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Synthesis of Enantiopure 6,11-Methylene Lipoxin B_4 Methyl Ester

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Dedicated to Prof. Dr. Horst Kunz on the occasion of his 80th Birthday.

The synthesis of Lipoxin B_4 analogs (LXB_4) to gain access to stabilized inflammation resolving compounds is an actual field of research. Focusing on variation and stabilization of the conjugated *E,Z,E,E* C6–C13 tetraene moiety of natural LXB_4, a methylene bridge introduced between C6 and C11 suppresses any *Z/E* isomerization of the C8–C9 olefin. Intending to enable prospective structure variations in connection with the C1–C5 and C14–C20 fragments, a convergent total synthesis has been developed. Optically active C1–C12 building blocks were build-up from cycloheptatriene 1-carbonester (C6–C11, C21) and glutaryl chloride (C1–C5) using Friedel-Crafts-type acylation and chiral HPLC. The C13–C20 segment had been generated via a five-step sequence starting from heptanoyl chloride. Horner key olefination enabled the assembly of the carbon backbone. A final five-step sequence including a chelate Cram reduction of the unsaturated ketone moiety afforded the target 6,11-methylene LXB_4 methyl ester.

Introduction

Acute inflammation is the protecting response of an organism against (local) tissue injury by various noxae such as physical injuries, chemical, and biotoxins as well as infections (bacteria, parasites, viruses).[1] Local inflammation can be described as a two-phase process.[1] Initiation is characterized by the activation of cytokines, chemokines, and the biosynthesis of pro-inflammation mediators (increasing levels of prostaglandins, leucotrienes from arachidonic acid) recruiting macrophages.[2,3] The second so-called resolution phase has to reverse the inflammatory response to initiate cellular repair.[4] In this connection so-called specialized pro-resolving mediators (SPMs: lipoxins from arachidonic acid, resolvins, protectins, maresins, likewise from eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, respectively) are biosynthesized.[5]

A poorly controlled return to homeostasis may develop into chronic inflammation with probable further severe tissue damage.[6] Actual investigations focus on the activation of the pro-resolving factors. Focusing on SPMs, biosynthesis of these compounds can be up-regulated, or the SPMs themselves can be used as drugs boosting the concentrations of pro-resolving mediators for accelerating termination of the acute inflammation.[7,8]

Lipoxin A_4 (LXA_4) and lipoxin B_4 (LXB_4) derived from arachidonic acid are known as potent pro-resolving mediators involved in inflammation resolution.[9] LXA_4 and LXB_4 had been isolated by Serhan, Samuelsson et al. from human leukocytes.[10] Structure elucidation gave 5(*S*),6(*R*),15(*S*) trihydroxy eicosa-7(*E*),9(*E*),11(*Z*),13(*E*) tetraenoic acid (LXA_4) and 5(S),14(R),15(S) trihydroxy eicosa-6(*E*),8(*Z*),10(*E*),12(*E*) tetraenoic acid (LXB_4), the so-called aspirin-triggered 15-*epi*-LXA_4 (15(*R*)) and 15-*epi*-LXB_4 (15(*R*)) had been discovered later (Figure 1).[11] Various publications elucidated the biosyntheses starting from arachidonic acid[12] as well as metabolism and degradation within the organism.

Until now, most research efforts concerning bio and chemical syntheses, metabolism as well as bioactivities focus on LXA_4, epimers, and defined analogs.[13,14] In comparison to the LXA_4 series, LXB_4 epimers and analogs are less intensely investigated. To date, a potential receptor is unknown, LXB_4 is described to be less stable, a limited number of analogs had

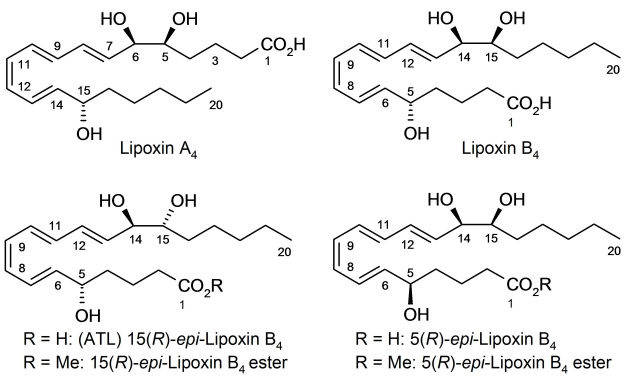

Figure 1. Lipoxins A_4 and B_4, C5 and C15 epimers (ATL: aspirin-triggered Lipoxin B_4), R = H, R = Me: methyl esters of LXB_4 epimers.

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been synthesized.[15] Since SPMs such as LXB_4 are discussed as potential new therapeutics to target pathogenic cells and potentiate resolution of chronic inflammation, the syntheses of desirable (bio)active LXB_4 analogs should be promoted.[16]

Since isolation, structure, and biological activity elucidation, chemical syntheses of LXB_4 have been published.[17] The rapid metabolism of the native material motivated the suggestion of a series of less sensitive and bioactive analogs.[18] Patent literature subdivided the LXB_4 core into a pharmacophore fragment (C5–C14) and metabolic transformation regions C14/15–C20, and C1–C4/5).[19] A detailed segmentation is given in Figure 2: Enhanced metabolic stability was addressed by introducing an ester, an amide, or an oxime function at C1 (carboxyl segment). A methyl group at C5, O5, and C15, respectively, as well as the exchange of C3 against O and the replacement of C17–C20 against suitable arene systems should suppress metabolism via dehydrogenation, β- and ω- oxidations (C14/15–C20 and C1–C4/5 segments).[20] Replacing a suitable triene segment by an arene, introduction of further double bonds, methyl, and aryl groups within C6–C13 as well as ring closures (e.g. a $(CH_2)_3$ segment between C9 and C12) should prevent the *Z* C8/C9 double bond from crucial *Z/E* isomerization (C5–C14 segment).[21]

Most efforts focus on the maintenance/optimization of the pharmacophore (C5–C14) Until now, limited information concerning the syntheses of such compounds is found within the literature. In this connection, a stereoselective total synthesis of *Z/E* isomerization stable 6,11-methylene LXB_4 was developed in our group. The convergent synthesis should enable the generation of stereoisomers as well as additional analogs using the same strategy as a new basis for investigation within the LXB_4 field.

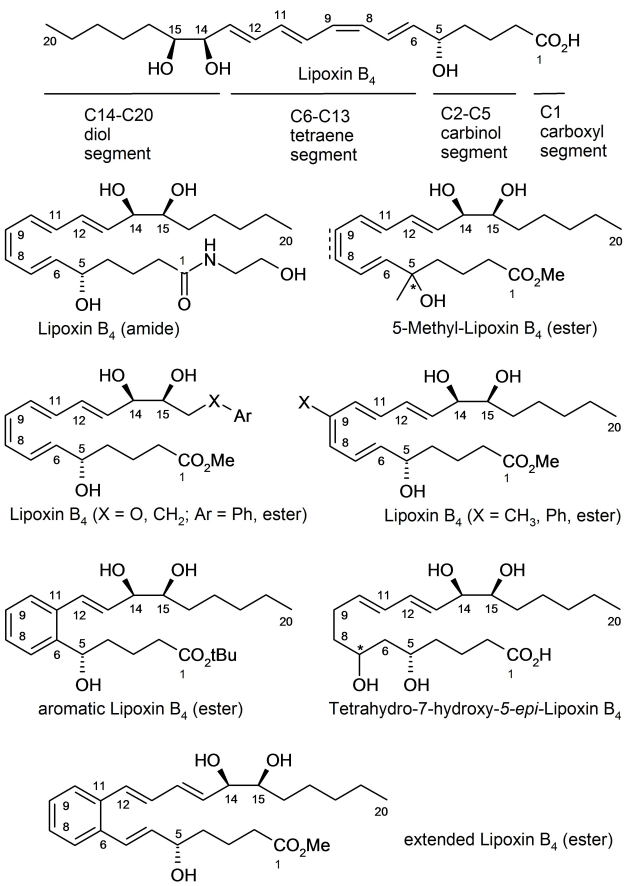


Figure 2. Lipoxin B_4 and analogues: metabolic stabilization (C1, C2–C5, C14–C20 segments) and modification of the pharmacophore (C6–C13 segment).

Results and Discussion

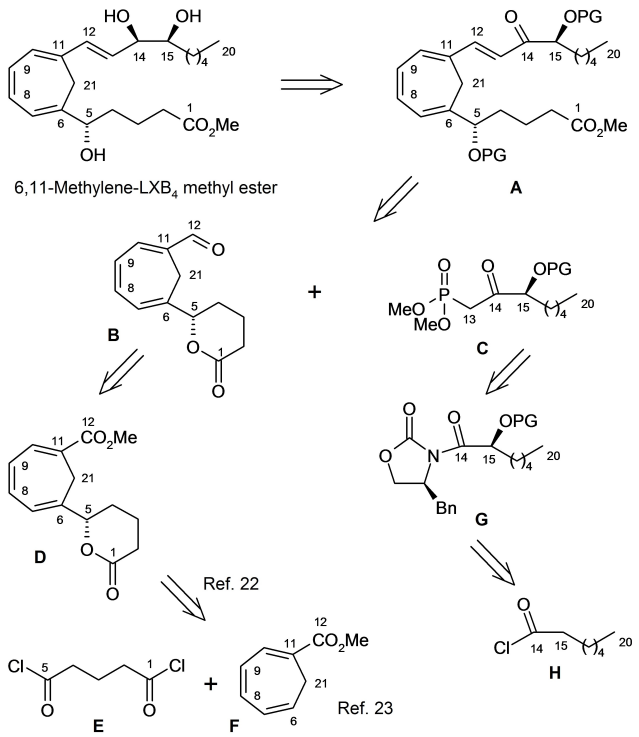
The synthesis of 6,11-methylene LXB_4 was planned in a convergent manner enabling the introduction of various C1–C5 and C14–C20 fragments. Because of the potential lability of the vinylcycloheptatriene moiety, the tetraene should be completed at a late stage of the total synthesis. Furthermore, the OH groups had to be protected as esters or silyl ethers to achieve a (single step) global final cleavage.

