Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Determination of the absolute configuration of two $\alpha_v\beta_6$ integrin inhibitors for the treatment of idiopathic pulmonary fibrosis and investigations on the asymmetric 1,4-addition of arylboronic acids to crotonate esters bearing a C4-oxygen substituent

Panayiotis A. Procopiou [a,*], Tim N. Barrett [a], Royston C. B. Copley [b], Christopher J. Tame [a]

[a] *Medicinal Chemistry, Fibrosis and Lung Injury DPU, Respiratory Therapeutic Area, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom*

[b] *Platform Technology & Science, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom*

ARTICLE INFO

Article history:
Received 1 August 2017
Revised 8 August 2017
Accepted 18 August 2017
Available online xxxx

Dedicated to the memory of Dr. Howard Flack

ABSTRACT

The absolute configuration of two novel $\alpha_v\beta_6$ integrin inhibitors was established via degradation to the corresponding C3-aryl substituted butyrolactone. The configuration of the resulting lactones was established by asymmetric synthesis using 1,4-addition of arylboronic acids to butenolide, catalysed by bis(norbornadiene)rhodium (I) tetrafluoroborate in the presence of (*R*)-BINAP, and confirmed by X-ray crystallography. Studies on arylboronic acid conjugate additions to acyclic crotonate esters bearing a γ-oxygen substituent are also reported. Three Rh catalysts were investigated and the one giving the highest enantioselectivity was bis(norbornadiene)rhodium (I) tetrafluoroborate.

1. Introduction

Idiopathic pulmonary fibrosis is a chronic lung disease, which is characterised by progressive deterioration of lung function, due to deposition of collagen within the lungs. It affects approximately 500,000 people in the USA and Europe, and patients' mean life-expectancy is approximately 3 years following diagnosis. Idiopathic pulmonary fibrosis is poorly treated and to improve quality and duration of life and alleviate suffering novel therapeutic approaches are urgently required.[1] Pirfenidone, a broad spectrum kinase inhibitor, and nintedanib, a multiple tyrosine-kinase inhibitor have recently been approved for use on patients with idiopathic pulmonary fibrosis.[2] Both compounds are administered orally at high doses, at least twice a day and, with low patient compliance due to gastro-intestinal issues. (*S*)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid hydrochloride **1** is a potent $\alpha_v\beta_6$ integrin inhibitor, suitable for dosing by inhalation, which is in clinical evaluation for the treatment of idiopathic pulmonary fibrosis (Fig. 1).[3] It was discovered by our group and so far we have only reported the determination of its absolute configuration using asymmetric total synthesis.[4] More recently, we have identified a new series of $\alpha_v\beta_6$ integrin inhibitors **2**, which are suitable for oral dosing, for example compound **2a** (X = $MeOCH_2CH_2O$–) and **2b** (X = *N*-morpholinyl).[5,6] Both of these compounds possess two stereogenic centres and we have very recently reported the determination of the absolute configuration of the 3-fluoropyrrolidine asymmetric centre.[7] Herein, we disclose our studies towards the establishment of the absolute configuration of the benzylic asymmetric centre of both **2a** and **2b**, and related work on asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters.

2. Results and discussion

2.1. Degradation studies

We considered initially performing an asymmetric total synthesis as we had previously done for the establishment of the absolute configuration of **1**;[4] however, we rejected this approach because of the long period of time anticipated to complete such a task, but also due to concerns regarding complications with individual chemical transformations, such as the reduction of a tertiary amide in the presence of the fluoride group. We opted instead for a shorter degradation approach leading to a fragment, which can be characterised more readily or be synthesised in a well-defined and predictive way. We envisaged reacting **2a** or **2b** with iodomethane to provide the respective quaternary ammonium iodide

* Corresponding author. Tel.: +44 1438 790496; fax: +44 1438 768302.
E-mail address: pan.a.procopiou@gsk.com (P.A. Procopiou).

http://dx.doi.org/10.1016/j.tetasy.2017.08.017
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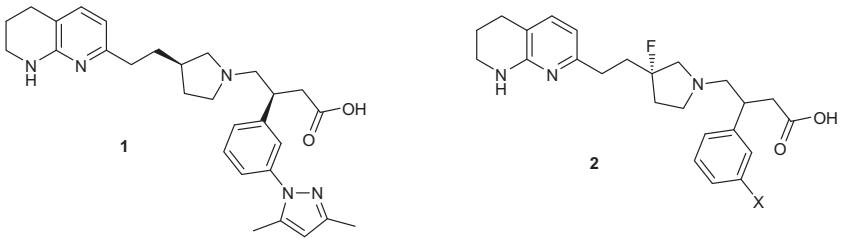


Figure 1. Novel $\alpha_v\beta_6$ integrin inhibitors designed for the treatment of idiopathic pulmonary fibrosis.

3, which upon addition of base and heating at elevated temperatures might cause cyclisation to occur with the simultaneous formation of the *N*-methyl pyrrolidine **4** and γ-lactone **5** (Scheme 1). The reaction of **2a** and **2b** with excess iodomethane in DCM at room temperature overnight proceeded smoothly forming in each case a new product **3** having a mass ion compatible with monomethylation by LCMS. Clearly there are other reactive centres where methylation could occur, such as methylation of the tetrahydronaphthyridine or conversion of the carboxylic acid to the methyl ester. These products were however less likely to form as the nucleophilicity of the naphthyridine and carboxylic acid groups is much lower than that of the pyrrolidine nitrogen. The addition of solid potassium carbonate to the quaternary ammonium salts **3a** and **3b** followed by heating at 120 °C for 1 h using microwave irradiation provided after chromatography lactones **5a** and **5b** in 82% and 64% yield over two steps. Both lactones were found to be pure by analytical HPLC on a chiral stationary phase, and to have a positive specific rotation $[\alpha]_D^{22}$ = +42 (*c* 1.06, $CHCl_3$) for **5a**, and $[\alpha]_D^{22}$ = +37 (*c* 1.40, $CHCl_3$) for **5b**. Lactones **5a** and **5b** have not previously been reported in the literature, so it was necessary to synthesise authentic samples of these using a stereospecific method for comparison with the lactones derived by degradation.

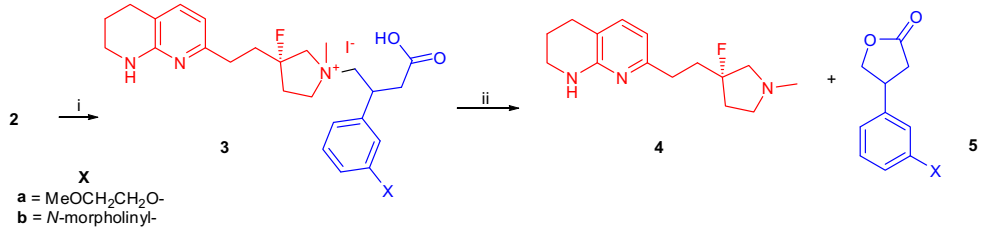
2.2. Asymmetric conjugate addition to butenolide 7

We envisaged synthesising lactones **5a** and **5b** in one step by the method of Hayashi et al.,[8] who reported the asymmetric conjugate addition of arylboronic acids **6** (5 equiv.) to a variety of acyclic α,β-unsaturated esters using acetylacetonatobis(ethylene)rhodium (I), [Rh(acac)$(C_2H_4)_2$], as the catalyst and in the presence of (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [(*S*)-BINAP] as the chiral ligand, at 100 °C (Scheme 2).

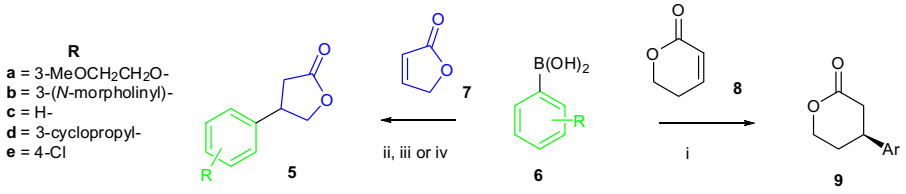
In addition, two cyclic substrates were examined, butenolide **7** and the six-membered homologue 5,6-dihydro-2*H*-pyran-2-one **8** to which a variety of arylboronic acids **6** were added in the presence of (*S*)-BINAP. High yields and high enantioselectivity were reported for all addition products **9**. However, only one addition product was reported for butenolide **7**, namely the addition of phenylboronic acid **6c** to provide lactone (*S*)-**5c** in 33% yield and with 96% ee. Despite the reported low yield of **5c**, we were still interested in utilising this methodology to obtain sufficient material for characterisation and comparison with the degradation derived lactones **5a** and **5b**. When we attempted to react **7** with commercially available boronic acid **6a** in the presence of a catalytic amount of chloro(1,5-cyclooctadiene)rhodium(II) dimer {[RhCl(cod)]$_2$}, and (*R*)-BINAP using aq. KOH solution as base in 1,4-dioxane at 100 °C for 1 h using microwave irradiation, conditions that we used very recently for adding arylboronic acids to acyclic α,β-unsaturated esters,[4] we found that although **5a** was obtained in 99% yield, there was no asymmetric induction (chiral HPLC indicated a mixture of 52:48). We repeated the reaction using the same conditions with 3-cyclopropylphenylboronic acid **6d**, which we synthesised for another project, and confirmed that the resulting lactone **5d** was also a mixture (50.4:49.6 by chiral HPLC). As the catalyst we used was different from the catalyst that Hayashi et al. had used, we repeated the 1,4-addition of **6d** (1.4 equiv.) to **7** using the same catalyst Rh(acac)$(C_2H_4)_2$, (*R*)-BINAP (3 mol% of each) and same reaction conditions, 1,4-dioxane–water (10:1), at 100 °C for 5 h and observed a very slow reaction with only a small amount of product **5d** forming by LCMS. The lack of reactivity of Rh(acac)$(C_2H_4)_2$ and selectivity of [RhCl(cod)]$_2$ prompted us to abandon this method and investigate the addition of boronic acids to acyclic α,β-unsaturated esters.

