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EPC Synthesis of (+)-Heptelidic Acid

G. Riehs and **E. Urban***

Institute of Pharmaceutical Chemistry, University of Vienna, A-1090 Vienna, Austria

Summary. An EPC (enantiomerically pure compound) synthesis of the antibiotic natural product (+)-heptelidic acid (**1**) is presented. Key step of the synthesis is a conjugate addition of the acetal protected vinyl cuprate **4** to the auxiliary shielded enoate **5n** which gives the adduct **7n** as a single diastereomer. After cleavage of the acetal protecting group and of the chiral auxiliary the enantiomerically pure β-ketoester **12** has been obtained which has been transformed to the title compound **1** (11 steps starting from **5n**, 10.6% overall yield).

Keywords. Antibiotics; Asymmetric synthesis; Conjugate addition; Cuprates; Heptelidic acid.

EPC-Synthese von (+)-Heptelidsäure

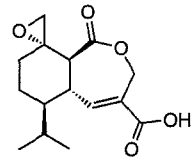
Zusammenfassung. Eine EPC-Synthese (EPC = enantiomerically pure compound) des antibiotischen Naturstoffes (+)-Heptelidsäure (**1**) wird präsentiert. Schlüsselschritt der Synthese ist die *Michael*-Addition des acetal-geschützten Vinylcuprates **4** an das auxiliargeschützte Enoat **5n**, wobei das Addukt **7n** in diastereomerenreiner Form erhalten wird. Nach der Abspaltung der Acetalschutzgruppe und des chiralen Auxiliars läßt sich der enantiomerenreine β-Ketoester **12** herstellen, der in die Titelverbindung **1** umgewandelt werden kann (11 Stufen ausgehend von **5n**, 10.6% Gesamtausbeute).

Introduction

Antibiotics represent an endless source of molecular structures for the development of drugs. However, only few of these natural products have reached an important place in the medical treatment of bacterial and fungal infections or therapy of human cancer, whereas many others have not received much attention since their discovery. One of these "forgotten antibiotics" is the sesquiterpene lactone (+)-heptelidic acid (**1**) which has attracted our attention because of its specific antibacterial activity and its interesting mechanism of action.

1 was isolated from different fungal strains (*Gliocladium virens, Chaetomium globosum, Trichoderma viride* and *Trichoderma koningii*) already 25 years ago [1–3]. The structure of **1** was resolved by spectroscopic methods [4] and confirmed by X-ray crystal structure analysis [5]. Its absolute configuration was determined after oxidative degradation to (*R*)-isopropyl-succinic acid [6]. A total synthesis of (±)-heptelidic acid was published by *Danishefsky* [7] in 1988.

Research on the biological potency of **1** has shown its specific activity against anaerobic bacteria, especially *Bacteroides fragilis* [3,8], and its ability to lower the



(+)-heptelidic acid (1)

Scheme 1

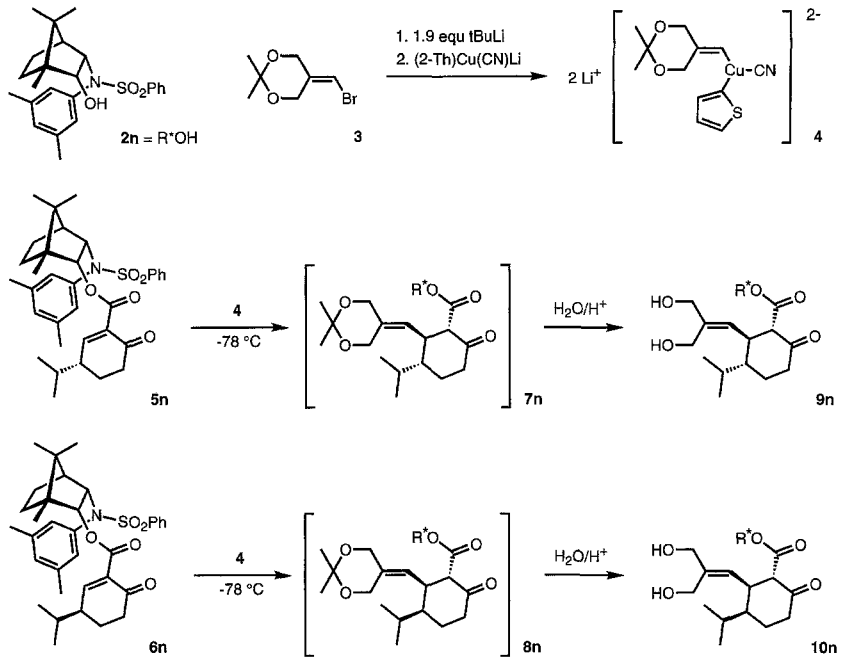
blood serum cholesterol level [9]. Studies on the mechanism of action of **1** revealed a specific inhibition of glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*), an important enzyme of the glycolytic pathway [10]. First, a reversible complex between *GAPDH* and **1** is formed in a competitive way against glyceraldehyde-3-phosphate with a K_i of 1.1 μM, but later an irreversible inhibition of the enzyme results [11]. Recent observations [12] have confirmed the postulation [10], that *GAPDH* is blocked by the formation of a covalent bond between the epoxide moiety of **1** and the thiol group of cystein 149 which has been recognized to be an amino acid responsible for substrate binding in the active center of the enzyme. The above findings suggest that **1** is a high-affinity active-side-directed inhibitor of *GAPDH*. Thus, we regard **1** as a valuable target molecule in our program aiming at an improvement of known antibiotics by synthetic structure modifications [13].

