COMMUNICATION

The use of π-allyltricarbonyliron lactone complexes in the synthesis of the resorcylic macrolides α- and β-zearalenol

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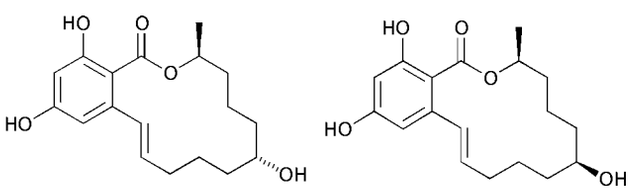
A highly stereoselective synthesis of α- and β-zearalenol 1 and 2 is accomplished utilising π-allyltricarbonyliron lactone complexes 5 and 6 to establish the 1,5-stereochemical relationship of oxygen functionalities present in the natural products.

The 14-membered resorcylic macrolides α- and β-zearalenol **1** and **2** are estrogenic mycotoxins produced by certain species



of the fungus *Fusarium*.[1] Their hormonal activity is linked to the close spatial similarity to 17β-estradiol,[2] with the α-isomer **1** being three to four times as active as the β-isomer **2**.[3] While several total syntheses of the parent compound zearalenone were accomplished over the last 30 years,[4] to our knowledge no independent synthesis of **1** or **2** has been reported so far. Here we report the first enantioselective preparation of **1** and **2** employing π-allyltricarbonyliron lactone complexes as key intermediates.

We have previously shown that organoaluminium reagents possessing active β-hydrogens, like tripropyl- and triisobutylaluminium, reduce carbonyl groups appended to the allyl ligand of π-allyltricarbonyliron lactone complexes with excellent diastereoselectivity.[5] Also, we recently reported that sodium triacetoxyborohydride efficiently decomplexes π-allyltricarbonyliron lactone complexes bearing a hydroxy group in the side-chain to afford stereodefined 1,5-diols.[6] By exploiting this methodology in this work, we show that π-allyltricarbonyliron lactone complexes can be used to set up the relative oxygen atom stereochemistry present in the natural products.

The route to α- and β-zearalenol **1** and **2** relied upon the formation of the π-allyltricarbonyliron lactone intermediates **5** and **6**, respectively, whose preparation is delineated in Scheme 1. Reduction of the ester **3**[7] using lithium aluminium hydride followed by Swern oxidation and Horner–Wadsworth–Emmons homologation with the phosphonate **18**,† prepared according to the methodology of Grieco,[8] gave the corresponding (*E*)-enone in 83% yield over three steps. Deprotection of the acetonide under acidic conditions and transformation of the liberated diol to the cyclic sulfite using thionyl chloride[9] afforded the compound **4** in 82% overall yield. Treatment of **4** with diironnonacarbonyl in benzene under sonication conditions[10] provided the two diastereoisomeric π-allyltricarbonyliron lactone complexes, *endo*-**5** and *exo*-**6**, in 70% combined yield and in a ratio of *ca.* 1:1. Separation of the two isomers **5** and **6** was readily achieved by flash column chromatography.

With these key intermediates in hand we were able to proceed to the target molecules α- and β-zearalenol **1** and **2** (Scheme 1). For example, for α-zearalenol **1**, reduction of the side-chain ketone in the *endo* complex **5** was achieved in 94% yield using tripropylaluminium[5] to give **7**, as the sole product as determined by 600 MHz ^{1}H NMR analysis. Treatment of **7** with sodium triacetoxyborohydride in tetrahydrofuran[6] resulted in a highly stereoselective decomplexation to afford, after TBDMS-protection and hydrogenation, the alcohol **8**. Swern oxidation of **8** provided the corresponding aldehyde which in turn was transformed into the vinylstannane **9** by applying the procedure developed by Hodgson[11] utilising chromium(II) chloride and Bu_3SnCHI_2 in *N*,*N*-dimethylformamide. Stille coupling of the stannane **9** with the known aromatic iodide **10**[4f] using Farina's catalyst[12] provided the coupled product **11** in 82% yield. Treatment of **11** with HF·pyridine followed by hydrolysis of the methyl ester functionality using aqueous potassium hydroxide in ethane-1,2-diol at 120 °C provided the seco acid **12** in 83% yield over two steps.