2.3. Asymmetric conjugate addition to acyclic esters

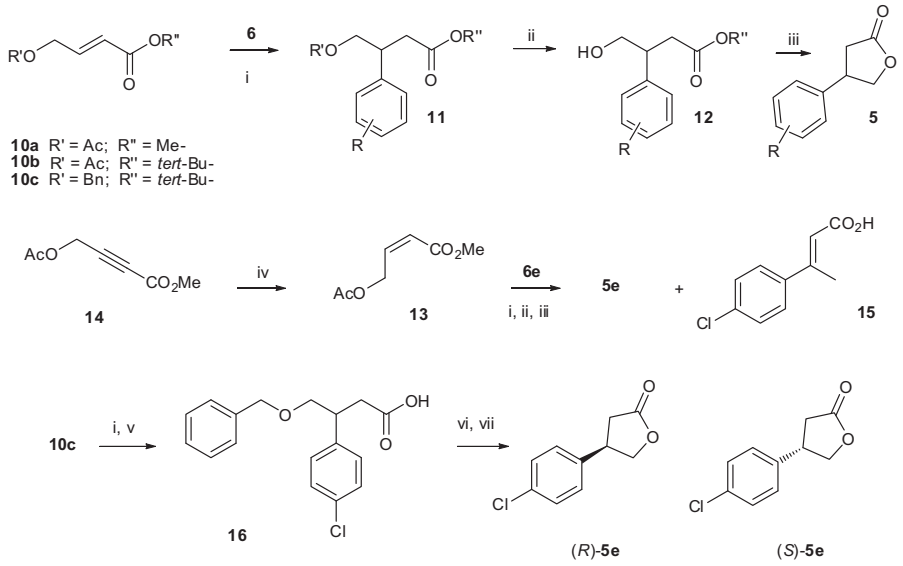
The systematic investigation of crotonic acid esters possessing a γ-oxygen substituent has not been reported so far, apart from a single application to ethyl 2-(oxetan-3-ylidene)acetate to which 4-chlorophenylboronic acid was added in 56% yield.[9] In contrast, investigations with γ-amino substituted crotonate esters have been reported and found applications in Helmchen's synthesis of Baclofen,[10] (*R*)-Rolipram,[11] Belyk's application to ethyl *N*-benzylpyrroline carboxylate,[12] Collier's ethyl 2-(azetidin-3-ylidene)acetate[13] and our own integrin work.[4,14] We envisaged using γ-oxygen substituted crotonate esters **10** as substrates for the 1,4-addition of arylboronic acids **6** to provide **11** (Scheme 3). A suitable γ-oxygen substituent would be an ester group, such as an acetate group, which would be readily removed by hydrolysis to give the hydroxy acid **12**. Alternatively, an ether group such as a γ-benzyloxy group, which could readily be converted into **12** would be worth investigating. Finally, cyclisation of the hydroxycrotonic acid **12** with anhydrous acid would be expected to provide the



Scheme 1. *Reagents and conditions*: i) MeI, DCM, room temperature, 18 h; ii) K_2CO_3, 120 °C, 1 h, 82% (two steps) for **5a** and 64% for **5b**.



Scheme 2. *Reagents and conditions* i) **6** (5 equiv.), $Rh(acac)(C_2H_4)_2$ (0.03 equiv.), (*S*)-BINAP (0.03 equiv.), 1,4-dioxane, 100 °C, 3 h; ii) $[RhCl(cod)]_2$, and (*R*)-BINAP, aq. KOH, 1,4-dioxane, 100 °C, 99% for (±)-**5a**, 52% for (±)-**5d**; iii) $Rh(acac)(C_2H_4)_2$, (*R*)-BINAP (3 mol% of each), 1,4-dioxane–water (10:1), 100 °C, 5 h slow reaction, low conversion; iv) $[Rh(nbd)_2]BF_4$ and (*R*)-BINAP, aq. KOH, 1,4-dioxane, 100 °C, 1 h, 21% for (*R*)-5 a, 27% for (*R*)-**5b**, 17% for (*R*)-**5d**.



Scheme 3. *Reagents and conditions*: i) (*R*)-BINAP (0.1 equiv.), $[RhCl(cod)]_2$ or $[Rh(nbd)_2]BF_4$ (0.05 equiv.), aq. KOH (2 equiv.), 1,4-dioxane, 95–100 °C; ii) aq. KOH (2 equiv.), 20–95 °C; iii) TFA, DCM, 20 °C; iv) H_2, Lindlar's catalyst, toluene-cyclohexane 30%; v) TFA, DCM; vi) 1 M BCl_3 in heptane, DCM; vii) 4 M HCl in 1,4-dioxane, 18% (four steps).

required γ-lactone **5**. Although this route is longer than the direct addition to butenolide **7**, the hydrolysis or cleavage of ether and the cyclisation steps could be easily telescoped and performed in one pot.

It was critical to use an arylboronic acid **6**, which provided a well characterised lactone **5** that we could use as a reference for our studies on asymmetric conjugate additions. We used commercially available 4-chlorophenylboronic acid **6e** because the absolute configuration of the enantiomers of **5e** has been thoroughly investigated by many groups using a variety of robust methodologies over several decades.[15–23] Furthermore, we wished to rapidly investigate the effect of the alkyl ester group (R″ = Me- or *tert*-Bu-), the geometry of the olefin (*E* and *Z*), the γ-oxygen substituent (R′ = acetyl or benzyl), and the rhodium catalyst, initially $[RhCl(cod)]_2$. The substrate esters **10a-c** were all known compounds and were synthesised following the reported procedures, (*E*)-methyl 4-acetoxybut-2-enoate[3] **10a**, (*E*)-*tert*-butyl 4-acetoxybut-2-enoate[4] **10b** and (*E*)-*tert*-butyl 4-(benzyloxy)but-2-enoate[24] **10c**. The (*Z*) isomer of **10a**, (*Z*)-methyl 4-acetoxybut-2-enoate **13** has not been reported previously, and was prepared by hydrogenation of methyl 4-acetoxybut-2-ynoate[25] **14** over Lindlar's catalyst in toluene-cyclohexane in 30% yield. For the first set of reactions we used $[RhCl(cod)]_2$ catalyst, which is the catalyst we had successfully utilised for the additions to γ-amino crotonate esters.[3,4] Reactions were performed in parallel in an Integrity apparatus, under nitrogen, using the following ratios of reagents: substrate (1 equiv.), boronic acid **6e** (2 equiv.), (*R*)-BINAP (0.1 equiv.), $[RhCl(cod)]_2$ (0.05 equiv.), aq. KOH (2 equiv.) and 1,4-dioxane as solvent at 95 °C. Two equiv. of boronic acid were used to ensure sufficient quantities were present to drive the reaction to completion, since arylboronic acids undergo reduction (de-borylation) under these reaction conditions. The reaction was heated thermally for 1 h, then the mixture containing the addition product **11** was allowed to cool to 20 °C, after which additional quantities of aq. KOH were added to hydrolyse the acetate and methyl esters, and then the resulting hydroxy acid/*tert*-butyl ester **12** was cyclised with acid to give lactone **5e**. Before starting the investigations we synthesised (±)-**5e** in 74% yield starting from **6e** and *tert*-butyl ester **10b** using $[RhCl(cod)]_2$ as catalyst and in the absence of any chiral ligand. This racemic material was resolved by chiral HPLC on a Chiralpak IA column, eluting with 7.5% EtOH-heptane, which provided authentic samples of the enantiomers (*R*)-(−)-**5e** and (*S*)-(+)-**5e** {$[\alpha]_D^{20}$ +51 in $CHCl_3$, lit.[21] for (*R*)-(−)-**5e** $[\alpha]_D^{20}$ −51 in $CHCl_3$}, which were used as reference materials for the identification of products in our studies. Reactions were monitored by LCMS, the enantiomeric purity of products was determined by analytical chiral HPLC, and the results are summarised in Table 1. When using the methyl ester **10a**, the enantiomeric ratio of **5e** (*S*):(*R*) was 60:40 (entry 1, Table 1), whereas for the *tert*-butyl ester **10b** was **5e** (*S*):(*R*) 72:28 (entry 2). The yield of **5e** however was low 15% from **10a** and 12% from **10b**. The fact that *tert*-butyl esters provided higher enantiomeric excesses than the methyl esters has been reported previously.[8,15,26] In an attempt to increase the yield, we also examined the use of an alternative rhodium catalyst. Process chemists at Abbott Laboratories have used the commercially available catalyst bis(norbornadiene)rhodium (I) tetrafluoroborate $[Rh(nbd)_2]BF_4$, in combination with (*S*)-BINAP to form in situ the Miyaura catalyst $\{Rh(nbd)[(S)\text{-BINAP}]\}BF_4$, which they have used

Table 1
Addition of arylboronic acids to acyclic α,β-unsaturated esters **10a**, **10b**, **10c**, **13** and butenolide **7** in the presence of rhodium catalyst, (*R*)-BINAP and KOH

