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Total synthesis of (−)-cleistenolide and formal synthesis of herbarumin I via a diastereoselective modulable allylation

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ABSTRACT

A modulable tin based allylation method for the synthesis of 1,2,3-triols is described. The optimization of the reaction was aided by ^{1}H and ^{119}Sn low temperature NMR spectroscopic investigations, which support the formation of two cyclic intermediates after transmetallation. Depending on the nature of the Lewis acid, either *syn/anti* or *anti/syn* configured triols could be obtained with good stereocontrol. To demonstrate the value of this methodology and the resulting scaffolds, they were used to install the signature triol motifs of (−)-cleistenolide and of herbarumin I.

1. Introduction

Polyketide natural products represent an enormous class of structurally diverse compounds that exhibit a wide-range of biological activities. Molecules from this family have already found significant medicinal applications. A few examples include Rapamycin [1] (organ transplants), Paclitaxel [2] and Doxorubicin [3] (oncology), and Amphotericin B [4] and Rifamycins [5] (treatment of fungal or bacterial infections, respectively). As such, polyketides represent challenging and valuable synthetic targets.

From a biosynthetic point of view, polyketides are assembled by polyketide synthases (PKSs) via multiple Claisen condensations of acetates or other short carboxylates. Modifications of the resulting carbonyl moieties (reductions, dehydrations, …) and post-PKSs processing of the native chain can lead to extreme complexity and diversity in structure [6]. An ubiquitous and complex motif in polyketides is the contiguous triol. Due to the high density of chiral information packed on the three neighboring carbons and the potential to exist as eight possible isomers, methods to synthesize 1,2,3-triols in a stereoselective manner are of significant interest to the synthetic community [7].

In order to address this problem and to prepare highly oxygenated architectures in a stereodivergent way, Markó and coworkers became previously interested in the allyl donor **2** (Scheme 1) [8]. The stereochemistry of the orthogonally protected contiguous di- or triol could be modulated, depending on the nature and the stoichiometry of the Lewis acid [9]. When one equivalent of $SnCl_4$ was used, *syn/anti* **3** was obtained as the major product. In the presence of two equivalents of $SnCl_4$, selective formation of the *syn/syn* isomer **4** was observed. For the isomer **5**, $BF_3{\cdot}OEt_2$ failed to promote the allylation of **1** and the *anti/syn* triol remained unavailable. Nevertheless, aliphatic aldehydes lacking an α-alkoxy group, analogous to **6**, reacted smoothly in the presence of $BF_3{\cdot}OEt_2$ giving *syn* diols similar to **7**.

Inspired by these findings, it became interesting to apply this approach to reagent **9**, lacking the methylenesilane group relative to its parent **2** (Scheme 1) [10]. It was surmised that subjecting **9** to the previously developed reaction conditions would allow access to differently configured triads of type **10**. These compounds, as a consequence of the latent functionality in the double bond and the orthogonally protected polyol, are valuable advanced scaffolds for further synthetic planning. Combined with the versatility of the

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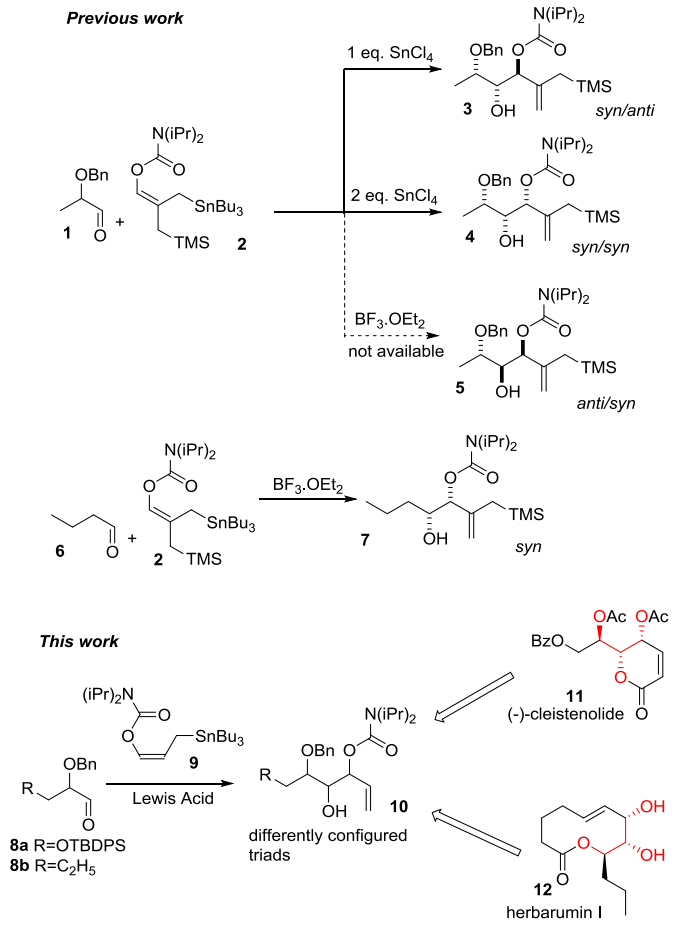
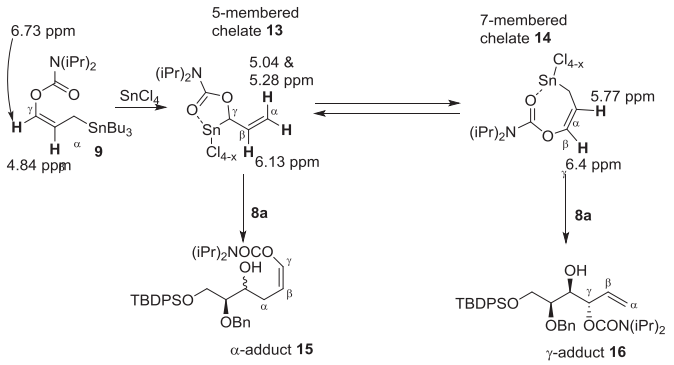


Scheme 1. Context of the current work.



Scheme 2. Transmetallation and proposed equilibrating isomers. ^{1}H NMR chemical shifts are shown.

allylation methodology, these products can readily allow access to a variety of polyketide derivatives.

In this report, the extension of the previous tin based allylation methodology to the allyltin carbamate reagent **9** is described. The optimization of the reaction was aided by ^{1}H and ^{119}Sn low temperature NMR spectroscopic investigations, which support the formation of two cyclic intermediates after transmetallation. Importantly, in addition to being able to obtain the previously described *syn/anti* stereochemistry for the new triol when $SnCl_4$ was used as the Lewis acid, the optimization of reaction conditions using $BF_3{\cdot}OEt_2$ allowed the previously inaccessible *anti/syn* stereochemistry to be obtained for the triol in good diastereomeric ratio. To showcase the versatility of the obtained scaffolds, their application towards the synthesis of two natural products, (−)-cleistenolide **11** [11,12] and herbarumin I [13,14], is described.

2. Results and discussion

2.1. Preparation of the syn/anti triad

As an initial trial for allylation with **9**, the allylstannane was premixed with one equivalent of $SnCl_4$ at −78 °C for **10** min, before aldehyde **8a** [15] was added slowly to the reaction. Surprisingly, these conditions gave a mixture of the α- and γ-addition products **15** and **16** in a 2:1 ratio (Scheme 2). While the desired product **16** was obtained as mostly one diastereoisomer, the α-addition product **15** formed as a 1.6 to 1 mixture of isomers, with scrambling of the homoallylic center. $SnCl_4$ is known to promote a fast and irreversible transmetallation in similar cases, leading to mixtures of equilibrating isomers via a 1,3-metalotropic shift [9,16]. Thus, the formation of these two products was rationalized through the formation of the two different intermediates **13** and **14**, proposed to have a chelating structure based on spectroscopic studies, *vide infra*.

