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Graphical Abstract

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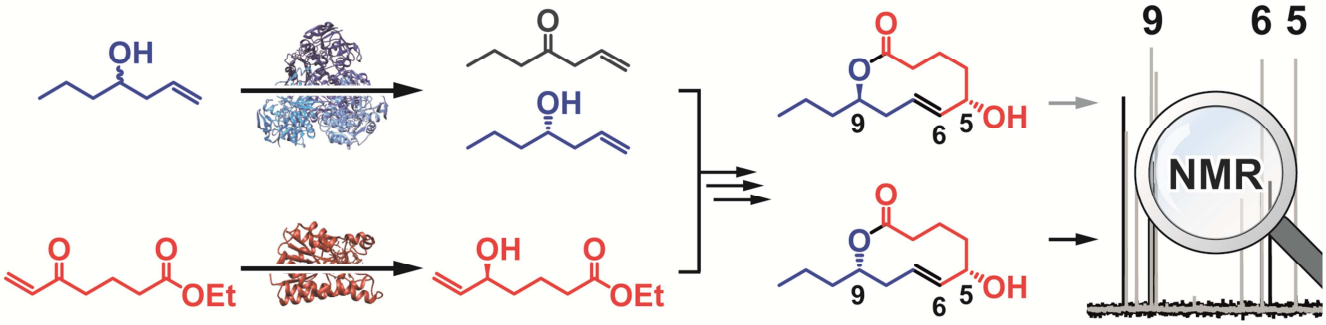

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ABSTRACT

The limitations of an alcohol dehydrogenase regarding the oxidative kinetic resolution of homoallylic alcohol containing alkyl chains were investigated, leading to a valuable building block for the total synthesis of phytotoxic nonenolide putaminoxin. The enzymatic approach towards the enantioenriched homoallylic alcohol was compared to classical, nonenzymatic approaches using asymmetric reagent controlled allyl additions and the obtained building block was used for the total synthesis of putaminoxin and its (5*S*,6*E*,9*S*)-diastereomer. After the spectroscopic analysis of the synthesized compounds, discrepancies were observed to already published data of isolated and synthesized putaminoxin. Therefore, a systematic comparison of NMR data was carried out. The result underlines the necessity of total synthesis for the absolute assignment of configuration.

1. Introduction

Putaminoxin (**1**) is a phytotoxic compound from *Phoma putaminum*, the causal agent of leaf necrosis of a common weed of field, *Erigeron annuus*.[1-2] It is a 10-membered macrolactone with a hydroxyl group in position 5, a *trans*-configured double bond at position 6 and a propyl-sidechain at position 9. After isolation from liquid culture of *Phoma putaminum* the structure of putaminoxin was investigated and the stereogenic center at position 5 was determined as being (*S*)-configured.[1] The stereogenic center at position 9 could not be assigned initially, but was found to be (*R*)-configured after total synthesis and comparison of the spectroscopic data to the isolated sample.[3] Due to its biological activity, putaminoxin (**1**) and its analogs putaminoxin B and D (**2**), hypocreolide A (**3**), and aspinolide A (**4**), were the basis of several synthetic studies (Figure 1).[3-14]

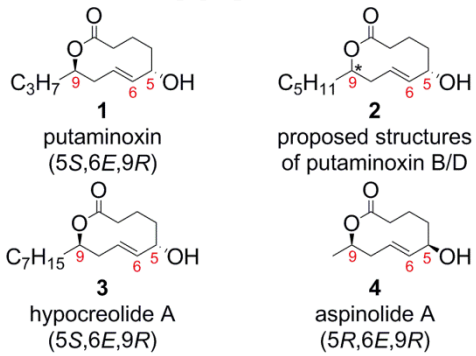
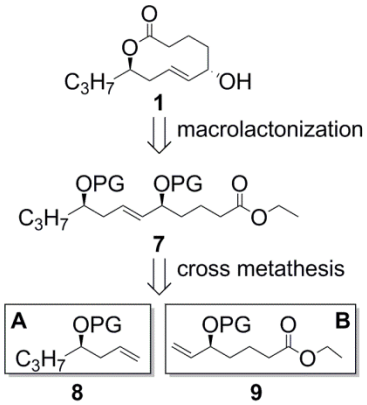


Figure 1: Structure of putaminoxin and related nonelides.

Recently the chemoenzymatic total synthesis of the proposed structures of putaminoxins B and D (**2**) were achieved by employing alcohol dehydrogenases for the selective generation of the two stereogenic centers.[14] Both enantiomers of the employed non-1-en-4-ol (**5**) building block were obtained in good yield and up to excellent *ee*-values in either oxidative kinetic resolution of racemic non-1-en-4-ol (*rac*-**5**), or asymmetric reduction of the corresponding ketone **6** (*vide infra*), by utilization of an alcohol dehydrogenase from *Thermoanaerobacter brockii*. (Tb-ADH). In the present study the limitations of this enzyme regarding the length of the alkyl-chain were investigated, giving potential access to more analogs of these interesting macrolactones via the identical retrosynthetic approach thus also providing an answer of questions raised concerning their configuration (Scheme 1).



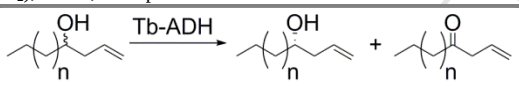
Scheme 1: Retrosynthesis of nonenolide **1** (PG: protection group).

2. Results and Discussion:

2.1. Oxidative kinetic resolution of aliphatic homoallylic alcohols

Key to the successful synthesis of the proposed structures of putaminoxin B and D was a convenient enantioselective synthesis of the required homoallylic alcohol *via* an oxidative kinetic resolution utilizing an alcohol dehydrogenase. Here, the alcohol dehydrogenase from *Thermoanaerobacter brockii*. was shown to be able to sterically distinguish between the two alkyl moieties of non-1-en-4-ol (**5**).[14-15] To analyze the scope of the Tb-ADH in the oxidative kinetic resolution of aliphatic homoallylic alcohols, homoallylic alcohols with increased and decreased chain length were employed. The oxidation of the longer chain homoallylic alcohols was slow and their limited solubility impaired the reliable measurement of conversion, because the samples were no longer homogenous under the tested reaction conditions. This effect could unfortunately not be circumvented by reducing to analytical transformations and working up the entire reaction since we had to work with stock solutions. Nevertheless, it could be observed that dec-1-en-4-ol (**10**) was oxidized and enantiomerically pure after 8 hours, whereas undec-1-en-4-ol (**11**) and dodec-1-en-4-ol (**12**) were nearly left untouched, even after prolonged reaction times (see supplementary material). These observations are in line with those reported for the asymmetric reduction of aliphatic ketones of comparable chainlength.[16] Reducing the concentration of the longer aliphatic homoallylic alcohols (**10**-**12**) from 10 mM to 7.5 mM led to a decreased reaction time and enantiopure or enantioenriched alcohols after 4 to 24 hours (Table 1). On the other hand, (*S*)-oct-1-en-4-ol [(*S*)-**13**] and (*S*)-non-1-en-4-ol [(*S*)-**5**] could be obtained with an *ee* >99% at 50% conversion after just 3 hours. Surprisingly the Tb-ADH was also able to differentiate between the alkyl moieties of the nearly symmetrical hept-1-en-4-ol (**14**). After 58% conversion an *ee* of 94% could be achieved (Table 1).

Table 1: Oxidative kinetic resolution of homoallylic alcohols with Tb-ADH. Reaction conditions: Homoallylic alcohol (10 mM), acetone (5 Vol.-%), Tb-ADH (0.5 U/mL), $NADP^+$ (300 µM), KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$), 30 °C, 130 rpm.



Substrate	Product	Conversion [%]	*ee* [%]	Time [h]
14 (n = 1)	(*S*)-**14** (n = 1)	58	94	3
13 (n = 2)	(*S*)-**13** (n = 2)	50	>99	3
5 (n = 3)	(*S*)-**5** (n = 3)	50	>99	3
10 (n = 4)	(*S*)-**10** (n = 4)		>99[a]	4[a]
11 (n = 5)	(*S*)-**11** (n = 5)		99[a]	8[a]
12 (n = 6)	(*S*)-**12** (n = 6)		90[a]	24[a]

[a] Substrate concentration was reduced to 7.5 mM.

