Asymmetric Total Synthesis of (−)-Callystatin A and (−)-20-*epi*-Callystatin A Employing Chemical and Biological Methods

Dieter Enders,*[a] Jose L. Vicario,[a] Andreas Job,[a] Michael Wolberg,[b] and Michael Müller[b]

Dedicated to Professor Hans Paulsen on the occasion of his 80th birthday

Abstract: An efficient asymmetric total synthesis of the potent cytotoxic marine natural product (−)-callystatin A and its 20-*epi* analogue has been achieved. The synthetic pathway involved the preparation of three fragments to be coupled with each other at the end of the route. The first fragment **3** was obtained using a biocatalytic enantioselective reduction of a 3,5-dioxocarboxylate as the key step. For the second intermediate **4** the asymmetric α-alkylation of an O-protected derivative of 4-hydroxybutanal was performed exploiting the SAMP/RAMP hydrazone alkylation methodology, and followed by a highly *Z*-selective Horner–Wadsworth–Emmons reaction under modified conditions. For the synthesis of the polypropionate fragment **5** a diastereoselective *syn*-aldol reaction was employed between a chiral ethyl ketone and an α-substituted chiral aldehyde, both prepared in enantiopure form again by means of the asymmetric alkylation of their corresponding RAMP hydrazones. Finally, these three building blocks were coupled using highly *E*-selective Wittig reactions via allyltributylphosphonium ylides to afford the target compounds after a final oxidation/deprotection sequence.

Keywords: asymmetric synthesis · enzymes · hydrazones · natural products · total synthesis

Introduction

(−)-Callystatin A is a potent cytotoxic polyketide isolated from the marine sponge *Callyspongia truncata* by Kobayashi et al. in 1997.[1] Its structure was elucidated by physicochemical methods[2] and shortly afterwards its absolute configuration was confirmed by the same authors through total synthesis.[3] Some structural analogues were also synthesised to establish some structure–activity relationships.[4] The structure of (−)-callystatin A shows a polypropionate chain and a lactone ring connected to each other by two diene systems separated by two sp^3-hybridised carbon atoms (Figure 1). This arrangement is structurally related to several antitumour antibiotics such as anguinomycin,[5] (−)-leptomycin B,[6] (−)-kazusamycin,[7] (+)-fostriecin,[8] (+)-leptofuranin[9] or (+)-ratjadone,[10] (−)-pironetin A,[11] (+)-discoder-

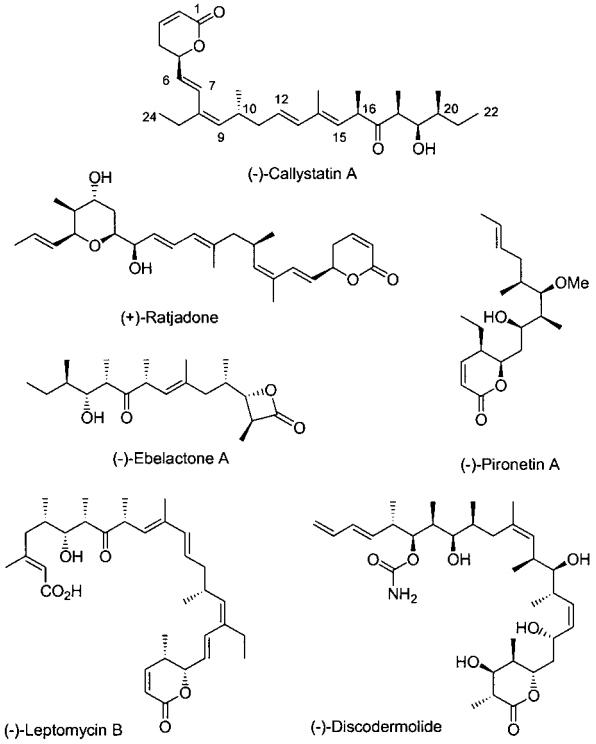

Figure 1. (−)-Callystatin A and other structurally related natural products.

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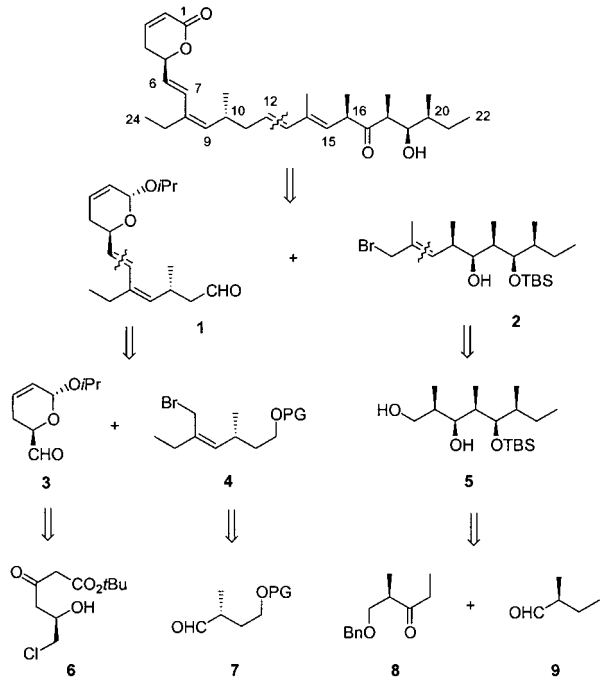
molide[12] as well as (−)-ebelactone A[13] (enzyme inhibitor). These compounds have been the focus of much attention from organic chemists in recent years, not only because of the promising biological activities shown, but also for the elegant total syntheses in which several research groups have been involved.

The fact that only very small amounts of this compound can be obtained from natural sources (1.0 mg of the natural product was isolated from 10 kg of sponge) makes (−)-callystatin A a very attractive target for total synthesis. In fact, some reports have very recently appeared covering the preparation of this polyketide. Shortly after the isolation and first total synthesis by Kobayashi et al. in 1998,[3] a total synthesis was published by Crimmins et al.,[14] in which a chiral auxiliary aldol methodology was employed to build up the polypropionate chain which was coupled with the other subunits by means of allylic Wittig reactions. In 2001 Smith et al.[15] reported the total synthesis of (−)-callystatin A using a combination of the Evans aldol methodology with two Julia olefination reactions. Kalesse et al.[16] accomplished a total synthesis employing Heck and Wittig reactions to construct the C_1–C_{20} chain and performed a final diastereoselective aldol reaction in order to complete the synthesis. Most recently Marshall et al.[17] have reported a total synthesis of this polyketide in which the key attribute implicated the formation of the polypropionate chain by stereoselective addition of chiral allenylmetals to aldehydes. One common feature in all reported syntheses so far is that at least one of the stereogenic centres present in the skeleton of the natural product was introduced from a chiral-pool building block.

In this context, and in view of the challenging structure of (−)-callystatin A, in 1998 we determined to engage in its total synthesis[18] as a unique opportunity to expand the scope of our SAMP/RAMP asymmetric hydrazone alkylation methodology for the introduction of several of the stereogenic centres.[19] In addition, a flexible and convergent synthetic route should be of great interest in the sense that structural analogues with potentially improved biological activity could be readily accessible.

Our retrosynthetic approach (Scheme 1) is based on disconnections of the C_6–C_7 and C_{12}–C_{13} double bonds, which can be built up by means of highly *E*-selective Wittig olefinations between allyltributylphosphorous ylides derived from the corresponding allylic bromides **2** and **4**.[20] Aldehyde **3** is accessible from keto ester **6**, which can be prepared in an almost enantiopure form by biocatalytic enantioselective reduction of a 6-chloro-3,5-dioxohexanoate under conditions recently published by us.[21] Bromide **4** can be obtained by selective olefination of functionalised aldehyde **7**, which is a suitable compound to be prepared by asymmetric α-alkylation of the corresponding (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone. Finally, bromide **2** can be synthesised from triol **5**, which should be obtained by means of a *syn*-selective aldol reaction between the enolate derived from **8** and chiral aldehyde **9**. The latter compounds can also be provided as virtually single enantiomers by standard SAMP/RAMP hydrazone alkylation procedures.

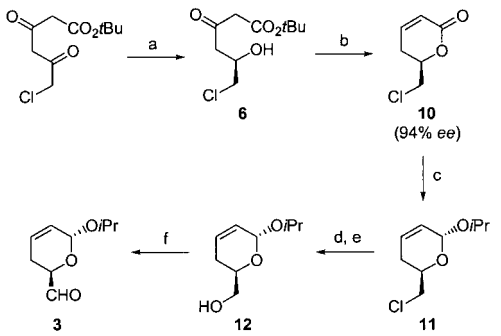


Scheme 1. Retrosynthetic analysis for (−)-callystatin A.

Abstract in German: *Durch eine effiziente asymmetrische Totalsynthese wurde der stark cytotoxische marine Naturstoff (−)-Callystatin A und dessen 20-epi Analogon erhalten. Die Syntheseroute basiert auf der Darstellung von drei Fragmenten, die gegen Ende der Synthese miteinander gekuppelt werden. Das erste Fragment **3** wurde mittels einer biokatalytischen, enantioselektiven Reduktion eines 3,5-Dioxocarboxylats als Schlüsselschritt erhalten. Zur Darstellung des zweiten Intermediats **4** wurde eine asymmetrische α-Alkylierung eines O-geschützten 4-Hydroxybutanals unter Anwendung der SAMP/RAMP-Hydrazon-Methode durchgeführt, gefolgt von einer hoch Z-selektiven modifizierten Horner–Wadsworth–Emmons-Reaktion. Für die Synthese des Polypropionatfragments **5** wurde eine diastereoselektive syn-Aldol-Reaktion zwischen einem chiralen Ethylketon und einem α-substituierten chiralen Aldehyd, beide in enantiomerenreiner Form über asymmetrische Alkylierung der entsprechenden RAMP-Hydrazone hergestellt, verwendet. Schließlich wurden die drei Bausteine unter Verwendung von hoch E-selektiven Wittig-Reaktionen via Allyltributylphosphonium Ylide miteinander gekuppelt, um nach Oxidation und Entfernung der Schutzgruppe die Zielmoleküle zu erhalten.*

Results and Discussion

Synthesis of the aldehyde 3: For the generation of the stereogenic centre in the key intermediate **3** (Scheme 2), we exploited the already mentioned enantioselective biocatalytic reduction of 3,5-dioxocarboxylates developed recently.[21a, b] Treatment of *tert*-butyl 6-chloro-3,5-dioxohexanoate with dried baker's yeast in a biphasic system (water/XAD-7 adsorber resin) furnished the regio- and enantioselective reduced hydroxy keto ester **6** in 94% enantiomeric excess. The



Scheme 2. Synthesis of the aldehyde **3**. a) dried baker's yeast, XAD-7/H_2O, RT, 50%. b) 1) $NaBH_4$, EtOH, 0°C; 2) *p*TsOH (cat), toluene, 120°C, 78%. c) 1) DIBAL-H, CH_2Cl_2, −78°C; 2) *i*PrOH, PPTS, benzene, 80°C, 79%. d) TBAA, NMP, 85°C, 89%. e) K_2CO_3, MeOH, 97%. f) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, −78°C, 95%. TBAA = tetrabutylammonium acetate, NMP = *N*-methyl-2-pyrrolidinone.

remaining keto group in this compound was then reduced with sodium borohydride and upon treatment with a catalytic amount of *p*TsOH in refluxing toluene underwent lactonisation together with elimination to provide the α,β-unsaturated δ-lactone **10** in good yield. The enantiomeric excess of **10** was determined by means of HPLC analysis on a chiral stationary phase.[22]

Our first attempts towards the exchange of the chlorine atom into the desired hydroxy functionality by applying tetrabutylammonium acetate (TBAA) in the presence of *N*-methylpyrrolidinone (NMP)[23] to lactone **10** led to decomposition of the starting material. Similar observations were made by Lichtenthaler and co-workers during the reaction of the iodosubstituted lactone with triphenylphosphine.[24]

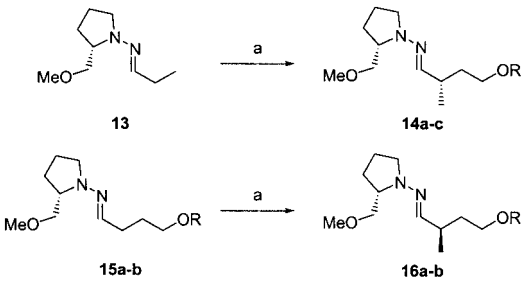
As a consequence we protected the lactone moiety as an acetal by DIBAL-H reduction followed by an acid-catalysed acetalisation with isopropanol in refluxing benzene. The reaction was highly diastereoselective, providing the thermodynamically preferred α-anomer **11**[25] together with 5–8% of the other epimer. Because this acetal would be reoxidised in the final step of the synthesis it could be used as a mixture of diastereoisomers, even though the separation of both was possible using column chromatography. The conversion of the chlorine atom into a hydroxy group was achieved by a chloroacetoxy substitution reaction of the protected intermediate **11** with TBAA in NMP, followed by saponification of the newly generated ester functionality with potassium carbonate in MeOH.[23] Finally, treatment of **12** under standard Swern oxidation conditions furnished the aldehyde **3**.

Synthesis of allylic bromide 4: To obtain the required chiral α-substituted aldehyde **7**, our first approach was to alkylate the SAMP hydrazone of propanal (**13**) with several O-protected 2-iodo- or 2-bromoethanol derivatives (Scheme 3, Table 1). The selection of the protecting groups was made according to their ability to be removed under non-reductive conditions in the presence of C–C double bond moieties, as it is required in our case. Although the configuration of the newly created stereogenic centre is the opposite to the desired one, the reaction should give us information about the viability of this approach. Unfortunately, all attempts to obtain the

Table 1. Alkylation of hydrazones **13** and **15a–b**. All reactions were carried out by deprotonation of the hydrazone with LDA in THF at 0°C for 5 h followed by addition of the electrophile at −100°C.

	Substrate	Electrophile	Product	R	Yield [%]	*de* [%][a]
1	**13**	$BrCH_2CH_2OTBS$	**14a**	TBS	14	87
2	**13**	$BrCH_2CH_2OIPS$	**14b**	IPS	34	84
3	**13**	ICH_2CH_2OPMB	**14c**	PMB	79	72[b]
4	**15a**	MeI	**16a**	TBS	85	>95
5	**15b**	MeI	**16b**	TBDPS	80	>95

[a] Determined by ^{13}C NMR of the crude reaction mixture. [b] Determined by ^{13}C NMR on product **25** (OPMB instead of OTBDPS) obtained afterwards during the synthesis. TBS = *tert*-butyldimethylsilyl, IPS = isopropyldimethylsilyl, PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl.

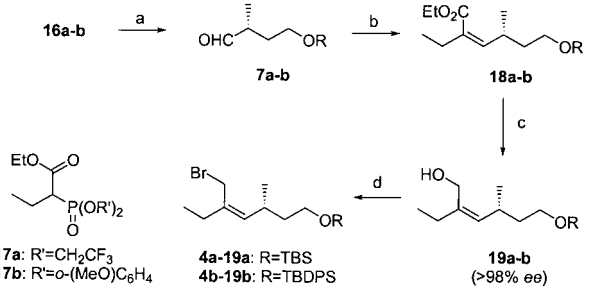


Scheme 3. Synthesis of the α-alkylated hydrazones **14a–c** and **16a–b**. a) see Table 1.

α-alkylated products by this procedure suffered from lack of selectivity or low yields (see Table 1).

Therefore, we inverted the order of assembly of the reagents in the construction of the stereogenic centre and proceeded with the alkylation of the SAMP hydrazones of O-protected 4-hydroxybutanal **15a–b** with iodomethane. In this case the reactions occurred with good yields and very high diastereoselectivities, affording the α-alkylated products with the required (*R*) configuration at the newly created stereogenic centre (Scheme 3, Table 1).

