The Use of Butane Diacetals of Glycolic Acid as Precursors for the Synthesis of the Phytotoxic Calmodulin Inhibitor Herbarumin II

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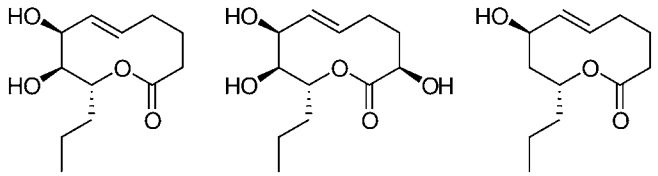
Dedicated with respect and appreciation to one of the world's great chemists, *Duilio Arigoni*, on the occasion of his 75th birthday

The total synthesis of phytotoxic nonenolide herbarumin II (**1**) has been achieved by implementation of butane diacetal (BDA)-desymmetrised glycolate building blocks. Three of the four stereogenic centres present in the key coupling fragments were generated from both enantiomeric forms of the BDA building block in highly diastereoselective alkylation and aldol reactions.

1. Introduction. – The medium-sized lactones herbarumin I (**1**), II (**2**), and the recently isolated III (**3**) are phytotoxic nonenolides produced from the fermentation broth and mycelium of the fungus *Phoma herbarum* Westend (Sphaeropsidaceae) (*Fig. 1*) [1][2].



1 **2** **3**

Fig. 1. *Herbarumin I* (**1**), *II* (**2**) *and III* (**3**)

These nonenolides have been tested by a petri-dish bioassay and show important phytotoxic effects against seedlings of *Amaranthus hypocondriacus* L. (Amaranthaceae). Enzyme-inhibition studies of compounds **1**–**3** also suggested an interesting behaviour as calmodulin inhibitors. In fact, bovine brain calmodulin, treated with the lactones, showed lower electrophoretic mobility than the untreated sample in a SDS-PAGE electrophoresis [3–5]. It was also found that different concentrations of herbarumin I (**1**) and II (**2**) inhibited the activation of the calmodulin-dependent enzyme cyclic nucleotide (cAMP) phosphodiesterase without interfering with the basal activity and either the independent form of the enzyme [2].

Owing to their physiological effects of agrochemical interest and the recently discovered activity as calmodulin inhibitors, these nonenolides were considered as highly attractive synthetic targets. A further level of interest arises from the structural

features present in the molecule: a ten-membered macrolide core, a vicinal diol, a (*E*)-substituted C=C bond and an appended Pr unit.

The herbarumins, as well as two close relatives, pinolidoxin (**4**), isolated from the phytopathogenic fungus *Ascochyta pinoides* Jones [6][7], and lethaloxin (**5**) [8][9], isolated from *Mycosphaerella lethalis* (*Fig. 2*), are part of a large family of ten-membered lactones that have recently attracted the interest of many synthetic chemists.

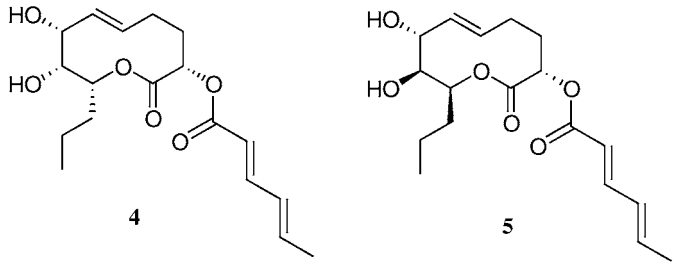


Fig. 2. *Two close relatives of the herbarumins family: pinolidoxin* (**4**) *and lethaloxin* (**5**)

Several approaches towards the synthesis of these ten-membered lactones have appeared in the literature during the past two years [10–13]. In many cases, ring closing metathesis (RCM) has been the method of choice owing to its inherently convergent route to the molecules [14]. This approach has posed considerable challenges since the ring strain predisposes cycloalkenes of eight to eleven ring atoms for the reverse process, that is, for ring-opening metathesis or ring opening metathesis polymerization (ROMP) [15][16]. There is no reliable and general method of controlling the geometry of the newly formed double bond, and, in general, RCM reactions in the macrocyclic series tend to give mixtures of the (*E*)- and (*Z*)-configured cyclic olefins [17][18]. This family of compounds has been tested for the kinetic *vs.* thermodynamic outcome of this metathesis reaction, and interesting results have been obtained by the use of different RCM catalysts by the different groups [10–12].

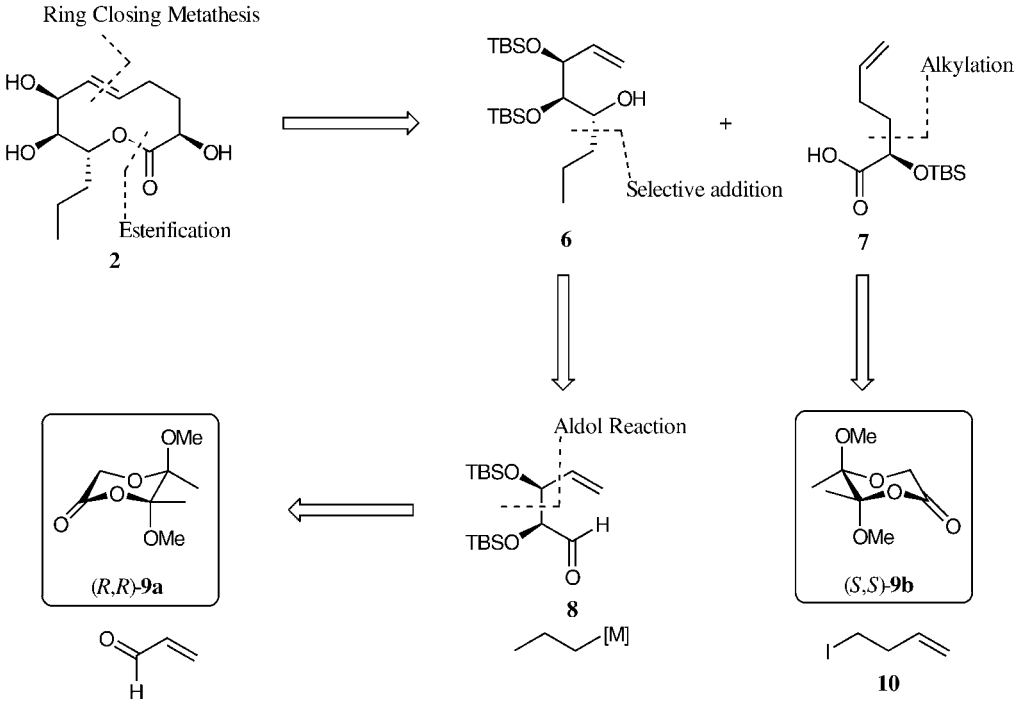
We have chosen to apply a method developed by our group to the synthesis of herbarumin II (**2**) to highlight the synthetic utility of butane diacetal-desymmetrised glycolic acid. We have published extensively on the use of butane diacetal (BDA) glycolic acid as a primary building block for the stereoselective synthesis of functionalised α-hydroxy acids and polyols [19–25]. The BDA chiral glycolate equivalent has been recently developed as a method alternative to the dispiro-ketal-desymmetrised glycolic acid previously introduced by our group several years ago [26][27]. The success of the BDA as a building block for the stereoselective synthesis of functionalised α-hydroxy acids and polyol motifs [28–33] suggested that it would be possible to extend this methodology to the creation of a suitable natural product such as herbarumin II (**2**). It was noticed that the required synthons for a convergent synthesis to this macrolide would necessitate the use of both enantiomers of these glycolic acid species.

