. (2*R*,3*S*,3a*S*,4*S*,6a*R*)-3-Allyl-3a,4-bis(*tert*-butyldimethylsilyloxy)hexahydro-2-hydroxy-2*H*-pentalen-1-one *exo*-3 and (2*S*,3*S*,3a*S*,4*S*,6a*R*)-3-allyl-3a,4-bis(*tert*-butyldimethylsilyloxy)hexahydro-2-hydroxy-2*H*-pentalen-1-one *endo*-3.** The exact procedure (and scale) of Section 4.1.9 above was followed until work-up. After 30 min at −78°C the reaction was quenched with saturated aq. $NH_4Cl$ solution (20 mL). Extraction with $Et_2O$ (3×20 mL) was followed by combining the organic layers and drying. The solvent was removed in vacuo, and the resulting residue was passed through a short pad of Florisil (eluting with petroleum ether) to yield silyl enol ether **18** (390 mg, 60%). The silyl enol ether was then rapidly used in the next step. To a mixture of $KHCO_3$ (84 mg, 0.84 mmol) and *m*-CPBA (50 mg, 0.20 mmol) in hexanes (3 mL) at −15°C was added silyl enol ether **18** (84 mg, 0.17 mmol) in hexanes (2 mL) at −15°C. The mixture was allowed to warm to 25°C over 2 h, then filtered, extracted with $Et_2O$ (30 mL) and washed with a saturated aq. $Na_2SO_3$ (10 mL), saturated aq. $NaHCO_3$ (10 mL) and dried. Column chromatography of the residue gave the α-hydroxy ketones *exo*-**3** (48 mg, 64%) and *endo*-**3** (16 mg, 21%) as colourless oils; data for *exo*-**3**: $R_f$ 0.55 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/$cm^{-1}$ 3460s, 2969s, 2933s, 1746s, 1641m, 1361m, 1257w; $\delta_H$ (400 MHz, $D_2O$ in $CDCl_3$) 5.98–5.83 (1H, m, C*H*=$CH_2$), 5.13 (1H, dd, *J*=17, 2 Hz, CH=C$H_2$),

5.02 (1H, dd, $J$=10, 2 Hz, CH═C$H_2$), 4.22 (1H, dd, $J$=8, 5 Hz, C(4)H), 4.13 (1H, d, $J$=5 Hz, C(2)H), 2.74 (1H, dd, $J$=10, 4 Hz, C(6a)H), 2.63–2.53 (1H, m, allylic $CH_2$), 2.42–.33 (2H, m, allylic $CH_2$ and C(3)H), 2.00–1.90 (2H, m, C(5)H *exo*, C(6)H *exo*), 1.89–1.80 (1H, m, C(6)H *endo*), 1.45–1.33 (1H, m, C(5)H *endo*), 0.91 (9H, s, C$Me_3$), 0.90 (9H, s, C$Me_3$), 0.18 (3H, s, Si*Me*), 0.16 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 216.6 (C═O), 137.4 (*C*H═$CH_2$), 116.3 (CH═*C*$H_2$), 90.0 (*C*OSi), 82.4 (*C*HOSi), 76.6 (*C*HOH), 55.8 (*C*HCO), 44.5 (homoallylic *C*H), 33.7 (*C*$H_2$CHOSi), 28.3 (allylic *C*$H_2$), 25.8 (C$Me_3$), 25.8 (C$Me_3$), 23.0 ($CH_2$), 18.3 (*C*$Me_3$), 17.9 (*C*$Me_3$), −2.3 (Si*Me*), −2.4 (Si*Me*), −4.1 (Si*Me*), −4.8 (Si*Me*); *m*/*z* (CI+) 458 (100%, M +$NH_4^+$), (Found (ES+) M+$NH_4^+$ 458.3126, $C_{23}H_{48}NO_4Si_2$ requires 458.3122); data for *endo*-**3**: $R_f$ 0.39 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/cm$^{-1}$ 3480w, 2956s, 2938s, 1749s, 1362w, 1096s, 836s, 775s; $\delta_H$ (400 MHz, $D_2O$ in $CDCl_3$) 6.09 (1H, dddd, $J$=17, 10, 8, 6 Hz, C*H*═$CH_2$), 5.17 (1H, dm, $J$=17 Hz, CH═C$H_2$), 5.06 (1H, dm, $J$=8 Hz, CH═C$H_2$), 4.37 (1H, dd, $J$=13, 3 Hz, C(2)H), 4.13 (1H, dd, $J$=11, 6 Hz, C(4)H), 2.90–2.85 (1H, m, allylic $CH_2$), 2.68–2.63 (1H, m, C(6a)H), 2.47–2.35 (1H, m, allylic $CH_2$), 2.09–1.80 (4H, m, C(3)H, C(6)H *exo* and *endo*, C(5)H *exo*), 1.36–1.26 (1H, m, C(H)5 *endo*), 0.94 (9H, s, C$Me_3$), 0.91 (9H, s, C$Me_3$), 0.14 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*), 0.10 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 216.0 (C═O), 138.5 (*C*H═$CH_2$), 115.4 (CH═*C*$H_2$), 86.1 (*C*OSi), 82.8 (*C*HOSi), 80.5 (*C*HOH), 54.1 (*CH*CO), 46.9 (homoallylic *C*H), 35.1 (allylic *C*$H_2$), 32.9 (*C*$H_2$CHOSi), 25.8 (2×C$Me_3$), 21.6 (*C*$H_2$), 18.3 (*C*$Me_3$), 17.9 (*C*$Me_3$), −2.5 (Si*Me*), −2.6 (Si*Me*), −4.1 (Si*Me*), −4.8 (Si*Me*); *m*/*z* (CI+) 458 (100%, M+$NH_4^+$), (Found (ES+) M+$NH_4^+$ 458.3127, $C_{23}H_{48}NO_4Si_2$ requires 458.3122).

**4.1.11. (4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2*H*-pentalen-1-one 19.** DBU (117 μL, 0.78 mmol) was added to a stirred solution of ketone **14** (150 mg, 0.39 mmol) in anhydrous MeCN (3.0 mL), and stirred at 25°C for 2 days. The solvent was evaporated and the crude mixture was subjected to flash chromatography (7:3 petroleum ether/$Et_2O$) to give the enone **19** (88 mg, 90%) as a colourless oil; $R_f$ 0.19 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/cm$^{-1}$ 2954s, 2938s, 1705s, 1257m, 1096m, 838m, 775m; $\delta_H$ (200 MHz) 5.00–4.93 (1H, m, C(4)H), 2.77–2.60 (4H, m), 2.57–2.31 (2H, m), 2.30–2.08 (2H, m), 0.92 (9H, s, C$Me_3$), 0.12 (3H, s, Si*Me*), 0.11 (3H, s, Si*Me*); $\delta_C$ (50 MHz) 204.6 (C═O), 184.8 (C═*C*CHOSi), 148.9 (*C*═CCHOSi), 74.7 (*C*HOSi), 40.8, 38.9, 25.8 (C$Me_3$), 23.3, 22.8, 18.3 (*C*$Me_3$), −4.6 (Si*Me*), −4.8 (Si*Me*); *m*/*z* (CI+) 140 (100%), 123 (70), 270 (40), 253 (30); (Found (ES+) M+$H^+$ 253.1622, $C_{14}H_{25}O_2Si$ requires 253.1624); the ee (80%) was determined by chiral GC (100–140°C, 1°C min$^{-1}$, 1 mL min$^{-1}$) $t_R$mj, 116.0; $t_R$mn, 121.4.

