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Total Synthesis of (−)-Cleistenolide

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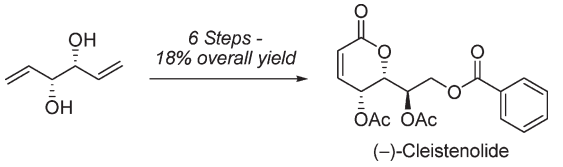

The first total synthesis of Cleistenolide, a novel natural product recently isolated from the Annonaceae species *Cleistochlamys kirkii* Oliver, is described. The synthesis proceeds in six steps and 18% overall yield, starting from an enantiopure C2-symmetric building block and using a Sharpless epoxidation, a selective epoxide opening, and a ring-closing metathesis reaction.

Introduction

Natural products and their semisynthetic derivatives are traditionally important drugs, drug candidates, or lead structures for novel drugs.[1,2] The comparatively high success rate for lead structures based on natural products is commonly attributed to the presence of privileged structures.[3] In particular, numerous antibacterial agents are derived from natural sources, and the search for novel compounds, their synthesis, and synthetic modification is an important task which is further stimulated by the emergence of drug-resistant bacteria strains.[4]

Cleistochlamys kirkii Oliver is an Annonaceae species occurring in Tanzania and Mozambique.[5] Extracts of this plant are used in traditional medicine as a remedy for the treatment of wound infections, rheumatism, and tuberculosis.[6] Recently, Nkunya et al. investigated the chemical composition of organic extracts from fruits, leaves, and stem and root barks of *C. kirkii* Oliver and discovered, apart from some known heptenolides, two novel plant constituents, which were named cleistenolide (**1**) and cleistodienol (**2**) (Figure 1).[7]

For cleistenolide, antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, as well as antifungal activity against *Candida albicans*, were reported by these authors. It was reasoned that these biological activities substantiate the effectiveness of the traditional use of *C. kirkii* Oliver. Herein, we report the first total synthesis of cleistenolide (**1**), starting from an enantiomerically pure mannitol-derived compound. Our synthesis confirms the absolute configuration assigned to (−)-cleistenolide.

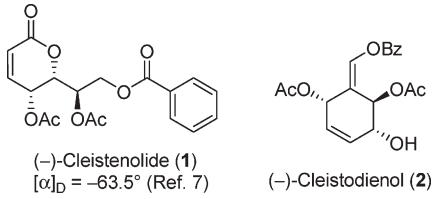

FIGURE 1. Novel natural products from *C. kirkii*.

Results and Discussion

We envisaged (*R*,*R*)-1,5-hexadiene-3,4-diol (**3**) as a starting material, which was first synthesized from D-mannitol by Rama Rao et al. in 1987.[8] Later, an alternative procedure was described by Burke et al.[9,10] and a slight modification by us.[11] A synthesis of *ent*-**3** from L-tartrate and its application in natural product synthesis have also been published.[12] Compound **3** has been used as a building block in the synthesis of natural products[13−31] and

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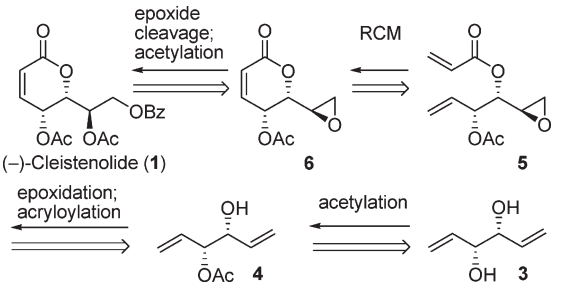
SCHEME 1. Proposed Synthesis of Cleistenolide

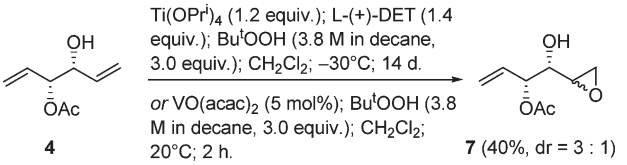


non-natural carbohydrate analogues.[32,33] Very recently, **3** and its derivatives were used as chiral ligands in rhodium-catalyzed conjugate additions.[34]

