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A general synthesis of aromatic and heteroaromatic lipoxin B_4 analogues†

Benjamin Owen and Patrick J. Guiry *

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Lipoxins are an important class of pro-resolving mediators that play a crucial role in the resolution of inflammation. Thus, the synthesis of more chemically and metabolically stable synthetic lipoxin analogues is an area of significant interest. Whereas synthetic analogues of lipoxin A_4 (LXA_4) have been well studied, analogues of lipoxin B_4 (LXB_4) have been the focus of considerably less attention. Herein we report the asymmetric synthesis of a focused library of LXB_4 mimetics in which the triene core of the molecule has been replaced with different aromatic and heteroaromatic rings. The synthesis of each of these analogues was achieved by a general strategy in which the key steps were a Suzuki cross coupling between a common upper chain fragment and an aromatic lower chain, followed by a stereoselective ketone reduction.

Introduction

Specialized pro-resolving mediators (SPMs) are a class of endogenously derived lipid mediators that are known to play a crucial role in the resolution of the innate inflammatory response.[1,2] The two lipoxins, lipoxin A_4 (**1**) and lipoxin B_4 (**2**) (Fig. 1a), are important members of this class of compounds and both have been shown to stimulate a range of pro-resolving bioactions such as slowing the recruitment of polymorphonuclear neutrophils (PMNs) to the site of inflammation, while accelerating the recruitment of monocytes and stimulating the phagocytosis of apoptotic PMNs.[3–5] However, a major drawback that limits the therapeutic use of these compounds is their chemical instability and rapid enzymatic degradation *in vivo*. As a result, there has been a lot of interest in designing synthetic lipoxin analogues that are more metabolically stable, easier to handle, and more synthetically accessible.[6,7] Alongside oxidation of a hydroxy group to the corresponding ketone, one of the major pathways of enzymatic degradation for both LXA_4 and LXB_4 is known to be reduction of one of the C=C double bonds in the triene core to form the metabolites 13,14-dihydro-LXA_4 and 6,7-dihydro-LXB_4 respectively.[8] Inspired by this observation, we have previously reported the synthesis and biological evaluation of a number of different aromatic analogues of LXA_4 in which the triene core of the molecule has been replaced with a more chemically stable aromatic or heteroaromatic ring (Fig. 1b). The first analogue synthesized, benzo-LXA_4 (**3**), was shown to stimulate an increase in the phagocytosis of apoptotic PMNs comparable to native LXA_4.[9] Since then, we have demonstrated the favourable anti-

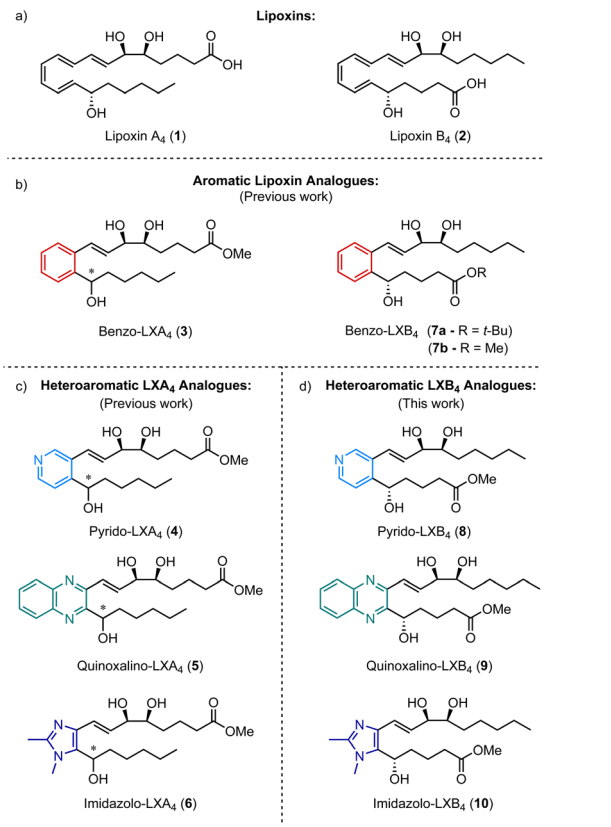

Fig. 1 Overview of previously synthesized analogues of LXA_4 and the corresponding LXB_4 analogues synthesized in this work.

Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: p.guiry@ucd.ie

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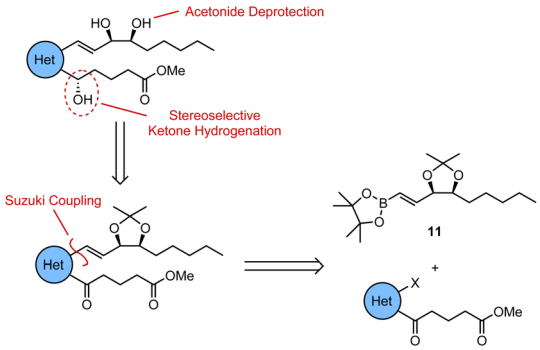
inflammatory properties of LXA_4 mimetics containing a heterocyclic core such as pyrido-LXA_4 (**4**),[10] quinoxalino-LXA_4 (**5**)[11] and imidazolo-LXA_4 (**6**) (Fig. 1c).[12] However, despite the progress made in the development of synthetic analogues of LXA_4, the synthesis and evaluation of stable analogues of its isomer LXB_4 has been the focus of considerably less attention. Although the biological properties of LXA_4 and LXB_4 are similar, they are not identical. For example, LXB_4 has been shown to have consistently more potent neuroprotective effects on retinal ganglion cells than LXA_4 both *in vitro* and *in vivo*.[13] Furthermore, it is clear that LXA_4 and LXB_4 operate through completely different signalling pathways.[14] LXA_4 is known to bind to FPR2 (also known as the ALX receptor) expressed in the cell membranes of human PMNs and other immune cells.[15] In contrast, no receptor for LXB_4 has so far been identified. As a result, the mechanism of action of LXB_4 is less well understood and research into the therapeutic benefits of LXB_4 and its analogues has been somewhat neglected in comparison to LXA_4. We initially reported a stereoselective synthesis of benzo-LXB_4 (**7a**) alongside benzo-LXA_4 (**3**) and showed that **7a** was also able to stimulate phagocytosis of apoptotic PMNs.[9] Since then, however, the only other examples of LXB_4 analogues have been reported by Nubbemeyer and co-workers who developed a synthesis of analogues based on a cycloheptatriene core.[16,17]

Given our experience with heteroaromatic analogues of LXA_4, we aimed to develop a general synthetic route that would allow for the efficient stereoselective synthesis of a focused library of LXB_4 mimetics containing a variety of different aromatic and heteroaromatic cores. This would rapidly expand the number of LXB_4 analogues accessible and hopefully lead to better understanding of LXB_4 and the potential therapeutic applications of its stable synthetic analogues in the future. To demonstrate this, we selected four different LXB_4 analogues as targets to be synthesized: benzo-LXB_4 (**7**), pyrido-LXB_4 (**8**), quinoxalino-LXB_4 (**9**) and imidazolo-LXB_4 (**10**) (Fig. 1d). Targets containing these particular heteroaromatic cores were chosen based on the findings of our SAR studies on heteroaromatic LXA_4 mimetics. In particular, analogues containing a dimethylimidazole core[12,18] and a quinoxaline core[11] have been shown to be especially potent and effective inhibitors of LPS-induced NF-κB activity. The success of LXA_4 analogues based on a dimethylimidazole core and a quinoxaline core encouraged us to also investigate the synthesis of LXB_4 analogues containing these key heterocycles. A summary of the results of our previous SAR studies on synthetic LXA_4 mimetics is shown in the ESI (ESI, Table S1†).

