Total Synthesis of the Phytotoxic Agent Herbarumin II Using Butane Diacetals of Glycolic Acid as Building Blocks

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Abstract: The total synthesis of the phytotoxic agent herbarumin II has provided an ideal stage to exploit the utility of butane diacetal (BDA) desymmetrised glycolic acid as a primary building block.

Key words: acetals, aldol, alkylation, asymmetric synthesis, natural products, metathesis

The quest for novel potential herbicidal agents led in the year 2000 to the isolation of two new nonenolides, herbarumin I (**1**) and II (**2**), from the culture of *Phoma erbarum* fungus (Figure 1).[1] These lactones showed high levels of phytotoxic effect on seedling growth and proved to be closely related to other known compounds such as pinolidoxin,[2] lethaloxin.[3] The typical structure of these natural products is characterised by a ten-membered macrolide core, a vicinal diol, a *trans*-substituted double bond and an appended *n*-propyl unit. Owing to their activity as potential new herbicides, these nonenolides have recently become attractive synthetic targets.[4] Here we report the synthesis of herbarumin II since it provides an ideal platform to demonstrate the utility of butane diacetal (BDA) desymmetrised glycolic acid as a building block for the stereoselective synthesis of functionalised α-hydroxyacids and polyol motifs.[5] In particular, our plan was to exploit the use of both enantiomers of these glycolic acid species, employing alkylation or aldol reactions to set up the key coupling compounds required for the synthesis.[5b,c]

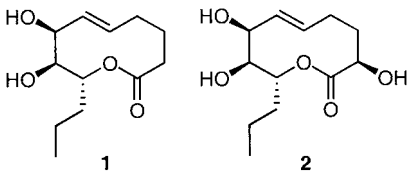
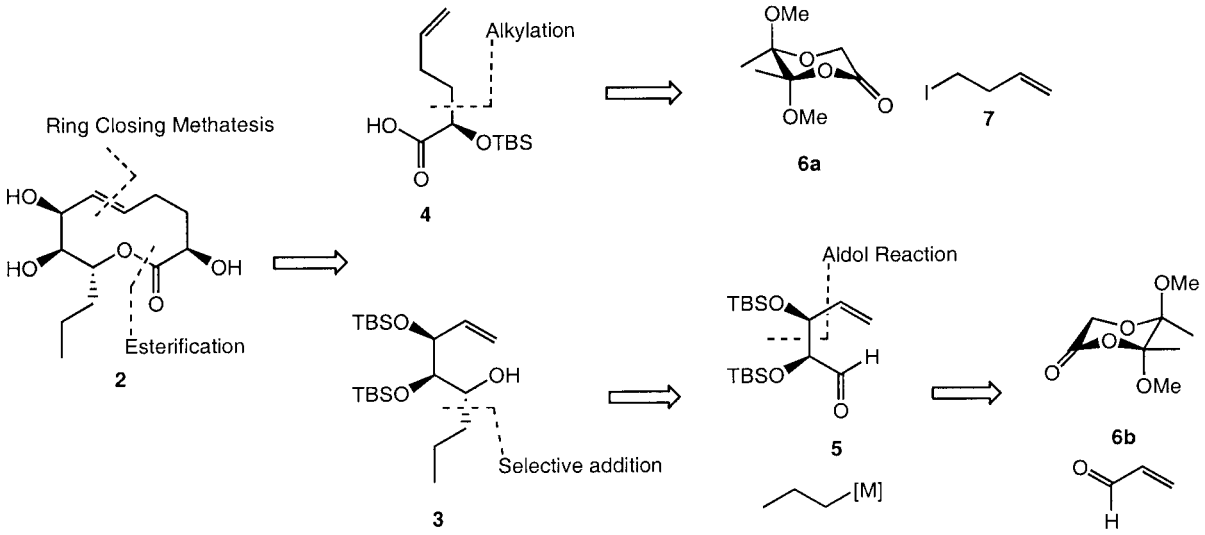


Figure 1 Structures of herbarumin I (**1**) and herbarumin II (**2**).

The synthetic plan for herbarumin II (**2**) (Scheme 1) relies on the union of two fragments **3** and **4** in a convergent fashion to give, after esterification, ring closing metathesis and deprotection, the desired natural product. The protected triol component **3** was expected to be derived by a non-chelation controlled addition of a propyl-metal reagent to aldehyde **5**, which, in turn, should be readily obtained from an aldol reaction between (*R*,*R*)-glycolate **6b** and acrolein.[6] Fragment **4** on the other hand should be easily obtained by alkylation of the enantiomeric (*S*,*S*)-glycolate **6a** with iodide **7**.[7]



Scheme 1 Synthetic plan.

