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Asymmetric Synthesis of a Structurally Simplified Analogue of the Antibiotic Heptelidic Acid[a]

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Summary. A structurally simplified analogue of the antibiotic (+)-heptelidic acid was synthesized in ten steps with an overall yield of 9%. Key step was a conjugate addition of a silyl protected vinylcuprate to an asymmetrically shielded enoate, which gave an adduct as a single diastereomer. Transesterification in the presence of triethylamine allowed a selective cleavage of the chiral auxiliary and afforded an enantiomerically pure methyl ester. This easily enolizable β-ketoester was transformed to the *trans* configurated methylene derivative using a four-step reaction sequence. Finally, the desired epoxylactone was accessible from the methylene derivative by lactone ring formation and successive oxidation in four steps.

Keywords. Antibiotics; Asymmetric synthesis; Conjugate addition; Cuprates; *Helmchen*'s auxiliary.

Introduction

(+)-Heptelidic acid (**1**) is a sesquiterpene lactone of fungal origin which shows selective activity against *Bacteroides fragilis* [1], an anaerobic pathogen causing serious septic infections, and is active against the human malaria parasite *Plasmodium falciparum* [2]. In studies about the mechanism of action it has turned out that **1** is a high-affinity active site directed inhibitor of glyceraldehyde-3-phosphate dehydrogenase [3], which is an important enzyme of the anaerobic glycolytic pathway. The epoxide moiety of **1** has been postulated to be the essential structural element responsible for enzyme inactivation caused by covalent binding of **1** to the thiol groups at the active site of the enzyme [4].

A total synthesis of (±)-heptelidic acid has been published by *Danishefsky* [5] in 1988. Our contribution in this field of research has been the development of a synthetic method allowing an access to enantiomerically pure 6-alkenyl-2-oxo-cyclohexane-carboxylates [6] which have been key intermediates for the first asymmetric synthesis of (+)-heptelidic acid [7–10].

Only few papers [11–13] have been published on structural modifications of **1** until now, mainly for the purpose of structure determination of the natural product.

[a] Dedicated to Prof. *Wilhelm Fleischhacker* with our best wishes on the occasion of his 70th birthday

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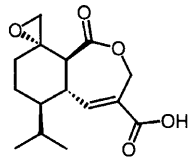
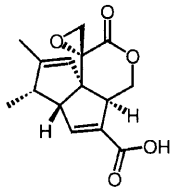
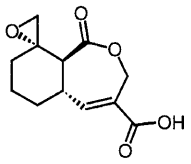


(+)-Heptelidic acid (**1**)



Pentalenolactone (**2**)



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Scheme 1

Syntheses have started exclusively from **1**, modifying the reactive epoxide or lactone ring. Recently, **1** has been transformed to its chlorohydrine derivative which shows antitumor activity [13]. Hence, an interesting progress in this area of research would be the total synthesis and biological evaluation of derivatives of **1** which are not accessible from the fermentatively produced natural product by semisynthetic transformations.

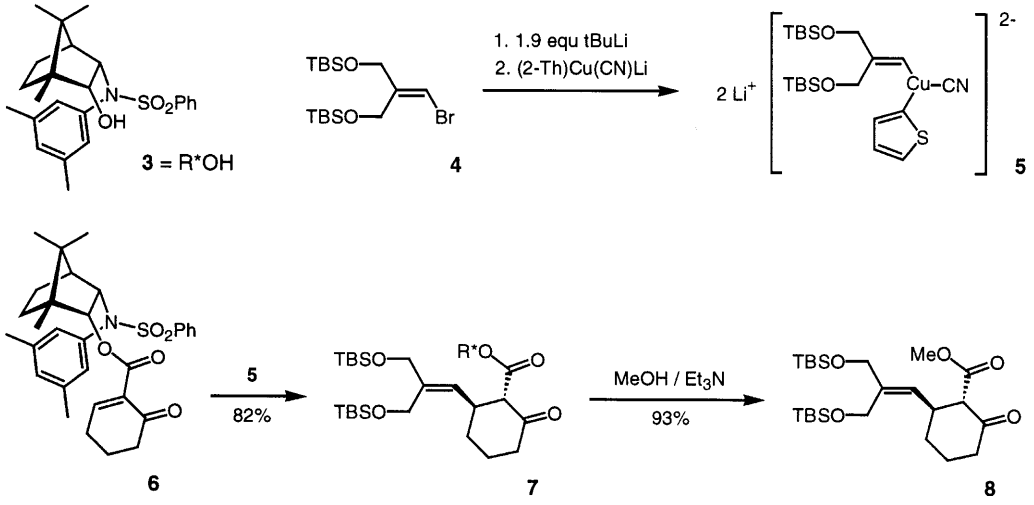
Conserving the pharmacophoric groups and modifying the remaining structure pattern is generally recognized as a reliable method to design analogues of an agent with improved activity. A comparison of the structural lead (+)-heptelidic acid (**1**) with pentalenolactone (**2**) [14], which both inhibit glyceraldehyd-3-phosphate dehydrogenase, has persuaded us that the oxirane moiety, the lactone ring, and the acrylic acid substructure are essential for the activity of **1** and **2**. Surprisingly, the disposition of the pharmacophoric groups and the underlying ring system are quite different in **1** and **2**, although both antibiotics have the same mechanism of action. Hence, it is an interesting question how far the nature of the substituent at the carbocyclic ring of **1** or the ring size of the carbocyclic ring may be changed without loss of activity.