In previous experiments, Keinan *et al*. could not observe product formation in the asymmetric reduction of symmetrical heptan-4-on, in presence of Tb-ADH, presumably because the *n*-pentyl chain does not fit into the small pocket of the substrate binding site of the alcohol dehydrogenase.[16] The oxidative kinetic resolution of racemic hept-1-en-4-ol (*rac*-**14**) revealed that the *n*-pentyl chain is indeed not readily accepted in contrast to the slightly smaller *n*-pentenyl chain. The discrimination is not as accurate as for the *n*-butyl chain of oct-1-en-4-ol (**13**) though, leading to a decreased enantiomeric excess after 50% conversion and much slower, but continuous oxidation of the remaining (*S*)-hept-1-en-4-ol [(*S*)-**14**] (Figure 2).

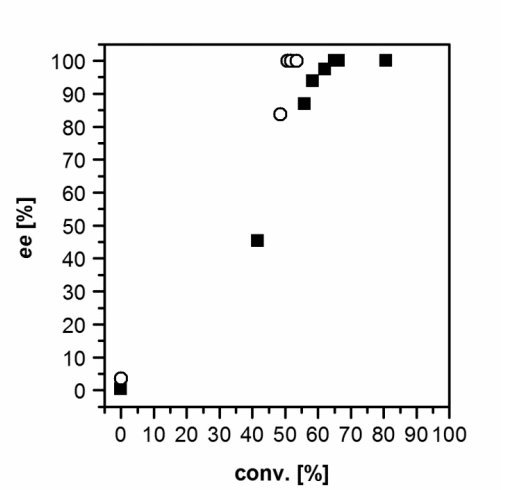
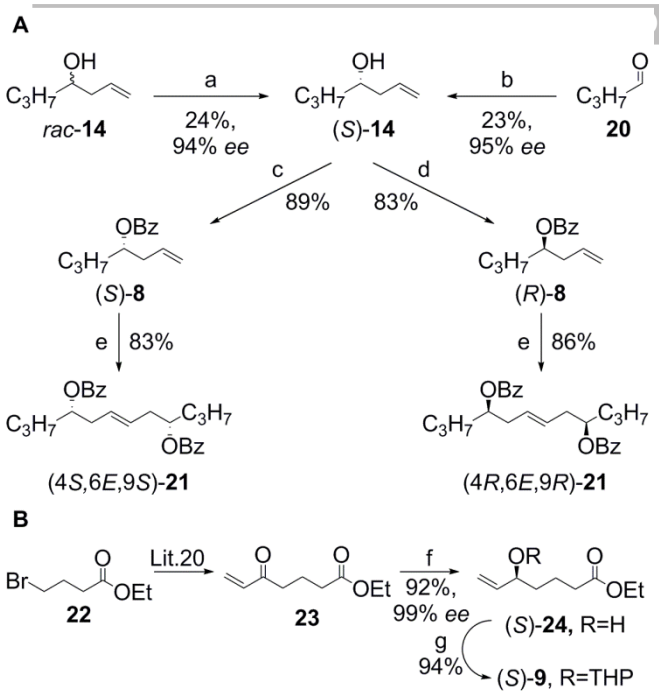


Figure 2: Oxidative kinetic resolution of hept-1-en-4-ol (**14**) ■ and oct-1-en-4-ol (**13**) ○ with the alcohol dehydrogenase from *Thermoanaerobacter brockii*. Reaction conditions: Homoallylic alcohol (10 mM), acetone (5 Vol.-%), Tb-ADH (0.5 U/mL), $NADP^+$ (300 µM), KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$), 30 °C, 130 rpm. Samples were taken after 0 h, 1 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h.

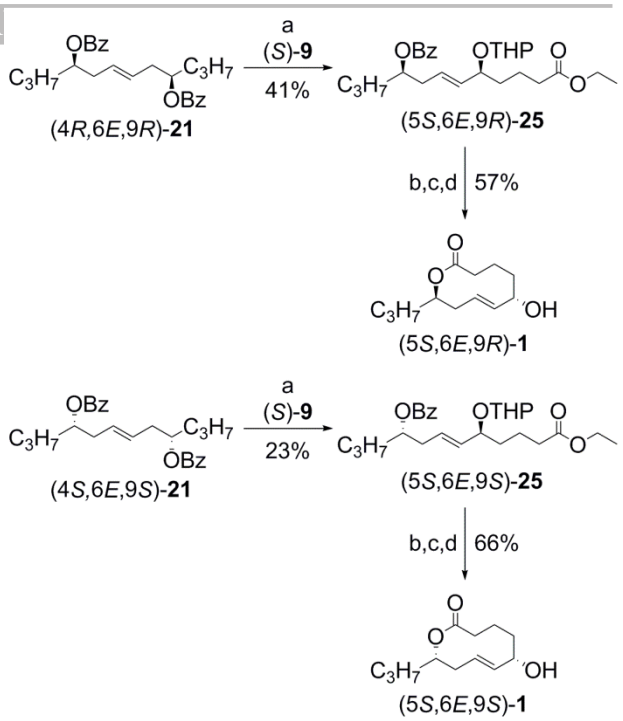
For the total synthesis of putaminoxin (**1**) the reaction was upscaled from 50 to 250 mL and (*S*)-hept-1-en-4-ol [(*S*)-**14**] could be isolated in 25% yield with an *ee* of 94%. The stereogenic center was found to be (*S*)-configured by comparison with products from the *Brown* asymmetric reagent controlled allyl addition to butanal (**20**) (Scheme 2).[17] This selectivity of the Tb-ADH is in line with previously reported results and is retained even in case of the smaller, and nearly symmetrical substrate.[15-16, 18] The low yield of this kinetic resolution can probable be attributed to the volatility of the product, something that was observed in the *Brown* asymmetric reagent controlled allyl addition as well. The selective allyl addition with commercial *Brown* reagent led to 23% yield with a maximum (*S*)-*ee* of 95% and was highly dependent on the quality of every single charge of the reagent. Selective allyl additions with commercially available *Leighton*-reagent were unsuccessful.[19]

*2.2. Total synthesis of putaminoxin (**1**) and its (5S,6E,9S)-diastereomer [(5S,6E,9S)-**1**]*

The enantiomerically enriched (*S*)-hept-1-en-4-ol [(*S*)-**14**] was further used for the synthesis of putaminoxin (**1**) and its (5*S*,6*E*,9*S*)-diastereomer [(5*S*,6*E*,9*S*)-**1**]. The synthetic route was planned based on previous publications, with a cross-metathesis of the two major building blocks **8** and **9** and a macrolactonization as the key steps.[6, 14] Therefore the homoallylic alcohol (*S*)-**14** was protected with a benzoylic protection group, because the acetate protected hept-1-en-4-ol proved to be even more volatile than the unprotected alcohol. For the synthesis of putaminoxin (**1**) the protection of the homoallylic alcohol was performed via *Mitsunobu*-esterification to invert the configuration.[20] Both protected alcohols (*S*)-**8** and (*R*)-**8**, were obtained in 89% and 83% yield respectively (Scheme 2).



Scheme 2: THP = tetrahydropyranyl. Bz = benzoyl. Reaction conditions for A: (a) Tb-ADH, acetone, $NADP^+$, KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$), 30 °C, 120 rpm, 3.5 h; (b) (+)-*B*-Allyldiisopinocampheylborane, Et_2O, -78 °C, 1 h; (c) benzoyl chloride, pyridine, CH_2Cl_2, 24 h; (d) benzoic acid, triphenyl phosphine, diisopropyl azodicarboxylate, THF, 4.5 h; (e) Grubbs 2nd generation catalyst, CH_2Cl_2, 40 °C, 24 h; (f) Lb-ADH, 2-propanol, $NADP^+$, KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$); (g) pyridinium para-toluenesulfonate, 3,4-dihydro-2H-pyran, CH_2Cl_2, rt, 14 h.