The virtually enantiopure aldehydes **7a–b** were obtained after clean removal of the auxiliary by ozonolysis (Scheme 4). In this reaction, (*S*)-2-(methoxymethyl)-1-nitrosopyrrolidine, produced together with the aldehyde **7a–b**, can be separated from the latter by column chromatography and recycled to SAMP by $LiAlH_4$ reduction.[26] For the *Z*-selective installation of the double bond in the α,β-unsaturated esters **18a–b** we



Scheme 4. Synthesis of the allylic bromides **4a–b**. a) O_3, CH_2Cl_2, −78°C, 86% (**7a**), 77% (**7b**). b) **17b**, NaH, THF, 0°C, 85% (**18a**), 91% (**18b**). c) DIBAL-H, CH_2Cl_2, −78°C, 95% (**19a**), 96% (**19b**). d) CBr_4, PPh_3, CH_3CN, RT, 5% (**4a**, R = TBS), 95% (**4b**, R = TBDPS).

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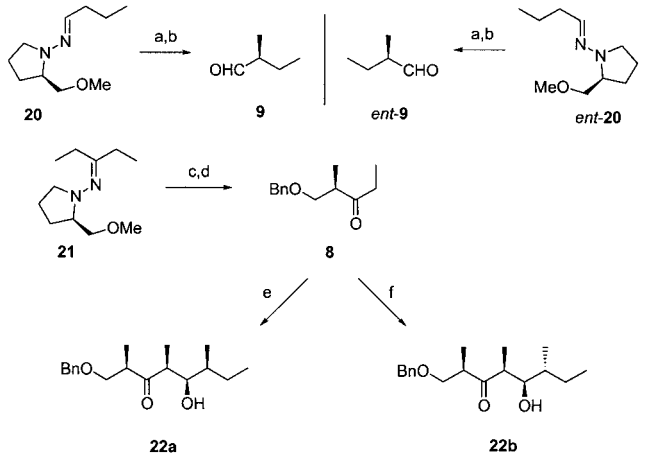
investigated modified Horner–Wadsworth–Emmons conditions. In this context, the use of the reagent **17a** introduced by Still and Gennari[27] gave the olefination product with a moderate degree of diastereoselection (*Z*/*E* ratio of 8:1), as known from the literature.[2, 14–17] Further investigations revealed a much higher Z-selectivity employing the aryl substituted phosphonate **17b**, obtained according to a protocol developed by Ando.[28] This protocol uses simpler reaction conditions (e.g. no crown ether is needed), and the esters **18a–b** were obtained in good yields and with excellent diastereoselectivities (*Z*/*E* ratio of 34:1).

DIBAL-H reduction of the α,β-unsaturated esters **18a–b** afforded cleanly the corresponding allylic alcohols **19a–b**. At this point the enantiomeric excess could be accurately determined by GC analysis to be >98% for each compound. Finally, the bromination of **19a–b** employing CBr_4/PPh_3 in acetonitrile led to the allylic bromides **4a–b**. In the case of **4a**, only a small amount of material (5%) together with a complex mixture of by-products could be isolated after the reaction. We thought that cleavage of the TBS group under the reaction conditions could occur due to the formation of HBr as by-product.[29] Although the yields were increased when the reaction was repeated in the presence of a base such as triethylamine (14%), pyridine (19%) or 2,6-lutidine (21%), they did not reach the level required for preparative purposes. Nevertheless, the bromination reaction of the O-TBDPS protected allylic alcohol **19b** afforded the desired bromide **4b** with excellent yield and without the presence of a base.

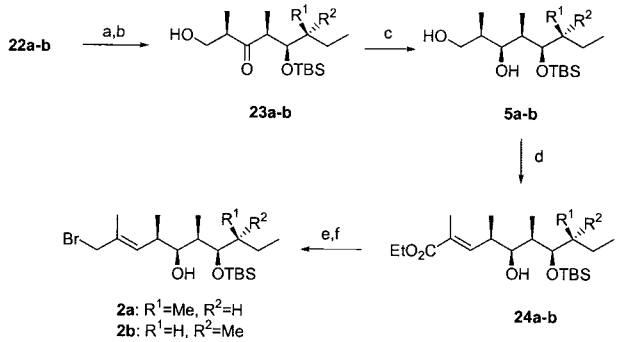
Synthesis of the polypropionate fragment 2:[30] For the synthesis of the allylic bromide **2** we first had to provide the chiral building blocks **8** and **9**. Asymmetric alkylation of 3-pentanone via its (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazone derivative **21** with benzyloxymethyl chloride (BOMCl) and subsequent cleavage of the auxiliary afforded ketone **8** in 96% *ee* and good yield (Scheme 5).[31] In a similar approach, we prepared (*S*)- and (*R*)-2-methylbutanal **9** and *ent*-**9** by α-alkylation of butanal-RAMP or butanal-SAMP hydrazones **20** or *ent*-**20** with iodomethane, respectively. Again it should be pointed out that the chiral auxiliaries SAMP or RAMP could be recycled by $LiAlH_4$ reduction of the nitrosamine isolated after the ozonolysis step.[26]



Scheme 5. Diastereoselective aldol coupling between **8** and **9**. a) 1) LDA, THF, 0 °C; 2) MeI, −100 °C. b) O_3, CH_2Cl_2, −78 °C, 72% (**9**), 67% (*ent*-**9**) over two steps. c) 1) LDA, Et_2O, 0 °C; 2) BOMCl, −100 °C. d) O_3, CH_2Cl_2, −78 °C, 79% over two steps. e) 1) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C; 2) **9**, −78 °C, 87% (97% *ds*). f) 1) $TiCl_4$, $EtN(iPr)_2$, CH_2Cl_2, −78 °C; 2) *ent*-**9**, −78 °C, 96% (94% *ds*).

The next task was to install two new stereogenic centres through a *syn*-selective aldol reaction between **8** and **9**. (Scheme 5).[32] In a first attempt, the Ti^{IV} enolate of **8** was reacted with aldehyde **9** and, although the aldol adduct was obtained in good yields and excellent 4,5-*syn* selectivity, the facial diastereoselectivity was not good enough and aldol adduct **22a** was obtained together with the corresponding 2,4-*anti*-4,5-*syn* diastereomer (62:38 ratio). When the same reaction conditions were employed on the enantiomeric aldehyde *ent*-**9**, the *matched* aldol product **22b** was obtained in good yield and 94% *ds*. On the other hand, when we tried the Sn^{II} mediated *mismatched* aldol reaction between ketone **8** and aldehyde **9**,[33] aldol **22a** was obtained in excellent yield and 97% *ds*. It should be noted that the use of commercially available $Sn(OTf)_2$ for this reaction led to 0% yield,[34] only after washing the purchased material several times with dry diethyl ether did the reaction proceed with the given results. In any case both aldol products **22a** and **22b** were obtained as single diastereomers after column chromatography. This *matched*/*mismatched* behaviour of the substrates in the aldol reaction enabled us to access the natural product employing the adduct **22a** and its C-20-epimer using **22b**, which constitutes also the correct configuration of the ebelactone A side chain.

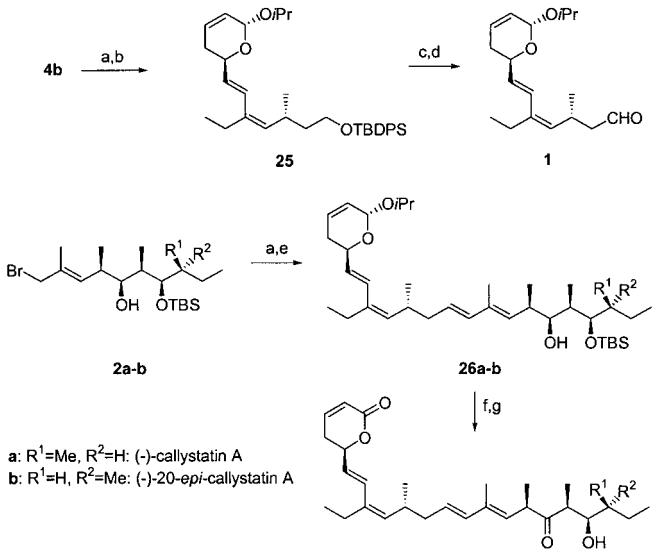
Continuing with the synthesis, aldols **22a–b** were protected as the corresponding TBS ethers and subsequent debenzylation with hydrogen over Pd/C afforded β-hydroxy ketones **23a–b** (Scheme 6). The enantiomeric excess of these compounds was determined to be >96% by the NMR analysis of the corresponding Mosher esters. Reduction with DIBAL-H in CH_2Cl_2 at low temperature yielded stereopentads **5a–b** with excellent diastereoselectivities (*de* 91% and 86% for **5a** and **5b**, respectively).[35] Subsequent Swern oxidation of the



Scheme 6. Synthesis of allylic bromides **2a–b**. a) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 98% (**22a**), 99% (**22b**). b) H_2, Pd/C, EtOH, RT, 95% (**23a**), 98% (**23b**). c) DIBAL-H, CH_2Cl_2, −78 °C, 87% (**5a**), 86% (**5b**). d) 1) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, −78 °C; 2) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, reflux, 79% (**24a**), 52% (**24b**). e) DIBAL-H, CH_2Cl_2, −78 °C. f) CBr_4, PPh_3, 2,6-lutidine, CH_3CN, RT, 76% (**2a**), 81% (**2b**) over two steps.

primary hydroxy group followed by a Wittig reaction with $Ph_3P{=}C(CH_3)CO_2Et$ afforded the *E* isomers of α,β-unsaturated esters **24a–b** as the only detectable products. No oxidation of the secondary alcohol functionality could be observed even though an excess of oxidative reagent was applied. Because ester **24a** is a known compound we could confirm the proposed absolute configuration of this building block by comparison with the data reported in the literature.[30a] Finally, DIBAL-H reduction of the ester moiety and selective bromination[36] of the primary alcohol with CBr_4/PPh_3 furnished the desired polypropionate fragment **2a–b**. Notably, in this case, the bromination reaction had to be carried out in the presence of one equivalent of a base such as 2,6-lutidine to prevent the generation of a significant amount of the corresponding TBS-deprotected analogue.

Assembling of the synthetic intermediates and synthesis of (−)-callystatin A and (−)-20-*epi*-callystatin A: In order to build up the skeleton of the target compounds, allylic bromide **4b** was converted into the corresponding tributylphosphonium salt by treatment with PBu_3 in acetonitrile. The Wittig reaction of the salt with aldehyde **3** in the presence of KO*t*Bu afforded the Western part **25** of the target molecules in good yield and as a single *E* isomer concerning the newly formed double bond (Scheme 7). Deprotection of the TBDPS ether



Scheme 7. Synthesis of (−)-callystatin A and its C-20-epimer. a) PBu_3, CH_3CN, RT. b) **3**, KO*t*Bu, toluene, 0 °C, 86% over two steps. c) TBAF, THF, RT. d) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, −78 °C, 91% over two steps. e) **1**, $LiCH_2S(O)CH_3$, toluene, −78 °C, 76% (**26a**), 73% (**26b**). f) PCC, AcOH, 4 Å MS, C_6H_6, RT. g) HF·pyridine, THF, RT, 72% (callystatin A), 69% (20-*epi*-callystatin A). TBAF = tetrabutylammonium fluoride, PCC = pyridinium chlorochromate.

took place smoothly employing TBAF in THF and Swern oxidation yielded aldehyde **1** ready for the next Wittig coupling reaction with the polypropionate fragments **2a–b**.

During the final assembly step the allyltributylphosphonium salt derived from allylic bromide **2a** failed to react with aldehyde **1** under the conditions previously employed (KO*t*Bu in toluene at 0 °C). Nevertheless, the use of $LiCH_2S(O)CH_3$ as base at lower temperature (−78 °C) instead enable the coupling of both phosphonium salts derived from **2a** and **2b** with aldehyde **1**. The pentaenes **26a–b** were obtained in good yield and again as single *E*-isomers concerning the newly generated double bond. Treatment of these pentaenes with PCC led to oxidation of the lactol moiety and the unprotected hydroxy group in C_1 and C_{17} position, respectively. Finally the TBS ether was deprotected with HF/pyridine complex in THF to obtain the natural (−)-callystatin A and its 20-*epi* analogue. The spectroscopic data observed for our synthetic (−)-callystatin A were identical in all respects with those reported for the natural material (^1H and ^{13}C NMR, HRMS, $[\alpha]_D^{20}$ and IR).[1–3]

Conclusion

A concise and flexible asymmetric total synthesis of the cytotoxic polyketide (−)-callystatin A has been achieved. The key steps of this synthesis rely on the creation of all stereogenic centres in the first stages by using the SAMP/RAMP hydrazone alkylation protocol together with an enantioselective biocatalytic reduction and a *syn*-selective aldol protocol. We therefore achieved the first asymmetric and non ex-chiral pool synthesis of this natural product. As another interesting feature of this synthesis the two diene systems have been built up using highly diastereoselective Wittig and Horner–Wadsworth–Emmons reactions. While optimising the reaction conditions for the diastereoselective aldol reaction that was intended for the preparation of the polypropionate chain of the target compound, efficient conditions for the synthesis of an epimeric intermediate were found. This intermediate was also employed in the reaction sequence providing the previously unknown 20-*epi* analogue of (−)-callystatin A. The overall yield of both the natural product (18%) and its C-20 epimer (17%, 13 steps for the longest linear reaction sequence) is comparable or better as in the previous reported syntheses.[3, 14–17]

Experimental Section

General methods: Solvents were purified and dried prior to use. Tetrahydrofuran (THF), diethyl ether, benzene and toluene were freshly distilled from sodium/benzophenone under argon. Dichloromethane, acetonitrile, dimethylsulfoxide (DMSO), diisopropylamine, triethylamine, diisopropylethylamine (DIPEA) and *N*-methyl-2-pyrrolidinone (NMP) were distilled from CaH_2 and stored under argon. Methanol was distilled from magnesium methoxide. Diethyl ether and pentane for column chromatography were distilled prior to use. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (400–630 mesh) were purchased from Merck. *n*BuLi was used as 1.5–1.4 M solution in hexane (Merck) and titrated regularly with diphenylacetic acid before use. (*S*)- and (*R*)-1-Amino-2-methoxymethylpyrrolidine,[37] hydrazones **13**,[38] **20a–b**,[38] and **21**,[39] benzyloxymethyl chloride (BOMCl)[40] and lactone **10**[21b] were prepared according to literature procedures. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Ozone was generated with Fischer Ozon apparatus M502, the flow of oxygen is given in the reaction procedures. Melting points were measured on a Büchi apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer P241 polarimeter and solvents of Merck UVASOL quality. Microanalyses were obtained with a CHN-O-RAPID

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elemental analyser. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 500 (500 and 125 MHz, respectively), Varian Inova 400 (400 and 100 MHz, respectively) or Varian Gemini 300 (300 and 75 MHz, respectively) in $CDCl_3$ using tetramethylsilane as internal standard unless otherwise noted. IR spectra were measured on Perkin-Elmer FT/IR 1750 and 1720X spectrophotometers as films or in $CHCl_3$ solutions. Mass spectra were obtained on a Varian MAT 212 or a Finigan MAT SSQ 7000, EI 70 eV or CI 100 eV (relative intensities in parentheses). High resolution mass spectra were measured on a Finigan MAT 95.

