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Lewis Acid-Catalyzed Stereoselective α-Addition of Chiral Aldehydes to Cyclic Dienol Silanes: Aqueous Synthesis of Chiral Butenolides

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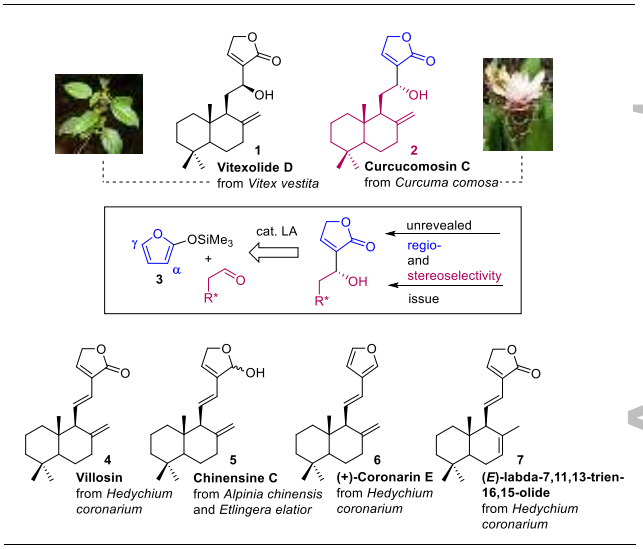
Abstract. The stereoselective α-addition to cyclic dienol silanes has rarely been exploited, in contrast to the well-studied γ-addition of conjugated butenolides. In this study, an unprecedent catalytic Mukaiyama aldol α-addition of 2-trimetylsiloxy furan to optically pure aldehydes in water-containing solvents is reported. The synthetic utility of this concept was demonstrated in the efficient synthesis of six bioactive natural products: vitexolide D, curcucomosin C, villosin, chinensine C, (+)-coronarin E and (*E*)-labda-7,11,13-trien-16,15-olid.

Keywords: Diastereoselectivity; Labdane diterpenes; Mukaiyama aldol reaction, Natural products, α-Regioselectivity

Introduction

Optically active butenolides serve as a prominent class of chiral building blocks for the synthesis of diverse biological active compounds[1] and complex molecules.[2] In particular, various types of butadiene-based silyl dienol ethers and cyclic dienoxysilanes[3] cleverly served to implement butenoate fragments into diverse, structurally complex polyketide frameworks and targets[4] *via* vinylogous Mukaiyama aldol reaction (VMAR)[5] with nicely controlled regio- and stereoselectivity.[6] However, in contrast to the widely studied γ-attack of silyl dienol ethers, catalytic diastereoselective Mukaiyama aldol formation of α-butenolides from silyloxyfuran and chiral aldehydes have not been reported.[7,8] Such methodology would be extremely important tool in the synthesis of naturally occurring compounds contain the 2(*5H*)-furanone ring substituted at α-position. For example, Scheme 1 presents six labdane-type diterpenoids (**1**-**2** and **4**-**7**) which belong to structurally diverse class of natural terpenoids[9] showing significant analgesic, anti-inflamatory and cytotoxic properties.[10]

Despite the differences in the furan ring structure, all these compounds (**1**, **2**, **4**-**7**) could be obtained through regioselective aldol addition of 2-trimethylsiloxy furan (**3**) to optically pure aldehyde skeleton, which in fact, is not known. Apart from regioselectivity issue, such newly developed efficient methodology should occur with catalytic amount of promoter controlling reaction stereoselectivity. This seems to be far from trivial as the synthesis of compounds **1** and **2** requires 1,3-stereocontrol accomplished most probably through an acyclic transition state of β-chiral aldehyde substrate.



Scheme 1. Biologically active compounds containing α-substituted 2(5*H*)-furanone ring.

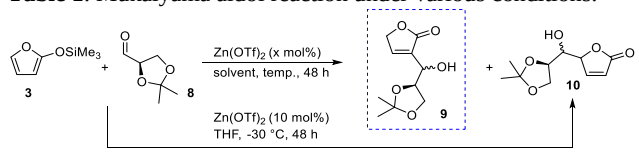
Development of such general catalytic strategy would simplify the synthesis of α-substituted α,β-unsaturated-γ-lactone containing the decalin core considerably in relation to known procedures reported previously.[11,12]

Recently, we showed that water plays significant impact on the regioselective Mukaiyama aldol reaction between cyclic dienol silanes and aromatic aldehydes[13] or ketoesters.[14] This new attempt was demonstrated also by other authors as a highly regioselective route to α-substituted furan derivatives,[15] but even more appreciated diastereoselective variant of this methodology have not yet been realized. Herein, we report the utility of these concept by documenting the first diastereoselective catalytic aqueous Mukaiyama aldol reaction as an alternative method for efficient construction of α-substituted 2(*5H*)-furanone moiety.

Results and discussion

We initiated this work by evaluating the model reaction between 2-trimethylsilyloxy furan **3** and optically pure (*R*)-glyceraldehyde acetonide **8** promoted by various Lewis acids to find out which catalyst, if any, promote α-regioselective reaction of siloxyfurans with aliphatic sugar aldehyde in water-containing solvents.

Table 1. Mukaiyama aldol reaction under various conditions.[a]



Entry	Solvent	$Zn(OTf)_2$ [mol%]	Temp. [°C]	Yield[b] [%]	
				9	**10**
1	MeOH	10	4	32	trace
2	MeOH/H_2O (9:1)	10	4	36	8
3	THF/H_2O (9:1)	10	4	30	10
4	EtOH/H_2O (9:1)	10	4	38	trace
5	*i*PrOH/H_2O (9:1)	10	4	30	12
6	THF/MeOH (1:1)-10% H_2O	10	4	20	8
7	THF/*i*PrOH (1:1)-10% H_2O	10	4	25	10
8	EtOH/MeOH (1:1)-10% H_2O	10	4	20	12
9	THF/EtOH (1:1)-10% H_2O	10	4	36	trace
10	THF/EtOH (1:1)-10% H_2O	5	-30	58	10
11		10	-30	62	trace
12		15	-30	50	12
13		20	-30	45	15
14	EtOH/H_2O (9:1)	10	-30	55	12

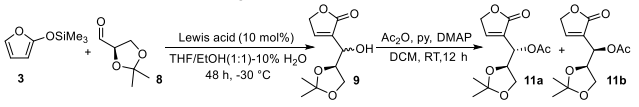
[a]The reaction was performed with silyloxyfuran **3** (1.2 equiv., 0.85 mmol), chiral aldehyde **8** (1.0 equiv., 0.71 mmol) and various catalyst loading in 2 mL of solvent at the specified temperature for 48h. [b]Isolated yield after silica gel chromatography.