Results and Discussion

Our first contribution in this field of research was the development of an EPC synthesis of the natural product (+)-heptelidic acid (**1**) using the auxiliary protected enoate **5n** as a chiral building block. In a preceeding paper [14] we reported on asymmetrically shielded 2-oxo-5-isopropyl-cyclohexenecarboxylates **5n** and **6n** (see Scheme 2) prepared by a five step synthesis. In accordance with our expectations, the additional chiral centers of the auxiliary stabilized the labile asymmetric carbon (C-5′) of the vinylogous β-ketoesters **5n** and **6n**. Thus we were able to obtain the well crystallizable enoates **5n** and **6n** in diastereomerically pure form (>99%, HPLC) after separation by medium pressure chromatography.

First the configuration at C-5′ of the auxiliary protected enoates **5n** and **6n** was determined by chemical correlation [14]. Later, we were able to prove the postulated configuration of **5n** (5′*R*) and **6n** (5′*S*) by X-ray crystal structure analysis [15].

Conjugate addition of the acetal protected vinylcuprate **4** to the 5′*R* configurated enoate **5n** gave the adduct **7n** (75%) as a single diastereomer [15]. After selective removal of the acetal protecting group we obtained the diol **9n** which proved to be the favourable intermediate for purity determination by HPLC (**9n** predominately exists in the keto form and is hardly enolizable). The main difficulty was to enlarge the scale of preparation for **9n** which was necessary keeping in mind that further ten steps were needed for the completion of the natural product synthesis (Scheme 3). The limiting factor was the separation of **5n** and **6n** by medium pressure chromatography which could not be manufactured in the multigram scale.