The retrosynthesis of 6,11-methylene LXB_4 methyl ester starts with a diastereoselective reduction of ketoester **A**. Then, an olefination key step at C12/C13 disconnects the target in a C1–C12 aldehyde **B** and a C13–C20 ketophosphonate **C**. Aldehyde **B** had been built-up from an ester lactone **D** via an activation reduction sequence. Lactonoester **D** is the C6 acylation product of methyl cycloheptatrienyl 1-carboxylate **F** using glutaryl chloride **E** (C1–C5) and a proceeding reduction/cyclization as described recently.[22,23]

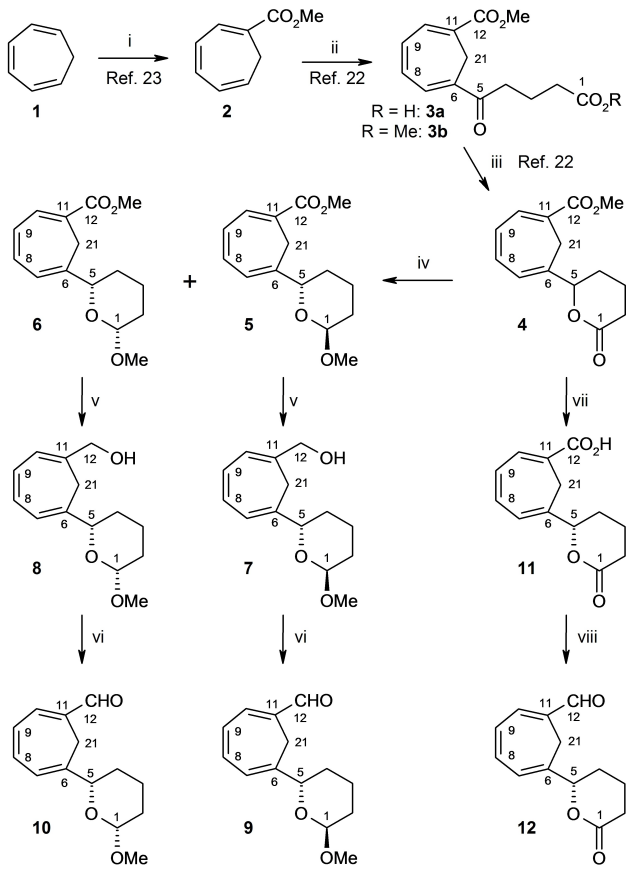
Ketophosphonate **C** is the Corey-Kwiatkowski condensation product of dimethyl methane phosphonate (C13) and the known protected α-hydroxyester (C14–C20, not shown)[24] derived from oxazolidinyl heptanoate **G**.[25a] The defined configured OH function at C15 had been introduced using Davis oxaziridine in combination with the *N*-oxazolidonyl heptanoate (Evans auxiliary strategy).[25a] Finally, heptanoyl chloride **H** served as C14–C20 starting material (Scheme 1).[25b]

The synthesis of the C1–C12 fragment **B** started from cycloheptatriene **1** adapting the well-known sequence published by E. Vogel et al.[23] A three-step sequence of C1 acetylation with acetyl chloride and $ZnCl_2$, a haloform reaction with Br_2/aq. NaOH and esterification with MeOH/AcCl afforded methyl cycloheptatriene 1-carboxylate **2** with about 40% yield overall. The second acylation using glutaryl chloride and $AlCl_3$ in refluxing CH_2Cl_2 enabled to generate ketocarboxylic acid **3a** with up to 73% yield.[22,26] $NaBH_4$/MeOH reduction of the keto groups of **3a** and **3b** and subsequent heating of the crude hydroxy acid and hydroxymethyl ester in toluene gave racemic δ-valerolactone **4** with 76% yield (2 steps). Preparative chiral HPLC resolution enabled to separate the enantiomers **4**(5*S*) and **4**(5*R*) with high optical purity (Scheme 2).[27]

Establishing of the C12 aldehyde function was achieved via two different strategies.[28] For installation of a stable protecting group for both, C1 lactone and C5 carbinol moieties, selective DIBAL–H reduction of lactone **4** delivered 1(*S*),5(*S*) and 1(*R*),5(*S*) lactols with >98% yield.[29] The remaining hemiacetal was treated with MeOH/*p*TsOH to give the product methyl THP ethers 1(*S*),5(*S*)-**5** and 1(*R*),5(*S*)-**6** with 75% yield and a 3:1 ratio of diastereomers **5** and **6** after HPLC separation and structure



Scheme 1. Retrosynthesis of 6,11-Methylene Lipoxin B_4. (PG = TBS (*tert*-butyldimethylsilyl), Ac, R = H, *tert*-butyl).



Scheme 2. Synthesis of the C1–C12 Fragment. Conditions and Yields: i) (a) $ZnCl_2$, AcCl, CH_2Cl_2, HOAc, 40–45%, (b) Br_2, NaOH, dioxane, H_2O, 95%, (c) MeOH, AcCl, heating, 95.5%, Ref. [23]; (ii) Glutaryl chloride, $AlCl_3$, CH_2Cl_2, reflux, 90–120 min, then: AcOH, H_2O, up to 73%; iii) (a) $NaBH_4$, MeOH, 0 °C, 18 h, (b) PhMe, heating, 12 h, yield *rac*-**4**: 69% from **3a**, 89% from **3b** (76%, 2 steps without separation/purification of intermediates), Ref. [22], [28]; iv) (a) DIBAL–H, THF, −60 °C, 2.5 h, 98.5%, (b) MeOH, *p*TsOH, 23 °C, 20 h, 75% (**5**:**6** = 3:1); (v) DIBAL–H, THF, −10 °C, 2 h, **7**: 99%, **8**: 91%; vi) Dess Martin-ox. CH_2Cl_2, 23 °C, 3 h, **9**: 74%, **10**: 70% ; vii) (a) LiOH, MeOH, H_2O, 0 °C to 23 °C, 18 h, (b) PhMe, reflux, 2 h, 97–98%; viii) (a) DMF, $(COCl)_2$, CH_2Cl_2, 0 °C, 1 h, then acid **11**, pyridine, THF, MeCN, −20 °C, 1 h, then LTBA (lithium tri (*tert*-butoxy aluminum hydride), THF, −78 °C, 2 h, (b) PhMe, reflux, 18 h, 98–99%.

elucidation (NMR).[30] A second DIBAL–H reduction of diastereomer **5** gave carbinol **7** with 99% yield, the analogous transformation of methyl THP ether **6** afforded alcohol **8** with 91% yield.[31] Oxidizing of carbinols **7** and **8** required maintaining of the cycloheptatriene moiety and the C5 configuration. In this connection, Swern variants and MnO_2 oxidations were hampered by several side product formations.[32] Best results were obtained using Dess Martin periodinane reagent.[33] The product THP aldehydes **9** and **10** were isolated with 74% and 70% yield, respectively, displaying fully protected C1 and C5 positions (Scheme 2).

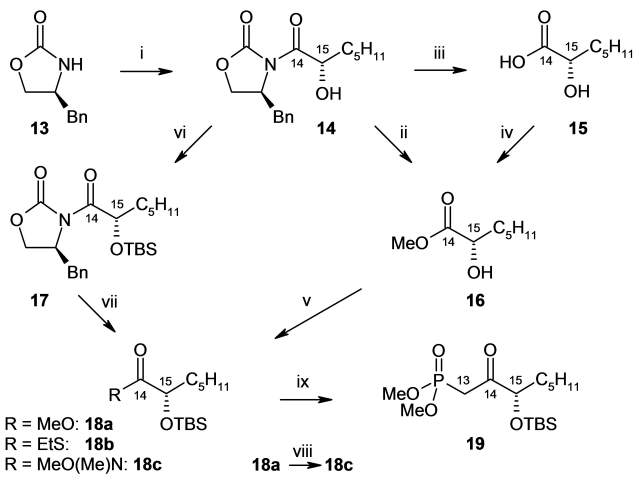
Alternatively, direct conversion of the δ-lactonoester **4** into the aldehyde **12** was tested in the presence of the non-protected lactone moiety. Cleavage of ester and lactone succeeded using LiOH in MeOH/H_2O,[34] the δ-lactone could be easily regenerated upon heating of the intermediate hydroxy C1/C12 dicarboxylic acid in toluene to give δ-lactonoacid **11** with 97–98% yield. Reduction of the acid without affecting the lactone moiety required a carefully optimized sequence of C12 acid activation and subsequent LTBA reduction (lithium tri (*tert*-butoxy aluminum hydride). Activation of the acid could be achieved upon building the corresponding Weinreb amide, thiol ester, and mixed anhydride (e.g. acyl methyl carbonate), but always the subsequent reductions failed.[35] The formation of acid chloride intermediates (highly activated acid derivatives) required the application of more or less neutral conditions (such as Ghosez reagent cyanuric chloride/base).[36] A carefully developed one-pot-procedure of acid activation (DMF/oxalyl chloride, acid **11**/MeCN), and reduction with LTBA, THF (lithium tri (*tert*-butoxy aluminum hydride) afforded the aldehyde group at C12.[37] Heating in dry PhMe induced re-lactonization of any intermediate hydroxycarboxylic acid, overall, δ-lactonoaldehyde **12** was generated with 98–99% yield (2–3 transformations, Scheme 2).

