doi.org/10.1002/hlca.202100127

FULL PAPER

HELVETICA chimica acta

Highly Stereoselective Aldol Reactions by Memory of Chirality: Synthesis of Quaternary β-Hydroxy α-Amino Acids

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Dedicated to Prof. *Ernst Peter Kündig*, on the occasion of his 75th birthday

We describe here an asymmetric aldol reaction based on the principle of Memory of Chirality. From α-amino acids such as leucine and methionine, we have synthesized in two steps quaternary α-amino acid derivatives with high diastereoselectivity and enantioselectivity, using the chirality of the initial α-amino acid as the only chirality source. Furthermore, we were able to determine the relative and absolute configurations of the aldol products thanks to crystallographic structures and thus showed that the relative configuration depended on the aldehyde employed. We proposed a stereoselectivity explanation and obtained also quaternary β-hydroxy α-amino acids after acidic hydrolysis.

Keywords: aldol reaction, amino acids, asymmetric synthesis, memory of chirality, tertiary aromatic amides.

Introduction

Quaternary α-amino acids are very interesting compounds for their proven or potential biological activities. Examples of biologically active quaternary α-amino acids are antibiotics, such as peptaibols,[1] antihypertensive drug such as methyldopa or among β-hydroxy α-amino acids,[2] lactacystin, kaitocephalin, calcaridine A or sphingofungins which have potent antifungal activities. They are also found in peptide chemistry, because the presence of the quaternary center induces a conformational change, even a flexibility decrease of the structure, while increasing its metabolic stability.[3] They can furthermore be used as reaction intermediates, as in the synthesis of (−)-penibruguieramine A.[4,5] Because of their multiple interests, many ways to access quaternary α-amino acids have been developed.[6–10] Among these, methods based on the principle of memory of chirality (MOC)[11–24] use as the only source of chirality the chirality of a natural α-amino acid, the initial reactant, although it disappears transiently during the reaction. Our group has been interested in the development of asymmetric syntheses based on this principle for many years. We have developed a synthesis of quaternary α-amino acids by alkylation in only three steps,[25,26] a method that we have applied to the synthesis of methyldopa[27] and to microflow reactors.[28] We also extended this strategy to oxidative coupling of enolate[29] and to the aldol reaction of alanine derivatives.[30] In the latter case, we have been able to demonstrate a control of the second asymmetric center by the nature of the aromatic aldehyde used (*Scheme 1*). We wanted to know if this control was specific to the alanine derivative or was also valid for

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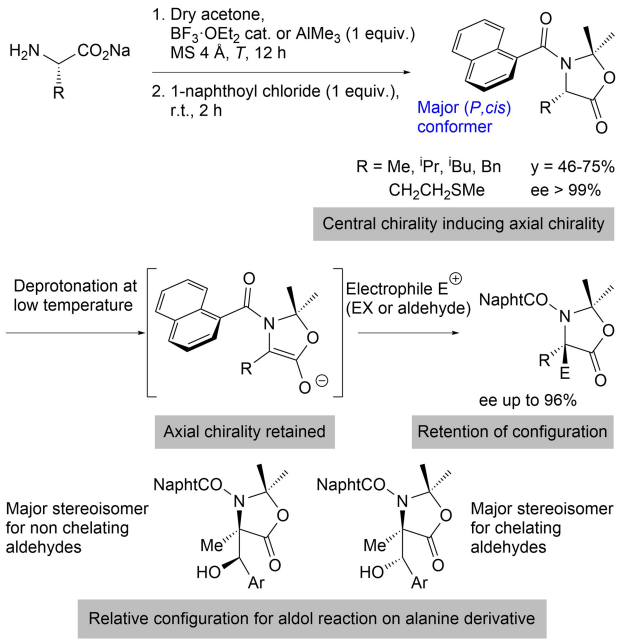
Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.202100127



Scheme 1. Previous results for alkylation and aldol reactions by Memory of Chirality.

other amino acids. We present here our latest results concerning this MOC aldol reaction applied to other amino acids and thanks to some crystallographic structures of some major diastereomers, we were able to confirm the dependence of the configuration of the second center with the nature of the aldehyde.

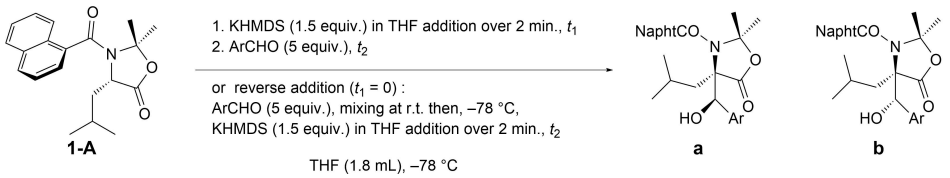
Results and Discussion

We targeted mainly two amino acids, leucine, which showed good results in alkylation reactions and methionine, as an example of functionalized amino acid. According to our previous strategy, an oxazolidinone is formed without racemization in a single step from the sodium salt of the corresponding α-amino acid, acetone and naphthoyl chloride. The presence of a tertiary aromatic amide function in the compound thus formed induces the creation of a dynamic axial chirality (these compounds are not planar and possess two slow rotations, the Ar–CO and the N–CO rotations). The preferred orientation of the naphthyl group is on the same side as the amino acid residue (major (*P,cis*) conformer) and it allows to preserve, at low temperature, the chiral information during the planar enolate formation step. This major conformer thus induces a stereoselective approach of the electrophile (whether it is an alkyl group or an aldehyde) by the face opposite to the naphthyl group, leading to a global retention of configuration for the initial asymmetric center (*Scheme 1*). It should be noted here that the major (*P,cis*) conformer is not the only one present but that we probably have a dynamic kinetic resolution.

We thus synthesized the corresponding oxazolidinones and used the reaction conditions developed for the aldol reaction of alanine: mixing of the aromatic aldehyde with the oxazolidinone (at room temperature or low temperature), then slow addition at −78 °C of the base – KHMDS (over two minutes) – to avoid racemization due to heating of the medium; treatment of the reaction at −78 °C with a 5% aqueous $NaHCO_3$ solution to avoid hydrolysis of the oxazolidinone as well as retro-aldol reaction. For leucine derivative **1-A**, we tested two types of conditions: a sequential reaction (deprotonation for t_1 minutes and then addition of the aldehyde) and an *in situ* reaction (mixing the aldehyde with the oxazolidinone at room temperature, before lowering the temperature to −78 °C to perform the deprotonation). The results are collected in *Table 1*. It appears that the aldol reaction takes place in all cases with very good diastereomeric ratios, better than those observed for the alanine derivative (the assignments of the relative configuration were based on crystallographic structures of major diastereomer of some aldol products – see below for determination and stereoselectivity explanation). The enantiomeric excesses are higher than 70% in the optimized reactions and can go up to enantiopure compounds, as in the case of compound **3** (the enantiomeric excess can also be improved by recrystallization, *Entry 7*). We did not need to replace THF with the ether/DME mixture that had been used for the alkylation reactions. In general, it is better to perform the reaction *in situ*, to obtain better enantiomeric excesses (*Entries 1* and *4* or *9* and *11*). This probably limits the racemization of the enolate, which is trapped directly by the aldehyde. Some aldol products, such as the 3-pyridine compound have a tendency to degrade rapidly, so it is sometimes simpler to acetylate them for purification (yields are in this case calculated on compound **Ac-4**, on two steps). The change in the amount of THF does not have a great influence (*Entries 1–3*) and the introduction of the aldehyde at −78 °C (*Entries 6* and *10*) generally induces a decrease in yield, probably due to a decrease in its solubility and consequently to a less homogeneous mixture.

On the methionine derivative **1-B**, we also tested various aromatic aldehydes and the results are

Table 1. Aldol reaction with Leucine oxazolidinone **1-A** (in situ or sequential procedure).[a]



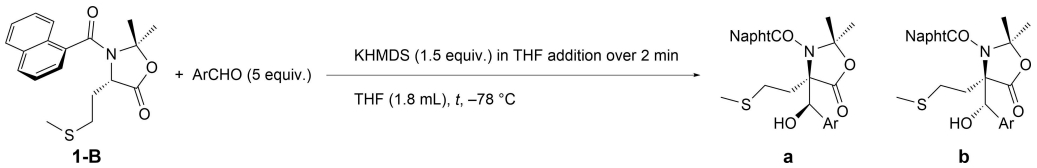
Entry	ArCHO	t_1/t_2 [min]	Comp.	dr[b]	ee[c] [%]	Yield[d] [%]
1	*m*-Br-C_6H_4CHO	8/10	**2**	>99:1	69/–	92
2[e]	*m*-Br-C_6H_4CHO	8/10	**2**	>99:1	64/–	63
3[f]	*m*-Br-C_6H_4CHO	8/10	**2**	>99:1	59/–	84
4	***m*-Br-C_6H_4CHO**	0/18	**2**	**>99:1**	**72**/–	**95**
5	**2-pyridine-CHO**	0/18	**3**[g]	**4:96**	**>99/>99**	**56**
6[h]	3-pyridine-CHO	0/12	**Ac-4**	>99:1	48/–	48[i]
7	**3-pyridine-CHO**	0/12	**Ac-4**	**>99:1**	**76[j]/–**	**55**[i]
8[k]	3-pyridine-CHO	0/12	**Ac-4**	>99:1	80/–	38[i]
9	*o*-F-C_6H_4CHO	8/10	**5**	97:3	67/59	60
10[h]	***o*-F-C_6H_4CHO**	0/18	**5**[l]	**>99:1**	**82**/–	**61**
11	*o*-F-C_6H_4CHO	0/18	**5**	96:4	82/86	81

[a] General procedure: *In situ* - to a stirred solution of oxazolidinone **1-A** (100 mg) and aldehyde (5 equiv.) in THF (1.8 mL) cooled to −78 °C was added a solution of KHMDS (1.5 equiv.) in THF dropwise (over 2 min) and the mixture was stirred for t_2 min at −78 °C; *sequential* - Identical to *in situ* procedure, except that KHMDS is added first and aldehyde is then added after t_1 min. Unless specified, absolute and relative configurations were assumed by analogy. [b] ratio **a:b** determined by chiral stationary-phase HPLC on the crude product. [c] ee of **a**/**b** determined by chiral stationary-phase HPLC after purification. [d] combined yield of **a** and **b**. [e] THF volume 1.2 mL instead of 1.8 mL. [f] THF volume 2.4 mL instead of 1.8 mL. [g] Absolute configuration of major diastereomer **3b** was assigned by X-Ray crystallography (*Figure 1*). [h] Aldehyde was added at −78 °C instead of r.t. [i] Yield calculated after acetylation on two steps. [j] ee = 91 % after recrystallization. [k] Only 1 equiv. of KHMDS was used. [l] Absolute configuration of major diastereomer **5a** was assigned after acetylation by X-Ray crystallography (*Figure 1*).

collected in *Table 2*. We applied only the *in situ* conditions, the aldehyde being introduced prior to the base, either at r.t. or at −78 °C depending on the case. By default, the aldehyde was added at −78 °C. However, when the enantiomeric excesses were low, probably due to a lack of solubility of the aldehyde, it was then introduced at room temperature and the mixture cooled to −78 °C (*Entries 1* and *2*). The observed diastereomeric ratios are always higher than those of the alanine derivative. The enantiomeric excesses are generally higher than 70 %, except in the disappointing case of *ortho*-bromobenzaldehyde (*Entries 3–6*). For the latter, replacing THF with ether or decreasing the number of aldehyde equivalents did not result in a better enantiomeric excess (*Entries 5* and *6*). For 3-pyridine-carboxaldehyde, the enantiomeric excess could be improved by decreasing the amount of base employed and addition of the aldehyde at room temperature (*Entries 11* and *12*). Changing the reaction time does not have a significant influence on the enantiomeric excess (*Entries 7* and *8*, or *9* and *10*). Again, the best enantiomeric excess was obtained with 2-pyridine carboxaldehyde (97 % ee for the major diastereomer, *Entry 7*).