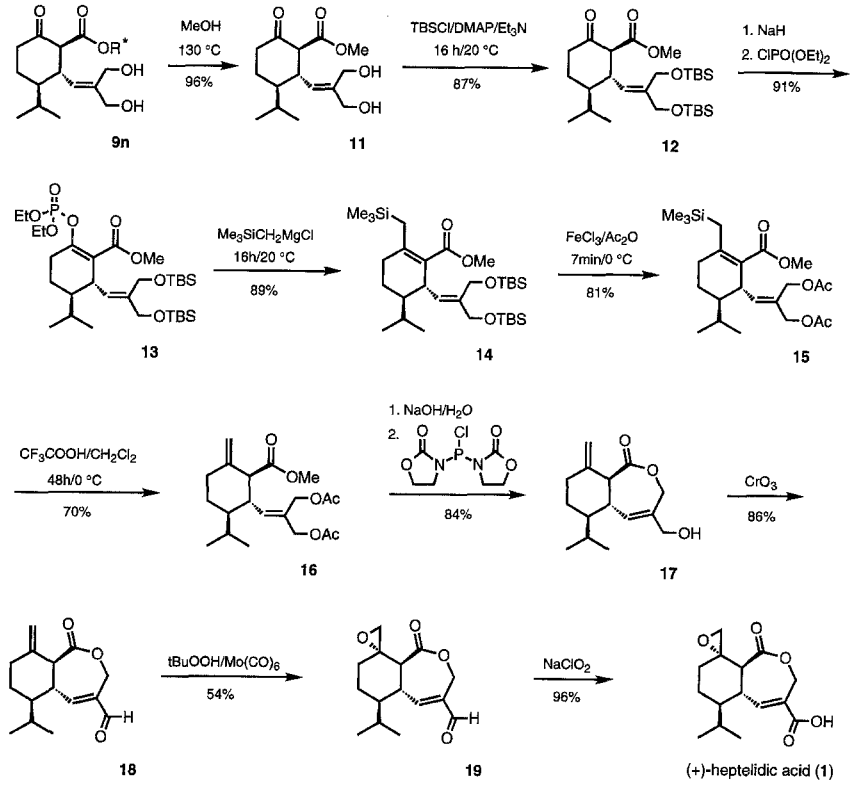
Scheme 2

Thus, we studied the conjugate addition of **4** to the easily available mixture of **5n** and **6n**. Whereas the less hindered enoate **5n** was completely converted to the *trans*-adduct **7n**, the main part of the more hindered enoate **6n** remained unreacted giving only small amounts of the *cis*-adduct **8n**. The unreacted enoate **6n** was easily separable by flash chromatography. After removal of the acetal protecting group from the raw adducts the resulting mixture of **9n** and **10n** was separated by flash chromatography giving **9n** (74%) and **10n** (38%) in diastereomerically pure form (>99%, HPLC). With this method well in hand, we are able to prepare sufficient amounts of diastereomerically pure **9n** to complete the natural product synthesis (Scheme 3).

Cleavage of the chiral auxiliary from the highly crowded β-ketoester **9n** was accomplished by transesterification with methanol at 130°C as previously described for simpler β-ketoesters [16]. Reprotection of the enantiomerically pure diol **11** with *TBS*Cl/Et_3N gave the silylprotected derivative **12**. For the further eight steps we used the reaction sequence of *Danishefsky* [7] which proved to be well reproduceable.

Finally, we obtained the target molecule of the synthesis, (+)-heptelidic acid (**1**), in 11 steps starting from **5n** (10.6% overall yield). The synthetic material gave spectroscopic data fully in accordance with the published data of the natural product [3–5]. Surprisingly, the optical rotation of our product ($[\alpha]_D^{20} = +16.97$ ($c = 1.002$ in $CHCl_3$)) was 2.2 fold higher than that reported for the fermentatively produced material [3].

In conclusion, our EPC synthesis of (+)-heptelidic acid has demonstrated the usefulness of auxiliary shielded 2-oxo-cyclohexenecarboxylates as key intermediates in natural product syntheses. The main advantages of our auxiliary approach to



Scheme 3

(+)-heptelidic acid are that (*i*) the absolute configuration could be verified by X-ray structure analysis of the crystalline intermediate **5n** and (*ii*) that the purity could be determined by conventional HPLC analysis of the auxiliary protected key intermediate **9n** at a very early stage of the synthesis.

Experimental

Melting points were determined with a Kofler melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian unity plus 300 spectrometer by *B. Richter* using *TMS* as an internal standard. The HPLC system consisted of a Shimadzu pump (LC-10AD), a Reodyne injection valve (20 µl), a Merck column (250 × 5 mm, LiChrospher Si 60, 5 µm), a Shimadzu UV/Vis detector (SPD-10A, 254 nm), and a Hewlett Packard integrator (3396 A). Optical rotations were measured on a Perkin Elmer 241 polarimeter. Microanalyses were performed by *J. Theiner* (Institute of Physical Chemistry, University of Vienna).

(1R,2R,3S,4S)-(3-(N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino)-2-bornyl)-(1S,5R,6S)-6-(3-hydroxy-2-hydroxymethyl-prop-1-en-1-yl)-2-oxo-5-isopropyl-cyclohexanecarboxylate (**9n**)