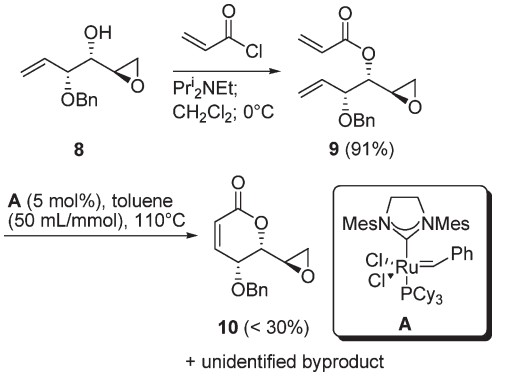
Originally, we planned to desymmetrize diol **3** by monoacetylation and to convert the resulting monoacetate **4** via stereoselective OH-directed epoxidation and acryloylation to compound **5**. As final steps of the sequence we envisaged a nucleophilic epoxide opening with benzoate, acetylation of the newly formed OH-group, and ring-closing olefin metathesis for the formation of the C3−C4 double bond. Because scrambling of labile functional groups or protecting groups, such as esters or silyl ethers, upon nucleophilic cleavage of proximal epoxides is often a problem,[35] we thought it might be advantageous to perform the RCM step prior to the epoxide opening (Scheme 1).

To our surprise, the envisaged stereoselective epoxidation of allylic alcohol **4**[36] proceeded only in poor yield and unsatisfactory diastereoselectivity. Thus, the required epoxide **7** was obtained in approximately 40% yield as a 3:1 mixture of epimers, using either $VO(acac)_2$ or Sharpless conditions (Scheme 2).[37,38]

SCHEME 2. Epoxidation of Allylic Alcohol 4



SCHEME 3. RCM of an Acrylate Derived from 8



Taking this disappointing result into account, we expected that the use of a protecting group would be overall advantageous. In a previous project, we used benzyl-protected epoxide **8**, which is, in contrast to **7**, conveniently available from the enantiomerically pure precursor via Sharpless epoxidation in excellent yield and diastereoselectivity if L-(+)-DET is used as a ligand.[11] Epoxide **8** was previously synthesized from racemic starting material using Sharpless conditions.[39] Although we are aware of the difficulties associated with the selective removal of a benzyl protecting group in the presence of C−C-double bonds, we decided to use this starting material to check the feasibility of the subsequent steps (Scheme 3).

Epoxide **8** was first converted to the required acrylate **9**, which was then subjected to the conditions of a metathesis reaction using the second-generation precatalyst **A**.[40−42] Complete consumption of the starting material was observed after a few hours; however, we could not isolate the desired lactone **10** in pure form and in preparatively useful yield due to formation of an unidentified byproduct, which could not be removed by chromatography or crystallization. NMR spectroscopy revealed an unsaturated lactone structure for this byproduct, and several signals in the ether/epoxide range. It should be stated that the integrity of the starting material **9** was checked immediately before the RCM step; thus, the RCM conditions are apparently responsible for the rather sluggish conversion of acrylate **9** into lactone **10**. These problems prompted us to reconsider the choice of