Cyclisation of **12** using Mukaiyama's protocol[13] afforded the desired MEM-protected α-zearalenol in 64% yield. Final deprotection of the MEM-ethers with aqueous hydrochloric acid in tetrahydrofuran at 40 °C provided α-zearalenol **1** in 93% yield and with a de of 94% as determined by 600 MHz ^{1}H NMR analysis {$[a]_D^{32}$ −93.6 (*c* 0.55 in acetone) [optical rotation obtained on an authentic sample‡ $[a]_D^{32}$ −97.3 (*c* 0.55 in acetone)]}.

Application of the same sequence of reactions to the *exo* complex **6** afforded the diastereoisomeric β-zearalenol **2** in similar overall yield *via* the intermediates **13** to **17**, as shown in Scheme 1 {de >95% as determined by 600 MHz ^{1}H NMR analysis; $[a]_D^{32}$ −12.5 (*c* 1.00 in acetone) [optical rotation obtained on an authentic sample‡ $[a]_D^{32}$ −12.9 (*c* 1.00 in acetone)]}.

These highly stereoselective syntheses of α- and β-zearalenol **1** and **2** clearly demonstrate the utility of carbonyl substituted π-allyltricarbonyliron lactone complexes in organic synthesis. Using the *endo* complex **5** as well as the *exo* complex **6** we were able to set up the required 1,5-stereochemical relationship of oxygen functionalities present in the natural products.

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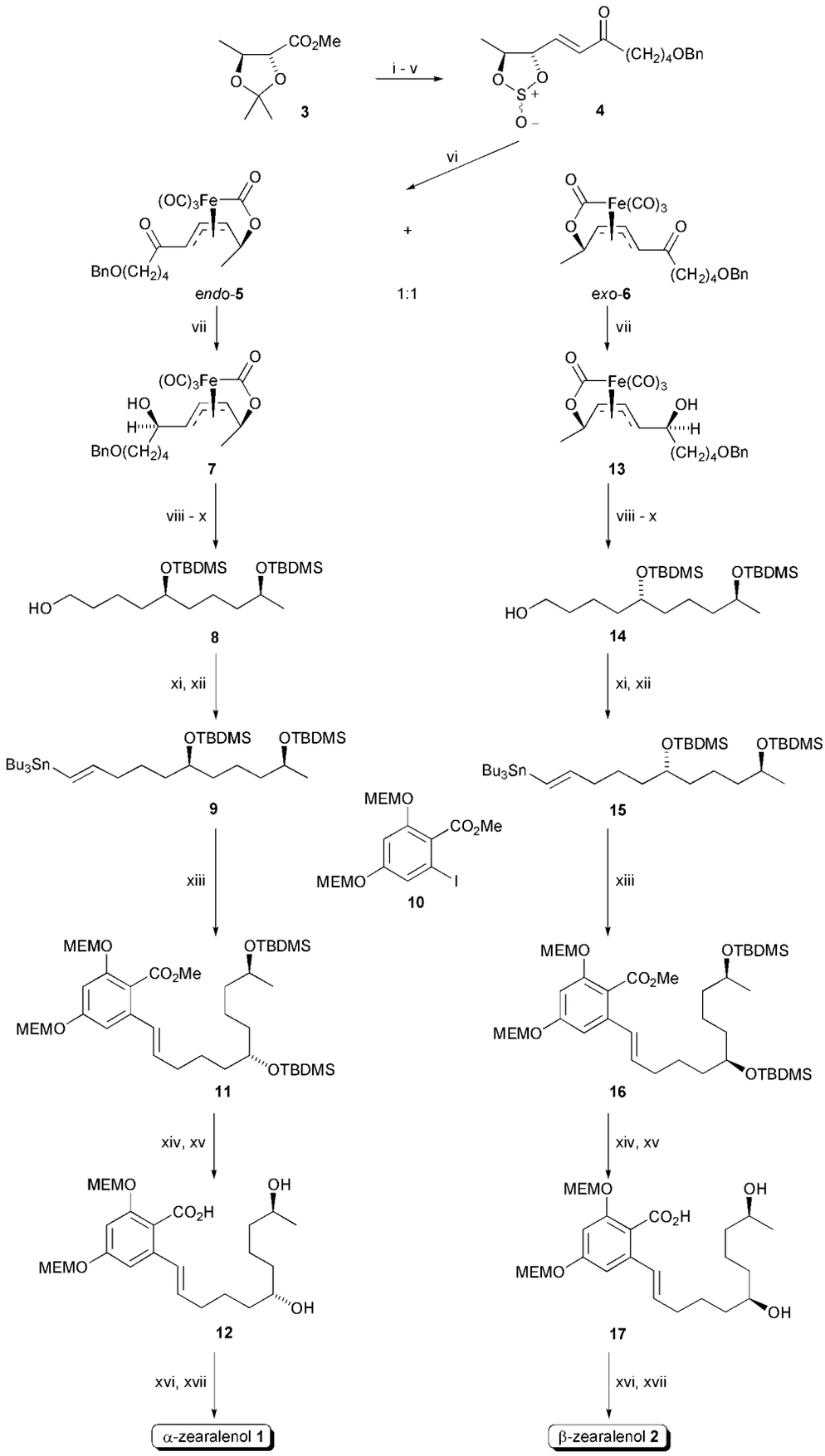