2. Results and Discussion. – 2.1. *Proposed Synthesis and Preliminary Studies.* The proposed synthetic plan requires the union of two fragments **6** and **7** by well-known

synthetic methods such as esterification and RCM to provide the desired phytotoxin (*Scheme 1*).

The stereoselective addition of the Pr unit to generate fragment **6** is expected to arise from a non-chelation-controlled addition of an propylmetal reagent to the aldehyde **8** whose upper face should be sterically hindered by the presence of two bulky protecting units. In turn, the aldehyde should be obtained from an aldol reaction between (*R*,*R*)-glycolate **9a** and acrolein [32]. The right-hand fragment **7** should be readily available from an alkylation of the enantiomeric (*S*,*S*)-glycolate **9b** with homoallylic iodide **10** [30].

Scheme 1. *Proposed Synthetic Plan*



At this point, the choice of protecting groups was investigated. We were well aware of the great influence that different protecting units could exert on the final RCM, and how they could force the cyclization precursors to adopt favorable conformations to perform ring closure. Therefore, we carried out semi-empirical calculations [34] for the (*t*-Bu)Me_2Si (TBS)-protected precursor of herbarumin II, to investigate the relative energy stabilities of the possible isomers generated by a RCM reaction. It was found that the (*E*)-isomer was only *ca.* 2.5 kcal/mol more stable than the corresponding (*Z*)-isomer (*Fig. 3*).

Macromodel calculations have shown the role of the TBS protecting groups in favoring an (*E*)-conformation. In the (*E*)-isomer, the two bulky units are able to sit in a pseudoaxial position that brings them as far apart as possible, reducing the steric clash

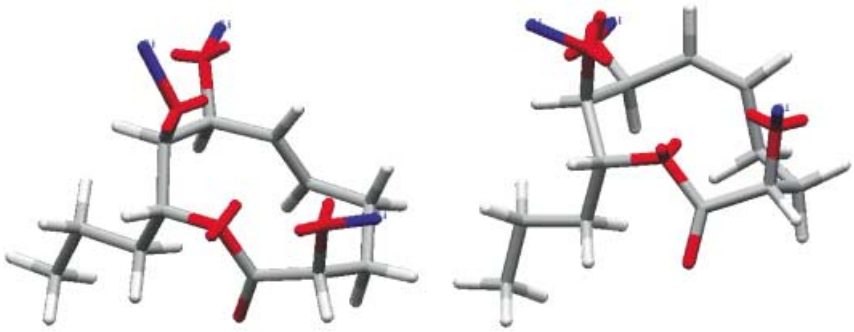


Fig. 3. *(*E*)-Isomer on the left and (*Z*)-isomer on the right*

between the two. It is also clear that the ten-membered ring exists in a double-fused-chair arrangement that minimises the energy. By examining the (*Z*)-isomer, it is apparent that the two protecting groups end up being close, and the ring is, therefore, constrained, thus justifying the higher energy of this unfavourable conformation. Therefore, we envisaged that employing the *Grubbs* second-generation catalyst to perform the final RCM should provide us with the thermodynamically more-stable (*E*)-isomer [35–37].

The synthesis commenced with the preparation of the two enantiomers of the BDA building block. These were prepared according to our procedures [30]. The two enantiomeric building blocks obtained were proven identical by spectroscopic analysis to the ones previously synthetised and reported in literature[1]) [38].

2.1. *Synthesis of Fragment* **6**. The synthesis of fragment **6** began with the aldol reaction between the (*R*,*R*)-glycolate **9a** and acrolein, performed as previously reported in literature [29]. Lithium hexamethyldisilazide (LHMDS) was added to a solution of the glycolate (*R*,*R*)-**9a** in THF at −78°, followed by the addition of acrolein, to provide alcohol **11** in 86% yield and better than 96% de (*Scheme 2*).

The configuration of the major diastereoisomeric product arises through the attack of the aldehyde to the *si*-face of the glycolate enolate, avoiding the steric clash with the 1,3 axially disposed MeO group (*Fig. 4*).

Deprotection of the BDA with MeOH/hydrochloric acid afforded the corresponding *anti*-1,2-dihydroxy methyl ester in 72% yield (*Scheme 2*). The two newly generated

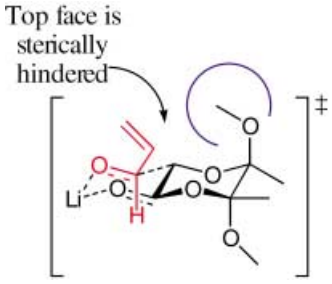
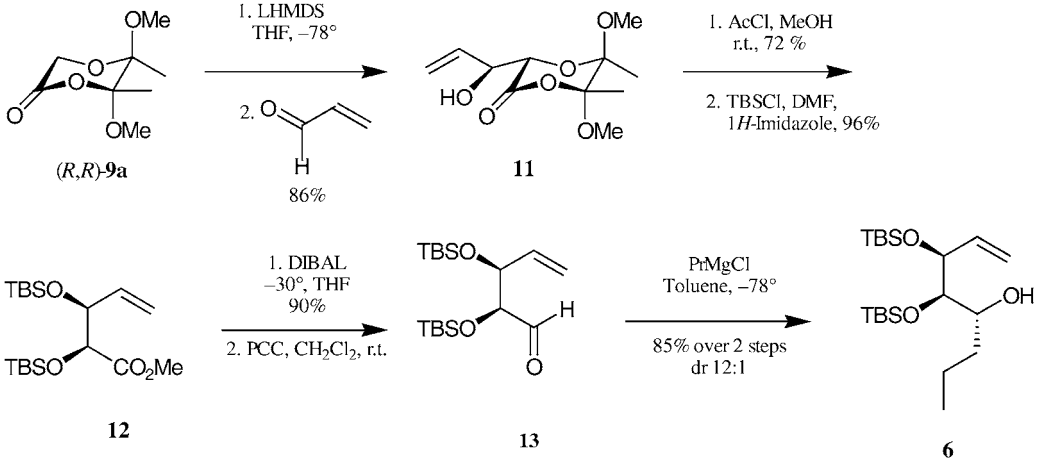


Fig. 4. *Proposed transition state model leading to the major diastereoisomer*

[1]) (*S*,*S*)-**9b**: $[\alpha]_D^{25} = +208.3$ ($c = 1.2$, $CHCl_3$), m.p. 41–42°; (*R*,*R*)-**9a**: $[\alpha]_D^{25} = -211.5$ ($c = 0.4$, $CHCl_3$), m.p. 40–41°, in agreement with [38].

Scheme 2. *Synthesis of Fragment* **6**



OH groups were protected as TBS ethers to obtain **12** in 96% yield. Reduction of the ester functionality with diisobutylaluminum hydride (DIBAL) in THF at $-30°$ gave the corresponding primary alcohol in 90% yield. Oxidation of the alcohol with pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature gave the desired aldehyde **13**. The final step to obtain fragment **6** required a non-chelation-controlled addition of an propylmetal nucleophile to aldehyde **13**. Optimisation studies on the yields and diastereoselectivities were carried out.