(2*R*,6*R*)-(+)-2-Chloromethyl-6-isopropoxy-3,6-dihydro-2*H*-2-pyran (11): A 1M solution of DIBAL-H in CH_2Cl_2 (7.48 mL, 7.48 mmol) was slowly added to a cold (−78 °C) solution of chlorolactone **10** (1.00 g, 6.80 mmol) in CH_2Cl_2 (30 mL). After stirring for 30 min, the reaction was quenched with 1M HCl solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting oil was taken up in benzene (30 mL) and isopropanol (1.56 mL, 20.41 mmol) and PPTS (25 mg) was added. The mixture was heated under reflux for 3 h and quenched with water. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording lactol **11** after flash column chromatography (Et_2O/pentane 1:9) as a colourless oil (1.03 g, 79 %). $[\alpha]_D^{20} = +19.1$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 1.18$ (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.0$ Hz, 3H), 2.04 (dddd, $J = 17.5$, 5.4, 3.9, 1.5 Hz, 1H), 2.13 (ddtd, $J = 17.5$, 10.7, 2.5, 1.5 Hz, 1H), 3.59 (d, $J = 5.5$ Hz, 2H), 4.07 (sept, $J = 6.2$ Hz, 1H), 4.18 (dtd, $J = 10.7$, 5.3, 3.9 Hz, 1H), 5.13 (dd, $J = 1.5$, 1.3 Hz, 1H), 5.74 (dtd, $J = 10.0$, 2.9, 1.5 Hz, 1H), 5.98 (dddd, $J = 10.0$, 5.6, 2.3, 1.3 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = 21.80$, 23.76, 27.97, 46.98, 66.17, 69.35, 92.91, 126.12, 127.58; IR (film): $\tilde{\nu} = 2971$, 2928, 2901, 1660, 1466, 1428, 1402, 1382, 1318, 1260, 1230, 1183, 1141, 1126, 1101, 1066, 1035, 1017, 977, 956, 931, 897, 874, 856, 841, 815, 797, 742, 717, 686, 636, 578, 506, 492 cm^{-1}; MS (CI, 100 eV, isobutane): *m*/*z* (%): 193 (15), 191 (47) [M^++H], 133 (34), 131 (100); elemental analysis calcd (%) for $C_9H_{15}ClO_2$: C 56.69, H 7.93; found: C 56.55; H 7.85.

(2*R*,6*R*)-(+)-(6-Isopropoxy-3,6-dihydro-2*H*-6-pyran-2-yl)methanol (12): Tetrabutylammonium acetate (2.28 g, 17.15 mmol) was placed in a flask under argon and a solution of the chlorolactol **11** (1.31 g, 6.86 mmol) in NMP (10 mL) was added. The mixture was heated to 85 °C for 3 h, cooled to RT and water (30 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording the desired acetoxylactol after flash column chromatography purification (Et_2O/pentane 1:2) as a colourless oil (1.31 g, 89 %). $[\alpha]_D^{20} = +31.7$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (300 MHz): $\delta = 1.18$ (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.94 (m, 1H), 2.06 (m, 1H), 2.09 (s, 3H), 4.02 (sept, $J = 6.3$ Hz, 1H), 4.16 (m, 2H), 4.20 (m, 1H), 5.11 (dd, $J = 1.5$, 1.1 Hz, 1H), 5.75 (dtd, $J = 10.2$, 2.7, 1.5 Hz, 1H), 5.99 (dddd, $J = 10.2$, 5.8, 1.9, 1.1 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = 20.83$, 22.11, 23.68, 26.47, 64.42, 66.27, 69.83, 93.14, 126.15, 127.76, 170.88; IR (film): $\tilde{\nu} = 3046$, 2971, 2930, 2899, 1743, 1659, 1455, 1429, 1407, 1369, 1318, 1285, 1238, 1184, 1127, 1096, 1042, 1032, 978, 961, 933, 915, 862, 845, 826, 802, 719, 646, 607, 513, 472 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 213 (0.6) [$M^+ - H$], 155 (86), 141 (21), 112 (19), 95 (100), 81 (9), 70 (23), 67 (20); elemental analysis calcd (%) for $C_{11}H_{18}O_4$: C 61.66, H 8.47; found: C 61.53, H 8.31.

The acetoxylactol (1.30 g, 6.07 mmol) was dissolved in dry methanol (15 mL) and K_2CO_3 (420 mg, 3.04 mmol) was added in one portion. After stirring for 30 min at RT the solvent was removed under reduced pressure and the residue was taken up in water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording the hydroxylactol **12** after flash column chromatography (Et_2O/pentane 1:1) as a white solid (1.01 g, 97 %). M.p. 39–42 °C; $[\alpha]_D^{20} = +36.5$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 1.18$ (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.89 (dddd, $J = 17.6$, 5.8, 3.3, 1.4 Hz, 1H), 2.15 (dddt, $J = 17.6$, 11.3, 2.5, 1.9 Hz, 1H), 2.21 (brs, 1H), 3.60 (dd, $J = 11.5$, 6.0 Hz, 1H), 3.72 (dd, $J = 11.5$, 3.2 Hz, 1H), 4.00 (sept, $J = 6.2$ Hz, 1H), 4.07 (m, 1H), 5.11 (m, 1H), 5.73 (dtd, $J = 10.0$, 3.0, 1.5 Hz, 1H), 5.99 (dddd, $J = 10.0$, 5.6, 1.4, 1.4 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = 21.91$, 23.78, 25.98, 65.17, 66.61, 69.41, 92.66, 125.75, 127.99; IR (film): $\tilde{\nu} = 3447$, 3044, 2971, 2927, 2889, 1658, 1466, 1425, 1402, 1382, 1318, 1242, 1138, 1126, 1104, 1039, 1017, 976, 954, 931, 906, 846, 825, 794, 719, 633, 508 cm^{-1}; MS (CI, 100 eV, isobutane): *m*/*z* (%): 173 (42) [M^++H], 114 (7), 113 (100); elemental analysis calcd (%) for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.63, H 9.08.

(2*R*,6*R*)-6-Isopropoxy-3,6-dihydro-2*H*-pyran-2-carbaldehyde (3): Oxalyl chloride (0.57 mL, 6.52 mmol) was added at −78 °C to a solution of DMSO (0.92 mL, 13.04 mmol) in dry CH_2Cl_2 (20 mL). After stirring for 10 min, a solution of the alcohol **12** (1.02 g, 5.93 mmol) in CH_2Cl_2 (15 mL) was carefully added and the mixture was stirred for an additional 15 min. DIPEA (5.16 mL, 29.65 mmol) was added at once and, after 10 min, it was allowed to reach RT and quenched with water (30 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The obtained oil was dissolved in Et_2O and filtered through a short path of silica gel, eluting with Et_2O/pentane 1:1, and afforded crude aldehyde **3** as a yellowish oil, which was used directly in the next step without further purification (0.96 g, 95 %). ^{1}H NMR (400 MHz): $\delta = 1.20$ (d, $J = 6.2$ Hz, 3H), 1.25 (d, $J = 6.2$ Hz, 3H), 2.11–2.27 (m, 2H), 4.06 (sept, $J = 6.2$ Hz, 1H), 4.41 (dd, $J = 11.3$, 4.7 Hz, 1H), 5.21 (m, 1H), 5.75 (dtd, $J = 10.2$, 2.9, 1.7 Hz, 1H), 6.02 (m, 1H), 9.73 (s, 1H); ^{13}C NMR (100 MHz): $\delta = 21.94$, 23.73, 24.88, 70.06, 70.95, 92.92, 126.32, 126.64, 200.78.

4-(*tert*-Butyldimethylsilyloxy)butanal: 1,4-Butanediol (720 mg, 8.09 mmol) was slowly added to a suspension of NaH (194 mg, 8.09 mmol) in dry THF (50 mL) at 0 °C. After stirring for 1 h at this temperature and for 2 h at RT, the mixture was cooled down to 0 °C and TBSCl (1.17 g, 8.09 mmol) was added at once. The mixture was stirred at RT for 2 h and quenched with water (20 mL). The obtained oil was dissolved in dry CH_2Cl_2 (10 mL) and added to a cold (−78 °C) solution of Swern reagent (prepared by addition of oxalyl chloride (0.78 mL, 8.90 mmol) to a solution of DMSO (1.26 mL, 17.79 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C followed by 30 min stirring at this temperature). The mixture was stirred for 1 h and Et_3N (6.23 mL, 44.48 mmol) was added at once. After stirring for 30 min at −78 °C the mixture was allowed to reach to RT, stirred for further 30 min and quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording the pure aldehyde after flash column chromatography (Et_2O/pentane 1:3) as a colourless oil (1.45 g, 89 % yield over two steps). ^{1}H NMR (400 MHz): $\delta = 0.04$ (s, 6H), 0.89 (s, 9H), 1.87 (m, 2H), 2.51 (dt, $J = 7.2$, 1.6 Hz, 2H), 3.66 (t, $J = 6.0$ Hz, 2H), 9.79 (t, $J = 1.9$ Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -5.41$, 18.25, 25.47, 25.85, 40.72, 61.98, 202.26; IR (film): $\tilde{\nu} = 2930$, 2887, 2857, 2716, 1727, 1472, 1440, 1410, 1389, 1361, 1255, 1099, 1017, 980, 939, 836, 810, 777, 663 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 145 (75) [$M^+ - C_4H_9$], 127 (11), 115 (12), 89 (6), 75 (100), 59 (9), 45 (5).

4-(*tert*-Butyldiphenylsilyloxy)butanal: The same procedure as described for the previous aldehyde using 1,4-butanediol (3.50 g, 38.83 mmol), NaH (0.93g, 38.83 mmol) TBDPSCl (10.67 g, 38.83 mmol), oxalyl chloride (3.74 mL, 42.72 mmol), DMSO (6.06 mL, 85.44 mmol) and Et_3N (27.1 mL, 194.15 mmol) afforded the aldehyde as a colourless oil (12.10 g, 95 %). ^{1}H NMR (400 MHz): $\delta = 1.05$ (s, 9H), 1.89 (m, 2H), 2.54 (dt, $J = 7.1$, 1.5 Hz, 2H), 3.69 (t, $J = 7.1$ Hz, 2H), 7.35–7.45 (m, 6H), 7.63–7.68 (m, 4H), 9.78 (t, $J = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz): $\delta = 19.14$, 25.19, 26.77, 40.67, 62.81, 127.49, 129.47, 133.36, 135.15, 202.13; IR (film): $\tilde{\nu} = 3070$, 3049, 2955, 2931, 2890, 2858, 2720, 1726, 1471, 1428, 1390, 1110, 1012, 823, 739, 704, 613, 506 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 269 (100) [$M^+ - C_4H_9$], 227 (6), 199 (72), 191 (20), 181 (15), 161 (11), 139 (34), 131 (19), 129 (12), 105 (19).

(*S*)-(−)-1′-(4-*tert*-Butyldimethylsilyloxy-1-butylidenamino)-2′-(methoxymethyl)pyrrolidine (15a): SAMP (0.65 g, 4.95 mmol) was added to 4-*tert*-butyldimethylsilyloxybutanal (1.00 g, 4.95 mmol) at 0 °C and the mixture was stirred for 3 h at RT. Et_2O (10 mL) and Na_2SO_4 were added and the mixture was stirred for a further 30 min. After filtration and removal of the solvent under reduced pressure, pure hydrazone **15a** was obtained after flash column chromatography (Et_2O/pentane 1:1+3 % Et_3N) as a colourless oil. (1.34 g, 86 %). $[\alpha]_D^{20} = -34.9$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.05$ (s, 6H), 0.89 (s, 9H), 1.21 (t, $J = 7.1$ Hz, 2H), 1.70 (m, 2H), 1.92 (m, 2H), 2.27 (m, 2H), 2.74 (q, $J = 8.5$ Hz, 1H), 3.27 (m, 1H), 3.37 (s, 3H), 3.43 (m, 1H), 3.49 (q, $J = 7.1$, 1H), 3.56 (dd, $J = 8.8$, 3.6 Hz, 1H), 3.65 (t, $J = 6.3$ Hz, 2H), 6.65 (t, $J = 5.5$ Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -5.26$, 18.34, 22.13, 25.95, 26.56, 29.56, 30.84, 50.33, 59.10, 62.58, 63.41, 74.74,

138.40; IR (film): $\tilde{\nu}$ = 2953, 2928, 2886, 2856, 1471, 1462, 1387, 1361, 1255, 1196, 1099, 1006, 972, 836, 813, 776 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 314 (11) [M^+], 269 (100), 106 (6), 101 (5), 89 (6), 73 (28), 70 (10), 59 (10); 45 (9); elemental analysis calcd (%) for $C_{16}H_{34}N_2O_2Si$: C 61.10, H 10.90, N 8.91; found: C 61.01, H 11.11, N 9.16.

(*S*)-(−)-1′-(4-*tert*-Butyldiphenylsilyloxy-1-butylidenamino)-2′-(methoxymethyl)pyrrolidine (15b): The same procedure as described for the previous hydrazone using SAMP (2.22 g, 17.07 mmol), and 4-*tert*-butyldiphenylsilyloxybutanal (5.60 g, 17.07 mmol) afforded **15b** as a colourless oil (7.13 g, 95%). $[\alpha]_D^{20} = -69.4$ (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 1.06 (s, 9H), 1.72–1.96 (m, 6H), 2.33 (q, J = 7.1 Hz, 2H), 2.54 (dq, J = 7.1, 2.5 Hz, 1H), 2.68 (q, J = 8.2 Hz, 1H), 3.21 (m, 1H), 3.36 (s, 3H), 3.41 (m, 1H), 3.55 (dd, J = 8.2, 3.0 Hz, 1H), 3.71 (t, J = 6.3, 1H), 6.61 (t, J = 5.5 Hz, 1H), 7.34–7.43 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR (100 MHz): δ = 19.18, 22.11, 26.54, 26.82, 29.55, 30.66, 50.26, 59.09, 63.30, 63.35, 74.73, 127.39, 129.31, 133.76, 135.33, 138.29; IR (film): $\tilde{\nu}$ = 3070, 2930, 2891, 2858, 1472, 1462, 1428, 1196, 1111, 823, 740, 703, 688, 614, 506 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 438 (8) [M^+], 393 (100), 197 (7), 168 (16), 135 (17), 70 (6), 45 (5); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2Si$: C 71.19, H 8.73, N 6.39; found: C 71.08, H 8.70, N 6.27.

(2′*S*,2*R*)-(−)-1′-(4-*tert*-Butyldimethylsilyloxy-2-methyl-1-butylidenamino)-2′-(methoxymethyl)pyrrolidine (16a): A solution of the hydrazone **15a** (0.90 g, 3.19 mmol) in dry THF (15 mL) was added to a cooled (0 °C) solution of LDA (0.38 g, 3.51 mmol) in THF (20mL). After stirring for 5 h, the mixture was cooled down to −105 °C and a solution of MeI (0.22 mL, 3.51 mmol) in THF (10 mL) was slowly added. The mixture was stirred at this temperature for 3 h, allowed to warm to RT and quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the α-alkylated hydrazone **16a** after flash column chromatography (Et_2O/pentane 1:5+3% Et_3N) as a colourless oil (0.81 g, 85%). $[\alpha]_D^{20} = -79.7$ (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.06 (d, J = 6.9 Hz, 3H), 1.55 (m, 1H), 1.70 (m, 1H), 1.75–1.98 (m, 4H), 2.45 (m, 1H), 2.70 (m, 1H), 3.31 (m, 2H), 3.37 (s, 3H), 3.42 (m, 1H), 3.57 (dd, J = 9.1, 3.6 Hz, 1H), 3.66 (t, J = 6.6 Hz, 2H), 6.50 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz): δ = −5.25, −5.23, 18.31, 19.15, 22.01, 25.95, 26.52, 33.74, 38.31, 50.16, 59.08, 61.18, 63.35, 74.62, 143.20; IR (film): $\tilde{\nu}$ = 2955, 2929, 2859, 1463, 1386, 1254, 1197, 1101, 1005, 987, 898, 837, 810, 776, 898, 837, 810, 776 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 328 (18) [M^+], 283 (100), 214 (6), 170 (5), 113 (7), 89 (16), 73 (25), 70 (14), 59 (5), 45 (5); elemental analysis calcd (%) for $C_{17}H_{36}N_2O_2Si$: C 62.14, H 11.04, N 8.53; found: C 62.03, H 10.92, N 8.58.