The synthesis of the C13–C20 fragment of 6,11-methylene LXB_4 commenced with a sequence according to S. Omura et al.[25,38] N-acylation of Evans oxazolidinone **13** with heptanoyl chloride (95% yield) delivered a starting imide.[25b] Diastereoselective introduction of the OH group succeeded after NaHMDS deprotonation and treatment with Davis oxaziridine[25c] to give hydroxyimide **14** with 69% yield.[25a] Exchange of the oxazolidinone moiety against methanol and protection of the α-OH function as a silyl ether required careful elaboration. Treatment of hydroxyimide **14** with freshly prepared SmI_2 in MeOH and MeMgBr/MeOH, respectively, delivered hydroxyester **16** with a

disappointing yield of 31%.[39] Alternatively, cleavage of the imide **14** using 3 N HCl afforded acid **15** (79% yield),[40] subsequent ester formation with $SOCl_2$/MeOH gave hydroxyester **16** (87% yield).[41] TBS protection of the OH group delivered protected ester **18a** (R = OMe) with acceptable 81% yield (Scheme 3).[41d]

Running the OH group protection as the first step, treatment of hydroxyimide **14** with TBSCl/imidazole in CH_2Cl_2 gave TBS ether **17** with nearly quantitative yield.[25a] However, various attempts of direct ester **18a** formation using LiOMe in THF, as well as imide cleavage with ethane thiole (→**18b**, R = SEt) gave low to moderate yields of silyl protected ester **18** (9–44%).[42] Finally, the method published by J. Stevens and D. Frantz led to a break-through: conversion using $Yb(OTf)_3$ in MeOH enabled the direct oxazolidinone - methoxide exchange, the silylester **18a** was isolated with 96% yield maintaining the high optical purity (Scheme 3).[43]

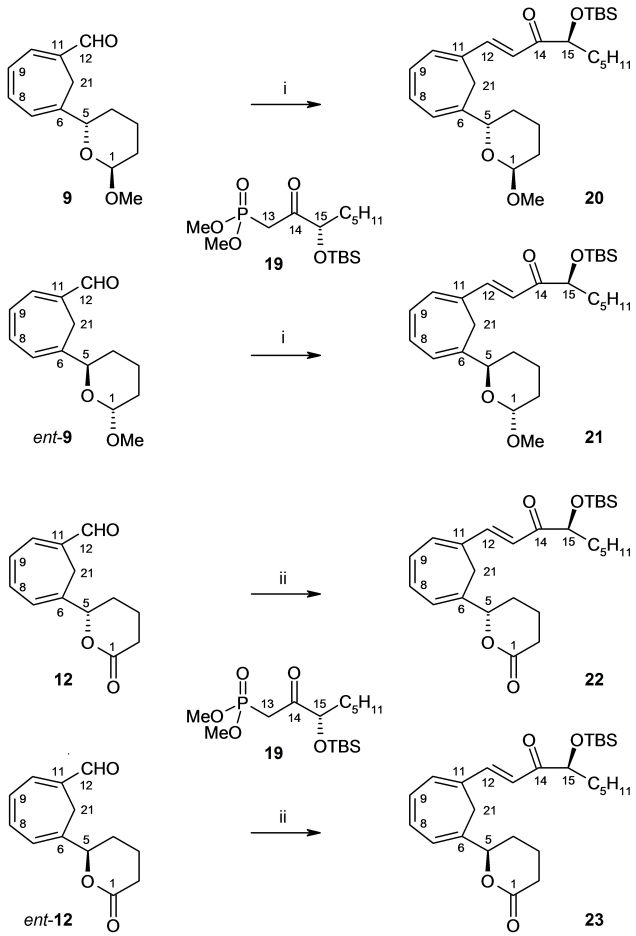
The assembly of the β-keto phosphonate moiety required a final Corey-Kwiatkowski condensation:[44] deprotonation of dimethyl methane phosphonate with *n*BuLi and subsequent reactions with ester **18**/imide **17** had been tested. Initial trials focused on ester condensation using activated oxazolidinone **17** and thiolester **18b** (R = SEt) as starting materials. Maximal yields of about 44% of ketone **19** could be achieved. Weinreb amide **18c** (from ester **18a**, 87% yield) proved to represent the better choice, keto phosphonate **19** was generated with 96% yield.[35a,42c] After careful optimization, the reaction of lithiated methane phosphono ester and methyl ester **18a** delivered the C13–C20 **19** fragment with 98% yield (Scheme 3).[44c–e]



Scheme 3. Synthesis of the C13–C20 Fragment. Conditions and yields: i) (a) NaH, THF, 0 °C, 0,5 h, then heptanoyl chloride, 0 °C to 23 °C, 18 h, 95%, (b) NaHMDS, THF, −78 °C, 1 h, then Davis reagent (phenyl *N*-phenylsulfonyl oxaziridine), THF, −78 °C, 1 h, 69%; ii) SmI_2, THF/MeOH, 23 °C, 18 h, 31%; iii) 3 M aq. HCl, reflux 48 h, 79%; iv) $SOCl_2$, MeOH, 0 °C to 23 °C, 3 h, 87%, v) TBSCl, imidazole, DMF, 0 °C to 23 °C, 18 h, 81%; vi) TBSCl, imidazole, DMF, 0 °C to 23 °C, 18 h, > 99%, vii) variation 1: MeMgBr, MeOH, 23 °C, 0.5 h, 31% of **18a**, variation 2: EtSH, *n*BuLi, THF, −78 °C, 0.5 h, then **17**, THF, −78 °C to −20 °C, 0.5 h, 73% of **18b**; variation 3: $Yb(OTf)_3$, MeOH, 23 °C 18 h, 96% of **18a**; viii) $MeO(Me)NH_2Cl$, THF, *i*PrMgCl, 0 °C, 4.5 h, 87% of **18c**. ix) $(MeO)_2P(O)Me$, *n*BuLi, THF, −78 °C, 1 h, then ester **18a**, THF, −78 °C to 23 °C, 2 h, 98%. Reaction with **18c**, −78 °C to 23 °C, 2 h: 96%. Reaction with **18b**: −78 °C to 23 °C, 2 h: 44%.

Starting from C13–C20 ketophosphonate **19** and C1–C12 aldehydes **9** and **12** (both enantiomers), fragment coupling employing Horner olefinations had been tested.[45] Standard conditions (phosphonate **19**/LDA) using THP-substituted aldehyde **9** gave disappointing results, only 8% yield of α,β-unsaturated ketone **20** could be isolated after about 2 weeks of reaction time. Applying the Masamune-Roush variant (**19**/LiCl/$i Pr_2NEt$ in CH_2Cl_2), ketone **20** had been obtained with about 20% yield.[44d,45c,d] In contrast, Paterson's conditions (**19**/$Ba(OH)_2$ in THF/H_2O) enabled smooth olefination, the THP-keto olefin **20** could be obtained with 93% yield, the diastereomer **21** (from *ent*-**9**) could be isolated with 41% yield (Scheme 4).[45e,f]

Initial investigations using δ-lactono aldehyde **12** as starting material in combination with the Paterson variant failed. Traces of H_2O and hydroxide/alkoxide ions caused a rapid opening of the lactone moiety in **12** delivering 5-hydroxy acids and esters, respectively. Unfortunately, these compounds prevented any further Horner olefination. A breakthrough could be developed by switching to carefully dried Cs_2CO_3/MeCN conditions:[44e,45g,h] Horner olefination involving δ-lactono aldehydes **12**/*ent*-**12** and keto phosphonate **19** afforded δ-lactono α,β-unsaturated

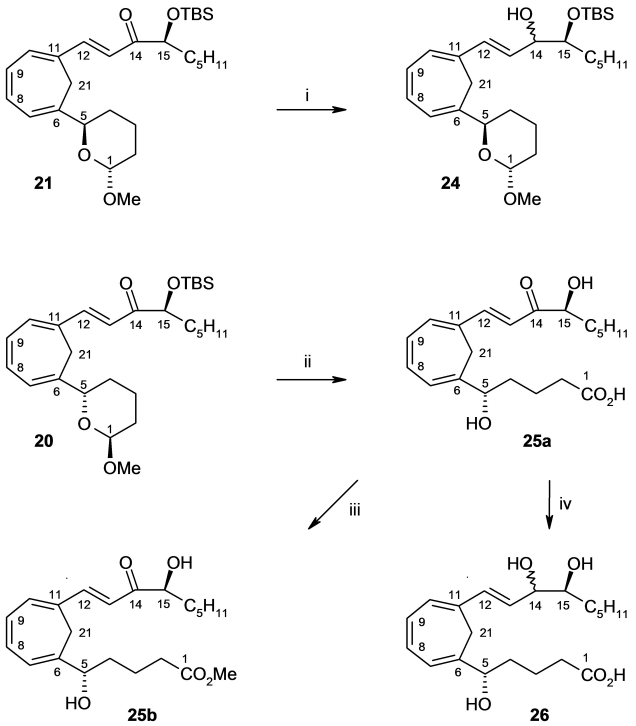


Scheme 4. Horner olefinations involving C1–C12 fragments **9**, **12** and the C13–C20 fragment **19**. Conditions and yields: i) $Ba(OH)_2$, THF, **19**, 23 °C, 1 h, then **9**/*ent*-**9**, THF, 0 °C to 23 °C, 72 h, **20**: 93%, **21**: 41%; ii) Cs_2CO_3, MeCN, −10 °C to 23 °C 7 d (if necessary: Na_2SO_4, PhMe, reflux, 12 h for re-lactonization of accompanying δ-hydroxy acid), **22**: 87%, **23**: 60%.

ketones **22** with 87% yield and **23** with 60% yield, respectively. Both ketones **22** and **23** proved to be easily separable by means of preparative column chromatography (PSC) and preparative HPLC enabling to remove any residual minor diastereomer (Scheme 4).

After assembling the complete 6,11-methylene LXB_4 framework **20**–**23**, final steps of diastereoselective ketone reductions, protecting group removals, and regeneration of the C1 carboxylic acid had to be developed using THP-systems **20** and **21**.

Starting from THP-ether derived unsaturated ketone **21** (*epi*-5(*R*) series), DIBAL–H reduction gave a nearly 1:1 mixture of epimer diols **24** in unoptimized 30% yield.[31] All attempts removing the THP ether and oxidative regeneration of the C1 carboxylic acid failed (destruction of the material because of the electron-rich tetraene system). Exchanging the steps of ketone reduction and acid regeneration turned to be more successful (maintaining the less electron-rich tetraene until the last step). Treatment of the methyl THP ether **20** (5(*S*) series) with $HClO_4$ enabled the removal of the methoxy and the silyl protective group in a single step.[46] Pinnick oxidation of the lactol delivered ketocarboxylic acid **25a** with 47% yield (2 steps).[47] For analytical purposes, acid **25a** was reacted with diazomethane to give ester **25b** (98% yield). A final Luche reduction ($NaBH_4$/$CeCl_3$) of acid **25a** delivered a 1:1 epimer mixture of 14(*R*) and 14(*S*) 6,11-methylene LXB_4 **26** with 98% yield.[48] Unfortunately, all attempts separating the diastereomers via PSC and HPLC failed. According to these observations, esterification and C5 OH protection of ketoacid **25a** prior to the final ketone reduction occurred mandatory in respect to the separation of the C14 diastereomers (Scheme 5).