Screening of different organometallic compounds under various reaction conditions showed that optimum results could be achieved by addition of PrMgCl in toluene at $-78°$ (*Table 1*). Under these conditions, alcohol **6** was obtained in 85% isolated yield and greater than 12 : 1 diastereoselectivity.

Table 1. *Propylmetal Nucleophile Addition to Aldehyde* **13**

Reagent	Solvent	Temp.	dr[a])	Yield [%]
$BuLi/CeCl_3$	THF	$-78°$	7 : 1	86[bc])
$PrLi/LiI/Et_2O$	THF	$-78°$	2.5 : 1	76[b])
PrLi	THF	$-78°$	9 : 1	82[b])
PrMgCl	Toluene	$-78°$	12 : 1	85[d])

[a]) Determined by analysis of the ^{1}H-NMR of the crude mixture. [b]) Yield referred to the mixture of the major and minor diastereoisomer. [c]) 74% of the major diastereoisomer was isolated. [d]) Yield referred to isolated major diastereoisomer **6**.

To rationalize the diastereoselectivity of this reaction, it is assumed that the reacting conformation of the aldehyde is the one that places the electronegative O-atom perpendicular to the C=O bond in the *Felkin–Anh* transition state (*Fig. 5*).

A chelation-controlled transition state is not expected, as the presence of a large protecting group such as TBS prevents chelation of Mg^{2+} between the two O-atoms. The relative and absolute configurations of the newly generated stereogenic centre was determined by analogy with compound **15**, derived from alcohol **14**, by the *Mosher*'s

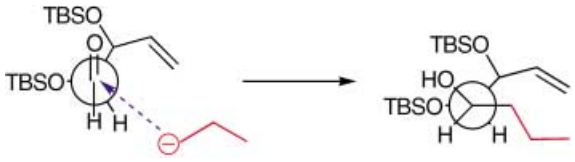
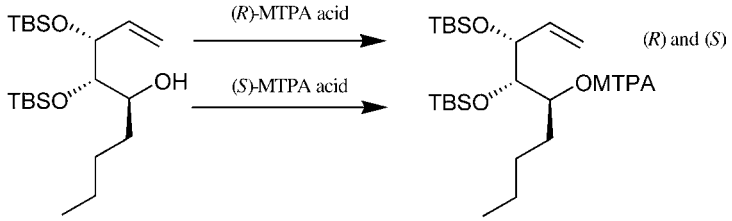


Fig. 5. *The attack on the aldehyde proceeds* via *a non-chelation* Felkin–Anh *transition state*

ester method [39][40] (*Scheme 3*). Compound **14** was synthesised from the (*S*,*S*)-glycolate **9b** by the same route as the synthesis of compound **6** from (*R*,*R*)-glycolate **9a**, the only difference being the introduction of a Bu chain instead of a Pr one.

Scheme 3. *Determination of the Absolute and Relative Configurations by the* Mosher *Method*



14 **15**

2.2. *Synthesis of Fragment* **7**. The synthetic strategy towards **7** centres on the idea of utilising the enantiomeric (*S*,*S*)-glycolate **9b** in a diastereoselective alkylation to create the desired configuration at the stereogenic centre C(2) [30]. As seen previously for the aldol reaction, the stereochemical outcome of this reaction arises from the presence of the axial MeO group that hinders the *si*-face of the enolate. Therefore, the attack on the halide occurs on the *re*-face, introducing the new alkyl group on the equatorial position (*Fig. 6*).

Fragment **7** was obtained in just three steps. First, LHMDS was added to the (*S*,*S*)-glycolate **9b** in THF at $-78°$ to generate the lithium enolate in the usual way. This was then allowed to react with an excess of iodide **10** to give the alkylated product **16** in 58% yield (*Scheme 4*).

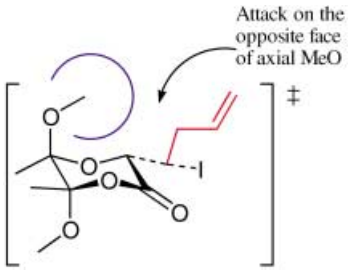
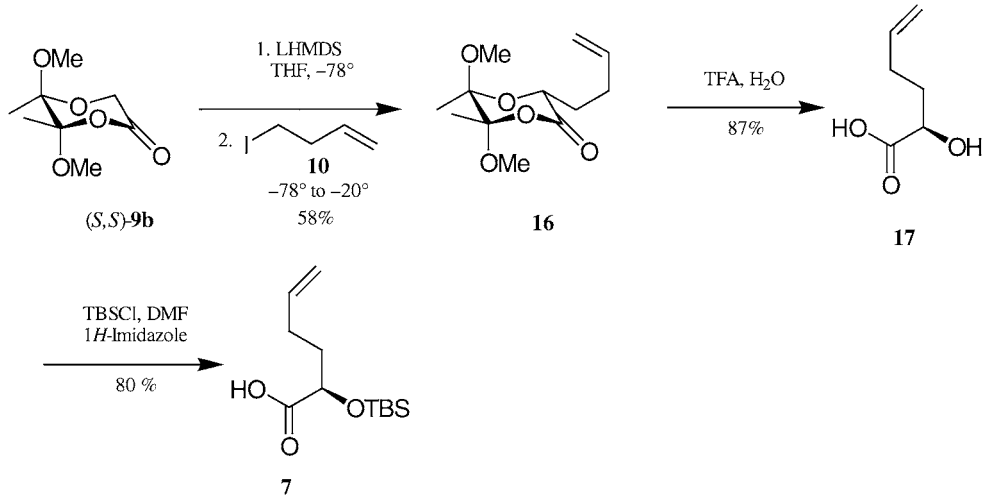


Fig. 6. *Rationalization of the stereochemical outcome of the alkylation reaction*

Scheme 4. *Synthesis of the Right-Hand Fragment* **7**



This yield was considered respectable in light of the side reactions possible with the iodide. Deprotection of the acetal with TFA/H_2O gave the hydroxy acid **17** in 87% yield [41]. The OH group was then selectively protected as the TBS ether through the addition of TBDSCl and 1*H*-imidazole in DMF to afford fragment **7** in 80% yield.

2.3. *Fragment Coupling and Cyclisation.* The convergent assembly of herbarumin II (**2**) from the two fragments **6** and **7** involves two key bond-forming steps. The first coupling reaction between **6** and **7** forms the ester bond of the macrolide, while the second intramolecular coupling event creates the ring skeleton through a RCM between the two terminal olefins.

Initial attempts at bringing the two fragments together were disappointing; the use of coupling reagents such as 1,3-dicyclohexylcarbodiimide (DCC) and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) afforded the ester **18** in low yields after extended reaction times (*Table 2*).

