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Enantioselective total synthesis of (–)-xialenon A

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The first total synthesis of (−)-xialenon A (1) *via* conjugate allylation of a 1,5-cyclooctadiene-derived bicyclo[3.3.0]octenone 3 and an α′-hydroxylation on the more hinderd face of enone 9 using hypervalent iodine chemistry, is described.

Xialenon A (**1**) and its more highly oxygenated congeners are naturally occurring secondary metabolites recently isolated by Thiericke and coworkers from culture broths of the *Streptomyces* genus (Fig. 1).[1] The xialenons all possess a bicyclo[3.3.0]octane skeleton, which is rarely found without additional rings appended 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.

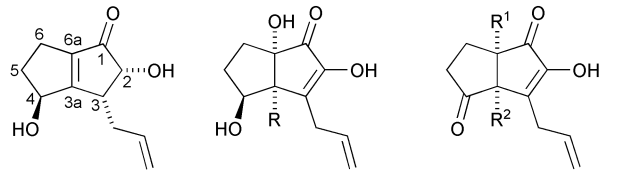
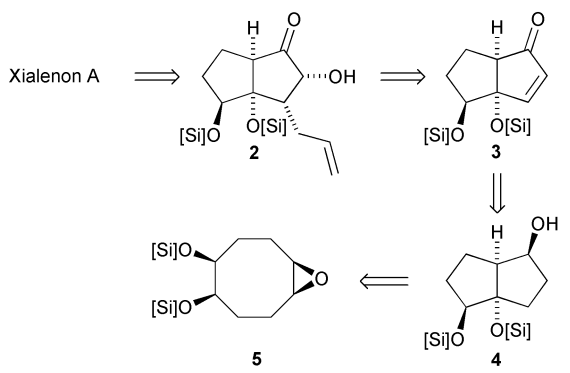


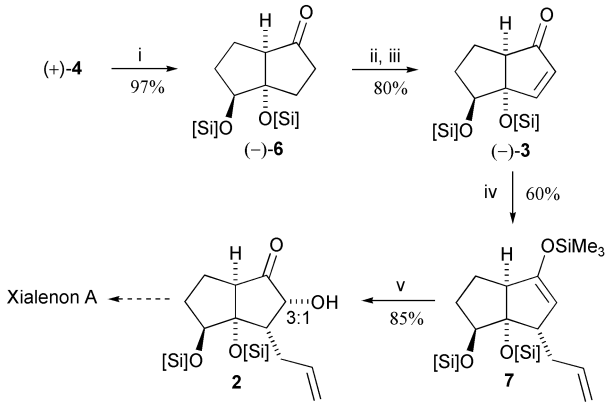
Fig. 1

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 cyclooctene oxide **5** ([Si] = $SiMe_2Bu^t$) using organolithium/(−)-sparteine (or (−)-α-isosparteine) combinations,[2,3] we considered that alcohol **4** could be used to address the above issues and, if successful, provide an attractive entry point to the xialenons, especially (−)-xialenon A (**1**) (Scheme 1). Thus, we planned to elaborate the alcohol **4** into the enone **3**. It was anticipated that the envelope shape of enone **3** should bias both allyl conjugate addition and, hopefully, oxidation of the intermediate enolate from the convex face to give hydroxyketone **2** with the desired stereochemistry; xialenon A would then be obtained *via* elimination of the tertiary silyloxy group.



Scheme 1

Alcohol (+)-**4** (80% ee) was efficiently prepared in four steps from 1,5-cyclooctadiene as previously described.[2] Conversion of alcohol **4** to the enone **3** was best effected in a stepwise manner *via* oxidation[4] to the ketone **6** (97% yield, Scheme 2), followed by further oxidation of the derived enol ether using $Pd(OAc)_2$ (80% yield from ketone **6**).[5] The more concise oxidation procedures recently reported by Nicolaou *et al.*[6] were less effective in the present case. With enone **3** in hand, introduction of the allyl side-chain and *in situ* silyl enol ether formation were performed using the procedure of Lipshutz and coworkers.[7] The corresponding silyl enol ether **7** or allylated ketone (+)-**8** were obtained (depending on if the reaction was worked-up with a saturated solution of NH_3 (aq)/NH_4Cl, or with water first for 30 min then addition of a saturated solution of NH_3 (aq)/NH_4Cl) in 60% yield and with complete stereoselectivity. That delivery of the allyl group had occurred to the convex face of enone **3** was supported by NOE analysis of allylated ketone **8** (and, ultimately, by synthesis of **1**). Rubottom oxidation[8] of silyl enol ether **7** gave hydroxyketone **2** as an easily separable mixture of epimers (85% yield in total, 3:1 in favour of the desired diastereomer, as determined by NOE experiments).†



Scheme 2 *Reagents and conditions:* i, TPAP (5%), NMO (1.5 eq.), 4Å sieves, CH_2Cl_2, 25 °C, 1 h; ii, LDA (2 eq.), Me_3SiCl (2 eq.), THF, −78 °C to 25 °C, 3 h; iii, $Pd(OAc)_2$ (1 eq.), MeCN, 25 °C, 12 h; iv, (allyl)MgBr (5.5 eq.), CuI (6.25 eq.), LiBr (6.25 eq.), Me_3SiCl (5.5 eq.), THF, −78 °C, 1 h; v, MCPBA (1.5 eq.), $KHCO_3$ (5.0 eq.), hexane, −15 °C to 25 °C, 3 h.