**4.1.12. (3*S*,4*S*)-3-Allyl-4-(*tert*-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2*H*-pentalen-1-one 20.** DBU (152 μL, 1.02 mmol) was added to a stirred solution of ketone **17** (288 mg, 0.69 mmol) in anhydrous MeCN (3.0 mL), and stirred at 25°C for 2 days. The solvent was evaporated and the crude mixture was subjected to flash chromatography (8:2 petroleum ether/$Et_2O$) to give the enone **20** (190 mg, 94%) as a colourless oil. $[\alpha]_D^{25}$=−35.3 (*c* 1.0, $CHCl_3$); $R_f$ 0.40 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/cm$^{-1}$ 2956s, 2936s, 1704s, 1253m, 1098m, 836m, 775m; $\delta_H$ (400 MHz) 5.71 (1H, ddt, $J$=17, 10, 7 Hz, C*H*═$CH_2$), 5.06 (1H, dm, $J$=17 Hz, CH═C$H_2$), 5.06–5.04 (1H, m, CH═C$H_2$), 5.02 (1H, br t, $J$=6 Hz, C(4)H), 3.08–3.00 (1H, m, C(2)H), 2.85 (1H, dd, $J$=19, 6 Hz, allylic $CH_2$), 2.68–2.60 (1H, m, C(3)H), 2.50–2.40 (2H, m), 2.41 (1H, dd, $J$=19, 2 Hz, allylic $CH_2$), 2.28–2.19 (1H, m), 2.15–2.05 (2H, m), 0.91 (9H, s, C$Me_3$), 0.12 (3H, s, Si*Me*), 0.11 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 203.5 (C═O), 186.8 (C═*C*CHOSi), 148.9 (*C*═CCHOSi), 134.9 (CH═*C*$H_2$), 117.4 (*C*H═$CH_2$), 73.0 (*C*HOSi), 46.3, 38.9, 36.6, 34.7 (homoallylic *C*H), 25.7 (C$Me_3$), 22.8, 18.0 (*C*$Me_3$), −4.4 (Si*Me*), −4.9 (Si*Me*); *m*/*z* (CI+) 161 (100%, M−31), 293 (80, $MH^+$); (Found (ES+) M+$H^+$ 293.1934, $C_{17}H_{29}O_2Si$ requires 293.1937).

**4.1.13. (2*R*,3*R*,4*S*)-3-Allyl-4-(*tert*-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2-hydroxy-2*H*-pentalen-1-one 22 and (2*S*,3*R*,4*S*)-3-allyl-4-(*tert*-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2-hydroxy-2*H*-pentalen-1-one *epi*-22.** KOH (432 mg, 7.68 mmol) in dry MeOH (4 mL) was stirred until dissolved, then the solution was cooled to −15°C and a solution of **20** (150 mg, 0.51 mmol) in MeOH (2 mL) was added. After 15 min, $PhI(OAc)_2$ (249 mg, 0.78 mmol) was added in one portion. The reaction mixture was stirred at −15°C for 1 h and then at 25°C for 2 h and concentrated under reduced pressure to give the crude α′-hydroxydimethylacetals **21** [7:1 mixture as determined by $^1$H NMR of C(2)H, for **21** $\delta_H$ (400 MHz) 4.40 (d, $J$=7 Hz) and for *epi*-**21** $\delta_H$ 4.01 (d, $J$=5 Hz)]. [In a separate experiment column chromatography (8:2 petroleum ether/$Et_2O$) gave separable **21** and *epi*-**21**, as well as compounds **22**. While **21** was stable enough to be characterised by NMR, *epi*-**21** was almost immediately hydrolysed in $CDCl_3$. Data for **21**: $\delta_H$ (250 MHz, $CDCl_3$ in $D_2O$) 5.97–5.80 (1H, m, C*H*═$CH_2$), 5.07 (1H, dm, $J$=17 Hz, CH═C$H_2$), 5.02–4.96 (1H, brd, $J$=10 Hz, CH═C$H_2$), 4.89–485 (1H, m, C(4)H), 