Entry	Catalyst	$ArB(OH)_2$	Substrate	Product	% (*S*)	% (*R*)	% yield
1	$[RhCl(cod)]_2$	**6e**	**10a**	**5e**	60	40	15
2	$[RhCl(cod)]_2$	**6e**	**10b**	**5e**	72	28	12
3	$[Rh(nbd)_2]BF_4$	**6e**	**10a**	**5e**	79	21	3
4	$[Rh(nbd)_2]BF_4$	**6e**	**10b**	**5e**	91	9	4
5	$[Rh(nbd)_2]BF_4$	**6e**	**13**	**5e**	36	64	10
6	$[RhCl(cod)]_2$	**6e**	**10c**	**5e**	62	38	18
7	$[Rh(nbd)_2]BF_4$	**6e**	**7**	**5e**	5	95	34
8	$[Rh(nbd)_2]BF_4$	**6d**	**7**	**5d**	2	98	17
9	$[Rh(nbd)_2]BF_4$	**6a**	**7**	**5a**	6	94	21
10	$[Rh(nbd)_2]BF_4$	**6b**	**7**	**5b**	6	94	27

Reactions involved addition of arylboronic acid (2 equiv.) to α,β-unsaturated substrate (1 equiv.) in the presence of (*R*)-BINAP (0.1 equiv.), rhodium catalyst (0.05 equiv.) and aqueous KOH as base (2 equiv.). In the case of acyclic ester substrates the resulting lactone product was obtained after hydrolysis and cyclisation. Enantiomeric ratios were obtained by chiral HPLC conducted on either a Chiralpak IA or a Chiralpak AD-H column.

for the 1,4-addition of a range of arylboronic acids to enones in >91.6% ee, including one addition to an acyclic ester (ethyl crotonate) in 79% yield.[27] When we reacted boronic acid **6e** with methyl ester **10a** in the presence of $[Rh(nbd)_2]BF_4$ and (*R*)-BINAP, we isolated after hydrolysis and cyclisation **5e** (*S*):(*R*) in 79:21 in 3% yield (entry 3), whereas the *tert*-butyl ester **10b** gave **5e** (*S*):(*R*) in 91:9 and in 4% yield (entry 4). The asymmetric conjugate addition of **6e** to the (*Z*) isomer **13** gave lactone **5e** in 36:64 (*S*):(*R*) in 10% yield (entry 5), but in this case another by-product, the α,β-unsaturated acid **15** was also isolated in 11% yield (Scheme 3). ^1H NMR, ^{13}C, HSQC, HMBC, ROESY and 1D-ROESY spectra were recorded, which allowed for the elucidation of the structure of **15** as depicted. The regiochemistry and (*E*)-geometry of **15** were in accordance with the correlations observed (Fig. 2). The (*E*) geometry of the olefinic double bond was established from the 1D-ROESY spectrum, where irradiation of the olefinic proton at 6.16 ppm gave an NOE enhancement to the two *ortho* aromatic protons at 7.47–7.40.

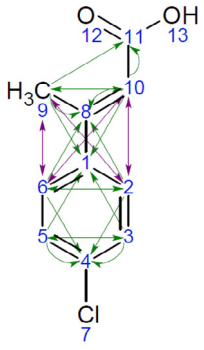


Figure 2. NOESY, ^1H and ^{13}C HMBC correlations for **15**.

Having isolated and characterised both lactone **5e** [LCMS RT = 0.97 min with a weak mass-ion in ES+ve *m*/*z* 197, 199 $(M+H)^+$] and acid **15** [LCMS RT = 1.07 min with strong mass-ion in ES−ve *m*/*z* 195, 197 $(M-H)^-$] ($C_{10}H_9^{35}ClO_2$ Exact Mass: 196) it was now worth re-examining the crude products from the addition of **6e** to the (*E*) isomers **10a** and **10b** (entries 1 and 2) to establish if the formation of **15** was unique to the (*Z*)-isomer **13**. Carboxylic acid **15** was found to be present in the LCMS chromatograms of the crude reaction mixtures of both entries 1 and 2, and a small amount of **15** was isolated from the reaction with the *tert*-butyl ester **10b** (entry 2). The very close LCMS retention times of **5e** and **15**, identical mass-ion, and the fact that reaction mixtures were washed with $NaHCO_3$ during work-up made detection of **15** more difficult in the early experiments. In the case of the *tert*-butyl ester **10b** the intermediates *tert*-butyl 4-acetoxy-3-(4-chlorophenyl)butanoate **11e** and *tert*-butyl 4-hydroxy-3-(4-chlorophenyl) butanoate alcohol **12e**, were also isolated and characterised. The presence of alcohol **12e** suggested that hydrolysis of the acetate ester was a competing reaction, despite the fact that 2 equiv. of base were used together with 2 equiv. of boronic acid **6e**, which was expected to buffer the reaction mixture. Alcohol **12e** was converted into lactone **5e** with TFA in DCM and analysed by chiral HPLC to establish the enantiomeric ratio of **5e** (*S*):(*R*) 72:28. The formation of **15** during the asymmetric 1,4-addition of **6e** to both (*E*)- and (*Z*)- substrate esters **10a**, **10b**, **13** indicated that its formation was more general. In order to eliminate the possibility that the aqueous hydroxide was the cause of the side-reaction leading to formation of acid **15**, the addition of **6e** (2 equiv.) to *tert*-butyl crotonate **10b** (1 equiv.) was repeated, but in the presence of triethylamine (2 equiv.) replacing aq. KOH, and in the presence of (*R*)-BINAP (0.1 equiv.), $[RhCl(cod)]_2$ (0.1 equiv.) in 1,4-dioxane-water (9:1) and heating to 95 °C for 1 h as before. The reaction was followed by LCMS, which showed consumption of the starting material and the formation of a complex mixture. None of the products contained chlorine (isotope ratio of 3:1), and there was no evidence for the presence of any of the products **5e**, **11**, **12** or **15** identified previously.

Replacement of the acetate ester group of **10b** with the benzyl ether moiety, was also investigated in order to eliminate the potential for base-induced side-reactions. (*E*) *tert*-Butyl 4-benzyloxycrotonate ester **10c** was reacted with boronic acid **6e** using $[RhCl(cod)]_2$ catalysis and (*R*)-BINAP in the presence of aq. KOH at 95 °C for 65 min. The reaction was worked up and the crude product treated with TFA in DCM to provide **16** (LCMS RT = 1.22 min, ES−ve *m*/*z* 303, 305 $(M-H)^-$). Carboxylic acid **16** was treated with 1 M BCl_3 solution in heptane in DCM, which rapidly cleaved the benzyl ether to the corresponding alcohol, and then 4 M HCl in 1,4-dioxane was added to provide lactone **5e** in 18%. This was still a low yield of lactone formation, however the by-product **15** was not observed in this case.

2.4. Conjugate addition to butenolide 7 catalysed by $[Rh(nbd)_2]BF_4$

Having established higher enantiomeric ratios with $[Rh(nbd)_2]BF_4$ and (*R*)-BINAP we returned to the asymmetric conjugate addition of arylboronic acids **6** to butenolide **7**. Lactone **5e** was obtained in a ratio of 5:95 (*S*):(*R*) and in 34% yield (entry 7), whereas, lactone **5d** was obtained in a ratio of 2:98 (*S*):(*R*) and in 17% yield (entry 8). With these excellent enantioselectivities in hand we re-examined the addition of **6a** and **6b** to **7** in the presence of (*R*)-BINAP and $[Rh(nbd)_2]BF_4$, and isolated lactone **5a** in 21% yield, with a ratio of 6:94 (entry 9) and the optical rotation of this mixture was $[\alpha]_D^{23} = -37$ (*c* 1.10, $CHCl_3$). Lactone **5b** was obtained in 27% yield in the ratio of 6:94 (entry 10) and the specific

rotation for this mixture was $[\alpha]_D^{22} = -28$ (*c* 1.70, $CHCl_3$). Based on the negative sign of the specific rotation of lactones **5a** and **5b** derived by asymmetric 1,4-addition to butenolide **7** and comparing with the published[21] specific rotation for (*R*)-**5e** $[\alpha]_D^{25} = -51$ (*c* 0.5, $CHCl_3$) but also with other lactones **5** possessing different substituents,[18] for example R = H, 2-Br, 4-Me, 4-F, 4-Br, the configuration of lactones **5a** and **5b** was assigned as (*R*). The lactones derived by degradation of **2a** and **2b** as mentioned above had positive specific rotations (*dextro*-rotatory) and were assigned the (*S*)-configuration. Therefore, the parent compounds **2a** and **2b** had also the (*S*) absolute configuration. The absolute configuration of **5b** was further confirmed by an X-ray study on the degradation lactone **5b**, hence **2b** was identified as (*S*)-4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-morpholinophenyl)butanoic acid. The absolute configuration of **2a** was assigned by inference as (*S*)-4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(2-methoxyethoxy)phenyl)butanoic acid.

2.5. X-ray study on 5b, derived from the degradation of 2b

There are two independent molecules within the asymmetric unit of the **5b** crystal structure and these are approximately related by a non-crystallographic two-fold axis (Fig. 3). The conformations of these molecules differ mainly in the arrangements of the morpholinyl rings, with a least-squares fit for the non-hydrogen atoms O1-N13 with O21-N33 giving an RMS deviation of just 0.146 Å. There are no classical hydrogen bonds but the structure does contain weaker C–H···O interactions, where the oxygen atoms of the lactone groups act as acceptors. The absolute structure parameter (synonymous with Howard Flack)[28] was refined to –0.02(12) using either of the approaches available within SHELXTL 2008/4. The standard uncertainty here was slightly larger than the upper safe limit recommended for an enantiomerically pure compound in 2000.[29] However, using the more recent Parsons method[30] (available in the programs SHELXL-2014 and PLATON) a value of –0.04 (3) was obtained, thus unambiguously confirming the absolute configuration of **5b** as being (*S*).