Results and discussion

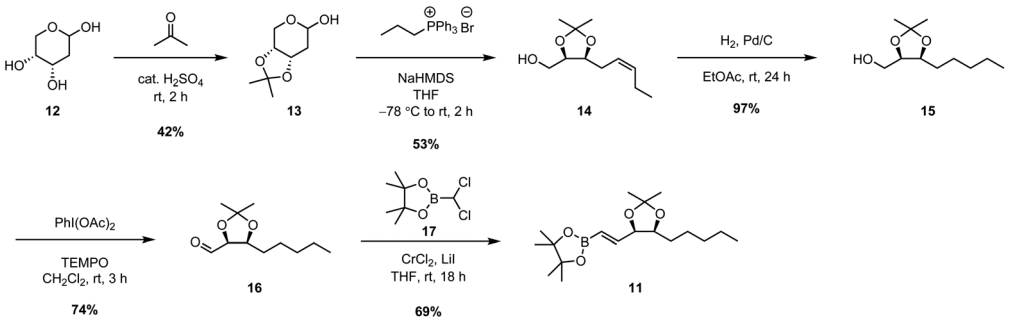
For all four of the target analogues, we proposed a general retrosynthetic analysis that would allow us to vary the heterocyclic core in a modular fashion without needing to redesign the synthesis each time (Scheme 1). The key steps of this general strategy were anticipated to be (i) a Suzuki coupling between a boronic ester "upper chain" and an aromatic δ-keto ester "lower chain", (ii) a stereoselective ketone reduction, and (iii) an acetonide deprotection of the 1,2-diol. Upper chain **11** would thus serve as a common fragment in the synthesis of each of the target analogues, while the synthesis of the lower chain would be slightly different each time in order to successfully vary the aromatic or heterocyclic core.



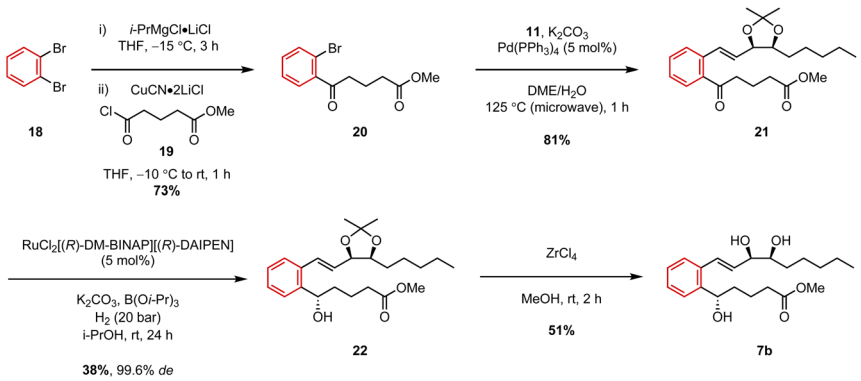
Scheme 1 Proposed general retrosynthetic analysis for the target (hetero)aromatic LXB_4 analogues.

To begin with, the synthesis of upper chain **11** was achieved *via* a chiral pool strategy starting from 2-deoxy-D-ribose (**12**) (Scheme 2). Following acetonide protection of the 1,2-diol, a Wittig olefination was carried out between **13** and the ylide generated *in situ* by deprotonation of propyl phosphonium bromide with NaHMDS. This afforded alkene **14** in 53% yield exclusively as the *Z*-geometric isomer. However, the *E*/*Z*-selectivity of the Wittig reaction was inconsequential as alkene **14** was subsequently reduced to the corresponding alkane **15** in 97% yield by H_2 gas and Pd/C. To complete the synthesis, alcohol **15** was first oxidized to aldehyde **16** in 74% yield using catalytic TEMPO, and PIDA as the co-oxidant. After that, the key vinyl boronic ester functionality was successfully installed *via* a chromium(II)-mediated Takai olefination with (dichloromethyl)boronic ester **17**. This afforded upper chain **11** in 69% yield with only the desired *E*-geometric isomer being detectable by ^{1}H-NMR spectroscopic analysis.