A solution of **3** (2.78 g, 13.4 mmol) in ether (50 ml) was cooled to −78°C. A solution of *t*-BuLi in pentane (15.0 ml, 1.74 *M*, 26.1 mmol) was added, and the mixture was stirred at −78°C for 2h. Then the mixture was transferred to a precooled (−78°C) solution of lithium 2-thienyl-cyano-cuprate (118 ml, 0.17 *M* in *THF*, 20.1 mmol) with a double-tipped needle, and the mixture was stirred at −78°C for 1 h. A solution of **5n** and **6n** (7.74 g, 1:1, 13.4 mmol) in *THF* (50 ml) was added, and stirring was

continued at −78°C for 2 h. Then the reaction mixture was transferred to a flask filled with a mixture of NH_3 (125 ml, 2 *M*) and a solution of NH_4Cl (125 ml, 5%). The mixture was stirred at 20°C for 1 h and extracted with CH_2Cl_2 (3 × 150 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (850 g, silica gel, hexane/EtOAc=80:20) gave the raw adduct (6.56 g) and **6n** (2.07 g, 53%, colourless crystals from *i*-PrOH, m.p.:123–125°C). The raw adduct was dissolved in methanol (100 ml); HCl (4.0 ml, 1*M*) was added, and the mixture was stirred at 20°C for 1 h. Then $NaHCO_3$ (1.0 g) was added, the mixture was diluted with EtOAc (200 ml), the organic layer was dried (Na_2SO_4), and the solvent was distilled off *in vacuo*. Purification of the residue by flash chromatography (850 g, silica gel, CH_2Cl_2/*i*-PrOH = 96:4) gave **9n** (3.31 g, 74%, colourless oil) and **10n** (1.71 g, 38%, colourless oil).

HPLC (Lichrospher Si 60, 5 μm, CH_2Cl_2/*i*-PrOH=96:4, flow 1.0 ml/min; **9n** (ketone:enol = 97.5:2.5): R_t (ketone) = 4.56 min, R_t(enol) = 7.10 min; **10n** (ketone:enol = 74.5:25.5): R_t (ketone) = 6.23 min, R_t(enol) = 8.32 min) revealed a purity of > 99% for adducts **9n** and **10n**.

Further analytical and spectroscopic data: **9n** see preceeding paper [15]; **10n**: see below.

(1R,2R,3S,4S)-(3-(N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino)-2-bornyl)-(1R,5S,6S)-6-(3-hydroxy-2-hydroxymethyl-prop-1-en-1-yl)-2-oxo-5-isopropyl-cyclohexanecarboxylate (**10n**)

A solution of **3** (197 mg, 0.95 mmol) in ether (7 ml) was cooled to −78°C. A solution of *t*-BuLi in pentane (1.07 ml, 1.74 *M*, 1.86 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 lithium 2-thienyl-cyano-cuprate (8.0 ml, 0.125 *M* in *THF*, 1.00 mmol) and the mixture was stirred at −78°C for 1 h. A solution of **6n** (440 mg, 0.76 mmol) in *THF* (10 ml) was added, and stirring was continued at −78°C for 3 h. Then the reaction mixture was transferred to a flask filled with a mixture of NH_3 (30 ml, 2 *M*) and a solution of NH_4Cl (30 ml, 5%). The mixture was stirred at 20°C for 1 h and extracted with CH_2Cl_2 (3 × 50 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (100 g, silica gel, hexane/EtOAc = 75:25) gave the raw adduct (392 mg) and **6n** (53 mg, 12%, colourless crystals from *i*-PrOH, m.p.:123–125°C). The raw adduct was dissolved in methanol (20 ml), HCl was added (2.0 ml, 2*M*) and the mixture was stirred at 20°C for 1 h. Then $NaHCO_3$ (200 mg) was added, the mixture was diluted with EtOAc (40 ml), the organic layer was dried (Na_2SO_4), and the solvent was distilled off *in vacuo*. Purification of the residue by flash chromatography (40 g, silica gel, CH_2Cl_2/*i*-PrOH = 96:4) gave **10n** (296 mg, 58%, colourless oil).