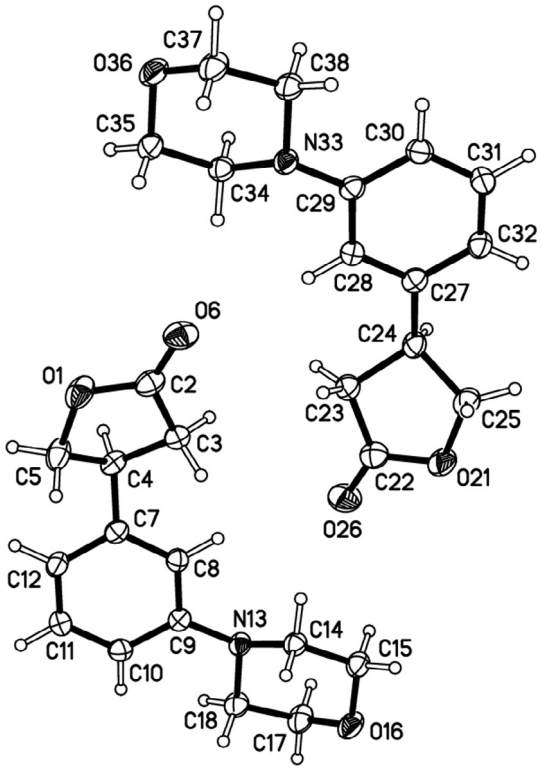


Figure 3. A view of both independent molecules from the **5b** crystal structure, showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

3. Conclusion

The 1,4-addition of arylboronic acids **6a**, **6d** and **6e** to butenolide **7** using $[RhCl(cod)]_2$ as catalyst and in the absence of the chiral ligand (*R*)-BINAP provided lactones (±)-**5a**, (±)-**5d** and (±)-**5e**, in good yields (69, 57 and 74% respectively). When the reactions were repeated in the presence of (*R*)-BINAP to make the lactones enantioselectively **5a** and **5d** were obtained in 99 and 52% yields respectively, however, there was no asymmetric induction when $[RhCl(cod)]_2$ was used as catalyst. The reaction of **6d** with **7** in the presence of $Rh(acac)(C_2H_4)_2$ was very slow and low yielding. $[Rh(nbd)_2]BF_4$ in combination with (*R*)-BINAP was a much more useful commercially available catalyst, providing (*R*)-**5a**, (*R*)-**5b** and (*R*)-**5d** with high enantioselectivity (up to 98:2). In contrast the reactions of **6e** with (*E*)- and (*Z*)-crotonate esters (methyl or *tert*-butyl) bearing a γ-oxygen substituent, such as **10a**, **10b** and **13** were more complicated due to the formation of the by-product (*E*)-3-(4-chlorophenyl)but-2-enoic acid **15**, in addition to the expected conjugate addition products. The exact source of this product was not identified. The by-product was not observed when the γ-oxygen substituent was a benzyl ether **10c** or when KOH was replaced by triethylamine.

The reaction of the $\alpha_v\beta_6$ integrin inhibitors **2a** and **2b** with iodomethane, followed by heating the resulting quaternary salts in the presence of potassium carbonate provided lactones **5a** and **5b**, which were *dextro*-rotatory. Enantioselective synthesis of both **5a** and **5b** established the absolute configuration of the degradation lactones **5a** and **5b** as (*S*). An X-ray study on degradation lactone **5b** confirmed its configuration as (*S*). The absolute configuration of the benzylic asymmetric centre of the parent compounds **2a** and **2b** was thus shown to be (*S*) and hence **2a** was (*S*)-4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(2-methoxyethoxy)phenyl)butanoic acid and **2b** was (*S*)-4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-morpholinophenyl)butanoic acid.

4. Experimental

4.1. General

TLC was performed on Merck 0.25 mm Kieselgel 60 F_{254} plates. Products were visualised under UV light and/or by staining with aqueous $KMnO_4$ solution. LCMS analysis was conducted on one of the following two systems: System A an Acquity UPLC BEH or CSH C18 column (2.1 mm × 50 mm i.d. 1.7 μm packing diameter) eluting with 0.1% formic acid in water (solvent A), and 0.1% formic acid in acetonitrile (solvent B), using the following elution gradient 0.0–1.5 min 3–95% B, 1.5–1.9 min 95% B, 1.9–2.0 min 95–3% B, at a flow rate of 1 mL min^{-1} at 40 °C; System B an Acquity UPLC CSH C18 column (2.1 mm × 50 mm i.d. 1.7 μm packing diameter) eluting with 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution (solvent A), and acetonitrile (solvent B), using the following elution gradient 0.0–1.5 min 3–95% B, 1.5–1.9 min 95% B, 1.9–2.0 min 95–3% B, at a flow rate of 1 mL min^{-1} at 40 °C The UV detection was an averaged signal from wavelength of 210 nm to 350 nm, and mass spectra were recorded on a mass spectrometer using alternate-scan electrospray positive

and negative mode ionisation (ES+ve and ES-ve). Column chromatography was performed on disposable, normal phase, SPE cartridges (2 –100 g). Mass-directed auto-preparative HPLC (MDAP) was conducted on a Sunfire C18 column (150 mm × 30 mm i.d. 5 μm packing diameter) at ambient temperature eluting with aqueous 0.1% HCO_2H solution (solvent A) and 0.1% HCO_2H solution in acetonitrile (solvent B), using an appropriate elution gradient over 10 min at a flow rate of 40 mL min^{-1} and detecting at 210–350 nm at room temperature. Mass spectra were recorded using electro spray positive and negative mode, alternate scans. The accurate mass measurements were performed on an Orbitrap Biomax mass spectrometer or a Bruker maXis Impact TOF mass spectrometer equipped with an ESI interface. ^{1}H NMR spectra were recorded at 400 (Bruker AVII), 500 (Bruker AVI) or 600 MHz (Bruker AVII). The chemical shifts are expressed in ppm relative to tetramethylsilane. Optical rotations were measured with an Optical Activity AA100 digital polarimeter and are given in 10^{-1} deg cm^2 g^{-1}.

4.2. (*S*)-(+)-4-(3-(2-Methoxyethoxy)phenyl)dihydrofuran-2(3*H*)-one (*S*)-5a

4.2.1. Conversion of 2a into 3a and degradation into 5a

A solution of 4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-l, 8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(2-methoxyethoxy)phenyl) butanoic acid[5] **2a** (200 mg, 0.412 mmol) in DCM (20 mL) was treated with iodomethane (0.400 mL, 6.40 mmol) at room temperature and stirred for 18 h. The reaction mixture was concentrated in vacuo to remove the excess iodomethane, the residual solid was re-dissolved in DCM (10 mL) and then potassium carbonate (250 mg, 1.81 mmol) was added. The reaction mixture was heated in a microwave reactor to 120 °C for 1 h. The solution was filtered and concentrated in vacuo and the residual oil was purified by chromatography on a silica column (10 g) eluting with a gradient of 0–100% TBME in cyclohexane detecting at 220 nm. The relevant fractions were concentrated *in vacuo* affording **5a** (80 mg, 82%) as a colourless oil: LCMS (System A) RT = 0.80 min, 100%, ES+ve *m/z* 237 $(M+H)^+$; IR ν_{max} (neat) 1771, 1584, 1489, 1448, 1263, 1164, 1124, 1061, 1017, 843, 784, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.30–7.25 (1H, m), 6.88–6.79 (3H, m), 4.66 (1H, dd, *J* = 9, 8 Hz), 4.27 (1H, dd, *J* = 9, 8 Hz), 4.16–4.10 (2H, m), 3.80–3.72 (3H, m), 3.46 (3H, s), 2.91 (1H, dd, *J* = 17.5, 8.7 Hz), 2.67 (1H, dd, *J* = 17.5, 9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) 176.2, 159.4, 141.0, 130.2, 119.1, 113.7, 113.1, 73.8, 71.0, 67.4, 59.2, 41.0, 35.6; HRMS (ESI) calc'd for $C_{13}H_{17}O_4$ $(M+H)^+$ 237.1121, found 237.1117. $[\alpha]_D^{22}$ = +42 (*c* 1.06, $CHCl_3$); Anal. chiral HPLC RT = 9.72 min, 100% on a Chiralpak AD column (250 mm × 4.6 mm) eluting with 40% EtOH in heptane, flow-rate = 1 mL/min, detecting at 215 nm.

4.2.2. (±)-4-(3-(2-Methoxyethoxy)phenyl)dihydrofuran-2(3*H*)-one (±)-5a

To a solution of $[RhCl(cod)]_2$ (49.3 mg, 0.100 mmol) and **6a** (980 mg, 5.00 mmol) in 1,4-dioxane (10 mL) was added **7** (0.142 mL, 2.0 mmol). The resulting solution was heated to 100 °C for 1 h in a microwave apparatus. The reaction was allowed to cool and partitioned between water (20 mL) and DCM (20 mL). The layers were separated and the organic phase was passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by chromatography on a KPNH cartridge (50 g). eluting with 0–100% TBME in cyclohexane over 45 min. The relevant fractions were concentrated in vacuo to give (±)-**5a** (328 mg, 69%) as a colourless oil. LCMS (System A) RT = 0.81 min, 100%, ES +ve *m/z* 237 $(M+H)^+$, 254 $(M+NH_4)^+$; Anal. Chiral HPLC RT = 9.79 min, 50.0% and RT = 12.0 min, 50.0% on a Chiralpak AD column (4.6 mm × 250 mm), eluting with 40% EtOH-heptane, flow-rate 1 mL/min, detecting at 215 nm.