This study exposed zinc triflate as the best candidate for the initial studies. Reaction of TMSOF (**3**) with aldehyde **8** in the presence of zinc salt afforded mixtures of corresponding α-substituted α,β-unsaturated γ-lactone **9** in low to good yields, contaminated by the undesired γ-addition product of vinylogous reaction (Table 1). Reaction yield and regioselectivity depends on the solvent and catalyst loading. Good yields and regioselectivity were observed when the Mukaiyama aldol reaction was carried out in aqueous protic solvents such as MeOH and EtOH with 10% of water (Table 1, entries 2 and 4). Lowering the temperature from 4 °C down to –30 °C and using the mixture of ethanol and tetrahydrofuran (1:1, v/v) with 10% addition of water in the presence of 10 mol% of zinc triflate resulted in improved yields of α-substituted α,β-unsaturated-γ-lactone (62%). Only trace of undesirable product substituted in γ position (**10**) was observed under optimized reaction conditions (Table 1, entry 11). Reaction carried out in the mixture of aqueous THF-EtOH with 10 mol% catalyst at –30 °C guaranteed optimal yield and stereoselectivity (Table 1, entry 11). It is important to notice that reaction carried out in dry tetrahydrofuran resulted in exclusive formation of the γ-aldol product in 70 % yield. This additional experiments unambiguously confirmed crucial impact of water additive on the reaction regioselectivity.

Encouraged by the promising results in Table 1, stereoselective variants of the aldol reaction by using optically pure glyceraldehyde **8** were investigated. We assumed that the kind of catalyst could have a general effect on the formation of *syn*-and *anti*-configured aldol products. To test the viability of our proposed protocol and asses the reaction stereoselectivity, a variety of water compatible Lewis acids including zinc, copper, magnesium, calcium and lanthanide salts have been employed under previously elaborated reaction conditions (Table 2, entry 1-9). To our delight, the majority of tested metal triflates promoted the formation of product **9** in water containing solvent with strong preferential formation of one stereoisomer. Interestingly, iron- bismuth- and silver salts turned out to be entirely ineffective in this reaction (Table 2, entry 10-12).

From among all tested Lewis acids we selected zinc and ytterbium triflates as the most promising catalysts in terms of yields and stereoselectivity. The later reaction parameter was determined by using ^1H NMR of crude reaction mixture and was also measured for individual stereoisomers. For this reason alcohol **9** was protected in form of acyl esters under standard reaction conditions (Ac_2O, Py) resulting in the formation of diastereoisomers **11a** and **11b** with better separation of signals in NMR spectra.

Table 2. Stereoselectivity studies.[a]



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Entry	Lewis acid	Yield of α-product[b] [%]	dr[c]
1	$Zn(OTf)_2$	62	4:1
2	$Cu(OTf)_2$	20	3:1
3	$Ca(OTf)_2$	30	7:1
4	$Mg(OTf)_2$	28	7:1
5	$Yb(OTf)_3$	68	10:1
6	$Sc(OTf)_3$	53	5:1
7	$La(OTf)_3$	46	3:1
8	$Eu(OTf)_3$	60	5:1
9	$Sm(OTf)_3$	57	5:1
10	AgOTf	-	-
11	$Fe(OTf)_2$	-	-
12	$Bi(OTf)_3$	-	-

[a]The reaction was performed with silyloxyfuran **3** (1.2 equiv., 0.85 mmol), chiral aldehyde **8** (1.0 equiv., 0.71 mmol) and 10 mol% of $Zn(OTf)_2$ in 2 mL of solvent at the -30 °C for 48 h. [b]Isolated yield after silica gel chromatography. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopy.

Analysis of NMR spectra suggested that all metal triflates promoted the formation of α-substituted products in a highly *anti*-diastereoselective manner. The use of any ligands have not been required. The absolute configuration of alcohols **9a** and **9b** was unambiguously assigned by HPLC-ECD methodology by comparison of the experimental ECD spectrum obtained online during the HPLC separation with the computed ECD spectra of possible diastereoisomers. Such stereochemical analysis of chiral compounds was successfully applied for stereochemical analysis of various compounds.[16]

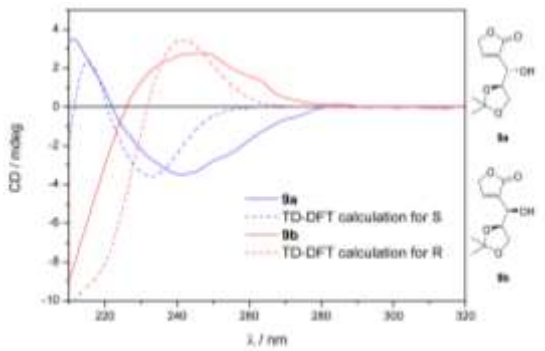
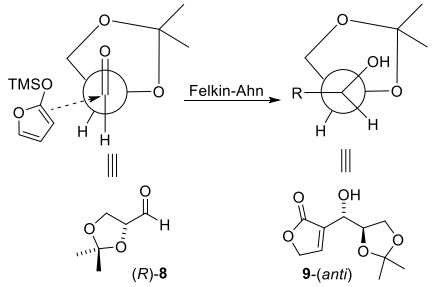


Fig 1. Comparison of on-line ECD (solid lines) and simulated (dashed lines) ECD spectra of **9a** and **9b**. In simulations the CAM-B3LYP/aug-cc-pVDZ/PCM computational level was applied.

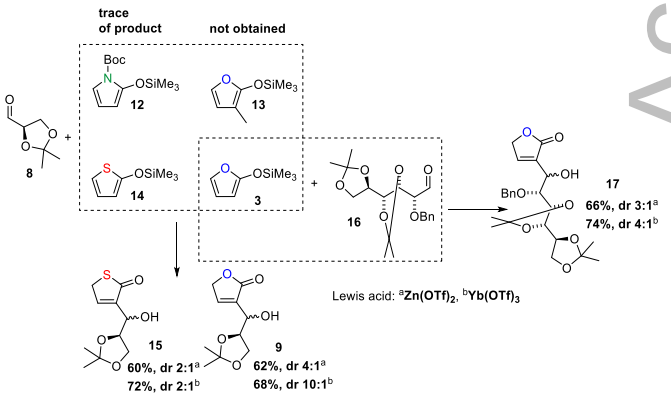
As shown in Figure 1, the simulated ECD spectrum of (*S*)-product of Mukaiyama aldol reaction (at the CAM-B3LYP/aug-cc-pVDZ/PCM level) corresponds to the experimental online ECD data of **9a**, in turn the spectrum of (*R*)- product fits to online spectra of **9b** (for experimental details see the Supporting Information Materials). Both simulated ECD spectra show satisfactory compliance with appropriate experiment and allow to assign absolute configuration of reaction products.

Observed preferential formation of *anti*-configured isomer **9a** from (*R*)-**8** could be easily explained by stereoselective addition of 2-TMS furan to optically pure aldehyde. Considering Felkin−Anh transition state oxygen at C-2 of aldehyde, being electronegative, it will lie perpendicular to the carbonyl group in the most reactive conformer delivering *anti*-**9** (Scheme 2). This explains clearly formation of the (3*S*)-configured product. The same rules can be adopted to the preferential formation of *anti*-configured **11**, **15** and **17**. In all cases, stereogenic center in the chiral aldehyde control the formation of anti-configured product under non-chelating Felkin−Anh transition state control.