Results and Discussion

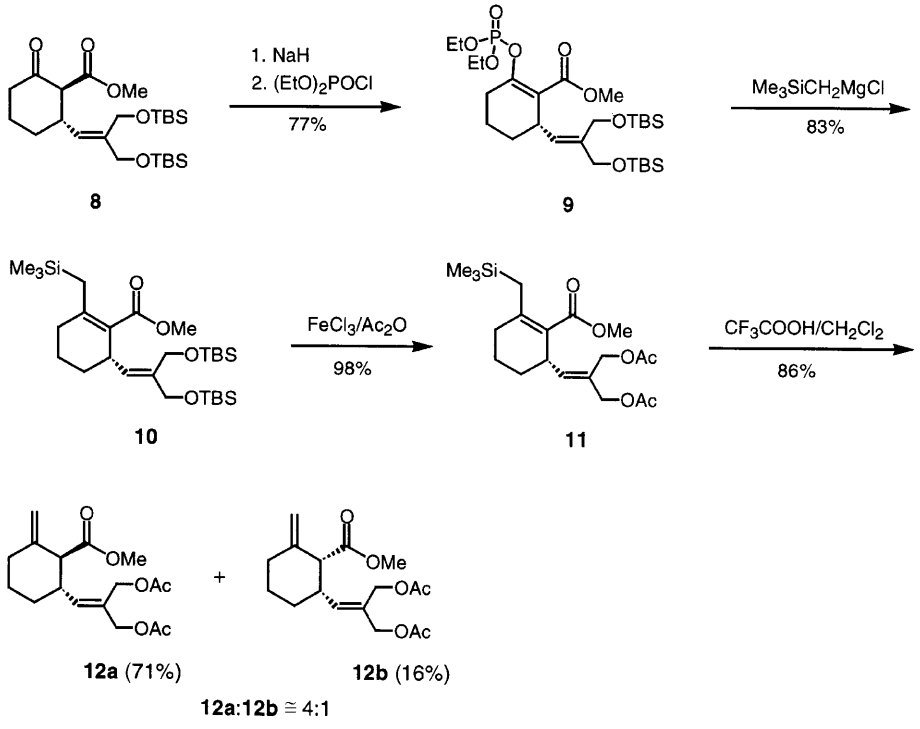
In this contribution we want to present an asymmetric synthesis of the epoxylactone **16**, which is a structurally simplified analogue of **1** bearing no alkyl substituent in the six-membered carbocyclic ring. Whereas the synthesis of **1** requires an alkyl substituted building block, which must be prepared by a five step reaction sequence including a chromatographic separation of diastereomers [7], the synthesis of the simplified analogue **16** starts from the easily accessible 2-oxo-cyclohexane-carboxylate **6** [6].

In the first step of the synthesis the vinylcuprate **5** was added to the asymmetrically protected enoate **6**, giving the adduct **7** (82%) as a single diastereomer. This result was in accordance with our previous observations on high diastereoselectivity obtained in additions of simpler organocopper compounds to enoate **6** [7]. The thienylcyanocuprate **5** was the reagent of choice for this reaction step, because only one equivalent of this readily accessible reagent was required for a complete conversion of **6** at $-78°C$. ^{1}H and ^{13}C NMR spectra of the adduct **7** showed a mixture of keto and enol forms in a ratio of 40:60 which is typical for alkenyl substituted 2-oxo-cyclohexane-carboxylates [6].

In the next reaction step, the chiral auxilary was selectively removed from the sterically highly crowded β-ketoester **7** by transesterification with an excess of



Scheme 2



Scheme 3

methanol in the presence of triethylamine at 115°C. We obtained a mixture of the methyl ester **8** and *Helmchen*'s auxilary **3** (R^*OH) which was separated by column chromatography to give the enantiomerically pure methyl ester **8** (93%). The presence of triethylamine was essential to avoid a cleavage of the silyl ether protecting groups from the chiral building block **8**.

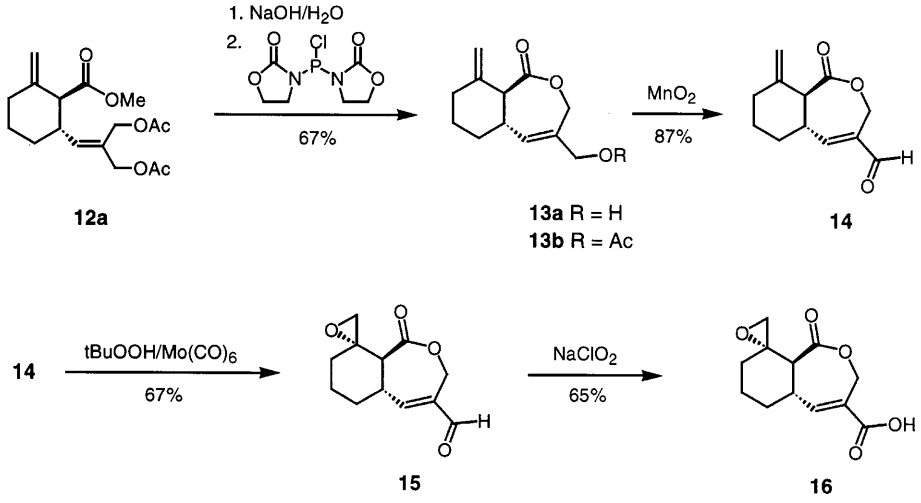
Next, we focused our efforts on the preparation of the methylene derivative **12a**. Transformation of the keto group of **8** to the methylene substituent was not quite trivial, because literature-known reagents usually failed due to the β-ketoester substructure of **8**. The enolization potential of **8** was indicated by its ^{1}H and ^{13}C NMR spectra which showed a mixture of keto and enol forms in a ratio of 31:69 and 43:57, respectively. Nevertheless, we obtained derivatives **12a**,**b** in good yields using a four-step sequence (see Scheme 3) which had previously been used successfully for the synthesis of heptelidic acid [9]. Thus, β-ketoester **8** was transformed to enol phosphate **9**, which was subsequently reacted with trimethylsilylmethylmagnesium chloride to the allylsilane derivative **10**. Next, a change of the silylether protecting groups to acetyl groups was necessary to avoid cleavage during the protodesilylation step. This was achieved by reaction of the silylether derivative **10** with $FeCl_3$ in acetic anhydride to give the diacetate **11**. Protodesilylation of the allylsilane derivative **11** using trifluoroacetic acid in dichloromethane gave a mixture of **12a** and **12b** in a ratio of 4:1. This result was in accordance with our previous observations on the synthesis of **1** [9]. Obviously, presence or absence of an isopropyl substituent in position 5 of **11** gave no difference in the diastereoselectivity during formation of the diastereomeric methylene derivatives.