In model studies on the key elimination (*cf.* **2** to **1**) using ketone **6** we found that either acid (*e.g.* 3 equiv. of PPTS in Bu^tOH at reflux for 24 h) or base (*e.g.* 2 equiv. of DBU in MeCN at 25 °C for 48 h) effected elimination of the tertiary silyloxy group. Unfortunately, application of all of these methods to hydroxyketone **2** only resulted in its complete decomposition. Suspecting that the presence of the hydroxyl

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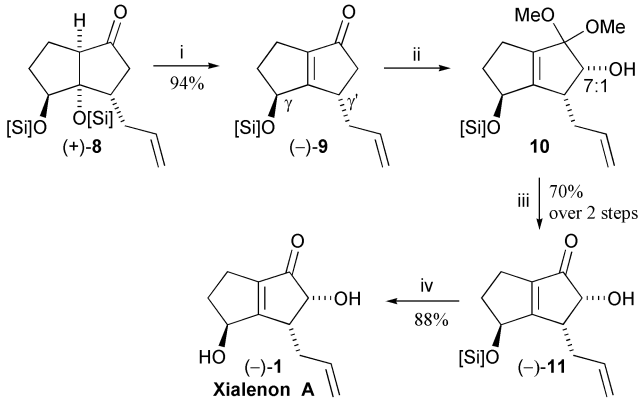
group in hydroxyketone **2** was the origin of the problem, we investigated reversing the sequence of elimination and hydroxylation steps. In order to examine hydroxylation by this latter strategy, enone **9** was prepared in 94% yield from allylated ketone **8** *via* a smooth (E1cB) elimination using DBU in MeCN (Scheme 3).



Scheme 3 *Reagents and conditions:* i, DBU (1.5 eq.), MeCN, 25 °C, 48 h; ii, $PhI(OAc)_2$ (1.5 eq.), KOH (15.0 eq.), MeOH, −15 to 25 °C, 3 h; iii, H_2SO_4 (10%), CH_2Cl_2, 25 °C, 10 min. iv, TBAF (2.0 eq.), THF, 0 °C, 1 h.

Many procedures are known for the oxidation of an α,β-unsaturated ketone to an α′-acetoxyenone or α′-hydroxyenone,[9] but most of them would likely oxidise enone **9** from the undesired, less-hindered face (*trans* to the allyl side chain). 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.[10] In the event, when enone **9** was exposed to a solution of KOH in dry MeOH at −15 °C for 15 min, followed by addition of iodobenzene diacetate (IBD), a mixture of α′-hydroxydimethylacetals **10** was obtained (7:1, as determined by ^{1}H NMR analysis of the H-2 signals). The crude mixture of α′-hydroxydimethylacetals **10**, 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 **11** and 10% of the isomer epimeric at the hydroxyl group.‡ 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).[10,11] In the present case, the presence of both the γ-silyloxy group and the γ′-allyl side chain on opposite faces of enone **9** may be shielding[11] the enone system from such unwanted side reactions.

Desilylation of hydroxyenone **11** using TBAF in THF gave (−)-xialenon A (**1**) {88% yield, $[\alpha]_D^{25}$ −83.3 (*c* 0.54, MeOH) [lit.,[1] $[\alpha]_D$ −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 (+)-**4** 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 and coworkers,[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.[12]

In summary, we have accomplished the first total synthesis of xialenon A in 12 steps from 1,5-cyclooctadiene *via* the previously known alcohol **4**. The allyl side chain has been introduced with complete stereoselectivity, and a highly stereoselective α′-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.

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Notes and references

† For the major epimer **7** NOEs were observed between H-2 and H-5/H-6. For the minor epimer **7** NOEs were observed between H-2 and H-6a and no NOEs were detected between H-2 and H-3.

‡ The *cis* relative stereochemistry between C-2 and C-3 in hydroxyenone **11** was provisionally assigned from the larger ^3J value between H-2 and H-3 (6.1 Hz) relative to that observed for C-2 epi-**11** (2.5 Hz), and comparison with ^3J between H-2 and H-3 (6.1 Hz) reported for natural xialenon A (**1**)[1] and, ultimately, by conversion of **11** to **1**.

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