Scheme 2. Plausible model of transition state.

After establishing optimal reaction conditions, we next sought to examine the scope and generality of the current stereoselective α-addition for other substrates. Scheme 3 illustrates reactivity of chiral aldehyde and a variety of cyclic dienol silanes based of furan, thiophen and pyrrole structure under elaborated methodology. Similarly to TMS-furan (**3**), thiophene-based 2-siloxy diene reacted with model chiral aldehyde **8** afforded desired product **15**. Application of this substrate suppressed the competitive formation of the γ-substituted side products. Both ytterbium and zinc triflates catalyzed this unique reaction in exclusively α-selective manner in which comparable, good results were obtained (60-70% yield and dr 2:1). In contrast to reactivity of furan- and thiophene-type substrates similar investigation made for l-methyl-2-(trimethylsiloxy)pyrrole **12** was unsuccessful. We also examined methyl-substituted siloxyfuran skeleton in the vinylogous Mukaiyama aldol reaction. Starting from commercially available 3-methyl-2(5*H*)-furanone, which was treated with TMSOTf in the presence of Et_3N we obtained silyloxyfuran **13** in 78% yield. The α-product formation of the Mukaiyama aldol reaction between synthetized 3-methyl-2-(trimethylsilyloxy)furan **13** and optically pure aldehyde **8** under optimized reaction condition was not observed. One of the possible explanations of this phenomena may be shielding effect of the additional methyl substituent attached to the terminal position of the reactive silyl enol ether fragment.



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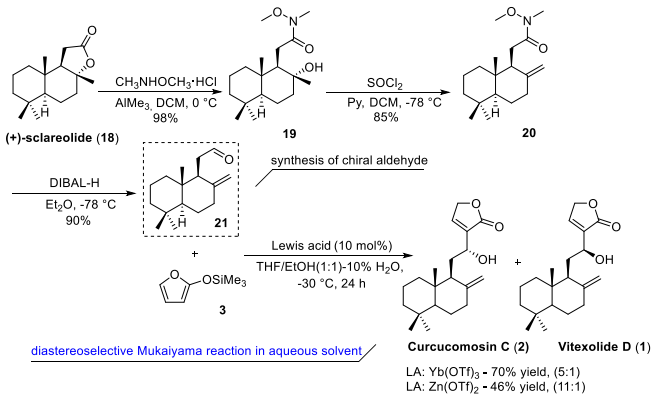
Scheme 3. Substrate scope for the Mukaiyama aldol α-addition.

This methodology was also successfully applied to the more demanding protected aldohexose **16**. This more sterically rigid 2,3-*O*-isopropylidene derivative of D-mannose led to lower selectivity but better yield when compared to 2,3-*O*-isopropylidene-D-glyceraldehyde (Scheme 3). For this substrate preferential formation of *anti*-configured aldol products was also observed with (3:1) or (4:1) diastereoselectivity depending of Lewis acid.

The scope of this reaction was further investigated by using more challenging group of aldehydes featuring β-stereogenic centers which represent a class of important building blocks for the synthesis of various natural products and pharmaceuticals. It was remarkably important to test the level of asymmetric induction caused by remoted stereocenters. This opportunity was investigated in order to prepare the biologically active compounds containing α-substituted 2(5*H*)-furanone ring collected at Scheme 1. For this family of compounds two types of aldehyde substrates with *exo*-**21** and *endo*-placed double bond (**22**, **23**) could be applied.

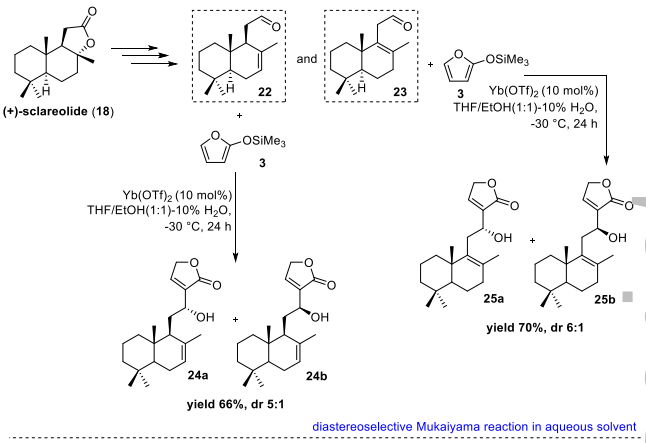


Scheme 4. Preparation of aldehyde **21** and its application in diastereoselective synthesis of curcucomosin C and vitexolide D.

The required aldehyde with trisubstituted *exo*-olefin structure **21** was efficiently prepared from commercially available (+)-sclareolide.[17] First, the (+)-sclareolide was converted to Weinreb's amide in the presence of dimethylaluminium amide derived from *N*-methoxy-*N*-methylamine (98% yield). Then, the dehydration of tertiary alcohol **19** with thionyl chloride in pyridine at –78 °C followed by DIBAL-H reduction afforded the desired aldehyde with high yield (90%).[11]

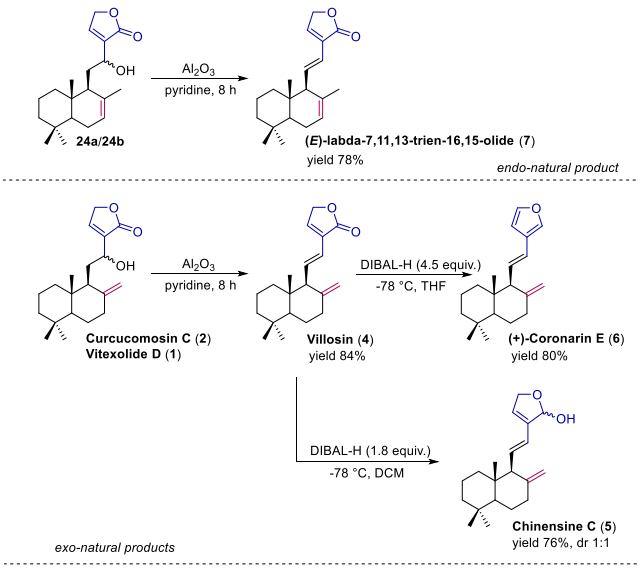
Diastereoselective Mukaiyama aldol reaction of **21** with **3** (2.0 equiv.) under elaborated conditions resulted in the mixture of two separable natural products: curcucomosin C - **2** and vitexolide D - **1** with 70% and 46% overall yields depending on Lewis acid applied. Structure of both natural products have been confirmed by comparison of NMR spectra of obtained samples with previously published data. These data are included in Supporting Information material.