The mixture of diastereomeric methylene derivatives **12a**,**b** was separated by column chromatography to give the diastereomerically pure methyl ester **12a**. The structures of **12a** and **12b** were assigned based upon characteristic ^{1}H NMR shift effects [9] of the carboxyl group on methylene hydrogens (**12a**: 4.56 and 4.87 ppm; **12b**: 4.85 and 4.87 ppm).

Cyclization of the lactone ring was achieved by removal of the ester protecting groups by means of sodium hydroxide, extraction of the free dihydroxy acid, and cyclization using N,N-*bis*-(2-oxo-3-oxazolidinyl)-phosphorodiamidic chloride [15]

Table 1. ^{13}C NMR shifts (ppm) of cyclohexanecarboxylates **7**–**12**

	7		**8**		**9**	**10**	**11**	**12a**	**12b**
	Ketone	Enol	Ketone	Enol					
C-1	62.46	101.86	63.28	100.92	119.32	123.67	122.11	55.20	53.18
C-2	205.93	172.29	205.23	172.99	151.42	148.86	150.76	144.21	144.76
C-3	41.37	29.11	40.93	29.02	28.54	33.98	34.00	34.66	31.47
C-4	24.71	17.93	25.04	17.82	19.40	19.48	19.36	25.67	26.07
C-5	30.76	30.76	31.03	29.57	28.66	29.74	29.15	31.00	27.92
C-6	39.29	30.36	40.26	30.22	33.77	33.95	34.58	39.60	39.46
COO	168.62	171.34	169.52	172.90	166.54	169.11	168.72	172.65	172.11
OCH_3	–	–	51.84	51.21	51.30	50.64	50.65	51.47	51.49
CH_2Si	–	–	–	–	–	27.36	27.55	–	–
$Si(CH_3)_3$	–	–	–	–	–	−0.71	−0.79	–	–
$=CH_2$	–	–	–	–	–	–	–	109.49	111.98
–HC=	127.89	131.83	125.66	129.42	126.55	128.98	138.73	137.06	137.26
=C<	140.25	137.24	139.76	136.46	139.02	137.24	128.41	129.96	129.34
CH_2O	65.00	64.54	64.17	64.71	64.43	64.53	66.45	66.19	66.45
CH_2O	59.17	58.98	59.13	58.90	58.72	58.88	60.01	60.04	59.75



Scheme 4

to yield **13a**. During the hydrolysis of **12a** two equivalents of acetic acid are formed which must be removed before cyclization to avoid the formation of the acetate derivative **13b** as a byproduct.

Selective oxidation of the allylalcohol moiety of **13a** was obtained by reaction with manganese dioxide, which proved to give higher yields (87%) of aldehyde **14** than the reaction with *Jones* reagent (51%). Diastereoselective epoxidation of **14** was achieved using *t*-butylhydroperoxide in the presence of molybdenum hexacarbonyl affording the epoxyaldehyd **15** in satisfying yield (67%) as a single diastereomer. This result was in accordance with our previous observations

Table 2. ^{13}C NMR shifts (ppm) of 3,5a,6,7,8,8a-Octahydro-1*H*-cyclopent[*c*]oxepin-1-ones

	13a	**13b**	**14**	**15**	**16**
C-1	172.76	171.99	171.53	169.92	170.57
C-3	64.00	63.92	59.03	59.20	61.93
C-4	134.60	130.13	137.51	137.76	128.32
C-5	132.88	136.77	157.34	155.94	147.14
C-5a	41.02	40.98	42.25	40.95	41.82
C-6	33.15	32.86	32.10	31.15	31.99
C-7	25.90	25.74	25.83	23.25	24.53
C-8	35.26	35.11	35.00	33.82	35.21
C-9	141.31	140.98	139.84	57.76	58.64
C-9a	46.58	46.25	45.48	45.00	44.57
CH_2OH	66.50	67.73	–	–	–
CHO	–	–	191.37	191.08	–
COOH	–	–	–	–	167.26
$=CH_2$	112.43	112.63	113.55	–	–
Epoxide CH_2	–	–	–	52.15	51.65

obtained on the oxidation of (+)-heptaldehyde [9]. Obviously, presence or absence of an isopropyl substituent in position 6 of **14** gave no difference of diastereoselectivity during formation of epoxylactones. The structure of **15** was assigned according to characteristic shift effects [9] of the carboxyl group to the oxirane hydrogens (2.59 and 3.96 ppm). In the last reaction step, the epoxyaldehyd **15** was oxidized with sodium chlorite in sodium dihydrogenphosphate buffered *t*-butanol to afford the desired carboxylic acid **16**.

