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# Synthesis of Optically Active Hydroxyalkyl Cycloheptatrienes: A Key Step in the Total Synthesis of 6,11-Methylene-LXB$_4$

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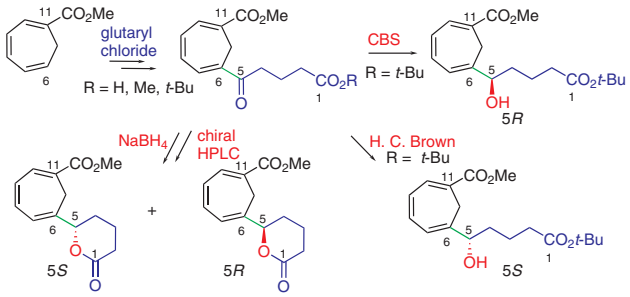
Dedicated to Prof. Dr. Helmut Vorbrüggen on the occasion of his 90th birthday

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**Abstract** Starting from methyl cycloheptatrienyl-1-carboxylate, 6-acylation was successfully achieved employing glutaryl chloride in the presence of $AlCl_3$ under controlled reaction conditions to furnish keto carboxylic acid product. After protection of this keto carboxylic acid as *tert*-butyl ester, reagent-controlled enantioselective reductions delivered configuration-defined methyl-6-hydroxylalkyl cycloheptatriene-1-carboxylates with up to 80% ee. Whereas simple $NaBH_4$ reduction of the keto carboxylic acid and subsequent lactonization afforded a methyl-6-tetrahydropyranonyl cycloheptatriene-1-carboxylate. Resolution using chiral HPLC delivered the product enantiomers with up to >99% ee Finally, ECD analyses enabled structure elucidation. The products are used as key intermediates in enantioselective 6,11-methylene-lipoxin $B_4$ syntheses.

**Key words** lipoxin analogue, cycloheptatriene, electrophilic acylation, enantioselective reduction, chiral HPLC, ECD analysis

Lipoxin A and Lipoxin B natural products are known as highly active arachidonic acid metabolites produced in human tissue for down regulation of inflammation processes.[2] The use of the original natural products as anti-inflammatory drugs hampers from the very short half life time within the organism.[3] The synthesis of more stable and still biologically active analogues represents a focus of recent and actual research.[4]

The introduction of a cycloheptatriene core in a lipoxin backbone might stabilize the crucial *E*,*E*,*Z*,*E* segment suppressing any *Z*–*E* isomerization of the 11,12 and 8,9 double bond in $LXA_4$ and $LXB_4$, respectively. Such an isomerization is known to be connected with a severe loss of biological activity (Figure 1).[5]

The syntheses of 9,14-methylene-lipoxin $A_4$ and 6,11-methylene-lipoxin $B_4$ require efficient access to suitable optically active building blocks. A configuration-defined methyl-6-(1-hydroxyalkyl) cycloheptatriene-1-carboxylate **D** served as a key intermediate in a 9,14-methylene-lipoxin $A_4$ total synthesis. Starting from cycloheptatriene **A**, a three-step sequence according the protocol of E. Vogel delivered methyl-cycloheptatriene-1-carboxylate **B**.[6] Acylation of the 6-position using hexanoyl chloride afforded ketone **C**,[5,7] which then was treated with H. C. Brown[8] and Corey–Bakshi–Shibata[9] reagents, respectively, to give the *epi*-(15*S*) and the (15*R*) enantiomers **D** with high ee. Always, the absolute configurations of the new stereogenic centers were elucidated via Mosher analyses (Scheme 1).[10]

Intending to use an analogous sequence for synthesizing both enantiomers of the C1–C12 segment of lipoxin $B_4$, methyl-cycloheptatrienyl-1-carboxylate **B** was chosen as starting reactant.[6] For C6 acylation glutaryl chloride, glutaryl chloride monomethyl ester, and glutaryl anhydride were envisaged as C1–C5 building blocks. All attempts involving glutaryl anhydride, a broadly varied set of Lewis acids, and reaction conditions in $CH_2Cl_2$ as solvent failed. The first progress was observed running the reaction at higher temperature in refluxing 1,2 dichloroethane. 12% (23% brsm) of keto acid **1** could be isolated after 50 h, 48% of