In addition to β-chiral aldehyde bearing an *exo*-double bond its two *endo*-isomers **22** and **23** were also successfully converted to the expected alcohols **24** and **25** with similarly high levels of diastereoselectivity and yields (Scheme 5). Aldehydes **22** and **23** were synthetized using described above three-step procedure starting from (+)-sclareolide except the dehydration step that was achieved with $SOCl_2$ at elevated temperature (0 °C).



Scheme 5. Mukaiyama aldol α-addition of synthetized chiral aldehydes **22** and **23** to 2-trimethylsilyloxyfuran **3** in new reaction conditions.

Elimination of water from **1**, **2**, **24** molecules gave access to next members of the labdane diterpenoids family named: villosin, (+)-coronarin E, chinensine C and (*E*)-labda-7,11,13-trien-16,15-olide as presented in Scheme 6. *Endo*-natural product **7** was obtained from diastereomeric mixture of alcohols: **24a** and **24b** by the refluxing in pyridine with the presence of Al2O3 with 78% yield. Similar reaction conditions have been used for the villosin synthesis. The requisite *exo*-olefin **4** was prepared from the combination of two diastereoisomers **2** and **1** with 84% yield. Further employing different amounts of DIBAL-H in THF at –78 °C allowed to obtained two additional natural products. Reduction of villosin with 1.8 equivalent of reducing agent provides directly to the diastereomeric lactols **5** (chinensine C) in very good 76% yield. Increasing the amount of DIBAL-H (4.5 equiv.) was necessary to complete the conversion to biologically active compound - (+)-coronarin E.



Scheme 6. Synthesis of biologically active compounds based on the 2(*5H*)-furanone structure substituted at α-position.

Conclusion

In conclusion, we have developed unprecedent catalytic diastereoselective Mukaiyama aldol reaction of chiral aldehydes with cyclic dienoxy silanes promoted by metal triflates in water-containing solvents. This efficient protocol offers a facile access to α-substituted α,β-unsaturated-γ-lactones with excellent regiocontrol and stereoselectivity. Furthermore, described methodology has been successfully applied to the formation of six labdane-type diterpenoids **1**-**2** and **4**-**7**, which are knowns for their pharmacological properties such as anti-inflammatory, analgesic and cytotoxic activity. Although there are no rational conclusion on how the water influences the reaction regioselectivity, we demonstrate in this paper further synthetic utility of this phenomena. Considering the unusual regioselectivity of the reaction carried out in the aqueous solvents and its usefulness in the synthesis of subsituted α-butenolides[2,15] further studies on the reaction mechanism are performing in our laboratory.

Experimental section

General information. All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. Reaction products were purified by flash chromatography using silica gel 60 (240-400 mesh). Reactions were controlled using TLC on silica [alu-plates (0.2 mm)]. Plates were visualized with UV detection or by use of a basic UV light (254 nm) and by treatment with aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid or treatment with acidic *p*-anisaldehyde stain followed by heating. High-resolution mass spectra were in general recorded on ESI-MS-TOF (MicrOTOF II, Bruker, Germany). Infrared (IR) spectra were recorded on a Fourier transform infrared attenuated total reflectance (ATR) FTIR spectrometer. ^{1}H NMR spectra were recorded on spectrometers operating at 600 MHz and 300 MHz in $CDCl_3$. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad), coupling constants (in Hz), and assignment. ^{13}C NMR spectra were measured at 151 MHz and 75 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. Optical rotations were measured at room temperature with a digital polarimeter. Trimethylsilyl enol ethers **12**,[18] **13**,[19] and **14**[20] were prepared according to the reported procedures. (*R*)-2,3-*O*-isopropylidene-glyceraldehyde (**8**)[21] and 2-*O*-benzyl-3,4:5,6-di-*O*-isopropylidene-D-glucose (16)[22] were prepared according to the reported procedures. β-Substituted aldehydes **21**, **22**, and **23**, starting materials for the synthesis of natural products, were prepared, according to the reported procedures.[11a] All of the spectral data of the synthesized aldehydes were in accordance with the reported ones.

General procedure for the synthesis of α-butenolides (9, 15, 17), curcucomosin (2), vitexolid D (1, 24, 25). The solution of metal triflate (0.077 mmol, 10 mol%) in EtOH/THF (1:1)-H_2O (10%) (2 mL) was stirred at –30 °C for 10 min. Subsequently chiral aldehyde (0.71 mmol, 1.0 equiv.) and trimethylsilyl enol ether (0.85 mmol, 1.2 equiv.) were added and the resulting mixture was stirred at –30 °C for 48 h. After complete consumption of starting materials reaction mixture was purified directly using column chromatography on silica gel (hexane/ethyl acetate 9:1→6:1→4:1→2:1 v/v). The volatiles were removed under reduced pressure to give pure products.

*3-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)furan-2(5H)-one (**9a**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.143 ml, 0.85 mmol, 1.2 equiv.) and aldehyde **8** (92.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **9a** (94.0 mg, 0.6 mmol) was obtained in 62% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 3.7, 1.7 Hz, 1H), 4.87 (dd, *J* = 3.1, 1.7 Hz, 2H), 4.58 (ddd, *J* = 5.4, 3.5, 1.8 Hz, 1H), 4.43 (dt, *J* = 6.5, 5.7 Hz, 1H), 3.96 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.93 (dd, *J* = 8.5, 5.8 Hz, 1H), 3.14 (s, 1H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 147.1, 132.1, 109.4, 75.1, 70.5, 67.0, 64.5, 26.1, 24.4; ν_{max} (neat)/cm^{-1}: 3398, 2987, 2935, 1739, 1649, 1373, 1251, 1207, 1155, 1055, 841, 791; HRMS (ESI-TOF): calculated for $C_{10}H_{14}O_5Na^+$ $[M+Na]^+$ 237.0733 found 237.0732; $[\alpha]^{25}_D = -20.5$ (c = 1.0 in $CHCl_3$).

*3-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-furan-2(5H)-one (**9b**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.143 ml, 0.85 mmol, 1.2 equiv.) and aldehyde **8** (92.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **9b** (9.4 mg, 0.04 mmol) was obtained in 6% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 3.1, 1.6 Hz, 1H), 4.84 (m, 2H), 4.51 (d, *J* = 5.5 Hz, 1H), 4.38 (dd, *J* = 12.2, 5.9 Hz, 1H), 3.95 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.91 (dd, *J* = 8.5, 5.7 Hz, 1H), 2.27 (s, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (151

MHz, $CDCl_3$) δ 172.9, 147.4, 132.6, 109.9, 76.1, 71.0, 67.5, 65.0, 26.6, 24.9; ν_{max} (neat)/cm^{-1} : 3390, 2985, 2932, 1740, 1655, 1375, 1261, 1210, 1158, 1059, 840, 787; HRMS (ESI-TOF): calculated for $C_{10}H_{14}O_5Na^+$ $[M+Na]^+$ 237.0733 found 237.0734; $[\alpha]^{25}{}_D = -4.5$ (c = 1.0 in $CHCl_3$).