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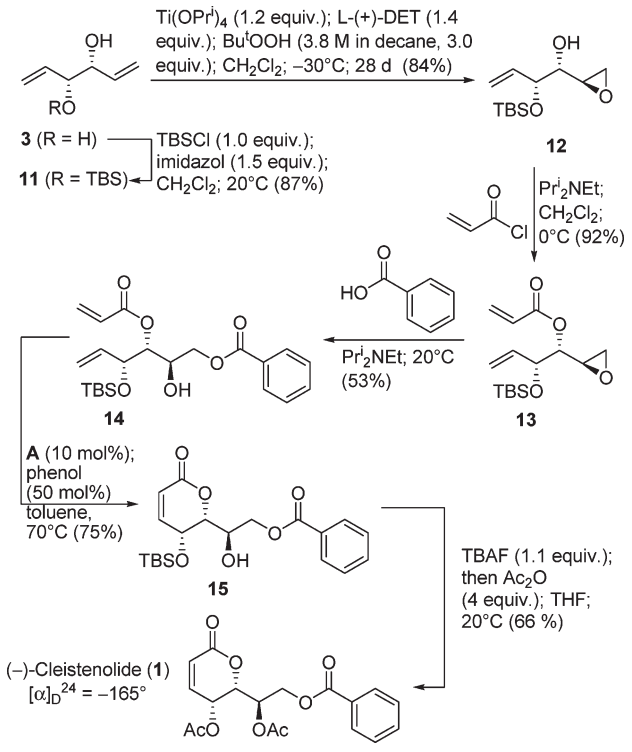
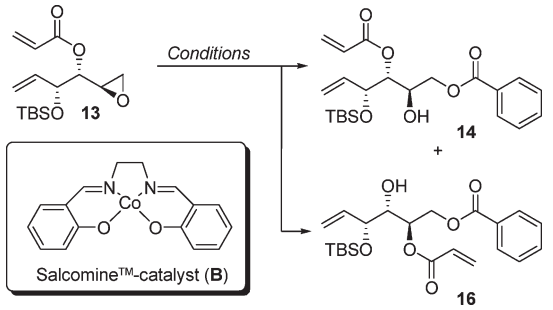
SCHEME 4. Synthesis of (−)-Cleistenolide (1)



protecting groups and the order of steps. A route which was eventually found to be viable is shown in Scheme 4.

Diol **3** was first protected as a TBS ether **11**,[43] which was then subjected to the conditions of a Sharpless epoxidation. As previously described for acetate **4** (Scheme 2), the VO(acac)$_2$-catalyzed epoxidation of **11** is very fast but proceeds only with unsatisfactory stereoselectivity.[44] By using L-(+)-DET in the Sharpless epoxidation the required epoxide **12**[44] was obtained in good yield and excellent selectivity (dr > 19:1, ^{1}H NMR spectroscopy), but the reaction required rather long reaction times of up to 28 days. Reducing the reaction time to 14 days provided the product in a lower but still useful yield of 72%. The long reaction times are somewhat surprising because the combination of (*R*,*R*)-**3** and L-(+)-DET represents a matched pair. Fortunately, the long reaction times are outweighed by the fact that quantities of several grams of **12** are easily obtained per batch. In the next step, the acrylate required for the RCM step was introduced. We were aware of the potential problems resulting from this order of steps because the subsequent nucleophilic epoxide cleavage with benzoic acid or a benzoate might be hampered by a competing 1,4-addition or inter- or intramolecular acrylate-transfer reactions. Nevertheless, we opted for this order of steps to minimize the number of protecting group operations. The first attempts to synthesize **14** from **13** and benzoic acid were indeed rather discouraging. The use of Li-, Na-, K-, or Cs-benzoates in solvents such as toluene, THF, DMF, or DMSO at various temperatures resulted either in no conversion or in complete decomposition of the starting material. Similar results were

TABLE 1. Conditions for Epoxide Opening of 13



entry	benzoic acid (equiv)	Pr$^i_2$NEt (equiv)	cat. **B** (mol %)	**13**^{a} (%)	**14**^{a} (%)	**16**^{a} (%)
1^{b,c}	1.1	1.1	5	n.d.		
2^c	1.1	1.1	5	n.d.	33	16
3^c	2.2	1.1	5	n.d.	53	12
4^c	2.2	1.1		n.d.	47	12
5^d	4.0	2.0		20	53^e	6

^{a}Yields of isolated products. ^{b}Reaction conducted in MTBE (0.2 mL/mmol). ^{c}Product composition determined after 76 h at 20 °C. ^{d}Product composition determined after 46 h at 20 °C. ^{e}Yield of **14** based on recovered starting material is 66%.