In conclusion, we obtained the simplified heptelidic acid analogue **16** starting from the asymmetric protected enoate **6** in ten steps with an overall yield of 9%.

Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance DPX 200 or a Varian Unity Plus 300 spectrometer using *TMS* as an internal standard. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Microanalyses were performed by *J. Theiner* (Institute of Physical Chemistry, University of Vienna) and corresponded to the calculated values with an accuracy of 0.4%.

(1R,2R,3S,4S)-(3-(N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino)-2-bornyl)-(1S,6S)-6-(3-t-butyldimethylsilyloxy-2-(t-butyldimethylsilyloxy)-methyl-prop-1-en-1-yl)-2-oxo-cyclohexanecarboxylate (**7**; $C_{47}H_{73}NO_7SSi_2$)

A solution of 11.86 g vinylbromide **4** (30.0 mmol) in 120 cm^3 diethylether was cooled to −78°C. A solution of 22.52 g *t*-BuLi in pentane (1.65 *M*, 57.0 mmol) was added, and the mixture was stirred at −78°C for 2 h. Then the mixture was transferred with a double-tipped needle to a precooled (−78°C) solution of 132.0 cm^3 lithium 2-thienyl-cyanocuprate (0.25 *M* in *THF*, 33.0 mmol), and the resulting mixture was stirred at −78°C for 1 h. A solution of 16.07 g **6** (30.0 mmol) in 120 cm^3 *THF* was added, and stirring was continued at −78°C for 2 h. Then the reaction mixture was transferred to a flask containing a mixture of 500 cm^3 CH_2Cl_2 and 500 cm^3 of a NH_4Cl solution (5%). The mixture was stirred at 20°C for 1 h and extracted with 2 × 250 cm^3 CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was distilled off at reduced pressure. Purification of the residue by flash chromatography (2 × 750 g silica gel, hexane:EtOAc = 9:1) gave 21.00 g (82%) **7** as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ketone:enol (k:e) = 40:60): −0.06 (s, 3H, $SiCH_3$, k), −0.04 (s, 3H, $SiCH_3$, k), 0.02 (s, 6H, $SiCH_3$, e), 0.06 (s, 6H, $SiCH_3$, k), 0.13 (s, 3H, $SiCH_3$, e), 0.16 (s, 3H, $SiCH_3$, e), 0.62–2.60 (m, 15H, CH_3, H-3′, H-4′, H-5′, k + e), 0.81 (s, 9H, *t*-Bu CH_3, k), 0.87 (s, 9H, *t*-Bu CH_3, e), 0.89 (s, 9H, *t*-Bu CH_3, k), 0.94 (s, 9H, *t*-Bu CH_3, e), 3.46 (m, 1H, H-6′, k), 3.51 (d, J = 8.6 Hz, 1H, H-1′, k), 3.59 (m, 1H, H-6′, e), 4.00–4.37 (m, 4H, H-3, CH_2O, k + e), 4.43 (d, J = 11.8 Hz, 1H, CH_2O, k), 4.49 (d, J = 12.0 Hz, 1H, CH_2O, e), 5.37 (d, J = 6.0 Hz, 1H, =CH–, e), 5.40 (d, J = 6.0 Hz, 1H, =CH–, k), 5.47 (d, J = 8.8 Hz, 1H, H-2, e), 5.51 (d, J = 9.4 Hz, 1H, H-2, k), 5.87 (s, 1H, NAr H-2, k), 6.39 (s, 1H, NAr H-2, e), 6.59 (s, 1H, NAr H-6, e), 6.78 (s, 1H, NAr H-4, e), 6.82 (s, 1H, NAr H-4, k), 7.08 (s, 1H, NAr H-6, k), 7.28–7.43 (m, 4H, SO_2ArH, k + e), 7.43–7.56 (m, 1H, SO_2ArH, k + e), 12.09 (s, 1H, =C–OH, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, δ, ketone:enol (k:e) = 40:60): −5.41 (OSi CH_3, e), −5.35 (OSi CH_3, k), −5.28 (OSi CH_3, k), 13.44 (CH_3, e), 14.22 (CH_3, k), 18.17 (*t*-Bu C, e), 18.22 (*t*-Bu C, e), 18.26 (*t*-Bu C, k), 19.28 (CH_3, e), 19.36 (CH_3, k), 19.48 (CH_3, e), 19.51 (CH_3, C-5, k), 19.91 (C-5, e), 21.17 (Ar–CH_3, k + e), 25.89 (*t*-Bu CH_3, k + e), 26.71 (C-6, k), 27.01 (C-6, e), 45.18 (C-7, e), 45.70 (C-7, k), 49.49 (C-4, k), 50.72 (C-1, e), 50.89 (C-4, e), 51.46 (C-1, k), 58.93 (C-3, e), 59.32 (C-3, k), 75.14 (C-2, e), 77.03 (C-2, k), 127.97 (NAr C-2, C-6, k + e), 128.01 (SO_2Ar C-3, C-5, e), 128.08 (SO_2Ar C-3, C-5, k), 128.49 (SO_2Ar C-2, C-6, e), 128.69 (SO_2Ar C-2, C-6, k), 129.14 (NAr C-4, k + e), 132.15 (SO_2Ar C-4, k), 132.51 (SO_2Ar C-4, e),

137.50 (NAr C-3, k, C-5, k + e), 136.35 (NAr C-1, e), 137.97 (NAr C-1, k), 138.86 (SO_2Ar C-1, e), 139.26 (SO_2Ar C-1, k) ppm; for further signals, see Table 1.