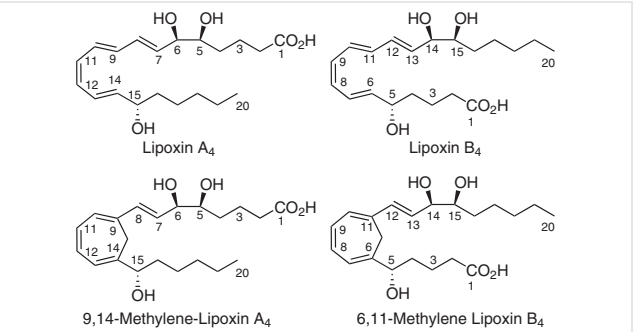



**Figure 1** Lipoxins $A_4$ and $B_4$ and methylene-bridged analogues



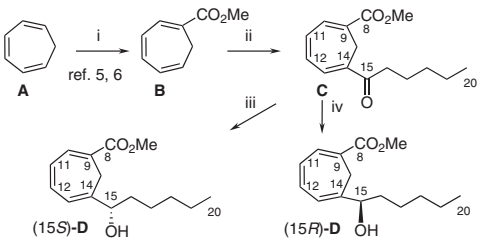
starting ester **B** remained.[11] Extension of the reaction time caused increased formation of side products and decomposition. The C6 acylation using glutaryl chloride monomethyl ester required harsh reaction conditions, too. Addition of ester **B** to a mixture of acid chloride and $AlCl_3$ in 1,2-dichloroethane afforded keto diester **2** with 11% yield (35% brsm, 68% of **B** remained) after aqueous workup. Longer reaction times caused the undesired formation of side products and degradation.[12]

Best results were achieved employing glutaryl chloride as reactant. The reaction was found to require less harsh conditions: $AlCl_3$ in refluxing $CH_2Cl_2$. Analyzing the mixture after 4 h reaction time, the product ketocarboxylic acid **1** was isolated with 37% yield (70% brsm). Furthermore, keto chloride **3** and chloro enollactone **4** were found as side products with 1% (2% brsm) and 16% (30% brsm) yield. About 47% of reactant ester **B** could be recovered. Prolongation of the reaction time caused increased formation of enollactone **5** (13.5%, 22% brsm), several regioisomers and degradation products.[13] In selected runs, the glutaryl chloride/$AlCl_3$ method in refluxing $CH_2Cl_2$ gave the desired product ketocarboxylic acid **1** in up to 73% yield (Scheme 2).[14]

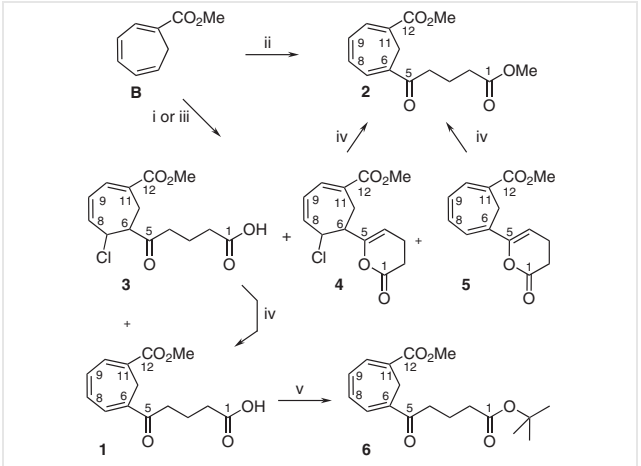
The chloro acyl compounds **3** and **4** had been used as valuable intermediates to generate the desired product cycloheptatrienes **1** and **2**. Upon treatment with NaOMe in MeOH, chloroacid **3** underwent β-elimination to give keto acid **1** (83% yield), chloro enollactone **4** was converted into ketoester **2** with 85% yield, respectively. Surprisingly, basic transesterification of enollactone **5** delivered ketoester **2** with 15% yield only, most of the material formed displayed the corresponding enol of ketoester **2** (not shown).[15]

Before investigating enantioselective reductions of the keto group, the acid function of **1** had been protected as *tert*-butyl ester **6** with 82% yield (Scheme 2).