obtained under Lewis- or Brønsted-acidic conditions. A first success was achieved when the conditions described by Khalafi-Nezhad et al.[45] were used. These authors described the cleavage of epoxides with benzoic acid catalyzed by 10 mol % of NBu$_4$Br (TBAB) in acetonitrile. Application of these conditions to our substrate **13** led to the recovery of unreacted starting material. Therefore, the amount of TBAB was gradually increased, and full conversion was achieved with 2.0 equiv of TBAB. Unfortunately, numerous byproducts were formed, and only one defined product could be isolated in 30% yield. A careful inspection of the ^{1}H NMR spectrum of this compound revealed that we did not obtain the expected **14**, but a regioisomer **16**, which is obviously the result of an intramolecular acrylate transfer. The next method tested was inspired by work published by Jacobsen et al., who used Co−salen complexes for the desymmetrization of *meso*-epoxides with benzoic acid in the presence of Pr$^i_2$NEt.[46] To avoid complications potentially arising from matched/mismatched pairs, we did not use a chiral salen complex but the commercially available achiral salcomine catalyst **B**, which has previously been used for epoxide-opening reactions.[47] The results obtained for these experiments are summarized in Table 1. In the first experiments (entry 1), small volumes of MTBE were used as a solvent and 5 mol % of the cobalt catalyst **B**. Both the base and the nucleophile, benzoic acid were used in a slight excess. TLC revealed that no conversion occurred after 76 h, and upon workup the starting material **13** was recovered unchanged. In the following experiments the reaction was conducted in the absence of any solvent under otherwise identical conditions. The regioisomers **14** and **16** were obtained as a separable 2:1 mixture in a combined yield of 49% (entry 2). Increasing the amount of benzoic acid to 2.2 equiv results in a significantly improved yield of the desired **14** and a significantly improved

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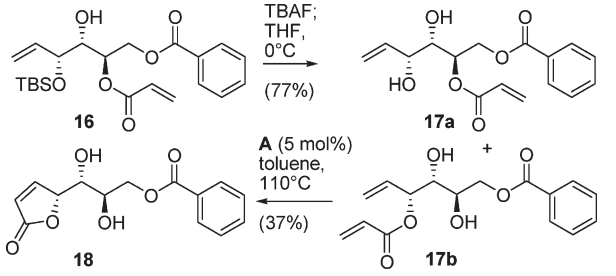
TABLE 2. Optimization of RCM Conditions for Acrylate 14

entry	precatalyst **A** (mol %)	solvent	concn of **14**[a] (mol/L)	*T*/°C	phenol (equiv)	time (h)	ratio **14**:**15**[b]	yield of **15** (%)
1	5	toluene	0.005	110	none	16	2.5:1	n.d.
2	5	C_6F_6	0.005	80	none	16	>19:1	n.d.
3	5	toluene	0.005	110	0.5	3	1.1:1	n.d.
4	5	CH_2Cl_2	0.0025	40	0.5	4	2.0:1	n.d.
5	10	toluene	0.002	110	0.5	3	1:1.1	36
6[c]	5	toluene	0.004[d]	60	0.5	6	1:1.7	56
7[c]	10	toluene	0.003[d]	70	0.5	6	1:4.0	75

[a]Initial concentration of substrate **14**, unless otherwise stated. [b]Determined from the ^{1}H NMR spectra of the crude reaction mixtures by integration of baseline-separated signals. [c]Solutions of **14** and of precatalyst **A** in toluene were added to a solution of phenol in toluene at the appropriate temperature over a period of 3 h; stirring was then continued for further 3 h. [d]Concentrations of **14** and **15** after completed addition: $c = (n(\mathbf{14}) + n(\mathbf{15}))$/(total volume of solvent).

SCHEME 5. Acrylate Migration under Desilylating Conditions



ratio of regioisomers (entry 3). Interestingly, virtually the same result was obtained in the absence of the cobalt catalyst **B**, with the isolated yield of the desired epoxide cleavage product **14** being only slightly lower (entry 4). Eventually, the best conditions were found with 4.0 equiv of nucleophile and 2.0 equiv of base in the absence of any solvent (entry 5). Under these conditions, 53% of **14** was isolated, along with only minor amounts of the regioisomer **16** and 20% of unreacted starting material **13**.