(2′*S*,2*R*)-(−)-1′-(4-*tert*-Butyldiphenylsilyloxy-2-methyl-1-butylidenamino)-2′-(methoxymethyl)pyrrolidine (16b): The same procedure as described for the previous alkylation using hydrazone **15b** (3.0 g, 6.85 mmol), LDA (0.81 g, 7.53 mmol) and MeI (0.45 mL, 7.53 mmol) afforded **16b** as a colourless oil (2.47 g, 80%). $[\alpha]_D^{20} = -105.7$ (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 1.03 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H), 1.61 (m, 2H), 1.68–1.94 (m, 4H), 2.54 (m, 2H), 2.68 (m, 1H), 3.21 (m, 1H), 3.33 (s, 3H), 3.64 (m, 1H), 3.55 (dd, J = 8.8, 3.3 Hz, 1H), 3.75 (m, 2H), 6.48 (d, J = 8.2 Hz, 1H), 7.34 (m, 6H), 7.68 (m, 4H); ^{13}C NMR (100 MHz): δ = 19.02, 19.21, 22.07, 26.65, 28.85, 33.77, 38.13, 50.15, 59.12, 62.01, 63.31, 74.60, 127.57, 129.33, 133.93, 135.45, 143.00; IR (film): $\tilde{\nu}$ = 2957, 2929, 2857, 1472, 1461, 1428, 1389, 1195, 1111, 998, 899, 823, 739, 703, 688, 614, 506 cm^{-1}; MS (EI, 70eV): *m*/*z* (%): 452 (19) [M^+], 407 (100), 197 (6), 183 (6), 175 (10), 135 (15), 70 (7); elemental analysis calcd (%) for $C_{27}H_{40}N_2O_2Si$: C 71.63, H 8.91, N 6.19; found: C 71.73, H 8.82, N 6.23.

(*R*)-(−)-4-*tert*-Butyldimethylsilyloxy-1-methylbutanal (7a): Hydrazone **16a** (3.17 g, 10.71 mmol) was dissolved in CH_2Cl_2 and the solution was cooled to −78 °C. Ozone (60 L h^{-1}) was bubbled through the solution until persistent blue colour was observed and then argon was bubbled until the blue colour disappeared. The solution was allowed to warm to RT and the solvent was removed under reduced pressure. Pure aldehyde **7a** (1.99 g, 86%) was obtained after flash column chromatography (Et_2O/pentane 1:2). $[\alpha]_D^{20} = -17.6$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 0.04 (s, 6H), 0.89 (s, 9H), 1.12 (d, J = 7.1 Hz, 3H), 1.54 (m, 1H), 1.96 (m, 1H), 2.52 (m, 1H), 3.64–3.78 (m, 2H), 9.65 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz): δ = −5.45, 13.07, 18.24, 25.84, 33.66, 43.48, 60.15, 204.59; IR (film): $\tilde{\nu}$ = 2955, 2931, 2885, 2858, 1728, 1709, 1471, 1388, 1256, 1103, 836, 811, 777, 734 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 201 (1) [$M^+ - CH_3$], 159 (100), 141 (15), 129 (39), 89 (17), 75 (94), 73 (17), 59 (11); elemental analysis calcd (%) for $C_{11}H_{24}O_2Si$: C 61.05, H 11.18; found: C 60.98, H 11.17.

(*R*)-(−)-4-*tert*-Butyldiphenylsilyloxy-1-methylbutanal (7b): The same procedure as described for the previous ozonolysis using hydrazone **16b** (2.16 g, 4.78 mmol) afforded **7b** as a colourless oil (1.15 g, 77%). $[\alpha]_D^{20} = -29.5$ (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 1.04 (s, 9H), 1.08 (d, J = 6.8 Hz, 3H), 1.63 (m, 1H), 1.98 (m, 1H), 2.53 (m, 1H), 3.71 (m, 2H), 7.36 (m, 6H), 7.62 (m, 4H), 9.67 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz): δ = 13.12, 19.21, 26.77, 33.44, 43.44, 61.02, 127.56, 129.46, 133.36, 135.39, 204.54; IR (film): $\tilde{\nu}$ = 2959, 2931, 2858, 1728, 1708, 1472, 1462, 1428, 1112, 1006, 998, 823, 738, 703, 688, 614, 505 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 325 (3) [$M^+ - CH_3$], 294 (11), 283 (100), 253 (15), 227 (11), 205 (51), 199 (93), 183 (19), 181 (20), 175 (43), 139 (25), 135 (11), 105 (12); elemental analysis calcd (%) for $C_{21}H_{28}O_2Si$: C 74.07, H 8.29; found: C 73.94, H 8.23.

Ethyl di-(2-methoxyphenyl)phosphonobutyrate (17b): Phosphorus pentachloride (50.4 g, 240 mmol) was added in portions to triethyl 2-phosphonobutyrate (24.1 g, 95 mmol) at RT. After stirring for 15 min at this temperature the mixture was heated to 75 °C in a distillation apparatus for 8 h. After cooling to RT the flask with the crude product was connected with a receiver flask which was cooled with liquid nitrogen and $POCl_3$ was vacuum transferred at RT. After 30 min maintaining this temperature the flask was heated to 100 °C and surplus PCl_5 was vacuum transferred to the receiver flask. After 1 h the receiver flask was disconnected and the yellowish oil (21.7 g) was used in the next steps without further purification. ^{1}H NMR (300 MHz): δ = 1.11 (td, J = 7.4, 1.4 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 2.18 (m, 2H), 3.50 (ddd, J = 17.6, 9.4, 5.3 Hz, 1H), 4.31 (m, 2H); ^{13}C NMR (75 MHz): δ = 12.56 (d, J = 6.9 Hz), 14.02, 21.38 (d, J = 5.1 Hz), 60.19 (d, J = 90.5 Hz), 62.64, 165.79 (d, J = 3.5 Hz).

Triethylamine (30 mL) were added at 0 °C to a solution of the crude dichloride (19.2 g) and guajacol (27.9 g, 225 mmol) in benzene (120 mL). After stirring for 1.5 h at this temperature and an additional 1.5 h at RT the solution was filtered, diluted with diethyl ether (80 mL) and washed with 1M NaOH solution (3 × 15 mL). After washing with pH 7 buffer (1 × 15 mL) and brine (1 × 15 mL) the organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure the pure phosphonate (15.5 g, 45%) was obtained after flash chromatography (Et_2O/petroleum ether 1:2). ^{1}H NMR (300 MHz): δ = 1.09 (td, J = 7.3, 1.1 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 2.26 (m, 2H), 3.34 (ddd, J = 23.4, 9.3, 5.2 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.23 (q, J = 7.0 Hz, 2H), 6.81–7.25 (m, 8H); ^{13}C NMR (75 MHz): δ = 13.09 (d, J = 17.2 Hz), 14.09, 20.86 (d, J = 5.7 Hz), 48.18 (d, J = 135.1 Hz), 55.88, 55.90, 61.48, 112.76, 120.69, 125.81, 122.07 (d, J = 5.7 Hz), 122.18 (d, J = 5.7 Hz), 139.60 (d, J = 9.1 Hz), 139.72 (d, J = 9.1 Hz), 150.83 (d, J = 4.6 Hz), 150.86 (d, J = 4.6 Hz), 168.49 (d, J = 4.6 Hz); IR (film): $\tilde{\nu}$ = 2976, 2939, 2879, 1735, 1604, 1589, 1504, 1458, 1263, 1210, 1197, 1170, 1112, 1043, 1026, 946, 800, 754 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 409 (12) [M^++H], 408 (61) [M^+], 363 (20), 293 (9), 286 (14), 285 (100) [$M^+ - C_7H_7O_2$], 257 (29), 239 (24), 215 (35), 211 (10), 187 (95), 172 (26), 138 (13), 124 (23), 123 (9), 109 (13), 77 (13); HRMS: calcd for $[C_{20}H_{25}PO_7]^+$: 408.1338; found: 408.1337.

(3*Z*,5*R*)-(+)-7-*tert*-Butyldimethylsilyloxy-3-ethoxycarbonyl-5-methylhept-3-ene (18a): A solution of the phosphonate **17b** (319 mg, 0.78 mmol) in dry THF (5 mL) was added over a cooled (0 °C) suspension of NaH (32 mg, 0.78 mmol) in THF (5 mL). After stirring for 3 h at this temperature, a solution of the aldehyde **7a** (130 mg, 0.60 mmol) in THF (5 mL) was added at once and the reaction was stirred for 1 h at 0 °C, allowed to warm to RT and quenched with water (15 mL) when TLC analysis of aliquots indicated full conversion (typically 4–5 h). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the α,β-unsaturated ester after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (160 mg, 85%). $[\alpha]_D^{20} = +21.4$ (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 0.03 (s, 6H), 0.89 (s, 9H), 1.00 (d, J = 6.4 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.45–1.63 (m, 2H), 2.25 (dq, J = 1.1, 7.4 Hz, 2H), 3.06 (m, 1H), 3.58 (t, J = 6.9 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 5.58 (dt, J = 10.2, 1.4 Hz, 1H); ^{13}C NMR (100 MHz): δ = −5.33, −5.31, 13.66, 14.25, 18.29, 20.78, 25.91, 27.58, 30.35, 40.34, 59.91, 61.52, 132.52, 144.78, 168.09; IR (film): $\tilde{\nu}$ = 2957, 2929, 2898, 2857, 1717, 1471, 1463, 1380, 1254, 1237, 1203, 1161, 1138, 1098, 1028, 1006, 902, 837, 811, 776 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 299 (3) [$M^+ - CH_3$], 269 (10), 257 (100), 211 (12), 133 (9), 109 (28), 103

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(15), 95 (13), 75 (27), 73 (18), 59 (15), 57 (14), 55 (13); elemental analysis calcd (%) for $C_{17}H_{34}O_3Si$: C 64.92, H 10.90; found: C 64.84, H 11.17.

(3*Z*,5*R*)-(+)-7-*tert*-Butyldiphenylsilyloxy-3-ethoxycarbonyl-5-methylhept-3-ene (18b): The same procedure as described previously using aldehyde **7b** (300 mg, 0.96 mmol), phosphonate **17b** (471 mg, 1.15 mmol) and NaH (28 mg, 1.15 mmol) afforded **18b** as a colourless oil (418 mg, 91%). $[\alpha]_D^{20} = +23.6$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.95$ (d, $J = 5.8$ Hz, 3H), 0.99 (t, $J = 6.2$ Hz, 3H), 1.03 (s, 9H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.51–1.73 (m, 2H), 2.24 (m, 2H), 3.15 (m, 1H), 3.62 (m, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 5.52 (dt, $J = 9.9$, 1.4 Hz, 1H), 7.48 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (100 MHz): $\delta = 13.65$, 14.42, 19.18, 20.76, 26.87, 27.61, 30.34, 40.10, 59.97, 62.20, 127.49, 129.37, 132.59, 133.88, 135.38, 144.80, 168.06; IR (film): $\tilde{\nu} = 3071$, 2961, 2931, 2897, 2858, 1715, 1472, 1462, 1428, 1388, 1237, 1203, 1161, 1137, 1110, 1028, 823, 793, 739, 704, 614, 506 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 393 (5) [$M^+ - C_2H_5O$], 381 (100), 231 (5), 227 (13), 199 (15), 183 (13), 135 (5), 109 (4); elemental analysis calcd (%) for $C_{27}H_{38}O_3Si$: C 73.92, H 8.73; found: C 74.11, H 8.66.

(3*Z*,5*R*)-(−)-7-*tert*-Butyldimethylsilyloxy-3-hydroxymethyl-5-methylhept-3-ene (19a): A 1M solution of DIBAL-H in CH_2Cl_2 (0.86 mL, 0.86 mmol) was slowly added to a cold (−78 °C) solution of the α,β-unsaturated ester **18a** (110 mg, 0.35 mmol) in CH_2Cl_2 (10 mL). After stirring for 30 min, the reaction was quenched with 1M HCl solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording allylic alcohol **19a** after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (83 mg, 95%). GC analysis on chiral stationary phase (chirasil-dex 25 m), showed an *ee* of >98% for **19a** ($t_R = 36.75$ and 37.12 min for the *R* and *S* enantiomers, respectively). $[\alpha]_D^{20} = -51.8$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.07$ (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 0.97 (d, $J = 6.6$ Hz, 3H), 1.04 (t, $J = 7.4$ Hz, 3H), 1.24 (m, 1H), 1.65 (m, 1H), 2.11–2.25 (m, 2H), 2.73–2.85 (m, 1H), 3.56–3.67 (m, 2H), 3.72–3.82 (m, 2H), 4.29 (d, $J = 11.8$ Hz, 1H), 4.94 (dd, $J = 10.4$, 0.6 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -5.31$, −5.01, 12.97, 18.29, 21.91, 25.86, 27.97, 28.82, 40.19, 60.35, 61.02, 131.82, 140.72; IR (film): $\tilde{\nu} = 3406$, 2957, 2858, 1472, 1463, 1389, 1362, 1256, 1095, 1018, 986, 955, 899, 873, 836, 810, 776, 662 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 272 (1) [M^+], 215 (5), 197 (5), 145 (16), 123 (95), 105 (74), 97 (15), 95 (18), 81 (91), 75 (100), 73 (24), 67 (20), 57 (26), 55 (23); elemental analysis calcd (%) for $C_{15}H_{32}O_2Si$: C 66.11, H 11.84; found: C 65.94, H 11.89.

(3*Z*,5*R*)-(−)-7-*tert*-Butyldiphenylsilyloxy-3-hydroxymethyl-5-methylhept-3-ene (19b): The same procedure as described previously using α,β-unsaturated ester **18b** (444 mg, 1.08 mmol) and 1M DIBAL-H solution (2.71 mL, 2.71 mmol) afforded **19b** as a colourless oil (412 mg, 96%). GC analysis on chiral stationary phase (chirasil-dex 25 m) showed an *ee* of >98% for **19e** ($t_R = 36.53$ and 36.91 min for the *R* and *S* enantiomers, respectively). $[\alpha]_D^{20} = -12.9$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.92$ (d, $J = 6.6$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H), 1.07 (s, 9H), 1.22 (m, 1H), 1.53 (m, 1H), 2.01 (br s, 1H), 2.14 (qt $J = 7.4$, 1.6 Hz, 2H), 2.81 (m, 1H), 3.58–3.70 (m, 2H), 3.97 (d, $J = 11.8$ Hz, 1H), 4.24 (d, $J = 12.4$ Hz, 1H), 4.95 (d, $J = 10.2$ Hz, 1H), 7.35–7.45 (m, 6H), 7.63–7.69 (m, 4H); ^{13}C NMR (100 MHz): $\delta = 12.96$, 19.11, 21.82, 26.85, 28.10, 28.31, 39.93, 60.53, 61.99, 127.45, 127.46, 129.44, 129.50, 132.41, 133.39, 133.58, 135.33, 135.43, 139.96; IR (film): $\tilde{\nu} = 3405$, 3070, 2959, 2930, 2859, 1471, 1428, 1111, 1011, 823, 738, 703, 614, 506 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 397 (1) [M^+], 339 (7), 269 (8), 229 (13), 211 (5), 199 (100), 181 (7), 139 (7), 137 (6), 123 (74), 81 (28), 67 (6), 57 (8), 55 (7); elemental analysis calcd (%) for $C_{25}H_{36}O_2Si$: C 75.70, H 9.15; found: C 75.67, H 9.08.