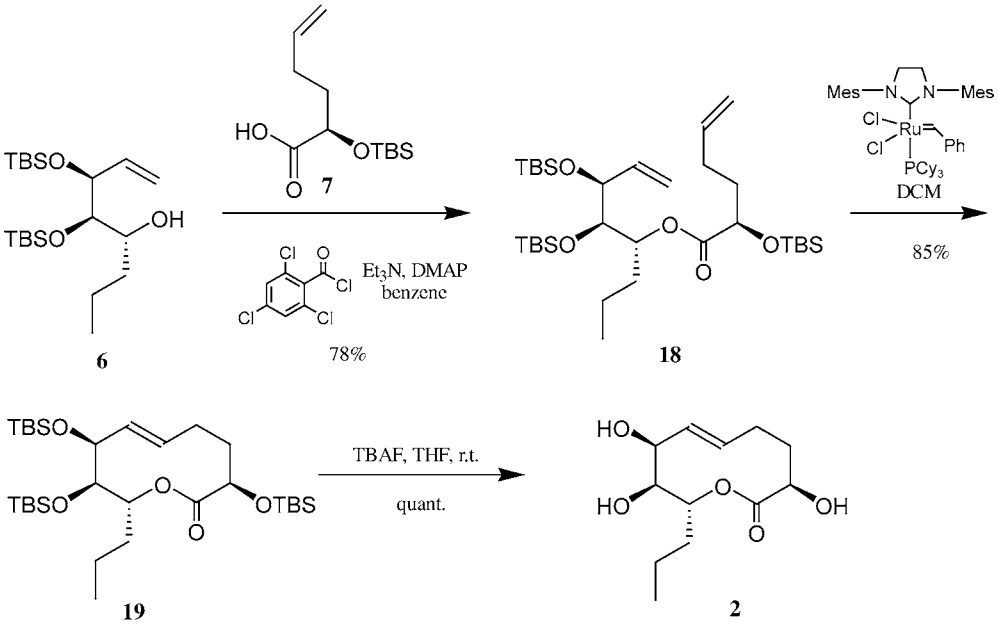
Table 2. *Conditions Tried for Esterification*

Acid **7**	Alcohol **6**	Reagent	Solvent	Time	Results
1.1 equiv.	1 equiv.	DCC/DMAP	CH_2Cl_2	3 d	Low conversion
1 equiv.	1.1 equiv.	HATU/DIPEA	CH_2Cl_2	4 d	Low conversion
4 equiv.	1 equiv.	DIEA/EDC/DMAP	CH_2Cl_2	4 d	Low conversion

These results may be attributed to the steric hindrance of the secondary alcohol caused by the presence of the two protecting units. The *Yamaguchi* protocol [42] proved to be a successful coupling alternative, and, when a solution of alcohol **6** and acid **7** in benzene was treated with 2,4,6-trichlorobenzoyl chloride and 4-(dimethylamino)pyridine (DMAP), the ester **18** was afforded in 78% yield (*Scheme 5*).

The results obtained with different metathesis catalysts were in perfect agreement with the calculations and predictions made. Accordingly, treatment of the ester **18** in

Scheme 5. Yamaguchi *Esterification and Final Ring Closure*



refluxing CH_2Cl_2 with *Grubbs* first-generation catalyst $RuCl_2(=CHPh)(PCy_3)_2$ [43] (10 mol-%) produced the (*E*)-isomer as the major product in a modest yield after 48 h. Pleasingly, exposure of **18** to the *Grubbs* second-generation catalyst 1,3-dimesityl-4,5-dihydroimidazol-2-yilidene catalyst [44] (20 mol-%) affected the selective formation of the thermodynamically more-stable (*E*)-lactone that was isolated in 85% yield (*Scheme 5*). For a further confirmation of our predictions, *Fürstner*'s indenylidene catalyst [45] (10 mol-%) was added to a solution of the ester **18** in CH_2Cl_2 to afford a 2:1 mixture of (*Z*)- and (*E*)-isomers after 24-h reflux. This result provides a further example of the tendency of this catalyst towards the formation of the thermodynamically less-stable isomer as a result of kinetic control (*Scheme 5*).

Global deprotection was achieved by treatment with Bu_4NF (TBAF) in THF to give herbarumin II (**2**) as a white solid in quantitative yield. The spectroscopic data for synthetic **2** (melting point, specific rotation, IR, ^1H- and ^{13}C-NMR, and X-ray structure (*Fig. 7*)) were all in good agreement with those reported for the naturally produced herbarumin II (**2**).

3. Conclusions. – In summary, the synthesis of herbarumin II (**2**) has been achieved by implementing our methods for the stereoselective preparation of both key fragments. Three out of four stereogenic centres formed in the polyol have, therefore, been set up from these key building blocks in efficient and highly diastereoselective alkylation and aldol reactions. The fourth centre is created by a *Felkin–Anh* addition of an organometallic reagent to an α-hydroxy aldehyde. Our route has the longest linear

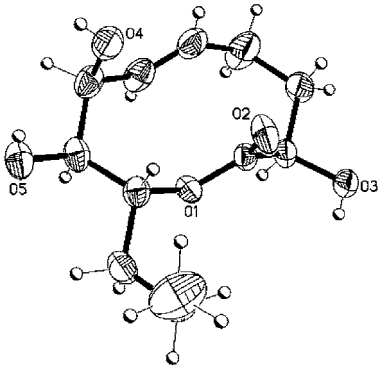


Fig. 7. *ORTEP Diagram of one of the two molecules of herbarumin II* (**2**) *in the asymmetric unit* (CH_2Cl_2 solvent omitted for clarity)

sequence of six steps, and furnishes herbarumin II (**2**) in twelve steps with an average yield of 75%. In future, these methods could be readily adapted to the synthesis of the enantiomeric series and other new analogues of the herbarumin family. Finally, studies of the RCM reaction exemplify how single olefinic stereoisomers can be rationally designed and synthetised with different catalysts.

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Experimental Part

General. All reactions were performed under an Ar atmosphere and carried out with oven-dried glassware, cooled under a continuous stream of Ar prior to use unless otherwise stated. Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and toluene from CaH_2; Et_3N and $(i\text{-}Pr)_2NH$ from KOH. All other reagents and solvents were purified by standard procedures or were used as obtained from commercial sources as appropriate. Light petroleum ether used had a b.p. 40–60°, unless otherwise stated and was distilled prior to use. Aq. solns. were all saturated, unless otherwise stated. Flash column chromatography (FC) was carried out with *Merck Kieselgel* (230–240 mesh) or prepacked silica-gel columns (*FLASH Biotage*). Anal. TLC was performed on precoated glass plates (*Merck Kieselgel 60* F_{254}) and visualised by UV fluorescence or acidic ammonium molybdate (IV). M.p.: *Reichert* hot-stage apparatus; uncorrected. Optical rotations: *Optical Activity AA-1000* polarimeter, $[\alpha]_D$ values in 10^{-1} deg cm^2 g^{-1}. IR Spectra: *Perkin-Elmer* '*Spectrum-One*' spectrometer equipped with an attenuated total reflectance (ATR) sampling accessory; thin films deposited from $CHCl_3$ soln. ^{1}H-NMR Spectra: at 400 or 600 MHz on a *Bruker AM-400* or *Bruker DRX-600* instruments, resp., chemical shifts δ in ppm; residual protic solvent was used as the internal reference. ^{13}C-NMR Spectra: at 100 MHz on a *Bruker AM-400* instrument; chemical shifts δ in ppm and referenced to the appropriate solvent peak. Microanalyses were determined in microanalytical laboratories at the Department of Chemistry, University of Cambridge. MS: *Kratos MS890MS* or *Bruker BIOAPEX 4.7 FTICR* spectrometers; with electron impact (EI) or electronspray techniques (ESI), at the Department of Chemistry, University of Cambridge. X-Ray structures were determined at the Department of Chemistry, University of Cambridge.