Acetylation of α-butenolides 9a and 9b. To a stirred solution of α-butenolide **9a/b** (103 mg, 0.5 mmol) in dry DCM (4 mL) subsequently pyridine (0.06 mL, 0.75 mmol), acetic anhydride (0.07 mL, 0.75 mmol), and catalytic amount of DMAP were added. The resulting mixture was stirred at room temperature for 12 h and then slightly acidified with 1.0 M HCI. The organic phase was washed with saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using hexane/ethyl acetate (3:2, v/v) as eluent, to afford product **11** (84 mg, 0.33 mmol, 68%) as a pale yellow oil. This product was isolated as an inseparable mixture of diastereomers in (10:1) ratio (Table 2, entry 5, for $Yb(OTf)_3$ as catalyst). The reported *dr* was determined by ^{1}H NMR analysis. Major diastereomer **11a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 2.7, 1.6 Hz, 10H), 5.60 (ddd, *J* = 5.7, 2.2, 1.1 Hz, 10H), 4.84 – 4.83 (m, 20H), 4.55 (dt, *J* = 6.6, 5.5 Hz, 10H), 4.02 (dd, *J* = 8.8, 6.7 Hz, 10H), 3.88 (dd, *J* = 8.8, 5.3 Hz, 10H), 2.09 (s, 30H), 1.37 (s, 30H), 1.31 (s, 30H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 169.6, 149.8, 130.3, 110.2, 74.9, 70.4, 68.3, 65.6, 26.4, 25.0, 20.8; Minor diastereomer **11b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 3.0, 1.6 Hz, 1H), 5.62 (ddd, *J* = 4.3, 2.9, 1.4 Hz, 1H), 4.85 – 4.84 (m, 2H), 4.55 (dt, *J* = 5.3, 4.4 Hz, 1H), 4.02 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.82 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.01 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 169.9, 149.0, 130.6, 110.2, 74.9, 70.6, 68.5, 65.7, 26.2, 25.2, 21.0; ν_{max} (neat)/cm^{-1}: 2988, 2937, 1756, 1448, 1373, 1226, 1156, 1067, 979, 838; HRMS (ESI-TOF): calculated for $C_{12}H_{16}O_6Na^+$ $[M+Na]^+$ 279.0839 found 279.0839.

*3-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)thiophen-2(5H)-one (**15a**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-thiophene **14** (146 mg, 0.85 mmol, 1.2 equiv.) and aldehyde **8** (92.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **15a** (93.7 mg, 0.4 mmol) was obtained in 48% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (td, *J* = 2.8, 1.3 Hz, 1H), 4.49 (m, 1H), 4.33 (td, *J* = 6.4, 4.0 Hz, 1H), 4.06 (dd, *J* = 7.6, 5.8 Hz, 1H), 4.05 – 4.04 (m, 2H), 3.96 (dd, *J* = 8.5, 6.1 Hz, 1H), 2.79 (d, *J* = 6.9 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.3, 150.3, 145.0, 109.8, 76.9, 68.1, 66.0, 35.8, 26.3, 24.9; ν_{max} (neat)/cm^{-1}: 3300, 2972, 2945, 1693, 1600, 1464, 1339, 1210, 1138, 1072, 833, 796; HRMS (ESI-TOF): calculated for $C_{10}H_{14}O_4SNa^+$ $[M+Na]^+$ 253.0505 found 253.0503; $[\alpha]^{25}{}_D = -15.4$ (c = 1.0 in $CHCl_3$).

*3-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)thiophen-2(5H)-one (**15b**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-thiophene **14** (0.146 ml, 0.85 mmol, 1.2 equiv.) and aldehyde **8** (92.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **15b** (46.8 g, 0.2 mmol) was obtained in 24% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (td, *J* = 2.8, 1.4 Hz, 1H), 4.63 (m, 1H), 4.42 (dd, *J* = 12.1, 5.9 Hz, 1H), 4.06 (ddd, *J* = 5.1, 2.8, 1.8 Hz, 2H), 3.95 (dd, *J* = 8.5, 6.7 Hz, 1H), 3.91 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.01 (d, *J* = 4.3 Hz, 1H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.9, 150.1, 143.7, 109.8, 76.0, 68.3, 64.9, 36.1, 26.5, 24.9; ν_{max} (neat)/cm^{-1}: 3297, 2966, 2932, 1680, 1590, 1458, 1335, 1206, 1130, 1069, 824, 790; HRMS (ESI-TOF): calculated for $C_{10}H_{14}O_4SNa^+$ $[M+Na]^+$ 253.0505 found 253.0507; $[\alpha]^{25}{}_D = -2.8$ (c = 1.0 in $CHCl_3$).

*3-((1S,2R)-2-(benzyloxy)-1-hydroxy-2-((4S,4'S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)-ethyl)furan-2(5H)-one (**17a**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.143 ml, 0.85 mmol, 1.2 equiv.) and aldehyde **16** (249 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **17a** (182 mg, 0.42 mmol) was obtained in 58% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.33 – 7.24 (m, 5H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.76-7.30 (m, 2H), 4.55 (dt, *J* = 18.5, 2.0 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.32 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.21 (dd, *J* = 8.7, 6.3 Hz, 1H), 4.10 (dt, *J* = 8.5, 6.2 Hz, 1H), 4.04 (dd, *J* = 5.0, 1.8 Hz, 1H), 4.01 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.94 (dd, *J* = 8.7, 6.1 Hz, 1H), 1.46 (s, 3H), 1.42 (d, *J* = 1.6 Hz, 6H), 1.38 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.6, 147.7, 138.1, 133.7, 128.3 (2C), 128.1 (2C), 127.8, 110.2, 110.1, 83.4, 78.3, 78.0, 77.3, 74.9, 70.8, 68.7, 68.3, 27.1, 26.8, 26.3, 25.1; ν_{max} (neat)/cm^{-1}: 3479, 2987, 2934, 1744, 1454, 1372, 1250, 1210, 1154, 1058, 1035, 844, 732, 698; HRMS (ESI-TOF): calculated for $C_{23}H_{30}O_8Na^+$ $[M+Na]^+$ 457.1833 found 457.1832; $[\alpha]^{25}{}_D = -4.7$ (c = 1.0 in $CHCl_3$).