(3*Z*,5*R*)-(+)-3-Bromomethyl-7-*tert*-butyldimethylsilyloxy-5-methylhept-3-ene (4a): PPh_3 (287 mg, 1.09 mmol) and CBr_4 (363 mg, 1.09 mmol) were sequentially added to a solution of allylic alcohol **19a** (118 mg, 0.47 mmol) in CH_3CN (10 mL) at RT. After stirring for 30 min the mixture was quenched with water (10 mL) and extracted with pentane (5 × 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording allylic bromide **4a** after flash column chromatography (pentane) as a colourless oil (7.4 mg, 5%). $[\alpha]_D^{20} = +23.1$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.07$ (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 0.98 (d, $J = 6.6$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H), 1.73 (m, 1H), 1.86 (m, 1H), 2.11 (dq, $J = 7.1$, 1.1 Hz, 2H), 2.67 (m, 1H), 3.28 (m, 1H), 3.39 (m, 1H), 4.15 (dd, $J = 11.5$, 0.6 Hz, 1H), 4.22 (dd, $J = 11.8$, 0.8 Hz, 1H), 4.87 (dt, $J = 10.1$, 0.5 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -5.33$, −5.28, 12.88, 18.30, 21.22, 25.91, 27.31, 30.55, 32.24, 40.45, 60.65, 129.36, 140.82; IR (film): $\tilde{\nu} = 2958$, 2930, 2857, 1462, 1255, 1068, 839, 775 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 307 (1), 279 (10), 277 (10), 123 (100), 95 (11), 81 (43), 75 (32), 73 (22), 69 (29), 59 (18), 55 (14), 45 (13); elemental analysis calcd (%) for $C_{15}H_{31}BrOSi$: C 53.72, H 9.32; found: C 53.78, H 9.28.

(3*Z*,5*R*)-(+)-3-Bromomethyl-7-*tert*-butyldiphenylsilyloxy-5-methylhept-3-ene (4b): The same procedure as previously described using α,β-unsaturated ester **19b** (37 mg, 0.093 mmol), PPh_3 (61 mg, 0.21 mmol) and CBr_4 (77 mg, 0.21 mmol) afforded **4b** as a colourless oil (41 mg, 95%). $[\alpha]_D^{20} = +51.6$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 1.44 (m, 1H), 1.60 (m, 1H), 2.15 (dq, $J = 7.1$, 1.1 Hz, 2H), 2.71 (m, 1H), 3.62 (dt, $J = 5.8$, 1.4 Hz, 2H), 3.88 (d, $J = 9.9$ Hz, 1H), 4.12 (d, $J = 9.6$ Hz, 1H), 5.08 (dt, $J = 9.9$, 0.6 Hz, 1H), 7.34–7.44 (m, 6H), 7.66 (m, 4H); ^{13}C NMR (100 MHz): $\delta = 12.55$, 19.14, 20.66, 26.84, 27.94, 28.88, 31.08, 39.83, 61.79, 127.39, 129.34, 133.74, 135.33, 135.71, 135.92; IR (film): $\tilde{\nu} = 2960$, 2930, 2858, 1471, 1460, 1428, 1205, 1110, 823, 737, 703 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 403 (10), 401 (10), 263 (26), 261 (25), 199 (12), 197 (11), 183 (10), 181 (9), 135 (11), 123 (100), 97 (10), 95 (11), 81 (36), 67 (10); elemental analysis calcd (%) for $C_{25}H_{35}BrOSi$: C 65.34, H 7.68; found: C 65.43, H 7.71.

(*R*)-(−)-1-Benzyloxy-2-methylpentan-3-one (8): A solution of the hydrazone **21** (397 mg, 2.00 mmol) in dry Et_2O (5 mL) was added to a cooled (0 °C) solution of LDA (235 mg, 2.20 mmol) in Et_2O (7 mL). After stirring for 5 h, the mixture was cooled down to −105 °C and a solution of BOMCl (375 mg, 2.40 mmol) in Et_2O (10 mL) was slowly added. The mixture was stirred at this temperature for 3 h, allowed to warm to RT and quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, to afford the α-alkylated hydrazone after flash column chromatography (Et_2O/pentane 1:2+3% Et_3N) as a colourless oil (522 mg, 82%). $[\alpha]_D^{20} = -114.6$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): $\delta = 0.88$ (d, $J = 7.1$ Hz, 3H), 1.23 (t, $J = 7.3$ Hz, 3H), 1.58–1.79 (m, 3H), 2.02 (m, 1H), 2.13 (dq, $J = 13.5$, 7.3 Hz, 2H), 2.53 (m, 1H), 2.94 (m, 1H), 3.13 (s, 3H), 3.18–3.57 (m, 5H), 3.98 (m, 1H), 4.27 (d, $J = 12.1$ Hz, 1H), 4.37 (d, $J = 12.1$ Hz, 1H), 7.05–7.33 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 11.35$, 14.60, 22.35, 24.53, 27.59, 34.96, 55.90, 58.81, 66.76, 72.70, 72.79, 76.26, 126.82, 127.62, 128.52, 139.20, 173.08; IR (film): $\tilde{\nu} = 2970$, 2932, 2873, 2732, 2066, 1950, 1872, 1808, 1716, 1631, 1587, 1496, 1455, 1375, 1361, 1280, 1252, 1201, 1184, 1100, 1049, 1028, 995, 970, 914, 737, 698, 608, 533, 463 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 318 (7) [M^+], 273 (96), 227 (8), 98 (9), 91 (100), 70 (11), 56 (9); elemental analysis calcd (%) for $C_{19}H_{30}N_2O_2$: C 71.66, H 9.50, N 8.80; found: C 71.89, H 9.40, N 8.34.

The above α-alkylated hydrazone (485 mg, 1.52 mmol) was dissolved in CH_2Cl_2 and the solution was cooled to −78 °C. Ozone (60 L h^{-1}) was bubbled through the solution until persistent blue colour was observed and then argon was bubbled until the blue colour disappeared. The solution was allowed to warm to RT and the solvent was removed under reduced pressure. Pure ketone **8** (302 mg, 96%) was obtained after flash column chromatography (Et_2O/pentane 1:2). GC analysis on chiral stationary phase (chirasil-dex 25 m) showed an *ee* of 96% for ketone **8** ($t_R = 31.74$ and 32.07 min for the *R* and *S* enantiomers, respectively). $[\alpha]_D^{20} = -25.3$ ($c = 1.0$, $CHCl_3$); lit.[33b] $[\alpha]_D^{20} = +25.8$ ($c = 8.2$, $CHCl_3$) for the opposite enantiomer; ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.87$ (d, $J = 7.1$ Hz, 3H), 0.97 (t, $J = 7.3$ Hz, 3H), 2.10 (dq, $J = 18.1$, 7.3 Hz, 1H), 2.20 (dq, $J = 18.1$, 7.3 Hz, 1H), 2.56 (qdd, $J = 7.1$, 7.7, 5.4 Hz, 1H), 3.21 (dd, $J = 8.8$, 5.4 Hz, 1H), 3.46 (dd, $J = 8.8$, 7.7 Hz, 1H), 4.24 (m, 2H), 7.06–7.23 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 7.75$, 13.57, 35.23, 46.15, 72.62, 73.11, 127.50, 127.52, 128.36, 138.67, 211.19. All analytical data match with those given in the literature.[33b]

(*S*)-(+)-2-Methylbutanal (9): A solution of the hydrazone **20** (1.00 g, 5.43 mmol) in dry THF (7 mL) was added to a cooled (0 °C) solution of LDA (640 mg, 5.98 mmol) in THF (10 mL). After stirring for 5 h, the mixture was cooled to −105 °C and a solution of MeI (0.37 mL, 5.98 mmol) in THF (10 mL) was added slowly. The mixture was stirred at this temperature for 3 h, allowed to warm to RT and quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, to afford the α-alkylated hydrazone after flash column chromatography (Et_2O/pentane 1:2+3% Et_3N) as a colourless oil (978 mg, 91%). The α-alkylated hydrazone thus obtained was dissolved in CH_2Cl_2 and the solution was cooled to −78 °C. Ozone (60 L h^{-1}) was bubbled through the

solution until persistent blue colour was observed and then argon was bubbled until the blue colour disappeared. The solution was allowed to warm to RT and water (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were washed with 4 M HCl (2×20 mL) and water (2×20 mL), dried over Na_2SO_4 and filtered. CH_2Cl_2 was removed by distillation and the pure aldehyde **9** (336 mg, 79%) was obtained after distillation of the residue through a short vigreux column. $[\alpha]_D^{20}=+33.1$ ($c=1.3$, $CHCl_3$); lit.[41] $[\alpha]_D^{20}=+32.6$ ($c=2.7$, acetone); ^{1}H NMR (500 MHz): $\delta=0.95$ (t, $J=7.6$ Hz, 3H), 1.09 (d, $J=7.0$ Hz, 3H), 1.45 (m, 1H), 1.74 (m, 1H), 2.23 (m, 1H), 9.62 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta=11.41$, 12.96, 23.60, 47.88, 205.34. All analytical data match with those given in the literature.[41] We proceeded analogously for the synthesis of (*R*)-2-methylbutanal (*ent*-**9**) starting from hydrazone *ent*-**20** (67%).

(2*R*,4*S*,5*R*,6*S*)-(−)-1-Benzyloxy-5-hydroxy-2,4,6-trimethyloctan-3-one (22a): Commercially available $Sn(OTf)_2$ was washed several times with dry Et_2O under argon. After drying under high vacuum for 12 h the acid free $Sn(OTf)_2$ (728 mg, 1.74 mmol) was suspended in dry CH_2Cl_2 (10 mL) and Et_3N (0.28 mL, 2.04 mmol) was added at once. The mixture was then cooled to −78 °C and a solution of ketone **8** (300 mg, 1.46 mmol) in CH_2Cl_2 (7 mL) was added slowly. After 2 h a solution of the aldehyde **9** (138 mg, 1.60 mmol) in CH_2Cl_2 (10 mL) was slowly added and the mixture was stirred for an additional 4 h before it was quenched with a 4 M HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the desired aldol product **22a** after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (370 mg, 87%). $[\alpha]_D^{20}=-39.7$ ($c=0.3$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.86$ (t, $J=7.3$ Hz, 3H), 0.95 (d, $J=6.4$ Hz, 3H), 1.03 (d, $J=6.7$ Hz, 3H), 1.08 (d, $J=7.0$ Hz, 3H), 1.37 (m, 1H), 1.46 (m, 1H), 2.6–2.8 (m, 2H), 2.88 (dq, $J=7.0$, 3.0 Hz, 1H), 3.14 (m, 1H), 3.45 (dd, $J=8.8$, 4.9 Hz, 1H), 3.63 (t, $J=8.8$ Hz, 1H), 3.73 (dd, $J=7.9$, 3.0 Hz, 1H), 4.43 (d, $J=12.2$ Hz, 1H), 4.47 (d, $J=12.2$ Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (125 MHz): $\delta=8.92$, 10.97, 13.70, 14.95, 25.42, 36.53, 44.64, 48.58, 73.24, 73.50, 73.85, 127.76, 127.86, 128.44, 137.63, 218.01; IR ($CHCl_3$): $\tilde{\nu}=3494$, 2959, 2927, 2856, 1707, 1456, 1216, 759, 669 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 274 (1) [M^+-H_2O], 235 (5), 186 (4), 172 (7), 107 (11), 100 (25), 91 (100), 87 (8), 85 (7), 57 (13); elemental analysis calcd (%) for $C_{18}H_{28}O_3$: C 73.93, H 9.65; found: C 73.88, H 9.56.

(2*R*,4*S*,5*R*,6*R*)-(−)-1-Benzyloxy-5-hydroxy-2,4,6-trimethyloctan-3-one (22b): A 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.53 mL, 1.53 mmol) was added to a cold (−78 °C) solution of ketone **8** (287 mg, 1.39 mmol) in dry CH_2Cl_2 (10 mL). After stirring for 5 min, DIPEA (0.29 mL, 1.67 mmol) was added and the mixture was stirred for 2 h at this temperature. A solution of aldehyde *ent*-**9** (144 mg, 1.69 mmol) in CH_2Cl_2 (10 mL) was slowly added and the mixture was allowed to stir for additional 2 h before it was quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the desired aldol product **22b** after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (391 mg, 96%). $[\alpha]_D^{20}=-15.4$ ($c=0.9$, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta=0.68$ (d, $J=6.9$ Hz, 3H), 0.80 (d, $J=6.9$ Hz, 3H), 0.91 (t, $J=7.6$ Hz, 3H), 1.08 (d, $J=7.1$ Hz, 3H), 1.26 (m, 1H), 1.52 (m, 1H), 1.96 (m, 1H), 2.69 (dq, $J=7.1$, 2.4 Hz, 1H), 2.84 (m, 1H), 3.10 (dd, $J=8.5$, 4.7 Hz, 1H), 3.12 (br s, 1H), 3.48 (dd, $J=9.3$, 8.5 Hz, 1H), 3.79 (m, 1H), 4.10 (d, $J=11.8$ Hz, 1H), 4.14 (d, $J=11.8$ Hz, 1H), 7.06–7.20 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=$ 8.16, 11.11, 13.69, 14.99, 25.62, 36.85, 44.30, 48.73, 73.33, 73.46, 73.62, 127.59, 127.72, 128.39, 137.96, 216.87; IR (film): $\tilde{\nu}=3501$, 3088, 3064, 2966, 2934, 2876, 1706, 1496, 1455, 1377, 1329, 1308, 1243, 1206, 1147, 1098, 1029, 987, 738, 699, 609, 519, 456 cm^{-1}; MS (CI, 100 eV, isobutane): *m*/*z* (%): 293 (67) [M^++H], 275 (12), 207 (100); elemental analysis calcd (%) for $C_{18}H_{28}O_3$: C 73.93, H 9.65; found: C 73.85, H 9.74.

(2*R*,4*S*,5*R*,6*S*)-(−)-5-*tert*-Butyldimethylsilyloxy-1-hydroxy-2,4,6-trimethyloctan-3-one (23a): 2,6-Lutidine (0.39 mL, 3.39 mmol) was added to a solution of **22a** (330 mg, 1.13 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After stirring for 1 h at this temperature TBSOTf (0.4 mL, 1.47 mmol) was added at once. Then, the mixture was stirred for 18 h at RT and it was quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the desired *O*-protected product after flash column chromatography (Et_2O/pentane 1:9) as a colourless oil (429 mg, 98%). $[\alpha]_D^{20}=-18.5$ ($c=0.4$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.04$ (s, 3H), 0.06 (s, 3H), 0.79 (d, $J=6.7$ Hz, 3H), 0.82 (t, $J=7.3$ Hz, 3H), 0.90 (s, 9H), 1.07 (d, $J=6.1$ Hz, 3H), 1.11 (d, $J=6.1$ Hz, 3H), 1.30 (m, 2H), 1.41 (m, 1H), 2.89 (m, 1H), 3.02 (m, 1H), 3.40 (dd, $J=9.1$, 5.8 Hz, 1H), 3.65 (dd, $J=9.1$, 7.6 Hz, 1H), 3.90 (dd, $J=7.3$, 2.4 Hz, 1H), 4.44 (d, $J=11.9$ Hz, 1H), 4.49 (d, $J=11.9$ Hz, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR (125 MHz): $\delta=-3.99$, −3.69, 12.20, 13.59, 14.09, 14.49, 18.48, 26.09, 26.99, 40.19, 46.17, 49.78, 72.26, 73.26, 75.33, 127.53, 127.58, 128.28, 138.13, 215.90; IR (film): $\tilde{\nu}=3031$, 2960, 2932, 2857, 1712, 1460, 1362, 1254, 1108, 1059, 1004, 836, 798, 775, 736, 698, 673 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 349 (9) [$M^+-C_4H_9$], 263 (36), 201 (9), 171 (16), 145 (9), 91 (100), 75 (16), 73 (15); elemental analysis calcd (%) for $C_{24}H_{42}O_3Si$: C 70.88, H 10.41; found: C 70.73, H 10.24.