For $SnCl_4$ the initial addition should occur at the γ-position [9], leading to intermediate **13** which upon reaction with the aldehyde would give the α-adduct **15**. Isomerization of **13** to **14** is needed to obtain the desired γ-product **16**. In order to improve the yield of the desired product **16** and study the nature of the intermediates, low temperature ^{1}H and ^{119}Sn NMR studies were performed, Fig. 1.

At 0 °C the ^{1}H NMR spectra shows a single set of signals for the starting allylstannane **9**. While most of these are sharp, the single resonance for the two C–H of the isopropyl groups on the carbamate at 3.9 ppm is partially broadened as a result of a fluxional process. Upon cooling the sample to −78 °C, this signal splits into two separate resonances separated by ~550 Hz. Splitting of the isopropyl CH_3 signals is also observed. Based on the coalescence temperature of −40 °C, the energy barrier for this process can be estimated as ~43 kJ/mol. This behavior is consistent with the ceasing of rotation around the carbamate C–N bond resulting in the two isopropyl groups being different. However, two other observations indicate that this process is potentially more complicated. At 0 °C the methylene protons α to Sn (1.7 ppm) present as a sharp doublet with noticeable coupling to Sn. Upon cooling this signal splits into two broad doublets each integrating for ~1 relative to the vinylic protons. Additionally, while presenting as a single signal at 0 °C, the ^{119}Sn NMR at −78 °C of carbamate **9** shows two different signals at −9.2 and −12.8 ppm, within the expected range for trialkylallyl tin species (Fig. 1) [17]. For both of the above observations, the estimated energy barriers for the processes that equate the different signals are essentially identical (43–45 kJ/mol) to the barrier calculated from the isopropyl groups. The presence of two signals for the tin at low temperature implies that two different conformations should be present, which cannot be explained only by the slow rotation of the $^{i}Pr_2N$ group. Nevertheless, the similarity of the energy barriers for the exchange suggests that both the exchange between these conformations and the slowing of the C–N rotation are connected. One possible explanation could be that rigidification of the structure allows the formation of a weak carbamate O–Sn interaction. Thus, the presence or absence of this interaction could lead to the observation of two signals. Despite the weak Lewis acidity of tetraalkyl Sn species, similar weak intramolecular interactions have been previously described for tetraorganotin species bearing a Lewis basic O in the alkyl chains [18]. Such an interaction could also explain the splitting of the

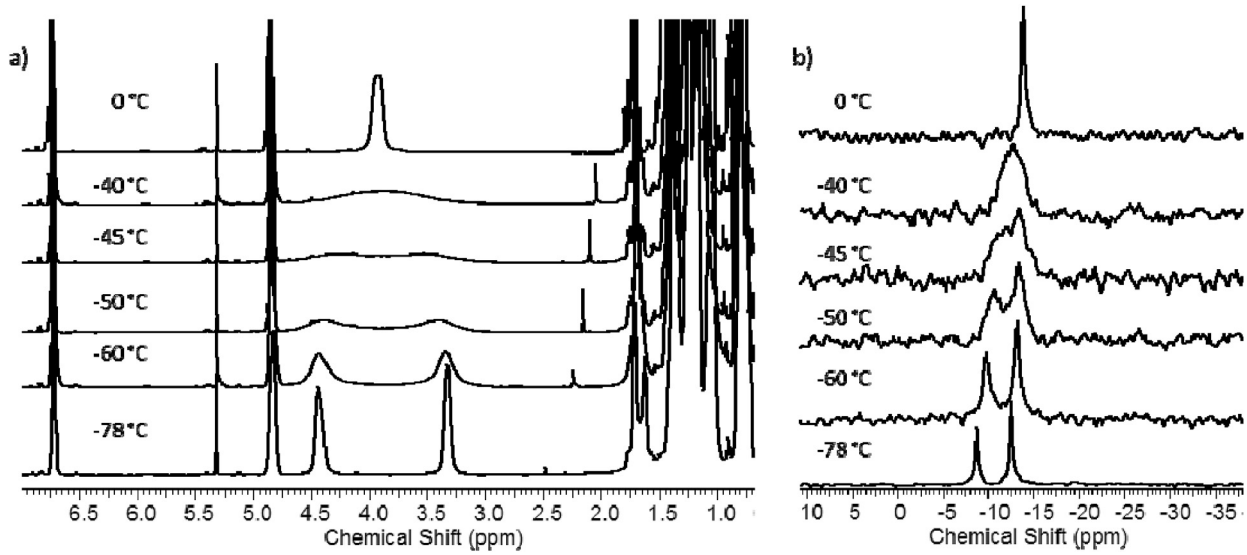


Fig. 1. a) ^{1}H and b) ^{119}Sn variable temperature NMR spectra of starting allyltin reagent **9**.

methylene proton signals observed at low temperature in the ^{1}H NMR. Nevertheless, given that the remaining signals in the ^{1}H NMR, while broad, do not necessarily show clear evidence of splitting this hypothesis is still tentative.

After the addition of $SnCl_4$ at −70 °C, the signals corresponding to **9** in the ^{1}H NMR spectra, Fig. 2, disappear completely within the acquisition time of the spectrum (~90 s) and give rise to two sets of signals in a roughly 1:1 ratio (Scheme 2). For one of the sets of signals, three clear proton resonances were found at 6.13; 5.28 and 5.04 ppm indicative of a terminal olefin, as would be expected in **13**. For the other set of signals, two characteristic resonances (6.40 and 5.77 ppm) were found, suggesting an internal polarized double bond as postulated for intermediate **14**. The coupling between the vinylic protons in this species ($^{3}J = 6$ Hz) is consistent with a Z configuration of the double bond. Further evidence for the structure of these two species comes from the ^{119}Sn NMR.

In agreement with the ^{1}H NMR analyses, the ^{119}Sn spectra show that **9** was entirely consumed within the 3 min of spectrum acquisition after addition of $SnCl_4$ (Scheme 2). Two new signals are observed, one between +165 and + 167 ppm, attributed to tributyltin chloride, and the second between −210 and −214 ppm [18].

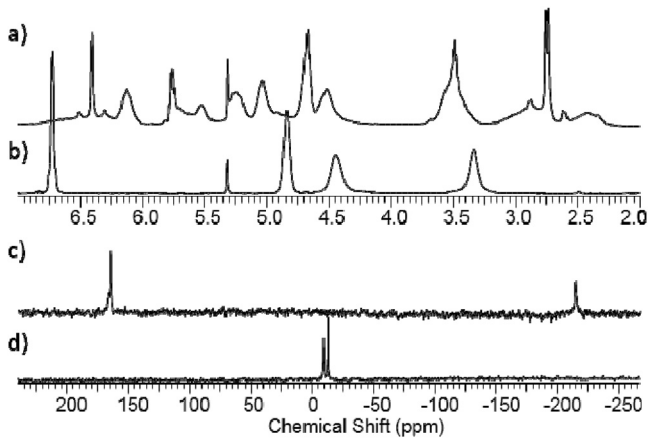


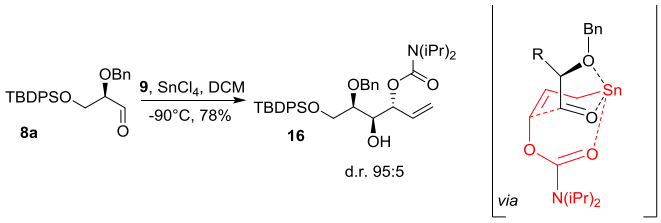
Fig. 2. Low temperature ^{1}H (a&b) and ^{119}Sn (c&d) NMR spectra of 9 before (b&d) and after (a&c) addition of 1 eq. of $SnCl_4$.