*(–)-(3*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-[(S)-1-hydroxyprop-2-enyl][1,4]dioxan-2-one* (**11**). Lithium bis(trimethylsilyl)amide in THF (1M; 8.3 ml, 8.3 mmol) was added to a stirred soln. of the (*R*,*R*)-glycolate **9a** (1.50 g, 7.89 mmol) in THF (40 ml) at −78°. After 10 min, freshly distilled acrolein (0.63 ml, 9.47 mmol) was added, and the soln. stirred at −78° for further 5 min. The reaction was then quenched by addition of AcOH (0.9 ml, 15.78 mmol) at −78° and was allowed to warm to r.t. Et_2O was added (20 ml), and the heterogeneous

mixture was filtered through a short plug of silica gel eluting with Et_2O (150 ml). The filtrate was concentrated under reduced pressure. The de of the reaction was found to be > 95% by integration of the signals in the 600-MHz ^{1}H-NMR spectrum. FC with Et_2O/petroleum ether 1:2 gave 11 (1.66 g, 86%). Colourless oil. R_f (Et_2O/petroleum ether 1:1) 0.12. $[\alpha]_D^{25} = -151.6$ ($c = 1.24$, $CHCl_3$). IR (film): 3487, 2951, 1741, 1032. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.04–5.96 (*m*, C*H*CH_2); 5.37 (*d*, *J* = 17.2, CHC*H*H); 5.26 (*d*, *J* = 10.5, CHCH*H*); 4.49 (*m*, C*H*OH); 4.19 (*d*, *J* = 3.5, COCH); 3.42 (*s*, MeO); 3.32 (*s*, MeO); 1.49 (*s*, Me); 1.42 (*s*, Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.7 (CO); 134.8 (*C*HCH_2); 117.3 (CH*C*H_2); 104.8 (C_q); 98.2 (C_q); 75.0 (CH); 73.7 (CH); 50.1 (MeO); 49.3 (MeO); 17.8 (Me); 16.8 (Me). ESI-MS: 246 (M^+). HR-MS: 269.1005 [$(M + Na)^+$, $C_{11}H_{18}NaO_6^+$; calc. 269.1001). Anal. calc. for $C_{11}H_{18}O_6$ (246.25): C 53.65, H 7.37; found: C 52.07, H 7.27.

(+)-(2S,3S)-Methyl 2,3-Dihydroxypent-4-enoate. AcCl (0.5M in MeOH, 1.48 ml) was added in one portion to a stirred soln. of **11** (1.67 g, 6.7 mmol) in MeOH (5 ml). The soln. was stirred for 30 min, and then all volatiles were removed *in vacuo*. This process was repeated, then purification by FC with Et_2O afforded the desired ester (560.4 mg, 72%). Colourless oil. R_f (Et_2O) 0.42. $[\alpha]_D^{25} = +10.5$ ($c = 1.06$, $CHCl_3$). IR (film): 3426, 1732. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.87–5.79 (*m*, C*H*CH_2); 5.24 (*d*, *J* = 17.3, CHC*H*H); 5.17 (*d*, *J* = 10.6, CHCH*H*); 4.28 (*t*, *J* = 6.5, C*H*CHCH$_2$); 4.04 (*d*, *J* = 6.5, C*H*CO); 3.71 (*s*); 3.43 (br. *s*, OH); 3.03 (br. *s*, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.9 (CO); 135.1 (*C*HCH_2); 118.3 (CH*C*H_2); 74.4 (*C*H); 74.2 (CH); 52.9 (MeO). ESI-MS: 146 (M^+). HR-MS: 169.0473 ([$M + Na$]$^+$, $C_6H_{10}NaO_4^+$; calc. 169.0471).

*(−)-(2S,3S)-Methyl-2,3-Bis[(*tert*-butyl)dimethylsilanyloxy]pent-4-enoate* (**12**). 1*H*-Imidazole (1.46 g, 21.45 mmol) was added in one portion to a soln. of methyl 2,3-dihydroxypent-4-enoate (522 mg, 3.57 mmol) in DMF (5 ml) at 0°. (*t*-Bu)Me_2SiCl (TBDS; 1.61 g, 10.71 mmol) was added, and the soln. was stirred overnight at r.t. H_2O (5 ml) was added, and the mixture was extracted with Et_2O (3 × 15 ml). The combined org. layers were washed with sat. aq. NaCl (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. FC with Et_2O/petroleum ether 1:8 gave **12** (1.28 g, 96%). Colourless oil. R_f (Et_2O/1:1) 0.53. $[\alpha]_D^{25} = -13.5$ ($c = 0.96$, $CHCl_3$). IR ($CHCl_3$): 2929, 1752, 1091. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.83–5.75 (*m*, C*H*CH_2); 5.20 (*d*, *J* = 16, C*H*HCH); 5.13 (*d*, *J* = 10, CH*H*CH); 4.24 (*t*, *J* = 6.5, C*H*CHCO); 4.00 (*d*, *J* = 3.5, CHCO); 3.67 (*s*, MeOCO); 0.83 (*s*, *t*-Bu); 0.82 (*s*, *t*-Bu); 0.00–0.01 (*m*, MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.1 (CO); 138.4 (*C*HCH_2); 117.4 (CH*C*H_2); 77.2 (CH); 76.6 (CH); 51.9 (MeO); 26.1 (*Me*$_3$C); 26.0 (*Me*$_3$C); 18.6 (*Me*$_3$C); 18.4 (*Me*$_3$C); −3.9 (MeSi); −4.7 (MeSi); −4.8 (MeSi). ESI-MS: 374 (M^+). HR-MS: 397.2203 ([$M + Na$]$^+$, $C_{18}H_{38}NaO_4Si_2^+$; calc. 397.2206).

*(−)-(2S,3R)-2,3-Bis[(*tert*-butyl)dimethylsilyloxy]pent-4-en-1-ol.* DIBAL-H (1M in CH_2Cl_2, 8.4 ml, 8.4 mmol) was added dropwise to a soln. of **12** (1.05 g, 2.80 mmol) in CH_2Cl_2 (19 ml) at −30°. After stirring at −30° for 1 h, the mixture was diluted with AcOEt (1.8 ml) and allowed to warm to 0°; then, finely ground $Na_2SO_4 \cdot 10\ H_2O$ (4.2 g) was added in one portion. The soln. was stirred for 4 h at r.t. and then filtered through a plug of silica gel eluting with Et_2O. Concentration *in vacuo*, then purification by FC with Et_2O/petroleum ether 1:5 gave the desired alcohol (868 mg, 90%). Colourless oil. R_f (Et_2O/petroleum ether 1:4) 0.45. $[\alpha]_D^{25} = -0.22$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 2929 (CH), 1254 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.79–5.71 (*m*, C*H*CH_2); 5.14 (*d*, *J* = 17, CHC*H*H); 5.07 (*d*, *J* = 10, CHCH*H*); 4.04 (*m*, C*H*CHCH$_2$); 3.63–3.38 (*m*, C*H*C*H*$_2$OH); 2.04 (br. *s*, COH); 0.82 (*s*, 2 *t*-Bu); 0.01–0.03 (*m*, 2 MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 139.6 (*C*HCH_2); 116.6 (CH*C*H_2); 76.3 (CH); 76.2 (CH); 64.3 (CH_2); 26.3 (*Me*$_3$C); 26.2 (*Me*$_3$C); 18.5 (*Me*$_3$C); 18.4 (*Me*$_3$C); −3.8 (MeSi); −3.9 (MeSi); −4.1 (MeSi). ESI-MS: 346 (M^+). HR-MS: 369.2251 ([$M + Na$]$^+$, $C_{17}H_{38}NaO_3Si_2^+$; calc. 369.2252).