Methyl-(1S,6S)-6-(3-t-butyldimethylsilyloxy-2-(t-butyldimethylsilyloxy)-methyl-prop-1-en-1-yl)-2-oxo-cyclohexanecarboxylate (**8**; $C_{24}H_{46}O_5Si_2$)

In an autoclave thermostated in an oil bath and equipped with a manometer a solution of 1.97 g **7** (2.31 mmol) and 230 mg Et_3N (2.31 mmol) in 100 cm^3 MeOH was heated for 15 h ($\approx$ 115°C/3.8 bar). The pressure was continuously observed and prevented to exceed 4 bar by adjusting the bath temperature. The solvent was removed under reduced pressure, and the residue was separated by flash chromatography (200 g silica gel, petroleum ether:ethyl acetate = 80:20) to yield 1.014 g (93%) **8** ($R_f = 0.65$) as a colourless oil and 0.955 g (99%) **3** ($R_f = 0.55$) as colourless crystals (MeOH), m.p.: 184°C.

$[\alpha]_D^{20} = +41.80$ ($c = 1.014$, $CDCl_3$, ketone:enol = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$, δ ketone: enol (k:e) = 31:69): 0.00 (s, 6H, $SiCH_3$, k), 0.03 (s, 12H, $SiCH_3$, k + e), 0.08 (s, 6H, $SiCH_3$, e), 0.89 (s, 9H, *t*-Bu CH_3, k + e), 0.91 (s, 9H, *t*-Bu CH_3, k + e), 1.55–1.95 (m, 4H, k + e), 2.20–2.40 (m, 2H, k + e), 3.20 (m, 2H, H-1, H-6, k), 3.52 (m, 1H, H-6, e), 3.67 (s, 3H, OCH_3, k + e), 4.04 (d, J = 12.2 Hz, 1H, CH_2O, k), 4.15 (s, 2H, CH_2O, k + e), 4.19 (d, $J = 12.0$ Hz, 1H, CH_2O, e), 4.33 (d, $J = 12.2$ Hz, 1H, CH_2O, k), 4.37 (d, $J = 12.0$ Hz, 1H, CH_2O, e), 5.30 (d, $J = 8.3$ Hz, 1H, =CH–, k), 5.41 (d, $J = 10.0$ Hz, 1H, =CH–, e), 12.36 (s, 1H, =C–OH, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, δ, ketone:enol (k:e) = 43:57): −5.47 (OSi CH_3, k), −5.43 (OSi CH_3, e), −5.39 (OSi CH_3, k), −5.32 (OSi CH_3, k), −5.26 (OSi CH_3, k), 18.20 (*t*-Bu C, k), 18.28 (*t*-Bu C, e), 18.37 (*t*-Bu C, e), 18.40 (*t*-Bu C, k), 25.89 (*t*-Bu CH_3, k + e) ppm; for further signals, see Table 1.

Methyl-(6S)-6-(3-(t-butyldimethylsilyloxy)-2-((t-butyldimethylsilyloxy)methyl)-prop-1-en-1-yl)-2-((diethyoxyphosphoryl)-oxy)-1-cyclohexenecarboxylate (**9**; $C_{28}H_{55}O_8PSi_2$)

758 mg NaH (95%, 30 mmol) were suspended in 70 cm^3 *THF*, and the mixture was cooled to 0°C. Then a solution of 5.65 g **8** (12 mmol) in 30 cm^3 *THF* was added, and the mixture was warmed to room temperature and stirred for 20 min. The reaction mixture was again cooled to 0°C, 2.48 g diethylchlorophosphate (14.4 mmol) were added, and the mixture was stirred for 2 h at 0°C and for 2 h at room temperature. The reaction mixture was transferred to a flask containing 80 cm^3 of a $NaHCO_3$ solution (5%) by a needle, stirred for 10 min, and extracted with 3 × 150 cm^3 diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (500 g silica gel, petroleum ether:ethyl acetate = 80:20) to yield 5.62 g (77%) **9** ($R_f = 0.14$).

$[\alpha]_D^{20} = +42.60$ ($c = 0.446$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.02 (s, 3H, OSi–CH_3), 0.03 (s, 3H, OSi–CH_3), 0.07 (s, 6H, OSi–CH_3), 0.88 (s, 9H, *t*-BuCH_3), 0.89 (s, 9H, *t*-BuCH_3), 1.33 (m, 6H, PO CH_3), 1.50 (m, 1H), 1.65–1.83 (m, 3H), 2.47 (m, 2H, H-3), 3.65 (s, 3H, OCH_3), 3.69 (m, 1H, H-6), 4.11 (d, $J = 11.8$ Hz, 1H, CH_2O), 4.13 (s, 2H, CH_2O), 4.18 (m, 4H, PO CH_2), 4.35 (d, J = 11.8 Hz, 1H, CH_2O), 5.35 (d, $J = 10.3$ Hz, 1H, –CH =) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, δ): −5.50 (OSi CH_3), −5.46 (OSi CH_3), −5.42 (OSi CH_3), −5.41 (OSi CH_3), 15.98 (d, $J_{PC} = 6.9$ Hz, $POCH_3$), 18.18, (*t*-Bu C), 18.29 (*t*-Bu C), 25.80, (*t*-Bu CH_3), 25.85 (*t*-Bu CH_3), 64.37 (d, $J_{PC} = 6.2$ Hz, $POCH_2$), 64.43 (d, $J_{PC} = 6.2$ Hz, $POCH_2$), 119.32 (d, $J_{PC} = 7.7$ Hz, C-1), 151.42 (d, $J_{PC} = 7.7$ Hz, C-2) ppm; for further signals, see Table 1.