Consequently, we wanted to test the aldol reaction with 2-pyridine carboxaldehyde on oxazolidinones derived from other amino acids. We thus tested the valine and phenyl alanine derivatives (*Table 3*). The valine derivative **1-C** leads to the expected compound with high diastereomeric ratio and enantiomeric excess for the major diastereomer. In the case of phenylalanine **1-D**, we directly acetylated the reaction product for ease of purification and product stability. The result was very disappointing, the diastereomeric ratio and enantiomeric excesses being both low. This derivative was the one that already gave the worst results in the alkylation reactions. The presence of the benzyl group disturbs the conformer proportions observed in NMR at low temperature (in THF, there was a (*P,cis*)/(*M,cis*) conformer ratio of 100/50 for this derivative, compared to 100/29 for alanine and especially a *cis/trans* conformer ratio of 100/10 compared to 100/2 in the case of alanine) and this probably impairs the selectivity.[25] This is likely to be even more pronounced for aldol reactions, as the aldehyde is an aromatic aldehyde, which can also interact with the benzyl group. We also tested 2-fluorobenzaldehyde on phenylalanine, but the enan-

Table 2. Aldol reaction with Methionine oxazolidinone **1-B** (in situ procedure).[a]

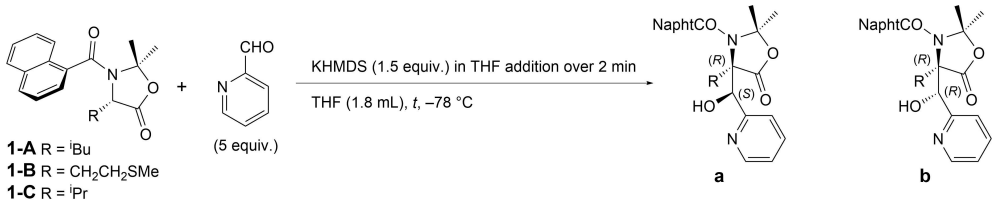


1-B **a** **b**

Entry	ArCHO	T[b] [°C]	t [min]	Comp.	dr[c]	ee[d] [%]	Yield[e] [%]
1	*m*-Br-C_6H_4CHO	−78	10	**6**	>99:1	30/–	42
2	***m*-Br-C_6H_4CHO**	r.t.	10	**6**	**>99:1**	**73**/–	**65**
3	*o*-Br-C_6H_4CHO	r.t.	18	**7**	87:13	61/89	30[f]
4	***o*-Br-C_6H_4CHO**	r.t.	12	**7**	**>99:1**	**60**/–	**72**
5[g]	*o*-Br-C_6H_4CHO	r.t.	18	**7**	>99:1	60/–	50
6[h]	*o*-Br-C_6H_4CHO	r.t.	12	**7**	98:2	50/–	73
7	**2-pyridine-CHO**	−78	15	**8**[i]	**15:85**	**82/97**	**65**
8	2-pyridine-CHO	−78	12	**8**	17:83	89/98	65
9	***o*-F-C_6H_4CHO**	−78	18	**9**	**>99:1**	**85**/–	**99**
10	*o*-F-C_6H_4CHO	−78	12	**9**	>99:1	81/–	92
11	3-pyridine-CHO	−78	12	**10**	98:2	47/–	80
12[j]	**3-pyridine-CHO**	r.t.	12	**10**	**98:2**	**75**/–	**88**

[a] General procedure: to a stirred solution of oxazolidinone **1-B** (100 mg) and aldehyde (5 equiv.) in THF (1.8 mL) at −78 °C was added a solution of KHMDS (1.5 equiv.) in THF dropwise (over 2 min) and the mixture was stirred for t min at −78 °C. [b] Temperature at which the aldehyde was added to the oxazolidinone. Unless specified, absolute and relative configurations were assumed by analogy. [c] Ratio **a:b** determined by chiral stationary-phase HPLC on the crude product. [d] ee of **a**/**b** determined by chiral stationary-phase HPLC after purification. [e] Combined yield of **a** and **b**. [f] Diastereomers are difficult to separate. [g] Diethyl ether was used instead of THF. [h] Only 3 equiv. of aldehyde were used. [i] Absolute configuration of major diastereomer **8b** was assigned by X-Ray crystallography (*Figure 1*). [j] Only 1 equiv. of KHMDS was used.

Table 3. Aldol reaction with oxazolidinones **1** with 2-pyridine carboxaldehyde.[a]



1-A R = ^{i}Bu
1-B R = CH_2CH_2SMe
1-C R = ^{i}Pr
1-D R = Bn

a **b**

Entry	R	t [min]	Comp.	dr[b]	ee[c] [%]	Yield[d] [%]
1	^{i}Bu	18	**3**[e]	4:96	>99/>99	56
2	CH_2CH_2SMe	15	**8**[e]	15:85	82/97	65
3	^{i}Pr	18	**11**[f]	7:93	45/90	47
4	Bn	12	**Ac-12**[g]	56:44	29/29	44[h]

[a] General procedure: to a stirred solution of oxazolidinone **1-A** (100 mg) and aldehyde (5 equiv.) in THF (1.8 mL) cooled to −78 °C was added a solution of KHMDS (1.5 equiv.) in THF dropwise (over 2 min) and the mixture was stirred for t_2 min at −78 °C. [b] Ratio **a:b** determined by chiral stationary-phase HPLC on the crude product. [c] ee of **a**/**b** determined by chiral stationary-phase HPLC after purification. [d] Combined yield of **a** and **b**. [e] Absolute configuration of major diastereomers **3b** and **8b** were assigned by X-Ray crystallography (*Figure 1*). [f] Absolute and relative configuration of major diastereomer **11a** were assumed by analogy. [g] Relative configuration of major diastereomer **Ac-12a** was assigned by X-Ray crystallography (*Figure 1*). [h] Yield calculated after acetylation on two steps.

tiomeric excess was only 34% (compound **13a** was obtained with a very good diastereomeric ratio of 98:2 and a yield of 52%). In all cases (except for the particular case of phenylalanine), the observed enantiomeric excesses are comparable to those obtained during alkylation reactions. When the enantiomeric excess is lower, this is probably due to a decrease in the reactivity of the aldehyde, as in the case of *ortho*-

bromobenzaldehyde, which is likely too hindered, or in the case of poorly soluble aldehydes added at −78 °C (*Entry 6*, *Table 1* and *Entry 1*, *Table 2*). Thus, the enantiomeric excess is presumably kinetically controlled and not compromised by retro aldol reaction and subsequent enolate racemization.

Regarding the control of the relative configuration of the aldol product by the substrate, we were able to obtain crystallographic structures on major diastereomer of some aldol products (*Figure 1*) and thus to have access to the relative and possibly absolute configuration (when the latter is accessible, we observe, as expected, the retention of configuration of the initial α-amino acid). The crystallographic structure of the compounds **3b** and **8b** thus shows that the relative configuration is identical to that obtained in the case of the reaction of oxazolidinone derived from alanine with furan-2-carboxaldehyde (we had not performed the aldol reaction of the alanine derivative with 2-pyridine-carboxaldehyde). In the case of the phenylalanine derivative (crystallographic structure of acetylated major diastereoisomer **Ac-12a**, *Figure 1*), the relative configuration of the major diastereomer does not correspond to that observed for the leucine and methionine derivatives **3b** and **8b**. However, this does not seem significant to us, as the diastereomeric ratio is close to 1 : 1. Thus, when 2-pyridinecarboxaldehyde is used, there is probably complexation of the potassium enolate by the pyridine nitrogen (pyridine, a good complexing agent, is regularly used to achieve a better control of the stereoselectivity[31]) as in transition state **II** (*Scheme 2*). More surprisingly, the crystallographic structure of the acetylated compound **Ac-5a** is different from that observed for the major diastereomer in the reaction with the alanine derivative. Therefore, there is probably no complexation with fluorine in this case. It can consequently be assumed that for all compounds resulting from aldol reaction with an aldehyde different from 2-pyridine-carboxaldehyde, the absolute configuration of the new asymmetric center created is identical (major diastereomer **a**). This corresponds to an aldol product controlled by a classical *Zimmerman–Traxler* transition state (transition state **I**, *Scheme 2*). There is thus a control of the second asymmetric center by the aldehyde, phenomenon to our knowledge not described in the literature (except in our previous publication).

The next step was the hydrolysis of the aldol products. This was performed on the products after acetylation, to avoid any problem of degradation of the aldol compounds. We applied the conditions developed previously in the laboratory (heating in a mixture of 6 N hydrochloric acid and acetic acid) and obtained for leucine derivatives **Ac-4a** and **Ac-5a** the expected amino acids hydrochloride **14** and **15** (*Scheme 3*). On the other hand, for methionine derivatives (on the compound resulting from the reaction with 2-fluorobenzaldehyde **9a** after acetylation), we observed the formation of a cyclic product **16**, whose sulfur is de-methylated, which we were able to characterize by NMR (proton, carbon, HSQC) and mass, but which we were unfortunately unable to isolate in