*(+)-(2S,3R)-2,3-Bis[(*tert*-butyl)dimethylsilyloxy]pent-4-en-1-al* (**13**). Bis[(*tert*-butyl)dimethylsilyloxy]-pent-4-en-1-ol (113 mg, 0.326 mmol) was dissolved in CH_2Cl_2 (3 ml) and cooled to 0°. Pyridinium chlorochromate (PCC; 141 mg, 0.653 mmol) and 4-Å molecular sieves (163 mg) were added, and the resulting black suspension was stirred for 1.5 h. Et_2O (5 ml) was added, and the suspension was filtered through a plug of *Celite*®, *Florisil*® and silica gel eluting with Et_2O (*ca.* 300 ml). The eluent was concentrated *in vacuo* to give **13** (105 mg, 94%). Yellow oil. R_f (Et_2O/petroleum ether 1:4) 0.66. $[\alpha]_D^{25} = +1.56$ ($c = 0.96$, $CHCl_3$). IR ($CHCl_3$): 3497, 1737, 1252. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.52 (*d*, *J* = 1.9, CHO); 5.84–5.76 (*m*, C*H*CH_2); 5.19 (*d*, *J* = 17.2, CHC*H*H); 5.13 (*d*, *J* = 10.4, CHCH*H*); 4.25 (*t*, *J* = 4.9, C*H*CHCH$_2$); 3.84 (*dd*, *J* = 4.5, 1.9, C*H*CHO); 0.84 (*s*, *t*-Bu); 0.81 (*s*, *t*-Bu); 0.01–0.02 (*m*, 4 MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.8 (CHO); 137.7 (*C*HCH_2); 117.2 (CH*C*H_2); 81.5 (CH); 76.7 (CH); 26.1 (*Me*$_3$C); 18.6 (*Me*$_3$C); 18.5 (*Me*$_3$C); −4.0 (MeSi); −4.4 (MeSi); −4.5 (MeSi). ESI-MS: 344 (M^+). HR-MS: 367.2105 ([$M + Na$]$^+$, $C_{17}H_{36}NaO_3Si_2^+$; calc. 367.2095).

*(+)-(4R,5R,6S)-5,6-Bis[(*tert*-butyl)dimethylsilyloxy]oct-7-en-4-ol* (**6**). PrMgCl (2M in Et_2O, 0.457 ml, 0.916 mmol) was added dropwise *via* syringe to a soln. of **13** (105 mg, 0.30 mmol) in toluene (3.5 ml) at −78°. The mixture was stirred for 2 h at −78°, then a sat. soln. of NH_4Cl (1 ml) was added dropwise, and the soln. was allowed to warm to 0°. $Na_2SO_4 \cdot 10\ H_2O$ (457 mg) was then added, and the mixture was stirred for 1 h at r.t., passed through a small pad of silica gel eluting with Et_2O and concentrated *in vacuo*. The de of the reaction

was found to be 86% by integration of the signals in the 600-MHz crude ^{1}H-NMR spectrum. Purification by FC with Et_2O/petroleum ether 1:12 gave **6** (97 mg, 85%). Colourless oil. R_f (Et_2O/petroleum ether 1:10) 0.38. $[\alpha]_D^{25} = +10.5$ ($c = 1.15$, $CHCl_3$). IR ($CHCl_3$): 2956, 1472, 1252, 1098, 833, 776. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.92–5.84 (*m*, C*H*CH_2); 5.18 (*d*, *J* = 16, CHC*H*H); 5.12 (*d*, *J* = 10, CHCH*H*); 4.23–4.21 (br. *s*, C*H*$CHCH_2$); 3.59 (br. *s*, C*H*OH); 3.46–3.45 (br. *s*, C*H*CHOH); 1.96 (br. *s*, COH); 1.62–1.44 (*m*, CH_2CH); 1.41–1.20 (*m*, MeCH_2); 0.95–0.83 (*m*, 2 *t*-Bu, $MeCH_2$); 0.03–0.01 (*m*, 4 MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 139.6 (*C*HCH_2); 116.3 (CH*C*H_2); 79.8 (*C*HCHOH); 77.2 (*C*$HCHCH_2$); 73.7 (COH); 35.2 (CH*C*H_2CH_2); 26.4 (*Me*$_3$C); 26.3 (*Me*$_3$C); 19.5 (Me*C*H_2); 18.7 (*Me*$_3$C); 18.6 (*Me*$_3$C); 14.5 (Me); −3.3 (MeSi); −3.7 (MeSi); −4.1 (MeSi). ESI-MS: 388 (M^+). HR-MS: 411.2698 ($[M+Na]^+$, $C_{20}H_{44}NaO_3Si_2^+$; calc. 411.2721). Anal. calc. for $C_{20}H_{44}O_3Si_2$ (388.73): C 61.79, H 11.41; found: C 62.25, H 11.35.

4-Iodobut-1-ene (**10**). NaI (14.76 g, 98.5 mmol) was added to 4-bromobut-1-ene (5 ml, 49.25 mmol) in acetone (370 ml) at r.t., and the mixture was refluxed for 3 h. After filtration, solvents were removed by distillation, and the remaining soln. was washed with H_2O (2 × 50 ml), brine, dried ($MgSO_4$) and filtered. Distillation of the solvent gave **10** (4.04 g, 45%). Brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.5–5.8 (*m*, CH); 5–5.2 (*m*, CH_2); 3.15 (*t*, *J* = 7.2, CH_2I); 2.5–2.7 (*m*, CH_2CH_2I). ^{13}C-NMR (100 MHz, $CDCl_3$): 137.3 (*C*HCH_2); 117.4 (CH*C*H_2); 38.1 (CH_2I); 4.9 (*C*H_2CH_2I). Anal. calc. for $C_{20}H_{44}O_3Si_2$ (388.73): C 61.79, H 11.41; found: C 62.25, H 11.35.