*3-((1R,2R)-2-(benzyloxy)-1-hydroxy-2-((4S,4'S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)-ethyl)furan-2(5H)-one (**17b**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.143 ml, 0.85 mmol, 1.2 equiv.) and aldehyde **16** (249 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **17b** (46 mg, 0.11 mmol) was obtained in 15% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.37 – 7.30 (m, 5H), 4.94 – 4.93 (m, 1H), 4.82 (dt, *J* = 6.8, 2.0 Hz, 2H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.07 (dd, *J* = 8.7, 6.2 Hz, 1H), 4.04 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.03 – 4.00 (m, 2H), 3.96 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.87 (d, *J* = 7.1 Hz, 1H), 3.77 (dd, *J* = 8.7, 5.4 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 147.7, 137.7, 134.3, 128.5 (2C), 127.9 (2C), 127.8, 110.3, 109.8, 79.6, 77.3, 76.9, 76.3, 72.4, 70.8, 68.1, 67.7, 27.3, 26.5, 26.4, 25.1; ν_{max} (neat)/cm^{-1}: 3484, 2986, 2934, 1749,

1455, 1371, 1210, 1155, 1059, 843, 734, 698; HRMS (ESI-TOF): calculated for $C_{23}H_{30}O_8Na^+$ $[M+Na]^+$ 457.1833 found 457.1832; $[\alpha]^{25}_D$ = +36.9 (c = 1.0 in $CHCl_3$).

*3-((1R)-1-hydroxy-2-((1S,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-furan-2(5H)-one - Curcucomosin C (**2**).*[9,11a] In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **21** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **2** (132 mg, 0.42 mmol) was obtained in 58% yield, as a colorless oil. All data were in excellent agreement with previously reported.; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (q, *J* = 1.5 Hz, 1H), 4.88 (dd, *J* = 2.7, 1.3 Hz, 1H), 4.81 (t, *J* = 1.7 Hz, 2H), 4.71 (dd, *J* = 2.7, 1.4 Hz 1H), 4.54 (d, *J* = 9.5 Hz, 1H), 2.48 (d, *J* = 5.0 Hz, 1H), 2.41 (ddd, *J* = 12.7, 4.1, 2.4 Hz, 1H), 2.06 (brd, *J* = 11.3 Hz, 1H), 2.01 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.88 (ddd, *J* = 13.7, 11.4, 2.0 Hz, 1H), 1.74 (ddt, *J* = 12.7, 4.9, 2.3 Hz, 1H), 1.71 – 1.66 (m, 2H), 1.58 – 1.51 (m, 1H), 1.50-1.47 (m, 1H), 1.41 – 1.37 (m, 1H), 1.34 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.21 – 1.16 (m, 2H), 1.06 (td, *J* = 12.9, 3.9 Hz, 1H), 0.87 (s, 3H), 0.80 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 148.3, 144.1, 137.7, 107.2, 70.5, 65.8, 55.5, 51.9, 42.1, 39.3, 39.0, 38.3, 33.6 (2C), 30.3, 24.4, 21.7, 19.3, 14.6; ν_{max} (neat)/cm^{-1}: 3440, 3078, 2930, 2845, 1742, 1642, 1449, 1390, 1345, 1214, 1039, 908, 890, 830, 732; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2088; $[\alpha]^{25}_D$ = +46.5 (c = 1.0 in $CHCl_3$).

*3-((1S)-1-hydroxy-2-((1S,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-furan-2(5H)-one - Vitexolide D (**1**).*[9a] In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **21** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **1** (26 mg, 0.08 mmol) was obtained in 12% yield, as a colorless oil. All data were in excellent agreement with previously reported.; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 2.7, 1.6 Hz, 1H), 4.90 (dd, *J* = 2.8, 1.3 Hz, 1H), 4.84 (t, *J* = 1.8 Hz, 2H), 4.72 (m, 1H), 4.53 (m, 1H), 2.61 (d, *J* = 4.7 Hz, 1H), 2.41 (ddd, *J* = 12.7, 4.1, 2.5 Hz, 1H), 2.07 (ddd, *J* = 14.1, 8.0, 1.7 Hz, 1H), 1.96 (td, *J* = 13.0, 5.1 Hz, 1H), 1.86 (ddd, *J* = 14.1, 10.6, 5.9 Hz, 1H), 1H), 1.78 – 1.73 (m, 2H), 1.60 (d, *J* = 10.5 Hz, 1H), 1.56 – 1.50 (m, 2H), 1.40 – 1.38 (m, 1H), 1.32 (dd, *J* = 12.9, 4.3 Hz, 1H), 1.16 (td, *J* = 13.3, 4.1 Hz, 1H), 1.07 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.95 (td, , *J* = 12.8, 3.9 4.5 Hz 1H), 0.86 (s, 3H), 0.79 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 149.3, 145.1, 136.1, 107.1, 70.4, 67.7, 55.6, 53.6, 42.0, 39.9, 39.0, 38.3, 33.6, 33.5, 30.0, 24.4, 21.7, 19.3, 14.5; ν_{max} (neat)/cm^{-1}: 3340, 3080, 2940, 2862, 2850, 1642, 1500, 1450, 1390, 1162, 1025, 877, 790, 730; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2089; $[\alpha]^{25}_D$ = +5.2 (c = 1.0 in $CHCl_3$).

*3-((1R)-1-hydroxy-2-((1S,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-ethyl)furan-2(5H)-one (**24a**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **22** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **24a** (124 mg, 0.39 mmol) was obtained in 54% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 2.9, 1.5 Hz, 1H), 5.44 (brs, 1H), 4.83 (t, *J* = 1.6 Hz, 2H), 4.59 (d, *J* = 8.2 Hz, 1H), 2.40 (brs, 1H), 2.10 (brs, 1H), 2.01-1.98 (m, 1H), 1.90 – 1.87 (m, 1H), 1.85-1.83 (m, 1H), 1.75 (s, 3H), 1.69 – 1.66 (m, 2H), 1.55 – 1.43 (m, 2H), 1.42 – 1.39 (m, 1H), 1.26 (m, 1H), 1.18 (td, *J* = 13.2, 3.8 Hz, 1H), 1.05 (td, *J* = 12.8, 3.7 Hz, 1H), 0.88 (s, 3H), 0.87 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 144.1, 137.3, 134.5, 123.0, 70.5, 67.7, 50.1, 49.8, 42.2, 39.2, 36.3, 33.9, 33.2, 33.0, 23.8, 22.3, 21.9, 18.8, 13.7; ν_{max} (neat)/cm^{-1}: 3468, 2922, 2847, 1739, 1446, 1345, 1205, 1156, 1092, 1034, 944, 879, 809, 673; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2085; $[\alpha]^{25}_D$ = +22.4 (c = 1.0 in $CHCl_3$).

*3-((1S)-1-hydroxy-2-((1S,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-ethyl)furan-2(5H)-one (**24b**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **22** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **24a** (24.9 mg, 0.08 mmol) was obtained in 11% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.46 – 5.45 (m, 1H), 4.86-4.85 (m, 2H), 4.58 – 4.56 (m, 1H), 2.67 (brs, 1H), 1.97 – 1.91 (m, 2H), 1.89 – 1.82 (m, 2H), 1.75 (s, 3H), 1.73 – 1.70 (m, 2H), 1.52 – 1.46 (m, 1H), 1.42 – 1.38 (m, 2H), 1.29 – 1.27 (m, 1H), 1.17 (dd, *J* = 12.1, 4.8 Hz, 1H), 1.10 (m, 1H), 0.87 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 145.4, 135.8, 134.1, 70.5, 68.8, 50.6, 50.1, 42.2, 39.3, 36.9, 33.4, 33.1, 33.0, 29.7, 23.8, 22.6, 21.8, 18.7, 13.5; ν_{max} (neat)/cm^{-1}: 3470, 2926, 2846, 1740, 1442, 1348, 1209, 1156, 1095, 1037, 945, 880, 809, 674; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2088; $[\alpha]^{25}_D$ = +5.1 (c = 1.0 in $CHCl_3$).