These latter broad signals are attributed to the transmetallated allyl tin chloride chelates. The severe shielding can be partially explained by the butyl to chloride exchange on the Sn atom. A ^{119}Sn chemical shift of −36 ppm was for instance reported for trichloroallylstannane at −90 °C by Keck [17]. The additional dramatic upfield δ_{Sn} after transmetallation compared to trichloroallylstannane could further be accounted for by the presence of the donating carbamate moiety which can participate in intramolecular hypervalent O···Sn interactions [17]. Intramolecular chelation with benzyl ethers in tin chloride species has been observed previously to lead to chemical shifts in the range of −169 to −187 similar to what is observed [19a].

The above observations, the presence of terminal and internal double bonds and the chemical shift range observed for the intermediates after exchange with $SnCl_4$, support the hypothesized chelate structures of the intermediates **13** and **14** proposed in Scheme 2. As intermediate **14** leads to the desired product **16**, additional studies looking at both temperature and mixing time with the $SnCl_4$ were carried out to see what factors affect the relative quantity of intermediate **14**. Notably, when kept at −70 °C for an extended period of time the ratio of **14** relative to **13** appears to increase based on the integration of the vinylic proton resonances in the ^{1}H NMR (Scheme 2). This occurs over the course of an hour indicating a potentially slow exchange between **13** and **14**. However, an increase in the temperature from −70 °C to −60 °C results in a rapid decrease of the amount of **14** within 10 min. While, based on integration, this appears to coincide with an increase in the amount of **13**, given the broadness of many of the signals present, the potential for degradation of **14** or its exchange with other conformers cannot be ruled out.

Nevertheless, based on these observations, we decided to lower the reaction temperature from −78 °C to −90 °C after premixing the Lewis acid with **9**. Furthermore, the aldehyde was only added to the reaction mixture after 60 min at −90 °C to ensure a higher ratio of **14** to **13**. To our satisfaction, using these optimized conditions the ɣ-addition product **16** was exclusively formed as a 95:5 mixture of diastereoisomers. (Scheme 3). X-ray diffraction analyses of the acetonide derivative **16b** revealed the triad to be of *syn/anti* relative configuration, similar to its homologue **3** [8], Fig. 3.

As a consequence of the similarity of **9** with allyl donor **2**, we propose that the transition state, leading from **14** to the product **16**



Scheme 3. Allylation and proposed transition state.

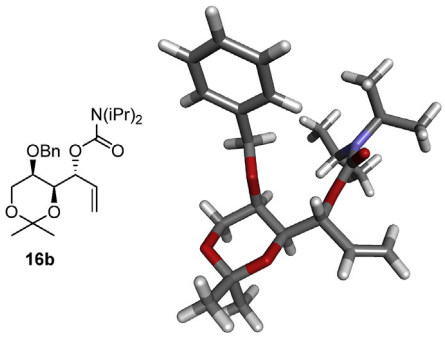


Fig. 3. Structure of the acetonide derivative of 16 (left) as confirmed by the X-ray crystal structure (right).

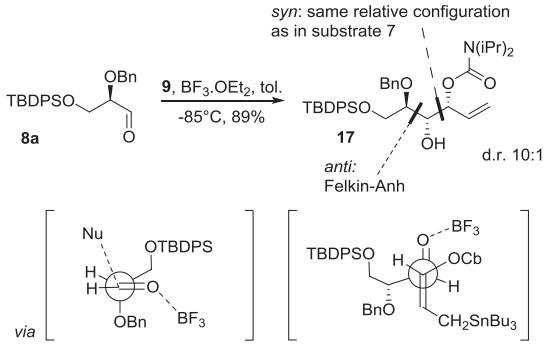
includes the same key features as described previously (Scheme 3) [8]. The transmetallated species would react with the aldehyde **8a** (or **8b**) through a bicyclic Cram chelate transition state as depicted in Scheme 3. Due to the ability to chelate the trichlorotin generated under our conditions, the carbamate would adopt a pseudo-axial orientation in order to interact with the tin which is also chelated by the benzyl ether and carbonyl of the aldehyde. Allyl transfer through this rigid transition state would then lead to the observed *syn/anti* selectivity.

While the formation of the *syn/anti* product was similar to the previous allylation reagent **2**, interestingly, **9** showed very different reactivity with regards to the stoichiometry of the Lewis acid. According to the previous study [8], the use of two equivalents of $SnCl_4$ in the presence of **9** should give the *syn/syn* configured triol of type **10**. Unfortunately, every attempt at using these conditions with the current reagent led to isolating the unwanted *syn/anti* product in poor yield, or extensive degradation of the starting material.

2.2. Preparation of the anti/syn triad

In order to broaden the range of triol diastereomers available from allylation with **9**, the use of a different Lewis acid, BF_3, was studied. Based on the assumption that the addition of **9** onto the α-hydroxy aldehyde should be face-selective as described by the Felkin-Anh model [20] and the *syn* stereochemistry previously observed for the formation of diol **7**, an overall *anti/syn* configuration for the product triol **17** was expected (Scheme 4). The incoming nucleophile and the aldehyde in its preferred conformation according to the polar Felkin-Anh model are shown. Furthermore, the Newman projection along the new C–C bond depicts the *Si-Si* interaction of the aldehyde and the allyl-donor that leads to the *anti/syn* configuration of adduct **17**. The addition of the nucleophile's Re face would reasonably be expected to have a significant steric clash between the OCb/CH_2SnBu_3 groups on the aldehyde.

It is important to note that when previously applied to allyltin reagent **2**, $BF_3 \cdot OEt_2$ failed to promote the allylation of protected α-



Scheme 4. Synthesis of 17 and rationale for the anti/syn selectivity; Lower left structure: Felkin-Anh model for the addition; The lower right Newman-projection depicts the Si–Si approach between the aldehyde and the nucleophile.

hydroxy aldehydes analogous to **1** [8]. The disappointing outcome was reportedly due to competitive destannylation of **2** under the reaction conditions. To see if this could be prevented with reagent **9**, the temperature, solvent and stoichiometry of Lewis acid used for the reaction were screened, Scheme 4 and Table 1. Surprisingly, even under the previously reported conditions [8], allyl addition onto aldehyde **8a** was observed. However, the best results were obtained with one equivalent of $BF_3 \cdot OEt_2$ in toluene at −95 °C. Using these conditions, the *anti/syn* triol could be obtained in good diastereoisomeric ratio (d.r. = 10:1). The stereochemistry of **17** was confirmed through X-ray diffraction of the crystalized material, Fig. 4.

2.3. Formal synthesis of herbarumin I

The successful optimization of the *anti/syn*- and the *syn/anti* triols with **9**, provides a useful scaffold for the further syntheses. To highlight the value of these compounds two synthetic applications were envisaged: herbarumin I and (−)-cleistenolide.

For the first target, the phytotoxic lactone herbarumin I, **12**, provides an interesting challenge as it contains a contiguous *anti/anti* triol (Scheme 5). In 2000, the phytotoxic medium-sized lactone herbarumin I (together with herbarumin II) was extracted from Phoma herbarum Westend [13]. After the structure elucidation, herbariums received much interest from synthetic chemists and in 2001, the first total synthesis of herbarumin I was described by the group of Fürstner [14a,b]. Many other examples followed and virtually all methods took either advantage of chiral templates such as D-ribose [14b], L-arabinose [14c] D-(−)-isoascorbic acid [14d], L-ascorbic acid [14e], glyceraldehyde [14h,j] or employed asymmetric aldol [14f] and epoxidation protocols [14g].

We planned to use a complementary method, consisting in the allylation procedure. Although the contiguous *anti/anti* triol that is

Table 1
Optimization of reaction between **8a** and **9**.

Solvent	Eq. BF_3	T (° C)	Ratio[a]
DCM	2	−78	1.9:1
DCM	2	−78- > r.t.	2.3:1
Et_2O	2	−78	2.7:1
THF	2	0	6.7:1
MeCN	2	r.t.	2.3:1
MeCN	1	−30	1.6:1
Toluene	2	−78	7.5:1
Toluene	4	−78	2.7:1
Toluene	1	−78	7.7:1
Toluene	1	−95	10:1

[a] Ratio of the anti-syn to anti-anti products; r.t.: room temperature.