Development of the enantioselective ketone reductions required generation of a racemic standard first. Treatment of *tert*-butyl ketoester **6** with $NaBH_4$ in MeOH afforded racemic *tert*-butyl hydroxyester **7** with 96% yield (Table 1, entry 1). Since the OH group represents an ideal anchoring position, the present racemate was analyzed using Eu(hfc)$_3$ shift reagents.[16] Careful optimization of the experimental conditions enabled baseline separation of the C5 protons of the (*R*)-**7** and (*S*)-**7** enantiomers enabling determination of the enantiomeric ratio by simple peak integration.[12]

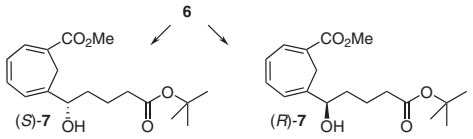



**Scheme 1** Synthesis of 15*S* and 15*R* C8–C20 segment of 9,14-methylene-lipoxin $A_4$. *Reagents and conditions*: i) three-step sequence according to ref. 5, 6 (acylation, haloform reaction, ester formation); ii) acylation with hexanoyl chloride/$AlCl_3$; iii) enantioselective reduction according H. C. Brown; iv) enantioselective reduction according Corey, Bakshi, and Shibata.




**Scheme 2** C6-Acylation of methyl-cycloheptatriene-1-carboxylate **B**. *Reagents and conditions*: i) glutaric anhydride, $AlCl_3$, 1,2-DCE, 0 °C to reflux 50 h; **1**: 12% (48% of remaining **B**); ii) glutaryl chloride monomethyl ester, $AlCl_3$, 1,2-DCE, 0 °C to reflux, 3 h; **2**: 11% (68% of remaining **B**); iii) glutaryl chloride, $AlCl_3$, $CH_2Cl_2$, 0°C to reflux, 4 h; **1**: 37%, **4**: 16%, **3**: 1% (47% of remaining **B**); extended reaction time of 44 h: **1**: 18.5%; **5**: 13%, + regioisomers, 40% of remaining **B**; iv) NaOMe, MeOH, 23 °C, 0.5–1.5 h; **1**: 83% (from **3**); **2**: 85% (from **4**), 5 h; **2**: 15%, 50% enol of **2** – not shown (from **5**); v) isobutene, cat. $H_2SO_4$, $CH_2Cl_2$, –5 °C to 23 °C, 3 h; **6**: 82%.

**Table 1** Enantioselective Reduction of Ketoester **6**




| Entry | Reagent[a] | Temp (°C) | Yield (%)[b] | e.r. (*S*-**7**/*R*-**7**)[c] | $[\alpha]_D$ |
|---|---|---|---|---|---|
| 1 | $NaBH_4$ | 0 | 96 | 1:1 | 0 |
| 2 | (–)-(Ipc)$_2$BCl | 0 | 85 | 2.5:1 | 2.7 |
| 3 | (–)-(Ipc)$_2$BCl | –25 | 19 | 7.5:1 | 11.6 |
| 4 | (–)-CBS/BMS | 0 | 67 | 1:6 | –7.3 |
| 5 | (–)-CBS/BMS | –40 | 17 | 1:4 | –7.2 |
| 6 | (–)-CBS/BMS | –60 | 18 | 1:2 | –2.1 |
| 7 | (–)-CBS/$BH_3$–DEA | 0 | 51 | 1:9 | –14.2 |
| 8 | (–)-CBS/$BH_3$–DEA | –40 | 0 | no reaction | – |

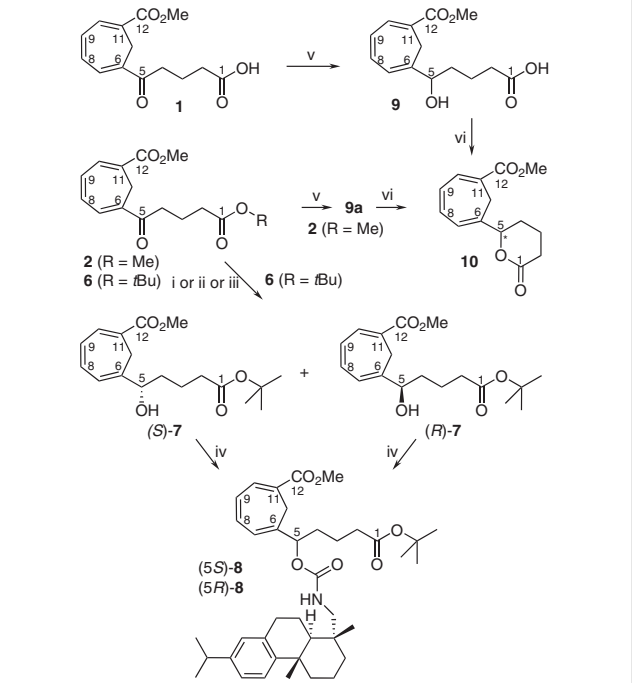
[a] (–)-(Ipc)$_2$BCl: diisopinocampheyl boron chloride; (–)-CBS: Corey–Bakshi–Shibata borolidine; BMS: $H_3B{\cdot}SMe_2$; DEA = *N*,*N*-diethylaniline.
[b] Yields based on reactant **6** used. Entries 3, 5, 6, 7: remaining reactant **6** (20–55%).
[c] The e.r. based on Eu(hfc)$_3$ shift experiments; hfc = 3-(heptafluoropropylhydroxymethylen)-(+)-campherato.