As the next step, we considered the cleavage of the TBS group prior to the RCM step. We thought that this order might be advantageous because OH-directing and activating effects[11,36,48−50] should facilitate the metathesis reaction. It has, however, been previously described in the literature that the cleavage of a TBS ether with an acetate in the vicinity can result in the formation of regioisomeric alcohols due to intramolecular acetyl group transfer.[51] We checked the chances of success for a desilylation in the presence of an acrylate and a benzoate in the same molecule for compound **16**: upon treatment with TBAF at 0 °C two products, most likely regioisomers **17a** and **17b**, were obtained as an inseparable mixture. To verify the formation of **17b**, the mixture was subjected to the conditions of a ring-closing metathesis using 5 mol % of **A**. Only one product was isolated, which was identified as the γ-butyrolactone **18** (Scheme 5).

The chances to suppress the acrylate migration are rather small, and we therefore decided to use the TBS-protected diene **14** for the RCM reaction. This step required considerable optimization (Table 2). In a first attempt to obtain **15**, 5 mol % of second-generation precatalyst **A** and an initial substrate concentration of 5×10^{-3} M were used. The beneficial effect of high dilution in the ring-closing metathesis of acrylates was noted some time ago[52] and was more recently systematically investigated by us.[53] Disappointingly, after 16 h in refluxing toluene a conversion of only 30% was observed (entry 1). Recently, Blechert et al.[54] and Grela et al.[55] reported a promoting effect of hexafluorobenzene and other fluorinated aromatic hydrocarbons on olefin metathesis reactions. We tried these conditions for the ring closure of **14** but could not detect any conversion after 16 h at 80 °C (entry 2). In the next experiment, we returned to the original conditions described in entry 1 and used 50 mol % of phenol as a promoting additive (entry 3). With these conditions, a significant improvement was observed: after just 3 h a 1:1 ratio of starting material **14** and product **15** was observed. The positive effect of phenol in difficult cross-metathesis reactions was originally reported by Forman et al.[56] and recently exploited by us in ring-closing enyne metathesis reactions.[36] We tried to further improve the reaction by using a lower initial substrate concentration and a lower reaction temperature, in order to enhance the catalyst lifetime, but this approach was not successful (entry 4). We then tested a higher catalyst loading of 10 mol %, in combination with an initial substrate concentration of 2×10^{-3} M (entry 5). Remarkably, the result was virtually identical with the one listed in entry 3: after 3 h, a conversion of approximately 50% was observed, and the isolated yield of **15** was 36%. Yields higher than 50% were eventually obtained by using the promoting effect of phenol in combination with pseudo-high-dilution conditions and a reduced reaction temperature for enhanced catalyst lifetime. In a first experiment along these lines, a 4.6×10^{-3} M solution of phenol in toluene was preheated to 60 °C, and a 1.8×10^{-2} M solution of **14** in toluene and a 0.9×10^{-3} M solution of precatalyst **A** in toluene were simultaneously added over 3 h. After the completed addition, the reaction temperature was maintained for another 3 h. Under these conditions, corresponding to an overall substrate concentration of 4×10^{-3} M and a catalyst loading of 5 mol %, a conversion of ca. 65% and a yield of 56% were obtained (entry 6). Finally, a

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conversion of 80% and a preparatively useful yield of 75% were obtained with a 2.3×10^{-3} M solution of phenol in toluene, preheated to 70 °C, and simultaneous addition of a 1.8×10^{-2} M solution of **14** in toluene and a 1.8×10^{-3} M solution of precatalyst **A** in toluene. This corresponds to a total concentration of 3×10^{-3} M and a catalyst loading of 10 mol % (entry 7).