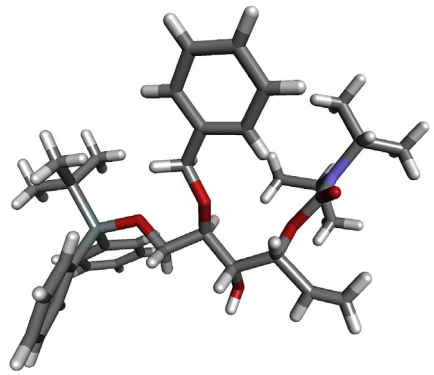
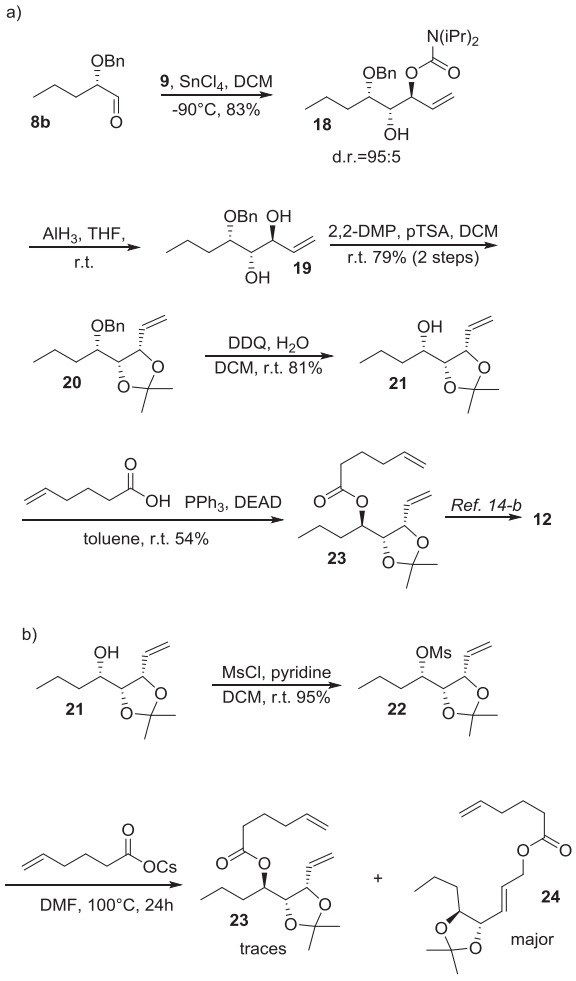


Fig. 4. X-ray structure of the anti/syn triad **17**.



Scheme 5. Formal synthesis of herbarumin I.

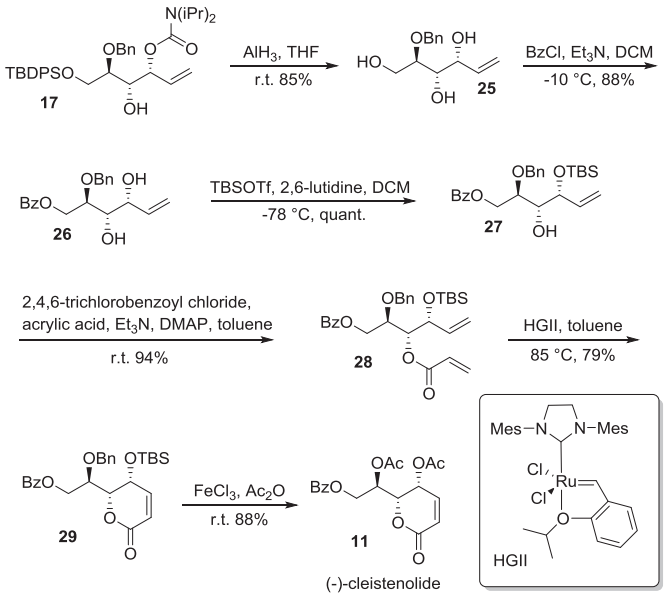
embodied in herbarumin I is not accessible in a direct manner by our method, the orthogonal protecting groups allow an easy and selective S_N2 type inversion of the absolute configuration of one hydroxy function. As such, the chiral information stored in the *syn/anti* adduct can be used to allow access to the *anti/anti* building block.

Starting from α-benzyloxyaldehyde **8b** [21], the allylation product **18**, containing the precursor *syn/anti* triol, was obtained in 83% yield via $SnCl_4$ promoted allylation with the allyltin carbamate **9** under the reaction conditions described above. The protected triol product was then submitted to an aluminum hydride promoted cleavage of the carbamate. The resulting diol **19** was then protected as the acetonide using 2,2-DMP to give **20** in 79% yield across the two steps [22]. A subsequent oxidative debenzylation using DDQ allowed access to the secondary alcohol **21**. The initial approach envisaged for inverting the stereochemistry of this alcohol, Scheme 5b, was the direct S_N2 substitution of the mesylate with the cesium salt of 5-hexenoic acid. While **23** was obtained in trace amounts using this procedure, the major product observed was **24** which is proposed to form through concomitant addition of the carboxylate onto the double bond with migration of the acetonide to displace the mesylate group. As a second approach, a Mitsunobu [23] substitution proved more reliable and afforded product **23** in acceptable yield. At this stage the synthesis intercepted the same intermediate previously reported by Fürstner and co-workers in their synthesis of herbarium I [14b]. As further confirmation of the stereochemistry, the spectral data and optical rotation of **23** were in perfect agreement with the previously reported data.

2.4. Total synthesis of (−)-cleistenolide

To further show the value and scope of the developed scaffolds, they provide an efficient starting point for the total synthesis of (−)-cleistenolide, **11**, a naturally occurring lactone isolated in 2007 from *Cleistochlamys kirkii* oliver [11] and that has been reported to have both antibacterial and antitumor activity [12k]. The three contiguous chiral centres embedded in this natural product, combined to its attractive biological properties have already set the stage for earlier syntheses [12]. The first total synthesis of the δ-lactone was already disclosed in 2010 by Schmidt and co-workers [12a]. After this initial report, the lactone received much attention from the scientific community. Its synthesis was addressed in several creative reports, starting from chiral building blocks such as d-mannitol [12a,b,d,f,g], D-arabinose [12c], (−)-isoascorbic acid [12e], or D-tartaric acid [12h]. Alternatively to these methods utilizing the chiral pool, a chemoenzymatic approach to (−)-6-*epi*-cleistenolide was described [12i]. More recently, the product was accessed from D-glucose either protected as the monoacetonide or as the diacetonide [12j,k]. The combination of the tin based allylation and the new scaffolds is orthogonal to these procedures since the chiral framework of the natural product is built from only one existing chiral center.

After obtaining the *anti/syn* triol **17** under the reaction conditions described above ($BF_3 \cdot OEt_2$ in toluene at −85 °C), the primary and allylic hydroxyl groups were deprotected using freshly synthesized aluminium hydride to give triol **25** in 85% yield (Scheme 6). Selective benzoylation of the primary alcohol at low temperature (−10 °C) using benzoyl chloride afforded intermediate **26** in 88% yield. Initial attempts to selectively acetylate the allylic alcohol proved unsatisfactory. However, TBS protection using a combination of TBSOTf and 2,6-lutidine at −78 °C resulted in quantitative silylation of the allylic alcohol. Subsequent acrylation of homoallylic alcohol **27** under Yamaguchi's conditions provided the desired ester **28** in excellent yield [24]. Ring closing metathesis using Hoveyda-Grubbs' second generation catalyst was then used to give the α,β unsaturated lactone **29** in 79% yield [25]. Finally, to obtain the desired natural product, $FeCl_3$ mediated deprotection of the TBS and benzyl groups was performed with the *in situ* acetylation of the resulting diol [26]. When acetic anhydride was used as the solvent, excellent yields of (−)-cleistenolide were obtained. X-ray diffraction analysis, Fig. 5, unambiguously revealed **10** to possess the same structure as the naturally occurring (−)-cleistenolide [10]. Additionally, the optical rotation of our sample was



Scheme 6. Total synthesis of (−)-cleistenolide.