Intending to induce a resolution of the enantiomers, the racemic carbinol **7** was reacted with freshly prepared dehydroabietylamine isocyanate.[17] Carbamate **8** formation was finished upon heating in toluene with 76% yield. The (5*R*)-**8** and (5*S*)-**8** diastereomers (ratio 1:1) could be carefully separated via preparative HPLC. Unfortunately, the carbamates **8** did not crystallize. Any structure elucidation concerning the absolute configuration of the new C5-stereogenic centers failed (X-ray, NMR techniques).

The enantioselective generation of (5*S*)-hydroxy ester (*S*)-**7** was carried out employing H. C. Brown's procedure.[8] Running the reduction at 0 °C using 2 equivalents of (–)-DIPCl ((–)-$(Ipc)_2BCl$, diisopinocampheyl boron chloride) gave carbinol **7** with 85% yield. Unfortunately, only about 2.5:1 e.r. (5*S*)-**7**/(5*R*)-**7** according to NMR shift-reagent analysis was found (Table 1, entry 2). A further experiment applying lower reaction temperature of –25 °C resulted in a higher e.r. of about 7.5:1, but the reaction turned to be very slow. A yield of 19% only was observed after 7 d of reaction time, the reaction had been stopped before complete consumption of starting ester **6** (Table 1, entry 3).[18]

The (5*R*)-hydroxy ester (*R*)-**7** was synthesized using Corey–Bakshi–Shibata (CBS) reduction.[9] Running the standard reaction ($H_3B{\cdot}SMe_2$) at 0 °C, a yield of 67% and an e.r. of about 1:6 (5*S*)-**7**/(5*R*)-**7** according to NMR shift-reagent analysis was detected (Table 1, entry 4).[19] Surprisingly, lower reaction temperatures led to slower reaction and decreased the e.r. of 1:4 (–40 °C) and 1:2 (–60 °C), respectively (Table 1, entries 5 and 6). Obviously, a racemic background reaction gained preference. In contrast, application of $H_3B$–diethylaniline as reducing agent resulted a higher e.r. of 1:9 (5*S*)-**7**/(5*R*)-**7** in combination with a somewhat lower yield (Table 1, entry 7). In comparison with the results of the $LXA_4$ analogue synthesis, the e.r. found within the actual series are somewhat lower despite of broad variation of the reaction conditions.[5a] In contrast to the inert *n*-pentyl side chain as present in the $LXA_4$ precursors, the achiral *tert*-butyl ester donor moiety of ketone **6** might have competed against the chirality-inducing pyrrolidine within complexation of the borane decreasing the crucial influence of the chiral ligands. For details see Table 1 and Scheme 3.

Another option to overcome the problems with the laborious enantioselective reductions is a resolution of the racemic material via chiral HPLC. Here, a simple $NaBH_4$ reduction of both keto carboxylic acid **1** and the corresponding methyl ester **2** delivered the product racemic carbinols **9** with 78% and the corresponding methyl ester (**9a**, not shown) with 96% yield.[20] Subsequent heating of the intermediates in refluxing toluene delivered δ-valerolactone ester **10** with 88% yield (from hydroxy acid **9**) and 93% yield (from hydroxy ester **9a**), respectively. Chiral HPLC using (*S*,*S*)-Whelk-O1 column and EtOAc/hexane as mobile phase enabled to achieve a complete separation of (+)- and (–)-lactones **10** with >99% and >96% ee (Scheme 3 and Figure 2).[21]