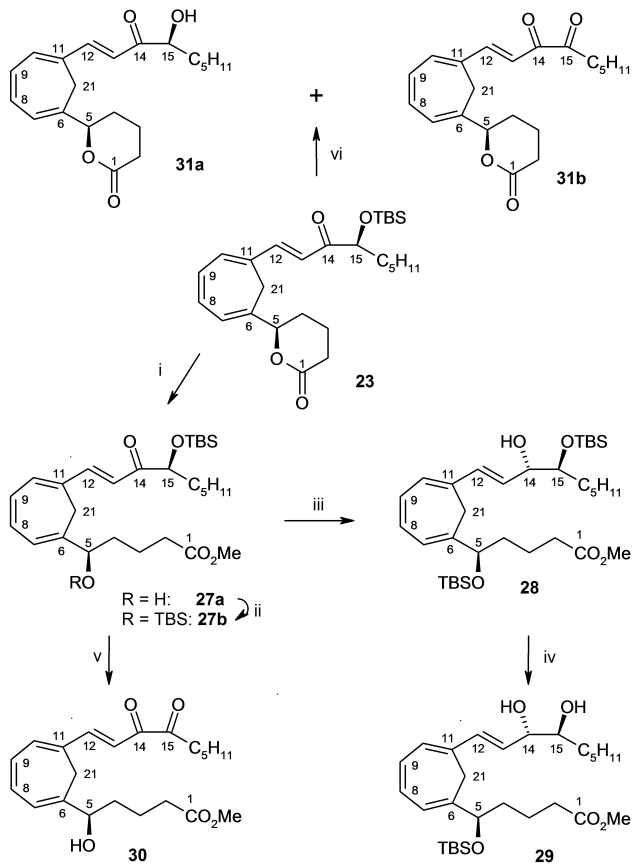


Scheme 5. Final steps synthesising 6,11-methylene LXB_4 from THP ketone **20**. Conditions and yields: i) DIBAL–H, THF, 0 °C, 72 h, 30%; ii) (a) 0.5 M $HClO_4$, THF, 23 °C, 8 h, (b) *t*BuOH, 2-methyl-2-butene, $NaClO_2$, KH_2PO_4, H_2O, 23 °C, 0.25 h, 47% of **25a**, iii) CH_2N_2, Et_2O, MeOH, H_2O, 23 °C, 1 h, 98% of **25b**; iv) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 15 min, 98% of **26** inseparable mixture of C14 epimers.

Starting from ketolactone **23** (*epi*-5(*R*) series), the initial modification of the C1–C5 segment started with a Zemplén-type ring-opening with Et_3N in MeOH to give methyl ester **27a** (R = H) with 96% yield.[49a,b] Immediate protection of the C5 OH group proved necessary to avoid any re-lactonization, introduction of a TBS ether under standard conditions gave the disilylether **27b** (R = TBS) with 95% yield.[33c,49c] Then, reduction of the C14 ketone was run under Luche conditions. Reaction with $NaBH_4$ and $CeCl_3$ in MeOH afforded carbinol **28** with nearly quantitative yield as a single diastereomer.[44d,45h,50] Mosher-analyses using freshly prepared (*R*) and (*S*) Mosher acid chlorides, respectively, gave the corresponding esters with 19% and 29% yields.[51] Structure elucidation proved the 14(*S*) configuration of the new alcohol moiety indicating a complete Cram-Felkin-Anh selectivity within the reduction. A final fluoride induced silyl group removal enabled to install the C15 OH group, the C5 silylether remained unaffected delivering the *epi*-5(*R*), *epi*-14(*S*), 15(*S*), 6,11-methylene LXB_4 as a monosilyl-protected methyl ester **29** with 95% yield (Scheme 6).

Since the reduction of the C14 ketone of **27b** induced the high Cram-Felkin-Anh selectivity adjacent to a C15(*S*) TBS protected carbinol, removal and exchange of the bulky silyl group should deliver the C14(*R*) Cram-chelate derived carbinol upon reduction. Therefore, cleavage of the C15 silylether had been tested in the presence of the C14 ketone function.[44e,52] Fluoride induced desilylation using hydroxyester **27a** gave complex mixtures of products partly regenerating the lactone moiety. After running a silylether cleavage and a subsequent Zemplén reaction sequence no C15 hydroxyketone had been found. Surprisingly, C14, C15 diketone **30** could be isolated with 17% yield only indicating a distinct oxidation lability of the hydroxyketone **27a** under the conditions employed.[53] Alternatively, C15 silylether cleavage had been tested prior to lactone opening. Starting from ketolactone **23**, treatment with TBAF in THF enabled desilylation delivering a mixture of hydroxylactone **31a** and ring opening side products.[44e,51] Thus, the crude silylether cleavage mixture was heated in toluene in the presence of Na_2SO_4 (complete regeneration of the lactone moiety). After final work-up, the C15-hydroxyketone **31a** could be isolated with moderate 38% yield. Again, some C-14, C-15 diketone **31b** was found as an oxidized side product with 21% yield (Scheme 6).[53]

Starting from keto lactone **22** (5(*S*) series), several attempts to reduce the ketone were not successful.[54] Even though the reduction might have worked, all processes were accompanied by the opening of the lactone leading to hardly isolable and detectable products, no hydroxylactone **32** had been found. Obviously, the lactone moiety required a carefully chosen functional group variation prior to the ketone reductions. Zemplén reaction using Et_3N/MeOH smoothly gave the corresponding hydroxyester **33a** (R = H) with 98% yield.[49a,b] Intending suppression of any re-lactonization, the C5 OH group



Scheme 6. Final steps within the 5-*epi*-6,11-methylene LXB_4-series from ketolactone **23**. Conditions and yields: i) MeOH, Et_3N, 23 °C, 20 h, 96% of **27a** (R = H); ii) TBSCl, imidazole, DMF, 0 °C to 23 °C, 20 h, 95% of **27b** (R = TBS), iii) $NaBH_4$, $CeCl_3$ (7 H_2O), MeOH 0 °C, 15 min, > 99% (for Mosher analysis see supporting information); iv) TBAF, THF, 0 °C to 23 °C, 1 h, 95%; v) from **27a** (R = H) (a) TBAF, THF, 0 °C to 23 °C, 1 h (b) Et_3N, MeOH, 23 °C 20 h, 17%; vi) TBAF, THF, 0 °C, 15 min (b) Na_2SO_4, PhMe, reflux, 20 h, 38% of **31a**, 21% of **31b**.

immediately had been protected as an acetate (**33b**, R = Ac) with 96% yield.[55] Upon planning the reduction of the ketone, a C15 OTBS protected carbinol should favor a Cram-Felkin-Anh selectivity concerning the hydride transfer, leading predominantly to the *epi* 14(*S*) configured alcohol. In contrast, establishing the 14(*R*) carbinol required Cram-chelate conditions. Consequently, the C15 OTBS group in ketoester **33b** was removed with buffered TBAF/HOAc in THF delivering C15 hydroxyester **34** with 83% yield.[45d] No competing C14, C15 diketone had been detected. Several tests incorporating the C15 OH group as an anchoring group for reducing agents such as $NaBH(OAc)_3$ failed.[54,56] In contrast, the use of $Zn(OTf)_2$ and $NaBH_4$ in Et_2O gave the desired carbinol as a 3:1 mixture of 14(*R*) and 14(*S*) diastereomers with nearly quantitative yield.[44e] Since the direct separation of the diastereomers via column chromatography and HPLC proved cumbersome, the C14/C15 diol moiety was converted into the cyclic carbonate. Reaction with triphosgene $(COCl_2)_3$ delivered *cis* C14, C15 carbonate **35** with 57% yield and the corresponding *trans* diastereomer **36** with 38% yield indicating a surprisingly lower 3:2 d. r.[57] In contrast, reaction with carbonyl diimidazole (CDI), afforded a mixture of *cis* 14(*R*)/15(*S*) carbonate **35** (38% yield), the corresponding *trans* 14(*S*)/15(*S*) epimer **36** (19% yield) and, additionally, some *cis* 14(*R*)/15(*S*) di-O-(imidazolyl carbonyl) derivative (28% yield, not shown), indicating a nearly 3.5:1 chelate-Cram selectivity favoring 14(*R*)/15(*S*).[58] However, separation of *trans* and *cis* carbonates **35** and **36** (and di-imidazolide) succeeded in applying simple column chromatography. Furthermore, the correct relative configuration of the adjacent stereogenic C14 and C15 centers in both diastereomers **35** and **36** could be unequivocally proven via NOESY experiments.[59] Finally, removal of both, C5 acetate and C14/C15 carbonate/carbamates using NaOMe in MeOH delivered the optically active target 6,11-methylene LXB_4 methylester **37** with 94% yield from carbonate **35**.[48b] In addition, cleavage of the di-imidazolide (not shown) gave additional derivative **37** with 64% yield.[60] The epimer 14(*S*) **38** was obtained by transesterification from carbonate **36** (91% yield). Surprisingly, the product ester **37** was found to be fairly stable, purification via PSC and preparative HPLC and storing in CD_2Cl_2 for several analyses did not induce significant degradation processes (Scheme 7).

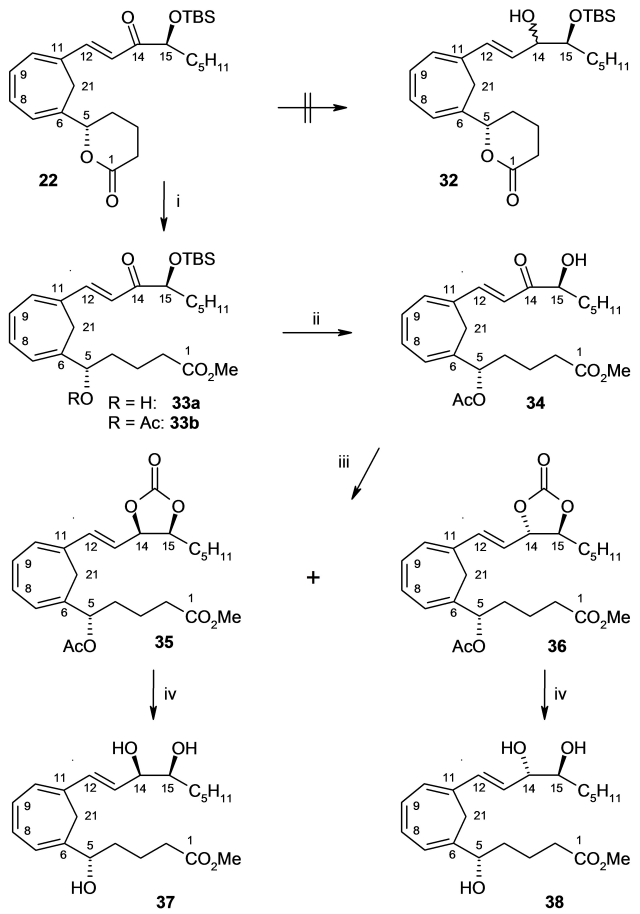
Conclusion

A convergent total synthesis of optically active 6,11-methylene lipoxin B_4 methylester **37** was developed using cycloheptatriene **1**, oxazolidinone **13**, and heptanoyl chloride as reactants.