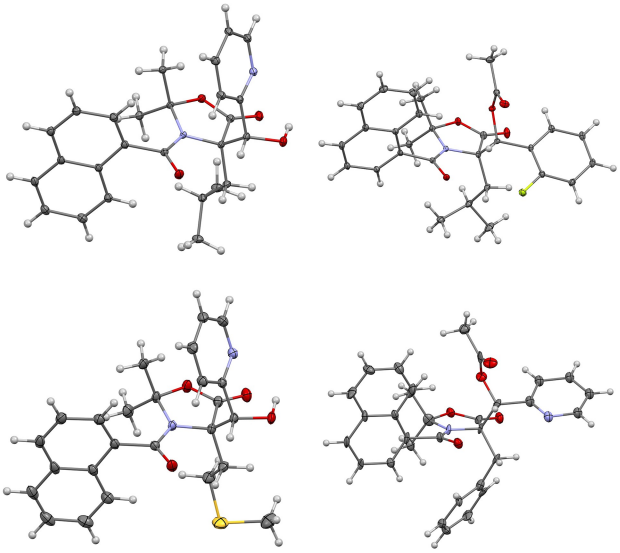
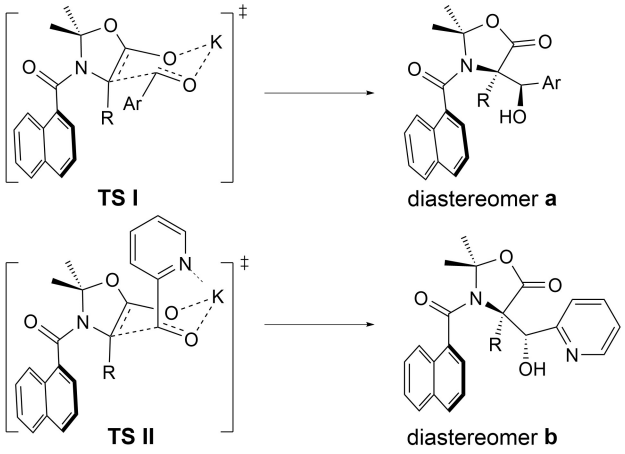
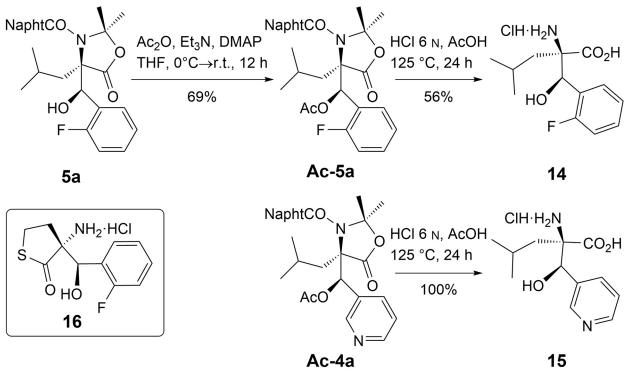


Figure 1. Crystallographic structures of compounds **3b** (up left), **Ac-5a** (up right), **8b** (bottom left), **Ac-12a** (bottom right, racemic).



Scheme 2. Proposed transition state for stereoselectivity explanation: with most aldehydes (up) and with 2-pyridine carboxaldehyde (bottom).



Scheme 3. Hydrolysis of diastereopure acylated aldol compounds.

pure form. This type of cyclization has already been described in the past.[32] We could consider deprotecting the methionine derivatives using milder conditions, as we described in the case of frozen chirality (basic hydrolysis of oxazolidinone, esterification of the acid, then reduction of the amide to imine by *Schwartz*'s reagent and mild hydrolysis),[33,34] in order to retain the methyl group. This is currently under investigation.

Conclusions

In conclusion, we extended the aldol reaction by Memory of Chirality that we had previously developed to other amino acids. We observed better diastereoselectivity and good enantiomeric excesses. In the best case, we were able to obtain the compound **3b** in enantiopure form. We also showed that there was a control of the second asymmetric center which depended on the nature of the aldehyde employed. β-Hydroxy α-amino acids were synthesized efficiently from leucine. The application of this strategy to the total synthesis of active molecules is under study in our laboratory.

Experimental Section

General Information

Unless otherwise stated, all reactions were conducted in oven dried glassware under an atmosphere of dry argon gas. THF was distilled over sodium/benzophenone under argon. Acetone was purchased with water <50 ppm. All other reagents were used as received. Potassium bis(trimethylsilyl)amide was used as a THF solution (1 M). Flash chromatography was performed on *Kieselgel 60* (35–70 μm) silica gel. Infrared spectra were recorded as thin films on NaCl plates using an FT-IR spectrophotometer. ^{1}H-NMR spectra were measured at 250, 300, 360 or 400 MHz using $CDCl_3$, MeOD, C_6D_6, toluene, CD_2Cl_2 or D_2O as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual solvent as an internal reference. Multiplicities are reported as follows: *s* = *singlet*, *d* = *doublet*, *t* = *triplet*, *q* = *quadruplet*, *m* = *multiplet*, br. *s* = broad *singlet*, br. *d* = broad *doublet*. ^{13}C-NMR spectra were measured at 62.5, 75, 90 or 100 MHz using $CDCl_3$, MeOD, CD_2Cl_2 or D_2O as solvent. Chemical shifts are reported in δ units to 0.1 ppm precision using residual solvent as an internal reference. Mass spectra were measured on an ESI Q-Tof mass spectrometer *Bruker* at the Institut de Chimie Moléculaire et des Matériaux (ICMMO) Mass Spectrometry Laboratory. HPLC Analyses were performed on a *Dionex* instrument (*Ultimate 3000*) in our laboratory. This instrument is principally composed of gradient pump, a columns selector valve, *Peltier* effect column oven and diode array detector. All enantiomeric excesses were determined by normal phase HPLC analyses with four different chiral stationary phase columns:

- *Daicel* column, *Chiralcel OJ-H* (250 mm × 4,6 mm i.d.); particle size: 5 μm
- *Daicel* column, *Chiralpak AD-H* (250 mm × 4,6 mm id); particle size: 5 μm
- *Daicel* column, *Chiralpak IC* (250 mm × 4,6 mm id); particle size: 5 μm
- *Régis* column Type *'Pirkle'*, (*S,S*) *Whelk-O 1* (250 mm × 4,6 mm id); particle size: 5 μm

Note: all the experimental procedures listed below apply to both racemic and enantiomerically pure material. All aldol reaction for racemic compounds were performed in two steps: first deprotonation with KHMDS at −78 °C for 6 min and then addition of the aldehyde, in order to get both diastereomers. Only the preparation of chiral compounds will be reported.

For all the compounds, there exist at least two conformers and were reported for the proton or carbon NMR as major (*M*) and the minor (*m*).

General Procedure for Oxazolidinone Synthesis

Procedure A. In a solution of amino acid salt (1 equiv.) and molecular sieves 4 Å (activated in the oven) in dry acetone at 0 °C under Ar was added, slowly, $BF_3 \cdot Et_2O$

(0.06 equiv.). The mixture was stirred 5 min at 0 °C and overnight at room temperature. Then, 1-naphthoyl chloride (1 equiv.) was added and the resulting solution was stirred 2 h. The mixture was filtered through silica gel and washed twice with Et_2O. The solvents were concentrated, and the residue was dried under vacuum. After dilution in ether and CH_2Cl_2, the organic phase was washed with saturated solution of $NaHCO_3$ and water. The crude product was obtained after concentration.

Procedure B. In a solution of amino acid salt (1 equiv.) and molecular sieves 4 Å (activated in the oven) in dry acetone at 0 °C under Ar was added, slowly, $AlMe_3$ (1 equiv., 2 M in toluene). The mixture was stirred 5 min at 0 °C and overnight at room temperature. Then, 1-naphthoyl chloride (1 equiv.) was added and the resulting solution was stirred 2 h. The mixture was filtered through silica gel and washed twice with Et_2O. The crude product was obtained after concentration.

General Procedure for Aldol Reaction of Oxazolidinone with Aldehydes

To a stirred solution of starting *N*-(1-naphthoyl)-oxazolidinone in THF (1.8 mL) at −78 °C was added 5 equiv. of the aldehyde (or in case of r.t. aldehyde addition, aldehyde was added prior to cooling). A solution of potassium bis(trimethylsilyl)amide (1 M in THF) was added dropwise over 2 min, and the resulting mixture was stirred for desired time (total reaction time including the base addition) at −78 °C. The reaction was then quenched by the addition of 1.0 mL of saturated ammonium chloride solution and diluted with 10 mL diethyl ether and 10 mL of ethyl acetate. Excess ammonium chloride was washed with 5 mL of 5 % sodium bicarbonate solution. The aqueous layer is back extracted with 5 mL ethyl acetate. Combined organic layers were washed with sat. NaCl, dried over sodium sulfate, filtered, and then concentrated to give the crude product which was then purified through column chromatography over silica gel to give the desired product.

General Procedure for the Acetylation Reaction

To a stirred solution of *N*-(1-naphthoyl)-oxazolidinone and 4-(dimethylamino)pyridine in THF at 0 °C were added acetic anhydride and triethylamine. The resulting mixture was stirred for the night at room temperature. The reaction was quenched by the addition of a 2 M of aqueous solution of hydrochloric acid. The mixture was washed with a saturated sodium bicarbonate solution and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and then concentrated to give the crude product which was then purified through column chromatography over silica gel to give the desired product.

General Procedure for the Hydrolysis of the Aldol Product

The acetylated aldol product was suspended in a mixture of acetic acid (0.5 mL) and 6 N HCl (1 mL) and was heated to 125 °C for 24 h. After cooling, the mixture was then diluted with water and washed with diethyl ether. The aqueous phase was concentrated to yield 2-amino-3-hydroxy-2-isobutyl-3-arylpropanoic acid derivatives as their hydrochloride salt.

(4*S*)-2,2-Dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**). Following the *Procedure A*, with sodium L-leucinate salt (2.20 g, 14.38 mmol), $BF_3 \cdot Et_2O$ (0.06 equiv., 100 µL, 0.82 mmol), and 1-naphthoyl chloride (1 equiv., 2.16 mL, 14.38 mmol). The residue was purified by flash column chromatography over silica gel (toluene/ethyl acetate 100 : 0 to 95 : 5) to give (4*S*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**; 2.21 g, 49 %, ee > 99 %). All spectroscopic data are in agreement with those previously reported.[25]

(4*S*)-2,2-Dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**). Following the *Procedure B*, with sodium L-methioninate salt (2.46 g, 14.38 mmol), $AlMe_3$ (1 equiv., 7.2 mL (2 M in toluene), 14.38 mmol), and 1-naphthoyl chloride (1 equiv., 2.16 mL, 14.38 mmol). The residue was purified by flash column chromatography over silica gel (cyclohexane/ethyl acetate/triethylamine 90 : 10 : 1) to give(4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl) ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 2.25 g, 45 %, ee > 99 %). All spectroscopic data are in agreement with those previously reported.[25]

(4*S*)-2,2-Dimethyl-3-(naphthalene-1-carbonyl)-4-(propan-2-yl)-1,3-oxazolidin-5-one (**1-C**). Following the *Procedure A*, with sodium L-valinate salt (2.00 g, 14.38 mmol), $BF_3 \cdot Et_2O$ (0.06 equiv., 100 µL, 0.82 mmol), and 1-naphthoyl chloride (1 equiv., 2.16 mL, 14.38 mmol). The residue was purified by flash column chromatography over silica gel (pentane/

diethyl ether 80:20) to give (4*S*)-2,2-dimethyl-3-(naphthalene-1-carbonyl)-4-(propan-2-yl)-1,3-oxazolidin-5-one (**1-C**; 3.28 g, 75%, ee > 99%). All spectroscopic data are in agreement with those previously reported.[25]

(4*S*)-4-Benzyl-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-D**). Following the *General Procedure B*, with sodium L-phenylalaninate salt (2.69 g, 14.38 mmol), $AlMe_3$ (1 equiv., 7.2 mL (2 M in toluene), 14.38 mmol), and 1-naphthoyl chloride (1 equiv., 2.16 mL, 14.38 mmol). The residue was purified by flash column chromatography over silica gel (cyclohexane/ethyl acetate/triethylamine 80:20:1) to give (4*S*)-4-Benzyl-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-D**; 3.14 g, 61%, ee > 99%). All spectroscopic data are in agreement with those previously reported.[25]