**Scheme 3** Reduction of the C5 ketone. *Reagents and conditions*: i) $NaBH_4$, MeOH, 0 °C, 4 h; *rac*-**7**: 96% (from **6**); ii) (–)-$(Ipc)_2BCl$, THF, ketoester **6**, 0 °C, h; **7**: 85%, d.r. = 2.5:1 (*S*/*R*); iii) (1*R*)-CBS-$BH_3$, $BH_3$, THF, –15 °C, 0.5 h, then ketoester **6**, THF, 0 °C, 18 h; **7**: 67%, d.r. = 1:6 (*S*/*R*); for further experiments, see Table 1; iv) dehydroabietylamine, $C(O)Cl_2$, pyridine, $CH_2Cl_2$, 0–23 °C, 2 h, then *rac*-**7**, PhMe, reflux, 24 h; 76% (5*S*-**8**/5*R*-**8** = 1:1; from *rac*-**7**); v) $NaBH_4$, MeOH, 0–23 °C, 2 h, 78% of hydroxy acid **9** from **1**; 96% hydroxymethyl ester **9a** (not shown) from **2**; vi) PhMe, reflux, 17 h, 88% *rac*-**10** (from **9**), 96 h; 93% *rac*-**10** (from hydroxymethyl ester **9a**); from **1**: reduction and lactonization without purification of intermediate **9**: 76% of *rac*-**10** (2 steps).

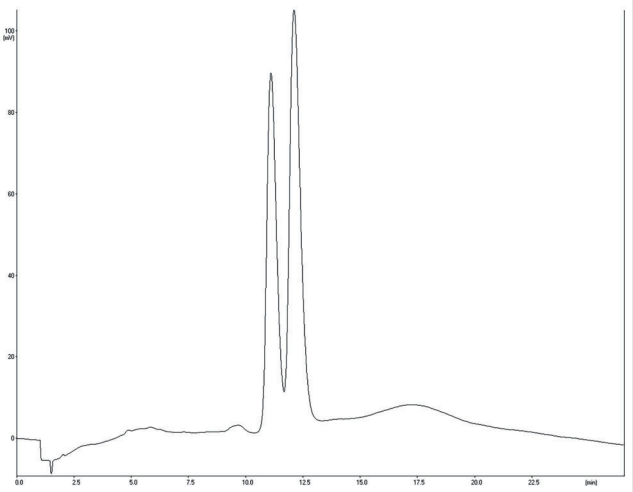


**Figure 2** Separation of (5*R*)- and (5*S*)-δ-valerolactone esters (**10**): (*S*,*S*) Whelk-O1, 100–10 m, 4.6 × 250 mm, 15% EtOAc/hexane, 2 mL/min, 25 bar, UV 254 nm, $k_R$ = 4.36, $k_S$ = 5.07.

For structure elucidation experimental and computational CD spectroscopy had been applied.[22] Comparison of the experimental CD curves of (+)- and (–)-δ-valerolactone esters **10** with the calculated versions for (5*R*)- and (5*S*)-δ-valerolactone esters **10** showed excellent matching for (+)-(5*R*)-**10** and (–)-(5*S*)-**10** (Figure 3).

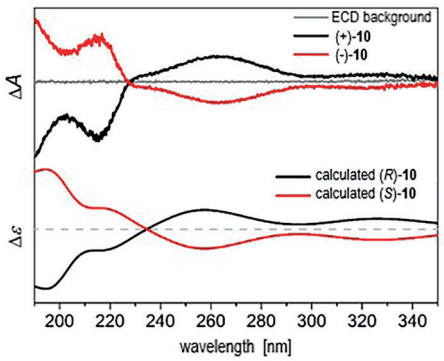



**Figure 3** ECD spectra of the enantiomers of δ-valerolactone esters **10**. Experimental: MeCN, *c* 1.0 mmol/L, scan rate 20 nm/s. Calculated: 17 conformers TD-B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p) level.

The introduction of a cycloheptatriene core in a lipoxin backbone required syntheses of suitably 1,6-disubstituted key fragments. Starting from known methyl-1,3,5-cycloheptatriene-1-carboxylate, C6 acylation involving glutaric acid derivatives still occurred as a challenging process, a bouquet of compounds was formed applying slightly varied reaction conditions. Intending to avoid formation of various degradation and rearrangement products, acylation using glutaryl chloride had to be stopped after about 50 % conversion of the reactant ester **B**.[23] Despite generation of a mixture of ketoacid **1**, acid chloride adduct **3**, and enol lactones **4** and **5**, most of these compounds could be used to build-up δ-lactone ester **10**. Overall, ester **B** had been converted into lactone **10** with 77% yield via two major reaction paths (via acid **1** and ester **2**, respectively).