4.2.3. Addition of 6a to 7 in the presence of $[RhCl(cod)]_2$ and (*R*)-BINAP

A solution of $[RhCl(cod)]_2$ (49.3 mg, 0.100 mmol), (*R*)-BINAP (125 mg, 0.200 mmol) and **6a** (980 mg, 5.00 mmol) in 1,4-dioxane (10 mL) was treated with **7** (0.142 mL, 2.0 mmol) and the mixture was heated to 100 °C for 1 h in a microwave reactor. The reaction mixture was allowed to cool and partitioned between water (20 mL) and DCM (20 mL). The layers were separated and the organic layer was passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by chromatography on a KPNH (50 g) cartridge eluting with a gradient of 0–100% TBME in cyclohexane over 45 min. The relevant fractions were concentrated in vacuo to give (±)-**5a** (467 mg, 99%) as a colourless oil: LCMS (System A) RT = 0.80 min, 98%, ES+ve *m/z* 237 $(M+H)^+$, 254 $(M+NH_4)^+$. Anal. Chiral HPLC RT = 9.70 min, 47.8% and RT = 11.94 min, 52.2% on a Chiralpak AD column (4.6 mm × 250 mm), eluting with 40% EtOH-heptane, flow-rate 1 mL/min, detecting at 215 nm.

4.2.4. Addition of 6a to 7 in the presence of $[Rh(nbd)_2]BF_4$ and (*R*)-BINAP. (*R*)-(−)-4-(3-(2-Methoxyethoxy)phenyl) dihydrofuran-2(3*H*)-one (*R*)-5a

A solution of $[Rh(nbd)_2]BF_4$ (37.4 mg, 0.100 mmol), (*R*)-BINAP (125 mg, 0.200 mmol) and **6a** (980 mg, 5.00 mmol) in 1,4-dioxane (10 mL) was treated with **7** (0.142 mL, 2.0 mmol) and aqueous 3.8 M KOH (1.053 mL, 4.00 mmol). The resulting solution was heated to 100 °C for 1 h in a microwave reactor. The reaction mixture was allowed to cool and partitioned between water (20 mL) and DCM (20 mL). The layers were separated and the organic layer was passed through a hydrophobic frit and concentrated in vacuo. The residual oil was purified by chromatography on a KPNH column (50 g) eluting with a gradient of 0–100% TBME in cyclohexane over 45 min, detecting at 220 nm. The relevant fractions were concentrated *in vacuo* to give (*R*)-**5a** (101 mg, 21%) as a colourless oil: LCMS (System A) RT = 0.80 min, 100%, ES+ve *m/z* 237 $(M+H)^+$; $[\alpha]_D^{23}$ = −37 (*c* 1.10, $CHCl_3$). Anal. Chiral HPLC RT = 11.82 min, 94% and RT = 9.67 min, 6% on a Chiralpak AD column (250 mm × 4.6 mm) eluting with 40% EtOH in heptane, flow rate = 1 mL/min, detecting at 215 nm.

4.3. (*S*)-4-(3-Morpholinophenyl)dihydrofuran-2(3*H*)-one (*S*)-5b

4.3.1. Conversion of 2b to 3b and degradation to 5b

A solution of (*S*)-4-((*S*)-3-fluoro-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-morpholinophenyl) butanoic acid[6] **2b** (100 mg, 0.201 mmol) in DCM (8 mL) at room temperature was treated with iodomethane (0.195 mL, 3.13 mmol) and stirred for 18 h. The reaction was concentrated *in vacuo* and the residue was re-dissolved in DCM (5 mL) and treated with solid potassium carbonate (122 mg, 0.884 mmol). The reaction mixture was heated in a microwave reactor to 120 °C for 1 h. The solution was filtered and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica (10 g) eluting with a gradient of 0–100% TBME in cyclohexane. The relevant fractions were concentrated *in vacuo* to give (*S*)-**5b** (32 mg, 64%) as a white solid: LCMS (System B) RT = 0.82 min, 100%, ES+ve *m/z* 248 $(M+H)^+$; IR ν_{max} (neat) 1772, 1604, 1159, 1116, 1016, 996, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32–7.26 (1H, m), 6.89–6.84 (1H, m), 6.79–6.73 (2H, m), 4.67 (1H, dd, *J* = 9, 8 Hz), 4.30 (1H, dd, *J* = 9, 7.5 Hz), 3.92–3.85 (4H, m), 3.76 (1H, quin, *J* = 8 Hz), 3.21–3.17 (4H, m), 2.93 (1H, dd, *J* = 17.5, 9 Hz), 2.93 (1H, dd, *J* = 17.5, 9 Hz), 2.70 (1H, dd, *J* = 17.5, 9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) 176.4, 151.9, 140.7, 130.0, 117.9, 114.8, 113.7, 74.1, 66.8, 49.2, 41.4, 35.7; HRMS (ESI) calc'd for $C_{14}H_{18}NO_3$ $(M+H)^+$ 248.1281, found 248.1286. $[\alpha]_D^{22}$ = +37 (*c* 1.40, $CHCl_3$). Anal. Chiral HPLC RT = 25.4 min, 100% on a Chiralpak ID column (250 mm × 4.6 mm)

eluting with 20% isopropanol-heptane, flow-rate 1 mL/min, detecting at 215 nm. Anal. Chiral HPLC for the racemic mixture: RT = 23.4 min, 49.8% and RT = 25.3 min, 50.2%. A portion of (*S*)-**5b** was recrystallised from chloroform by slow evaporation to provide crystals, which were suitable for an X-ray diffraction study.

4.3.2. X-ray diffraction study

Data were collected with an Oxford Diffraction Gemini A Ultra diffractometer at 150(2)K using Cu-Kα X-radiation (λ = 1.54178 Å). Crystal data and refinement summary: $C_{14}H_{17}NO_3$; *M* = 247.29; colourless tablet; 0.22 × 0.20 × 0.10 mm; monoclinic; space group $P2_1$ (#4); *a* = 13.91633(7) Å, *b* = 6.13096 (3) Å, *c* = 14.35229(9) Å, *β* = 93.9101(5)°, *V* = 1221.693(11) Å^3; *Z* = 4; D_{calc} = 1.344 Mgm^{-3}; θ_{max} = 67.70°; reflections collected = 42194; independent reflections = 4416; R_{int} = 0.0244; coverage = 99.4%; restraints = 1; parameters = 326; *S* = 1.055; R_1 [$I > 2\sigma(I)$] = 0.0234; wR_2 (all data) = 0.0635; absolute structure parameter = −0.02(12); and largest difference peak and hole = 0.147 and −0.135 e Å^{-3}. A description of the refinement and the full tables associated with the crystal structure are given in the supporting information. A crystallographic information file has been deposited with the Cambridge Crystallographic Data Centre. CCDC 1564994 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

4.3.3. Addition of 6b to 7 in the presence of [Rh(nbd)$_2$]BF$_4$ and (*R*)-BINAP. (*R*)-(−)-4-(3-Morpholinophenyl)dihydrofuran-2(3*H*)-one (*R*)-5b

A solution of [Rh(nbd)$_2$]BF$_4$ (18.70 mg, 0.05 mmol), (*R*)-BINAP (62.3 mg, 0.1 mmol) and (3-morpholinophenyl)boronic acid **6b** (1.035 g, 5.00 mmol) in 1,4-dioxane (10 mL) was treated with **7** (0.142 mL, 2.0 mmol) and KOH solution (3.8 M, 1.053 mL, 4.00 mmol). The resulting solution was heated to 100 °C for 1 h in a microwave reactor, allowed to cool and concentrated *in vacuo*. The residue was purified by chromatography (50 g KPNH cartridge) eluting with a gradient of 0–50% EtOAc in cyclohexane over 45 min. The relevant fractions were concentrated *in vacuo* to give (*R*)-**5b** (132 mg, 27%) as a white solid: LCMS (System B) RT = 0.82 min, 100%, ES+ve *m*/*z* 248 (M+H)$^+$; HRMS (ESI) calc'd for $C_{14}H_{18}NO_3$ (M+H)$^+$ 248.1281, found 248.1283. $[\alpha]_D^{22}$ = −28 (*c* 1.70, $CHCl_3$). Anal. Chiral HPLC RT = 23.4 min, 94%, RT = 25.4 min 6% on a Chiralpak ID column (250 mm × 4.6 mm) eluting with 20% isopropanol–heptane, flow-rate 1 mL/min, detecting at 215 nm.

4.4. (3-Cyclopropylphenyl)boronic acid 6d

A solution of 1-bromo-3-cyclopropylbenzene (2.0 g, 10 mmol) in THF (24 mL) was cooled to −78 °C, n-butyllithium solution in hexanes (1.6 M, 12.7 mL, 20.3 mmol) was added and the mixture was stirred for 30 min before adding triisopropylborate (3.06 mL, 13.2 mmol). The mixture was stirred for 45 min and then the reaction mixture was warmed to room temperature. After 1 h the reaction was quenched with aqueous 2 M HCl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was recrystallised from the minimum amount of hot TBME and the crystals were dried *in vacuo* to afford **6d** (1.16 g, 60%): LCMS (System A) RT = 0.80 min, 97% (no mass ion observed); ^{1}H NMR (CD_3OD, 400 MHz) 7.52–7.44 (1H, m), 7.37–7.28 (1H, m), 7.25–7.15 (1H, m), 7.12–7.06 (1H, m), 1.94–1.84 (1H, m), 0.97–0.88 (2H, m), 0.69–0.63 (2H, m).