Completion of the synthesis required desilylation of **15** and acetylation of the two secondary alcohols. This was most conveniently achieved as a one-flask reaction in THF by addition of TBAF and subsequently of acetic acid anhydride. Notably, the desilylation/double acetylation proceeds in the absence of additional base and gratifyingly without any migration of the benzoyl group. Thus, analytically pure (−)-cleistenolide (**1**) was obtained as a single regio- and stereoisomer in a yield of 66%. Melting point, elemental analysis, HRMS, IR, and ^{1}H and ^{13}C NMR data are in accord with the structure assigned to cleistenolide and match the values reported by Nkunya et al. for the material isolated from the natural source.[7] The only discrepancy was discovered for the specific rotation: we observed in repeated measurements a value of $[\alpha]^{24}_D = -165$ for synthetic cleistenolide (**1**), whereas a significantly lower value of $[\alpha]_D = -63.5$ was reported in the literature.[7] However, as both natural and synthetic cleistenolide are levorotatory, we conclude that the absolute configuration assigned to (−)-cleistenolide (Figure 1) is correct.

Conclusions

In conclusion, we report the first total synthesis of the recently discovered antibiotic and antifungal plant constituent (−)-cleistenolide. The synthesis was achieved in six steps and 18% overall yield from (*R*,*R*)-hexa-1,5-diene-3,4-diol (derived from D-mannitol) and confirms the assigned absolute configuration. Key features of our route to (−)-cleistenolide are the efficient utilization of the C_2 symmetry of the starting material, a Sharpless epoxidation, a selective epoxide opening with benzoic acid, and a ring-closing metathesis reaction.

Experimental Section

(1*R*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((*R*)-oxiran-2-yl)-but-3-enyl Acrylate (13). To a solution of **12** (2.00 g, 8.2 mmol) in CH_2Cl_2 (80 mL) were added DIPEA (7.6 mL, 24.6 mmol) and acryloyl chloride (1.7 mL, 21.3 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 3 h. The reaction was quenched by addition of water, and the aqueous layer was extracted three times with diethyl ether (30 mL). The combined organic layers were washed with NH_4Cl (aq) solution and with brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography to give **13** (2.25 g, 92%): $[\alpha]^{25}_D$ +37.5 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, J = 17.3, 1H), 6.10 (dd, J = 17.3, 10.4, 1H), 5.86 (ddd, J = 17.5, 10.5, 5.9, 1H), 5.85 (d, J = 10.7, 1H), 5.32 (d, J = 17.2, 1H), 5.20 (d, J = 10.4, 1H), 4.82 (dd, J = 5.0, 5.0, 1H), 4.40 (dd, J = 5.4, 5.3, 1H), 3.17 (ddd, J = 7.0, 4.8, 3.2, 1H), 2.80−2.70 (2H), 0.90 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 (0), 136.4 (1), 131.3 (2), 128.1 (1), 116.9 (2), 74.6 (1), 73.2 (1), 49.5 (1), 45.13 (2), 25.7 (3), 18.0 (0), −4.6 (3), −5.1 (3); IR (neat) ν 2930 (w), 2857 (w), 1730 (w), 1183 (m); LRMS (ESI) m/z 227 (100), 299 (M − H, 10), 321 (M + Na, 13); HRMS (ESI) calcd for $C_{15}H_{26}NaO_4Si^+$ (M^+ + Na) 321.1498, found 321.1505.