With the upper chain coupling partner in hand, we then turned our attention to completing the synthesis of our first target analogue, benzo-LXB_4 (**7b**). We have previously reported the synthesis of this particular compound, albeit as the *tert*-butyl ester **7a**, by employing a somewhat different strategy involving a Heck coupling as the key retrosynthetic disconnection.[9] This work therefore represents an alternative approach to the target analogue. The δ-keto ester lower chain **20** was prepared in a single step from 1,2-dibromobenzene (**18**) using turbo-Grignard methodology developed by Knochel and co-workers.[19] 1,2-Dibromobenzene was first treated with a solution of i-PrMgCl·LiCl to induce Br/Mg exchange, and the resulting ArMgCl·LiCl species was then transmetallated to copper by addition of CuCN·2LiCl and subsequently trapped with acid chloride **19** to afford lower chain δ-keto ester **20** in 73% yield (Scheme 3). A Suzuki coupling was then attempted



Scheme 2 Synthesis of upper chain boronic ester **11**.

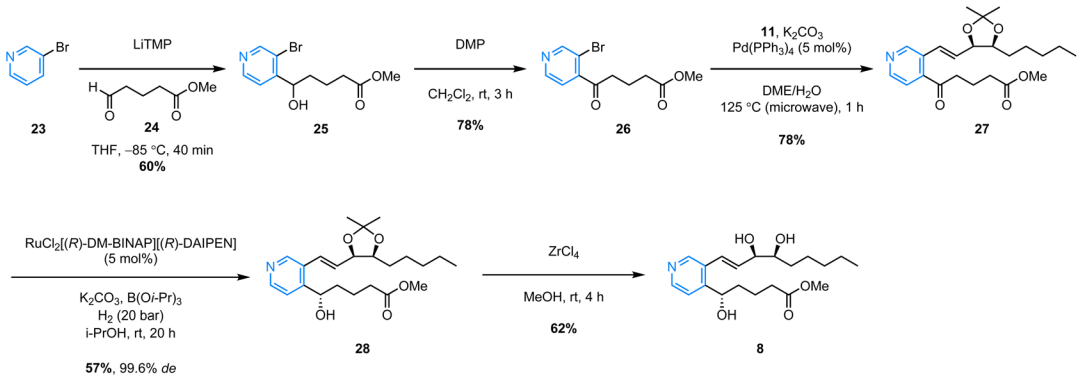


Scheme 3 Synthesis of benzo-LXB_4 (**7b**).

by heating the two coupling partners, **11** and **20**, under microwave-irradiation in the presence of $Pd(PPh_3)_4$ and K_2CO_3. Pleasingly, these microwave-assisted conditions furnished the desired couple product **21** in an excellent 81% yield after only 1 hour at 125 °C. After this, we then sought to carry out a stereoselective reduction of the ketone *via* a ruthenium-catalyzed Noyori hydrogenation. Due to its ability to tolerate a large number of different heterocyclic ketones,[20] we hoped this catalytic system would be the most general and reliable for the synthesis of our LXB_4 analogues. The reduction of **21** was thus carried out under 20 bar of H_2 gas in the presence of the catalyst, $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] which afforded the desired (*S*)-alcohol **22** in 38% yield after 24 h.

Although the isolated yield was somewhat moderate, the diastereoselectivity was excellent with **22** being obtained in 99.6% de (99.8 : 0.2 dr) as determined by SFC analysis. We also observed that it was important to use K_2CO_3 as the base instead of KO*t*-Bu in order to avoid transesterification of the methyl ester with the i-PrOH solvent. The stereochemistry of the product was tentatively assigned as (*S*)-based on the transition state model associated with the (*R*,*R*)-Ru catalyst,[21] but this assignment was not confirmed. Nevertheless, we have previously confirmed predictions made by the transition state model on multiple separate occasions by using both X-ray crystallography and Mosher's ester analysis, so we place high confidence in our stereochemical assignment of **22**.[11,12,18] Finally, to complete the synthesis, the acetonide protecting group was removed using $ZrCl_4$ in MeOH and the target analogue **7b** was obtained in 51% yield.