^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 56:44) δ(ketone)= 0.80 (s, 3H, CH_3), 0.87 (d, *J*=7.7 Hz, 3H, *i*-Pr-CH_3), 0.90 (d, *J*=7.5 Hz, 3H, *i*-Pr-CH_3), 1.05 (s, 6H, CH_3), 1.27–1.69 (m, 6H), 1.82–1.98 (m, 3H), 2.00 (s, 3H, Ar–CH_3), 2.16 (m, 1H), 2.38 (s, 3H, Ar-CH_3), 2.43–2.74 (m, 2H), 3.63 (d, *J*=3.2 Hz, 1H, 1′-H), 3.82 (ddd, *J*=11.1, 3.9 and 3.2 Hz, 1H, 6′-H), 4.10–4.30 (m, 4H, 3-H, CH_2O), 4.53 (d, *J*=13.0 Hz, 1H, CH_2O), 5.46 (d, *J*=8.8 Hz, 1H, 2-H), 5.62 (d, *J*=11.1 Hz, 1H, =CH-), 5.68 (s, 1H, NAr-2-H), 6.86 (s, 1H, NAr-4-H), 7.23 (s, 1H, NAr-6-H), 7.28–7.40 (m, 4H, SO_2ArH), 7.53 (m, 1H, SO_2ArH) ppm; δ (enol, separated signals) = 0.80 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, *i*-Pr-CH_3), 0.95 (d, *J*=6.6 Hz, 3H, *i*-Pr-CH_3), 1.05 (s, 3H, CH_3), 2.04 (s, 3H, Ar-CH_3), 2.29 (s, 3H, Ar-CH_3), 3.92 (dd, *J* = 11.1 and 2.9 Hz, 1H, 6′-H), 4.64 (d, *J* = 12.0 Hz, 1H, CH_2O), 5.38 (d, *J*=11.1 Hz, 1H, =CH–), 5.57 (d, *J* = 8.6 Hz, 1H, 2-H), 5.89 (s, 1H, NAr-2-H), 6.84 (s, 1H, NAr-4-H), 7.01 (s, 1H, NAr-6-H), not detectable (s, 1H, = C–OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, ketone: enol = 56:44): δ(ketone)=14.19 (CH_3), 19.05 (CH_3), 19.17 (C-5), 19.27 (CH_3), 20.72 (*i*-Pr-CH_3), 20.82 (*i*-Pr-CH_3). 20.92 (Ar-CH_3), 21.15 (Ar-CH_3), 25.19 (C-4′), 26.55 (C-6), 29.22 (*i*-Pr-CH), 39.83 (C-3′), 41.83 (C-6′), 44.83 (C-5′), 45.55 (C-7), 48.89 (C-4), 51.08 (C-1), 58.86 (CH_2O), 58.98 (C-3), 62.09 (C-1′), 65.86 (CH_2O), 76.97 (C-2), 124.73 (= CH–), 127.14 (NAr-C-6), 127.91 (SO_2Ar-C-3, C-5), 128.11 (SO_2Ar-C-2, C-6), 129.43 (NAr-C-2), 130.26 (NAr-C-4), 132.61 (SO_2Ar-C-4), 136.37 (NAr-C-5), 136.98 (NAr-C-1), 137.61 (NAr-C-3), 138.44 (SO_2Ar-C-1), 140.40 (=C<), 168.47

(COO), 207.05 (C-2) ppm; δ(enol)= 13.91 (CH_3), 19.17 (C-5), 19.22 (CH_3), 19.34 (CH_3), 20.09 (C-4′), 20.50 (*i*-Pr-CH_3), 20.86 (Ar-CH_3), 20.92 (Ar-CH_3), 21.62 (*i*-Pr-CH_3), 26.55 (C-6), 27.31 (C-3′), 29.12 (*i*Pr-CH), 33.67 (C-6′), 39.13 (C-5′), 45.29 (C-7), 49.28 (C-4), 50.75 (C-1), 58.98 (C-3), 59.68 (CH_2O), 66.68 (CH_2O), 76.44 (C-2), 102.07 (C-1′), 127.29 (NAr-C-6), 127.95 (SO_2Ar-C-3, C-5), 128.11 (SO_2Ar-C-2, C-6), 128.29 (= CH–), 128.29 (NAr-C-2), 130.26 (NAr-C-4), 132.67 (SO_2Ar-C-4), 135.62 (NAr-C-5), 136.90 (NAr-C-1), 138.10 (NAr-C-3), 138.21 (=C<), 138.86 (SO_2Ar-C-1), 168.42 (COO), 169.87 (C-2′) ppm; $C_{38}H_{51}NO_7S$ (665.9); calcd.: C 68.54, H 7.72, N 2.10; found: C 68.24, H 7.93, N 2.15.