The synthesis of the C1–C12 fragment started from cycloheptatriene **1**. After literature known steps building-up cycloheptatriene 2-carbonester **2** (C6–C12, C21), Friedel-Crafts type acylation with glutaryl chloride (C1–C5) delivered keto acid derivatives **3**. Ketone reduction, lactonization, and resolution gave lactonoester **4** (both enantiomers) as published recently.[22]

For completion of the C1–C12 moiety two strategies had been pursued. On one hand, chemoselective reduction of lactone and subsequent protection as a methyl THP ether delivered mixtures of epimers **5** and **6** (both enantiomers). A final DIBAL–H reduction and Dess-Martin oxidation sequence delivered the aldehydes **9** and **10** with 40% plus 12% yield over three steps. On the other hand, cleavage ester afforded a lactono acid **11**. Acid activation and LTBA reduction delivered lactono aldehyde **12** with 96% yield (both enantiomers). Summarized, the shortest sequence (**2**→**12**(*S*) and **12**(*R*), respectively) comprised six/seven steps and one HPLC resolution with about 72% yield overall (36% for **12**(*S*) plus 36% of **12**(*R*)).

The synthesis of the C13–C20 key building block started from heptanoyl chloride. Application of Evans auxiliary strategy (α-hydroxylation of Evans imide and subsequent protecting group operations) gave the desired enantiopure ester **18a** with 65.6% yield (3 steps). Finally, condensation with dimethyl methane phosphonate afforded the C13–C20 key building block **19** with 98% yield. Summarized, the shortest sequence (N-heptanoyloxazolidinone→**19**) comprised four steps with about 64% yield overall.



Scheme 7. Final steps synthesising 6,11-methylene LXB_4 from keto lactone **22**. Conditions and yields: i) (a) Et_3N, MeOH, 23 °C, 20 h, 98% **33a** (R = H); (b) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 23 °C, 18 h, 96%, **33b** (R = Ac); ii) TBAF, HOAc, THF, 0 °C to 23 °C, 3 d, 83%, iii) (a) $Zn(OTf)_2$, $NaBH_4$, Et_2O, 0 °C, 1 h, then 23 °C, 1 h, > 99% (1:3 mixture of diastereomer C14 carbinols, not separated); (b) triphosgene, DMAP (cat.) Pyrdine, CH_2Cl_2, 0 °C to 23 °C, 24 h, 57% of **35**, 38% of **36**; replacing the triphosgene by carbonyl diimidazole delivered **35** (38%), **36** (19%) and *cis*-C14, C15 bis-O-(imidazolyl carbonyl) derivative, not shown, see supporting information (28%); iv) NaOMe, MeOH, 0 °C to 23 °C, 20 h, 94% of **37**, 91% of **38**. Reaction of *cis*-14, 15 bis-O-(imidazolyl carbonyl)-derivative, not shown, gave 64% of **37**, see supporting information. 52.5% of **37**, two steps, 17.3% of **38**, two steps, via CDI.

With two C1–C12 aldehyde building blocks **9** and **12** (both enantiomers each) and the C13–C20 phosphono ester **19** in hand, (*E*)-selective Horner reactions for coupling had been tested. Despite a relatively long distance concerning the stereogenic centers of both fragments, a distinct substrate control (moderate to high yields) could be observed upon combining the reactants. Paterson's conditions enabled condensation of THP aldehyde **9** and phosphonate **19** to generate ketone **20** with 93% yield. For comparison: reaction of *ent*-**9** and **19** delivered ketone **21** with 41% yield only. Best results upon Horner olefination with lactono aldehydes **12** and phosphonate **19** were achieved using dry Cs_2CO_3 in MeCN. 87% yield of ketolactone **22** (from **12**) and 60% yield of ketolactone **23** (from *ent*-**12**) were obtained.

Complete assembly of the 6,11-methylene LXB_4 frameworks enabled the investigation of the final steps of the total syntheses. Starting from THP ethers **20** and **21**, acid group regeneration had to be carried out prior to the Luche reduction of the unsaturated C14 keto function. THP ether cleavage and Pinnick oxidation afforded keto carboxylic acid **25a** with 47% yield, the final Luche reduction of the keto function gave the product 6,11-methylene LXB_4 **26** (98% yield) as an inseparable mixture of C14 epimers.

Starting from *epi*-5(*R*)-ketolactone **23**, Zemplén reaction and TBS protection of the carbinol delivered protected ketone **27b**. Subsequent Luche reduction gave hydroxyester **28** with undesired 14(*R*) configuration only indicating a complete Cram-Felkin-Anh selectivity upon hydride transfer. A final treatment with fluoride enabled removal of the O15 TBS group only delivering 6,11-methylene LXB_4 methyl ester with *epi*-5(*R*) and *epi*-14(*R*) configuration as a 5(*R*)-OTBS ether (86%, 4 steps).

Starting from 5(*S*)-ketolactone **22**, Zemplén reaction and acetylation of the O-5(*S*)-carbinol delivered protected ketone **33b** (94%). After TBAF removal of the 15-O–TBS group, Luche reduction delivered a 3:1 mixture of epimer C14 carbinols (77%). O-14/O-15 cyclization using carbonyl diimidazole gave the carbonates **35** and **36** (separation via PSC) Final global deprotection applying Zemplén conditions afforded 6,11-methylene LXB_4 methyl ester **37** (52.5%) and *epi*-C14 6,11-methylene LXB_4 methyl ester **38** (17.3%).

Summarized, the shortest sequence (**22** to **37**) comprised six steps with about 46.5% yield overall. The shortest linear sequence of the 6,11-methylene LXB_4 methyl ester synthesis (**2** to **37**) was run via 13 steps and about 15% yield overall (HPLC resolution included).

Further investigations focus on syntheses of 6,11-methylene LXB_4 derivatives displaying modified C15–C20 and C2–C5 segments as suggested within Figure 2.

Experimental Section

General Remarks: Reaction solvents were dried by standard procedures prior to use when necessary. All reactions including moisture- or air-sensitive reagents were carried out under an argon atmosphere. ^1H NMR, ^{13}C NMR, and 2D Spectra (COSY, HSQC, HMBC, NOESY) spectra were recorded at room temperature with a Bruker AV300, AV400, or AV600 spectrometer in $CDCl_3$ or CD_3OD using the signal of residual $CHCl_3$ (7.26 ppm), and CD_3OD (3.31 ppm) as internal standards. Deuterated solvents were purchased from Deutero GmbH. IR spectra were recorded with a Jasco FT/IR-400 plus spectrometer with single reflection horizontal ATR (ZnSe window). FD Mass spectra were obtained using a Finnigan MAT 95, the high-resolution mass spectra (HRMS) were recorded with a Waters Q Tof Ultima 3 Micromasses spectrometer or Agilent 6545 Q-TOF spectrometer. Optical rotation was recorded with Perkin-Elmer's MC 241 polarimeter. Melting points were determined with an Elecrothermal Engineering Ltd. IA 9100 apparatus. Column chromatography was performed on MN silica gel 60 M from Macherey-Nagel (grain size: 0.040–0.063 mm). Progress of the reaction was monitored by thin-layer chromatography (TLC) performed on aluminium sheets pre-coated with silica gel 60 F254 silica gel from Merck and Macherey & Nagel. Analytical HPLC Systems were used to analyze the products: Knauer HPLC Pump 64 connected to a Phenomenex Gemini-NX C18 (110-5 4.6x 250 mm) column, a Knauer Variable Wavelength Monitor at λ = 254 nm or 220 nm, and Knauer Differential Refractometer. A standard column

(4×250 mm) Nucleosil 50–5 (5 μm) and a chiral column (4.6×250 mm) *S,S*-Whelk-O1 were employed. The remaining chromatographic conditions: flow rate and mobile phase are noted in analytical data. Preparative HPLC: Knauer WellChrom Preparative Pump K-1800 connected to a Nucleosil 50–5, 5 μm (32×250 mm) column, a Knauer Variable Wavelength Monitor at λ = 254 nm or 220 nm and Bischoff RI-detector 8110. A chiral column (20×280 mm) *S,S*-Whelk-O1 was employed as well. The remaining chromatographic conditions: flow rate and mobile phase are noted in analytical data. HPLC data: RT = peak retention time, k = retention factor = $(RT-t_0)/t_0$.

6-((6*S*)-3,4,5,6-Tetrahydropyran-2-on-6-yl)-1,3,5-cycloheptatriene 1-carboxylic acid 11(*5S*): The ester **4**(*5S*) (0.20 g, 0.81 mmol, 1.0 eq.) was dissolved in methanol (27 mL) and cooled to 0 °C. $LiOH{\cdot}H_2O$ (0.17 g, 4.00 mmol, 5.0 eq.) dissolved in water (13 mL) was slowly added via dropping funnel. The reaction was stirred overnight at room temperature. Then the reaction was concentrated in vacuo. The residue was acidified with 1 M citric acid and extracted with EtOAc (3×25 mL). The combined organic layers were washed (brine) and dried ($MgSO_4$). The solvent was removed in vacuo, the residue was taken up in toluene (40 mL) and refluxed for two hours. Then the solvent was removed in vacuo to afford the carboxylic acid **11**(*5S*) (0.18 g, 0.78 mmol, 97%) as a colorless oil. No further purification was needed. R_f (EtOAc/petroleum ether 1:2): 0.26. $[\alpha]_D = -34.5°$ (*c* = 1.0, 22 °C, CH_2Cl_2, *ee* 96%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.68 (s, 1H, COOH), 7.37 (d, $^3J_{HH}$ = 5.9 Hz, 1H, H-10), 6.83 (dd, $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 6.1 Hz, 1H, H-8), 6.67 (ddd, $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H-9), 6.32 (dd, $^3J_{HH}$ = 6.1 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H-7), 5.01–4.86 (m, 1H, H-5), 3.06 (d, $^2J_{HH}$ = 13.5 Hz, 1H, H-13′), 2.70–2.45 (m, 2H, H-2), 2.36 (d, $^2J_{HH}$ = 13.5 Hz, 1H, H-13″), 2.04 (dddd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, H-4′), 1.97–1.79 (m, 3H, H-3, H-4″). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 170.3 (C-1), 166.7 (C-12), 136.4 (C-6), 134.2 (C-8), 132.7 (C-10), 129.4 (C-9), 128.6 (C-11), 122.4 (C-7), 81.8 (C-5), 29.1 (C-2), 27.0 (C-4), 26.5 (C-13), 17.7 (C-3). IR (neat): $\tilde{\nu}$ = 3439 (mbr), 3025 (w), 2962 (w), 1657 (mbr), 1600 (m), 1495 (m), 1243 (m), 1024 (s), 1004 (s), 823 (m), 759 (s), 699 (w), 618 (w) cm^{-1}. HRMS-ESI $C_{13}H_{14}O_4Na$ calcd.: 257.0790, found: 257.0786.