The obtained O-protected aldol (418 mg, 1.08 mmol) was dissolved in EtOH and Pd/C was added. The mixture was stirred under H_2 atmosphere (balloon) for 6 h after which it was filtered and the solvent was removed under reduced pressure, affording ketone **23a** after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (323 mg, 95%). $[\alpha]_D^{20}=-3.6$ ($c=0.2$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.07$ (s, 6H), 0.85 (d, $J=7.0$ Hz, 3H), 0.87 (t, $J=7.3$ Hz, 3H), 0.91 (s, 9H), 1.09 (d, $J=7.0$ Hz, 3H), 1.15 (d, $J=7.6$ Hz, 3H), 1.19 (m, 1H), 1.31 (m, 1H), 1.43 (m, 1H), 2.40 (br s, 1H), 2.87 (m, 1H), 2.95 (m, 1H), 3.65 (dd, $J=11.3$, 4.3 Hz, 1H), 3.73 (dd, $J=$ 11.3, 7.0 Hz, 1H), 3.82 (dd, $J=7.6$, 2.4 Hz, 1H); ^{13}C NMR (125 MHz): $\delta=$ −3.98, −3.72, 12.26, 13.43, 13.84, 14.68, 18.45, 26.12, 27.02, 40.00, 48.39, 48.89, 64.22, 76.47, 218.32; IR (film): $\tilde{\nu}=3502$, 2965, 2934, 2875, 1706, 1496, 1455, 1376, 1147, 1099, 1028, 987, 737, 698 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 259 (6) [$M^+-C_4H_9$], 201 (10), 173 (100), 155 (11), 115 (5), 87 (5), 81 (5), 75 (26), 73 (11), 59 (10); elemental analysis calcd (%) for $C_{17}H_{36}O_3Si$: C 64.50, H 11.46; found: C 64.49, H 11.36.

(2*R*,4*S*,5*R*,6*R*)-(+)-5-*tert*-Butyldimethylsilyloxy-1-hydroxy-2,4,6-trimethyloctan-3-one (23b): The same procedure as previously described using aldol **22b** (555 mg, 1.90 mmol), 2,6-lutidine (0.66 mL, 5.70 mmol) and TBSOTf (653 mg, 2.47 mmol) afforded the corresponding O-protected derivative as a colourless oil (761 mg, 99%). $[\alpha]_D^{20}=+4.6$ ($c=1.3$, $CHCl_3$); ^{1}H NMR (300 MHz): $\delta=0.02$ (s, 3H), 0.06 (s, 3H), 0.82 (t, $J=7.2$ Hz, 3H), 0.87 (d, $J=6.7$ Hz, 3H), 0.89 (s, 9H), 1.00 (m, 1H), 1.07 (d, $J=7.1$ Hz, 3H), 1.10 (d, $J=7.1$ Hz, 3H), 1.40 (m, 2H), 2.86 (m, 1H), 3.03 (m, 1H), 3.38 (dd, $J=9.1$, 6.0 Hz, 1H), 3.64 (dd, $J=9.1$, 7.7 Hz, 1H), 3.94 (dd, $J=5.4$, 3.4 Hz, 1H), 4.43 (d, $J=12.1$ Hz, 1H), 4.48 (d, $J=12.1$ Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (75 MHz): $\delta=-4.25$, −3.98, 12.13, 13.68, 14.21, 15.83, 18.38, 24.56, 26.10, 40.85, 45.73, 48.73, 72.28, 73.26, 75.27, 127.55, 127.59, 128.30, 138.19, 215.43; IR (film): $\tilde{\nu}=2958$, 2931, 2879, 2857, 1713, 1496, 1471, 1462, 1407, 1382, 1361, 1254, 1103, 1057, 1028, 1004, 837, 776, 735, 698 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 349 (11) [$M^+-C_4H_9$], 263 (49), 241 (94), 201 (26), 171 (28), 155 (87), 145 (11), 91 (100), 75 (64), 73 (34), 69 (35); elemental analysis calcd (%) for $C_{24}H_{42}O_3Si$: C 70.88, H 10.41; found: C 70.53, H 10.25.

Hydrogenolysis of the obtained O-protected aldol (600 mg, 1.55 mmol) under the conditions previously described yielded hydroxyketone **23b** as a colourless oil (479 mg, 98%). $[\alpha]_D^{20}=+9.7$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta=0.09$ (s, 6H), 0.83 (t, $J=7.3$ Hz, 3H), 0.88 (d, $J=6.4$ Hz, 3H), 0.91 (s, 9H), 1.11 (d, $J=6.3$ Hz, 3H), 1.15 (d, $J=7.6$ Hz, 3H), 1.21 (m, 1H), 1.44 (m, 2H), 2.25 (br s, 1H), 2.86 (m, 1H), 2.94 (m, 1H), 3.66 (dd, $J=$ 11.0, 4.1 Hz, 1H), 3.73 (dd, $J=11.3$, 6.9 Hz, 1H), 3.82 (dd, $J=7.1$, 2.5 Hz, 1H); ^{13}C NMR (100 MHz): $\delta=-3.97$, −3.72, 12.19, 13.41, 13.82, 14.66, 18.41, 26.00, 26.08, 40.64, 47.95, 48.83, 64.19, 76.48, 218.05; IR (film): $\tilde{\nu}=$ 3502, 2963, 2928, 2875, 1704, 1495, 1147, 1111, 1028, 988, 737, 698 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 259 (12) [$M^+-C_4H_9$], 201 (9), 173 (100), 155 (35), 115 (28), 87 (10), 81 (15), 75 (33), 73 (9), 59 (7); elemental analysis calcd (%) for $C_{17}H_{36}O_3Si$: C 64.50, H 11.46; found: C 64.59, H 11.56.

(2*R*,3*S*,4*R*,5*R*,6*S*)-(−)-5-*tert*-Butyldimethylsilyloxy-2,4,6-trimethyloctan-1,3-diol (5a): DIBAL-H (0.38 mL, 0.38 mmol) was slowly added to a cooled (−78 °C) solution of hydroxyketone **23a** (60 mg, 0.19 mmol) in dry CH_2Cl_2 (15 mL). After stirring for 1 h at this temperature the mixture was quenched with 4 M HCl (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the diol **5a** after flash column chromatography (Et_2O/pentane 1:1) as a colourless oil (53 mg, 87%). $[\alpha]_D^{20}=-9.3$ ($c=0.3$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.10$ (s, 3H), 0.14 (s,

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3H), 0.83 (d, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.92 (s, 9H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.21 (m, 1H), 1.42 (m, 1H), 1.59 (m, 1H), 1.72 (m, 1H), 2.06 (m, 1H), 3.57 (dd, $J = 11.0$, 4.3 Hz, 1H), 3.71 (dd, $J = 9.1$, 3.0 Hz, 1H), 3.83 (t, $J = 2.7$ Hz, 1H), 3.93 (dd, $J = 11.0$, 3.0 Hz, 1H), OH's could not be detected; ^{13}C NMR (125 MHz): $\delta = -4.56$, −4.22, 12.26, 13.86, 15.28, 15.58, 18.09, 25.89, 28.46, 35.76, 36.60, 40.23, 64.62, 79.68, 80.22; IR (film): $\tilde{\nu} = 3365$, 2958, 1464, 1385, 1362, 1338, 1254, 1216, 1079, 1026, 972, 940, 836, 775, 669 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 261 (5) [$M^+ - C_4H_9$], 259 (9), 201 (100), 173 (32), 161 (91), 145 (11), 129 (40), 115 (18), 105 (11), 83 (15), 75 (54), 73 (42), 59 (12), 57 (16); elemental analysis calcd (%) for $C_{17}H_{38}O_3Si$: C 64.09, H 12.02; found: C 64.13, H 12.01.

(2*R*,3*S*,4*R*,5*R*,6*R*)-(−)-5-*tert*-Butyldimethylsilyloxy-2,4,6-trimethyloctan-1,3-diol (5b): The same procedure as previously described using hydroxyketone **23b** (456 mg, 1.44 mmol) and 1M solution of DIBAL-H in CH_2Cl_2 (2.88 mL, 2.88 mmol) afforded diol **5b** as a colourless oil (395 mg, 86%). $[\alpha]_D^{20} = -7.5$ ($c = 0.8$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.88–0.92 (m, 6H), 0.91 (s, 9H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H), 1.07 (m, 1H), 1.47 (m, 1H), 1.54 (m, 1H), 1.81 (m, 1H), 1.86 (m, 1H), 2.30 (br s, 2H), 3.56 (dd, $J = 5.5$, 1.9 Hz, 1H), 3.66–3.72 (m, 3H); ^{13}C NMR (100 MHz): $\delta = -4.07$, −3.60, 9.60, 10.53, 12.16, 15.26, 18.39, 26.04, 26.88, 36.98, 37.52, 40.69, 67.43, 77.32, 77.42; IR (film): $\tilde{\nu} = 3387$, 2958, 1463, 1385, 1361, 1077, 1025, 1005, 974, 939, 836, 773, 674 cm^{-1}; MS (CI, 100 eV, isobutane): *m*/*z* (%): 319 (100) [M^++H], 261 (8), 187 (30), 169 (17); elemental analysis calcd (%) for $C_{17}H_{38}O_3Si$: C 64.09, H 12.02; found: C 63.83, H 12.27.

(2*E*,4*R*,5*S*,6*R*,7*R*,8*S*)-(+)-Ethyl 7-*tert*-butyldimethylsilyloxy-5-hydroxy-2,4,6,8-tetramethyldec-2-enoate (24a): Oxalyl chloride (150 mg, 1.18 mmol) was added to a cooled (−78 °C) solution of DMSO (184 mg, 2.35 mmol) in dry CH_2Cl_2 (15 mL). After stirring for 10 min at this temperature, a solution of diol **5a** (340 mg, 1.07 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was stirred for further 10 min before DIPEA (0.93 mL, 5.35 mmol) was added at once. After stirring for 10 min at −78 °C the mixture was allowed to warm to RT and filtered through a pad of silica gel (5 cm), eluting with Et_2O/pentane 1:1. The obtained yellowish oil was dissolved in dry CH_2Cl_2 (10 mL) and $Ph_3P{=}C(CH_3)CO_2Et$ (543 mg, 1.50 mmol) was added. The mixture was refluxed for 4 h after which it was quenched with water (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford α,β-unsaturated ester **24a** after flash column chromatography (Et_2O/pentane 1:2) as a colourless oil (337 mg, 79%). $[\alpha]_D^{20} = +21.8$ ($c = 1.1$, $CHCl_3$); lit.[30a] $[\alpha]_D^{20} = +22.2$ ($c = 1.2$ $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.07$ (s, 3H), 0.12 (s, 3H), 0.75 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.93 (s, 9H), 1.02 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.25 (t, $J = 6.9$ Hz, 3H), 1.13–1.39 (m, 2H), 1.61 (m, 1H), 1.77 (m, 1H), 1.86 (d, $J = 1.7$ Hz, 3H), 2.60 (m, 1H), 3.44 (d, $J = 7.1$ Hz, 1H), 3.51 (t, $J = 3.5$ Hz, 1H), 4.11–4.22 (m, 2H), 4.2–4.35 (br s, 1H), 6.98 (dq, $J = 10.5$, 1.2 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -4.82$, −4.12, 12.13, 12.52, 14.01, 14.31, 15.36, 16.80, 18.09, 25.89, 29.20, 35.50, 36.40, 41.71, 60.35, 71.83, 80.86, 127.55, 142.56, 168.24; IR (film): $\tilde{\nu} = 3500$, 2957, 2933, 2871, 1685, 1464, 1374, 1302, 1247, 1146, 1099, 1060, 1004, 857, 837, 776, 755 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 343 (27) [$M^+ - C_4H_9$], 259 (14), 257 (12), 201 (100), 173 (21), 161 (27), 142 (17), 127 (11), 115 (13), 113 (14), 109 (16), 105 (6), 75 (29), 73 (31), 69 (13), 57 (11); elemental analysis calcd (%) for $C_{22}H_{44}O_4Si$: C 66.95, H 11.07; found: C 66.11, H 11.11.

(2*E*,4*R*,5*S*,6*R*,7*R*,8*R*)-(+)-Ethyl 7-*tert*-butyldimethylsilyloxy-5-hydroxy-2,4,6,8-tetramethyldec-2-enoate (24b): The same procedure as previously described using diol **5b** (138 mg, 0.43 mmol), oxalyl chloride (75 mg, 0.59 mmol), DMSO (93 mg, 1.20 mmol), DIPEA (0.43 mL, 2.50 mmol) and $Ph_3P{=}C(CH_3)CO_2Et$ (272 mg, 0.75 mmol) afforded ester **24b** as a colourless oil (60 mg, 67% conversion, 52%). $[\alpha]_D^{20} = +5.9$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR (300 MHz): $\delta = 0.09$ (s, 3H), 0.11 (s, 3H), 0.84–0.92 (m, 9H), 0.92 (s, 9H), 1.09 (d, $J = 6.6$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.34 (m, 1H), 1.55–1.74 (m, 3H), 1.87 (d, $J = 1.4$ Hz, 3H), 2.48 (br s, 1H), 2.63 (m, 1H), 3.46 (m, 1H), 3.74 (dd, $J = 4.1$, 3.6 Hz, 1H), 4.19 (m, 2H), 6.50 (dq, $J = 10.4$, 1.4 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = -4.49$, −3.42, 8.02, 12.39, 12.60, 14.27, 15.34, 16.51, 18.29, 25.89, 26.07, 37.15, 37.41, 40.72, 60.49, 79.74, 80.12, 127.33, 143.85, 168.13; IR (film): $\tilde{\nu} = 3525$, 2959, 2858, 1713, 1463, 1387, 1369, 1256, 1139, 1096, 1052, 1004, 836, 774, 753 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 343 (33) [$M^+ - C_4H_9$], 259 (8), 257 (21), 201 (100), 173 (60), 161 (39), 142 (30), 127 (8), 115 (28), 113 (24), 109 (18), 105 (11), 75 (69), 73 (59), 69 (18), 57 (8); HRMS: calcd for $[C_{22}H_{44}O_4Si - C_4H_9]^+$: 343.2305; found 343.2304.