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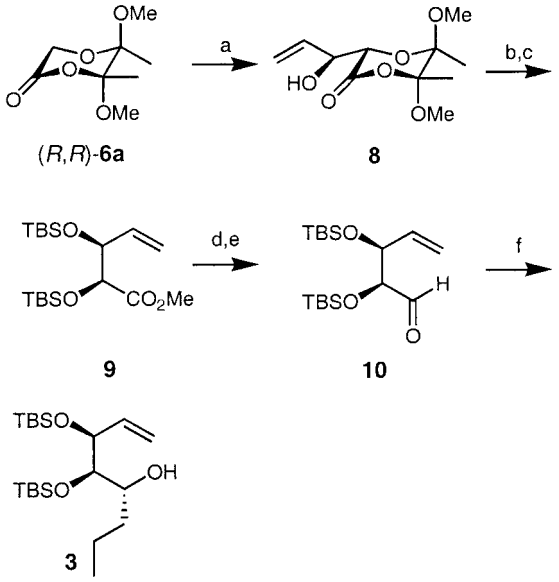
Accordingly, the aldol reaction between (*R*,*R*)-glycolate-**6b** and acrolein was performed in the usual way[5c] by deprotonation of the glycolate in THF at –78 °C followed by addition of the aldehyde to give alcohol **8** in 86% yield and better than 96% de.[8]

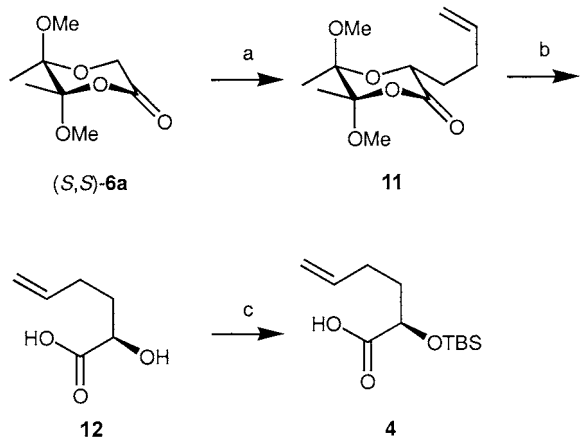
Deprotection of the butane diacetal using TMSCl in methanol gave the corresponding *anti*-1,2-diol methyl ester in 72% yield. Protection of the hydroxyl groups as their TBS ethers occurred in 96% yield to obtain **9**. From here, the desired aldehyde **10** was obtained in a two step procedure. Thus, DIBAL reduction of the ester functionality in THF at –30 °C gave the corresponding alcohol in 90% yield. This alcohol was immediately oxidised to the aldehyde **10** using PCC in dichloromethane at room temperature (Scheme 2).



Scheme 2 Synthesis of fragment **3**. a) LHMDS, THF, –78 °C, 20 min, acrolein, –78 °C, 1 h (86%); b) HCl, MeOH, r.t., 1 h (72%); c) TBSCl, Imidazole, DMF, r.t., on (96%); d) DIBAL, CH_2Cl_2, –30 °C, 1 h (90%); e) PCC, CH_2Cl_2, r.t., 1.5 h; f) *n*-PrMgCl, toluene, –78 °C, 2 h (dr >12:1, 68% over two step).

The only step remaining to obtain fragment **3** required a non-chelation controlled addition of an appropriate propylmetal nucleophile to aldehyde **10**. After several attempts using different organometallic compounds (*n*-PrLi, *n*-PrLi/$CeCl_3$, *n*-PrMgCl) under various reaction conditions and alternative solvents (THF, diethyl ether, toluene) it was found that the addition of *n*-PrMgCl in toluene at –78 °C gave the best results. Under these conditions the reaction proceeded with better than 12:1 diastereoselectivity ratio to give the alcohol **3** in 68% isolated yield over the last two steps (Scheme 2). The relative and absolute configuration of **3** was determined by examining Mosher ester derivatives of related compounds.[9]

Coupling partner **4** was obtained in just three steps from the enantiomeric (*S*,*S*)-glycolate **6a** (Scheme 3). The corresponding lithium enolate was obtained as before and then was allowed to react with an excess of iodide **7** to give **11** in 56% yield. Deprotection of the acetal using TFA/H_2O in the normal fashion gave hydroxy acid **12** in 87% yield and the following protection of the hydroxyl group as the TBS ether gave the desired fragment **4** in 80% yield.



Scheme 3 Synthesis of fragment **4**. a) LHMDS, THF, –78 °C, 20 min, 4-iodo-1-butene, –78° C to –20 °C, 20 h (56%); b) TFA/H_2O (87%); c) TBSCl, Imidazole, DMF (80%).

The union of fragments **3** and **4** initially proved to be difficult and methods involving the use of coupling reagents such as DCC and HATU gave the desired ester **16** but in low yields and involved long reaction times. Nevertheless the esterification step finally proved to be successful using the Yamaguchi protocol,[10] affording the coupled fragment in good yield (Scheme 4).

Once obtained, the ester **16** was subjected to ring closing metathesis reactions using different catalysts (Figure 2). The results obtained were congruent with our predictions based on semi-empirical calculations, which indicated that compound (*E*)-**17** was ca. 2.5 Kcalmol^{-1} more stable that the corresponding (*Z*)-**17** isomer.[11] Therefore our choice to protect with a TBS group was expected to lead to the desired *E*-isomer.