*3-((1R)-1-hydroxy-2-((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-ethyl)furan-2(5H)-one (**25a**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **23** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **25a** (135.7 mg, 0.4 mmol) was obtained in 60% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.84 (t, *J* = 1.8 Hz, 2H), 4.61 – 4.59 (m, 1H), 2.65 (dd, *J* = 14.3, 3.7 Hz, 1H), 2.32 (dd, *J* = 14.1, 11.0 Hz, 2H), 2.19 – 2.12 (m, 1H), 2.03 (dd, *J* = 17.9, 6.6 Hz, 1H), 1.99-1.97 (m, 1H), 1.67 (s, 3H), 1.62 – 1.56 (m, 1H), 1.53 – 1.40 (m, 4H), 1.20 (dd, *J* = 12.8, 2.0 Hz, 1H), 1.18 – 1.12 (m, 2H), 0.99 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 144.0, 137.4, 135.8, 132.2, 70.6, 67.2, 51.5, 41.7, 39.4, 37.4, 34.1, 33.8, 33.4, 33.3, 21.7, 21.1, 20.1, 19.0, 18.9; ν_{max} (neat)/cm^{-1}: 3500, 2931, 1739, 1456, 1352, 1307, 1176, 1099, 1063, 1032, 942, 831, 753 714, 730; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2089; $[\alpha]^{25}_D$ = −2.7 (c = 1.0 in $CHCl_3$).

*3-((1S)-1-hydroxy-2-((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-ethyl)furan-2(5H)-one (**25b**).* In the presence of $Yb(OTf)_3$ (47.8 mg, 0.077 mmol, 10 mol%) from TMS-furan **3** (0.238 ml, 1.42 mmol, 2.0 equiv.) and aldehyde **23** (166.4 mg, 0.71 mmol, 1.0 equiv.) following the general procedure described above, compound **25b** (22 mg, 0.07 mmol) was obtained in 10% yield, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 3.1, 1.5 Hz, 1H), 4.83 – 4.82 (m, 2H), 4.67 – 4.64 (m, 1H), 2.75 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.43 (brs, 1H), 2.33 (dd, *J* = 14.4, 10.2 Hz, 1H), 2.10-2.08 (m, 2H), 1.95 – 1.93 (m, 1H), 1.62 (s, 3H), 1.58 – 1.50 (m, 4H), 1.43 – 1.40 (m, 1H), 1.18 – 1.16 (m, 3H), 1.04 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 144.2, 136.9, 136.2, 131.4, 70.6, 67.0, 51.4, 41.7, 38.3, 38.0, 34.5, 33.7, 33.5, 33.4, 21.8, 21.6, 20.8, 19.1, 19.0; ν_{max} (neat)/cm^{-1}: 3505, 2931, 1740, 1452, 1350, 1307, 1179, 1099, 1066, 1037, 944, 831, 753 714, 730; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_3Na^+$ $[M+Na]^+$ 341.2087 found 341.2088; $[\alpha]^{25}{}_D = -1.8$ (c = 1.0 in $CHCl_3$).

Synthesis of villosin (4) and (E)-labda-7,11,13-trien-16,15-olide (7). Al_2O_3 (1.5 equiv.) was added to the α-butenolide (1.0 equiv.) in dry pyridine (3 mL). The mixture was refluxed for 12 h, allowed to room temperature and then filtrated to remove the Al_2O_3. The filter cake was washed with chloroform (20 mL). The solvent was removed from the filtrate under reduced pressure. The crude was purified by column chromatography using hexane/ethyl acetate (3:2, v/v) as eluent. The volatiles were removed under reduced pressure to give pure product.

*Villosin (**4**).*[9e] From the mixture of diastereomers **1** and **2** (110 mg, 0.35 mmol, 1.0 equiv.) and Al_2O_3 (52 mg, 0.53 mmol, 1.5 equiv.) following the general procedure described above, compound **4** (87 mg, 0.29 mmol) was obtained in 84% yield, as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.90 (dd, *J* = 15.8, 10.1 Hz, 1H), 6.11 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 1.3 Hz, 2H), 4.76 (q, *J* = 1.6 Hz, 1H), 4.50 (q, *J* = 1.6 Hz, 1H), 2.44 (ddd, *J* = 13.5, 4.3, 2.2 Hz, 1H), 2.37 (d, *J* = 10.1 Hz, 1H), 2.08 (ddd, *J* = 13.4, 9.3, 3.8 Hz, 1H), 1.70 (ddt, *J* = 12.9, 5.2, 2.5 Hz, 1H), 1.55 1.51 (m, 1H), 1.49-1.45 (m, 1H), 1.44 – 1.36 (m, 3H), 1.18 (dt, *J* = 13.3, 3.5 Hz, 1H), 1.09 (dd, *J* = 12.6, 2.7 Hz, 1H), 1.03 – 0.96 (td, *J* = 13.3, 3.2 Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 149.4, 142.5, 136.8, 129.5, 120.7, 108.4, 69.6, 62.2, 54.7, 42.3, 40.8, 39.3 , 36.7, 33.6 (2C), 23.4, 21.9, 19.1, 15.1; ν_{max} (neat)/cm^{-1}: 3079, 2925, 1757, 1642, 1085, 1050, 948, 900, 891; HRMS (ESI-TOF): calculated for $C_{20}H_{28}O_2Na^+$ $[M+Na]^+$ 323.1981 found 323.1982; $[\alpha]^{25}{}_D = -7.8$ (c = 1.0 in $CHCl_3$).

*(E)-labda-7,11,13-trien-16,15-olide (**7**).*[9i] From α-butenolide 24 (50 mg, 0.16 mmol, 1.0 equiv.) and Al_2O_3 (26.5 mg, 0.24 mmol, 1.5 equiv.) following the general procedure described above, compound **7** (7 mg, 0.12 mmol) was obtained in 78 % yield, as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 1.9 Hz, 1H), 6.65 (dd, *J* = 15.8, 10.6 Hz, 1H), 6.13 (d, *J* = 15.8 Hz, 1H), 5.52 (br s, 1H), 4.81 (br s, 2H), 2.44 (d, *J* = 9.8 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.95 – 1.88 (m, 1H), 1.57 (br d, *J* = 13.2, 1H), 1.52 – 1.51 (m, 4H), 1.43 – 1.38 (m, 2H), 1.20 (dd, *J* = 12.1, 4.7 Hz, 1H), 1.15 (dd, *J* = 14.2, 4.4 Hz, 1H), 0.99 (td, *J* = 13.2, 3.4 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 142.1, 138.6, 132.6, 129.5, 122.4, 121.0, 69.6, 60.8, 49.7, 42.4, 40.4, 36.5, 33.3, 33.1, 23.7, 22.6, 22.0, 18.7, 14.9; ν_{max} (neat)/cm^{-1}: 2930, 1754, 1658, 1090, 1047, 946, 885, 890; HRMS (ESI-TOF): calculated for $C_{20}H_{28}O_2Na^+$ $[M+Na]^+$ 323.1981 found 323.1984.