Scheme 3: THP = tetrahydropyranyl. Bz = benzoyl. Reaction conditions: (a) Grubbs 2nd generation catalyst, CH_2Cl_2, 40 °C, 3 d; (b) LiOH, THF:MeOH:H_2O (2:1:1), 60 °C, 48 h; (c) 1. 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 2 h; 2. 4-(*N*,*N*-dimethylamino)pyridine (DMAP), toluene, reflux, 3 h; (d) PPTS, *p*-TsOH·H_2O, EtOH, 40 °C, 16 h.

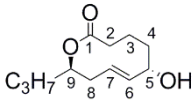
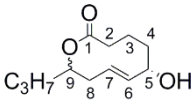
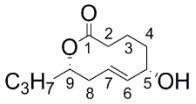
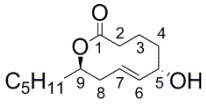
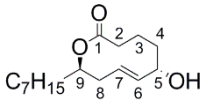
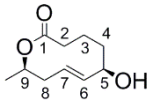
The second building block (*S*)-**24** could be provided in a three-step procedure by employing an ADH from *Lactobacillus brevis* for the asymmetric reduction of ketone **23**, which was obtained in two steps, starting from ethyl 4-bromobutanoate (**22**) in accordance to the previously described protocol.[21] Reduction of the ketone yielded the alcohol in 92% yield with an excellent *ee* of >99%. The allylic alcohol was protected with a THP-group in 94% yield before the following cross-metathesis reaction. The metathesis reaction of protected homoallylic alcohol **8** and protected allylic alcohol **9** with Grubbs second generation catalyst afforded the diastereomer **25** in 24% yield. The primary product was in both cases the homodimerized homoallylic alcohol **21**. Therefore, it was attempted to dimerize the homoallylic alcohol **8** first, before employing it in the cross-metathesis, which was beneficial in previous attempts with acetate protected non-1-en-4-ol.[6, 14] Even though the first metathesis led to good yields ranging from 83-86% yield, the second step did not exceed yields of 41%. However, unreacted allylic and homodimerized homoallylic alcohol could be reisolated and reused in a subsequent metathesis reaction giving nearly identical yields of the heterodimer **25** of 40%. The last step of the synthesis was a three-step procedure of saponification, followed by *Yamaguchi* macrolactonization, and subsequent deprotection of the THP-protection group. In accordance to a procedure of Götz *et al*., the intermediates were not isolated.[6] The synthesis of putaminoxin (**1**) and its (5*S*,6*E*,9*S*)-diastereomer [(5*S*,6*E*,9*S*)-**1**] were finalized with moderate yields of 57-66% over the last three steps (Scheme 3).

2.3. Comparison of ^{13}C NMR data of nonenolides

Since a previous publication revealed inconsistencies in the ^{13}C NMR data of a variety of putaminoxin analogs that just differ in the length of the alkyl chain at position 9,[14] a comparison of the synthesized molecules with already published data was drawn. Even though the MS and IR data are quite similar to those reported by Evidente *et al*.[1] for the isolated sample, and Sabitha *et al*.[3] for the synthesized compound, the differences in the ^{13}C NMR data are identical to those reported recently.[14] (Figure 3, A) The newly acquired ^{13}C NMR data of the synthesized (5*S*,6*E*,9*R*)-putaminoxin (**1**) do not fit to those reported by Evidente *et al*.[1] and Sabitha *et al*.[3] The data fits very well to the ^{13}C NMR data of the synthesis of the proposed structures of putaminoxin B and D (**2**)[14] and those of hypocreolide A (**3**)[6] though, which are likewise (5*S*,6*E*,9*R*) configurated (Table 2, Figure 3, A).

On the other hand the ^{13}C NMR data of the newly synthesized (5*S*,6*E*,9*S*)-diastereomer [(5*S*,6*E*,9*S*)-**1**] are in full agreement with the ^{13}C NMR data provided by Evidente *et al*.[1] and Sabitha *et al*.[3] for the (5*S*,6*E*,9*R*)-putaminoxin (**1**) (Figure 3, B). Additionally, the ^{13}C NMR data of the (5*S*,6*E*,9*S*)-diastereomer [(5*S*,6*E*,9*S*)-**1**] fit very well to the data of (5*S*,6*E*,9*S*)-**2** by Bisterfeld and Holec *et al*.[14] and the (5*R*,6*E*,5*R*) configurated. aspinolide A (**4**), isolated by Fuchser and Zeeck.[22] Significant differences in the data of the mentioned examples are just in the signals of the alkyl chains at position 9, which is to be expected because of their different length. A structural proposition that explains these correlations would therefore lead to a structure that is (5*R*,6*E*,9*R*) configurated, rather than (5*S*,6*E*,9*R*) (Figure 3).

Table 2: Comparison of ^{13}C NMR signals of the newly synthesized compounds (5*S*,6*E*,9*R*)-**1** and (5*S*,6*E*,9*S*)-**1** with previously reported data for the originally provided structures. Relevant ^{13}C NMR signals were highlighted by color (green = similar to (5*S*,6*E*,9*R*)-**1**, red = similar to (5*S*,6*E*,9*S*)-**1**).

Struc-tures	 (5*S*,6*E*,9*R*)-**1**		 (5*S*,6*E*,9?)-**1**	 (5*S*,6*E*,9*S*)-**1**	 (5*S*,6*E*,9*R*)-**2**	 (5*S*,6*E*,9*R*)-**3**	 (5*R*,6*E*,9*R*)-**4**
Ref.	This	Sabitha	Evidente *et al.* [1]	This paper	Bisterfeld and	Götz *et al.*[6]	Fuchser and
Atom	paper	*et al.*[3]			Holec *et al.* [14]		Zeeck[22]
C-1	176.8	175.6	175.8	175.9	176.7	176.6	175.5
C-2	35.9	35.7	35.6	35.8	35.7	35.9	35.6
C-3	18.0	22.3	22.2	22.5	17.8	18.0	22.3
C-4	36.8	38.7	38.7	38.9	36.6	36.8	38.7
C-5	68.6	74.1	74.0	74.3	68.4	68.6	74.1
C-6	136.8	137.1	137.2	137.3	136.6	136.8	137.1
C-7	126.4	131.7	131.5	131.8	126.3	126.5	131.8
C-8	40.9	40.4	40.3	40.5	40.8	40.9	42.1
C-9	76.6	75.3	75.3	75.5	76.8	76.9	71.6
C-10	36.5	36.4	36.3	36.6	34.2	34.4	19.8
C-11	19.3	19.1	19.1	19.3	25.6	26.1	
C-12	14.0	13.9	13.8	14.0	31.6	29.5	
C-13					22.7	29.3	
C-14					14.1	31.9	
C-15						22.8	
C-16						14.2	