4.42 (1H, d, $J$=7 Hz, C(2)H), 3.40 (3H, s, OMe), 3.35 (3H, s, OMe), 2.86–2.76 (1H, m), 2.76–2.23 (4H, m), 2.05–1.87 (2H, m), 0.90 (9H, s, C$Me_3$), 0.09 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); $\delta_C$ (63 MHz) 155.0 (*C*═*C*), 143.9 (C═*C*), 138.0 (CH═*C*$H_2$), 115.4 (CH═*C*$H_2$), 80.3 (*C*HO), 74.1 (*C*HO), 50.6 (OMe), 50.2 (OMe), 41.2 (homoallylic *C*H), 38.0, 33.8, 27.3, 25.8 (C$Me_3$), 18.1 (*C*$Me_3$), −4.3 (Si*Me*), 4.7 (Si*Me*)]. Crude **21** was dissolved in $CH_2Cl_2$ and treated with 10% sulphuric acid at 25°C for 10 min. After neutralisation with saturated aq. $NaHCO_3$ and extraction with ether, the combined organic layers were dried and removed under vacuum. Flash chromatography (7:3 petroleum ether/$Et_2O$) gave **22** (110 mg, 70%) and *epi*-**22** (16 mg, 10%); data for **22**: $[\alpha]_D^{25}$=−49.6 (*c* 1.0, $CHCl_3$), $R_f$ 0.24 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/cm$^{-1}$ 3424m, 2954s, 2930s, 1713s, 1638m, 1471m, 1255s, 837s, 776m; $\delta_H$ (400 MHz) 5.75 (1H, ddt, $J$=17, 10, 7 Hz, C*H*═$CH_2$), 5.06 (1H, dm, $J$=17 Hz, CH═C$H_2$), 5.00 (1H, dm, $J$=10 Hz, CH═C$H_2$), 4.96 (1H, m, C(4)H), 4.51 (1H, dd, $J$=6, 3 Hz, C(2)H), 3.28–3.21 (1H, m, C(3)H), 2.95 (1H, d, $J$=3 Hz, OH), 2.64–2.56 (1H, m), 2.54–2.42 (2H, m), 2.35–2.23 (2H, m), 2.11–2.02 (1H, m), 0.92 (9H, s, C$Me_3$), 0.14 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 204.0 (C═O), 184.0 (C═*C*CHOSi), 144.7 (*C*═CCHOSi), 136.1 (*C*H═$CH_2$), 116.9 (CH═*C*$H_2$), 78.9 (*C*HOH), 73.5

(*C*HOSi), 40.0 (homoallylic *C*H), 37.9, 33.4, 25.7 (C*Me*$_3$), 23.1, 18.1 (*C*Me$_3$), −4.4 (Si*Me*), −4.8 (Si*Me*); *m/z* (CI+) 149 (100%), 309 (80); 131 (65), (Found M+H$^+$ 309.1883, $C_{17}H_{29}SiO_3$ requires 309.1886); data for *epi*-**22**: $[\alpha]_D^{25}$= −64.0 (*c* 1.0, $CHCl_3$), $R_f$ 0.18 (50% $Et_2O$/petroleum ether); $\nu_{max}$(thin film)/cm$^{-1}$ 3428w, 2930s, 2857s, 1713s, 1472w, 1340w, 1257s, 838s, 776s; $\delta_H$ (400 MHz) 5.82 (1H, ddt, *J*=17, 10, 7 Hz, C*H*=CH$_2$), 5.19 (1H, dm, *J*=17 Hz, CH=C*H*$_2$), 5.13 (1H, dm, *J*=10 Hz, CH=C*H*$_2$), 5.07 (1H, dm, *J*=6 Hz, C(4)H), 4.15 (1H, d, *J*=3 Hz, C(2)H), 2.97–2.90 (1H, m, C(3)H), 2.95 (1H, br s, OH), 2.66–2.59 (2H, m), 2.57–2.51 (1H, m), 2.34–2.25 (2H, m), 2.12–2.06 (1H, m), 0.91 (9H, s, C*Me*$_3$), 0.13 (3H, s, Si*Me*), 0.11 (3H, s, Si*Me*). $\delta_C$ (100 MHz) 203.2 (C=O), 184.2 (C=*C*CHOSi), 145.8 (*C*=CCHOSi), 135.1 (CH=*C*H$_2$), 118.3 (*C*H=CH$_2$), 82.4 (*C*HOH), 74.1 (*C*HOSi), 44.7 (*C*H), 38.3, 34.7, 26.1 (C*Me*$_3$), 23.8, 18.4 (*C*Me$_3$), −3.8 (Si*Me*), −4.5 (Si*Me*); *m/z* (CI+) 148 (100%), 70 (35), 131 (20); (Found M+H$^+$ 309.1882, $C_{17}H_{29}SiO_3$ requires 309.1886).