4.4.1. (±)-4-(3-Cyclopropylphenyl)dihydrofuran-2(3*H*)-one (±)-5d

A nitrogen-degassed mixture of **6d** (100 mg, 0.62 mmol) and **7** (0.22 mL, 3.1 mmol) in 1,4-dioxane (2 mL) and water (0.2 mL) was treated with [RhCl(cod)]$_2$ (30 mg, 60 μmol) and aqueous 3.8 M KOH solution (0.49 mL, 1.9 mmol) sequentially at room temperature and the reaction mixture was stirred at room temperature for 10 min. Water (10 mL) and EtOAc (10 mL) were added and the separated aqueous phase was extracted twice with EtOAc (2 × 10 mL). The combined organic phase was passed through a hydrophobic frit and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on a silica column (20 g) eluting with 0–50% EtOAc in cyclohexane over 40 min. The relevant fractions were combined and concentrated under reduced pressure to afford (±)-**5d** (71 mg, 57%) as a clear oil: LCMS (System A) RT = 1.00 min, ES+ve *m*/*z* 203 (M+H)$^+$; IR ν_{max} (neat) 1771, 1164, 1015 cm^{-1}; ^{1}H NMR (CD_3CN, 400 MHz) 7.14 (1H, t, *J* = 8 Hz), 7.06–6.99 (2H, m), 6.90 (1H, d, *J* = 8 Hz), 4.55 (1H, t, *J* = 8 Hz), 4.12 (1H, t, *J* = 8 Hz), 3.74 (1H, quin, *J* = 8.5 Hz), 2.77 (1H, dd, *J* = 17, 8.5 Hz), 2.62 (1H, dd, *J* = 17, 9.5 Hz), 1.86–1.78 (1H, m), 0.86 (2H, ddd, *J* = 8, 4.5, 2 Hz), 0.64–0.56 (2H, m); ^{13}C NMR (DMSO-d_6, 101 MHz) 177.1, 144.7, 140.2, 129.0, 124.8, 124.5, 124.4, 73.9, 41.0, 35.6, 15.5, 9.9. HRMS (ESI) calc'd for $C_{13}H_{15}O_2$ (M+H)$^+$ 203.1072, found 203.1065.

4.4.2. 5d from 7 using [RhCl(cod)]$_2$ and (*R*)-BINAP

To a nitrogen-degassed mixture of **6d** (100 mg, 620 μmol) and **7** (0.22 mL, 3.1 mmol) in 1,4-dioxane (2 mL) and water (0.2 mL) was added a degassed solution of [RhCl(cod)]$_2$ (30 mg, 60 μmol) and (*R*)-BINAP (77 mg, 0.12 mmol) in 1,4-dioxane (0.5 mL). The mixture was then treated with aqueous 3.8 M KOH solution (0.5 mL, 1.9 mmol) and stirred at room temperature for 10 min. Water (10 mL) and EtOAc (10 mL) were added and the separated aqueous phase was extracted twice with EtOAc (2 × 10 mL). The combined organic phases were passed through a hydrophobic frit and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMSO (2 mL) and a 1 mL aliquot was purified by MDAP (Method A). The relevant fractions were combined and concentrated under reduced pressure to afford (±)-**5d** as a colourless oil (32 mg, 26%, adjusted to 52% if all the mixture was purified). Anal. Chiral HPLC RT = 16.7 min, 49.6% and RT = 19.1 min, 50.4% on a Chiralpak AD-H column (4.6 mm × 250 mm), eluting with 5% EtOH in heptane, flow-rate 1 mL/min).

4.4.3. 5d from 6d and 7 using [Rh(nbd)$_2$]BF$_4$ and (*R*)-BINAP

To a nitrogen-degassed solution of **6d** (101 mg, 620 μmol) and 1,4-dioxane (0.7 mL) was added [Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and (*R*)-BINAP (21 mg, 36 μmol) under a nitrogen atmosphere and the mixture was stirred for 2 h at room temperature. To the mixture was added water (109 μL), **7** (42 μL, 0.60 mmol) and triethylamine (83 μL, 0.60 mmol) sequentially and the mixture was stirred at 50 °C for 15 h. The mixture was diluted with EtOAc (20 mL) and water (20 mL) and the separated aqueous phase was extracted twice with EtOAc (2 × 20 mL). The combined organic phase was passed through a hydrophobic frit and the filtrate was concentrated under reduced pressure. The residue was purified by MDAP (Method A). The relevant fractions were combined and concentrated under reduced pressure to afford (*R*)-**5d** (20 mg, 17%) as a clear oil: LCMS (System A) RT = 1.00 min, ES+ve *m*/*z* 203 (M+H)$^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.25 (1H, t, *J* = 8 Hz), 7.03–6.94 (3H, m), 4.65 (1H, dd, *J* = 9, 8 Hz), 4.12 (1H, dd, *J* = 9, 8 Hz), 3.74 (1H, quin, *J* = 8.5 Hz), 2.91 (1H, dd, *J* = 17.5, 8.5 Hz), 2.67 (1H, dd, *J* = 17.5, 9 Hz), 1.93–1.85 (1H, m), 1.02–0.95 (2H,

m), 0.72–0.66 (2H, m). $[\alpha]_D^{22}$ −43 (c 1.8 in $CHCl_3$); Anal. Chiral HPLC RT = 16.1 min, 2.1% and RT = 18.4 min, 97.9% on a Chiralpak AD-H column (4.6 mm × 250 mm), eluting with 5% EtOH in heptane, flow rate = 1 mL/min), detecting at 215 nm.

4.5. (±)-4-(4-Chlorophenyl)dihydrofuran-2(3*H*)-one (±)-5e

A mixture of *tert*-butyl (*E*)-4-acetoxybut-2-enoate[4] **10b** (110 mg, 0.55 mmol), **6e** (172 mg, 1.1 mmol), $[RhCl(cod)]_2$ (14 mg, 0.03 mmol) and 3.8 M KOH (0.3 mL, 1.1 mmol) in 1,4-dioxane (2.5 mL) was deoxygenated by evacuating and re-filling with nitrogen gas three times, before the mixture was heated to 90 °C for 1 h. LCMS (System A) RT = 1.28 min, 313 $(M+H)^+$ (for addition product). Next, 3.8 M KOH aq solution (1.1 mL, 4.2 mmol) was added, followed by MeOH (3 mL) and the mixture was heated to 90 °C for 1.5 h. LCMS (System A) RT = 0.72 min, ES+ve *m*/*z* 293 $(M+Na)^+$ for hydroxy ester product. The mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was diluted with chloroform (4 mL) and treated with conc. sulfuric acid (1 mL, 18 mmol) and the mixture was stirred for 2 h. LCMS (System A) RT = 0.83 min and 0.91 min, ES+ve *m*/*z* 197 $(M+H)^+$ for both. The mixture was stood at room temperature overnight and then passed through a phase separator cartridge and washed with chloroform. The organic solution was concentrated to a small volume under reduced pressure and then applied to a silica cartridge (5 g). The cartridge was eluted with cyclohexane, ether, 50% EtOAc–cyclohexane and finally EtOAc (1CV each). The fractions were combined and evaporated under reduced pressure and the residue was further purified by MDAP (Method A) collecting fractions with RT = 8 min. The fractions were concentrated under reduced pressure to give (±)-**5e** (80 mg, 74%) as a yellow oil, which solidified on standing: LCMS (System A) RT = 0.93 min, ES+ve *m*/*z* 197 $(M+H)^+$ and 214 $(M+NH_4)^+$; IR ν_{max} (neat) 1775, 1495, 1064, 1092, 1013, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.35 (2H, d, *J* = 8 Hz), 7.18 (2H, d, *J* = 8 Hz), 4.66 (1H, dd, *J* = 9, 8 Hz), 4.24 (1H, dd, *J* = 9, 8 Hz), 3.77 (1H, quint, *J* = 8 Hz), 2.94 (1H, dd, *J* = 17.5, 9 Hz), 2.64 (1H, dd, *J* = 17.5, 9 Hz). Anal. Chiral HPLC RT = 28.3 min, 50%; and RT = 30.3 min, 50% on a Chiralpak IA column (4.6 mm × 250 mm) eluting with 5% EtOH-heptane, flow-rate = 1 mL/min at room temperature, detecting at 215 nm.

4.5.1. Resolution of (±)-5e

A racemic mixture of **5e** (75 mg) was resolved by preparative chiral HPLC, on a Chiralpak IA (250 × 30 mm) column, eluting with 7.5% EtOH-heptane, run-time 30 min, collecting the first compound to come off the column (eluting between 23 and 24.5 min), flow-rate = 35 mL/min, detecting at 280 nm to give after evaporation of the solvent (*S*)-**5e** (34 mg, 35%): $[\alpha]_D^{20}$ = +51 (*c* 0.71, $CHCl_3$), lit.[21] for (*R*)-**5e** $[\alpha]_D^{25}$ = −51 (*c* 0.5, $CHCl_3$). Anal. Chiral HPLC RT = 17.5 min, 99.5% on a Chiralpak IA (250 × 4.6 mm) column, eluting with 7.5% EtOH-heptane, flow-rate = 1 mL/min, detecting at 280 nm. Other spectral data as reported above.