6-((6*S*)-3,4,5,6-Tetrahydropyran-2-on-6-yl)-1,3,5-cycloheptatriene 1-carbaldehyde 12 (*5S*): Under Ar, *N,N*-Dimethylformamide (0.22 g, 0.24 mL, 3.7 mmol, 1.2 eq.) was dissolved in dry CH_2Cl_2 (18 mL) and cooled to 0 °C. Oxalyl chloride (1.30 g, 0.88 mL, 10.25 mmol, 4.0 eq.) was added carefully via syringe and stirred for an hour at 0 °C. Then the solvent was removed in vacuo and replaced with dry acetonitrile (12 mL) and dry THF (18 mL). The reaction was cooled to −10 °C and the acid **11** (*5S*) (0.60 g, 2.56 mmol, 1.0 eq.) and pyridine (0.20 g, 0.21 mL, 2.56 mmol, 1.0 eq.) dissolved in dry THF (18 mL) were added slowly. After an hour the reaction was further cooled to -78 °C and LTBA 1.1 M in THF (5.12 mL, 5.64 mmol, 2.2 eq.) was added dropwise via syringe. The reaction was stirred at that temperature for two hours before being warmed up to 0 °C being quenched with water. 1 M hydrochloric acid was added until all precipitate was dissolved and the aqueous layer was extracted with EtOAc (3×60 mL). The combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was taken up in toluene (120 mL). The reaction was heated to reflux overnight. The next day the solvent was removed in vacuo to afford aldehyde **12** (*5S*) (0.55 g, 2.52 mmol, 98%) as a pale-yellow oil. No further purification was needed. R_f (EtOAc/petroleum ether 1:2): 0.27. $[\alpha]_D = -50.2°$ (*c* = 1.0, 22 °C, CH_2Cl_2, *ee* 96%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.51 (s, 1H, H-12), 6.96 (d, $^3J_{HH}$ = 5.7 Hz, 1H, H-10), 6.89 (dd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, H-8), 6.78 (ddd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 0.9 Hz, 1H, H-9), 6.35 (d, $^3J_{HH}$ = 5.9 Hz, 1H, H-7), 4.95–4.86 (m, 1H, H-5), 3.03 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-13′), 2.70–2.44 (m, 2H, H-2), 2.38 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-13″), 2.03–1.92 (m, 1H, H-4′), 1.92–1.67 (m, 3H, H-3, H-4″). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 192.0 (C-12), 171.1 (C-1), 142.6 (C-10), 137.7 (C-6), 136.2 (C-8), 132.6 (C-11), 129.1 (C-9), 123.2 (C-7), 82.9 (C-5), 29.7 (C-2), 27.1 (C-4), 23.7 (C-13), 18.7 (C-3). IR (neat): $\tilde{\nu}$ = 3040 (w), 3016 (w), 2946 (w), 2926 (w), 1736 (s), 1672 (s), 1240 (m), 1184 (w), 1038 (m), 748 (m), 626 (w) cm^{-1}. HRMS-ESI $C_{13}H_{14}O_3Na$ calcd.: 241.0841, found: 241.0838.

(*S*)-6-(6-((*S,E*)-4-(*tert*-Butyldimethylsilyl)oxy)-3-oxonon-1-ene-1-yl) cyclohepta-1,3,5-triene-1-yl)tetrahydro-2*H*-pyran-2-one 22 (*5S*): Cesium carbonate (0.51 g, 1.56 mmol, 2.0 eq.) was dried under high vacuum (2×10^{-2} mbar) for at least two hours and was then suspended in dry acetonitrile (5 mL). Phosphonate **19** (0.57 g, 1.56 mmol, 2.0 eq.) dissolved in dry acetonitrile (5 mL) was added dropwise at room temperature and the mixture was stirred for an hour. Then the aldehyde **12** (*5S*) (0.17 g, 0.78 mmol, 1.0 eq) dissolved in dry acetonitrile (5 mL) was added slowly. The reaction was stirred at room temperature for 7 days. The reaction was quenched by adding 1 M hydrochloric acid. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed (brine) and dried ($MgSO_4$). The solvent was evaporated und the residue dissolved in toluene (30 mL). Anhydrous sodium sulfate was added and the mixture was heated to reflux overnight. The next day sodium sulfate was filtered off using a Buechner funnel and the filtrate was evaporated. The residue was purified via column chromatography (EtOAc/petroleum ether 1:5 to 1:2) affording the product **22** (*5S*) (0.31 g, 0.68 mmol, 87%) as a yellow oil. R_f (EtOAc/petroleum ether 1:5): 0.34, $[\alpha]_D = -73.9°$ (*c* = 1.0, 21 °C, CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, $^3J_{HH}$ = 15.8 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, H-12), 6.85 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-13), 6.70–6.61 (m, 2H, H-8, H-10), 6.56 (d, $^3J_{HH}$ = 5.5 Hz, 1H, H-9), 6.28 (d, $^3J_{HH}$ = 5.7, 1H, H-7), 4.86–4.79 (m, 1H, H-5), 4.17 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, H-15), 2.75 (d, $^2J_{HH}$ = 13.6 Hz, 1H, H-21′), 2.69–2.45 (m, 2H, H-2), 2.55 (d, $^2J_{HH}$ = 13.6 Hz, 1H, H-21″), 2.05–1.95 (m, 1H, H-4″), 1.94–1.83 (m, 2H, H-3), 1.80–1.69 (m, 1H, H-4′), 1.69–1.57 (m, 2H, H-16), 1.43–1.23 (m, 6H, H-17, H-18, H-19), 0.93 (s, 9H, H-25, H-26, H-27), 0.90–0.82 (m, 3H, H-20), 0.08 (s, 3H), 0.05 (s, 3H) (H-22, H-23). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.0 (C-14), 170.9 (C-1), 144.7 (C-12), 135.0 (C-9), 134.2 (C-6), 132.7 (C-8), 130.6 (C-10), 130.5 (C-11), 123.5 (C-7), 121.1 (C-13), 82.5 (C-5), 78.8 (C-15), 35.4 (C-16), 31.8 (C-18), 29.5 (C-2), 27.7 (C-21), 27.1 (C-4), 26.0 (C-25, C-26, C-27), 24.8 (C-17), 22.6 (C-19), 18.4 (C-3), 18.4 (C-24), 14.1 (C-20), −4.6, −4.8 (C-22, C-23). IR (neat): $\tilde{\nu}$ = 3053 (w), 3018 (w), 2952 (s), 2932 (s), 2855 (m), 1741 (s), 1681 (w), 1583 (s), 1465 (m), 1432 (w), 1357 (w), 1317 (w), 1254 (m), 1237 (m), 1090 (s), 1074 (s), 1042 (s), 970 (m), 838 (s), 778 (s), 693 (m), 620 (m), 605 (w), 586 (w) cm^{-1}. HRMS-ESI $C_{27}H_{43}O_4Si$ calcd.: 459.2925, found: 459.2936.

(*5S*, *15S*) 15-(O-*tert*-Butyldimethylsilyl)-6,11-methylene-14-oxo-LXB$_4$ methyl ester 33a: Under Ar, the lactone **22** (*5S*) (0.13 g, 0.28 mmol, 1.0 eq.) was dissolved in dry methanol (8 mL) and dry triethylamine (0.14 g, 0.20 mL, 1.42 mmol, 5.0 eq.) was added dropwise at room temperature. The reaction was stirred for 20 hours. Then the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:5) affording the methyl ester **33a** (0.14 g, 0.28 mmol, 98%) as a yellow oil. R_f (EtOAc/petroleum ether 1:5): 0.34, $[\alpha]_D = -38.6°$ (*c* = 1.0, 22 °C, CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, $^3J_{HH}$ = 15.7 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, H-12), 6.98 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-13), 6.67 (ddd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 0.9 hz, 1H, H-8), 6.63–6.53 (m, 2H, H-9, H-10), 6.24 (d, $^3J_{HH}$ = 5.7 Hz, 1H, H-7), 4.22 (t, $^3J_{HH}$ = 5.9 Hz, 1H, H-5), 4.18 (dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 5.2 Hz, 1H, H-15), 3.68 (s, 3H, H-22), 2.81 (d, $^2J_{HH}$ = 13.2, 1H, H-21′), 2.52 (d, $^2J_{HH}$ = 13.2 Hz, 1H, H-21″), 2.41–2.28 (m, 2H, H-2), 1.83–1.54 (m, 6H, H-3, H-4, H-16), 1.43–1.26 (m, 6H, H-17, H-18, H-19), 0.97 (s, 9H, H-26, H-27, H-28), 0.89 (t, $^3J_{HH}$ = 6.8 Hz, 3H, H-20), 0.10 (s, 3H), 0.07 (s, 3H) (H-23, H-24). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.3 (C-14), 174.0 (C-1), 144.8 (C-12),

140.3 (C-6), 134.9 (C-10), 133.1 (C-8), 130.6 (C-11), 129.8 (C-9), 122.5 (C-7), 121.0 (C-13), 78.8 (C-15), 75.1 (C-5), 51.7 (C-22), 35.4 (C-16), 34.7 (C-4), 33.8 (C-2), 31.8 (C-18), 27.5 (C-21), 26.0 (C-26, C-7, C-28), 24.8 (C-17), 22.6 (C-19), 21.1 (C-3), 18.4 (C-25), 14.1 (C-20), −4.6, −4.9 (C-23, C-24). IR (neat): $\tilde{\nu}$ = 3469 (br), 2954 (s), 2931 (s), 2858 (m), 1740 (s), 1682 (w), 1580 (s), 1437 (w), 1317 (w), 1253 (m), 1162 (w), 1092 (m), 838 (s), 779 (s), 742 (m), 611 (w), 596 (w), 584 (w). HRMS-ESI $C_{28}H_{46}O_5SiNa$ calcd.: 513.3007, found: 513.2998.