(1S,5R,6S)-Methyl-6-(3-hydroxy-2-hydroxymethyl-prop-1-en-1-yl)-2-oxo-5-isopropyl-cyclohexane-carboxylate (**11**)

9n (3.30 g, 4.96 mmol) was dissolved in methanol (70 ml) and heated in an autoclave at 130°C for 25 h. Then the solvent was evaporated at reduced pressure. After the main fraction of **2n** (924 mg, 45%) was removed by crystallization from MeOH, the residue was separated by flash chromatography (110 g, silica gel, hexane/EtOAc=3:7) to give **2n** (940 mg, 46%, $R_f = 0.92$ colourless crystals from MeOH), **9n** (100 mg, 3%, $R_f = 0.78$ colourless oil), and **11** (1.35 g, 96%, $R_f = 0.26$, colourless crystals from hexane/EtOAc, m.p.: 61–65°C). Analytical and spectroscopic data were identical with previously published values [15].

(1S,5R,6S)-Methyl-6-(3-tert-butyldimethylsilyloxy-2-(tert-butyldimethylsilyloxy)methyl-prop-1-en-1-yl)-2-oxo-5-isopropyl-cyclohexanecarboxylate (**12**)

Diol **11** (2.85 g, 10.0 mmol) was converted to the silylether **12** as described previously ([15]; 4.45 g, 87%). Analytical and spectroscopic data were identical with published values [7,15].

(3S,4R)-1-((Diethoxyphosphoryl)oxy)-2-(methoxycarbonyl)-4-(1-methylethyl)-3-(3-(tert-butyldimethylsilyl-oxy)-2-((tert-butyldimethylsilyl-oxy)methyl)prop-1-en-1-yl)cyclohex-1-ene (**13**)

β-Ketoester **12** (3.29 g, 6.42 mmol) was reacted as published previously [7] to the enolphosphate **13** (3.79 g, 91%).

$[\alpha]_D^{20} = +60.63$ ($c = 1.016$, $CHCl_3$), ^{1}H NMR: identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.51, -5.40$ (OSi-CH_3), 16.02 (d, $J_{PC} = 6.6$ Hz, PO-CH_3), 17.50 (*i*-Pr-CH_3), 18.22, 18.33 (*t*-Bu-C), 20.45 (C-5), 21.58 (*i*-Pr-CH_3), 25.81, 25.87 (*t*-Bu-CH_3), 26.92 (*i*-Pr-CH), 27.47 (C-6), 37.44 (C-3), 44.59 (C-4), 51.33 (OCH_3), 58.51 (CH_2O), 64.22 (CH_2O), 64.39 (d, $J_{PC} = 6.6$ Hz, PO-CH_2), 64.45 (d, $J_{PC} = 6.0$ Hz, PO-CH_2), 118.96 (d, $J_{PC} = 8.2$ Hz, C-2), 126.56 (-CH=), 140.39 (=C<), 150.66 (d, $J_{PC} = 7.7$ Hz, C-1), 166.75 (COO) ppm; $C_{31}H_{61}O_8P$ (649.0); calcd.: C 57.37, H 9.47; found: C 57.69 H 9.24.

(3S,4R)-2-(Methoxycarbonyl)-4-(1-methylethyl)-1-((trimethylsilyl)methyl)-3-(3-(tert-butyldimethyl-silyl-oxy)-2-((tert-butyldimethylsilyl-oxy)methyl)prop-1-en-1-yl)-cyclohex-1-ene (**14**)

Enolphosphate **13** (3.79 g, 5.84 mmol) and Ni(*acac*)$_2$ (130 mg, 0.5 mmol) were dissolved in *THF* (50 ml) in an argon atmosphere and cooled to 0°C. A solution of Me_3SiCH_2MgCl (14.6 ml, 1.0 *M* in ether, 14.6 mmol) was added in one portion and the mixture was stirred for 66 h at 20°C. The reaction was quenched with a solution of NH_4Cl (50 ml, 20%), the mixture was stirred for 45 min and then extracted with ether (3 × 100 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (250 g, silica gel, hexane/EtOAc=95:5) gave **14** (3.03 g, 89%).