(4*R*)-4-[(*R*)-(3-Bromophenyl)(hydroxy)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**2a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**; 100 mg, 0.307 mmol), 3-bromobenzaldehyde (5 equiv., 1.53 mmol, 180 µL) and KHMDS (1.5 equiv., 0.460 mmol, 460 µL (1 M in THF)) in THF gave compound **2a** after 18 min. The crude product was then purified by column chromatography over silica gel (heptane/THF 90:10 to 70:30) to give one diastereomer **2a** (150 mg, 95%, ee = 72%). HPLC Analysis: (*S,S*) *Whelk-O 1*, hexane/ethanol 90:10, 1 mL/min, $T = 25\,^{\circ}C$, $\lambda = 222$ nm; retention times of racemic mixture: 12.2 min (minor) and 17.3 min (major *RR*) *ee* = 72%. ^{1}H-NMR (360 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.6:0.4: 0.42 (*s*, 3H*m*); 0.54 (*s*, 3H*M*); 0.99 (*s*, 3H*M*); 1.10 (*d*, *J* = 6.3, 3H*m*); 1.11 (*d*, *J* = 6.5, 3H*M*); 1.20 (*d*, *J* = 6.6, 3H*m*); 1.28 (*d*, *J* = 6.7, 3H*M*); 1.43 (*s*, 3H*m*); 1.94–2.04 (*m*, 1H*m*); 2.09 (*dd*, *J* = 8.6, *J* = 14.5, 1H*m*); 2.13–2.18 (*m*, 1H*M*); 2.32 (*dd*, *J* = 9.2, *J* = 14.8, 1H*M*); 2.90 (*dd*, *J* = 2.5, *J* = 14.6, 1H*m*); 3.06 (*dd*, *J* = 2.1, *J* = 14.8, 1H*M*); 5.33 (*d*, *J* = 10.6, 1H*M*); 5.36 (*d*, *J* = 10.2, 1H*m*); 6.51 (*d*, *J* = 10.6, 1H*M*); 6.53 (*d*, *J* = 10.2, 1H*m*); 7.28–7.42 (*m*, 3H*M* + 3H*m*); 7.46–7.62 (*m*, 4H*M* + 4H*m*); 7.72–7.76 (*m*, 2H*M* + 2H*m*); 7.87–7.96 (*m*, 2H*M* + 2H*m*). ^{13}C-NMR (62.9 MHz, 300 K, $CDCl_3$): 22.6*M*; 22.9*m*; 24.5*M*; 24.7*m*; 25.4*m*; 25.5*M*; 28.5*M*; 28.6*M* + *m*; 30.1*m*; 40.7*m*; 40.8*M*; 75.8*M*; 76.2*m*; 78.4*M* + *m*; 96.4*M*; 96.5*m*; 123.1*M*; 123.2*m*; 123.7*m*; 124.2*M*; 124.4*M*; 125.5*m*; 125.6*M*; 126.0*m*; 126.2*M*; 126.4*m*; 126.8*M*; 126.9*m*; 127.5*M*; 128.2*m*; 128.6*m*; 128.8*M*; 129.6*M*; 129.8*m*; 129.9*M*; 130.0*M* + *m*; 130.3*M* + *m*; 130.7*m*; 131.6*M* + *m*; 132.8*M*; 132.9*m*; 133.2*M*; 133.5*m*; 143.2*m*; 143.4*M*; 170.8*M*; 171.3*m*; 171.4*m*; 171.6*M*. HR-ESI-MS): 510.1259 ($C_{27}H_{28}BrNO_4^+$, $[M+H]^+$; calc. 510.1274), 532.1074 ($C_{27}H_{28}BrNNaO_4^+$, $[M+Na]^+$; calc. 532.1094).

(4*R*)-4-[(*S*)-Hydroxy(pyridin-2-yl)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**3b**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**; 100 mg, 0.307 mmol), 2-pyridinecarboxaldehyde (5 equiv., 1.53 mmol, 146 µL) and KHMDS (1.5 equiv., 0.460 mmol, 460 µL (1 M in THF)) in THF gave compound **3b** after 18 min. The crude product (dr = 4:96) was then purified by column chromatography over silica gel (cyclohexane/ethyl acetate 85:15 to 30:70) to give diastereomer **3b** (75 mg, 56%, ee > 99%). HPLC Analysis: *Chiralpak AD-H*, hexane/ethanol 95:5, 1 mL/min, $T = 35\,^{\circ}C$, $\lambda = 222$ nm; retention times of racemic mixture: major diastereomer 29.3 min and 38.1 min (*RR*) *ee* = 99% (minor diastereomer 14.6 min (minor) and 29.3 min (major) ee > 99%). ^{1}H-NMR (300 MHz, 300 K, (D_8)toluene): Conformer ratio major (*M*)/minor (*m*): 1.0: 0.5: 0.50 (*s*, 3H*m*); 0.74 (*s*, 3H*m*); 0.93 (s,3H*M*); 1.10 (s,3H*M*); 1.12–1.23 (*m*, 6H*M* + 6H*m*); 2.10–2.17 (*m*, 1H*M* + 1H*m*); 2.36–2.44 (*m*, 1H*M* + 1H*m*); 3.12 (*dd*, *J* = 3.3, *J* = 13.9, 1H*m*); 3.28 (*dd*, *J* = 1.2, *J* = 14.1, 1H*M*); 5.10 (*d*, *J* = 8.7, 1H*M*); 5.19 (br. *s*, 1H*m*); 5.53 (*d*, *J* = 8.7, 1H*M*); 5.82 (br. *s*, 1H*m*); 6.56–6.64 (*m*, 1H*M* + 1H*m*); 6.95–7.52 (*m*, 8H*M* + 8H*m*); 7.93 (*d*, *J* = 8.1, 1H*M*); 8.10 (*d*, *J* = 9.1, 1H*m*); 8.25 (*d*, *J* = 5.1, 1H*M*); 8.33 (*d*, *J* = 4.2, 1H*m*). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 1.0:0.5: 0.89 (*s*, 3H*m*); 1.09 (*d*, *J* = 6.7, 3H*M*); 1.10 (*d*, *J* = 6.7, 3H*m*); 1.14 (*s*, 3H*M*); 1.17 (*d*, *J* = 6.7, 3H*m*); 1.22 (*d*, *J* = 6.7, 3H*M*); 1.25 (*s*, 3H*M*); 1.52 (*s*, 3H*m*); 1.89–1.97 (*m*, 1H*m*); 1.99–2.08 (*m*, 1H*M*); 2.25–2.35 (*m*, 1H*M* + 1H*m*); 3.01 (*dd*, *J* = 3.2, *J* = 14.2, 1H*m*); 3.18 (*d*, *J* = 12.7, 1H*M*); 5.01 (*d*, *J* = 9.1, 1H*M*); 5.06 (*d*, *J* = 9.0, 1H*m*); 5.43 (*d*, *J* = 9.1, 1H*M*); 5.66 (*d*, *J* = 8.6, 1H*m*); 7.29–7.36 (*m*, 2H*M* + 1H*m*); 7.41–7.56 (*m*, 4H*M* + 5H*m*); 7.60 (*d*, *J* = 7.6, 1H*M*); 7.70–7.93 (*m*, 3H*M* + 4H*m*); 8.61–8.67 (*m*, 1H*M* + 1H*m*). ^{13}C-NMR (100 MHz, 300 K, $CDCl_3$): 22.3*M*; 23.1*m*; 24.8*M* + *m*; 25.0*M* + *m*; 28.7*m*; 29.2*M*; 29.4*M*; 30.3*m*; 40.1*m*; 41.2*M*; 72.5*m*; 72.8*M*; 76.0*M*; 76.4*m*; 96.5 *M* + *m*; 123.4 *M*; 123.6*m*; 123.8 *M* + *m*; 124.0*M* + *m*; 125.0*M*; 125.4*M*; 125.6*m*; 126.0*m*; 126.5*M* + *m*; 127.3*M*; 128.4*m*; 128.6*M*; 129.8*m*; 130.0*M**2 + *m**2; 133.3*m*; 133.4*M*; 134.1*M*; 134.3*m*; 136.4*M* + *m*; 148.8*M* + *m*; 157.6*M*; 158.2*m*; 169.0*M* + *m*; 172.4*m*; 172.7*M*. HR-ESI-MS: 433.2124 ($C_{26}H_{29}N_2O_4^+$, $[M+H]^+$; calc. 433.2122), 455.1946 ($C_{26}H_{28}N_2NaO_4^+$, $[M+Na]^+$; calc. 455.1941).

(*R*)-[(4*R*)-2,2-Dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-5-oxo-1,3-oxazolidin-4-yl](pyridin-3-yl)methyl acetate (**Ac-4a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**; 100 mg, 0.307 mmol), 3-pyridinecarboxaldehyde (5 equiv., 1.53 mmol, 116 μL) and KHMDS (1.5 equiv., 0.460 mmol, 460 μL (1 M in THF)) in THF gave (4*R*)-4-[(*R*)-hydroxy(pyridin-3-yl)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**4**) after 12 min. Following the *General Procedure of Acetylation*, compound **4** (crude product), 4-(dimethylamino)pyridine (0.1 equiv., 0.03 mmol, 4 mg), acetic anhydride (5 equiv., 1.53 mmol,145 μL) and triethylamine (1 equiv., 0.307 mmol, 410 μL) in THF (3 mL) gave compound **Ac-4a** after one night. The crude product was then purified by column chromatography over silica gel (cyclohexane/ethyl acetate 60:40) to give diastereomer **Ac-4a** (80 mg, 55%, ee = 76%, and 91% after recrystallization). HPLC Analysis: *Chiralpak IC*, hexane/ethanol 80:20, 1 mL/min, $T = 25\,^{\circ}C$, $\lambda = 222$ nm; retention times of racemic mixture: 14.0 min and 20.1 min (*RS*). *ee* = 76%. ^{1}H-NMR (250 MHz, 300 K, CD_2Cl_2): Conformer ratio major (*M*)/minor (*m*): 0.7:0.3 (second minor, not described 0.2): 1.60 (*d*, *J* = 6.5, 3H*M*); 1.77 (*d*, *J* = 6.7, 3H*M*); 1.85 (*d*, *J* = 6.8, 3H*m*); 1.91–1.94 (*m*, 3H*m*); 1.93 (*s*, 3H*M*); 1.96 (*s*, 3H*m*); 2.42 (*s*, 3H*m*); 2.44 (*s*, 3H*M*); 2.51-2.64 (*m*, 1H*M*); 2.73–2.75 (*m*, 2H*m*); 2.83 (*d*, *J* = 14.1, 1H*M*); 2.93 (*s*, 3H*M*); 3.00 (*s*, 3H*m*); 3.48 (*dd*, *J* = 2.8, *J* = 13.8, 1H*M*); 3.64 (*dd*, *J* = 1.4, *J* = 13.7, 1H*m*); 7.58 (*s*, 1H*m*); 7.83 (*s*, 1H*M*); 8.09–8.38 (*m*, 6H*M* + 6H*m*); 8.66–8.79 (*m*, 3H*M* + 3H*m*); 9.29 (*dd*, *J* = 1.5, *J* = 4.9, 1H*M* + 1H*m*); 9.43 (*d*, *J* = 1.6, 1H*M* + 1H*m*). ^{13}C-NMR (62.9 MHz, 300 K, CD_2Cl_2): 22.7*M*; 22.8*m*; 23.4*m*; 24.1*M*; 26.0*M*; 26.2*m*; 26.4*M* + *m*; 30.2*M*; 30.7*m*; 31.5*m*; 31.9*M*; 43.4*M*; 44.6*m*; 72.4*M*; 72.8*m*; 75.6*m*; 75.7*M*; 98.7*M* + *m*; 125.4*M* + *m*; 126.0*m*; 126.1*M*; 126.2*M*; 126.5*m*; 127.1*M*; 127.7*m*; 128.7m; 128.8*M*; 129.4*M*; 129.5*m*; 130.7*M*; 130.8*m*; 131.7*m*; 131.9*M*; 132.3*M*; 132.4*m*; 134.1*M* + *m*; 135.2*M*; 135.3*M*; 135.4*m*; 135.5*m*; 139.0*M*; 139.2*m*; 151.1*M*; 151.2*m*; 151.3*M* + *m*; 171.5*M*; 171.6*M*; 171.7*m*; 171.8*m*; 171.9*M*; 172.0*m*. HR-ESI-MS: 475.2240 ($C_{28}H_{31}N_2O_5^+$, $[M+H]^+$; calc. 475.2227), 497.2046 ($C_{28}H_{30}N_2NaO_5^+$, $[M+Na]^+$; calc. 497.2047).