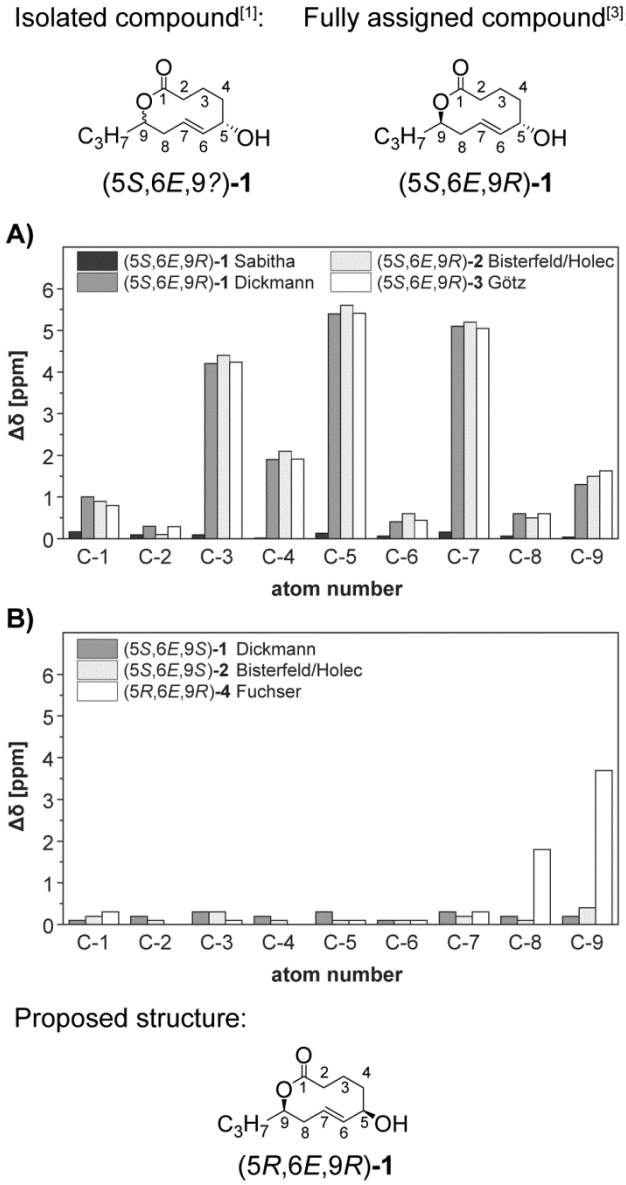


Figure 3: Comparison of the ^{13}C NMR shifts of nonenolides with the reported ^{13}C NMR shifts of the isolated compound (5*S*,6*E*,9*?*)-**1** by Evidente *et al.*[1] and a structural proposition on the basis of observed correlations. A) Comparison of ^{13}C NMR shifts of (5*S*,6*E*,9*?*)-**1** with the ^{13}C NMR shifts of synthesized (5*S*,6*E*,9*R*) configurated nonenolides.[3, 6, 14] B) Comparison of ^{13}C NMR shifts of (5*S*,6*E*,9*?*)-**1** with the ^{13}C NMR shifts of synthesized (5*S*,6*E*,9*S*) and isolated (5*R*,6*E*,9*R*) configurated nonenolides.[14, 22]

3. Conclusion:

In the present work we were able to realize the chemoenzymatic total synthesis of the phytotoxic compound putaminoxin (**1**) and its (5*S*,6*E*,9*S*)-diastereomer [(5*S*,6*E*,9*S*)-**1**] by employing alcohol dehydrogenases for the generation of both stereogenic centers. The oxidative kinetic resolution of aliphatic homoallylic alcohols revealed that the alcohol dehydrogenase from *Thermoanaerobacter brockii* is capable of distinguishing between the *n*-pentyl and *n*-pentenyl residue of the challenging substrate hept-1-en-4-ol (**14**), giving access to the valuable building block (*S*)-**14** with a cheap and easy reaction setup and under mild reaction conditions. The Tb-ADH is most suited for the conversion of oct-1-en-4-ol (**13**) and non-1-en-4-ol (**5**) though, combining short reaction times and excellent selectivities. Longer aliphatic homoallylic alcohols can still be converted with excellent selectivities, but the reaction time increases and the substrate concentration needs to be lowered, probably owing to their poor solubility in aqueous media (Table 1). The newly acquired ^{13}C NMR-data of the final products **1** and [(5*S*,6*E*,9*S*)-**1**] showed a discrepancy with already published data. A comparison with the ^{13}C NMR data of closely related analogs, which just differ in the length of the sidechain at position 9, indicate that the configuration of the stereogenic centers of putaminoxin (**1**) should be reconsidered (Table 2, Figure 3). Additionally, the rotatory powers of the isolated and synthesized nonenolides **1**-**4** demonstrate, that the stereogenic center at position 9 dictates the direction of the optical rotation, since all (9*R*)-configurated analogs of putaminoxin (**1**) showed a negative optical rotatory power, whereas (9*S*)-configurated analogs showed a positive optical rotatory power (Table 3).

Table 3: Optical rotatory powers of different nonenolides.

Author	Molecule	Optical rotatory power
Evidente *et al.*[1]	(5*S*,6*E*,9*?*)-**1**	$[\alpha]_D^{25}$ = -23.1, (c = 1.6), $CHCl_3$
Sabitha *et al.*[3]	(5*S*,6*E*,9*R*)-**1**	$[\alpha]_D^{25}$ = -25.2, (c = 1), $CHCl_3$
Dickmann *et al.*	(5*S*,6*E*,9*R*)-**1**	$[\alpha]_D^{25}$ = -13.4, (c = 0.7), $CHCl_3$
Dickmann *et al.*	(5*S*,6*E*,9*S*)-**1**	$[\alpha]_D^{25}$ = +22.3, (c = 0.7), $CHCl_3$
Bisterfeld and Holec *et al.*[14]	(5*S*,6*E*,9*R*)-**2**	$[\alpha]_D^{20}$ = -25.6, (c = 1), $CHCl_3$
Bisterfeld and Holec *et al.*[14]	(5*S*,6*E*,9*S*)-**2**	$[\alpha]_D^{20}$ = +16.1, (c = 1), $CHCl_3$
Götz *et al.*[6]	(5*S*,6*E*,9*R*)-**3**	$[\alpha]_D^{25}$ = -29.0, (c = 0.35), $CHCl_3$
Fuchser and Zeeck[22]	(5*R*,6*E*,9*R*)-**4**	$[\alpha]_D^{23}$ = -43.8, (c = 0.3), MeOH

Therefore, it is likely that the originally isolated compound by Evidente *et al.* is indeed (9*R*) configurated as well. By comparison of the ^{13}C NMR data of our synthesized compounds and those of putaminoxin B/D (**2**), hypocreolide A (**3**), and aspinolide A (**4**) one can assume though, that putaminoxin (**1**) may not be (5*S*)-, but (5*R*)-configurated instead. Taking these observations into consideration, we come to the conclusion, that the originally isolated putaminoxin from Evidente *et al.* might be (5*R*,6*E*,9*R*)-configurated, instead of (5*S*,6*E*,9*R*). The specific rotation of the newly synthesized enantiomer (5*S*,6*E*,9*S*)-**1** of +22.3 supports this argument, as it is the opposite of the reported -23.1 by Evidente *et al.* (Table 3) and the ^{13}C NMR data of these enantiomers are consistent as well (Table 2, Figure 3, B). A more concise comparison of ^{13}C NMR data of closely related nonenolides **2**-**4** revealed even more inconsistencies in the ^{13}C NMR data of these intriguing compounds (see supplementary material), emphasizing the importance of total synthesis of these biologically active lactones.

4. Experimental Section:

4.1. General:

Optical rotations were measured in $CHCl_3$ using a PerkinElmer 341 and Krüpps Optotronic polarimeter at the sodium D-line using a cell with 100 mm path length. Absorbance measurements were conducted using an UV-160 spectrophotometer. IR data were recorded on a PerkinElmer SpectrumOne and SpectrumTwo instrument as a thin film, and absorbance frequencies are reported in cm^{-1}. ^1H- and ^{13}C NMR spectra were recorded on an Avance/DRX 600 NMR spectrometer (Bruker) at ambient temperature in $CDCl_3$ at 600 and 151 MHz, respectively. The chemical shifts are given in ppm relative to the solvent signal [^1H: δ ($CHCl_3$) = 7.26 ppm] and [^{13}C: δ ($CDCl_3$) = 77.16 ppm, for the centerline of the $CDCl_3$ triplet]. NMR signals were assigned by means of COSY and HSQC experiments. GC/MS measurements were carried out using a Hewlett-Packard HP 6890 Series GC System/Hewlett-Packard 5973 mass selective detector or Thermo Scientific ISQ QD/Thermo Scientific Trace 1310 GC System. HRMS (ESI, positive ion) was performed by the analytical service of the Forschungszentrum Jülich (ZEA-3). GC analysis was performed on a Trace GC Ultra gas chromatograph (Thermo Finnigan, Thermo Scientific) or a GC-17A gas chromatograph (Shimadzu) with a flame ionization detector (FID). The Trace GC Ultra gas chromatograph was equipped with a FS-Lipodex G (25 m × 0.25 mm, Macherey Nagel)., FS-Hydrodex-βTBDAc (25 m × 0.25 mm, Macherey Nagel) or FS-Hydrodex-β3p column (25 m × 0.25 mm, Macherey Nagel). The injector and detector were operated at 250 °C, and H_2 was used as the carrier gas at a flow rate of 30 $mL \cdot min^{-1}$. The GC-17A gas chromatograph was equipped with a CP-Chirasil-Dex CB column (25 m × 0.25 mm, Varian), and He was used as the carrier gas at a flow rate of 1.3 $mL \cdot min^{-1}$. Substances were dissolved in MTBE and analyzed according to the given temperature protocols. Chiral stationary-phase HPLC measurements were performed on a Dionex system equipped with a pump with a gradient mixer and devolatilizer, including a WPS-3000TSL autosampler and a DAD-3000 UV-detector. A Lux Amylose-1 column (250 mm × 4.6 mm, Phenomenex) and a mixture of *n*-heptane/2-propanol (99.8:0.2) as solvent were used, applying a flow rate of 0.5 $mL \cdot min^{-1}$ at room temperature. Flash column chromatography was performed on silica gel 60, particle size 40−63 µm (230−240 mesh).