4.5.2. Preparation of 4-(4-chlorophenyl)dihydrofuran-2(3*H*)-one (5e) from 6e and 10b using $[RhCl(cod)]_2$ and (*R*)-BINAP

A mixture of (*E*)-*tert*-butyl 4-acetoxybut-2-enoate **10b** (241 mg, 1.2 mmol), $[RhCl(cod)]_2$ (29.7 mg, 0.06 mmol, 0.05 equiv.), (4-chlorophenyl)boronic acid **6e** (471 mg, 3.0 mmol, 2.5 equiv.), (*R*)-BINAP (75 mg, 0.12 mmol, 0.1 equiv.) and 3.8 M KOH (0.633 mL, 2.4 mmol, 2.0 equiv.) in 1,4-dioxane (6 mL) was deoxygenated for a few minutes by passing nitrogen gas through the solution and then the mixture was heated to 65 °C for 75 min, allowed to cool to 20 °C overnight. The crude reaction mixture was concentrated under reduced pressure and MeOH was added, whereupon a solid precipitated out. The solid, which was soluble in water, was removed by filtration and checked by LCMS; no mass-ions were obtained, presumed inorganic material and was discarded. The filtrate was checked by LCMS (System A) which showed the presence of lactone **5e** and acid **15** together with addition product **11** and hydrolysis product **12**. The solution was applied to an aminopropyl cartridge (20 g) eluting with MeOH. The solvent from the fractions was evaporated *in vacuo* to give an orange coloured oil (510 mg): LCMS (System A) indicated the presence of three products: RT = 1.05 min (1%), RT = 1.15 min (3%), and 1.35 min (9%). Elution of the cartridge with 2 M ammonia in MeOH gave a yellow solid (132 mg), which contained only BINAP oxides, and was discarded. The orange coloured oil was first purified by chromatography on a silica cartridge (25 g) eluting with a gradient of 0–100% EtOAc–cyclohexane and the fractions were further purified by MDAP (Method A): the fractions with RT = 8.7 min were combined and evaporated under reduced pressure to give *tert*-butyl 4-acetoxy-3-(4-chlorophenyl)butanoate **11e** (15.6 mg, 4%) as a colourless oil: LCMS (System A) RT = 1.35 min, ES+ve *m*/*z* 313, 315 $(M+H)^+$; ^1H NMR ($CDCl_3$, 600 MHz) 7.29 (2H, d, *J* = 8.4 Hz), 7.17 (2H, d, *J* = 8.4 Hz), 4.22 (1H, dd, *J* = 11.1, 6.5 Hz), 4.14 (1H, dd, *J* = 11.0, 7.0 Hz), 3.44 (1H, dq, *J* = 8.8, 6.7 Hz), 2.69 (1H, dd, *J* = 15.5, 6.5 Hz), 2.54 (1H, dd, *J* = 15.5, 8.9 Hz), 2.02 (3H, s), 1.33 (9H, s); ^{13}C NMR ($CDCl_3$, 151 MHz) 170.7 (s, 1C), 170.6 (s, 1C), 139.0 (s, 1C), 132.9 (s, 1C), 129.1 (s, 2C), 128.6 (s, 2C), 80.9 (s, 1C), 67.3 (s, 1C), 40.8 (s, 1C), 38.5 (s, 1C), 27.9 (s, 3C), 20.8 (s, 1C).

The fractions with RT = 8.3 min, were combined and evaporated under reduced pressure to give *tert*-butyl 3-(4-chlorophenyl)-4-hydroxybutanoate **12e** (26 mg, 8%) as a colourless oil: LCMS (System A) RT = 1.15 min, 100%; ^1H NMR ($CDCl_3$, 600 MHz) 7.28 (2H, d, *J* = 8.4 Hz), 7.16 (2H, d, *J* = 8.3 Hz), 3.73 (2H, qd, *J* = 10.8, 6.4 Hz), 3.26 (1H, quin, *J* = 7.0 Hz), 2.69 (1H, dd, *J* = 15.4, 7.2 Hz), 2.51 (1H, dd, *J* = 15.4, 7.9 Hz), 1.33 (9H, s); ^{13}C NMR ($CDCl_3$, 151 MHz): 171.5 (s, 1C), 139.7 (s, 1C), 132.7 (s, 1C), 129.2 (s, 2C), 128.7 (s, 2C), 80.8 (s, 1C), 66.8 (s, 1C), 44.1 (s, 1C), 38.5 (s, 1C), 27.9 (s, 3C).

The fractions with RT = 7.97 min, ES+ve *m*/*z* 197, 199 $(M+H)^+$ and ES−ve *m*/*z* 195, 197 $(M-H)^-$ were combined and evaporated under reduced pressure to give **15**, more characterisation was obtained in the reaction with **13:** ^1H NMR ($CDCl_3$, 400 MHz) 7.43 (2H, d, *J* = 8.5 Hz), 7.36 (2H, d, *J* = 8.5 Hz), 6.14 (1H, br s), 2.56 (3H, s).

The hydroxy ester **12e** (26 mg) was then treated with DCM (0.3 mL) and TFA (0.3 mL) and the solution was stood at RT for 3 h. The mixture was then evaporated in a blow-down unit using nitrogen gas at 40 °C to give **5e** (19 mg, 8%): LCMS (System A) RT = 0.97 min. Anal. Chiral HPLC RT = 29.1 min, 72.2% and RT = 31.2 min, 27.8% on Chiralpak IA (250 mm × 4.6 mm) eluting with 5% EtOH-heptane containing 0.1% isopropylamine, flow-rate = 1 mL/min and detecting at 235 nm.

4.5.3. (*R*)-5e from 7 and 6e using $[Rh(nbd)_2]BF_4$

A solution of $[Rh(nbd)_2]BF_4$ (18.7 mg, 0.05 mmol) and **6e** (391 mg, 2.5 mmol) in 1,4-dioxane (5 mL) was treated with **7** (0.071 mL, 1.0 mmol), 3.8 M KOH (0.5 mL, 1.9 mmol), and (*R*)-BINAP (62.3 mg, 0.1 mmol) and the mixture was evacuated and purged with nitrogen twice. The reaction mixture was heated to 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in DCM and applied to a silica cartridge (20 g). The cartridge was eluted with a gradient of 0–100% TBME-cyclohexane and the major peak was isolated and purified twice by MDAP (Method A) collecting the fraction with RT = 11.49 min. The fraction was evaporated under reduced pressure to give (*R*)-**5e** (33 mg, 17%): Anal. Chiral HPLC RT = 33.1 min, 5.2% and RT = 36.2 min, 94.8% using a Chiralpak IA column (4.6 mm × 250 mm) eluting with 5% EtOH-heptane, flow-rate = 1 mL/min, detecting at 215 nm. Major isomer having the (*R*) configuration.

Please cite this article in press as: Procopiou, P. A.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2017.08.017

4.5.4. 5e from 10a and 6e using $[RhCl(cod)]_2$

A mixture of (*E*)-methyl 4-acetoxybut-2-enoate[3] **10a** (158 mg, 1.0 mmol), **6e** (312 mg, 2.0 mmol), (*R*)-BINAP (62.2 mg, 0.1 mmol), $[RhCl(cod)]_2$ (25 mg, 0.05 mmol) and 3.8 M KOH (0.5 mL, 1.9 mmol) in 1,4-dioxane (5 mL) and the mixture was deoxygenated by purging with nitrogen gas before the mixture was heated to 95 °C for 1 h. The mixture was then treated with 3.8 M KOH (1 mL, 3.8 mmol) and heated for another hour at 95 °C. The mixture was concentrated under reduced pressure, the residue was dissolved in DCM (3 mL) and then TFA (3 mL) was added and stirred at room temperature for 3 d. LCMS (System A) of the crude reaction mixture indicated the presence of **15** (RT = 1.06 min, 13%, ES−ve *m*/*z* 195, 197 $(M-H)^-$) and lactone **5e** (RT = 0.96 min, 6%). The mixture was concentrated under reduced pressure, and the residue was partitioned between DCM and aq. $NaHCO_3$ solution. The organic phase was collected after passing through a hydrophobic frit and evaporated *in vacuo*. The residue was dissolved in MeCN and purified by MDAP (Method A) to give **5e** (30 mg, 15%) RT = 0.97 min, ES+ve *m*/*z* 197 $(M+H)^+$. Anal. Chiral HPLC RT = 33.1 min, 60.0% and RT = 36.4 min, 40% using a Chiralpak IA column (4.6 mm × 250 mm) eluting with 5% EtOH-heptane, flow-rate = 1 mL/min, detecting at 215 nm. Major isomer having the (*S*)-configuration.