(5*S*, 15*S*) 5-(O-Acetyl)-15-(O-*tert*-butyldimethylsilyl)-6,11-methylene-14-oxo-LXB$_4$ methyl ester 33 b: Under Ar, the alcohol **33 a** (0.070 g, 0.14 mmol, 1.0 eq.) dissolved in dry CH_2Cl_2 (5 mL) was treated with *N, N*-dimethylaminopyridine (7.0 mg, 0.057 mmol, 0.4 eq.) and dry triethylamine (0.022 g, 0.030 mL, 0.21 mmol, 1.5 eq.). Then acetic anhydride (0.022 g, 0.020 mL, 0.21 mmol, 1.5 eq.) was added slowly at room temperature. The reaction was stirred for 18 hours before being quenched with water. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with 1 M hydrochloric acid, sat aq. $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed in vacuo affording the product **33 b** (0.073 g, 0.14 mmol, 96%) as a yellow oil. R_f (EtOAc/petroleum ether 1:5): 0.42, $[\alpha]_D = -59.1°$ (c = 1.0, 22 °C, CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{HH}$ = 15.8 Hz, 1H, H-12), 6.96 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-13), 6.63–6.56 (m, 2H, H-8, H-9), 6.55–6.48 (m, 1H, H-10), 6.23–6.16 (m, 1H, H-7), 5.27 (ddd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H-5), 4.22–4.09 (m, 1H, H-15), 3.63 (s, 3H, H-22), 2.78 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-21′), 2.52 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-21″), 2.24 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H-2), 2.03 (s, 3H, H-30), 1.79–1.58 (m, 4H, H-4, H-16), 1.58–1.44 (m, 2H, H-3), 1.44–1.32 (m, 2H, H-17), 1.32–1.20 (m, 4H, H-18, H-19), 0.95 (s, 9H, H-26, H-27, H-28), 0.87 (t, $^3J_{HH}$ = 6.8 Hz, 3H, H-20), 0.08 (s, 3H), 0.06 (s, 3H) (H-23, H-24). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.3 (C-14), 173.6 (C-1), 170.1 (C-29), 144.8 (C-12), 135.1 (C-10), 134.8 (C-6), 132.8 (C-8), 131.1 (C-11), 130.4 (C-9), 124.9 (C-7), 121.1 (C-13), 78.7 (C-15), 76.8 (C-5), 51.7 (C-22), 35.5 (C-16), 33.5 (C-2), 32.2 (C-4), 31.8 (C-18), 27.0 (C-21), 26.0 (C-26, C-27, C-28), 24.8 (C-17), 22.6 (C-19), 21.2 (C-30), 21.0 (C-3), 18.3 (C-25), 14.1 (C-20), −4.6, −4.9 (C-23, C-24). IR (neat): $\tilde{\nu}$ = 3018 (w), 2952 (m), 2929 (m), 2857 (m), 1740 (s), 1682 (w), 1581 (m), 1468 (w), 1436 (w), 1369 (w), 1313 (w), 1234 (s), 1163 (w), 1092 (w), 1024 (w), 958 (w), 838 (m), 778 (m), 745 (m), 669 (w), 618 (w), 593 (w), 582 (w) cm^{-1}. HRMS-ESI $C_{30}H_{48}O_6SiNa$ calcd.: 555.3112, found: 555.3119.

(5*S* 15*S*) 5-(O-Acetyl)-6,11-methylene-14-oxo-LXB$_4$ methyl ester 34: Under Ar, the silyl ether **33 b** (0.020 g, 0.038 mmol, 1.0 eq.) was dissolved in dry THF (2 mL) and cooled to 0 °C. Then a 1:1 mixture of tetrabutylammonium fluoride 1.0 M in THF (0.19 mL, 0.19 mmol, 5.0 eq.) and acetic acid (0.011 g, 0.011 mL, 0.19 mmol, 5.0 eq.) in dry THF (3 mL) was added dropwise. The reaction was warmed to room temperature and stirring was continued for three days. The solvent was evaporated and the residue was purified via column chromatography (EtOAc/petroleum ether 1:3) affording the hydroxyketone **34** (0.013 g, 0.031 mmol, 83%) as a yellow oil. R_f (EtOAc/petroleum ether 1:3): 0.42, $[\alpha]_D = -72.4°$ (c = 1.0, 23 °C, CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, $^3J_{HH}$ = 15.7 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, H-12), 6.72–6.58 (m, 3H, H-8, H-9, H-13), 6.58–6.54 (m, 1H, H-10), 6.22 (d, $^3J_{HH}$ = 5.4 Hz, 1H, H-7), 5.29 (t, $^3J_{HH}$ = 6.7 Hz, 1H, H-5), 4.44 (s, 1H, H-15), 3.64 (s, 3H, H-22), 2.76 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-21′), 2.49 (d, $^2J_{HH}$ = 13.4 Hz, 1H, H-21″), 2.27 (t, $^3J_{HH}$ = 7.1 Hz, 2H, H-2), 2.04 (s, 3H, H-24), 1.93–1.79 (m, 1H, H-16′), 1.79–1.66 (m, 2H, H-4), 1.65–1.37 (m, 5H, H-3, H-16″, H-17), 1.36–1.26 (m, 4H, H-18, H-19), 0.88 (t, $^3J_{HH}$ = 6.5, 3H, H-20). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.1 (C-14), 173.7 (C-1), 170.2 (C-23), 145.3 (C-12), 135.7 (C-10), 135.1 (C-6), 133.4 (C-8), 130.3 (C-9), 129.9 (C-11), 124.6 (C-7), 121.0 (C-13), 76.6 (C-5), 75.9 (C-15), 51.8 (C-22), 34.6 (C-16), 33.4 (C-2), 32.3 (C-4), 31.8 (C-18), 27.3 (C-21), 24.7 (C-17), 22.7 (C-19), 21.2 (C-24), 21.0 (C-3), 14.2 (C-20). IR (neat): $\tilde{\nu}$ = 3460 (br), 3018 (w), 2949 (m), 2929 (m), 2863 (w), 1738 (s), 1682 (m), 1587 (s), 1436 (w), 1371 (m), 1313 (w), 1236 (s), 1058 (m), 746 (m), 642 (w) cm^{-1}. HRMS-ESI $C_{24}H_{36}O_6Na$ calcd.: 441.2247, found: 441.2243.

(5*S*, 14*R/S*, 15*S*) 5-(O-Acetyl)-6,11-methylene-LXB$_4$ methyl ester XIV: Zinc(II) triflate (0.070 g, 0.19 mmol, 4.0 eq.) was dried under high vacuum (2×10^{-2} mbar) at 200 °C for 20 minutes before being suspended in dry ether (2 mL) under Ar. The hydroxyketone **34** (0.020 g, 0.048 mmol, 1.0 eq.) dissolved in dry ether (3 mL) was added. After 15 minutes the reaction was cooled to 0 °C and sodium borohydride (0.018 g, 0.48 mmol, 10.0 eq.) was added. The reaction was stirred at 0 °C for one hour and then warmed up to room temperature and stirred for one hour until complete discoloration. The reaction was quenched with aq. sat. NH_4Cl and extracted with ether (3×15 mL). The combined organic layers were washed (brine) and dried (Na_2SO_4). The solvent was removed in vacuo at a temperature below 30 °C. The rotary evaporator was ventilated with argon. The mixture of C14 epimers of alcohol **XIV** (0.020 g, 0.048 mmol, quant.) was afforded as a colorless oil and used directly for the next reaction. R_f (EtOAc/petroleum ether 1:2): 0.16. For spectroscopic data see supporting information.

Under Ar, the diol **XIV** (0.025 g, 0.059 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (3 mL) and treated with *N, N*-dimethylaminopyridine (7.3 mg, 0.059 mmol, 1.0 eq.). The solution was cooled to 0 °C and 1,1′-carbonyldiimidazole (0.015 g, 0.089 mmol, 1.5 eq.) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with water and acidified with 1 M hydrochloric acid. The aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic layers were washed (brine) and dried (Na_2SO_4). The solvent was removed in vacuo at a temperature below 30 °C. The residue was purified via column chromatography (EtOAc/petroleum ether 1:3 to 2:1) affording the *trans*- **36** and *cis*-**35** carbonates as well as a dicarbamate **XV**. Yields: *Cis*-carbonate **35**: Yield: 0.010 g (0.022 mmol, 38%) as a colorless oil. *Trans*-carbonate **36** (14-*epi*): Yield: 5.0 mg (0.011 mmol, 19%) as a colorless oil. Dicarbamate **XV**: Yield: 0.010 g (0.016 mmol, 28%) as a pale-yellow oil. R_f (EtOAc/petroleum ether 2:1): 0.31. For spectroscopic data see supporting information.

(*S*)-5-Acetoxy-5-(6-((*E*)-2-((4*R*,5*S*)-2-oxo-5-pentyl-1,3-dioxolan-4-yl) vinyl)cyclohepta-1,3,5-trien-1-yl)pentanoic acid methyl ester (*cis*-carbonate) 35: R_f (EtOAc/petroleum ether 1:2): 0.50, $[\alpha]_D = +6.9°$ (c = 1.0, 22 °C, CH_2Cl_2), ^{1}H-NMR (600 MHz, C_6D_6): δ = 6.37–6.31 (m, 2H, H-8, H-9), 6.13–6.08 (m, 2H, H-7, H-12), 5.93–5.90 (m, 1H, H-10), 5.76 (dd, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, H-13), 5.41–5.38 (m, 1H, H-5), 4.39 (td, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 1.1 Hz, 1H, 14), 3.84 (ddd, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H-15), 3.34 (s, 3H, H-22), 2.77 (d, $^2J_{HH}$ = 13.3 Hz, 1H, H-21′), 2.31 (d, $^2J_{HH}$ = 13.3 Hz, 1H, H-21″), 2.11 (td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 2.0 Hz, 2H, H-2), 1.67 (s, 3H, H-24), 1.61–1.51 (m, 2H, H-4), 1.50–1.41 (m, 2H, H-3), 1.41–1.25 (m, 2H, H-16), 1.21–1.12 (m, 2H, H-19), 1.09–1.02 (m, 4H, H-17, H-18), 0.84 (t, $^3J_{HH}$ = 7.3 Hz, 3H, H-20). ^{13}C-NMR (150 MHz, C_6D_6): δ = 173.0 (C-1), 169.6 (C-23), 154.1 (C-25), 136.9 (C-12), 133.9 (C-6), 131.1 (C-8), 130.3 (C-9), 130.2 (C-11), 129.2 (C-10), 124.5 (C-7), 121.6 (C-13), 79.9 (C-14), 79.7 (C-15), 76.4 (C-5), 51.1 (C-22), 33.4 (C-2), 32.1 (C-4), 31.5 (C-18), 30.1 (C-16), 28.0 (C-21), 25.7 (C-17), 22.8 (C-19), 21.4 (C-3), 20.7 (C-24), 14.2 (C-20). IR (neat): $\tilde{\nu}$ = 3018 (w), 2956 (m), 2931 (m), 2862 (w), 1803 (s), 1737 (s), 1638 (w), 1437 (m), 1370 (m), 1238 (s), 1175 (m), 1041 (m), 975 (m), 851 (w), 745 (m), 668 (w), 643 (w), 634 (m), 623 (m), 608 (m), 596 (m) cm^{-1}. HRMS-ESI $C_{25}H_{34}O_7Na$ calcd.: 469.2197, found: 469.2188.