(4*R*)-4-[(*R*)-(2-Fluorophenyl)(hydroxy)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**5a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-A**; 100 mg, 0.307 mmol), 2-fluorobenzaldehyde (5 equiv., 1.53 mmol, 160 μL) and KHMDS (1.5 equiv., 0.460 mmol, 460 μL (1 M in THF)) in THF gave (4*R*)-4-[(*R*)-(2-fluorophenyl)(hydroxy)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one after 18 min. The crude product (dr = 96:4) was then purified by column chromatography over silica gel (heptane/THF 85:15) to give diastereomer **5a** (113 mg, 81%, ee = 82%). HPLC Analysis: (*S,S*) *Whelk-O 1*, hexane/ethanol 90:10, 1 mL/min, $T = 25\,^{\circ}C$, $\lambda = 222$ nm; retention times of racemic mixture: 10.6 min (minor) and 24.9 min (major) *ee* = 82% (minor diastereomer 12.4 min (minor) and 16.4 min (major) *ee* = 86%). ^{1}H-NMR (300 K, $CDCl_3$): Conformer ratio major (M_1): major (M_2): major (M_3):minor (*m*): 0.6:0.6:0.6: 0.1 (not described): 0.85 (*s*, 3H*M*); 0.87 (*d*, *J* = 6.0, 3H*M*); 0.98 (*d*, *J* = 7.3, 3H*M*); 0.99 (br. *s*, 6H*M*); 1.08 (*d*, *J* = 5.8, 3H*M*); 1.14 (*d*, *J* = 6.6, 3H*M*); 1.18 (*s*, 3H*M*); 1.27 (*d*, *J* = 6.1, 3H*M*); 1.54 (*s*, 3H*M*); 1.80–1.67 (*m*, 4H*M*); 2.19–2.12 (*m*, 5H*M*); 2.30 (*s*, 3H*M*); 2.94 (*dd*, *J* = 2.2, *J* = 14.3, 1HM_1); 3.17 (*d*, *J* = 12.5, 1HM_2 + 1HM_3); 4.59 (*d*, *J* = 7.0, 1HM_1); 4.69 (br. *s*, 1HM_2); 5.67 (*d*, *J* = 10.1, 1HM_3); 5.68 (br. *s*, 1HM_2); 5.76 (*d*, *J* = 10.1, 1HM_3); 6.12 (*d*, *J* = 6.2, 1HM_1); 6.64 (*t*, *J* = 9.2, 1H*M*); 8.01–7.00 (*m*, 32H*M*). ^{13}C-NMR (75.5 MHz, 300 K, $CDCl_3$): 3 conformers 1 major (*M*) and 2 minor, same proportion (*m*): 21.7*m*; 22.7*M*; 23.2*m*; 24.0*m*; 24.6*m**3; 24.9*m*; 25.2*M*; 25.7*M*; 27.0*m*; 28.6*m*; 28.8*M*; 28.9*M*; 30.5*m*; 39.9*m*; 40.7*M*; 41.4*m*; 69.1*m*; 70.4*m*; 73.3*m*; 74.6*m*; 74.9*M*; 77.5*M*; 96.4*M*; 96.5*m*; 98.4*m*; 114.5*m* (*d*, *J* = 23); 115.7*m* (*d*, *J* = 23); 116.2*M* (*d*, *J* = 23); 123.4–134.1; 159.6*m* (*d*, *J* = 249); 160.1*M* (*d*, *J* = 249); 160.2*m* (*d*, *J* = 249); 168.7*m*; 170.1*M*; 170.3*m*; 170.5*m*; 171.1*M* + *m*. HR-ESI-MS: 450.2059 ($C_{27}H_{29}FNO_4^+$, $[M+H]^+$; calc. 450.2075), 472.1879 ($C_{27}H_{28}FNNaO_4^+$, $[M+Na]^+$; calc. 472.1895).

(4*R*)-4-[(*R*)-(3-Bromophenyl)(hydroxy)methyl]-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**6a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 100 mg, 0.290 mmol), 3-bromobenzaldehyde (5 equiv., 1.45 mmol, 170 μL) and KHMDS (1.5 equiv., 0.430 mmol, 430 μL (1 M in THF)) in THF gave compound **6a** after 10 min. The crude product (single diastereomer) was then purified by column chromatography over silica gel (PE/ethyl acetate 100:0 to 70:30) to give diastereomer **6a** (100 mg, 65%, ee = 73%). HPLC Analysis: (*S,S*) *Whelk-O 1*, hexane/ethanol 90:10 for 30 min then with a gradient from 90:10 to 80:20 over 15 min and a step of 35 min, 1 mL/min, $T = 25\,^{\circ}C$, $\lambda = 222$ nm; retention times of racemic mixture: 23.3 min (minor) and

26.6 min (major) *ee* = 73 %. ^{1}H-NMR (250 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.7: 0.3: 0.44 (*s*, 3H*m*); 0.56 (*s*, 3H*M*); 0.99 (*s*, 3H*M*);1.47 (*s*, 3H*m*); 2.25 (*s*, 3H*m*); 2.31 (*s*, 3H*M*); 2.71–3.03 (*m*, 3H*M* + 4H*m*); 3.07–3.17 (*m*, 1H*M*);5.37 (*d*, *J* = 11.0, 1H*M*); 5.40 (*d*, *J* = 11.1, 1H*m*); 6.67 (*d*, *J* = 11.1, 1H*M*); 6.71 (*d*, *J* = 11.1, 1H*m*); 7.25–7.42 (*m*, 3H*M* + 3H*m*); 7.45–7.75 (*m*, 6H*M* + 6H*m*); 7.86–7.99 (*m*, 2H*M* + 2H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 3 conformers *M* + 2*m*: 14.6*m*; 15.5*m*; 15.6*M*; 26.2*m*; 27.0*m*; 28.3*M* + *m*; 28.7*m*; 28.4 *M* + *m*; 28.9*M*; 30.4*m*; 32.4*m*; 32.9*M*; 33.1*m*; 56.5*M* + 2*m*; 75.4*M*; 75.6*m*; 76.1*m*; 96.7*M*; 96.8*m*; 98.2*m*; 123.2–133.7; 137.3*m*; 142.8*m* 142.9*M*; 169.9 *M*; 170.3*m*2*; 170.6*m*; 171.2*m*; 171.5 *M*. HR-ESI-MS: 528.0823 ($C_{26}H_{27}BrNO_4S^+$, $[M+H]^+$; calc. 528.0839), 550.0645 ($C_{26}H_{26}BrNNaO_4S^+$, $[M+Na]^+$; calc. 550.0658).

(4*R*)-4-[(*R*)-(2-Bromophenyl)(hydroxy)methyl]-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**7a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 100 mg, 0.290 mmol), 2-bromobenzaldehyde (5 equiv., 1.45 mmol, 170 μL) and KHMDS (1.5 equiv., 0.430 mmol, 430 μL (1 M in THF)) in THF gave compound **7a** after 12 min. The crude product (single diastereomer) was then purified by column chromatography over silica gel (PE/ethyl acetate 100:0 to 70:30) to give diastereomer **7a** (110 mg, 72 %, ee = 60 %). HPLC Analysis: (*S,S*) *Whelk-O 1*, hexane/ethanol 88:12 for 30 min then with a gradient from 88:12 to 80:20 over 15 min and a step of 40 min, 1 mL/min, *T* = 25 °C, λ = 222 nm; retention times of racemic mixture: 15.5 min (minor) and 41.5 min (major) *ee* = 60 % (minor diastereomer 11.9 min (minor) and 25.5 min (major) – other trials). ^{1}H-NMR (300 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*):minor 1 (m_1):minor 2 (m_2): 0.4: 0.3: 0.2: 1.00 (*s*, 3Hm_1); 1.19 (*s*, 3Hm_1); 1.25 (*s*, 3Hm_2); 1.27 (*s*, 3Hm_2); 2.02 (*s*, 3H*M*); 2.03 (*s*, 3Hm_1); 2.06 (*s*, 3Hm_2); 2.19 (*s*, 3H*M*); 2.28 (*s*, 3H*M*); 2.37–2.88 (*m*, 3H*M* + 3Hm_1 + 3Hm_2); 3.27–3.50 (*m*, 1H*M* + 1Hm_1 + 1Hm_2); 4.86 (*d*, *J* = 7.3, 1Hm_1); 4.96 (*d*, *J* = 2.0, 1H*M*); 6.05 (*d*, *J* = 7.1, 1Hm_1); 6.63 (*d*, *J* = 3.2, 1Hm_2); 6.97–7.04 (*m*, 1H*M*); 7.13–7.25 (*m*, 1H*M* + 1Hm_1 + 2Hm_2); 7.36–7.66 (*m*, 6H*M* + 6Hm_1 + 6Hm_2); 7.24–7.36 (*m*, 1H*M* + 1Hm_1 + 1Hm_2); 7.85–7.98 (3H*M* + 3Hm_1 + 3Hm_2). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 15.3m_2; 15.4*M* + m_1; 24.8*M*; 27.2*M*; 28.1m_2; 28.6m_1; 28.7*M*; 28.9m_1; 29.0m_1; 29.4m_2; 30.3m_2; 30.6m_2; 32.2m_1; 33.1*M*; 71.8m_1; 72.3m_2; 73.7*M*; 74.1m_2; 74.2*M*; 74.3m_1; 96.5*M*; 98.4m_1 + m_2; 123.2-134.2; 135.4m_2; 137.6*M*; 138.5m_2; 139.2m_1; 168.5m_1; 169.0*M*; 169.4m_2; 169.5*M*; 170.3m_1; 170.4m_2. HR-ESI-MS: 528.0829 ($C_{26}H_{27}BrNO_4S^+$, $[M+H]^+$; calc. 528.0839), 550.0647 ($C_{26}H_{26}BrNNaO_4S^+$, $[M+Na]^+$; calc. 550.0658).