**4.1.14. (2*R*,3*R*,4*S*)-3-Allyl-3,4,5,6-tetrahydro-2,4-dihydroxy-2*H*-pentalen-1-one, xialenon A (1).** To a solution of **22** (85 mg, 0.28 mmol) in THF (10 mL) was added TBAF (1.0 M solution in THF, 0.50 mL, 0.50 mmol) at 0°C. After 2 h, the reaction mixture was quenched with water (10 mL) and extracted with ether (3×25 mL). The combined organic phases were dried and the solvent was removed under vacuum. The residue was subjected to flash column chromatography (1:3 petroleum ether/$Et_2O$) to give xialenon A (**1**) (49 mg, 88%) as a colourless oil; $[\alpha]_D^{25}$=−83.3 (*c* 0.54, MeOH) [lit.[1] $[\alpha]_D^{25}$=−108.0 (*c* 0.66, MeOH)], $R_f$ 0.33 (10% MeOH/$CH_2Cl_2$); $\nu_{max}$(thin film)/cm$^{-1}$ 3368s, 2934w, 2860w, 1699s, 1630m, 1438w, 1050s, 920s; $\delta_H$ (400 MHz) 5.83 (1H, dddd, *J*=17, 10, 8, 7 Hz, C*H*=CH$_2$), 5.12 (1H, dq, *J*=17, 2 Hz, CH=C*H*$_2$), 5.06 (1H, dm, *J*=10 Hz, CH=C*H*$_2$), 5.03 (1H, br dd, *J*=6 Hz, C(4)H), 4.50 (1H, d, *J*=6 Hz, C(2)H), 3.34–3.29 (1H, m, C(3)H), 2.79 (1H, br s, OH), 2.74–2.66 (1H, m, C(5)H), 2.63–2.55 (1H, m), 2.54–2.49 (1H, m), 2.36 (1H, dddd, *J*=16, 6, 3, 2 Hz, C(6)H), 2.20–2.07 (2H, m); $\delta_C$ (100 MHz) 204.0 (C=O), 183.7 (C=*C*CHOH), 145.5 (*C*=CCHOH), 136.2 (CH=*C*H$_2$), 117.2 (*C*H=CH$_2$), 78.6 ((*C*CO), 73.3 (*C*HOH), 40.0 (*C*H), 37.2, 33.4, 23.1; *m/z* (CI+) 195 (100%, M+H$^+$), (Found M+H$^+$ 195.1027, $C_{11}H_{15}O_3$ requires 195.1021); the ee (80%) was determined by chiral HPLC (50:50 EtOH/heptane, 0.1 mL min$^{-1}$) $t_R$mj, 52.1; $t_R$mn, 43.7.

**4.1.15. (3a*R*,4*S*,6a*R*)-3-Allyl-3a,4-bis(*tert*-butyldimethylsilyloxy)-4,5,6,6a-tetrahydro-2-hydroxy-3a*H*-pentalen-1-one 23.** Cu(OAc)$_2$·H$_2$O (37 mg, 0.19 mmol) was added in one portion to a solution of **3** (41 mg, 0.09 mmol) in MeOH (3 mL) at 25°C. After being stirred for 24 h, the reaction was hydrolysed with water (10 mL) and extract with ether (3×15 mL). The combined organic layers were dried and concentrated to leave a residue. Flash column chromatography (7:3 petroleum ether/$Et_2O$) gave hydroxyenone **23** (33 mg, 80%) as an oil; $R_f$ 0.51 (50% $Et_2O$/petroleum ether); $\delta_H$ (400 MHz) 6.08 (1H, dddd, *J*=17, 10, 7, 6 Hz, C*H*=CH$_2$), 6.00 (1H, s, OH), 5.18 (1H, dm, *J*=17 Hz, CH=C*H*$_2$), 5.09 (1H, dq, *J*=10, 2 Hz, CH=C*H*$_2$), 4.08–4.05 (1H, m, C(4)H), 3.26 (1H, ddt, *J*=17, 6, 2 Hz, allylic CH$_2$), 3.18 (1H, ddt, *J*=17, 7, 1 Hz, allylic CH$_2$), 2.62 (1H, br dd, C(6a)H), 1.87–1.76 (3H, m), 1.49–1.36 (1H, m), 0.89 (9H, s, C*Me*$_3$), 0.85 (9H, s, C*Me*$_3$), 0.08 (3H, s, Si*Me*), 0.05 (3H, s, 2×Si*Me*), 0.03 (3H, s, Si*Me*); $\delta_C$ (100 MHz) 202.0 (C=O), 149.9 (*C*OH=C), 143.5 (COH=*C*), 134.0 (*C*H=CH$_2$), 116.4 (CH=*C*H$_2$), 88.2 (*C*OSi), 81.4 (*C*HOSi), 53.8 (*CH*CO), 32.5 (*C*H$_2$), 31.5 (*C*H$_2$), 25.9 (C*Me*$_3$), 25.8 (C*Me*$_3$), 22.1 (*C*H$_2$), 18.2 (*C*Me$_3$), 18.0 (*C*Me$_3$), −3.1 (Si*Me*), −3.2 (Si*Me*), −4.5 (Si*Me*), −4.9 (Si*Me*).