For generation of the optically active C5 hydroxy function of the C1–C12 segment of the $LXB_4$ analogue, two strategies had been tested. Enantioselective reductions of the C5 keto group of ester **6** using H. C. Brown and CBS methods gave the desired 5*S*- and 5*R*-carbinols **7** with up to about 80% ee. Until now, laborious reactions, costly reagents, and moderate yields can be regarded as the major disadvantages. Furthermore, a final purification via preparative chiral HPLC was necessary to produce the key compounds with >95% ee. In contrast, the racemic sequence could be managed employing simple reactions and reagents upon generating racemic lactone **10** with high yield. Major challenge was the resolution of both enantiomers **10** via chiral preparative HPLC: (–)-(*S*)-**10**: 96% ee, (+)-(*R*)-**10**: >99% ee determined via ECD methods.

In summary, the racemic sequence in combination with the chiral HPLC gave both enantiomers **10** with 38% yield, in each case. The enantioselective CBS sequence affords about 42% yield of 5*R* material **7** and the Brown reduction 16% of 5*S* product **7**. The optically active C1–C12 key fragments are used in a 6,11-methylene-lipoxin $B_4$ total synthesis.[24]

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## Supporting Information

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(11) Most C6 acylations of methyl-cycloheptatriene-1-carboxylate **B** had been stopped after about 50% conversion. Always, remaining **B** had been recycled. The standard yields presented within the manuscript based on originally used **B**. Additionally, yields based on recovered starting material (brsm) are given in brackets.

(12) For experimental details and data see the Supporting Information.

(13) All cycloheptatriene derivatives suffer from reversible 6π-electrocyclization (norcaradiene intermediates). In the presence of nucleophiles such as chloride Michael–addition/elimination cyclopropane ring opening, etc. potentially cause the formation of regioisomeric norcaradienes and cycloheptatrienes (e.g., 1,3-diacyl, 2,7-diacyl). Longer reaction times led to the formation of further isomers.

(14) **Synthesis of Keto Acid 1**

Under Ar, in a three-necked flask equipped with a reflux condenser aluminum(III) chloride (6.66 g, 49.94 mmol, 1.5 equiv) was suspended in dry $CH_2Cl_2$ (100 mL) and cooled in an ice-bath. Glutaryl chloride (6.37 mL, 49.94 mmol, 1.5 equiv) was added, and the mixture was stirred at 0 °C for about 1 h until complete dissolution of aluminum(III) chloride. Then, the reaction mixture was heated to reflux and methyl ester **B** (5.00 g, 33.29 mmol, 1.0 equiv) dissolved in dry $CH_2Cl_2$ (20 mL) was added. Refluxing was continued for 4 h. After cooling of the reaction mixture to –10 °C, acetic acid (15 mL) was added slowly with stirring. After 30 min, water (100 mL) was added at –10 °C, and stirring was continued for another 30 min. Then the layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed (brine) and dried ($MgSO_4$). After removal of the solvent the residue was purified via column chromatography (EtOAc/petroleum ether, 1:5 to 1:2). Yields: re-isolated methyl ester **B** (2.37 g, 15.78 mmol, 47%), keto carboxylic acid **1** (3.24 g, 12.26 mmol, 37% (70% brsm)), chloro keto carboxylic acid **3** (0.11 g, 0.33 mmol, 1% (2% brsm)), chloro enollactone **4** (1.47 g, 5.20 mmol, 16% (30% brsm)).

**6-(1,5-Dioxo-5-hydroxypentyl)-1,3,5-cycloheptatriene 1-Carboxylic Acid Methyl Ester (1)**

Yellow oil; $R_f$ = 0.31 (EtOAc/petroleum ether, 1:5).$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 1 H, H-10), 7.18–7.13 (m, 1 H, H-8), 6.93–6.88 (m, 2 H, H-7, H-9), 3.80 (s, 3 H, H-14), 3.01 (s, 2 H, H-13), 2.86 (t, $^3J_{HH}$= 7.1 Hz, 2 H, H-4), 2.44 (t, $^3J_{HH}$= 7.1 Hz, 2 H, H-2), 1.99 (tt, $^3J_{HH}$= 7.1 Hz, 2 H, H-3). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 198.0 (C-5), 178.6 (C-1), 166.0 (C-12), 133.8 (C-9), 133.6 (C-8), 133.4 (C-6), 133.2 (C-10), 132.0 (C-7), 125.6 (C-11), 52.3 (C-14), 37.2 (C-4), 32.9 (C-2), 24.7 (C-13), 19.2 (C-3). IR (neat): ν = 3011 (m), 2988 (m), 2947 (w), 1717 (s, br), 1589 (m), 1438 (w), 1276 (s), 1261 (s), 1038 (w), 749 (s), 703 (m), 624 (w) cm$^{-1}$. MS (FD, 5 kV/8 mA/min): *m/z* (%) = 264.4 (100) [M]$^+$, 265.4 (57) [M + H]$^+$. HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_5Na$: 287.0895; found: 287.0887. For further data, see the Supporting Information.