Methyl-(6S)-6-(3-(t-butyldimethysilyloxy)-2-((t-butyl-dimethylsilyloxy)-methyl)-prop-1-en-1-yl)-2-((trimethylsilyl)-methyl)-1-cyclohexenecarboxylate (**10**; $C_{28}H_{56}O_4Si_3$)

In an Ar atmosphere, 75 mg nickel acetylacetonate (292 µmol) were mixed with a solution of 1.77 g enol phosphate **9** (2.92 mmol) in 16 cm^3 *THF*, and the mixture was cooled to 0°C. Then,

7.3 cm^3 Me_3SiCH_2MgCl (1 *M* in diethyl ether, 7.3 mmol) were added, and the mixture was stirred for 2 h at 0°C and for 26 h at room temperature. The reaction mixture was then transferred to 12 cm^3 of a NH_4Cl solution (20%) with a needle, the organic layer was separated, and the aqueous layer was extracted with 2×50 cm^3 diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography (200 g silica gel, petroleum ether:ethyl acetate = 95:5) yielded 1.313 g (83%) **10** ($R_f = 0.49$) as a colourless oil.

$[\alpha]_D^{20} = +103.7$ ($c = 0.190$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.01 (s, 3H, OSi–CH_3), 0.02 (s, 3H, OSi–CH_3), 0.03 (s, 9H, Si–CH_3), 0.08 (s, 6H, OSi–CH_3), 0.88 (s, 9H, *t*-BuCH_3), 0.90 (s, 9H, *t*-BuCH_3), 1.45–1.56 (m, 2H), 1.59–1.74 (m, 2H), 1.94 (dd, $J = 12.2$ and 1.0 Hz, 1H, $SiCH_2$), 2.07 (m, 2H, H-3), 2.13 (d, $J = 12.2$ Hz, 1H, $SiCH_2$), 3.59 (s, 3H, OCH_3), 3.59 (m, 1H, H-6), 4.14 (s, 2H, CH_2O), 4.17 (d, $J = 12.0$ Hz, 1H, CH_2O), 4.38 (d, $J = 12.0$ Hz, 1H, CH_2O), 5.32 (d, $J = 10.5$ Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, δ): −5.37 ($3 \times$ OSi–CH_3), −5.31 (OSi–CH_3), 18.27 (*t*-Bu C), 18.34 (*t*-Bu C), 25.90 (*t*-Bu CH_3), 25.92 (*t*-Bu CH_3) ppm; for further signals, see Table 1.

Methyl-(6S)-6-(3-(acetoxy)-2-((acetoxy)-methyl)-prop-1-en-1-yl)-2-((trimethylsilyl)-methyl)-1-cyclohexenecarboxylate (**11**; $C_{20}H_{32}O_6Si$)

310 mg of the allylsilane **10** (573 μmol) were dissolved in 0.5 cm^3 of acetic anhydride, and the solution was cooled to 0°C. Then, 27 mg $FeCl_3$ (172 µmol) were added, and the mixture was stirred at 0°C for 2 h. Afterwards, 404 mg $NaHCO_3$ (4.81 mmol) were added, the reaction mixture was warmed to room temperature, and stirring was continued for 20 min. Then, 4 cm^3 petroleum ether were added, and the mixture was filtered through 300 mg celite and washed with 50 cm^3 of a mixture of petroleum ether and ethyl acetate (3:7). The combined organic layers were washed with 20 cm^3 of a solution of $NaHCO_3$ (5%), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (25 g silica gel, petroleum ether:ethyl acetate = 8:2) to afford 222 mg (98%) **11**.

$[\alpha]_D^{20} = +106.2$ ($c = 0.130$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.03 (s, 9H, Si–CH_3), 1.41–1.58 (m, 2H), 1.64–1.82 (m, 2H), 2.04 (s, 3H, Ac CH_3), 2.07 (s, 3H, Ac CH_3), 2.10 (m, 4H, H-3, Si–CH_2), 3.61 (s, 3H, OCH_3), 3.66 (m, 1H, H-6), 4.53 (s, 2H, CH_2O), 4.63 (d, $J = 12.3$ Hz, 1H, CH_2O), 4.89 (d, $J = 12.3$ Hz, 1H, CH_2O), 5.56 (d, $J = 10.5$ Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.89 ($2 \times$ Ac CH_3), 170.62 (Ac COO), 170.83 (Ac COO) ppm; for further signals, see Table 1.

Protodesilylation of allylsilane **11**

911 mg of the allylsilane **11** (2.3 mmol) were dissolved in 3 cm^3 CH_2Cl_2, the solution was cooled to 0°C, and 2.62 g trifluoroacetic acid (23 mmol) were added. The mixture was warmed to room temperature and stirred for 60 h. Then, the reaction mixture was cooled to 0°C, 1.93 g $NaHCO_3$ (23 mmol) were added, and the slurry was stirred for 1 h. After addition of 15 cm^3 H_2O the product was extracted with 2×30 cm^3 CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The remaining mixture of diastereomeric esters (**12a**:**12b** = 4:1) was separated by flash chromatography (200 g silica gel, petroleum ether:ethyl acetate = 8:2) to yield 121 mg (16%) **12b** ($R_f = 0.38$) as a colourless oil and 530 mg (71%) **12a** ($R_f = 0.31$) as a colourless oil.