(4*R*)-4-[Hydroxy(pyridin-2-yl)methyl]-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**8**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 100 mg, 0.290 mmol), 2-pyridinecarboxaldehyde (5 equiv., 1.45 mmol, 140 μL) and KHMDS (1.5 equiv., 0.430 mmol, 430 μL (1 M in THF)) in THF gave compound **8** after 15 min. The crude product (dr = 15:85) was then purified by column chromatography over silica gel (PE/ethyl acetate/Et_3N 80:20:1 to 60:40:1) to give minor diastereomer **8a** (4 mg, 3 %, ee = 82 %) and major diastereomer **8b** (85 mg, 65 %, ee = 97 %). HPLC Analysis: *Chiralpak AD-H*, hexane/ethanol 95:5, 1 mL/min, *T* = 38 °C, λ = 222 nm; retention times of racemic mixture: 62.1 min (minor) and 67.8 min (major) *ee* = 97 % (isolated with ee > 99 %) (minor diastereomer 47.6 min (minor) and 56.8 min (major) *ee* = 82 %). *Minor Diastereomer* **8a**. ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 1.0:0.5: 0.87 (*s*, 3H*M*); 0.97 (*s*, 3H*m*); 1.15 (m_c, 3H*m*); 1.74 (*s*, 3H*M*); 2.25 (*s*, 3H*M*); 2.30 (*s*, 3H*m*); 2.37–2.47 (*m*, 2H*m*); 2.56–2.67 (*m*, 1H*m*); 2.98–3.11 (*m*, 4H*M*); 3.15–3.34 (*m*, 1H*m*); 5.53 (*d*, *J* = 11.0, 1H*m*); 5.57 (*d*, *J* = 11.7, 1H*M*); 6.04 (*d*, *J* = 8.4, 1H*M*); 6.44 (*d*, *J* = 11.7, 1H*m*); 6.51 (*d*, *J* = 11.9, 1H*M*); 6.62 (*d*, *J* = 6.2, 1H*m*); 7.07–7.13 (*m*, 1H*M*); 7.31–7.98 (*m*, 8H*M* + 9H*m*); 8.57–8.60 (*m*, 1H*M*); 8.66–8.69 (*m*, 1H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 15.6*M*; 15.7*m*; 27.3*M*; 28.0*M*; 28.1*m*; 28.6*m*; 29.7*m*; 30.4*M*; 33.6*m*; 34.5*M*; 72.6*M*; 73.3*m*; 74.9*M*; 76.1*m*; 96.2*M* + *m*; 121.2*m*; 121.4*M*; 122.8*M*; 123.0*m*; 124.0*M* + *m*; 124.4*M*; 124.5*m*; 124.7*M*; 125.3*m*; 126.5*M*; 126.8*m*; 127.1*M*; 127.7*m*; 128.3*M*; 128.7*m*; 129.4*m*; 130.0*M*; 130.2*M* + *m*; 132.7*m*; 133.1*M* + *m*; 133.2*M*; 136.9*M* + *m*; 148.3*M*; 148.6*m*; 160.1*m*; 160.2*M*; 169.6*M*; 170.0*m*; 174.4*M*; 170.5*m*. HR-ESI-MS: 451.1684 ($C_{25}H_{27}N_2O_4S^+$, $[M+H]^+$; calc. 451.1686), 473.1503 ($C_{25}H_{26}N_2NaO_4S^+$, $[M+Na]^+$; calc. 473.1505). *Major Diastereomer* **8b**. ^{1}H-NMR (360 MHz, 300 K, C_6D_6): Conformer ratio major (*M*)/minor (*m*): 1.0:0.5: 0.83 (*s*, 3H*m*); 0.93 (*s*, 3H*M*); 1.22 (m_c, 3H*M* + 3H*m*); 2.04 (*s*, 3H*m*); 2.10 (*s*, 3H*M*); 2.78–2.91 (*m*, 3H*m*); 2.95–3.15 (*m*, 3H*M*); 3.52–3.63 (*m*, 1H*m*); 3.70–3.80 (*m*, 1H*M*); 5.33 (*d*, *J* = 8.4, 1H*M*); 5.35 (*d*, *J* = 8.3, 1H*m*); 5.69 (*d*, *J* = 8.4, 1H*M*); 6.04 (*d*, *J* = 8.3, 1H*m*); 6.61–6.72 (*m*, 1H*M* + 1H*m*); 7.02–7.10 (*m*, 2H*M* + 2H*m*); 7.13–7.23 (*m*, 2H*M* + 3H*m*); 7.24–7.36 (*m*, 1H*M* + 1H*m*); 7.44 (*d*, *J* = 6.8,

1H*M*); 7.53–7.74 (*m*, 2H*M*+2H*m*); 7.96 (br. *s*, 1H*M*); 8.07 (br. *s*, 1H*m*); 8.30 (*d*, *J*=3.9, 1H*M*); 8.40 (*d*, *J*=3.7, 1H*m*). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.7:0.3: 0.87 (*s*, 3H*m*); 1.11 (*s*, 3H*M*); 1.28 (m_c, 3H*M*); 1.51 (*s*, 3H*m*); 2.21 (*s*, 3H*m*); 2.26 (*s*, 3H*M*); 2.56–2.65 (*m*, 3H*m*); 2.70–2.83 (*m*, 3H*M*); 3.20–3.30 (*m*, 1H*m*); 3.40–3.50 (*m*, 1H*M*); 5.03 (br. *s*, 1H*M*+1H*m*); 5.46 (br. *s*, 1H*M*); 5.71 (br. *s*, 1H*m*); 7.26–7.93 (*m*, 10H*M*+10H*m*); 8.60–8.67 (*m*, 1H*M*+1H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 15.5*M*+*m*; 28.4*m*; 29.0*M*; 29.6*m*; 29.7*M*2*; 30.5*m*; 31.5*m*; 32.4*M*; 72.3*m*; 73.2*M*; 75.3*M*+*m*; 96.7*M*+*m*; 123.3*M*; 123.6*m*; 123.8*M*; 123.9*m*; 124.1*m*; 124.2*M*; 124.8*M*; 125.4*M*; 125.6*m*; 125.7*m;* 126.4*m*; 126.6*M*; 126.7*m*; 127.4*M*; 128.4*m*; 128.7*M*; 129.8*m*; 129.9*M*; 130.0*m*; 130.2*M*; 133.3*m*; 133.4*M*; 133.8*M*; 134.1*m*; 136.6*M*+*m*; 148.9*M*+*m*; 157.2*M*; 158.0*m*; 169.1*m*; 169.3*M*; 171.4*M*; 172.0*m*. HR-ESI-MS: 451.1672 ($C_{25}H_{27}N_2O_4S^+$, $[M+H]^+$; calc. 451.1686), 473.1500 ($C_{25}H_{26}N_2NaO_4S^+$, $[M+Na]^+$; calc. 473.1505).

(4*R*)-4-[(*R*)-(2-Fluorophenyl)(hydroxy)methyl]-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**9a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 100 mg, 0.290 mmol), 2-fluorobenzaldehyde (5 equiv., 1.45 mmol, 180 μL) and KHMDS (1.5 equiv., 0.430 mmol, 430 μL (1 M in THF)) in THF gave compound **9a** after 18 min. The crude product (single diastereomer) was then purified by column chromatography over silica gel (heptane/THF 90:10 to 75:25) to give one diastereomer **9a** (135 mg, 99%, ee=85%). HPLC Analysis: (*S,S*) *Whelk-O 1*, hexane/ethanol 88:12 for 30 min then with a gradient from 88:12 to 80:20 over 15 min and a step of 40 min, 1 mL/min, *T*=25 °C, λ=222 nm; retention times of racemic mixture: 15.8 min (minor) and 29.8 min (major) *ee*=85% (minor diastereomer 11.9 min and 25.6 min from racemic). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.6:0.3: 0.75 (*s*, 3H*M*); 0.78 (*s*, 3H*m*); 0.98 (*s*, 3H*M*); 1.52 (*s*, 3H*m*); 2.20 (*s*, 3H*m*); 2.32 (*s*, 3H*M*); 2.54–2.63 (*m*, 1H*m*); 2.72–3.08 (*m*, 3H*m*+4H*M*); 5.28 (*d*, *J*=9.4, 1H*m*); 5.69 (*d*, *J*=11.1, 1H*M*); 5.92 (*d*, *J*=9.3, 1H*m*); 6.16 (*d*, *J*=11.0, 1H*M*); 7.06–7.21 (*m*, 2H*M*+2H*m*); 7.34–7.74 (*m*, 6H*M*+6H*m*); 7.06–7.95 (*m*, 3H*M*+3H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 15.4*m*; 15.6*M*; 28.2*m*; 28.4*M*; 28.5*M*; 28.9*m*; 29.0*M*; 30.4*m*; 32.2*m*; 32.8*M*; 70.6*m*; 72.2*M*; 74.0*M*; 74.4*m*; 96.4*M*+*m*; 115.7*m* (*d*, *J*=22); 116.0*M* (*d*, *J*=22); 124.1–133.4; 159.6*M*+*m* (*d*, *J*=248); 169.0*M*; 169.5*m*; 170.5*m*; 171.1*M*. HR-ESI-MS: 468.1623 ($C_{26}H_{27}FNO_4S^+$, $[M+H]^+$; calc. 468.1639), 490.1451 ($C_{26}H_{26}FNNaO_4S^+$, $[M+Na]^+$; calc. 490.1459).