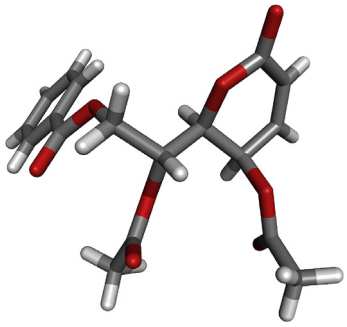


Fig. 5. X-ray crystal structure of (−)-cleistenolide obtained from this synthetic procedure.

similar to the value obtained for the natural product and for other synthetic samples [11,12].

3. Conclusions

In conclusion, the methodology developed previously with stannane **8** was successfully extended to the stannane **9** and the reaction optimized with the help of variable temperature ^{1}H and ^{119}Sn NMR spectroscopic studies. The *syn/anti* triad **16**, resulting from the use of one equivalent of $SnCl_4$, was successfully valorized as a building block for a formal synthesis of herbarumin I. The required *anti/anti* configuration in this natural product was prepared indirectly from the *syn/anti* compound **16** upon inversion of the stereochemistry of one of the centres, which is facilitated by the orthogonal protection of the triol. Additionally, through optimization of the boron trifluoride mediated allylation reaction, the *anti/syn* adduct **17** that was inaccessible in the previous study could be obtained. The resulting scaffold provides an efficient starting product for the synthesis of (−)-cleistenolide as described.

4. Experimental section

4.1. General

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an argon atmosphere. Commercial reagents were used as received. All anhydrous solvents were distilled prior to use: THF and Et_2O from Na and benzophenone; CH_2Cl_2 from CaH_2 and toluene from Na. Flash column chromatography was carried out on Merck silica gel 60 (40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance 300 and 500. ^{1}H NMR and ^{13}C NMR spectra were referenced to $CHCl_3$ ($\delta = 7.26$ ppm) and $CDCl_3$ ($\delta = 77.16$ ppm) respectively. ^{1}H NMR data are shown as follows: δ in ppm (multiplicity, coupling constant, integration). The following abbreviations are used to designate multiplicity: m (multiplet), b (broad), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), etc. ^{119}Sn NMR was recorded on a Bruker Avance 500, with $SnMe_4$ as reference (98% $SnMe_4$, 2% C_6D_6 90° pulse calibration, 0 ppm). A broadband inverse probe (5 mm) was used. All ^{119}Sn spectra were measured using zgig (Bruker terms) sequence (acquisition with inverse gated decoupling for ^{1}H). The 01p was changed in order to measure broader range of signals, as SW was restricted to 530 ppm. High-resolution mass data were obtained on a Kratos MS50TC. Infrared spectra were recorded in cm^{-1} on a SHIMATZU-FTIR-8400S. Melting points were determined by Büchi 545 and Büchi SMP-20 devices. Optical rotations $[\alpha]_D^{20}$ are given in $10^{-1}degcm^2g^{-1}$. X-ray crystallographic studies were performed by the Molecular Structural Analysis platform (ASM) of the Institute of condensed matter and nanosciences at the Université catholique de Louvain.

4.2. (3S,4R,5S)-5-(benzyloxy)-4-hydroxyoct-1-en-3-yl diisopropylcarbamate ***18***

To a stirred solution of **9** (2.59 g, 5.46 mmol, 1.05 eq.) in DCM (130 mL) at −78 °C was added $SnCl_4$ (0.6 mL, 5.2 mmol, 1 eq.) over 5 min and the resulting mixture was allowed to stir for 1 h at that temperature. Subsequently, the reaction mixture was cooled to −90 °C and aldehyde **8b** (1 g, 5.2 mmol, 1 eq.) in DCM (20 mL) was added over a period of 30 min. After 2 h, the reaction mixture was quenched by adding a saturated aqueous solution of $NaHCO_3$ (150 mL). The resulting suspension was first filtered and after phase separation, the aqueous layer was extracted with EtOAc (2 × 40 mL). Combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue that was further purified by flash column chromatography on silica gel (PE/EtOAc 10:1 to 6:1) to yield **18** as a colorless oil (1.63 g, 4.32 mmol, 83%). $[\alpha]_D^{20}$: −9.3 (c = 10.8, $CHCl_3$). HRMS *m/z* calcd for $C_{22}H_{35}NO_4Na$: 400.2464; found: 400.2451. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.00 (m, 5H), 6.03 (ddd, $J = 17.1$, 10.5, 6.8 Hz, 1H), 5.43–5.19 (m, 3H), 4.61 (d, $J = 11.0$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 3.99 (bs, 1H), 3.87 (bs, 1H), 3.66 (ddd, $J = 7.6$, 6.3, 3.5 Hz, 1H), 3.49 (td, $J = 6.2$, 3.6 Hz, 1H), 2.51 (d, $J = 7.6$ Hz, 1H), 1.76–1.57 (m, 2H), 1.50–1.32 (m, 2H), 1.22 (d, $J = 6.8$ Hz, 12H), 0.93 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 138.3, 134.6, 128.5, 128.2, 127.9, 118.2, 77.9, 75.3, 74.1, 72.8, 46.4, 45.8, 33.2, 21.6, 20.9, 18.7, 14.3. IR (film, cm^{-1}): 3462, 2962, 2933, 2873, 1693, 1304, 1284, 1049.

4.3. (4R,5S)-4-((S)-1-(benzyloxy)butyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane ***20***

To a stirred solution of $AlCl_3$ (0.6 g, 4.77 mmol, 1.5 eq.) in THF at 0 °C (15 mL) was added $LiAlH_4$ (3.58 mL, 4 M in THF, 14.3 mmol, 4.5 eq.) and the mixture was stirred for 20 min. Subsequently, alcohol **18** (1.2 g, 3.18 mmol, 1 eq.) in THF (5 mL) was added. After 30 min at r.t., the reaction was quenched by slow addition of water (10 mL) and EtOAc (20 mL). The ensuing mixture was left stirring at r.t. for 30 min. After phase separation, the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure to

yield **19** as a colorless oil that was immediately dissolved in 2,2-DMP (5 mL, 40.6 mmol, 12.8 eq.) and *p*TSA monohydrate (40 mg, 0.21 mmol, 0.06 eq.) was added. After 20 min, the reaction mixture was diluted with EtOAc (50 mL) and quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL). After phase separation, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel (PE/EtOAc 15:1 to 10:1) to yield **20** as a colorless oil (730 mg, 2.51 mmol, 79% on 2 steps). $[\alpha]_D^{20}$: −7.1 (c = 0.38, $CHCl_3$). HRMS *m/z* calcd for $C_{18}H_{26}O_3Na$: 313.1780; found: 313.1782. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–6.91 (m, 5H), 5.89 (tdd, *J* = 17.1, 10.8, 8.5 Hz, 1H), 5.26 (m, 2H), 4.82 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.43 (dd, *J* = 8.7, 6.1 Hz, 1H), 4.20 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.42 (td, *J* = 7.8, 3.5 Hz, 1H), 1.54 (s, 3H), 1.52–1.28 (m, 4H), 1.39 (s, 3H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 134.7, 128.3, 128.0, 127.5, 119.0, 109.0, 81.8, 79.5, 77.4, 73.1, 33.3, 28.3, 25.8, 18.7, 14.1. IR (film, cm^{-1}): 2983, 2958, 2933, 2871, 1706, 1454, 1429, 1379, 1369, 1307, 1288, 1247, 1217, 1153, 1145, 1097, 1076, 1039, 997.