Colourless oil $[\alpha]_D^{20} = +87.61$ ($c = 1.00$, $CHCl_3$); ^1H NMR: identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl)_3$ $\delta = -5.46$, -5.39, -5.35 (OSi-CH_3), -0.77 (Si-CH_3), 17.63 (*i*-Pr-CH_3), 18.28, 18.36 (*t*-Bu-C), 20.45 (C-5), 21.58 (*i*-Pr-CH_3), 25.87, 25.93 (*t*-Bu-CH_3), 27.08 (Si-CH_2), 27.25 (*i*-Pr-CH), 33.12 (C-6), 38.10 (C-3), 45.50 (C-4), 50.69 (OCH_3), 58.73 (CH_2O), 64.34 (CH_2O) 123.59 (C-2), 128.96 (-CH=), 138.68 (=C<), 147.61 (C-1), 169.48 (COO) ppm; $C_{31}H_{62}O_4Si_3$ (583.1); calcd.: C 63.86, H 10.72; found: C 64.03, H 10.71.

(3S,4R)-2-(Methoxycarbonyl)-4-(1-methylethyl)-1-((trimethylsilyl)methyl)-3-(3-(acetoxy)-2-((acetoxy)methyl)prop-1-en-1-yl)-cyclohex-1-ene (**15**)

Silylether **14** (3.03 g, 5.20 mmol) was converted to the acetate **15** as published previously ([7]; 1.85 g, 81%).

$[\alpha]_D^{20} = +120.0$ ($c = 1.071$, $CHCl_3$); ^1H NMR: identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -0.89$, (Si-CH_3), 17.44 (*i*-Pr-CH_3), 20.23 (C-5), 20.81, 20.86 (Ac-CH_3), 21.55 (*i*-Pr-CH_3), 27.18 (Si-CH_2), 27.43 (*i*-Pr-CH_3), 33.07 (C-6), 38.55 (C-3), 44.96 (C-4), 50.63 (OCH_3), 59.99 (CH_2O), 66.27 (CH_2O), 121.92 (C-2), 129.85 (=C<), 138.68 (-CH=), 149.44 (C-1), 168.98 (COO), 170.58, 170.80 (Ac COO) ppm; $C_{23}H_{38}O_6Si$ (438.6); calcd.: C 62.98, H 8.73; found: C 62.76, H 8.59.

(2S,3R,4R)-2-Methoxycarbonyl)-4-(1-methylethyl)-1-methylen-3-(3-acetoxy)-2-((acetoxy)methyl)-prop-1-en-1-yl) cyclohexane (**16**)

Allylsilane **15** (1.85 g, 4.21 mmol) was reacted as reported earlier [7] to the methylene derivative **16** (1.08 g, 84%).

$[\alpha]_D^{20} = +42.04$ ($c = 1.168$, $CHCl_3$); ^1H NMR: identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 15.34$ (*i*-Pr-CH_3), 20.69, 20.76 (Ac-CH_3), 21.36 (*i*-Pr-CH_3), 24.85 (C-5), 27.98 (*i*-Pr-CH), 35.06 (C-3), 43.18 (C-6), 46.52 (C-4), 51.21 (OCH_3), 55.68 (C-2), 60.03 (CH_2O), 65.88 (CH_2O), 108.22 (=CH_2), 131.44 (=C<), 136.48 (-CH=), 144.38 (C-1), 170.41, 170.58 (Ac COO), 172.48 (COO) ppm; $C_{20}H_{30}O_6$ (366.5); calcd.: C 65.55, H 8.25; found: C 65.84, H 8.02.

(5aR,6R,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-4-(hydroxymethyl)-6-(1-methylethyl)-9-methylen-1-oxo-2-benzoxepin (**17**)

Triester **16** (1.08 g, 2.95 mmol) was converted to the lactone **17** as published previously ([7]; 621 mg, 70%).

$[\alpha]_D^{20} = +59.24$ ($c = 1.001$, $CHCl_3$); ^1H NMR : identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.97$ (*i*-Pr-CH_3), 21.18 (*i*-Pr-CH_3), 24.76 (C-7), 27.18 (*i*-Pr-CH), 35.05 (C-8), 42.73 (C-5a), 47.54 (C-6), 49.01 (C-9a), 64.07 (C-3), 66.46 (CH_2OH), 110.74 (=CH_2), 131.11 (C-5), 136.60 (C-4), 142.65 (C-9), 173.00 (C-1) ppm; $C_{15}H_{22}O_3$ (250.3); calcd.: C 71.97, H 8.86; found: C 72.20, H 8.67.

(5aR,6R,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-9-methylen-1-oxo-2-benzoxepin-4-carbaldehyd (**18**)

Alcohol **17** (621 mg, 2.48 mmol) was oxidized to the aldehyde **18** as published previously ([7]; 529 mg, 86%).