4.2. Chemicals:

All reagents were used as purchased from commercial suppliers without further purification. The nicotinamide cofactor $NADP^+$ was a generous gift from Codexis. Petroleum ether, diethyl ether, *n*-pentane, and EtOAc for column chromatography were distilled before usage. The synthesis of ethyl 5-oxo-6-heptenoate (**23**) and ethyl (*S*)-5-hydroxyhept-6-enoate [(*S*)-**24**] were carried out according to a published procedure by Fischer and Pietruszka.[21]

4.3. Enzyme Production:

For heterologous protein expression, the *Escherichia coli* strain BL21 (DE3) was used. Expression, purification, and quantification of production and activity measurements of Lb-ADH and Tb-ADH, were performed as described earlier.[23]

4.4. Oxidative kinetic resolution of homoallylic alcohols:

Preparative Scale:

A 250 mL Erlenmeyer flask was charged with homoallylic alcohol (0.5 mmol), acetone (5 Vol.-%), Tb-ADH (25 U), and $NADP^+$ (300 µM) in KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$) to a final volume of 50 mL. The reaction was shaken at 30 °C and 130 rpm and after 0 h, 1 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h a 200 µL sample was taken. The sample was extracted by addition of 500 µL MTBE, containing 2.5 mM of 1-Hexanol as internal standard, and measured via gas chromatography over chiral stationary phase (individual programs are as stated in the supplementary material).

Analytical Scale:

A 5 mL glass vial was charged with homoallylic alcohol (0.02 mmol), acetone (5 Vol.-%), Tb-ADH (1 U), and $NADP^+$ (300 µM) in KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$) to a final volume of 2 mL. The reaction mixture was briefly vortexed and distributed into 200 µL aliquots. The aliquots were shaken at 30 °C and 130 rpm and after 0 h, 1 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h a 200 µL sample was extracted by addition of 500 µL MTBE, containing 2.5 mM of 1-hexanol as internal standard, and measured via gas chromatography over chiral stationary phase (individual programs are as stated in the supplementary material).

Ethyl (5*S*)-5-(tetrahydropyran-2´´-yloxy)-hept-6-enoate [(*S*)-9]: To a solution of allylic alcohol (*S*)-**24** (400 mg, 2.00 mmol.) in dry CH_2Cl_2 (38 mL) were added pyridinium *p*-toluenesulfonate (60.0 mg, 240 µmol, PPTS) and 3,4-dihydro-2H-pyran (550 µL, 6 mmol). The mixture was stirred at rt for 14 h and then quenched by the addition of saturated aqueous $NaHCO_3$-solution (60 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over $MgSO_4$, filtered over a pad of Celite, and concentrated under reduced pressure. Chromatography of the crude product on silica gel (petroleum ether/EtOAc, 90:10) afforded the product (*S*)-**7** (533 mg, 1.88 mmol, 94%) as a colorless oil. The analytical data were in accordance with the literature.[21] Compound (*S*)-**7** was due to the THP-protecting group obtained as a diastereomeric mixture indicated as A and B; *dr* (A:B) = 1:1.2. R_f 0.28 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{20}$ = -13.8 (c 1.0, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 2942, 2867, 1735, 1445, 1379, 1240, 1175, 1129, 1076, 1021, 967, 923, 869, 813 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ[ppm]= 1.25 (t, $^3J_{2´,1´}$ = 7.1 Hz, 6H, 2-$H^{AB´}$), 1.45-1.90 (m, 20H, 3-H^{AB}, 4-H^{AB}, 3-$H^{AB´´}$, 4-$H^{AB´´}$, 5-$H^{AB´´}$), 2.29-2.35 (m, 4H, 2-H^{AB}), 3.43-3.54 (m, 2H, 6-$H_b^{AB´´}$), 3.85-3.91 (m, 2H, 6-$H_a^{AB´´}$), 4.05-4.13 (m, 6H, 5-H^{AB}, 1-$H^{AB´}$), 4.65 (t, $^3J_{2B´´,3B´´}$ = 3.6 Hz, 1H, 2-$H^{B´´}$), 4.69 (t, $^3J_{2A´´,3A´´}$ = 3.8 Hz, 1H, 2-$H^{A´´}$), 5.11 (dt, $^3J_{7aA,6A}$ = 10.5 Hz, $^2J_{7aA,7bA}$ = 1.4 Hz), 1H, 7-H_a^A), 5.19 (m, 2H, 7-H^B), 5.23 (dt, $^3J_{7bA,6A}$ = 17.3 Hz, $^2J_{7bA,7aA}$ = 1.4 Hz, 1H, 7-H_b^A), 5.62 (ddd, $^3J_{6B,7bB}$ = 17.6 Hz, $^3J_{6B,7aB}$ = 10.0 Hz, $^3J_{6B,5B}$ = 7.7 Hz, 1H, 6-H^B), 5.86 (ddd, $^3J_{6A,7bA}$ = 17.3 Hz, $^3J_{6A,7aA}$ = 10.5 Hz, $^3J_{6A,5A}$ = 6.8 Hz, 1H, 6-H^A); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.40 (C-2´), 19.71/19.82/20.67/21.19/25.60/25.72/30.88/31.03/34.40/35.09 (C-3, C-4, C-3´´, C-4´´, C-5´´), 34.04/34.35 (C-2), 60.36/60.40 (C-1´), 62.44/62.74 (C-6´´), 76.17/77.77 (C-5), 95.17/97.92 (C-2´´), 115.20/117.5 (C-7), 138.36/139.50 (C-6), 173.72 (C-1); EIMS *m/z* 55, 70, 85, 98, 155.

(*S*)-Hept-1-en-4-ol (*Brown* allylation) [(*S*)-14]: A solution of 5 mL (+)-*B*-Allyldiisopinocampheylborane (5 mmol, 1 M in *n*-pentane) in 5 mL dry Et_2O was stirred and cooled to -78 °C and a solution of butanal (**20**) (403 µL, 4.5 mmol) in 500 µL dry Et_2O was slowly added. The mixture was stirred for 1 h after which the reaction was warmed to rt. 1.6 mL of a 3 M NaOH solution and 650 µL of H_2O_2 (30% (*w*/*w*)) were added and the reaction was refluxed for 1 h. The organic phase was separated, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography of the crude product over silica gel (*n*-pentane/Et_2O, 87:13) afforded product (*S*)-**14** as colorless oil (118 mg, 1,03 mmol, 23%, *ee* 95%). The analytical

data were in accordance with those reported in the literature.[24] R_f 0.21 (*n*-pentane/Et_2O, 87:13); $[\alpha]_D^{20}$ = -12.3 (c 1.0, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 3355, 2964, 2929, 2874, 1643, 995, 912 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.93 (t, $^3J_{7,6}$ = 7.2 Hz, 3H, 7-H), 1.32 – 1.58 (m, 5H, 4-OH, 5-H, 6-H), 2.14 (m, 1H, 3-H_a), 2.30 (m, 1H, 3-H_b), 3.66 (m, 1H, 4-H), 5.09-5.16 (m, 2H, 1-H), 5.79-5.87 (m, 1H, 2-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.23 (C-7), 19.01 (C-6), 39.14 (C-5), 42.11 (C-3), 70.55 (C-4), 118.21 (C-1), 135.06 (C-2). EIMS *m/z* 55, 71, 73.