*(+)-(3*R*,5*S*,6*S*)-3-(But-3′-enyl)-5,6-dimethoxy-5,6-dimethyl[1,4]dioxan-2-one* (**16**). Lithium bis(trimethylsilyl)amide in THF (LM, 2.5 ml, 2.5 mmol) was added to a soln. of (*S*,*S*)-glycolate **9b** (500 mg, 2.64 mmol) in THF (8 ml) at −78°. After 15 min, **10** (1.5 g, 7.92 mmol) was added and the soln. was stirred for 25 h at −60°. The reaction was then quenched by addition of AcOH (0.3 ml, 5.2 mmol) at −60°, and the mixture was warmed to r.t. Et_2O was added (4 ml), and the heterogeneous mixture was filtered through a short plug of silica gel, eluting with Et_2O (30 ml). The filtrate was concentrated under reduced pressure. The de of the reaction was found to be >95% by integration of the signals in the 600-MHz ^{1}H-NMR spectrum. FC with Et_2O/petroleum ether 1:13 gave **16** (749 mg, 58%). Colourless oil. R_f (Et_2O/petroleum ether 1:4) 0.31. $[\alpha]_D^{25} = +177$ ($c = 1.3$, $CHCl_3$). IR ($CHCl_3$): 2953, 1746, 1265. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.79–5.69 (*m*, C*H*CH_2); 4.99 (*d*, *J* = 17.1, CHC*H*H); 4.93 (*d*, *J* = 10.2, CHCH*H*); 4.09 (*t*, *J* = 5.5, CHCO); 3.35 (*s*, MeO); 3.22 (*s*, MeO); 2.26–2.10 (*m*, CH_2CHCH_2); 1.96–1.83 (*m*, CHCH_2); 1.41 (*s*, Me); 1.32 (*s*, Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.2 (CO); 137.4 (*C*HCH_2); 117.3 (CH*C*H_2); 104.9 (C_q); 98.0 (C_q); 69.6 (CH); 49.9 (MeO); 48.9 (MeO); 31.7 (CH_2); 29.1 (CH_2); 17.8 (Me); 17.0 (Me). ESI-MS: 244.28 (M^+). HR-MS: 267.1204 ($[M+Na]^+$, $C_{11}H_{18}NaO_6^+$; calc. 267.1208). Anal. calc. for $C_{13}H_{24}O_5$ (260.30): C 59.00, H 8.25; found: C 59.40, H 8.25.

*(−)-(2*R*)-2-Hydroxyhex-5-enoic Acid* (**17**). A soln. of TFA in H_2O (TFA/H_2O 2:1; 2 ml) was added to **16** (42 mg, 0.172 mmol) at r.t. After stirring at the same temp. for 1 h, the soln. was evaporated *in vacuo* to leave **17** (21 mg, 87%). Yellow oil. R_f (Et_2O/petroleum ether 1:1) 0.12. $[\alpha]_D^{25} = -16.4$ ($c = 0.93$, $CHCl_3$). IR (film): 3400, 1717, 1641, 1449, 1213, 1086. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.00 (br. *s*, COOH); 5.80–5.70 (*m*, C*H*CH_2); 5.02 (*d*, *J* = 17.2, C*H*HCH); 4.95 (*d*, *J* = 10, CH*H*CH); 4.23 (br. *s*, C*H*OH); 2.18–2.16 (*m*, CH_2CHCH_2); 2.07–1.91 (*m*, CH_aH$_b$CH_2); 1.85–1.76 (*m*, CH_aH$_b$CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.9 (CO); 136.9 (*C*HCH_2); 115.7 (CH*C*H_2); 70.0 (CH), 33.1 (CH_2), 28.8 (CH_2). ESI-MS: 130 (M^+). HR-MS: 153.0523 ($[M+Na]^+$, $C_6H_{10}NaO_3^+$; calc. 153.0528).

*(+)-(2*R*)-2-[(*tert*-Butyl)dimethylsilyloxy]hex-5-enoic Acid* (**7**). 1*H*-Imidazole (290 mg, 4.25 mmol) was added in one portion to a soln. of **17** (280.5 mg, 2.15 mmol) in DMF (1.5 ml) at 0°. (*t*-Bu)Me_2SiCl (1.23 g, 8.16 mmol) was added. After stirring for 22 h, the mixture was diluted with petroleum ether/AcOEt 1:1 (50 ml), washed with citric acid (10%, 35 ml), H_2O and sat. aq. Na_2SO_4. The org. layer was removed under vacuum. The residue was dissolved in MeOH (20 ml), cooled in an ice bath, and K_2CO_3 (690 mg, 5 mmol) in H_2O (6 ml) was added. The mixture was stirred at r.t. for 4 h. The solvent was then removed, and the residue was diluted with H_2O, cooled in an ice bath and acidified to pH 4 with 10% aq. citric acid, and extracted with AcOEt (3 × 20 ml). The AcOEt layer was dried (Na_2SO_4) and concentrated under vacuum to give **7** (420.7 mg, 80%). Yellow oil. R_f (Et_2O/petroleum ether 1:1) 0.57. $[\alpha]_D^{25} = +5.7$ ($c = 0.8$, $CHCl_3$). IR (film): 2955, 1717, 1472, 1253, 1139. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.72–5.62 (*m*, C*H*CH_2); 4.92 (*d*, *J* = 17, C*H*HCH); 5.87 (*d*, *J* = 10, CH*H*CH); 4.17 (*t*, *J* = 5.4, *CH*OH); 2.32–1.98 (*m*, CH_2CH_2); 1.81–1.69 (*m*, CH_2CH_2); 0.81 (*s*, *t*-Bu); 0.00 (*s*, 2 MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.0 (CO); 137.6 (*C*HCH_2); 115.8 (CH*C*H_2); 71.9 (CH); 34.3 (CH_2); 28.8 (CH_2); 26.1 (*Me*$_3$C); 18.5 (*Me*$_3$C); −4.5 (MeSi); −4.7 (MeSi). ESI-MS: 244 (M^+). HR-MS: 267.1385 ($[M+Na]^+$, $C_{12}H_{24}NaO_3Si^+$; calc. 295.1392). Anal. calc. for $C_{13}H_{28}O_3Si$ (244.40): C 58.97, H 9.90; found: C 60.31, H 9.97.

*(1*R*,2*R*,3*S*)-2,3-Bis[(*tert*-butyl)dimethylsilyloxy]-1-propylpent-4-enyl (+)-(2*R*)-2-[(*tert*-Butyl)dimethylsilyloxy]hex-5-enoate* (**18**). A soln. of **7** (165 mg, 0.67 mmol) in benzene was treated with **6** (197 mg, 0.50 mmol), Et_3N (0.18 ml, 1.35 mmol), 2,4,6-trichlorobenzoyl chloride (0.16 ml, 1.02 mmol) and DMAP (41 mg,

0.33 mmol). The mixture was stirred at r.t. for 16 h and then quenched with citric acid (10% aq. soln., 20 ml), extracted with Et_2O (3 × 20 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by FC with petroleum ether/Et_2O 1:1 gave **18** (238 mg, 78%). Colourless oil. R_f (Et_2O/petroleum ether 1:8) 0.67. $[\alpha]_D^{25} = +24$ ($c = 0.76$, $CHCl_3$). IR (film): 2858, 1753, 1472, 1253, 1129. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.86–5.75 (*m*, CH=CH_2); 5.16–4.97 (*m*, 2 CH_2=CH, CHOC=O); 4.17 (*dd*, *J* = 7.9, 4.4, CH); 4.06 (*dd*, *J* = 7.25, 4.06, CH); 3.66 (*t*, *J* = 4.2, CH); 2.23–2.09 (*m*, CH_2); 1.88–1.74 (*m*, CH_2); 1.72–1.55 (*m*, CH_2); 1.43–1.122 (*m*, CH_2); 0.91 (*s*, *t*-Bu); 0.89 (*s*, *t*-Bu); 0.86 (*t*, *J* = 7.2, Me); 0.84 (*s*, *t*-Bu); 0.09 (*s*, MeSi); 0.08 (*s*, MeSi); 0.08 (*s*, MeSi); 0.06 (*s*, MeSi); 0.05 (*s*, MeSi); 0.02 (*s*, MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.7 (C=O); 138.1 (CHCH$_2$); 137.6 (*C*HCH$_2$); 117.1 (CH*C*H$_2$); 115.1 (CH*C*H$_2$); 78.2 (CH); 76.1 (CH); 75.2 (CH); 71.6 (CH); 34.3 (CH_2); 32.1 (CH_2); 29.4 (CH_2); 25.9 (*Me*$_3$C); 25.8 (*Me*$_3$C); 25.7 (*Me*$_3$C); 18.5 (CH_2); 18.3 (*Me*$_3$C); 18.2 (*Me*$_3$C); 18.1 (*Me*$_3$C); 13.9 (Me); −3.90 (MeSi); −4.0 (MeSi); −4.6 (MeSi); −4.7 (MeSi); −5.3 (MeSi). ESI-MS: 614 (M^+). HR-MS: 637.4115 ($[M+Na]^+$, $C_{32}H_{66}NaO_5Si_3^+$; calc. 637.4116).