Methyl-(1S,6S)-6-(3-(acetoxy)-2-(acetoxymethyl)-prop-1-en-1-yl)-2-methylen-1-cyclohexanecarboxylate (**12a**; $C_{17}H_{24}O_6$)

$[\alpha]_D^{20} = +19.09$ ($c = 0.110$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.30–1.60 (m, 2H), 1.73–1.85 (m, 2H), 2.06 (s, 6H, Ac CH_3), 2.10 (m, 1H), 2.36 (m, 1H), 2.86–2.95 (m, 2H, H-1, H-6), 3.67 (s, 3H,

OCH_3), 4.53 (s, 2H, CH_2O), 4.56 (s, 1H, $=CH_2$), 4.57 (d, $J = 12.8$ Hz, 1H, CH_2O), 4.82 (d, $J =$ 12.8 Hz, 1H, CH_2O), 4.87 (s, 1H, $=CH_2$), 5.55 (d, $J = 10.0$ Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.85 ($2 \times$ Ac CH_3), 170.55 (Ac COO), 170.72 (Ac COO) ppm; for further signals, see Table 1.

Methyl-(1R,6S)-6-(3-(acetoxy)-2-(acetoxymethyl)-prop-1-en-1-yl)-2-methylen-1-cyclohexanecarboxylate (**12b**; $C_{17}H_{24}O_6$)

$[\alpha]_D^{20} = -23.75$ ($c = 0.160$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, δ): 1.67–1.98 (m, 3H), 2.07 (s, 6H, Ac CH_3), 2.16–2.42 (m, 3H), 2.70 (m, 1H, H-6), 3.26 (d, $J = 5.0$ Hz, 1H, H-1), 3.65 (s, 3H, OCH_3), 4.56 (s, 2H, CH_2O), 4.65 (s, 2H, CH_2O), 4.85 (s, 1H, $=CH_2$), 4.87 (s, 1H, $=CH_2$), 5.78 (d, $J =$ 10.0 Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.88 (Ac CH_3), 20.92 (Ac CH_3), 170.59 (Ac COO), 170.79 (Ac COO) ppm; for further signals, see Table 1.

(5aS,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-4-hydroxymethyl-9-methylen-2-benzoxepin-1-one (**13a**; $C_{12}H_{16}O_3$)

423 mg of the triester **12a** (1.30 mmol) were dissolved in 15 cm^3 of aqueous NaOH (10%) and stirred at room temperature for 65 h. Then, the reaction mixture was cooled to 0°C and acidified with 20 cm^3 conc. HCl (12 *N*). The aqueous layer was saturated with NaCl and extracted with 3×30 cm^3 ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was dried in a vaccum desiccator over KOH for 16 h to remove traces of acetic acid.

The remaining dihydroxy acid (348 mg) was dissolved in 20 cm^3 CH_2Cl_2 and cooled to 0°C. Then, 496 mg *bis*-(2-oxo-3-oxazolidinyl)-phosphonic chloride (1.95 mmol), 7.3 mg 4-dimethylamino-pyridine (60 µmol), and 373 mg triethylamine (3.69 mmol) were added, and the mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was cooled to 0°C, carefully neutralized with *ca.* 3.5 cm^3 HCl (0.5 *N*), the organic layer was separated, and the aqueous layer was extracted with 3×20 cm^3 CH_2Cl_2. The combined organic layers were washed with 40 cm^3 of a solution of $NaHCO_3$ (5%), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (30 g silica gel, petroleum ether:ethyl acetate = 1:1) to afford 181 mg (67%) **13a** ($R_f = 0.23$).

If the crude dihydroxy acid was not dried over KOH, lactonization occured, and a mixture of **13a** and **13b** was obtained which was separated by flash chromatography (30 g silica gel, petroleum ether:ethyl acetate = 1:1) to yield 14 mg (4%) **13b** ($R_f = 0.66$) and 160 mg (59%) **13a** ($R_f = 0.23$).

$[\alpha]_D^{20} = +54.4$ ($c = 0.090$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, δ): 1.68–2.14 (m, 5H), 2.20–2.50 (m, 3H), 3.70 (d, $J = 12.0$ Hz, 1H, H-9a), 4.02 (d, $J = 13.1$ Hz, 1H, CH_2O), 4.11 (d, $J = 13.1$ Hz, 1H, CH_2O), 4.40 (d, $J = 15.0$ Hz, 1H, H-3), 5.07 (s, 1H, $=CH_2$), 5.13 (d, $J = 15.0$ Hz, 1H, H-3), 5.50 (d, $J = 1.3$ Hz, 1H, $=CH_2$), 5.64 (d, $J = 0.7$ Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2.

(5aS,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-4-acetoxymethyl-9-methylen-2-benzoxepin-1-one (**13b**; $C_{14}H_{18}O_4$)

$[\alpha]_D^{20} = +44.8$ ($c = 0.101$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, δ): 1.65–2.15 (m, 5H), 2.06 (s, 3H, Ac CH_3), 2.31–2.52 (m, 2H), 3.67 (d, $J = 11.5$ Hz, 1H, H-9a), 4.35 (d, $J = 15.1$ Hz, 1H, H-3), 4.44 (d, $J = 12.4$ Hz, 1H, CH_2O), 4.53 (d, $J = 12.4$ Hz, 1H, CH_2O), 5.06 (s, 1H, $=CH_2$), 5.10 (d, $J = 15.1$ Hz, 1H, H-3), 5.50 (d, $J = 1.5$ Hz, 1H, $=CH_2$), 5.71 (d, $J = 0.7$ Hz, 1H, –CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.84 (Ac CH_3), 170.58 (Ac COO) ppm; for further signals, see Table 2.