4.5.5. 5e from 10a and 6e using $[Rh(nbd)_2]BF_4$

A mixture of methyl (*E*)-4-acetoxybut-2-enoate[3] **10a** (158 mg, 1.0 mmol), **6e** (312 mg, 2.0 mmol), (*R*)-BINAP (62.2 mg, 0.1 mmol), $[Rh(nbd)_2]BF_4$ (19 mg, 0.05 mmol) and 3.8 M KOH (0.5 mL, 2 mmol) in 1,4-dioxane (5 mL) and the mixture was deoxygenated by purging with nitrogen gas bubbling through the suspension. The mixture was heated to 100 °C for 1 h. The mixture was then treated with MeOH (2 mL) and 3.8 M KOH (1 mL, 3.8 mmol) and heated to 60 °C. The mixture was acidified with TFA and extracted with DCM twice. The organic phase was washed with water, 2 M HCl, aq. $NaHCO_3$ and the organic solution passed through a hydrophobic frit. The solvent was evaporated under reduced pressure and the residue was dissolved in MeOH-MeCN and purified by MDAP collecting the peak with RT = 8.36 min. The solvent was removed under nitrogen using a blow-down unit to give **5e** (6 mg, 3%) Anal. Chiral HPLC RT = 33.4 min,78.8% and RT = 36.7 min, 21.2% using a Chiralpak IA column (4.6 mm × 250 mm) eluting with 5% EtOH-heptane, flow-rate = 1 mL/min, detecting at 215 nm. Major isomer having the (*S*)-configuration

4.5.6. 5e from 10b and 6e using $[Rh(nbd)_2]BF_4$

A mixture of *tert*-butyl (*E*)-4-acetoxybut-2-enoate (200 mg, 1 mmol), $[Rh(nbd)_2]BF_4$ (19 mg, 0.05 mmol), **6e** (313 mg, 2.0 mmol), (*R*)-BINAP (62 mg, 0.1 mmol) and 3.8 M KOH (0.526 mL, 2 mmol) was deoxygenated for a few minutes by passing nitrogen gas through the solution and then the mixture was heated to 100 °C for 1 h. The mixture was then treated with 3.8 M KOH (1 mL, 3.8 mmol) and the mixture heated for 1 h, followed by concentration under reduced pressure, diluting with DCM (4 mL) and acidification with TFA (4 mL). The mixture was stood at room temperature for 2 h and then evaporated under reduced pressure. The residue was partitioned between DCM and water and the organic phase was washed with aq. $NaHCO_3$ twice. The organic phase was dried by passing through a phase separation frit and the filtrate was concentrated under reduced pressure. The residue was purified by MDAP (Method A) collecting the first peak (RT = 7.9 min), the fractions were concentrated *in vacuo* to give **5e** (7.5 mg, 4%). Anal. Chiral HPLC RT = 33.0 min, 91.2% and RT = 36.3 min, 8.8% using a Chiralpak IA column (4.6 mm × 250 mm) eluting with 5% EtOH-heptane, flow-rate = 1 mL/min, detecting at 215 nm. Major isomer having the (*S*)-configuration.

4.5.7. 5e from 13 and 6e using $[Rh(nbd)_2]BF_4$

A mixture of (*Z*)-methyl 4-acetoxybut-2-enoate **13** (158 mg, 1.0 mmol), **6e** (312 mg, 2.0 mmol), (*R*)-BINAP (62.2 mg, 0.1 mmol), $[Rh(nbd)_2]BF_4$ (19 mg, 0.05 mmol) and 3.8 M KOH (0.526 mL, 2 mmol) in 1,4-dioxane (5 mL) and the mixture was deoxygenated by bubbling nitrogen gas through the solution before the mixture was heated to 95 °C for 1 h. The mixture was then treated with 3.8 KOH (1.2 mL, 4.56 mmol) and heated to 95 °C for another 1 h. The mixture was treated with TFA (3 mL) and mixture was left standing at 20 °C overnight. The mixture was evaporated under reduced pressure and the residue was partitioned between DCM and sodium bicarbonate. The mixture was passed through a phase separation frit and the organic phase was concentrated under reduced pressure. The mixture was purified by MDAP (Method A) collecting the fraction with (RT = 7.43 min) to give after evaporation of the solvent **6e** (39 mg, 20%) as a white crystalline solid. $[\alpha]_D^{20} = -3$ (*c* 1.59, $CHCl_3$) almost racemic. Anal. Chiral HPLC RT = 29.4 min, 36% and RT = 31.4 min, 64% on Chiralpak IA (250 mm × 4.6 mm) eluting with 5% EtOH-heptane flow-rate = 1 mL/min, detecting at 215 nm.

The fraction with RT = 8.5 min in the MDAP was evaporated under reduced pressure to give (*E*)-3-(4-chlorophenyl)but-2-enoic acid **15** (22.3 mg, 11%) as an off-white solid: LCMS (System A) RT = 1.07 min, 95%, ES−ve *m*/*z* 195, 197 $(M-H)^-$; IR ν_{max} (neat) 3313–2157, 1674, 1621, 1296, 1214, 1095, 823, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) 7.47–7.40 (2H, m, *J* = 8.4 Hz), 7.40–7.34 (2H, m, *J* = 8.4 Hz), 6.16 (1H, br s), 2.57 (3H, s); ^{13}C NMR ($CDCl_3$, 151 MHz) 171.4 (br s, 1C), 156.6 (br s, 1C), 140.4 (s, 1C), 135.4 (s, 1C), 128.8 (s, 2C), 127.7 (s, 2C), 116.9 (s, 1C), 18.1 (s, 1C). HRMS (ESI) calc'd for $C_{10}H_{10}ClO_2$ 197.0364 (M+H), found: 197.0364. For HMBC and ROESY correlations see Figure 2.

4.5.8. 5e from 10c and 6e using $[Rh(nbd)_2]BF_4$ and $[RhCl(cod)]_2$

A mixture of *tert*-butyl (*E*)-4-(benzyloxy)but-2-enoate **10c** (248 mg, 1.0 mmol), **6e** (312 mg, 2.0 mmol), (*R*)-BINAP (62.2 mg, 0.1 mmol), $[RhCl(cod)]_2$ (25 mg, 0.05 mmol) and 3.8 M aq. solution of KOH (0.85 mL, 3.2 mmol) in 1,4-dioxane (5 mL) was deoxygenated by passing through nitrogen gas and then the mixture was heated to 95 °C for 65 min. The mixture was partitioned between DCM and aq. $NaHCO_3$ solution, the organic phase was washed with HCl, brine, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in DCM (5 mL) and treated with TFA (3 mL) and stood at room temperature for 2 h, then concentrated under reduced pressure. The residue was dissolved in MeOH and applied to an aminopropyl cartridge eluting with MeOH, followed by 2 M NH_3 in MeOH. The basic fractions were concentrated under reduced pressure to give 4-(benzyloxy)-3-(4-chlorophenyl)butanoic acid **16**: LCMS (System A) RT = 1.22 min, ES+ve *m*/*z* 305, 307 $(M+H)^+$ and ES−ve *m*/*z* 303, 305 $(M-H)^-$. The mixture was dissolved in DCM and treated with 1 M BCl_3 in heptane (1 mL), when the benzyl ether was consumed the mixture was evaporated *in vacuo* and the residue treated with 4 M HCl in dioxane (3 mL) at 20 °C. The mixture was treated with aq $NaHCO_3$ and diluted with EtOAc. The organic solution was washed with aq. $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in DCM and purified by chromatography on a silica cartridge (1 g) eluting with 25% EtOAc–cyclohexane (3CV) to give **5e** (35 mg, 18%): Anal. Chiral HPLC RT = 23.0 min, 62% (*S*) and RT = 25.2 min 38% (*R*) on a Chiralpak IA column (250 mm × 4.6 mm), eluting with 5% EtOH-heptane, flow-rate 1 mL/min, detecting at 215 nm; $[\alpha]_D^{20} = +24$ (*c* 0.95, chloroform).

4.6. Preparation of (*Z*)-methyl 4-acetoxybut-2-enoate 13

A solution of methyl 4-acetoxybut-2-ynoate[25] (1.14 g, 7.3 mmol) in cyclohexane (25 mL) and toluene (1 mL) was

hydrogenated over Lindlar's catalyst (50 mg) for 3 h. The reaction mixture was filtered through a silica cartridge (20 g) eluting with a gradient of 0–25% EtOAc–cyclohexane and the filtrate was concentrated under reduced pressure. The residual oil was further purified by chromatography on a Biotage KP Sil SNAP cartridge (50 g) eluting with 0–25% TBME-cyclohexane over 40 min. The fractions containing the less-polar compound were combined and evaporated under reduced pressure to give **13** (345 mg, 30%) as a colourless oil: LCMS (System A) RT = 0.71 min, ES+ve *m*/*z* 159 $(M+H)^+$; IR ν_{max} (neat) 1741, 1717, 1653, 1224, 1178, 1036, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 6.24 (1H, dt, *J* = 12, 5 Hz), 5.86 (1H, dt, *J* = 12, 2.5 Hz), 5.16 (2H, dd, *J* = 5, 2.5 Hz), 3.71 (3H, s), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$, 126 MHz) 170.5, 165.9, 144.8, 120.2, 62.5, 51.4, 20.7. HRMS (EIC) calc'd for $C_7H_{11}O_4$ $(M+H)^+$ 159.0652, found 159.0648.

4.7. Preparation of *tert*-Butyl (*E*)-4-(benzyloxy)but-2-enoate 10c

Was prepared by the method described by Davies[24] from 2-(benzyloxy)acetaldehyde (706 mg, 4.7 mmol), *tert*-butyl 2-(diethoxyphosphoryl)acetate (1.24 g, 4.90 mmol), LiCl (1.4 g, 33 mmol) in MeCN (20 mL) and diisopropylethylamine (0.61 mL, 3.5 mmol) to give **14** (0.6 g, 51%) as a colourless oil: LCMS RT = 1.36 min, 84%, ES+ve *m*/*z* 266 $(M+NH_4)^+$; IR ν_{max} (neat) 1713, 1146, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.39–7.29 (5H, m), 6.91 (1H, dt, *J* = 16, 4 Hz), 6.07 (1H, dt, *J* = 16, 2 Hz), 4.58 (2H, s), 4.18 (2H, dd, *J* = 4, 2 Hz), 1.51 (9H, s).

Acknowledgements

We thank Professor William Clegg and Dr. Michael R. Probert from Newcastle University for the GSK funded crystal structure of **5b**, Dr. Bill J. Leavens for collecting the HRMS data, Mr. Eric Hortense and Mr. Bill Jackson for the analytical chiral HPLC, Mr. Andy Knaggs for the resolution, and Mr. Sean M. Lynn for the additional NMR spectra on compound **15.**

Declaration.

The authors are GSK employess, have given approval to the manuscript, and have no other competing financial interests.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.08.017.

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