(*S*)-Hept-1-en-4-ol (oxidative kinetic resolution) [(*S*)-14]: A 1 L Erlenmeyer flask was charged with substrate **14** (500 µL, 3,68 mmol), acetone (5 Vol.-%), Tb-ADH (119 U) and $NADP^+$ (300 µM) in KP_i-buffer (50 mM, pH 7.0, 1 mM $MgCl_2$) to a final volume of 250 mL. The reaction was stirred at 30 °C and 130 rpm for 3.5 h after it was stopped and extracted by addition of CH_2Cl_2. Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography of the crude product on silica gel (*n*-pentane/Et_2O, 87:13) afforded product (*S*)-**14** as colorless oil (102.7 mg, 0,90 mmol, 24%, *ee* 94%) The analytical data were in accordance to those stated for compound (*S*)-**14** (see above).

(*S*)-Hept-1-en-4-yl benzoate [(*S*)-8]: To a stirring solution of (*S*)-**14** (150 mg, 1.31 mmol) in 5 mL dry CH_2Cl_2, benzoyl chloride (198 µL, 1.71 mmol) and pyridine (179 µL, 2.23 mmol) were slowly added, and the reaction was kept stirring at rt for 24 h. The reaction was stopped by addition of saturated Na_2HCO_3-solution and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with saturated copper(II) sulfate-solution and brine, afterwards dried over $MgSO_4$ and filtrated. The crude solution was concentrated under reduced pressure before chromatography over silica gel (*n*-pentane/Et_2O, 98:2) yielded the product (*S*)-**8** (254 mg, 1.16 mmol, 89 %) as a colorless oil. R_f 0.23 (*n*-pentane/Et_2O, 98:2); $[\alpha]_D^{20}$ = +15.7° (c 1.0, $CHCl_3$, 95% *ee*); FT-IR $\tilde{\nu}_{max}$ 2959, 2929, 2866, 1713, 1269, 1111, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.93 (t, $^3J_{1,2}$ = 7.4 Hz, 3H, 7-H), 1.34-1.49 (m, 2H, 6-H), 1.59-1.75 (m, 2H, 5-H), 2.45 (dd, $^3J_{3,2}$ = 7.2 Hz, $^3J_{3,4}$ = 5.9 Hz, 2H, 3-H), 5.06 (dt, $^2J_{1a,1b}$ = 1.6 Hz, $^3J_{1a,2}$ = 10.1Hz, 2H, 1-H_a), 5.11 (dt $^2J_{1b,1a}$ = 1.6 Hz, $^3J_{1b,2}$ = 17.2Hz, 2H, 1-H_b), 5.78-5.87 (ddt, $^3J_{2,1b}$ = 17.2Hz, $^3J_{2,1a}$ = 10.1Hz, $^3J_{2,3}$ = 7.2Hz, 1H, 2-H), 7.40-7.45 (m, 2H, 4-H_a´,4-H_b´), 7.52-7.56 (m, 1H, 5-H´), 8.00-8.04 (m, 2H, 3-H_a´, 3-H_b´); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.11 (C-7), 18.77 (C-6), 36.01 (C-5), 38,89 (C-5), 73.98 (C-4), 117.87 (C-1), 128.45 (C-4´), 129.69 (C-3´) 130.94 (C-2´), 132.87 (C-5´), 133.89 (C-2), 166.38 (C-1´); EIMS *m/z* 77, 105.

(*R*)-Hept-1-en-4-yl benzoate [(*R*)-8]: 116 mg (0.95 mmol) benzoic acid were dissolved in 5 mL dry THF and 251 mg (0.96 mmol) triphenyl phosphine and 100 mg (0.88 mmol) of (*S*)-hept-1-en-4-ol (*S*)-**14** were added before the reaction was cooled to 0 °C. 188 µL (0.95 mmol) of DIAD were slowly added to the stirring solution which was then left to warm to rt. After 4.5 h the reaction was stopped by addition of saturated $NaHCO_3$-solution and the organic phase was washed with brine and water. The crude product was concentrated under reduced pressure and then purified via chromatography over silica gel (*n*-pentane/Et_2O, 98:2) to yield the final product (*R*)-**8** as colorless oil (159 mg, 83%, 87 % *ee*). The configurational change of the stereogenic center was confirmed via HPLC over a chiral stationary phase (see supplementary material). R_f 0.23 (*n*-pentane/Et_2O, 98:2); $[\alpha]_D^{20}$ = -17.4 (c 1.0, $CHCl_3$, 94% *ee*); The analytical data are in accordance to those reported for compound (*S*)-**6** (see above).

(4*S*,6*E*,9*S*)-Dodec-6-ene-4,9-diyl dibenzoate [(4*S*,6*E*,9*S*)-21]: 151 mg (0.69 mmol) of the benzoyl-protected (*S*)-Hept-1-en-4-ol (*S*)-**8** and 30 mg (0.03 mmol) Grubbs 2nd generation catalyst were dissolved in 5 mL dry CH_2Cl_2 and the reaction was heated to 40 °C and stirred for 24 h. The reaction mixture was filtrated through a pad of celite and concentrated under reduced pressure. Chromatography over silica gel (*n*-pentane/Et_2O, 94:6) afforded the product (4*S*,6*E*,9*S*)-**21** (116 mg, 0.28 mmol, 83%) as a colorless oil. R_f 0.23 (*n*-pentane/Et_2O, 94:6); $[\alpha]_D^{20}$ = -19.5 (c 0.7, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 2958, 2873, 1714, 1451, 1270, 1111, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.82-0.93 (m, 6H , 1-H, 12-H), 1.23-1.45 (m, 4H, 2-H, 11-H), 1.51-1.70 (m, 4H, 3-H, 10-H), 2.33-2.53 (m, 4H,5-H, 8-H), 5.12 (m, 2H, 4-H, 9-H), 5.53 (m, 2H, 6-H, 7-H), 7.40-7.45 (m, 4H, 4-H_a´,4-H_b´, 4-H_a´´, 4-H_b´´), 7.52-7.56 (m, 2H, 5-H´,5-H´´), 8.00-8.04 (m, 4H, 3-H_a´, 3-H_b´, 3-H_a´´,3-H_b´´); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.07 (C-1, C-12), 18.73 (C-2, C-11), 35.76 (C-3, C-10), 37.56 (C-5, C-8), 74.19 (C-4, C-8), 128.43 (C-4´,C-4´´), 128.60 (C-6, C-7), 129.66 (C-3´,C-3´´), 130.88 (C-2´,C-2´´), 132.86 (C-5´,C-5´´) 166.31 (C-1´,C-1´´); EIMS *m/z* 77, 105; HRMS *m/z* 409.2374 (calcd for $C_{26}H_{33}O_4^+$ 409.2373).

(4*R*,6*E*,9*R*)-Dodec-6-ene-4,9-diyl dibenzoate [(4*R*,6*E*,9*R*)-21]: 151 mg (0.69 mmol) of the benzoyl-protected (*R*)-Hept-1-en-4-ol (*R*)-**8** and 30 mg (0.03 mmol) Grubbs 2nd generation catalyst were dissolved in 5 mL dry CH_2Cl_2 and the reaction was heated to 40 °C and stirred for 24 h. The reaction mixture was filtrated through a pad of celite and concentrated under reduced pressure. Chromatography over silica gel (*n*-pentane/Et_2O, 94:6) afforded the product (4*R*,6*E*,9*R*)-**21** (116 mg, 0.30 mmol, 86%) as a colorless oil. $[\alpha]_D^{20}$ = +28.3 (c 1, $CHCl_3$); The analytical data are in accordance to those of (4*S*,6*E*,9*S*)-**21** (see above).