Optimized Procedure for the Epoxide-Opening Reaction of 13 with Benzoic Acid. To a solution of benzoic acid (3.20 g, 26.8 mmol) in DIPEA (2.3 mL, 13.4 mmol) was added **13** (2.00 g, 6.7 mmol). The mixture was stirred at ambient temperature for 46 h. The reaction was diluted with CH_2Cl_2 (25 mL) and quenched by addition of water, and the aqueous layer was extracted three times with diethyl ether (20 mL). The combined organic layers were washed with $NaHCO_3$ (aq) solution and with brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica to give the title compound **14** (1.50 g, 53%), its regioisomer **16** (0.18 g, 6%), and unreacted starting material **13** (0.39 g, 20%). **(2*R*,3*R*,4*R*)-3-(Acryloyloxy)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxyhex-5-enyl benzoate (14):** $[\alpha]^{23}_D$ +51.5 (*c* 1.56, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−8.01 (d, J = 7.7, 2H), 7.53 (t, J = 7.3, 1H), 7.41 (dd, J = 7.7, 7.3, 2H), 6.42 (dd, J = 17.3, 1.4, 1H), 6.09 (dd, J = 17.3, 10.4, 1H), 5.93 (ddd, J = 17.1, 10.5, 5.3, 1H), 5.84 (dd, J = 10.4, 1.4, 1H), 5.38 (ddd, J = 17.2, 1.5, 1.5, 1H), 5.28 (ddd, J = 10.5, 1.4, 1.4, 1H), 5.08 (dd, J = 7.8, 4.4, 1H), 4.56 (dddd, J = 5.4, 4.4, 1.5, 1.3, 1H), 4.51 (dd, J = 9.1, 4.7, 1H), 4.28 (dd, J = 9.1, 5.1, 1H), 4.28 (m, 1H), 3.64 (d, J = 1.4, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (0), 164.9 (0), 135.3 (1), 133.0 (1), 131.9 (2), 129.9 (0), 129.7 (1), 128.3 (1), 127.8 (1), 117.6 (2), 73.3 (1), 72.9 (1), 69.0 (1), 65.7 (2), 25.7 (3), 18.1 (0), −4.8 (3), −5.2 (3); IR (neat) ν 3486 (bw), 2955 (w), 2930 (w), 2857 (w), 1723 (s), 1405 (m), 1255 (s); LRMS (ESI) m/z 289 (100), 403 (60), 421 (M^+ + H, 16); HRMS (ESI) calcd for $C_{22}H_{33}O_6Si^+$ (M^+ + H) 421.2046, found 421.2039. Anal. Calcd for $C_{22}H_{32}O_6Si$ (420.57): C, 62.8; H, 7.7. Found: C, 62.6; H, 7.7. **(2*R*,3*R*,4*R*)-2-(Acryloyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxyhex-5-enyl benzoate (16):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−7.99 (2H), 7.54 (t, J = 7.5, 1H), 7.42 (dd, J = 7.5, 7.5, 2H), 6.43 (dd, J = 17.3, 1.3, 1H), 6.14 (dd, J = 17.3, 10.4, 1H), 5.94 (ddd, J = 17.4, 10.4, 7.3, 1H), 5.85 (dd, J = 10.5, 1.4, 1H), 5.27 (ddd, J = 17.3, 1.2, 1.2, 1H), 5.22 (ddd, J = 10.5, 1.2, 1.2, 1H), 5.20 (ddd, J = 7.9, 5.7, 2.7, 1H), 4.82 (dd, J = 12.2, 2.7, 1H), 4.57 (dd, J = 12.2, 5.7, 1H), 4.21 (dd, J = 7.3, 3.3, 1H), 3.75 (ddd, J = 7.7, 7.7, 3.3, 1H), 2.71 (d, J = 7.6, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (0), 165.1 (0), 137.9 (1), 133.0 (1), 131.5 (2), 130.0 (0), 129.7 (1), 128.3 (1), 128.1 (1), 117.2 (2), 73.3 (1), 73.1 (1), 71.5 (1), 63.2 (2), 25.8 (3), 18.1 (0), −4.0 (3), −5.1 (3); IR (neat) ν 1724 (s), 1404 (m), 1254 (s), 834 (s); LRMS (ESI) m/z 217 (50), 289 (100), 421 (M^+ + H, 41), 443 (M^+ + Na, 38); HRMS (ESI) calcd for $C_{22}H_{33}O_6Si^+$ (M^+ + H) 421.2046, found 421.2057.