(*S*)-5-Acetoxy-5-(6-((*E*)-2-((4*S*,5*S*)-2-oxo-5-pentyl-1,3-dioxolan-4-yl) vinyl)cyclohepta-1,3,5-trien-1-yl)pentanoic acid methyl ester (*trans*-carbonate) 36 (14-*epi*): R_f (EtOAc/petroleum ether 1:2): 0.62, $[\alpha]_D = -59.8°$ (c = 1.0, 22 °C, CH_2Cl_2), ^{1}H-NMR (600 MHz, C_6D_6): δ = 6.38–6.31 (m, 2H, H-8, 9H-), 6.07 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.6 Hz, 1H,

H-7), 6.02 (d, $^3J_{HH}$ = 15.6 Hz, 1H, H-12), 5.93–5.90 (m, 1H, H-10), 5.73 (dd, $^3J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, H-13), 5.32 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, H-5), 4.09 (t, $^3J_{HH}$ = 7.9 Hz, 1H, H-14), 3.85 (td, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, H-15), 3.33 (s, 3H, H-22), 2.64 (d, $^2J_{HH}$ = 13.3 Hz, 1H, H-21′), 2.36 (d, $^2J_{HH}$ = 13.3 Hz, 1H, H-21″), 2.04 (t, $^3J_{HH}$ = 7.0, 2H, H-2), 1.71 (s, 3H, H-24), 1.66–1.62 (m, 1H, H-4′), 1.60–1.40 (m, 3H, H-3, H-4″), 1.30–1.14 (m, 6H, H-16, H-17, H-19), 1.12–1.04 (m, 2H, H-18), 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 3H, H-20). ^{13}C-NMR (150 MHz, C_6D_6): δ = 172.9 (C-1), 169.5 (C-23), 154.1 (C-25), 137.3 (C-12), 134.6 (C-6), 131.3 (C-8), 130.1 (C-9), 129.8 (C-11), 129.6 (C-10), 124.2 (C-7), 123.9 (C-13), 83.0 (C-14), 81.8 (C-15), 76.3 (C-5), 51.2 (C-22), 33.3 (C-2), 32.8 (C-16), 32.5 (C-4), 31.6 (C-18), 27.7 (C-21), 25.0 (C-17), 22.7 (C-19), 21.2 (C-3), 20.6 (C-24), 14.2 (C-20). IR (neat): $\tilde{\nu}$ = 3014 (w), 2952 (m), 2928 (m), 2861 (w), 1805 (s), 1737 (s), 1458 (w), 1438 (w), 1371 (m), 1239 (s), 1201 (m), 1174 (m), 1027 (m), 975 (w), 834 (w), 746 (m), 669 (w), 642 (w), 634 (w), 622 (w), 607 (w), 597 (w), 584 (w) cm^{-1}. HRMS-ESI $C_{25}H_{34}O_7Na$ calcd.: 469.2197, found: 469.2200.

(5*S*, 14*R*, 15*S*) 6,11-Methylene-LXB$_4$ methyl ester 37: Under Ar, the *cis*-carbonate **35** (0.010 g, 0.022 mmol, 1.0 eq.) was dissolved in dry methanol (2 mL) and cooled to 0 °C. Then sodium methoxide 0.5 M in methanol (0.22 mL, 0.11 mmol, 5.0 eq.) was added dropwise and the reaction was stirred at 0 °C for three hours. The reaction was brought to room temperature und stirred overnight before being quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed (brine) and dried (Na_2SO_4). The solvent was removed in vacuo at a temperature below 30 °C and the rotary evaporator was ventilated with argon. The residue was purified via HPLC affording the triole **37** (8.0 mg, 0.021 mmol, 94 %) as a colorless oil. R_f (EtOAc/petroleum ether 2:1): 0.20, HPLC: (Nucleosil 50/5, 4 × 250 mm, 2 mL/min, 130 bar, UV 254 nm) k = 3.88 (60 % EtOAc/Hex). $[\alpha]_D$ = + 13.1° (*c* = 0.7, 22 °C, CH_2Cl_2), ^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 6.54 (dd, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, H-9), 6.50 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, H8), 6.33 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-12), 6.16 (d, $^3J_{HH}$ = 5.8 Hz, 1H, H-10), 6.12 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, H-13), 6.12 (d, $^3J_{HH}$ = 5.6 Hz, 1H, H-7), 4.16 (t, $^3J_{HH}$ = 6.5 Hz, 1H, H-5), 4.10 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, H-14), 3.69 (dt, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, H-15), 3.62 (s, 3H, H-22), 2.99 (d, $^2J_{HH}$ = 13.1 Hz, 1H, H-21″), 2.30 (t, $^3J_{HH}$ = 6.8 Hz, 2H, H-2), 2.22 (d, $^2J_{HH}$ = 13.1 Hz, 1H, H-21′), 1.64–1.61 (m, 2H, H-4), 1.60–1.55 (m, 2H, H-3), 1.52–1.39 (m, 3H, H-16, H-17′), 1.34–1.28 (m, 5H, H-17″, H-18, H-19), 0.89 (t, $^3J_{HH}$ = 7.0, 3H, H-20). ^{13}C-NMR (150 MHz, CD_2Cl_2): δ = 174.9 (C-1), 139.0 (C-6), 134.2 (C-12), 132.2 (C-11), 130.5 (C-9), 130.4 (C-8), 129.6 (C-13), 127.6 (C-10), 122.9 (C-7), 76.6 (C-14), 76.1 (C-5), 75.0 (C-15), 52.1 (C-22), 34.7 (C-4), 34.2 (C-2), 33.0 (C-16), 32.4 (C-18), 27.2 (C-21), 26.1 (C-17), 23.2 (C-19), 21.8 (C-3), 14.4 (C-20). IR (neat): $\tilde{\nu}$ = 3415 (br), 3014 (w), 2952 (s), 2925 (s), 2856 (s), 1735 (s), 1465 (m), 1250 (m), 1064 (w), 838 (m), 741 (s), 672 (w), 629 (m), 618 (s), 595 (m), 585 (s) cm^{-1}. HRMS-ESI $C_{22}H_{34}O_5Na$ calcd.: 401.2298, found: 401.2308.

(5*S*, 14*S*, 15*S*) 6,11-Methylene-LXB$_4$ methyl ester 38 (14-*epi*): Under Ar, the *trans*-carbonate **36** (0.013 g, 0.029 mmol, 1.0 eq.) was dissolved in dry methanol (2 mL) and cooled to −0 °C. Then sodium methoxide 0.5 M in methanol (0.29 mL, 0.15 mmol, 5.0 eq.) was added dropwise and the reaction was stirred at 0 °C for one hour. The reaction was brought to room temperature und stirred overnight before being quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed (brine) and dried (Na_2SO_4). The solvent was removed in vacuo at a temperature below 30 °C and the rotary evaporator was ventilated with argon. The residue was purified via HPLC affording the triole **38** (0.010 g, 0.026 mmol, 91 %) as a colorless oil. R_f (EtOAc/petroleum ether 2:1): 0.20, HPLC: (Nucleosil 50/5, 4 × 250 mm, 2 mL/min, 130 bar, UV 254 nm) k = 3.89 (60 % EtOAc/Hex). $[\alpha]_D$ = −11.6° (*c* = 1.0, 22 °C, CH_2Cl_2), ^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 6.56–6.48 (m, 2H, H-8, 9), 6.36 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-12), 6.17 (d, $^3J_{HH}$ = 5.5 Hz, 1H, H-10), 6.13 (d, $^3J_{HH}$ = 5.3 Hz, 1H, H-7), 6.05 (dd, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, H-13), 4.16 (t, $^3J_{HH}$ = 5.9 Hz, 1H, H-5), 3.99 (t, $^3J_{HH}$ = 6.3 Hz, 1H, H-14), 3.63 (s, 3H, H-22), 3.49 (ddd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 2.6 Hz, 1H, H-15), 2.72 (d, $^2J_{HH}$ = 13.1 Hz, 1H, H-21′), 2.42 (d, $^2J_{HH}$ = 13.1 Hz, 1H, H-21″), 2.32–2.27 (m, 2H, H-2), 1.66–1.55 (m, 3H, H-3″, H-4), 1.53–1.44 (m, 3H, H-3′, H-16″, H-17′), 1.43–1.36 (m, 1H, H-16′), 1.36–1.26 (m, 5H, H-17″, H-18, H-19), 0.88 (t, $^3J_{HH}$ = 7.2 Hz, 3H, H-20). ^{13}C-NMR (150 MHz, CD_2Cl_2): δ = 174.7 (C-1), 139.2 (C-6), 133.5 (C-12), 132.0 (C-11), 131.1 (C-13), 130.5 (C-8), 130.4 (C-9), 127.4 (C-10), 122.6 (C-7), 76.5 (C-14), 75.6 (C-5), 75.2 (C-15), 52.0 (C-22), 34.8 (C-4), 34.1 (C-2), 33.6 (C-16), 32.4 (C-18), 27.7 (C-21), 25.9 (C-17), 23.2 (C-19), 21.7 (C-3), 14.4 (C-20). IR (neat): $\tilde{\nu}$ = 3413 (br), 3014 (w), 2952 (s), 2927 (s), 2856 (m), 1742 (s), 1600 (w), 1469 (m), 1373 (m), 1247 (s), 1048 (m), 838 (m), 781 (w), 746 (w), 697 (w), 668 (w), 648 (w), 620 (w), 608 (w), 592 (w) cm^{-1}. HRMS-ESI $C_{22}H_{34}O_5Na$ calcd.: 401.2298, found: 401.2305.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Convergent synthesis · Horner olefination · Luche reduction · Natural product · Total synthesis

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