4.4. (S)-1-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol **21**

To a stirred solution of **20** (420 mg, 1.45 mmol, 1 eq.) in DCM (7 mL) and phosphate buffer (1 mL) was added at r.t. DDQ (1.3 g, 5.8 mmol, 4 eq.). The resulting orange-brown reaction mixture was left stirring for 4 h, before being filtered over Celite®. The filtrate was then diluted with a saturated aqueous solution of $NaHCO_3$ (50 mL). After phase separation, the aqueous layer was extracted with EtOAc (2 × 20 mL). Combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was then purified by flash column chromatography on silica gel (PE/EtOAc 10:1) to yield **21** as colorless oil (235 mg, 1.17 mmol, 81%). HRMS *m/z* calcd for $C_{11}H_{20}O_3Na$: 223.13047; found: 223.1305. ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.2, 10.2, 8.1 Hz, 1H), 5.34 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 4.55 (dd, *J* = 7.8, 7.1 Hz, 1H), 4.00 (dd, *J* = 6.6, 5.5 Hz, 1H), 3.67–3.50 (m, 1H), 2.12 (d, *J* = 5.3 Hz, 1H), 1.51 (s, 3H), 1.62–1.25 (m, 4H), 1.39 (s, 3H), 0.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 119.4, 108.7, 80.9, 79.3, 69.5, 36.1, 27.6, 25.2, 18.8, 14.1. IR (film, cm^{-1}): 3429, 2955, 1682, 1458, 1377, 1304, 1254, 1215, 1169, 1068, 1030, 926.

4.5. (R)-1-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)butyl hex-5-enoate **23**

To a stirred solution of DEAD (0.158 mL, 1 mmol, 4 eq.) and Ph_3P (262 mg, 1 mmol, 4 eq.) at r.t. in toluene was added alcohol **21** (50 mg, 0.25 mmol, 1 eq.) The resulting mixture was left stirring for 1 h, resulting in a deep orange coloration. Subsequently, 5-hexenoic acid (0.12 mL, 1 mmol, 4 eq.) was added over a period of 5 min. After 12 h, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and EtOAc (100 mL). After phase separation, the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The orange residue was further purified by flash column chromatography on silica gel (PE/EtOAc 20:1 to 15:1) to yield **23** as a colorless oil (40 mg, 0.135 mmol, 54%). $[\alpha]_D^{20}$:+25.6 (c = 2.3, $CHCl_3$). HRMS *m/z* calcd for $C_{17}H_{28}O_4Na$: 319.18798; found: 319.1883. ^1H NMR (300 MHz, $CDCl_3$) δ 5.88–5.69 (m, 2H), 5.33 (dt, *J* = 17.0, 1.2 Hz, 1H), 5.21 (d, *J* = 10.3 Hz, 1H), 5.07–4.96 (m, 2H), 4.93 (td, *J* = 7.6, 3.8 Hz, 1H), 4.60 (td, *J* = 7.0, 6.5 Hz, 1H), 4.18 (dd, *J* = 7.3, 6.7 Hz, 1H), 2.25 (td, *J* = 7.5, 3.6 Hz, 2H), 2.08 (dd, *J* = 14.1, 7.3 Hz, 2H), 1.68 (m, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.36 (m, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 137.6, 133.3, 118.4, 115.3, 108.7, 78.9, 78.4, 71.6, 33.7, 33.4, 33.0, 27.5, 25.2, 23.9, 17.9, 14.0. IR (film, cm^{-1}): 3078, 2954, 2867, 1738, 1640, 1430, 1254, 1215.

4.6. (S)-1-((4S,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl) butylmethanesulfonate **22**

To a stirred solution of **21** (200 mg, 1.00 mmol, 1eq) in DCM (2 mL) was added sequentially pyridine (284 mg, 3.00 mmol, 3 eq.) and methane sulfonylchloride (137 mg, 1.20 mmol, 1.2 eq.) and the reaction was allowed to stir overnight. The reaction was then quenched by addition of an aqueous solution of saturated NH_4Cl. The solution was then extracted three times with DCM. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product purified by column chromatography on silica gel (AcOEt:petroleum ether/1:4) to give mesylate **22**. (0.111 mg, 0.4 mmol, 40%) ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.3, 13.5, 8.8 Hz, 1H), 5.35 (d, *J* = 5.7 Hz, 1H), 5.31 (s, 1H), 4.62 (td, *J* = 8.9, 2.7 Hz, 1H), 4.47 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.23 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.10 (s, 3H), 1.60–1.51 (m, 2H), 1.50 (s, 3H), 1.37 (s, 3H), 0.97–0.86 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 120.4, 109.3, 82.3, 78.9, 78.9, 39.0, 33.2, 28.0, 25.7, 18.0, 13.6.

4.7. (3R,4R,5R)-5-(benzyloxy)-6-((tert-butyldiphenylsilyl)oxy)-4-hydroxyhex-1-en-3-yl diisopropylcarbamate **16**

To a stirred solution of **9** (7.14 g, 0.015 mol, 1.05 eq.) in DCM (240 mL) at −78 °C was added dropwise $SnCl_4$ (3.92 g, 0.015 mol, 1.05 eq.) over 5 min. The resulting mixture was allowed to stir for 1 h at that temperature. Subsequently, the reaction mixture was cooled to −90 °C and aldehyde **8a** (6.00 g, 0.014 mol, 1 eq.) in DCM (10 mL) was added carefully. After 2 h, DCM (100 mL) and a saturated aqueous solution of $NaHCO_3$ (200 mL) were added to the reaction vessel. After phase separation, the combined organic fractions were dried over $MgSO_4$, concentrated under reduced pressure and resulting milky residue was purified by flash column chromatography on silica gel (PE 100% to PE/EtOAc 15:1) to furnish **16** as a colorless oil (5.49 g, 65%). HRMS *m/z* calcd for $C_{36}H_{49}NO_5NaSi$: 626.3278; found: 626.3283. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.27 (m, 15H), 6.08–5.94 (m, 1H), 5.40–5.26 (m, 3H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.04 (bs, 1H), 3.87 (td, *J* = 7.9, 2.1 Hz, 1H), 3.85 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.77 (dd, *J* = 10.3, 5.2 Hz, 2H), 3.73–3.63 (m, 1H), 2.52 (d, *J* = 8.2 Hz, 1H), 1.27–1.15 (m, 12H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 138.0, 135.7, 135.7, 135.0, 133.3, 133.2, 129.9, 129.9, 128.5, 128.3, 127.9, 127.9, 118.2, 77.6, 74.7, 73.3, 72.3, 63.1, 46.6, 45.6, 26.9, 21.8, 20.8, 19.3. IR (film, cm^{-1}) 3458, 3070, 3053, 3029, 2997, 2960, 2931, 2883, 2856, 1679, 1647, 1471, 1427, 1367, 1299, 1284, 1251, 1190, 1132, 1105, 1047, 1029.