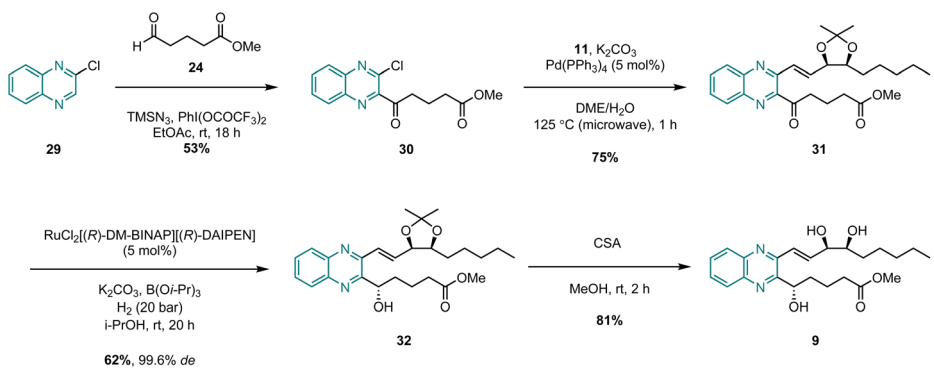
The successful synthesis of benzo-analogue **7b** confirmed the viability of our synthetic strategy, so in order to further explore the generality of the route, we then turned our attention to synthesizing examples of heteroaromatic analogues of LXB_4. Pyrido-LXB_4 (**8**) was thus chosen as our first target heteroaromatic analogue (Scheme 4). The synthesis of pyridine lower chain ketone **26** was achieved in two straightforward steps. The first step involved a LiTMP-mediated deprotonation of 3-bromopyridine (**23**) at −85 °C followed by trapping of the resulting lithiated species with aldehyde **24**. Provided that the temperature of the reaction was maintained below −80 °C, clean conversion to the desired product was observed and alcohol **25** was isolated in 60% yield following column chromatography.[22] The second step was a DMP-mediated oxidation of the secondary alcohol which afforded lower chain ketone **26** in 78% yield. With both coupling partners in hand, we were pleased to find that the same conditions used to synthesize the benzo-analogue **7b** could be extended to the synthesis of pyrido-analogue **8** with little difficulty. The microwave-assisted Suzuki coupling between lower chain **26** and upper chain **11** afforded coupled product **27** in an excellent 78% yield. After that, the stereoselective Noyori hydrogenation conditions converted ketone **27** to (*S*)-alcohol **28** in 57% yield. Once again,



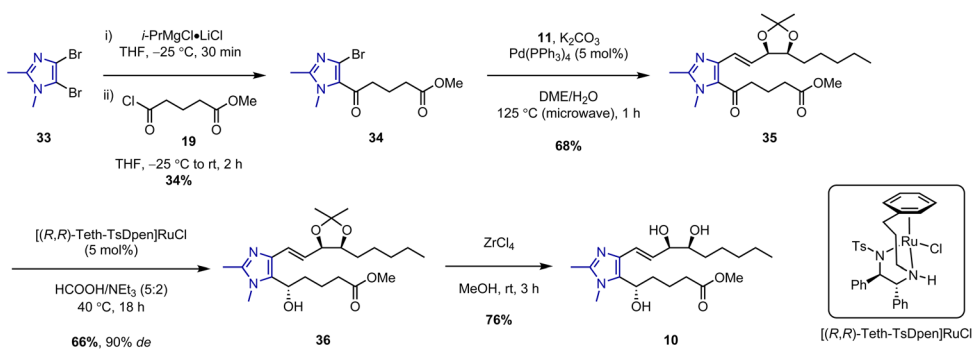
Scheme 4 Synthesis of pyrido-LXB_4 (**8**).

