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## Synthesis of (–)-Gloeosporone, a fungal autoinhibitor of spore germination using a $\pi$ -allyltricarbonyliron lactone complex as a templating architecture for 1,7-diol construction †

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The synthesis of the germination self-inhibitor (-)-Gloeosporone is reported. The embedded 1,7-diol motif in the product is constructed by an ironcarbonyl tether controlled Mukaiyama aldol reaction. The key step in the synthesis is the reductive removal of the ligating iron species by treatment of an acetoxycomplex 6 with lithium naphthalenide.

The isolation of the germination self-inhibitor (-)-Gloeosporone 1, from conidia of *Collectotrichum gloeosporioides*,<sup>1</sup> aroused considerable interest both structurally and for its biological properties. The synthesis of the now accepted correct macrocyclic structure (Fig. 1) has been reported by several groups.<sup>2</sup>



Fig. 1 (-)-Gloeosporone.

Here we wish to report a conceptually different synthetic approach using a  $\pi$ -allyltricarbonyliron lactone complex,<sup>3</sup> as the templating architecture to set-up the embedded 1,7-diol motif of the natural product. We have previously reported on the use of such complexes in natural product synthesis,<sup>4</sup> however, we wish to exploit not only the stereocontrolling aspects of these complexes,<sup>5</sup> but also a new reductive detachment of the ligating iron species using lithium napthalenide.<sup>6</sup>

The synthesis begins with the known  $\pi$ -allyltricarbonyliron lactone complex 2.<sup>7</sup> This complex is available in gramme quantities by an established route in greater than 95% e.e. at the key C-6 stereogenic centre. Following our established protocol, treatment of a dichloromethane solution of 2 with TMSOTf in the presence of NEt<sub>3</sub> gave an intermediate trimethylsilyl enol ether in an 84% yield. This silyl enol ether was used immediately in the highly diastereoselective Mukaiyama aldol coupling reaction with 3-benzyloxy-propionaldehyde 3,<sup>8</sup> giving rise to alcohol 4 in a 63% yield after work-up with HF–pyridine complex in THF. Reprotection of the alcohol with TBSOTf, followed by stereoselective reduction with 'Bu<sub>3</sub>Al in a toluene–dichloromethane mixture gave the mono-protected diol 5 in an 83% yield over two steps. The acetate intermediate for the reductive removal of the ligating iron moiety 6 was prepared in a 98% yield upon treatment of **5** with acetic anhydride in dichloromethane (Scheme 1).



Scheme 1 Synthesis of key intermediate (6). Reagents and conditions: (a) TMSOTF, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 84%; (b) OHC(CH<sub>2</sub>)<sub>2</sub>OBn (3), BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C then Et<sub>3</sub>N, HF–pyr, THF, 63%; (c) TBSOTF, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 18 h, 100%; (d) 'Bu<sub>3</sub>Al (1 M solution in toluene), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min, 83%; (e) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C  $\rightarrow$  rt, 2 h, 98%.

In the next phase of the synthesis 6 was treated with lithium naphthalenide in THF at -78 °C, and on warming the reaction mixture to room temperature afforded an inseparable mixture of alkenes 7-E,E, 7-Z,E and 7-E,Z in an excellent 98% yield,<sup>6,9</sup> (Scheme 2). Reduction of the diene mixture with simultaneous benzyl deprotection gave mono-protected triol 8 (83%). The primary alcohol was then selectively oxidised to aldehyde 9 using Oshima conditions.<sup>10</sup> It was noted that in order for this reaction to proceed smoothly two equivalents of K2CO3 needed to be added to the reaction mixture, this afforded aldehyde 9 in a respectable 78% yield. Acylation of 9 with 4-pentenoyl chloride occurred in a 65% yield. This reaction was found to be capricious and often led to incomplete conversion which necessitated recycling of unreacted 9. Nevertheless 10 could be readily methylenated with methyl phosphonium chloride upon treatment with KO'Bu in THF,11 to provide the known precursor 11 to (-)-Gloeosporone.<sup>2g</sup>

Treatment of a boiling dichloromethane solution of compound 11 with 3 mol% of tricyclohexylphosphine[1,3-bis(2,4,6trimethylphenyl)-4,5-dihydroimidazol-2-ylidine][benzylidine]ruthenium(Iv)-dichloride (Grubbs' second generation RCM catalyst),<sup>12</sup> formed cyclic lactone 12-*E* and 12-*Z* as a 1 : 1 mixture of alkene isomers in a 99% yield. The conversion of alkene mixtures of 12 to the natural product, using KMnO<sub>4</sub> in acetic anhydride,<sup>13</sup> followed by desilylation/cyclisation upon treatment with HF in acetonitrile affords 1 in a 56% yield.<sup>2b,g</sup>

<sup>†</sup> Electronic supplementary information (ESI) available: experimental procedure and data for 7. See http://www.rsc.org/suppdata/ob/b3/ b308793j/



Scheme 2 Synthesis (-)-Gloeosporone intermediate 1. Reagents and conditions: (a) Li naphthalenide, THF,  $-78 \,^{\circ}\text{C} \rightarrow \text{rt}$ , 17 h, 98%; (b) Pd/C, H<sub>2</sub>, EtOAc, 12 h, 83%; (c) RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, benzene, K<sub>2</sub>CO<sub>3</sub> (2 eq.), rt, 20 h, 78%; (d) 4-pentenoylchloride, DMAP (6 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 0  $^{\circ}\text{C} \rightarrow \text{rt}$ , 3 h, 65%; (e) (Ph)<sub>3</sub>PCH<sub>3</sub>Cl, KO'Bu, THF, 0  $^{\circ}\text{C} \rightarrow \text{rt}$ , 85%; (f) RuCl<sub>2</sub>-(=CHPh)[1,3-ImH<sub>2</sub>]P(Cy)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 40  $^{\circ}$ C, 5 h, 99%; (g) KMnO<sub>4</sub>, Ac<sub>2</sub>O, then, HF, MeCN, 4 h, 56%.

In conclusion, this work demonstrates the applicability of  $\pi$ -allyltricarbonyliron lactone complexes for natural product synthesis. In particular the use of the new lithium naphthalenide decomplexation protocol is an especially attractive route to enantiopure 1,7-diol units.

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