*Synthesis of chinensine C (**5**).*[9d] To a solution of villosin **4** (85 mg, 0.28 mmol, 1.0 equiv) in dry CH_2Cl_2 (2 mL) at −78 °C DIBAL-H (1.0 M in hexane, 492 μL, 0.50 mmol, 1.8 equiv) was added dropwise over a period of 15 min. The reaction was stirred for a further 30 min at −78 °C and quenched at the same temperature by adding MeOH (3 mL). The homogeneous mixture was allowed to warm to room temperature over a period of 1 h until a white precipitate appeared. The cloudy solution was filtered through a pad of celite that was washed with Et_2O (3 × 5 mL). The filtrate was concentrated under reduced pressure to give pure diastereomeric lactols **5** in 1:1 ratio as colorless oil (65 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 – 5.97 (m, 6H, 3H for each diastereomer), 5.91 (br s, 2H, 1H for each diastereomer), 4.79 (ddd, *J* = 6.8, 4.4, 2.4 Hz, 2H, 1H for each diastereomer), 4.74 (dd, *J* = 3.5, 1.7 Hz, 2H, 1H for each diastereomer), 4.61 – 4.52 (m, 2H, 1H for each diastereomer), 4.51 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.45 (q, *J* = 1.8 Hz, 1H), 2.79 (dd, *J* = 9.0, 5.0 Hz, 2H, 1H for each diastereomer), 2.44 (ddd, *J* = 13.5, 4.3, 2.2 Hz, 2H, 1H for each diastereomer), 2.34 (d, *J* = 8.3 Hz, 2H, 1H for each diastereomer), 2.15 – 2.03 (m, 2H, 1H for each diastereomer), 1.70 (ddd, *J* = 10.3, 5.4, 2.6 Hz, 2H, 1H for each diastereomer), 1.53 – 1.36 (m, 10H, 5H for each diastereomer), 1.23 – 1.17 (m, 2H, 1H for each diastereomer), 1.08 (dd, *J* = 12.6, 2.6 Hz, 2H, 1H for each diastereomer), 1.00 (dd, *J* = 12.8, 9.4 Hz, 2H, 1H for each diastereomer), 0.89 (s, 6H, 3H for each diastereomer), 0.83 (s, 6H, 3H for each diastereomer), 0.82 (s, 6H, 3H for each diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 150.3, 139.6, 139.5, 134.2, 134.0, 125.93, 125.90, 124.4, 124.3, 109.0, 108.6, 103.3 (2C), 74.2 (2C), 62.5 (2C), 55.4 (2C), 42.9 (2C), 41.5, 41.4, 39.9, 39.7, 37.33 (2C), 34.2 (2C), 30.9, 30.3, 24.0 (2C), 22.6 (2C), 19.7, 19.5, 15.64 (2C); ν_{max} (neat)/cm^{-1}: 3618, 3430, 3010, 2910, 2860, 1685, 1642; HRMS (ESI-TOF): calculated for $C_{20}H_{30}O_2Na^+$ $[M+Na]^+$ 325.2138 found 325.2138; $[\alpha]^{25}{}_D = +22.1$ (c = 1.0 in $CHCl_3$).

*Synthesis of coronarin E (**6**).*[9g,h] To a solution of villosin **4** (70 mg, 0.23 mmol, 1.0 equiv) in dry THF (10 mL) at −78 °C dropwise DIBAL-H (1.0 M in toluene, 1.1 mL, 1.1 mmol, 4.5 equiv) was added dropwise over a period of 30 min. The reaction was stirred for a further 4 h at −78 °C and quenched at the same temperature by adding 10% HCl (15 mL). The homogeneous mixture was allowed to warm to room temperature over a period of 1 h and stirred at this temperature over 20 min. The organic layer was separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and dried over $MgSO_4$. The residue obtained after evaporation of the solvent under reduced pressure was purified by silica

gel chromatography, eluted with hexanes-ethyl acetate (9:1 → 1:1, v/v) to provide pure product 6 as colorless oil (53 mg, 80%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.35 (s, 1H), 6.55 (s, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.7, 9.8 Hz, 1H), 4.76 (d, *J* = 1.8 Hz, 1H), 4.54 (d, *J* = 1.8 Hz, 1H), 2.46 (ddd, *J* = 13.5, 4.4, 2.3 Hz, 1H), 2.41 (d, *J* = 9.8 Hz, 1H), 2.11 (td, *J* = 13.4, 5.5 Hz, 1H), 1.74 – 1.68 (m, 1H), 1.54 – 1.40 (m, 5H), 1.20 (dt, *J* = 13.9, 4.0 Hz, 1H), 1.12 (dd, *J* = 12.6, 2.7 Hz, 1H), 1.03 (td, *J* = 13.8, 3.4 Hz, 1H), 0.90 (s, 3H), 0.85 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.3, 143.3, 139.6, 128.3, 124.5, 121.8, 108.0, 107.7, 61.5, 54.8, 42.3, 40.8, 39.2, 36.8, 33.6 (2C), 23.4, 22.0, 19.1, 15.0; ν_{max} (neat)/cm^{-1}: 3070, 2945, 2860, 1640, 1468, 1440, 1390, 1370, 1160, 1070, 1027, 970, 890, 598; HRMS (ESI-TOF): calculated for $C_{20}H_{28}ONa^+$ $[M+Na]^+$ 307.2032 found 307.2036; $[\alpha]^{25}{}_D$ = +21.4 (c = 1.0 in $CHCl_3$).

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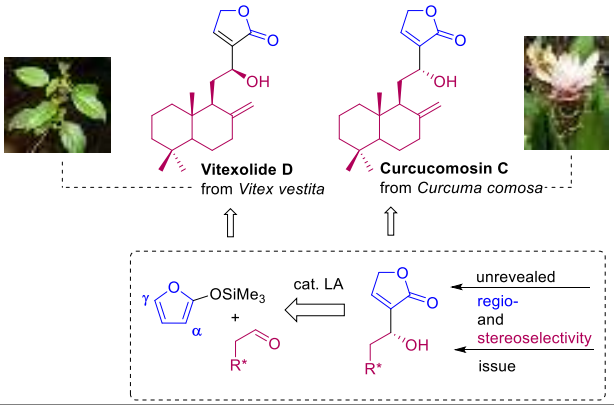

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