(2*E*,4*R*,5*S*,6*R*,7*R*,8*S*)-(−)-1-Bromo-7-*tert*-butyldimethylsilyloxy-5-hydroxy-2,4,6,8-tetramethyldec-2-ene (2a): A 1M solution of DIBAL-H in CH_2Cl_2 (2.34 mL, 2.34 mmol) was slowly added to a cold (−78 °C) solution of the α,β-unsaturated ester **24a** (312 mg, 0.78 mmol) in CH_2Cl_2 (10 mL). After stirring for 30 min, the reaction was quenched with 1M HCl solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording the corresponding allylic alcohol after flash column chromatography (Et_2O/pentane 1:1) as a colourless oil (238 mg, 85%). The obtained alcohol (57 mg, 0.16 mmol) was dissolved in dry acetonitrile (5 mL) and PPh_3 (96 mg, 0.37 mmol), 2,6-lutidine (18 mg, 0.16 mmol) and CBr_4 (121 mg, 0.37 mmol) were sequentially added at RT. After stirring for 30 min the mixture was quenched with water (10 mL) and extracted with pentane (5 × 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, affording allylic bromide **2a** after flash column chromatography (Et_2O/pentane 1:9) as a colourless oil (60 mg, 89%). $[\alpha]_D^{20} = -49.5$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.09$ (s, 3H), 0.11 (s, 3H), 0.72 (d, $J = 6.8$ Hz, 3H), 0.83 (t, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.94 (s, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.10 (m, 1H), 1.35 (m, 1H), 1.58 (m, 1H), 1.75 (m, 1H), 1.78 (d, $J = 1.6$ Hz, 3H), 2.12–2.25 (br s, 1H), 2.47 (m, 1H), 3.34 (dd, $J = 9.3$, 1.9 Hz, 1H), 3.72 (dd, $J = 4.7$, 2.7 Hz, 1H), 3.92 (d, $J = 9.6$ Hz, 1H), 3.96 (d, $J = 9.6$ Hz, 1H), 5.33 (d, $J = 10.2$ Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -4.54$, −3.39, 11.13, 12.43, 15.05, 15.03, 16.87, 18.24, 26.01, 26.11, 36.33, 36.71, 40.84, 41.36, 80.39, 131.69, 133.90; IR (film): $\tilde{\nu} = 3350$, 2965, 2920, 2870, 1460, 1355, 1214, 1190, 1162, 1095, 1073, 955, 840, 610, 524 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 365 (7) [$M^+ - C_4H_9$], 363 (8), 259 (15), 201 (100), 173 (38), 161 (58), 145 (8), 119 (12), 115 (15), 83 (9), 75 (36), 73 (32), 57 (8); elemental analysis calcd (%) for $C_{20}H_{41}BrO_2Si$: C 56.99, H 9.80; found: C 56.90, H 9.95.

(2*E*,4*R*,5*S*,6*R*,7*R*,8*R*)-(−)-1-Bromo-7-*tert*-butyldimethylsilyloxy-5-hydroxy-2,4,6,8-tetramethyldec-2-ene (2b): The same procedure as previously described using α,β-unsaturated ester **24b** (262 mg, 0.65 mmol) and 1M DIBAL-H (1.96 mL, 1.96 mmol) solution, yielded the corresponding allylic alcohol (231 mg, 99%). Bromination of this alcohol (200 mg, 0.56 mmol) with PPh_3 (335 mg, 1.28 mmol), 2,6-lutidine (60 mg, 0.56 mmol) and CBr_4 (425 mg, 1.28 mmol) afforded allylic bromide **2b** as a colourless oil (194 mg, 82%). $[\alpha]_D^{20} = -30.2$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (300 MHz): $\delta = 0.09$ (s, 3H), 0.11 (s, 3H), 0.86–0.94 (m, 9H), 0.92 (s, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.11 (m, 1H), 1.26–1.76 (m, 3H), 1.78 (d, $J = 1.4$ Hz, 3H), 2.38 (br s, 1H), 2.48 (m, 1H), 3.33 (dd, $J = 8.9$, 1.5 Hz, 1H), 3.72 (dd, $J = 4.9$, 3.0 Hz, 1H), 3.94 (m, 2H), 5.30 (dd, $J = 10.0$, 1.4 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = -4.57$, −3.38, 7.86, 12.45, 15.07, 15.09, 16.90, 18.25, 26.04, 26.14, 36.35, 36.74, 40.88, 41.42, 80.53, 131.89, 134.10; IR (film): $\tilde{\nu} = 3529$, 2958, 2930, 2876, 2857, 1462, 1387, 1255, 1094, 1051, 1005, 986, 836, 774 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 365 (4) [$M^+ - C_4H_9$], 363 (7), 259 (12), 201 (100), 173 (38), 161 (59), 145 (9), 131 (7), 119 (14), 115 (15), 109 (10), 83 (11), 75 (28), 73 (23), 69 (8); elemental analysis calcd (%) for $C_{20}H_{41}BrO_2Si$: C 56.99, H 9.80; found: C 57.01, H 9.93.

(2′*R*,6′*R*,1*E*,3*Z*,5*R*)-(+)-7-*tert*-Butyldiphenylsilyloxy-1-(5′,6′-dihydro-2′*H*-2′-isopropoxypyran-6′-yl)-3-ethyl-5-methylhepta-1,3-diene (25): Allylic bromide **4b** (84 mg, 0.18 mmol) was dissolved in dry acetonitrile (5 mL) and tributylphosphine (52 mg, 0.26 mmol) was added at once. After stirring for 30 min at RT the solvent was evaporated under reduced pressure and the resulting viscous oil was dried under high vacuum. The residue was dissolved in dry toluene, a solution of the aldehyde **3** (33 mg, 0.19 mmol) in toluene (5 mL) was added and the mixture was cooled to 0 °C, at which temperature a solution of KO*t*Bu (31 mg, 0.26 mmol) in THF (1 mL) was added slowly. After stirring for 1 h at this temperature, the reaction was quenched with water (5 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford triene **25** after flash column chromatography (Et_2O/pentane 1:9) as a colourless oil (82 mg, 86%). $[\alpha]_D^{20} = +53.6$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.94$ (d, $J = 6.8$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H), 1.03 (s, 9H), 1.16 (d, $J = 6.0$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.48 (m, 1H), 1.61 (m, 1H), 2.03–2.11 (m, 2H), 2.12–2.22 (m, 2H), 2.84 (m, 1H), 3.61 (t, $J = 6.6$ Hz, 2H), 3.98 (sept, $J = 6.0$ Hz, 1H), 4.46 (m, 1H), 5.09

(m, 2H), 5.72 (m, 2H), 5.95 (m, 1H), 6.59 (d, $J = 15.9$ Hz, 1H), 7.32 – 7.44 (m, 6H), 7.61 – 7.69 (m, 4H); ^{13}C NMR (100 MHz): $\delta = 13.44$, 19.24, 21.38, 22.06, 23.87, 26.30, 26.83, 28.05, 30.71, 40.37, 61.90, 65.85, 69.46, 93.18, 125.99, 127.40, 127.75, 128.13, 128.47, 129.33, 133.80, 134.80, 135.44, 136.07; IR ($CHCl_3$): $\tilde{\nu} = 3070$, 3046, 2964, 2930, 2894, 1469, 1428, 1381, 1316, 1182, 1108, 1029, 1001, 965, 947, 823, 800, 757, 704, 614, 506 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 532 (1) [M^+], 475 (27), 417 (11), 415 (16), 363 (53), 285 (16), 253 (10), 225 (17), 217 (12), 199 (100), 183 (33), 173 (11), 147 (25), 135 (34), 121 (21), 109 (17), 105 (16), 91 (14), 70 (34), 55 (10); elemental analysis calcd (%) for $C_{34}H_{48}O_3Si$: C 76.64, H 9.08; found: C 76.56, H 9.10.

(2′*R*,6′*R*,4*Z*,6*E*,3*R*)-7-(5′,6′-Dihydro-2′*H*-2′-isopropoxypyran-6′-yl)-5-ethyl-3-methylhepta-4,6-dien-1-al (1): Triene **25** (197 mg, 0.37 mmol) was dissolved in THF (5 mL) and TBAF (1M solution in THF, 0.74 mL, 0.74 mmol) was added at once. After stirring for 3 h at RT, the mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the corresponding alcohol after flash column chromatography (Et_2O/pentane 1:9) as a colourless oil (106 mg, 95%). $[\alpha]_D^{20} = +4.7$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 1.00$ (d, $J = 6.7$ Hz, 3H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.31 (m, 1H), 1.48 – 1.55 (m, 1H), 1.60 – 1.71 (m, 1H), 2.00 – 2.14 (m, 2H), 2.19 (q, $J = 7.4$ Hz, 2H), 2.86 (m, 1H), 3.58 – 3.63 (m, 2H), 4.07 (sept, $J = 6.0$ Hz, 1H), 4.52 (m, 1H), 5.09 (d, $J = 1.2$ Hz, 1H), 5.15 (d, $J = 8.5$ Hz, 1H), 5.70 – 5.81 (m, 1H), 5.88 (dd, $J = 15.9$, 6.0 Hz, 1H), 5.98 – 6.09 (m, 1H), 6.62 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (100 MHz): $\delta = 13.40$, 21.55, 22.14, 23.82, 26.32, 28.40, 30.80, 40.37, 61.14, 66.93, 69.66, 93.19, 126.98, 127.15, 128.31, 128.75, 134.87, 136.41; IR ($CHCl_3$): $\tilde{\nu} = 3420$, 2966, 2927, 1459, 1400, 1378, 1316, 1181, 1127, 1100, 1052, 1030, 1000, 964, 870, 718 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 294 (3) [M^+], 234 (18), 205 (19), 179 (11), 161 (12), 139 (11), 121 (11), 112 (34), 109 (24), 105 (11), 97 (13), 93 (15), 91 (17), 81 (17), 70 (100), 55 (24), 45 (31); elemental analysis calcd (%) for $C_{18}H_{30}O_3$: C 73.43, H 10.27; found: C 73.52, H 10.40.

The obtained alcohol (31 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and added to a cooled (−78 °C) solution of Swern reagent (prepared from oxalyl chloride (15 mg, 0.12 mmol) and DMSO (19 mg, 0.24 mmol) in CH_2Cl_2). After stirring for 10 min at this temperature, DIPEA (72 mg, 0.55 mmol) was added at once and the mixture was stirred for further 15 min at −78 °C. The reaction was allowed to warm to RT and filtered through a pad of silica gel (5 cm), eluting with Et_2O/pentane 1:1, to yield crude aldehyde **1** which was used in the following step without further purification 31 mg, 96%).

(2′*R*,6′*R*,8*E*,10*E*,14*Z*,16*E*,3*S*,4*R*,5*R*,6*S*,7*R*,13*R*)-(+)-4-*tert*-Butyldimethylsilyloxy-17-(5′,6′-dihydro-2′*H*-2′-isopropoxypyran-6′-yl)-15-ethyl-6-hydroxy-3,5,7,9,13-pentamethylheptadeca-8,10,14,16-tetraene (26a): *n*BuLi (0.047 mmol) was added to a cold (−78 °C) solution of DMSO (4.0 mg, 0.051 mmol) in dry toluene (5 mL). The mixture was stirred for 5 min at this temperature and for 15 min at RT, after which it was cooled again to −78 °C. In a separate flask, allylic bromide **2a** (18 mg, 0.043 mmol) was dissolved in dry acetonitrile (5 mL) and tributylphosphine (12 mg, 0.060 mmol) was added at once. After stirring for 30 min at RT the solvent was evaporated under reduced pressure and the resulting viscous oil was dried under high vacuum. The obtained residue was dissolved in dry toluene and added to the $LiCH_2S(O)CH_3$ solution at −78 °C. A solution of the aldehyde **1** (13 mg, 0.045 mmol) in toluene (5 mL) was also added and, after stirring for 2 h at −78 °C, the reaction was quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford pentaene **26a** after flash column chromatography (Et_2O/pentane 1:5) as a colourless oil (20 mg, 76%). $[\alpha]_D^{20} = +64.7$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.10$ (s, 3H), 0.16 (s, 3H), 0.71 (d, $J = 7.1$ Hz, 3H), 0.89 (d, $J = 7.4$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H), 1.02 (s, 9H), 1.07 (d, $J = 6.1$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 1.32 (m, 1H), 1.42 (m, 1H), 1.60 (m, 1H), 1.75 (d, $J = 1.1$ Hz, 3H), 1.79 (m, 1H), 1.91 (m, 1H), 2.08 (m, 3H), 2.19 (m, 2H), 2.67 (m, 1H), 2.78 (m, 1H), 3.43 (d, $J = 9.1$ Hz, 1H), 3.75 (t, $J = 4.1$ Hz, 1H), 3.98 (sept, $J = 6.0$ Hz, 1H), 4.69 (m, 1H), 5.19 (m, 3H), 5.57 (m, 1H), 5.75 (m, 2H), 5.87 (dd, $J = 15.9$, 5.8 Hz, 1H), 6.15 (d, $J = 15.7$ Hz, 1H), 6.81 (d, $J = 15.9$ Hz, 1H), OH could not be detected; ^{13}C NMR (100 MHz): $\delta = -4.21$, −3.42, 8.87, 12.64, 13.11, 13.90, 15.87, 17.82, 18.06, 21.04, 22.48, 24.27, 25.97, 26.30, 26.92, 31.44, 32.57, 37.31, 37.60, 41.08, 41.43, 67.39, 69.76, 79.85, 80.25, 93.83, 126.28, 126.69, 127.21, 127.57, 129.76, 133.15, 133.62, 135.05, 136.45; IR ($CHCl_3$): $\tilde{\nu} = 3396$, 2929, 2874, 2858, 1463, 1381, 1254, 1121, 1049, 1027, 1005, 979, 868, 836, 774 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 556 (1) [$M^+ - C_3H_9O$], 499 (3), 298 (15), 257 (39), 229 (8), 207 (12), 201 (100), 190 (41), 173 (23), 161 (23), 145 (11), 141 (26), 127 (9), 109 (40), 99 (15), 93 (14), 75 (21), 73 (30), 57 (8); elemental analysis calcd (%) for $C_{38}H_{68}O_4Si$: C 73.97, H 11.11; found: C 74.06, H 11.07.

(2′*R*,6′*R*,8*E*,10*E*,14*Z*,16*E*,3*R*,4*R*,5*R*,6*S*,7*R*,13*R*)-(+)-4-*tert*-Butyldimethylsilyloxy-17-(5′,6′-dihydro-2′*H*-2′-isopropoxypyran-6′-yl)-15-ethyl-6-hydroxy-3,5,7,9,13-pentamethylheptadeca-8,10,14,16-tetraene (26b): The same procedure as previously described using allylic bromide **2b** (12 mg, 0.028 mmol), aldehyde **1** (8.2 mg, 0.028 mmol), *n*BuLi (0.031 mmol), DMSO (2.7 mg, 0.034 mmol) and tributylphosphine (8 mg, 0.040 mmol) afforded pentaene **26b** as a colourless oil (12 mg, 73%). $[\alpha]_D^{20} = +64.7$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 0.07$ (s, 3H), 0.10 (s, 3H), 0.81 – 0.90 (m, 9H), 0.94 (s, 9H), 0.99 (d, $J = 6.6$ Hz, 3H), 1.02 – 1.11 (m, 6H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.30 (m, 1H), 1.45 (m, 1H), 1.58 (m, 1H), 1.70 (d, $J = 1.2$ Hz, 3H), 1.73 (m, 1H), 2.03 – 2.11 (m, 4H), 2.21 – 2.35 (m, 2H), 2.65 (m, 1H), 2.74 (m, 1H), 3.36 (d, $J = 9.0$ Hz, 1H), 3.70 (m, 1H), 4.03 (sept, $J = 6.0$ Hz, 1H), 4.64 (m, 1H), 5.06 (d, $J = 10.1$ Hz, 1H), 5.11 – 5.20 (m, 2H), 5.48 (m, 1H), 5.73 (m, 2H), 5.98 – 6.09 (m, 2H), 6.59 (d, $J = 15.8$ Hz, 1H), OH could not be detected; ^{13}C NMR (100 MHz): $\delta = -4.48$, −3.41, 7.98, 12.38, 12.82, 13.49, 15.27, 17.57, 18.27, 20.56, 22.14, 23.85, 25.88, 26.03, 26.32, 30.84, 31.97, 36.50, 36.59, 40.71, 40.88, 67.06, 69.57, 80.26, 80.50, 93.19, 125.64, 125.97, 127.19, 128.31, 129.81, 132.09, 133.28, 135.31, 135.98; IR ($CHCl_3$): $\tilde{\nu} = 3510$, 2961, 2929, 1720, 1689, 1462, 1381, 1254, 1216, 1106, 1004, 976, 939, 877, 836, 757, 668 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 543 (1) [$M^+ - C_4H_{10}O$], 299 (15), 257 (21), 229 (33), 201 (100), 190 (15), 173 (61), 161 (22), 145 (10), 115 (20), 109 (18), 75 (58), 73 (42), 57 (61); elemental analysis calcd (%) for $C_{38}H_{68}O_4Si$: C 73.97, H 11.11; found: C 74.08, H 11.19.