(15) For data of enol ester, see the Supporting Information. Furthermore, cleavage of enol lactone **5** was run under acidic conditions (AcCl, MeOH, 50 °C) delivering **2** in 12%, enol ester of **2** in 42% yield and several isomers.

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(18) **H. C. Brown Reduction: (1'*S*)-6-(5-*tert*-Butyloxy-5-oxo-1-hydroxypentyl)-1,3,5-cycloheptatriene 1-carboxylic acid methyl ester ((*S*)-7)**

Under Ar, to a solution of (–)-diisopinocampheylchloroborane (0.15 g, 0.47 mmol, 1.5 equiv) in dry THF (2 mL) was added ketoester **6** (0.10 g, 0.31 mmol, 1.0 equiv) in dry THF (2 mL) at –25 °C with stirring. After seven days the solvent was removed in vacuo and replaced by EtOAc (5 mL). Then, diethanolamine (0.07 g, 0.63 mmol, 2.2 equiv) was added and stirred at room temperature for 2 h in which a white precipitate formed. The solid was filtered off and washed with $Et_2O$. The solvent was removed in vacuo, and α-pinene could be removed in high vacuum (8 × 10$^{-3}$ mbar, 5 h). The residual crude product was purified via column chromatography (EtOAc/petroleum ether, 1:4) affording hydroxyester (*S*)-**7** (0.02 g, 0.06 mmol, 19%) as a colorless oil. $R_f$ = 0.20 (EtOAc/petroleum ether, 1:4). $[\alpha]_D$ = +11.6° (*c* 1.0, 25 °C, $CH_2Cl_2$, ee 40%). For further analytical data, see the Supporting Information.

(19) **CBS Reduction: (1'*R*)-6-(5-*tert*-Butyloxy-5-oxo-1-hydroxypentyl)-1,3,5-cycloheptatriene 1-Carboxylic Acid Methyl Ester ((*R*)-7)**

Under Ar, (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborol (0.02 g, 0.07 mmol, 0.1 equiv) was dissolved in dry toluene (1 mL) and treated with borane dimethylsulfide (0.05 g, 0.63 mL, 0.84 mmol, 1.2 equiv 2 M) at 0 °C. After 1 h ketoester **6** (0.23 g, 0.70 mmol, 1.0 equiv) was added to the mixture and stirred for 5 h at 0 °C. Workup started by quenching with methanol (2 mL) and after 15 min 1 M hydrochloric acid. The aqueous layer was extracted with toluene (3 × 5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:9) affording hydroxyester (*R*)-**7** (0.15 mg, 0.42 mmol, 67%) as a colorless oil. $R_f$ = 0.20 (EtOAc/petroleum ether, 1:4). $[\alpha]_D$ –7.3° (*c* 1.0, 25 °C, $CH_2Cl_2$, ee 71%). For further analytical data, see the Supporting Information.

(20) **6-(1,5-Dihydroxy-5-oxopentyl)-1,3,5-cycloheptatriene 1-Carboxylic Acid Methyl Ester (9)**

The ketoacid **1** (1.03 g, 3.90 mmol, 1.0 equiv) was dissolved in methanol (60 mL) and cooled to 0 °C. Sodium borohydride (0.44