Ethyl (5*S*,6*E*,9*R*)-9-benzoyl-5-(tetrahydropyran-2´´-yloxy)-dodec-6-enoate [(5*S*,6*E*,9*R*)-25]: To a solution of 100 mg (0.24 mmol) of (4*R*,6*E*,9*R*)-**21** and 121 mg (0.47 mmol) (*S*)-**7** in 5 mL dry CH_2Cl_2, 22 mg (0.02 mmol) of Grubbs 2nd generation catalyst were added, and the reaction stirred at 40 °C for 3 d. The reaction was filtrated through a pad of celite and concentrated under reduced pressure. Chromatography over silica gel (*n*-pentane/Et_2O, 93:7→83:17→75:25) yielded the product (5*S*,6*E*,9*R*)-**25** as a colorless oil (90 mg, 0.20 mmol, 41%). Unreacted substrates (4*R*,6*E*,9*R*)-**21** (44 mg, 0.11 mmol, 44%) and (*S*)-**7** (34 mg, 0.13 mmol, 28%) could be reisolated. Due to the THP-protecting group compound (5*S*,6*E*,9*R*)-**25** was obtained as a diastereomeric mixture indicated as A and B; dr = 1:1.2 (^1H NMR). R_f 0.33 (*n*-pentane/Et_2O, 75:25); $[\alpha]_D^{20}$ = -9.5 (c 1, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 2938, 2873, 1716, 1272, 1112, 1022, 712 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.93 (t, $^3J_{12,11}$ = 7.4 Hz, 6H, 12-H^{AB}), 1.24 (t, $^3J_{2´,1}$= 7.1 Hz, 6H, 2-$H^{AB´}$), 1.28-1.76 (m, 28H, 3-H^{AB}, 4-H^{AB}, 10-H^{AB}, 11-H^{AB}, 3-$H^{AB´´}$,4-$H^{AB´´}$, 5-$H^{AB´´}$), 2.25 (m, 4H, 2-H^{AB}), 2.43 (q, $^3J_{8,9}$ = 5.8 Hz, $^3J_{8,7}$ = 5.6 Hz, 4H, 8-H^{AB}), 3.31-3.36 (dt, $^2J_{6bB´´,6aB´´}$= 10.5 Hz, $^3J_{6bB´´,5aB´´}$ = 4.5 Hz, $^3J_{6bB´´,5bB´´}$ = 4.5 Hz, 1H, 6-$H_b^{B´´}$), 3.36-3.41 (dt, 1H, $^2J_{6bA´´,6aA´´}$= 10.5 Hz, $^3J_{6bA´´,5aA´´}$ = 4.8 Hz, $^3J_{6bA´´,5bA´´}$ =4.8 Hz, 6-$H_b^{A´´}$) 3.72-3.78 (ddd, $^2J_{6aB´´,6bB´´}$= 11.5 Hz, $^3J_{6aB´´,5bB´´}$ =8.5 Hz, $^3J_{6aB´´,5aB´´}$ =3.3 Hz, 1H, 6-$H_a^{B´´}$), 3.78-3.83 (dt, $^2J_{6aA´´,6bA´´}$= 11.5 Hz, $^3J_{6aA´´,5aA´´}$ = 5.6 Hz, $^3J_{6aA´´,5aA´´}$ =5.6 Hz, 1H, 6-$H_a^{A´´}$), 4.00-4.04 (m, 2H, 5-H^A, 5-H^B), 4.11 (q, $^3J_{1´,2´}$ = 7.1 Hz, 4H, 1-$H^{AB´}$), 4.47 (t, $^3J_{2B´´,3B´´}$ = 3.6 Hz, 1H, 2-$H^{B´´}$), 4.64 (t, $^3J_{2A´´,3A´´}$ = 3.7 Hz, 1H, 2-$H^{A´´}$), 5.18 (m, 2H, 9-H^A, 9-H^B), 5.32 (dd, $^3J_{6B,7B}$ = 15.5 Hz, $^3J_{6B,\ 5B}$ = 8.3 Hz, 1H, 6-H^B), 5.54-5.70 (m, 3H, 6-H^A, 7-H^{AB}), 7.40-7.45 (m, 4H, 4-$H_a^{AB´´´}$, 4-$H_b^{AB´´´}$), 7.52-7.57 (m, 2H, 5-$H^{AB´´´}$), 8.01-8.05 (m, 4H, 3-$H_a^{AB´´´}$, 3-$H_b^{AB´´´}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.11 (C-12), 14.40 (C-2´), 18.75/18.76 (C-11), 19.66/19.81 (C-4´´), 20.78/21.27 (C-3), 25.60/25.67, 30.83/30.94, 35.31 (C-10, C-3´´,C-5´´) , 34.36/34.38 (C-2), 36.02/36.20 (C-4), 37.27/37.36 (C-8), 60.31/60.34 (C-1´) 62.48/62.60 (C-6´´) 73.87/74.17 (C-9), 75.39/76.76 (C-5), 95.04 (C-$2^{B´´}$), 97.52 (C-$2^{A´´}$) 126.64 (C-7), 128.43/128.47 (C-4´´´), 129.36/129.70 (C-3´´´), 130.83/130.94

(C-2´´), 132.86/132.93 (C-5´´), 133.64/134.68 (C-6), 166.22/166.28 (C-1´´), 173.62/173.70 (C-1); EIMS *m/z* 77, 105, 164, 341; HRMS *m/z* 469.2560 (calcd for $C_{26}H_{38}O_6Na^+$ 469.2561).

Ethyl (5*S*,6*E*,9*S*)-9-benzoyl-5-(tetrahydropyran-2´´-yloxy)-docec-6-enoate [(5*S*,6*E*,9*S*)-25]: To a solution of 94 mg (0.22 mmol) of (4*S*,6*E*,9*S*)-**21** and 124 mg (0.48 mmol) (*S*)-**7** in 5 mL dry CH_2Cl_2, 22 mg (0.02 mmol) of Grubbs 2nd Generation Catalyst were added, and the reaction stirred at 40 °C for 3 d. The reaction was filtrated through a pad of celite and concentrated under reduced pressure. Chromatography over silica gel (*n*-pentane/Et_2O, 92:8→8:2→7:3) yielded the product (5*S*,6*E*,9*S*)-**25** as a colorless oil (47 mg, 0.11 mmol, 23%). Unreacted substrates (4*S*,6*E*,9*S*)-**21** (59 mg, 0.14 mmol, 63%) and (*S*)-**7** (60 mg, 0.23 mmol, 48%) could be reisolated. Due to the THP-protecting group compound (5*S*,6*E*,9*S*)-**25** was obtained as a diastereomeric mixture indicated as A and B; dr = 1:1.2 (^{1}H NMR). R_f 0.37 (*n*-pentane/Et_2O, 7:3); $[\alpha]_D^{20}$ = -17.0 (c 1, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 2937, 2873, 1716, 1272, 1112, 1022, 713 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.93 (t, $^3J_{12,11}$ = 7.4 Hz, 6H, 12-H^{AB}), 1.24 (t, $^3J_{2´,1´}$= 7.1 Hz, 6H, 2-H$^{AB´}$), 1.28-1.76 (m, 28H, 3-H^{AB}, 4-H^{AB}, 10-H^{AB}, 11-H^{AB}, 3-H$^{AB´´}$,4-H$^{AB´´}$, 5-H$^{AB´´}$), 2.19 (m, 4H, 2-H^{AB}), 2.44 (m, 4H, 8-H^{AB}), 3.37-3.45 (m, 2H 6-H$_b^{A´´}$, 6-H$_b^{B´´}$) 3.79-3.85 (m, 2H 6-H$_a^{A´´}$, 6-H$_a^{B´´}$), 3.98 (q, $^3J_{5A,\ 4aA}$ = 6.2 Hz, $^3J_{5A,6A}$ = 6.2 Hz, 1H, 5-H^A), 4.03 (q $^3J_{5B,6B}$ = 6.5 Hz, $^3J_{5B,4aB}$ = 6.5 Hz, 1H, 5-H^B) 4.10 (q, $^3J_{1´,2´}$ = 7.1 Hz, 4H, 1-H$^{AB´}$), 4.57 (t, $^3J_{2B´´,3B´´}$ = 3.7 Hz, 1H, 2-H$^{B´´}$), 4.64 (t, $^3J_{2A´´,3A´´}$ = 3.7 Hz, 1H, 2-H$^{A´´}$), 5.18 (m, 2H, 9-H^A, 9-H^B), 5.31 (dd, $^3J_{6B,7B}$ = 15.5 Hz, $^3J_{6B,\ 5B}$ = 8.3 Hz, 1H, 6-H^B), 5.53-5.59 (dd, $^3J_{6A,7A}$ = 15.5 Hz, $^3J_{6A,5A}$ =7.1 Hz, 1H, 6-H^A), 5.64 (m, 2H, 7-H^{AB}), 7.40-7.45 (m, 4H, 4-H$_a^{AB´´´}$, 4-H$_b^{AB´´´}$), 7.52-7.57 (m, 2H, 5-H$^{AB´´´}$), 8.01-8.05 (m, 4H, 3-H$_a^{AB´´´}$, 3-H$_b^{AB´´´}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.12 (C-12), 14.39 (C-2´), 18.76 (C-11), 19.77/19.82 (C-4´´), 20.70/21.20 (C-3), 25.59/25.70, 30.86/30.98, 35.24 (C-10, C-3´´, C-5´´), 34.28/34.31 (C-2), 36.01/36.04 (C-4), 37.26/37.50 (C-8), 60.31/60.34 (C-1´), 62.46/62.68 (C-6´´), 73.78/74.00 (C-9), 75.36/77.23 (C-5), 94.92/97.74 (C-2´´), 126.76/129.22 (C-7), 128.42/128.46 (C-4´´´), 129.67 (C-3´´´), 130.76/130.85 (C-2´´), 132.88/132.94 (C-5´´´), 133.59/134.74 (C-6), 166.24/166.28 (C-1´´´), 173.61/173.68 (C-1); EIMS *m/z* 77, 105, 164, 341; HRMS *m/z* 469.2560 (calcd for $C_{26}H_{38}O_6Na^+$ 469.2561).