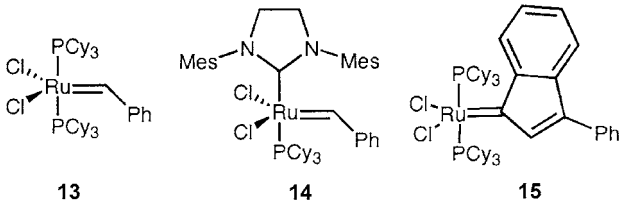
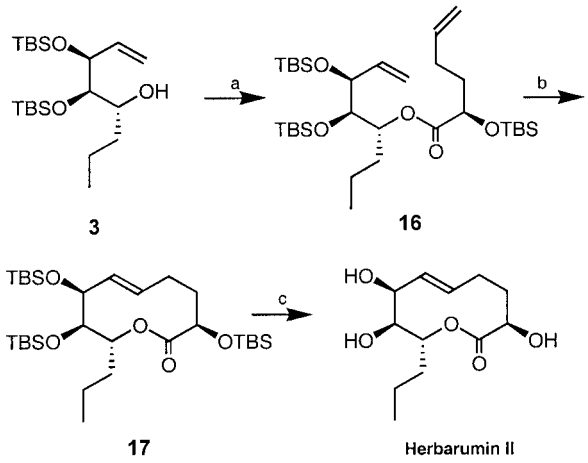


Figure 2 Ring closing metathesis catalysts used.

Specifically, the use of catalyst **13**[12] in boiling CH_2Cl_2 afforded the desired (*E*)-isomer as the major product but in less that 50% yield after 48 h, while the exposure of diene **16** to the 'second generation' metathesis catalyst **14**[13] gave rise to selective formation of the thermodynamically more stable (*E*)-lactone **17** that was isolated in an excellent 85% yield. On the other hand catalyst **15**[14] afforded a 2:1 mixture of *Z*:*E* isomers, indicating competing kinetic



Scheme 4 End game. a) Acid **4**, NEt_3, 2,4,6-trichlorobenzoyl chloride, DMAP, r.t., 16 h (78%); b) catalyst **16**, CH_2Cl_2, reflux, 8 h (85%); b) TBAF, THF, r.t., 1.5 h (quantitative).

control that allows the selective formation of the thermodynamically less stable (*Z*)-isomer.

Finally treatment of **17** with tetrabutylammonium fluoride in THF afforded herbarumin II **2** in quantitative yield and identical by ^{1}H NMR (600 MHz), ^{13}C NMR (100 MHz) analysis and X-ray crystallography to the natural product.[15]

In summary we have demonstrated the power of using both enantiomeric butane-diacetal glycolic acid building blocks to set up all the stereogenic centres formed in the polyol, phytotoxic agent herbarumin II. Clearly these methods could be readily adapted to the synthesis of the enantiomeric series and novel analogues.

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(7) Data for (*S*,*S*): $[\alpha]_D^{25}$ +208.3 (*c* 1.2, $CHCl_3$); mp 41–42 °C in agreement with the following reference: Michel, P.; Ley, S. V. *Synthesis* **2003**, in press.
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(15) Data for herbarumin II: δ_H (600 MHz, MeOH-d_4) 5.57 (1 H, ddd, *J* = 15.6 Hz, 2.0 Hz, 1.0 Hz, C*H*=CH), 5.51 (1 H, dddd, *J* = 15.6 Hz, 9.9 Hz, 4.1 Hz, 2.0 Hz, CH=C*H*), 5.17 (1 H, td, *J* = 9.3 Hz, 2.6 Hz, CHOCO), 4.34 (1 H, quint, *J* = 1.9 Hz, C*H*OH), 3.85 (1 H, dd, *J* = 10.5 Hz, 2.9 Hz, C*H*OHCH$_2$), 3.52 (1 H, dd, *J* = 9.6 Hz, 2.3 Hz, C*H*OH), 2.28 (1 H, m, CH=CHCH_aH$_b$), 2.08 (1 H, m, CH$_a$$H_b$), 1.87 (1 H, m, CH$_aH_bCH_cH_d$) 1.80 (1 H, m, CHC$H_eH_f$), 1.76 (1 H, m, CH$_c$$H_d$), 1.55 (1 H, m, CH$_e$$H_f$), 1.44 (1 H, m, C$H_gH_hCH_3$), 1.34 (1 H, m, CH$_g$$H_h$), 0.93 (3 H, t, *J* = 7.4 Hz, CH$_3$); δ_C (100 MHz, MeOH-d_4) 177.7 (C=O), 134.5 (CH), 123.9 (CH), 74.5 (CH), 74.3 (CH), 74.0 (CH), 72.3 (CH), 35.6 (CH$_2$), 35.4 (CH$_2$), 30.1 (CH$_2$), 19.1 (CH$_2$), 14.8 (CH$_3$).