4.8. Acetonide formation from 16. **16b**

Following TBS protection, the resulting Dihydroxycarbamate (250 mg, 0.684 mmol, 1 eq.) was solubilized in DCM (5 mL, 0.14 M). Subsequently, PTSA hydrate (13 mg, 0.068 mmol, 0.1 eq.) was added. At room temperature, 2,2-dimethoxypropane (1.7 mL, 13.68 mmol, 20 eq.) was added and reaction mixture was heated with stirring for 2 h (heating in a silicone oil bath, bath temperature 65 °C). TLC shows no presence of alcohol. Reaction was quenched with $NaHCO_3$ (sat. sol.) (20 mL). Subsequently, aqueous phase was back extracted with DCM (3 × 20 mL), combined organic layers were dried over MgSO4, concentrated in vacuo. Resulting oil was purified by flash silica gel chromatography (petroleum ether/ethyl

acetate, 10/1) to yield a white solid (250 mg, 0.616 mmol, 90%). Rf = 0.51 (PE/AcOEt = 4/1, dark blue with vanillin). Mp = 103–105 °C. HRMS, *m/z*: calcd. ($C_{23}H_{35}NO_5$): 406.25880; found ($C_{23}H_{35}NO_5$): 406.25882. 1H NMR (300.13 MHz, C_6D_6) δ 7.54 (d, J = 7.3 Hz, 2H), 7.36–7.24 (m, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.36 (ddd, J = 17.2, 10.7, 5.3 Hz, 1H), 6.18 (ddt, J = 7.9, 5.5, 1.3 Hz, 1H), 5.58 (dt, J = 17.3, 1.3 Hz, 1H), 5.30 (dt, J = 10.7, 1.2 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.08 (dd, J = 8.1, 2.1 Hz, 1H), 4.01 (dd, J = 12.8, 2.2 Hz, 1H), 3.91 (bs, 2H), 3.64 (dd, J = 12.8, 2.2 Hz, 1H), 3.36 (q, J = 2.0 Hz, 1H), 1.56 (s, 3H), 1.34 (s, 3H), 1.22 (bs, 12H). ^{13}C NMR (75.48 MHz, C_6D_6) δ 153.7, 138.8, 136.3, 128.5, 128.2, 116.4, 98.9, 73.7, 72.6, 71.7, 70.9, 61.4, 46.1, 29.1, 21.1, 19.3. IR (film, cm^{-1}): 2966, 2924, 2854, 1697, 1651, 1435, 1366, 1312, 1285, 1200, 1134, 1088, 1049, 984, 910.

4.9. (3R,4S,5R)-5-(benzyloxy)-6-((tert-butyldiphenylsilyl)oxy)-4-hydroxyhex-1-en-3-yl diisopropylcarbamate **17**

To a stirred solution of **8a** (4.94 g, 11.81 mmol, 1 eq.) in toluene (200 mL) was added **9** (5.6 g, 11.81 mmol, 1 eq.) and the resulting mixture was cooled to −85 °C. Subsequently, $BF_3{\cdot}OEt_2$ (1.5 mL, 11.81 mmol, 1 eq.), was added over 15 min and the reaction mixture was maintained at this temperature for 5 h. The reaction mixture was then poured onto a mixture of a saturated aqueous solution of $NaHCO_3$ (500 mL) and diethyl ether (100 mL). After phase separation, the aqueous layer was extracted with DCM (2 × 50 mL). Combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (PE/EtOAc 15:1 to 10:1) to yield **17** as a white solid (6.35 g, 89%). Mp = 75 °C. $[\alpha]_D^{20} = -6.3$ (c = 2.3, $CHCl_3$). HRMS *m/z* calcd for $C_{36}H_{50}NO_5Si$: 604.34528; found: 604.3453. 1H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.48–7.27 (m, 11H), 5.97 (ddd, J = 17.3, 10.6, 5.7 Hz, 1H) 5.65–5.58 (ddt, J = 5.9, 3, 1.5 Hz, 1H), 5.34 (dd, J = 17.3, 1.5 Hz, 1H), 5.28 (dd, J = 10.7, 1.2 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.46 (d, J = 10.8 Hz, 1H), 4.09–3.84 (m, 5H), 3.57 (dt, J = 7.9, 4.7 Hz, 1H), 2.93 (d, J = 5.0 Hz, 1H), 1.24 (d, J = 6.8 Hz, 12H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 138.1, 135.8, 135.0, 133.2, 133.1, 130.0, 128.5, 128.4, 127.9, 117.4, 78.7, 74.5, 74.3, 73.1, 64.4, 46.4, 45.8, 27.0, 21.7, 20.8, 19.3. IR (film, cm^{-1}): 3423, 2930, 1683, 1647, 1471, 1107, 1070.

4.10. (2R,3S,4R)-2-(benzyloxy)hex-5-ene-1,3,4-triol (5–57) **25**

To a stirred solution of $AlCl_3$ (0.45 g, 3.36 mmol, 1 eq.) in THF (10 mL) was added, at 0 °C, $LiAlH_4$ (4 M in Et_2O, 2.5 mL, 10.09 mmol, 3 eq.). The resulting mixture was left stirring at r.t. for 25 min before addition of **17** (2.03 g, 3.36 mmol, 1 eq.) in THF (20 mL). After 2 h of stirring at r.t., the reaction was quenched with aqueous HCl (2.0 M) until a pH of 1 was reached. The resulting mixture was left stirring for 1 h and a saturated aqueous solution of $NaHCO_3$ (80 mL) was added. After phase separation, the aqueous layer was extracted with DCM (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a residue that was further purified by flash column chromatography on silica gel (PE/EtOAc 2:1 to EtOAc 100%) to yield **25** as a white solid (0.68 g, 85%). Mp = 43 °C. $[\alpha]_D^{20} = -11.1$ (c = 0.7, $CHCl_3$). HRMS *m/z* calcd for $C_{13}H_{18}O_4Na$: 261.11097; found: 261.11097. 1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5H), 5.93 (ddd, J = 17.2, 10.6, 5.3 Hz, 1H), 5.41 (dd, J = 17.3, 1.5 Hz, 1H), 5.28 (dd, J = 10.6, 1.4 Hz, 1H), 4.69–4.63 (m, 2H), 4.41–4.33 (m, 1H), 3.90–3.72 (m, 3H), 3.66–3.59 (m, 1H), 2.43 (d, J = 5.4 Hz, 1H), 2.30 (d, J = 6.0 Hz, 1H), 1.89 (t, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 136.2, 128.6, 128.2, 128.1, 116.8, 78.8, 73.3, 72.5, 71.7, 61.4. IR (film, cm^{-1}) 3479, 3448, 2878, 1454, 1396, 1051.

4.11. (2R,3S,4R)-2-(benzyloxy)-3,4-dihydroxyhex-5-en-1-yl benzoate **26**

To a stirred solution of **25** (350 mg, 1.469 mmol, 1 eq.) at 0 °C in DCM (26 mL) was added subsequently, pyridine (0.24 mL, 2.94 mmol, 2 eq.) and benzoyl chloride (0.17 mL, 1.47 mmol, 1 eq.). After 30 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL) and DCM (30 mL). After phase separation, the aqueous layer was extracted with DCM (2 × 20 mL). Combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (PE/EtOAc 2:1) to yield **26** as a colorless oil (457 mg, 91%). $[\alpha]_D^{20}$: −10.3 (c = 3.1, $CHCl_3$). HRMS *m/z* calcd for $C_{20}H_{23}O_5$: 343.15400; found: 343.15430. 1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 5.2, 3.3 Hz, 2H), 7.58 (ddd, J = 6.8, 4.0, 1.3 Hz, 1H), 7.44 (dd, J = 10.5, 4.7 Hz, 2H), 7.40–7.28 (m, 5H), 5.95 (ddd, J = 17.2, 10.5, 5.2 Hz, 1H), 5.40 (dt, J = 17.3, 1.5 Hz, 1H), 5.27 (dt, J = 10.6, 1.4 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.74 (dd, J = 12.1, 3.3 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.55 (dd, J = 12.1, 4.8 Hz, 1H), 4.47 (m, 1H), 3.92 (ddd, J = 7.1, 4.7, 3.3 Hz, 1H), 3.71 (td, J = 6.6, 2.5 Hz, 1H), 2.63 (d, J = 6.2 Hz, 1H), 2.39 (d, J = 5.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 137.5, 137.1, 133.2, 129.7, 128.6, 128.5, 128.1, 128.1, 116.7, 77.8, 72.9, 72.4, 71.3, 63.6. IR (film, cm^{-1}): 3438, 1716, 1601, 1070.