(4*R*)-4-[(*R*)-Hydroxy(pyridin-3-yl)methyl]-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**10a**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-4-[2-(methylsulfanyl)ethyl]-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-B**; 100 mg, 0.290 mmol), 3-pyridinecarboxaldehyde (5 equiv., 1.45 mmol, 160 μL) and KHMDS (1 equiv., 0.290 mmol, 290 μL (*1* M in THF)) in THF gave compound **10a** after 12 min. The crude product (dr=98/2) was then purified by column chromatography over silica gel (cyclohexane/ethyl acetate 60:40 to 50:50) to give diastereomer **10a** (115 mg, 88%, ee=75%). HPLC Analysis: *Chiralpak IC*, hexane/ethanol 90:10, 1 mL/min, *T*=25 °C, λ=222 nm; retention times of racemic mixture: 30.1 min (minor) and 34.0 min (major) *ee*=75% (minor diastereomer 38.3 min (minor) and 41.3 min (major)). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.7:0.3: 0.57 (*s*, 3H*M*+3H*m*); 0.97 (*s*, 3H*M*); 1.51 (*s*, 3H*m*); 2.19 (*s*, 3H*m*); 2.27 (*s*, 3H*M*); 2.56–3.11 (*m*, 4H*M* +4H*m*); 5.41 (*d*, *J*=10.4, 1H*M*); 5.59 (*d*, *J*=8.5, 1H*m*); 6.23 (*d*, *J*=9.4, 1H*m*); 6.58 (*d*, *J*=10.7, 1H*M*); 7.16 (*d*, *J*=7.0, 1H*M*); 7.37–7.76 (*m*, 6H*M*+6H*m*); 7.82–7.94 (*m*, 2H*M*+3H*m*); 8.64–8.66 (*m*, 1H*M*+1H*m*); 8.72 (br. *s*, 1H*M*); 8.79 (br. *s*, 1H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 15.5*m*; 15.6*M*; 28.4*M*; 28.6*M*; 28.7*m*; 28.9*M*; 29.7*m*; 30.3*m*; 32.8*m*; 32.9*M*; 74.1*m*; 74.8*m*; 75.2*M*; 75.5*M*; 96.7*M*; 96.8*m*; 123.2*m*; 123.5*M*; 123.9*m*; 124.1*M*+*m*; 124.2*M*; 125.2*M*; 125.6*m*; 126.9*m*; 127.0*M*; 127.5*m*; 127.8*M*; 128.6*m*; 128.9*M*; 129.5*M*; 129.8*m*; 130.5*M*; 130.7*m*; 132.4*M*; 132.8*m*; 133.1*M*; 133.4*m*; 134.7*M*; 135.1*m*; 135.7*m*; 136.0*M*; 148.5*M*; 148.7*m*; 149.7*m*; 149.9*M*; 169.7*M*; 170.3*m*; 170.8*m*; 171.4*M*. HR-ESI-MS: 451.1676 ($C_{25}H_{27}N_2O_4S^+$, $[M+H]^+$; calc. 451.1686), 473.1492 ($C_{25}H_{26}N_2NaO_4S^+$, $[M+Na]^+$; calc. 473.1505).

(4*R*)-4-[(*S*)-Hydroxy(pyridin-2-yl)methyl]-2,2-dimethyl-3-(naphthalene-1-carbonyl)-4-(propan-2-yl)-1,3-oxazolidin-5-one (**11b**). Following the *General Procedure*, (4*S*)-2,2-dimethyl-3-(naphthalene-1-carbonyl)-4-(propan-2-yl)-1,3-oxazolidin-5-one (**1-C**; 100 Mg, 0.320 mmol), 2-pyridinecarboxaldehyde (5 equiv., 1.60 mmol, 152 μL) and KHMDS (1.5 equiv., 0.48 mmol, 480 μL (1 M in THF)) in THF gave compound **11b** after 18 min. The crude product (dr=7:93) was then purified by column chromatography over silica gel (cyclohexane/ethyl acetate 85:15 to 30:70) to give diastereomer (63 mg, 47%, ee=90%). HPLC

Analysis: *Chiralpak AD-H*, hexane/ethanol 90:10, 1 mL/min, $T=30\,^{\circ}C$, $\lambda=222$ nm; retention times of racemic mixture: 12.9 min (minor) and 32.7 min (major) *ee* = 90% (minor diastereomer 19.2 min (minor) and 39.2 min (major) *ee* = 45%). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.7:0.3: 0.94 (*s*, 3H*m*); 1.15 (*s*, 3H*M*); 1.28 (*s*, 3H*M*); 1.34 (*d*, *J* = 6.9, 3H*M*); 1.35 (*d*, *J* = 6.8, 3H*m*); 1.50 (*d*, *J* = 7.1, 3H*m*); 1.51 (*s*, 3H*m*); 1.61 (*d*, *J* = 7.0, 3H*M*); 3.40 (*sept*, *J* = 7.0, 1H*m*); 3.70 (*sept*, *J* = 7.0, 1H*M*); 5.74 (*s*, 1H*M*); 6.07 (*s*, 1H*m*); 7.23–7.56 (*m*, 7H*M* + 6H*m*); 7.67–7.80 (*m*, 2H*M* + 2H*m*); 7.82–7.90 (*m*, 2H*M* + 3H*m*); 8.56 (*d*, *J* = 4.6, 1H*M*); 8.63 (*d*, *J* = 4.8, 1H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 18.5*M*; 19.2*m*; 19.9*m*; 20.0*M*; 29.0*M*; 29.1*m*; 29.7*M* + *m*; 29.8*M*; 31.3*m*; 72.3*M*; 73.9*m*; 76.1*m*; 77.7*M*; 96.1*m*; 96.2*M*; 122.8*M*; 123.5*m*; 123.6*m*; 123.8*M*; 123.9 *M* + *m*; 125.2*M*; 125.7*M*; 125.8*m*; 125.9*m*; 126.4*M*; 126.5*m*; 126.7*m*; 127.2*M*; 128.4*m*; 128.5*M*; 129.9*M* + *m*; 130.0*M*; 130.1*m*; 133.4*M* + *m*; 134.5*M* + *m*; 136.5*M* + *m*; 148.1*M*; 148.6*m*; 157.0*M*; 158.5*m*; 169.6*M*; 169.8*m*; 170.3*M*; 171.4*m*. HR-ESI-MS: 419.1959 ($C_{25}H_{27}N_2O_4^+$, $[M+H]^+$; calc. 419.1965), 441.1777 ($C_{25}H_{26}N_2NaO_4^+$, $[M+Na]^+$; calc. 441.1785).

(*R*)-[4-Benzyl-2,2-dimethyl-3-(naphthalene-1-carbonyl)-5-oxo-1,3-oxazolidin-4-yl](pyridin-2-yl) methyl Acetate (Ac-12)

Following the general procedure, (4*S*)-4-benzyl-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-D**; 200 mg, 0.556 mmol), 2-pyridinecarboxaldehyde (5 equiv., 2.78 mmol, 264 μL) and KHMDS (1.5 equiv., 0.834 mmol, 834 μL (1 M in THF)) in THF (3 mL) gave (4*R*)-4-benzyl-4-[hydroxy(pyridin-2-yl) methyl]-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**12**) after 12 min. Following the *General Procedure of Acetylation*, compound **12** (crude product – 452 mg), 4-(dimethylamino)pyridine (0.1 equiv., 0.056 mmol, 7 mg), acetic anhydride (5 equiv., 2.78 mmol, 260 μL), triethylamine (1.5 equiv., 0.834 mmol, 116 μL) in THF (5.5 mL) gave compound **Ac-12** after one night. The crude product (dr 56:44) was then purified by column chromatography over silica gel (PE/ethyl acetate 80:20 to 70:30) then (CH_2Cl_2/ethyl acetate 95:5 at 90:10) to give two diastereomers **Ac-12** (125 mg : first diastereomer **Ac-12a** 54 mg, ee = 29%, mixture 15 mg, second diastereomer **Ac-12b** 56 mg, ee = 29%, 44% in two steps). HPLC Analysis: *Chiralpak IC*, hexane/ethanol 90:10, 1 mL/min, $T=25\,^{\circ}C$, $\lambda=222$ nm; retention times of racemic mixture: 26.5 min (minor) and 28.2 min (major) *ee* = 29% (minor diastereomer 35.0 min (minor) and 55.6 min (major), ee = 29%). *First Diastereomer* **Ac-12a**. ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.7:0.3: 0.19 (*s*, 3H*M*); 0.29 (*s*, 3H*m*); 0.33 (*s*, 3H*M*); 0.76 (*s*, 3H*m*); 2.28 (*s*, 3H*m*); 2.29 (*s*, 3H*M*); 3.85 (*d*, *J* = 13.2, 1H*M*); 3.89 (*d*, *J* = 13.1, 1H*m*); 4.21 (*d*, *J* = 13.3, 1H*M*); 4.39 (*d*, *J* = 13.4, 1H*m*); 6.81 (*s*, 1H*m*); 7.20 (*d*, *J* = 7.1, 1H*M*); 7.30–7. 65 (*m*, 10H*M* + 12H*m*); 7.69 (*d*, *J* = 7.8, 1H*M*); 7.77–7.86 (*m*, 3H*M* + 3H*m*); 8.41 (*d*, *J* = 8.2, 1H*M*); 8.76 (*d*, *J* = 3.9, 1H*M* + 1H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 21.1*m*; 21.2*M*; 27.5*M*; 28.5*m*; 29.0*M* + *m*; 37.4*M*; 39.3*m*; 73.1*M*; 73.4*m*; 76.0*M*; 76.2*m*; 96.4*M*; 96.8*m*; 123.4*m*; 123.7*M*; 123.8*M*; 123.9*m*; 124.3*M*; 125.1*M*; 125.9*m*; 126.2*m*; 126.3*m*; 126.5*M* + *m*; 126.8*M*; 127.9*m*; 128.0*M*; 128.1*M*; 128.3*m*; 128.6*M*; 129.0*M**2 + *m**2; 129.7*m*; 129.8*M* + *m*; 130.4*m*; 131.2*M**2 + *m**2; 131.4*M*; 133.1*M*; 133.2*m*; 134.0*M*; 134.1*m*; 135.4*m*; 135.7*M*; 136.9*m*; 137.0*M*; 149.3*M*; 149.5*m*; 156.0*m*; 156.1*M*; 169.2*M*; 169.4*m*; 169.5*m*; 169.7*M*; 169.8*M*; 170.5*m*. HR-ESI-MS: 509.2060 ($C_{31}H_{29}N_2O_5^+$, $[M+H]^+$; calc. 509.2071), 531.1878 ($C_{31}H_{28}N_2NaO_5^+$, $[M+Na]^+$; calc. 531.1890). *Second Diastereomer* **Ac-12b**. ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*)/minor (*m*): 0.8:0.2: 0.38 (*s*, 3H*m*); 0.51 (*s*, 3H*M*); 1.02 (*s*, 3H*M*); 1.38 (*s*, 3H*m*); 2.27 (*s*, 3H*M*); 2.33 (*s*, 3H*m*); 2.87 (*d*, *J* = 13.4, 1H*M*); 2.97 (*d*, *J* = 13.5, 1H*m*); 4.40 (*d*, *J* = 13.4, 1H*M*); 4.48 (*d*, *J* = 13.8, 1H*m*); 7.23–7.93 (*m*, 16H*M* + 17H*m*); 8.73 (*d*, *J* = 4.1, 1H*M*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): only *M* described: 21.3; 28.3; 28.6; 37.7; 73.0; 75.8; 96.6; 122.7; 123.5; 124.0; 124.6; 124.7; 126.6; 127.3; 127.9; 128.5; 128.8*2; 129.9; 130.7; 131.1*2; 133.2; 133.8; 135.7; 136.2; 148.9; 155.3; 168.5; 169.1; 169.3. HR-ESI-MS: 509.2051 ($C_{31}H_{29}N_2O_5^+$, $[M+H]^+$; calc. 509.2071), 531.1872 ($C_{31}H_{28}N_2NaO_5^+$, $[M+Na]^+$; calc. 531.1890).