(5aS,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-9-methylen-1-oxo-2-benzoxepin-4-carbaldehyde (**14**; $C_{12}H_{14}O_3$)

Method A: 70 mg of **13a** (336 µmol) were dissolved in 4 cm^3 acetone, and the solution was cooled to 0°C. Then, 147 mg *Jones* reagent (prepared from 77.9 mg H_2O, 41.8 mg H_2SO_4, and 26.8 mg CrO_3) were added, and the mixture was stirred for 10 min at 0°C. For work-up, 100 mm^3 MeOH and 4 cm^3 of a $NaHCO_3$ solution (5%) were added. The mixture was filtered through celite, the filter agent was washed with 20 cm^3 ethyl acetate, the organic layer was separated, and the aqueous layer was extracted with 2 × 10 cm^3 ethyl acetate. The combined organic layers were washed with 20 cm^3 of a saturated solution of NaCl, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (7 g silica gel, petroleum ether:ethyl acetate = 3:1) to afford 35 mg (51%) **14** ($R_f = 0.23$).

Method B: 408 mg of **13a** (1.96 mmol) were dissolved in 8 cm^3 CH_2Cl_2, 1.7 g manganese(IV) oxide (19.6 mmol) were added, and the suspension was heated to reflux for 12 h. The mixture was filtered through celite, the filter cake was washed with 3 × 40 cm^3 ethyl acetate, and the solvent was evaporated under reduced pressure to afford 350 mg **14** (87%).

$[\alpha]_D^{20} = -38.1$ ($c = 0.110$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.35–1.72 (m, 2H), 1.84–2.22 (m, 3H), 2.47 (dt, $J = 13.6$ and 4.5 Hz, 1H, H-8), 2.71 (tq, $J = 12.0$ and 3.0 Hz, 1H, H-5a), 3.75 (d, $J = 12.0$ Hz, 1H, H-9a), 4.96 (dt, $J = 14.3$ and 2.0 Hz, 1H, H-3), 5.11 (d, $J = 14.3$ Hz, 1H, H-3), 5.13 (s, 1H, $=CH_2$), 5.60 (d, $J = 1.3$ Hz, 1H, $=CH_2$), 6.63 (dd, $J = 3.0$ and 2.0 Hz, 1H, –CH=), 9.40 (s, 1H, aldehyde H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2.

(5aS,9S,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-1-oxo-spiro-(2-benzoxepin-9,2′-oxirane)-4-carbaldehyde (**15**; $C_{12}H_{14}O_4$)

257 mg of the methylene derivative **14** (1.25 mmol) were dissolved in 12 cm^3 dry benzene, 0.35 cm^3 *t*-BuOOH (5.5 *M* in decane, 1.925 mmol) and 20 mg $Mo(CO)_6$ (76 µmol) were added, and the mixture was refluxed for 3 h. After cooling to room temperature, 0.33 cm^3 dimethylsulfide (4.48 mmol) were added, and stirring was continued for 30 min. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (20 g silica gel, petroleum ether:ethyl acetate = 6:4) to yield 184 mg (67%) **15** ($R_f = 0.15$).

$[\alpha]_D^{20} = -43.2$ ($c = 0.200$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.35–1.59 (m, 2H), 1.62–1.89 (m, 2H), 2.04 (m, 1H), 2.15 (m, 1H), 2.59 (dd, $J = 5.3$ and 0.5 Hz, 1H, epoxide CH_2), 2.84 (tq, $J = 12.0$ and 3.2 Hz, 1H, H-5a), 3.50 (d, $J = 12.0$ Hz, 1H, H-9a), 3.96 (dd, $J = 5.3$ and 1.6 Hz, 1H, epoxide CH_2), 4.92 (dt, $J = 15.4$ and 2.2 Hz, 1H, H-3), 5.10 (dd, $J = 15.4$ and 0.5 Hz, 1H, H-3), 6.65 (dd, $J = 3.2$ and 2.2 Hz, 1H, –CH=), 9.40 (s, 1H, aldehyde) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): see Table 2.

(5aS,9S,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-1-oxo-spiro-(2-benzoxepin-9,2′-oxirane)-4-carboxylic acid (**16**; $C_{12}H_{14}O_5$)

100.3 mg of **15** (0.45 mmol) were dissolved in 4 cm^3 *t*-BuOH, 3 cm^3 2-methyl-2-butene were added, and the mixture was cooled to 0°C. Then, a solution of 509 mg $NaClO_2$ (80%, 4.5 mmol) and 621 mg $NaH_2PO_4 \cdot H_2O$ (4.5 mmol) in 1.6 cm^3 H_2O were added, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. For work-up, the reaction mixture was acidified with 300 mm^3 acetic acid, saturated with 600 mg NaCl, and extracted with 5 × 10 cm^3 ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Traces of acetic acid were removed by aceotropic distillation using 2 × 4 cm^3 benzene. The residue was purified by flash chromatography (6 g silica gel, ethyl acetate:acetic acid = 99:1) to give 69.7 mg (65%) **16** ($R_f = 0.67$).

Colourless crystals (*n*-hexane), m.p.: 110–112°C; $[\alpha]_D^{20} = -31.3$ ($c = 0.150$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.50–2.20 (m, 7H), 2.45 (d, $J = 5.8$ Hz, 1H, epoxide CH_2), 2.72 (m, 1H, H-5a),

3.86 (d, $J = 12.0$ Hz, 1H, H-9a), 3.89 (dd, $J = 5.8$ and 1.8 Hz, 1H, epoxide CH_2), 4.94 (d, $J = 15.2$ Hz, 1H, H-3), 5.34 (dt, $J = 15.2$ and 2.1 Hz, 1H, H-3), 7.04 (t, $J = 2.8$ Hz, 1H, –CH=) ppm; ^{13}C NMR (75 MHz, acetone-d_6): see Table 2.

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