4.12. (2R,3R,4R)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxyhex-5-en-1-yl benzoate **27**

To a stirred solution of **26** (60 mg, 0.175 mmol, 1 eq.) in DCM (3 mL) was added subsequently at 0 °C, 2,6-lutidine (0.045 mL, 0.386 mmol, 2.2 eq.) and TMSOTf (0.04 mL, 0.175 mmol, 1 eq.). After 30 min, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and DCM (50 mL). After phase separation, the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was further purified by flash column chromatography on silica gel (PE/EtOAc 20:1 to 15:1) to yield **27** as a colorless oil (78 mg, 97%). $[\alpha]_D^{20} = -3.9$ (c = 3.7, $CHCl_3$). HRMS *m/z* calcd for $C_{26}H_{37}O_5Si$: 457.24048; found: 457.24006. 1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H), 7.61–7.52 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.37–7.23 (m, 5H), 5.96 (ddd, J = 17.4, 10.3, 7.2 Hz, 1H), 5.28 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.4 Hz, 1H), 4.91 (dd, J = 12.1, 2.5 Hz, 1H), 4.82 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.51 (dd, J = 12.2, 4.7 Hz, 1H), 4.46 (m, 1H), 3.74 (ddd, J = 7.3, 4.5, 2.5 Hz, 1H), 3.64 (td, J = 7.6, 2.6 Hz, 1H), 2.64 (d, J = 8.0 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.6, 138.2, 133.1, 130.3, 129.8, 128.5, 128.5, 127.9, 116.9, 77.7, 74.0, 73.1, 72.1, 63.5, 26.0, 18.3, −3.6, −4.7. IR (film, cm^{-1}): 3491, 2928, 2854, 1720, 1647, 1454, 1389, 1273, 1258, 1219, 1099, 1057, 1026, 1003.

4.13. (2R,3R,4R)-3-(acryloyloxy)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy) hex-5-en-1-yl benzoate **28**

To a stirred solution of acrylic acid (0.66 mL, 9.64 mmol, 1.1 eq.) in toluene (80 mL) was added sequentially triethylamine (7.33 mL, 52.6 mmol, 6 eq.) and 2,4,6-trichlorobenzoyl chloride (1.5 mL, 9.64 mmol, 1.1 eq.) which resulted in a white precipitate. After 1 h, alcohol **27** (4.0 g, 8.76 mmol, 1 eq.) and DMAP (0.53 g, 4.38 mmol, 0.5 eq.) in toluene (20 mL) were added. After 2 h, the reaction mixture was poured onto a saturated aqueous solution of $NaHCO_3$ (100 mL) and Et_2O (50 mL). After phase separation, the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown residue was further purified by flash

column chromatography on silica gel (PE/EtOAc 15:1) to yield **28** as a colorless oil (3.85 g, 86%). $[\alpha]_D^{20} = +46.9$ (c = 2.5, $CHCl_3$). HRMS *m/z* calcd for $C_{29}H_{39}O_6Si$: 511.25104; found: 511.25195. ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (dt, J = 7, 1.5 Hz, 2H), 7.57 (tt, J = 7.4, 1.3 Hz, 1H), 7.45 (tt, J = 7.5, 1.4 Hz, 2H), 7.37–7.24 (m, 5H), 6.45 (dd, J = 17.3, 1.5 Hz, 1H), 6.17 (dd, J = 17.3, 10.4 Hz, 1H), 5.88 (ddd, J = 17.3, 10.3, 6.6 Hz, 1H), 5.86 (dd, J = 10.3, 1.5 Hz, 1H), 5.39 (dd, J = 6.4, 4.0 Hz, 1H), 5.35 (td, J = 17.3, 1.3 Hz, 1H), 5.23 (dt, J = 10.4, 1.2 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.70 (dd, J = 12.0, 3.1 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.41 (dt, J = 6.5, 1.3 Hz, 1H), 4.37 (dd, J = 12.1, 7.0 Hz, 1H), 4.03 (q, J = 3.5 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.3, 137.9, 136.9, 133.2, 131.4, 130.1, 129.8, 128.5, 128.1, 127.8, 117.9, 75.7, 75.2, 72.7, 71.8, 63.8, 25.9, 18.2, −4.2, −4.7. IR (film, cm^{-1}): 2908, 1724, 1633, 1454, 1404, 1261, 1223, 1184, 1110, 1092, 1068, 1030.

4.14. (R)-2-(benzyloxy)-2-((2R,3R)-3-((tert-butyldimethylsilyl) oxy)-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate **29**

To a stirred solution of **28** (110 mg, 0.215 mmol, 1 eq.) in toluene (10 mL) was added HG-II (6.5 mg, 10 μmol). The resulting reaction mixture was allowed to stir at 85 °C for 2 h, before a second portion of HGII (8 mg, 12 μmol) was added to ensure full conversion after 4 additional hours. The reaction mixture was then filtered through a pad of celite®/silica (1/1); which was thoroughly washed with Et_2O (2 × 15 mL). The combined organic fractions were concentrated under reduced pressure and the brown residue was purified by flash column chromatography on silica gel (PE/EtOAc 10:1 to 2:1) to yield lactone **29** (82 mg, 79%) as a colorless oil. $[\alpha]_D^{20} = -105.7$ (c = 0.8, $CHCl_3$). HRMS *m/z* calcd for $C_{27}H_{35}O_6Si$: 483.21974; found: 483.21986. ^1H NMR (300 MHz, $CDCl_3$) δ 8.09–7.97 (m, 2H), 7.56 (tt, J = 7.1, 1.3 Hz, 1H), 7.50–7.37 (m, 2H), 7.34–7.26 (m, 5H), 7.00 (dd, J = 9.7, 5.8 Hz, 1H), 6.15 (d, J = 9.7 Hz, 1H), 5.14 (dd, J = 12.5, 2.2 Hz, 1H), 4.91 (d, J = 10.7 Hz, 1H), 4.51 (m, 4H), 4.23 (dt, J = 5.3, 2.4 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 162.8, 144.8, 137.7, 133.2, 130.2, 129.8, 128.5, 128.0, 127.8, 123.5, 78.8, 74.5, 71.9, 61.1, 60.2, 25.9, 18.2, −3.2, −4.2. IR (film, cm^{-1}): 2932, 2854, 1724, 1454, 1342, 1315, 1273, 1250, 1111, 1068, 1030.

4.15. (−)-Cleistenolide **11**

To a stirred solution of **29** (350 mg, 0.725 mmol, 1 eq.) in acetic anhydride (2 mL) was added $FeCl_3$ (40 mg, 0.247 mmol, 0.34 eq.). The resulting mixture was left stirring at r.t. for 30 min. DCM (60 mL) and a saturated aqueous solution of $NaHCO_3$ (200 mL) were then added. After phase separation, the red turbid aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/EtOAc 10:1 to 1:1) to yield (−)-cleistenolide **11** (230 mg, 88%) as white crystals. Mp = 130 °C. $[\alpha]_D^{20} = -144.3$ (c = 3.85, $CHCl_3$). HRMS *m/z* calcd for $C_{18}H_{19}O_8$: 363.10744; found: 363.10745. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.1 Hz, 2H), 7.58 (tt, J = 7.4, 1.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.00 (dd, J = 9.7, 6.1 Hz, 1H), 6.29 (d, J = 9.7 Hz, 1H), 5.51 (ddd, J = 9.6, 4.4, 2.4 Hz, 1H), 5.42 (dd, J = 6.1, 2.7 Hz, 1H), 4.93 (dd, J = 12.5, 2.4 Hz, 1H), 4.80 (dd, J = 9.6, 2.7 Hz, 1H), 4.53 (dd, J = 12.5, 4.5 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.6, 166.1, 161.3, 139.9, 133.4, 129.8, 129.7, 128.7, 125.5, 75.6, 67.8, 62.1, 59.9, 20.8, 20.6. IR (film, cm^{-1}): 2993, 2966, 1728, 1639, 1443, 1373, 1277, 1215, 1180, 1153, 1072, 1022, 1003.

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