(5*S*,6*E*,9*R*)-5-Hydroxy-9-propyl-6-nonen-9-olide [1]: 11.3 mg LiOH (0.47 mmol) were added to a solution of 44 mg (0.10 mmol) (5*S*,6*E*,9*R*)-**25** in 10.2 mL of THF:MeOH:H_2O (2:1:1) and heated to 60 °C for 48 h. The reaction was diluted with 30 mL of Et_2O washed with saturated KH_2PO_4-solution and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. 12 mL dry THF was added to the crude product together with 86 µL (0.55 mmol) 2,4,6-trichlorobenzoyl chloride and 84 µL (0.60 mmol) of triethylamine. The reaction mixture was stirred for 60 min at rt, diluted with 25 mL dry toluene and then filtrated through a pad of celite. 40 mL of dry toluene were added and the mixture was slowly added to a refluxing solution of 86 mg (0.69 mmol) DMAP in 50 mL dry toluene over the course of 2.5 h. The reaction was stirred for another 30 min before it was allowed to cool to rt. The mixture was quenched with 1 M aqueous HCl and washed with saturated $NaHCO_3$-solution and brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 12 mL EtOH and treated with 27 mg PPTS (0.11 mmol) and 5.6 mg (0.03 mmol) *p*-TsOH monohydrate. The reaction mixture was heated to 40 °C and stirred for 16 h before being quenched with 40 mL of ice water and saturated $NaHCO_3$-solution. The mixture was extracted with EtOAc (3× 20 mL), dried over $MgSO_4$, filtered over a pad of celite and concentrated under reduced pressure. Chromatography of the crude product (*n*-pentane/Et_2O, 65:35) yielded 12 mg (0.06 mmol, 57%) of the final product (**1**). R_f 0.16 (*n*-pentane/Et_2O, 65:35); $[\alpha]_D^{25}$ = -13.4 (c 0.7, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 3441, 2963, 2931, 2874, 1727, 1442, 1226, 1158 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.93 (t, $^3J_{12,11}$ = 7.4 Hz, 3H, 12-H), 1.32-1.60 (m, 4H, 4-H$_a$, 10-H$_a$, 11-H), 1.62-1.70 (m, 2H, 3-H$_a$, 10-H$_b$), 1.75-1.91 (br s, 1H, 5-OH), 1.93-2.16 (m, 4H, 2-H$_a$, 3-H$_b$, 4-H$_b$, 8-H$_a$), 2.40-2.50 (m, 2H, 2-H$_b$, 8-H$_b$), 4.44 (br s, 1H, 5-H), 5.04 (ddd, *J* = 10.5 Hz, 8.3 Hz, 4.7 Hz, 1H, 9-H),5.44 (dd, *J* = 15.5 Hz, 1.7 Hz, 1H, 6-H),5.55 (dddd, *J* = 15,5 Hz, 10.5 Hz, 4.9 Hz, 2.4 Hz, 1H, 7-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.01 (C-12), 18.01 (C-3), 19.31 (C-11), 35.91 (C-2), 36,45 (C-10), 36.84 (C-4), 40,91 (C-8), 68.60 (C-5), 76.60 (C-9), 126.42 (C-7), 136.82 (C-6), 176.79 (C-1); HRMS *m/z* 213.1486 (calcd for $C_{12}H_{21}O_3^+$ 213.1485).

(5*S*,6*E*,9*S*)-5-Hydroxy-9-propyl-6-nonen-9-olide [(5*S*,6*E*,9*S*)-1]: 9 mg LiOH (0.38 mmol) were added to a solution of 35 mg (0.08 mmol) (5*S*,6*E*,9*S*)-**25** in 8.1 mL of THF:MeOH:H_2O (2:1:1) and heated to 60 °C for 24 h. The reaction was diluted with 25 mL of Et_2O washed with saturated KH_2PO_4-solution and brine. The organic phase was dried of $MgSO_4$ and concentrated under reduced pressure. 8 mL dry THF was added to the crude product together with 71 µL (0.44 mmol) 2,4,6-trichlorobenzoyl chloride and 67 µL (0.48 mmol) of triethylamine. The reaction mixture was stirred for 120 min at rt, diluted with 20 mL dry toluene and then filtrated through a pad of celite. 20 mL of dry toluene were added and the mixture was slowly added to a refluxing solution of 67 mg (0.55 mmol) DMAP in 57 mL dry toluene over the course of 2.5 h. The reaction was stirred for another 30 min before it was allowed to cool to rt. The mixture was quenched with 1M aqueous HCl and washed with saturated $NaHCO_3$-solution and brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 7 mL EtOH and treated with 27 mg PPTS (0.09 mmol) and 4.5 mg (0.02 mmol) *p*-TsOH monohydrate. The reaction mixture was heated to 40 °C and stirred for 16 h before being quenched with 20 mL of ice water and saturated $NaHCO_3$-solution. The mixture was extracted with EtOAc (3× 20 mL), dried over $MgSO_4$, filtered over a pad of celite and concentrated under reduced pressure. Chromatography of the crude product (*n*-pentane/Et_2O, 60:40->50:50) yielded 11 mg (0.05 mmol, 66%) of the final product (5*S*,6*E*,9*S*)-**1**. R_f 0.19 (*n*-pentane/Et_2O, 50:50); $[\alpha]_D^{25}$ = +22.3 (c 0.7, $CHCl_3$); FT-IR $\tilde{\nu}_{max}$ 3426, 2956, 2926, 2866, 1728, 1442, 1181, 1002 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ[ppm]= 0.92 (t, $^3J_{12,11}$ = 7.2 Hz, 3H, 12-H), 1.32-1.59 (m, 5H, 4-H$_a$, 5-OH, 10-H$_a$, 11-H), 1.62-1.70 (m, 1H, 10-H$_b$), 1.86-1.97 (m, 3H, 3-H, 8-H$_a$), 1.98-2.06 (m, 2H, 2-H$_a$, 4-H$_b$), 2.35 (m, 1H, 8-H$_b$), 2.44 (m, 1H, 2-H$_b$), 4.01 (m, 1H, 5-H), 5.03 (m, 1H, 9-H), 5.32 (dt, *J* = 15.0 Hz, 6.5 Hz, 1H, 6-H), 5.54 (m, 1H, 7-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ[ppm]= 14.01 (C-12), 19.28 (C-11), 22.45 (C-3), 35.82 (C-2), 36.58 (C-10), 38.88 (C-4), 40.51 (C-8), 74.28 (C-5), 75.48 (C-9), 131.83 (C-7), 137.30 (C-6), 175.93 (C-1); HRMS *m/z* 213.1485 (calcd for $C_{12}H_{21}O_3^+$ 213.1485).

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