the stereoselectivity was excellent with **28** being obtained in 99.6% de as confirmed by SFC analysis. Finally, the $ZrCl_4$/MeOH acetonide deprotection conditions afforded the target analogue, pyrido-LXB_4 (**8**), in 62% yield. The synthesis of a second heteroaromatic target, quinoxalino-LXB_4 (**9**) also proceeded as planned (Scheme 5). The quinoxaline lower chain **30** was prepared in one step from 2-chloroquinoxaline (**29**) and aldehyde **24** *via* a cross-dehydrogenative coupling using conditions reported by Antonchick and co-workers.[23] After that, the microwave-assisted Suzuki coupling between **11** and **30** furnished coupled ketone **31** in 75% yield, and the subsequent stereoselective Noyori hydrogenation led to the successful formation of (*S*)-alcohol **32** in 62% yield and excellent 99.6% de. However, a slight complication arose in the final step. It was found that $ZrCl_4$/MeOH could not be used to remove the acetonide protecting group as these conditions led to decomposition of the starting material. Camphorsulfonic acid (CSA) in MeOH was therefore used instead to afford the target analogue, quinoxalino-LXB_4 (**9**) in 81% yield.

The synthesis of a fourth and final LXB_4 analogue based on a dimethylimidazole core was then investigated (Scheme 6). Imidazole lower chain **34** was prepared in a single step *via*



Scheme 5 Synthesis of quinoxalino-LXB_4 (**9**).



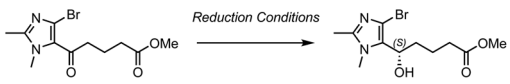
Scheme 6 Synthesis of imidazolo-LXB_4 (**10**).

addition of i-PrMgCl·LiCl to dibromoimidazole **33** followed by trapping of the resulting magnesiated intermediate with acid chloride **19**. This led to regiospecific acylation at C-5 with no trace of any C-4 acylated product observed. However, the isolated yield of **34** was somewhat low due to competing protonation of the magnesiated intermediate. Protonation was typically observed in an equal ratio to acylation even when the reaction was conducted under an inert atmosphere with anhydrous THF. This proved difficult to avoid, presumably due to the presence of acidic α-protons in acid chloride **19**. Nevertheless, despite the low yield, we believed the ability to rapidly access **34** in one step was still preferable to developing an alternative multi-step route. δ-Keto ester **34** was thus carried forward to the subsequent microwave-assisted Suzuki coupling with upper chain **11** to give the desired coupled product **35** in 68% yield. However, when a stereoselective Noyori hydrogenation of **35** was attempted in the presence of the (*R*,*R*)-Ru catalyst and 20 bar of H_2 gas, no reaction was observed after 24 h. This was surprising because we had previously used these conditions to successfully carry out asymmetric reductions of related imidazole substrates.[11,12,18]

We therefore decided to use uncoupled ketone **34** as a model substrate to screen for suitable alternative stereoselective reduction conditions (Table 1). As with coupled ketone **35**, lower chain **34** was also unreactive under the asymmetric Noyori hydrogenation conditions regardless of whether K_2CO_3 or KO*t*-Bu was used as the base (Table 1, entries 1 and 2). A number of other asymmetric reduction conditions were attempted, but all were unsuccessful (Table 1, entries 3–5).

Eventually, a breakthrough was made when tethered transfer hydrogenation catalyst, [Teth-TsDpen]RuCl was identified.

Table 1 Attempted asymmetric reduction conditions



34 (*S*)-**37**

Entry	Conditions	Yield	er
1	$RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (5 mol%) K_2CO_3, B(Oi-Pr)$_3$, i-PrOH, rt, 24 h, H_2 (20 bar)	No reaction	n/a
2	$RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (5 mol%) KO*t*-Bu, B(Oi-Pr)$_3$, i-PrOH, rt, 24 h, H_2 (20 bar)	No product[a]	n/a
3	(−)-DIP-chloride, Et_2O, −20 °C, 72 h	No reaction	n/a
4	(*R*)-CBS cat. (10 mol%), BH_3·THF, THF, rt, 24 h	No reaction	n/a
5	RuCl[*p*-cymene][(*S*,*S*)-TsDpen] (5 mol%) HCOOH/NEt_3 (5 : 2), rt, 4 days	Trace	n/a
6	[(*S*,*S*)-Teth-TsDpen]RuCl (5 mol%) HCOOH/NEt_3 (5 : 2), 40 °C, 24 h	46%	22 : 78[b]

[a] Transesterification to the i-propyl ester observed. [b] Major enantiomer was the unexpected (*R*)-enantiomer.