(4*R*)-4-Benzyl-4-[(*R*)-(2-fluorophenyl)(hydroxy) methyl]-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (13a)

Following the *General Procedure*, (4*S*)-4-benzyl-2,2-dimethyl-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**1-D**; 100 mg, 0.278 mmol), 2-fluorobenzaldehyde (5 equiv., 1.39 mmol, 146 μL) and KHMDS (1.5 equiv., 0.417 mmol, 417 μL (1 M in THF)) in THF gave compound **13a** after 15 min. The crude product (dr = 98:2) was then purified by column chromatography over silica gel (PE/ethyl acetate 100:0 to 80:20) to give diastereomer **13a** (70 mg, 52%, ee = 34%). HPLC Analysis: *Chiralpak IC*, hexane/ethanol 90:10, 1 mL/min, $T=25\,^{\circ}C$, $\lambda=222$ nm; retention times of racemic mixture: 6.5 min (major) and 7.4 min (minor) *ee* = 34% (minor diastereomer 13.0 min and 15.3 min from racemic). ^{1}H-NMR (400 MHz, 300 K, $CDCl_3$): Conformer

ratio major (*M*)/minor (*m*): 1:0.3: 0.29 (*s*, 3H*m*); 0.44 (*s*, 3H*M*); 0.78 (*s*, 3H*M*); 0.84 (*s*, 3H*m*); 3.26 (*d*, *J* = 13.7, 1H*M*); 3.57 (*d*, *J* = 14.0, 1H*m*); 4.29 (*d*, *J* = 13.7, 1H*M*); 4.48 (*d*, *J* = 7.3, 1H*M*); 4.53 (*d*, *J* = 14.2, 1H*m*); 5.18 (*d*, *J* = 8.7, 1H*m*); 5.92 (*d*, *J* = 8.8, 1H*m*); 6.34 (*d*, *J* = 7.2, 1H*M*); 7.11–7.20 (*m*, 1H*M* + 1H*m*); 7.24–7.60 (*m*, 11H*M* + 11H*m*); 7.69–7.92 (*m*, 4H*M* + 4H*m*). ^{13}C-NMR (100.0 MHz, 300 K, $CDCl_3$): 28.1*M*; 28.3*m*; 28.6*M*; 28.7*m*; 36.9*M*; 38.5*m*; 70.2*M*; 72.9*m*; 96.6*M* + *m*; 115.6*M* (*d*, *J* = 22); 115.9*m* (*d*, *J* = 22); 123.9*M* + *m*; 124.0*M*; 124.3*m*; 125.3*M*; 125.6*M*; 125.8*m*; 126.1*m*; 126.5*M* + *m*; 126.7*m*; 126.8*M* (*d*, *J* = 15); 127.0*M*; 127.2*m* (*d*, *J* = 14); 128.0*M*; 128.1*m*; 128.4*M*; 128.7*m*; 128.8*M*2* + *m*2*; 129.9*m*; 130.1*M* + *m*; 130.2*M*; 130.3*M*; 130.4*m*; 131.0*M*2* + *m*2*; 131.3*M*; 133.3*m*; 133.1*m*; 133.3*M*; 133.6*M* + *m*; 135.3*m*; 135.9*M*; 160.1*M* + *m* (*d*, *J* = 248); 169.9*M*; 170.2*M*; 170.3*m*; 171.6*m* (one carbon *M* and *m* are under $CDCl_3$ signal). HR-ESI-MS: 484.1908 ($C_{30}H_{27}FNO_4^+$, $[M+H]^+$; calc. 484.1919); 506.1727 ($C_{30}H_{26}FNNaO_4^+$, $[M+Na]^+$; calc. 506.1738).

(*R*)-[(4*R*)-2,2-Dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-5-oxo-1,3-oxazolidin-4-yl](2-fluorophenyl)methyl Acetate (Ac-5a). To a stirred solution of (4*R*)-4-[(*R*)-(2-fluorophenyl)(hydroxy)methyl]-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-1,3-oxazolidin-5-one (**5a**; 120 mg, 0.222 mmol) and 4-(dimethylamino)pyridine (0.01 equiv., 0.0022 mmol, 0.27 mg) in CH_2Cl_2 (2.2 mL) at 0 °C were added acetic anhydride (1.2 equiv., 0.267 mmol, 25 μL) and triethylamine (1.2 equiv., 0.267 mmol, 37 μL). The resulting mixture was stirred for 12h at room temperature. The reaction was quenched by the addition of methanol. The mixture was washed with a 1 M HCl solution and water. The organic layer was dried over sodium sulfate, filtered, and then concentrated to give the crude product which was then purified through column chromatography over silica gel (PE/ethyl acetate 100:0 to 80:20) to give compound **Ac-5a** (75 mg, 69%). ^{1}H-NMR (250 MHz, 300 K, $CDCl_3$): Conformer ratio major (*M*): minor (m_1): minor (m_2): 0.5:0.3:0.2: −0.30 (*d*, *J* = 6.6, 3Hm_2); 0.63 (*d*, *J* = 6.4, 3Hm_2); 0.89 (*d*, *J* = 6.6, 3H*M*); 0.90 (*s*, 3Hm_1); 0.83–0.93 (*m*, 1Hm_1); 1.02 (*d*, *J* = 6.4, 3Hm_1); 1.06 (*d*, *J* = 6.7, 3H*M*); 1.15 (*d*, *J* = 6.8, 3Hm_1); 1.19 (*s*, 3H*M*); 1.22 (*s*, 3Hm_2); 1.33–1.45 (*m*, 1H*M* + 1Hm_2); 1.67 (*s*, 3Hm_2); 1.69 (*s*, 3H*M*); 1.77–1.89 (*m*, 1Hm_1 + 1Hm_2); 2.06 (*s*, 3Hm_1); 2.09–2.20 (*m*, 1H*M* + 1Hm_1); 2.16 (*s*, 3H*M*); 2.21 (*s*, 3Hm_1); 2.27 (*s*, 3Hm_2); 2.99 (br. *d*, *J* = 13.9, 1H*M*); 3.13 (br. *d*, *J* = 13.8, 1Hm_2); 5.22 (br. *s*, 1Hm_2); 6.66 (*t*, *J* = 9.4, 1Hm_2); 6.80–7.78 (*m*, 10H*M* + 10Hm_1 + 8Hm_2); 7.82–8.04 (*m*, 2H*M* + 2Hm_1 + 2Hm_2). ^{13}C-NMR (90 MHz, 300 K, $CDCl_3$): 21.5*M*; 21.8*m*; 23.0*M*; 24.0*m*; 24.6*m*; 24.8*M*; 27.0*m*; 27.1*M*; 28.9*M*; 29.6*m*; 30.1*m*; 30.7*M*; 39.2M + *m*; 71.2*M*; 72.1*m*; 96.2*M*; 98.2*m*; 115.5*M* (*d*; *J* = 22); 124.0–134.2; 168.7*m*; 168.8*M*; 169.0*M* + *m*; 170.0*m*; 170.1*M* (one carbon *M* and *m* are under $CDCl_3$ signal). HR-ESI-MS: 492.2174 ($C_{29}H_{31}FNO_5^+$, $[M+H]^+$; calc. 492.2181), 514.2003 ($C_{29}H_{30}FNNaO_4^+$, $[M+Na]^+$; calc. 514.2000).

2-Fluoro-β-hydroxy-α-(2-methylpropyl)-D-Phenylalanine–Hydrogen Chloride (14). Following the *General Procedure*, (*R*)-[(4*R*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-5-oxo-1,3-oxazolidin-4-yl](2-fluorophenyl)methyl acetate (**Ac-5a**; 30 mg, 0.061 mmol), acetic acid (0.5 mL) and 6 M HCl (1 mL) gave compound **14** after 24 h (10 mg, 56%). ^{1}H-NMR (400 MHz, 300 K, CD_3OD): 0.89 (*d*, *J* = 5.4, 3H); 0.99 (*d*, *J* = 5.4, 3H); 1.71–1.85 (*m*, 2H); 2.03 (*d*, *J* = 8.8, 1H); 5.19 (*s*, 1H); 7.09 (*t*, *J* = 9.5, 1H); 7.20 (*t*, *J* = 7.1, 1H); 7.37 (*q*, *J* = 6.9, 1H); 7.60 (*t*, *J* = 7.0, 1H). ^{13}C-NMR (100 MHz, 300 K, CD_3OD): 22.7; 24.9; 25.2; 42.2; 68.8; 71.0; 116.0 (*d*, *J* = 23); 125.1; 127.0 (*d*, *J* = 14); 131.3; 131.5; 161.5 (*d*, *J* = 244); 171.2. HR-ESI-MS: 256.1339 ($C_{13}H_{19}FNO_3^+$, $[M+H]^+$; calc. 256.1343); 278.1157 ($C_{13}H_{18}FNNaO_3^+$, $[M+Na]^+$; calc. 278.1163).

2-[(*R*)-Hydroxy(pyridin-3-yl)methyl]-L-Leucine–Hydrogen Chloride (15). Following the general procedure, (*R*)-[(4*R*)-2,2-dimethyl-4-(2-methylpropyl)-3-(naphthalene-1-carbonyl)-5-oxo-1,3-oxazolidin-4-yl](-pyridin-3-yl)methyl acetate (**Ac-4a**; 45 mg, 0.095 mmol), acetic acid (0.5 mL) and 6 M HCl (1 mL) gave compound **15** after 24 h (26 mg, quantitative yield). ^{1}H-NMR (400 MHz, 300 K, CD_3OD): 0.90 (*d*, *J* = 6.5, 3H); 1.03 (*d*, *J* = 6.6, 3H); 1.69 (*dd*, *J* = 9.4, *J* = 14.3, 1H); 1.82–1.96 (*m*, 1H); 2.21 (*dd*, *J* = 3.1, *J* = 14.3, 1H); 5.28 (*s*, 1H); 8.14 (*dd*, *J* = 5.1, *J* = 7.9, 1H); 8.71 (*d*, *J* = 7.9, 1H); 8.90 (*d*, *J* = 5.1, 1H); 8.96 (*s*, 1H). ^{13}C-NMR (100 MHz, 300 K, CD_3OD): 22.3; 24.8; 25.1; 43.2; 68.1; 73.8; 127.9; 140.9; 142.7*2; 147.2; 171.0.

Supplementary Material

CCDC 2093028–2093030 and 2094493 contain the supplementary crystallographic data for compounds **3b**, **Ac-5a**, **8b** and **Ac-12a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre through https://www.ccdc.cam.ac.uk/structures/.

Acknowledgements

We thank the Marie Curie program for an IIF fellowship (post-doctoral fellowship to *B. V.*, grant PIIF-GA-2011-300491). We also thank the synthesis support facility (Pôle Synthèse) at ICMMO for their help.

Author Contribution Statement

L. R. and *B. V.* performed the experiments and analyzed the data; *R. G.* was in charge of all the crystal analyses and *D. G.* of HPLC analyses. *C. K.* helped to write the paper. *V. A.* conceived and designed the experiments, analyzed the data and wrote the paper.

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Received July 13, 2021
Accepted August 31, 2021