$[\alpha]_D^{20} = +21.93$ ($c = 1.049$, $CHCl_3$); ^1H NMR: identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.00$ (*i*-Pr-CH_3), 21.02 (*i*-Pr-CH_3), 24.60 (C-7), 27.43 (*i*-Pr-CH), 34.50 (C-8), 43.99 (C-5a), 46.36 (C-6), 47.30 (C-9a), 58.86 (C-3), 112.13 (=CH_2), 138.76 (C-4), 140.75 (C-9),

156.15 (C-5), 171.85 (C-1), 191.29, (aldehyde) ppm; $C_{15}H_{20}O_3$ (248.3); calcd.: C 72.55, H 8.12; found: C 72.41, H 8.25.

(5aR,6R,9S,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro-(2-benzoxepin-9,2′-oxirane)-4-carbaldehyd (**19**)

Methylene derivative **18** (529 mg, 2.13 mmol) was oxidized to the epoxide **19** as reported previously ([7]; 304 mg, 54%).

Colourless crystals from *n*-hexane/CH_2Cl_2; m.p.: 107–110°C; $[\alpha]_D^{20} = +18.14$ ($c = 1.003$, $CHCl_3$); ^{1}H NMR : identical with the racemate [7]; ^{13}C NMR (75 MHz, $CDCl_3$ $\delta = 14.99$ (*i*-Pr-CH_3), 21.09 (*i*-Pr-CH_3), 22.11 (C-7), 27.31 (*i*Pr-CH), 33.05 (C-8), 42.48 (C-5a), 45.39 (C-9a), 46.56 (C-6), 52.12 (epoxide CH_2), 57.95 (C-9), 58.96 (C-3), 138.86 (C-4), 154.94 (C-5), 170.42 (C-1), 191.18, (aldehyde) ppm; $C_{15}H_{20}O_4$ (264.3); calcd.: C 68.16, H 7.63; found: C 68.23, H 7.42.

(5aR,6R,9S,9aS)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro-(2-benzoxepin-9,2′-oxirane)-4-carboxylic acid ((+)-Heptelidic acid, **1**)

Aldehyde **19** (304 mg, 1.15 mmol) was oxidized to (+)-heptelidic acid (**1**) as published previously ([7]; 310 mg, 96%).

Colourless amorphous powder; $C_{15}H_{20}O_5$ (280.3); calcd.: C 64.27, H 7.19; found C 64.10, H 7.44; crystallization from cyclohexane gave colourless crystals ((+)-**1**·3/8 cyclohexane, ^{1}H NMR); m.p.: 52–56°C; $[\alpha]_D^{20} = +16.97$ ($c = 1.002$, $CHCl_3$); Ref.: $[\alpha]_D^{20} = +7.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$ $\delta = 0.90$ (d, $J = 6.8$ Hz, 3H, *i*-Pr-CH_3), 0.99 (d, $J = 6.8$ Hz, 3H, *i*-Pr-CH_3), 1.43 (s, 4.5 H, cyclohexane-H), 1.47 (m, 1H), 1.53–1.67 (m, 1H), 1.82 (m, 1H), 1.93 (m, 1H), 2.14 (m, 1H), 2.60 (d, $J = 4.7$ Hz, 1H, epoxide-CH_2), 2.65 (m, 1H, H-5a), 3.58 (d, $J = 12.2$ Hz, 1H, H-9a), 3.84 (d, $J = 4.7$ Hz, 1H, epoxide-CH_2), 5.03 (d, $J = 15.5$ Hz, 1H, H-3), 5.10 (d, $J = 15.5$ Hz, 1H, H-3), 7.39 (d, $J = 2.8$ Hz, 1H, H-5), ppm; ^{13}C NMR (75 MHz, $CDCl_3$ $\delta = 15.09$ (*i*-Pr-CH_3), 21.09 (*i*-Pr-CH_3), 22.34 (C-7), 26.85 (cyclohexane-C), 27.43 (*i*-Pr-CH), 33.24 (C-8), 42.26 (C-5a), 45.34 (C-9a), 46.96 (C-6), 52.19 (epoxide-CH_2), 58.23 (C-9), 61.19 (C-3), 128.50 (C-4), 147.63 (C-5), 170.10 (COOH), 170.35 (C-1) ppm.

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