This catalytic system has been extensively studied by Wills and co-workers,[24] and we were encouraged by their reports of its application to the reduction of similar imidazole-containing substrates.[25] We thus reacted **34** with [(*S*,*S*)-Teth-TsDpen]RuCl in the presence of an azeotropic mixture of formic acid and triethylamine, and to our delight, complete conversion to alcohol **37** was observed after 24 h (Table 1, entry 6). However, despite this being the only catalytic system to result in the successful formation of the alcohol product, the enantioselectivity of the reaction was somewhat low (78 : 22 er). Additionally Mosher's ester analysis (ESI, Fig. S1 and S2†) was used to confirm that the major product was actually (*R*)-**37**, which is the opposite enantiomer to that predicted by the transition state model associated with ruthenium/(η^6-arene)(TsDpen) catalysts of this type. The selectivity of the transfer hydrogenation is believed to be driven by a stabilizing C–H/π-intereaction in the transition state between an electron-deficient C–H bond on the η^6-arene ligand and the aromatic substituent of the ketone.[26,27] However, in this case, it is possible that the dimethyl-imidazole substituent is not sufficiently electron rich and too sterically encumbered to make this C–H/π-interaction favourable. Therefore, this would mean that the selectivity is instead driven by the avoidance of unfavourable steric interactions between the η^6-arene ligand and the bulky imidazole substituent.

Based on the observation that [(*S*,*S*)-Teth-TsDpen]RuCl converted **34** preferentially to (*R*)-**37**, these transfer hydrogenation conditions were then repeated with coupled ketone **35** using the opposite hand of the catalyst, [(*R*,*R*)-Teth-TsDpen]RuCl, with the expectation that the desired (*S*)-epimer would be obtained as the major product. This reaction proceeded well, and the desired product **36** was obtained in 66% yield after 18 h. Pleasingly, only a single diastereomer was detectable in the ^{1}H-NMR spectrum and SFC analysis confirmed that **36** was obtained in 90% de (95 : 5 dr). This showed much higher selectivity can be obtained when the stereoselective transfer hydrogenation is carried out on the more sterically hindered coupled ketone as opposed to the less sterically hindered uncoupled ketone **34**. With **36** finally obtained in high diastereomeric purity, the synthesis of the target analogue could be completed. Acetonide deprotection of **36** was conducted using $ZrCl_4$/MeOH to afford imidazolo-LXB_4 (**10**) in 76% yield.

Conclusion

An efficient and modular synthesis of aromatic and heteroaromatic lipoxin B_4 analogues has been developed, and a focused library of compounds was generated in order to demonstrate the robustness and generality of the synthetic strategy. In total, the asymmetric synthesis of four aromatic LXB_4 analogues was successfully completed. This included a new synthesis of benzo-LXB_4 as well as the first syntheses of LXB_4 analogues containing a heterocyclic core. The heteroaromatic analogues that were successfully synthesized in this study were based on a pyridine, a dimethylimidazole and a quinoxaline heterocyclic

core. However, the general principles of this synthetic strategy could, in theory, be extended to the synthesis of analogues containing a variety of other heterocyclic cores. We hope to report a detailed evaluation of the anti-inflammatory properties of each of the heteroaromatic LXB_4 analogues synthesized in this study in due course. The results of these studies could then potentially form the basis of a larger study probing the structure–activity relationships of (hetero)aromatic mimetics of lipoxin B_4 which would allow us to learn more about the important differences between lipoxin A_4 and lipoxin B_4.

Conflicts of interest

There are no conflicts to declare.

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