*(+)-(2R,7S,8S,9R)-2,7,8-Tris[(*tert*-butyl)dimethylsilyloxy]-9-propylnon-5-en-9-olide* (**19**). A soln. of **18** (100 mg, 0.16 mmol) and *Grubbs* second-generation catalyst (14 mg, 0.016 mmol) in CH_2Cl_2 (80 ml) was refluxed for 8 h until TLC showed complete conversion. The mixture was then quenched with ethyl vinyl ether (0.25 ml) and concentrated *in vacuo*, the resulting crude was passed through a column (Et_2O/petroleum ether 1:70 → 1:40) of $AgNO_3$-impregnated silica gel [46], affording **19** (80 mg, 85%). Colourless solid. R_f (petroleum ether/Et_2O 30:1) 0.37. M.p. 77–78°. $[\alpha]_D^{25} = +38.3$ ($c = 1.0$, $CHCl_3$). IR (Film): 2956, 2928, 2857, 1751, 1472, 1252, 1085. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.53–4.47 (*m*, CH=C*H*); 5.42 (*d*, *J* = 15.5, C*H*=CH); 5.34 (br. *t*, *J* = 8.9, CHOCO); 4.28 (br. *s*, C*H*CH=CH); 3.85–3.82 (*m*, COCH); 3.54 (*dd*, *J* = 8.9, 1.4, C*H*CHCO); 2.35–2.29 (*m*, CH_cH$_d$); 2.04–1.92 (*m*, CH_aH$_b$); 1.77–1.70 (*m*, CH_eH$_f$); 1.67–1.63 (*m*, CH$_c$H$_d$); 1.35–1.10 (*m*, CH$_e$H$_f$CH$_g$H$_h$); 0.95 (*s*, *t*-Bu); 0.93 (*s*, *t*-Bu); 0.89 (*t*, *J* = 7.2, Me); 0.86 (*s*, *t*-Bu); 0.12 (*s*, MeSi); 0.10 (*s*, MeSi); 0.07 (*s*, MeSi); 0.05 (*s*, MeSi); 0.04 (*s*, MeSi); 0.00 (*s*, MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.7 (C=O); 132.7 (CH); 124.8 (CH); 75.8 (CH); 75.1 (CH); 74.2 (CH); 71.1 (CH); 34.7 (CH_2); 34.4 (CH_2); 29.3 (CH_2); 26.6 (*Me*$_3$C); 26.2 (*Me*$_3$C); 26.0 (*Me*$_3$C); 18.7 (*Me*$_3$C); 18.6 (*Me*$_3$C); 18.6 (*Me*$_3$C); 18.5 (CH_2); 14.1 (Me); −2.98 (MeSi); −3.9 (MeSi); −4.0 (MeSi); −4.2 (MeSi); −4.5 (MeSi); −4.6 (MeSi). ESI-MS: 587 (M^+). HR-MS: 609.3821 ($[M+Na]^+$, $C_{30}H_{62}NaO_5Si_3^+$; calc. 609.3803); Anal. calc. for $C_{30}H_{62}O_5Si_3$ (587.40): C 61.38, H 10.64; found: C 61.65, H 10.37.

Herbarumin II (**2**) [1]. To a stirred soln. of **19** (36.8 mg, 0.063 mmol) in THF (3 ml) at r.t. was added in one portion Bu_4NF (0.63 ml; 1M soln. in THF), and the soln. was stirred for 1.5 h. The mixture was then passed through a silica-gel plug, eluting with AcOEt, and the resulting soln. was concentrated *in vacuo*. FC (pentane/AcOEt 1:1) afforded **2** (15 mg, quant.). Pale yellow solid. R_f (pentane/AcOEt 1:1) 0.3. M.p. 100–101°. $[\alpha]_D^{25} = +15.2$ ($c = 0.7$, MeOH). IR (Film): 3423, 2958, 1721, 1439, 1197, 1054. ^{1}H-NMR (600 MHz, $CDCl_3$): 5.57 (*ddd*, *J* = 15.6, 2.0, 1.0, C*H*=CH); 5.51 (*dddd*, *J* = 15.6, 9.9, 4.1, 2.0, CH=C*H*); 5.17 (*td*, *J* = 9.3, 2.6, CHOCO); 4.34 (*q*, *J* = 1.9, CHOH); 3.85 (*dd*, *J* = 10.5, 2.9, C*H*OHCH$_2$); 3.52 (*dd*, *J* = 9.6, 2.3, CHOH); 3.30 (*m*, CH=CHCH_aH$_b$); 1.87 (*m*, CH$_a$H$_b$); 1.80 (*m*, CHCH_eH$_f$); 1.76 (*m*, CH$_a$H$_b$CH$_c$H$_d$); 1.55 (*m*, CH$_e$H$_f$); 1.44 (*m*, CH$_g$H$_h$Me); 1.34 (*m*, CH$_g$H$_h$); 0.93 (*t*, *J* = 7.4, Me). ^{13}C-NMR (100 MHz, CD_3OD): 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 (Me). ESI-MS: 244 (M^+). HR-MS: 267.1209 ($[M+Na]^+$, $C_{12}H_{20}NaO_5^+$; calc. 267.1208).

X-Ray Crystallographic Structure Determination of Herbarumin II (**2**) [47]. Crystal data: $C_{12}H_{20}O_5 \cdot 1/2\ C_1H_2Cl_2$, M_r 286.74, colourless prism 0.23 × 0.14 × 0.05 mm, monoclinic $P2_1$ (No. 4), $a = 9.4298(3)$, $b = 9.4168(4)$, $c = 16.6593(5)$ Å, $\beta = 93.670(2)°$, $V = 1476.3(1)$ Å^3, $T = 180(2)$K, $D_X = 1.290$ g cm^{-3}, $\lambda = 0.71073$ Å, $\mu = 0.270$ mm^{-1}, *Nonius Kappa CCD* diffractometer, $3.68° < \theta < 25.06°$, 10668 measured reflections, 4895 independent, 3837 with $I > 4\sigma(I)$. The crystals did not diffract very well, as is reflected in the relatively high *R* factors. The structure was solved by direct methods (SHELXS-97) and refined by least-squares (SHELXL-97) with *Chebyshev* weights on F_o^2 to $R1 = 0.087$, $wR2 = 0.225$ [$I > 2\sigma(I)$], 355 parameters, all H-atoms in calculated positions except the three OH H-atoms, which were located and refined successfully. Goodness-of-fit on F^2 1.051, residual electron density 0.953 e · Å^{-3}. Crystallographic data (excluding structure factors) for this structure have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-217165. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

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