**4.1.16. (3a*R*,4*S*,6a*R*)-3-Allyl-4,5,6,6a-tetrahydro-2,3a,4-trihydroxy-3a*H*-pentalen-1-one 24.** HF (40 % w/w $H_2O$; 1 mL, 22.0 mmol) was added to a stirred solution of **23** (35 mg, 0.08 mmol) in MeCN (3 mL) at 25°C. After 1 h the reaction was neutralised with a saturated aq. $NaHCO_3$, and after filtration the solvent was evaporated under reduced pressure. Flash column chromatography (1:20 MeOH/$CH_2Cl_2$) gave **24** (12 mg, 70%); $R_f$ 0.54 (10% $Et_2O$/methanol); $\delta_H$ (400 MHz, $CD_3OD$) 6.07 (1H, ddt, *J*=17, 10, 7 Hz, C*H*=CH$_2$), 5.16 (1H, dm, *J*=17 Hz, CH=C*H*$_2$), 5.01 (1H, br dq, *J*=10 Hz, CH=C*H*$_2$), 4.10 (1H, dd, *J*=7, 5 Hz, C(4)H), 3.30–3.20 (2H, m, allylic CH$_2$), 2.43 (1H, dd, *J*=9, 4 Hz, C(6a)H), 2.02–1.94 (1H, m), 1.92–1.83 (1H, m), 1.77–1.70 (1H, m), 1.55–1.47 (1H, m); $\delta_C$ (100 MHz, $CD_3OD$) 203.0 (C=O), 151.1(*C*OH=C), 143.5 (COH=*C*), 135.0 (*C*H=CH$_2$), 115.1 (CH=*C*H$_2$), 86.3 (*C*OH), 78.9 (*C*HOH), 56.4 (*CH*CO), 33.1 (*C*H$_2$), 30.8 (*C*H$_2$), 22.1(*C*H$_2$).

**4.1.17. (3a*R*,4*S*,6a*R*)-3-Allyl-3a-(*tert*-butyldimethylsilyloxy)-4,5,6,6a-tetrahydro-2,4-dihydroxy-3a*H*-pentalen-1-one 25.** $H_2SiF_6$ (20–25% w/w in $H_2O$; 100 μL, 0.22 mmol) was added to a stirred solution of **23** (39 mg, 0.09 mmol) in MeCN/*tert*-butanol (9:1, 3 mL). After 24 h the reaction was neutralised with saturated aq. $NaHCO_3$ (10 mL) and extracted with ether. The organic layer was dried and concentrated to leave a residue. Flash column chromatography (1:1 petroleum ether/$Et_2O$) gave **24** (2 mg, 12%), **25** (10 mg, 35%) and starting material **23** (14 mg, 35%); data for **25**: $R_f$ 0.25 (1:1 petrol/ether); $\delta_H$ (400 MHz, $CDCl_3$) 6.11 (1H, dddd, *J*=17, 10, 8, 7 Hz, C*H*=CH$_2$), 5.27 (1H, dq, *J*=17, 2 Hz, CH=C*H*$_2$), 5.18 (1H, dq, *J*=10, 2 Hz, CH=C*H*$_2$), 4.05 (1H, br dd, *J*=5 Hz, C(4)H), 3.33 (1H, ddm, *J*=15, 6 Hz, allylic CH$_2$), 3.15 (1H, ddm, *J*=15, 8 Hz, allylic CH$_2$), 2.70 (1H, dd, *J*=10, 5 Hz, C(6a)H), 2.10–2.02 (1H, m), 1.98–1.82 (2H, m), 1.72–1.65 (1H, m), 0.91 (9H, s, C*Me*$_3$), 0.09 (3H, s, Si*Me*), 0.06 (3H, s, Si*Me*).

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24. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 221381 (**13**) and CCDC 221382 (**6**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
25. For the preparation of $Pr^{i}Li$, see: http://www.syntheticpages.com/search.php.