Scheme 1 *Reagents and conditions*: i. $LiAlH_4$, Et_2O, 0 °C, 2 h; ii. $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 3 h; iii. $(EtO)_2P(O)CH_2CO(CH_2)_4OBn$ **18**,† NaH, THF, −78 °C, 1 h, 83% (over 3 steps); iv. AcOH–H_2O (1 : 1), 40 °C, 24 h, 92%; v. $SOCl_2$, Et_3N, Et_2O, 0 °C, 30 min, 89%; vi. $Fe_2(CO)_9$, benzene, sonication, 30 °C, 3 h, 35% **5**, 35% **6**; vii. $AlPr^n_3$, DCM, 0 °C, 94% (80%);§ viii. $NaBH(OAc)_3$, THF, 3 d, 75% (83%); ix. TBDMSCl, imidazole, DMF, 0 °C, 30 min, then rt 24 h, 87% (85%); x. Pd/C (10%), H_2, EtOAc, 30 min, 94% (93%); xi. $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 3 h, 86% (80%); xii. Bu_3SnCHI_2, $CrCl_2$, DMF, 0 °C, 67% (69%); xiii. methyl 4,6-bis[(2-methoxyethoxy)methoxy]-2-iodobenzoate **10**, $Pd_2(dba)_3$, $P(2\text{-furyl})_3$, toluene, 100 °C, 4 h, 82% (85%); xiv. HF·pyridine, pyridine, THF, 12 h, 95% (93%); xv. 10 M aqueous KOH, ethane-1,2-diol, 120 °C, 4 h, 87% (91%); xvi. syringe pump addition of a solution of the seco acid and Et_3N in MeCN over 10 h to 1-methyl-2-chloropyridinium iodide, MeCN, reflux, 64% (62%); xvii. 1.5 M aqueous HCl, THF, 40 °C, 93% (93%).

Notes and references

† Compound **18** was prepared by alkylation of the dianion of diethyl (2-oxopropyl)phosphonate (NaH, BuLi, 0 °C) with benzyl 3-bromopropyl ether (82%).
‡ Authentic samples of α- and β-zearalenol were purchased from Sigma Aldrich.
§ Yields given refer to the synthesis of α-zearalenol **1**, while those given in parentheses correspond to the synthesis of β-zearalenol **2**.

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