(−)-Callystatin A: A solution of the pentaene **26a** (8.0 mg, 0.013 mmol) in benzene (1 mL) was treated with PCC (14 mg, 0.065 mmol), 4 Å molecular sieves (3 g, 3 beads, crushed) and AcOH (7.8 mg, 0.13 mmol). After stirring at RT for 2.5 h, water (2 mL) was added and the reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the corresponding O-TBS protected derivative of callystatin A (6.0 mg, 81%) after flash column chromatography (Et_2O/pentane 1:1). Afterwards, this derivative (3.7 mg, 0.0065 mmol) was placed in a plastic vial, dissolved in THF (0.2 mL) and HF·pyridine (0.2 mL) was added at once. After stirring for 72 h the reaction was quenched with 1M Na_2CO_3 (3 mL) and extracted with Et_2O (5 × 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford synthetic (−)-callystatin A (2.6 mg, 89%) after column chromatography (Et_2O/pentane 1:1). $[\alpha]_D^{20} = -102.6$ ($c = 0.02$, MeOH); lit[1] $[\alpha]_D^{20} = -107$ ($c = 0.1$, MeOH); lit[14] $[\alpha]_D^{20} = -105$ ($c = 0.1$, MeOH); ^{1}H NMR (500 MHz): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.05 (t, $J = 7.5$ Hz, 3H), 1.09 (d, $J = 7.1$ Hz, 3H), 1.15 (d, $J = 7.0$ Hz, 3H), 1.28 – 1.46 (m, 4H), 1.82 (d, $J = 1.2$ Hz, 3H), 2.12 (m, 2H), 2.18 (m, 2H), 2.48 (m, 2H), 2.68 (m, 1H), 2.84 (m, 1H), 3.51 (dd, $J = 7.0$, 4.4 Hz, 1H), 3.68 (m, 1H), 5.00 (m, 1H), 5.15 (d, $J = 9.6$ Hz, 1H), 5.25 (d, $J = 9.6$ Hz, 1H), 5.59 (m, 1H), 5.74 (dd, $J = 15.9$, 7.1 Hz, 1H), 6.01 (d, $J = 15.5$ Hz, 1H), 6.07 (dq, $J = 9.8$, 1.8 Hz, 1H), 6.65 (d, $J = 16.1$ Hz, 1H), 6.90 (m, 1H); ^{13}C NMR (125 MHz): $\delta = 10.92$, 11.23, 13.02, 13.33, 14.28, 16.01, 20.74, 25.76, 26.23, 30.15, 32.11, 36.65, 40.78, 45.61, 45.50, 74.43, 78.90, 121.66, 124.53, 127.58, 128.30, 129.91, 135.22, 135.40, 136.27, 137.04, 144.75, 164.15, 216.33; IR ($CHCl_3$): $\tilde{\nu} = 3516$, 3407, 2965, 2930, 1715, 1459, 1381, 1250, 1112, 970, 818, 756, 667 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 456 (0.7) [M^+], 206 (100), 159 (10), 121 (24), 108 (31), 97 (33), 93 (28), 86 (12), 69 (13), 57 (39); HRMS: calcd for $[C_{29}H_{44}O_4]^+$: 456.3239; found: 456.3238.

(−)-20-*epi*-Callystatin A: The same procedure as previously described using pentaene **26b** (10 mg, 0.016 mmol), PCC (17 mg, 0.081 mmol), 4 Å molecular sieves (3 g, 3 beads, crushed), AcOH (9.6 mg, 0.16 mmol) and HF·pyridine (0.2 mL) afforded 20-*epi*-callystatin A (1.9 mg, 69% yield over two steps) after column chromatography (Et_2O/pentane 1:1). $[\alpha]_D^{20} = -97.4$ ($c = 0.01$, MeOH); ^{1}H NMR (400 MHz): $\delta = 0.87$ (t, $J = 7.4$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 1.10 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 7.1$ Hz, 3H), 1.21 – 1.43 (m, 4H), 1.79 (d,

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$J = 1.4$ Hz, 3H), 2.09 (m, 2H), 2.15 (m, 2H), 2.43 (m, 2H), 2.61 (m, 1H), 2.80 (m, 1H), 3.63 (m, 1H), 3.91 (m, 1H), 5.00 (m, 1H), 5.12 (d, $J = 9.4$ Hz, 1H), 5.22 (d, $J = 9.7$ Hz, 1H), 5.53 (m, 1H), 5.79 (dd, $J = 15.7$, 7.2 Hz, 1H), 6.01 (d, $J = 15.7$ Hz, 1H), 6.06 (dq, $J = 9.7$, 1.8 Hz, 1H), 6.61 (d, $J = 16.3$ Hz, 1H), 6.87 (m, 1H); ^{13}C NMR (100 MHz): $\delta = 11.04$, 12.24, 12.97, 13.41, 14.85, 16.04, 20.64, 23.99, 26.34, 30.04, 32.06, 36.65, 40.78, 45.31, 47.98, 75.83, 78.68, 121.51, 124.44, 126.92, 128.44, 129.56, 135.53, 135.91, 136.88, 137.43, 144.40, 164.23, 216.10; IR ($CHCl_3$): $\tilde{\nu} = 3356$, 2964, 2929, 2877, 1716, 1460, 1381, 1256, 1118, 817, 757, 619 cm^{-1}; MS (EI, 70 eV): m/z (%): 456 (1) [M^+], 206 (100), 188 (12), 159 (20), 121 (22), 108 (30), 97 (39), 93 (25), 86 (15), 69 (16), 57 (38); HRMS: calcd for $[C_{29}H_{44}O_4]^+$: 456.3239; found: 456.3236.

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[1] M. Kobayashi, K. Higuchi, N. Murakami, H. Tajima, S. Aoki, *Tetrahedron Lett.* **1997**, *38*, 2859–2862.
[2] N. Murakami, W. Wang, M. Aoki, Y. Tsutsui, K. Higuchi, S. Aoki, M. Kobayashi, *Tetrahedron Lett.* **1997**, *38*, 5533–5536.
[3] N. Murakami, W. Wang, M. Aoki, Y. Tsutsui, M. Sugimoto, M. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 2349–2352.
[4] a) N. Murakami, M. Sugimoto, T. Nakajima, M. Kawanishi, Y. Tsutsui, M. Kobayashi, *Bioorg. Med. Chem.* **2000**, *8*, 2651–2661; b) N. Murakami, M. Sugimoto, M. Kobayashi, *Bioorg. Med. Chem.* **2001**, *9*, 57–67.
[5] a) Y. Hayakawa, K. Adachi, N. Komeshima, *J. Antibiot.* **1987**, *40*, 1349–1352; b) Y. Hayakawa, K. Sohda, K. Shin-ya, T. Hidaka, H. Seto, *J. Antibiot.* **1995**, *48*, 954–961.
[6] a) T. Hamamoto, S. Gunji, H. Tsuji, T. Beppu, *J. Antibiot.* **1983**, *36*, 639–645; b) T.R. Hurley, R. H. Bunge, N. E. Willer, G. C. Hokanson, J. C. French, *J. Antibiot.* **1986**, *39*, 1651–1656; c) J. P. Schaumberg, G. C. Hokanson, J. C. French, *J. Chem. Soc. Chem. Commun.* **1984**, 1450–1452; d) M. Kobayashi, W. Wang, Y. Tsutsui, M. Sugimoto, N. Murakami, *Tetrahedron Lett.* **1998**, *39*, 8291–8294.
[7] a) I. Umezawa, K. Komiyama, H. Oka, K. Okada, S. Tomisaka, T. Miyano, S. Takano, *J. Antibiot.* **1984**, *37*, 706–711; b) K. Komiyama, K. Okada, H. Oka, S. Tomisaka, T. Miyano, S. Funayama, I. Umezawa, *J. Antibiot.* **1985**, *38*, 220–223.
[8] a) J. B. Tunac, B. D. Graham, W. E. Dobson, *J. Antibiot.* **1983**, *36*, 1595–1600; b) S.S. Stampwala, R. H. Bunge, T.R. Hurley, N. E. Willmer, A. J. Brankiewicz, C. E. Steinman, T. A. Smitka, J. C. French, *J. Antibiot.* **1983**, *36*, 1601–1605; c) D. L. Boger, S. Ichikawa, W. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 4161–4167.
[9] Y. Hayakawa, K. Sohda, H. Seto, *J. Antibiot.* **1996**, *49*, 980–984.
[10] a) K. Gerth, D. Schummer, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1995**, *48*, 973–976; b) D. Schummer, K. Gerth, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1995**, 685–688; c) M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, M. Kalesse, *Angew. Chem.* **2000**, *112*, 4535–4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364–4366; d) U. Bhatt, M. Christmann, M. Quitschalle, E. Claus, M. Kalesse, *J. Org. Chem.* **2001**, *66*, 1885–1893; e) D.R. Williams, D. C. Ihle, S. V. Plummer, *Org. Lett.* **2001**, *3*, 1383–1386.
[11] a) S. Kobayashi, K. Tsuchiya, T. Harada, M. Nishide, T. Kurokawa, T. Nagakawa, N. Shimada, K. Kobayashi, *J. Antibiot.* **1994**, *47*, 697–702; b) S. Kobayashi, K. Tsuchiya, M. Nishide, N. Fakaaki, N. Taizo, S. Nobuyoshi, *J. Antibiot.* **1995**, *48*, 893–895; c) M. K. Gurjar, J. T. Henri, D.S. Bose, A. V.R. Rao, *Tetrahedron Lett.* **1996**, *37*, 6615–6618; d) M. K. Gurjar, A. Chakrabarti, A. V.R. Rao, *Heterocycles* **1997**, *45*, 7–10; e) H. Watanabe, H. Watanabe, T. Kitahara, *Tetrahedron Lett.* **1998**, *39*, 8313–8316; f) N. Chida, M. Yoshinaga, T. Tobe, S. Ogawa, *Chem. Commun.* **1997**, 1043–1044; g) G. E. Keck, C. E. Knutson, S. A. Wiles, *Org. Lett.* **2001**, *3*, 707–710.
[12] a) S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912–4915; b) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622; c) S. L. Schreiber, J. Chen, D. T. Hung, *Chem. Biol.* **1996**, *3*, 287–293.
[13] a) H. Umezawa, A. Takaaki, K. Uotani, M. Hamada, T. Takeuchi, S. Takahashi, *J. Antibiot.* **1980**, *33*, 1594–1596; b) K. Uotani, H. Naganawa, S. Kondo, T. Aoyagi, H. Umezawa, *J. Antibiot.* **1982**, *35*, 1495–1499; c) I. Paterson, A. N. Hulme, *J. Org. Chem.* **1995**, *60*, 3288–3300.
[14] M. T. Crimmins, B. W. King, *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085.
[15] A. B. Smith III, B. M. Brandt, *Org. Lett.* **2001**, *3*, 1685–1688.
[16] M. Kalesse, M. Quitschalle, C. P. Khandavalli, A. Saeed, *Org. Lett.* **2001**, *3*, 3107–3109.
[17] J. A. Marshall, M. P. Bourbeau, *J. Org. Chem.* **2002**, *67*, 2751–2754.
[18] a) Part of this work has been published in a preliminary form: J. L. Vicario, A. Job, M. Wolberg, M. Müller, D. Enders, *Org. Lett.* **2002**, *4*, 1023–1026; b) A. Job, Dissertation, RWTH Aachen (Germany), **2001**.
[19] a) D. Enders, in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, Orlando, **1984**, p. 275–339; b) D. Enders, M. Klatt, in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 1* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 178–182; c) review: A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.
[20] R. Tamura, K. Saegusa, M. Kakihana, D. Oda, *J. Org. Chem.* **1988**, *53*, 2723–2728.
[21] a) M. Wolberg, W. Hummel, C. Wandrey, M. Müller, *Angew. Chem.* **2000**, *112*, 4476–4478; *Angew. Chem. Int. Ed.* **2000**, *39*, 4306–4308; b) M. Wolberg, W. Hummel, M. Müller, *Chem. Eur. J.* **2001**, *7*, 4562–4571; c) A. Job, M. Wolberg, M. Müller, D. Enders, *Synlett* **2001**, 1796–1798.
[22] Lactone **10** can also be obtained in >98% *ee* by diastereoselective reduction of hydroxy keto ester **6** followed by crystallisation and subsequent lactonisation/elimination (see ref. [21b]).
[23] J. K. Thottathil, Y. Pendri, W.-S. Li, D.R. Kronenthal, US 5278313A, **1994** [*Chem. Abstr.* **1994**, *120*, 217699r].
[24] F. W. Lichtenthaler, K. Lorenz, W.-Y. Ma, *Tetrahedron Lett.* **1987**, *28*, 47–50.
[25] The configuration of the newly created stereogenic centre was determined by NOE experiments.
[26] D. Enders, L. Wortmann, R. Peters, *Acc. Chem. Res.* **2000**, *33*, 157–169.
[27] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
[28] K. Ando, *J. Org. Chem.* **1997**, *62*, 1934–1939.
[29] R. Appel, *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–810.
[30] Other published syntheses of the C_{13}–C_{22} fragment of callystatin A: a) J. A. Marshall, R. N. Fitzgerald, *J. Org. Chem.* **1999**, *64*, 4477–4481; b) L. C. Dias, P.R.R. Meira, *Tetrahedron Lett.* **2002**, *43*, 185–187.
[31] A. Job, R. Nagelsdiek, D. Enders, *Collect. Czech. Chem. Commun.* **2000**, *65*, 524–538.
[32] For the use of ketone **8** in the synthesis of polypropionate chains see: I. Paterson, *Pure Appl. Chem.* **1992**, *64*, 1821–1830 and references therein.
[33] a) I. Paterson, R. D. Tillyer, *Tetrahedron Lett.* **1992**, *33*, 4233–4236; b) I. Paterson, R. D. Norcross, R. A. Ward, P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314; for other Sn^{II}-mediated aldol reactions see: c) T. Mukaiyama, N. Iwasawa, R. W. Stevens, T. Haga, *Tetrahedron* **1984**, *40*, 1381–1390; d) Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, E. Fujita, *J. Org. Chem.* **1986**, *51*, 2391–2396; e) D. A. Evans, M. DiMare, *J. Am. Chem. Soc.* **1986**, *108*, 2476–2478; f) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761; g) D. A. Evans, J.R. Gage, *J. Org. Chem.* **1992**, *57*, 1961–1963.
[34] $Sn(OTf)_2$ purchased from Aldrich, catalog no. 38812-2.
[35] The configuration of the newly created chiral centre was determined by NOE experiments on the corresponding dimethylacetals of diols **5a**–**b**.
[36] P. J. Kocienski, G. Cernigliaro, G. Feldstein, *J. Org. Chem.* **1977**, *42*, 353–355.

  0947-6539/02/0818-4283 $ 20.00+.50/0

[37] D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173 – 182.
[38] D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *112*, 2933 – 2960.
[39] D. Enders, H. Eichenauer, U. Baus, H. Schubert, K. A. M. Kremer, *Tetrahedron* **1984**, *40*, 1345 – 1359.
[40] D. S. Connor, G. W. Klein, G. N. Taylor, *Org. Synth.* **1974**, *52*, 16 – 19.
[41] J. D. White, D. L. Bolton, A. P. Dantanarayana, C. M. J. Fox, R. N. Hiner, R. W. Jackson, K. Sakuma, U. S. Warrier, *J. Am. Chem. Soc.* **1995**, *117*, 1908 – 1939.

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  0947-6539/02/0818-4284 $ 20.00+.50/0