Optimized Procedure for the Synthesis of (*R*)-2-((2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-2-hydroxyethyl Benzoate (15). A solution of phenol (37 mg, 0.39 mmol) in toluene (200 mL) was heated to 70 °C. Precatalyst **A** (67 mg, 10 mol %) in toluene (50 mL) and **14** (330 mg, 0.78 mmol) in toluene (50 mL) were added simultaneously over 3 h at 70 °C. The solution was stirred for another 3 h at this temperature and then cooled to ambient temperature, and the solvent was evaporated. The residue was purified by column chromatography on silica to give the title compound **15** (230 mg, 75%) as a colorless solid: mp 118−120 °C; $[\alpha]^{23}_D$ −130.9 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.4, 1.3, 2H), 7.56 (t, J = 7.4, 1H), 7.42 (dd, J = 7.8, 7.8, 2H), 6.93 (dd, J = 9.7, 5.8, 1H), 6.10 (d, J = 9.7, 1H), 4.83 (dd, J = 12.2, 2.3, 1H), 4.57 (dd, J = 12.1, 4.5, 1H), 4.47 (dd, J = 5.8, 2.3, 1H), 4.31 (m, 1H), 4.28 (dd, J = 9.2, 2.2, 1H), 3.14 (d, J = 4.1, 1H), 0.87 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6 (0), 162.6 (0), 144.4 (1), 133.3 (1), 129.7 (1), 129.4 (0), 128.4 (1), 122.6 (1), 79.1 (1), 67.6 (1), 60.0 (1), 66.1 (2), 25.6 (3), 18.0 (0), −4.3 (3), −4.9 (3); IR (neat) ν 3533 (bw), 2927 (w), 2855 (w), 1704 (s), 1260 (m), 1120 (m), 1094 (m), 1064 (m); LRMS (ESI) m/z 375 (12), 393 (M^+ + H, 100); HRMS (ESI) calcd for $C_{20}H_{29}O_6Si^+$ (M^+ + H) 393.1733, found 393.1702. Anal. Calcd for $C_{20}H_{28}O_6Si$ (392.54): C, 61.2; H, 7.2. Found: C, 61.0; H, 7.2.

(−)-Cleistenolide (1). To a solution of **15** (150 mg, 0.38 mmol) in dry and degassed THF (10 mL) was added TBAF (133 mg, 0.42 mmol). The mixture was stirred at ambient temperature for 5 min, and then acetic anhydride (144 μL, 1.52 mmol) was

added. The solution was stirred for 1 h at ambient temperature. The reaction was quenched by addition of water, and the aqueous layer was extracted three times with diethyl ether (10 mL). The combined organic layers were washed with NH_4Cl (aq) solution and with brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography to give (−)-cleistenolide (**1**) (90 mg, 66%) as a colorless solid: mp 133−134 °C; $[\alpha]^{24}_D$ −164.6 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7, 2H), 7.57 (t, J = 7.5, 1H), 7.44 (dd, J = 7.7, 7.4, 2H), 7.00 (dd, J = 9.7, 6.1, 1H), 6.29 (d, J = 9.7, 1H), 5.51 (ddd, J = 9.6, 4.4, 2.4, 1H), 5.41 (dd, J = 6.1, 2.6, 1H), 4.93 (d, J = 12.5, 2.4, 1H), 4.80 (dd, J = 9.6, 2.7, 1H), 4.52 (dd, J = 12.5, 4.4, 1H), 2.08 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (0), 169.4 (0), 165.9 (0), 161.0 (0), 139.7 (1), 133.2 (1), 129.6 (0), 129.6 (1), 128.5 (1), 125.3 (1), 75.5 (1), 67.7 (1), 62.0 (2), 59.7 (1), 20.6 (3), 20.4 (3); IR (neat) ν 2963 (w), 1725 (s), 1452 (m), 1372 (m), 1224 (s), 1099 (s), 1070 (s); LRMS (ESI) m/z 139 (48), 241 (100), 303 (35), 363 (M^+ + H, 61); HRMS (ESI) calcd for $C_{18}H_{19}O_8^+$ (M^+ + H) 363.1080, found 363.1093. Anal. Calcd for $C_{18}H_{18}O_8$ (362.33): C, 59.7; H, 5.0. Found: C, 59.4; H, 4.9.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.