g, 11.70 mmol, 3.0 equiv) was added in small portions. The reaction stirred for 1 h at 0 °C and for 1 h at room temperature. Afterwards methanol was removed in vacuo. The residue was taken up in water and acidified with 1 M hydrochloric acid. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent alcohol **9** (0.82 g, 3.06 mmol, 78%) was obtained as a colorless oil. $R_f$ = 0.18 (EtOAc/petroleum ether, 1:2). $^1$H NMR (300 MHz, $CD_3OD$): δ = 7.22 (d, $^3J_{HH}$ = 5.9 Hz, 1 H, H-10), 6.82 (dd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H-8), 6.63 (ddd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 0.8 Hz, 1 H, H-9), 6.26 (dd, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 0.8 Hz, 1 H, H-7), 4.21 (t, $^3J_{HH}$ = 6.4 Hz, 1 H, H-5), 3.77 (s, 3 H, H-14), 3.24 (d, $^2J_{HH}$ = 13.1 Hz, 1 H, H-13'), 2.24 (t, $^3J_{HH}$ = 7.3 Hz, 2 H, H-2), 2.16 (d, $^2J_{HH}$ = 13.1 Hz, 1 H, H-13''), 1.97–1.37 (m, 4 H, H-3, H-4). $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 175.7 (C-1), 167.9 (C-12), 143.6 (C-6), 136.2 (C-10), 136.2 (C-8), 129.3 (C-9), 123.1 (C-7), 123.0 (C-11), 76.0 (C-5), 52.6 (C-14), 35.9 (C-4), 34.6 (C-2), 27.7 (C-13), 22.5 (C-3). IR (neat): ν = 3443 (b), 3024 (w), 2951 (w), 1705 (s), 1615 (w), 1542 (w), 1436 (m), 1277 (s), 1245 (m), 1212 (s), 1162 (s), 1090 (s), 1038 (m), 741 (s) cm$^{-1}$. MS (FD 5 kV/8 mA/min): m/z (%): 287.1 (100) $[M+Na]^+$. HRMS-ESI $C_{14}H_{16}O_5Na$ calcd.: 287.0887, found: 287. 0895.

(21) **6-(3,4,5,6-Tetrahydropyran-2-on-6-yl)-1,3,5-cycloheptatriene 1-Carboxylic Acid Methyl Ester (10)**

The alcohol **9** (0.82 g, 3.06 mmol) was dissolved in toluene (50 mL) and heated to reflux for 17 h until no alcohol could be detected (TLC). The solvent was removed in vacuo and the residue purified via column chromatography (EtOAc/petroleum ether, 1:2) to afford racemic lactone **10** (0.67 g, 2.71 mmol, 88%). The enantiomers could be separated via chiral HPLC. $R_f$ = 0.40 (EtOAc/petroleum ether, 1:2). HPLC: racemic purification (Nucleosil 50/5, 4 × 250 mm, 2 mL/min, 133 bar) k = 2.50 (40% EtOAc/Hex), chiral HPLC: (*S*,*S*-Whelk-O1, 20 × 280, 30 mL/min, 64 bar) $k_{5R}$= 5.79, $k_{5S}$ = 6.42 (15% EtOAc/Hex). $[\alpha]_D$ (5*R* enantiomer) = +72.2° (*c* 0.9, 25 °C, $CH_2Cl_2$, ee 100%), $[\alpha]_D$ (5*S* enantiomer) = –71.1° (*c* 1.0, 25 °C, $CH_2Cl_2$, ee 96%), mp 83–85 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, H-10), 6.80 (dd, $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 5.9 Hz, 1 H, H-8), 6.65 (ddd, $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 0.8 Hz, 1 H, H-9), 6.31 (d, $^3J_{HH}$ = 5.9 Hz, 1 H, H-7), 5.01–4.87 (m, 1 H, H-5), 3.78 (s, 3 H, H-14), 3.06 (d, $^2J_{HH}$ = 13.5 Hz, 1 H, H-13'), 2.73–2.45 (m, 2 H, H-2), 2.37 (d, $^2J_{HH}$ = 13.5 Hz, 1 H, H-13''), 2.10–1.96 (m, 1 H, H-4'), 1.96–1.78 (m, 3 H, H-4'', H-3). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C-1), 166.3 (C-12), 136.2 (C-6), 134.4 (C-8), 133.4 (C-10), 129.1 (C-9), 122.7 (C-7), 121.9 (C-11), 82.7 (C-5), 52.1 (C-14), 29.5 (C-2), 27.4 (C-4), 26.9 (C-13), 18.5 (C-3). IR (neat): ν = 3014 (w), 2951 (w), 2859 (w), 1732 (s), 1706 (s), 1538 (w), 1437 (m), 1278 (s), 1213 (s), 1162 (w), 1096 (m), 1052 (m), 933 (w), 740 (s), 627 (w), 602 (w) cm$^{-1}$. HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_4Na$: 271.0946; found: 271.0939.

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(23) Obviously, the formation of side products from starting material and products was a slow process. Thus, short reaction times enabled to avoid the generation of rearrangement and degradation products. Disadvantage was the incomplete consumption of reactant **B**. However, excess of **B** had been recycled enabling to avoid severe loss of starting material.

(24) The total synthesis of 6,11-methylene-lipoxine $B_4$ will be published in due course.