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Stereoselective alkylation–reduction of β-keto nitriles by the fungus *Curvularia lunata*

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Abstract—The alkylation–reduction (AR) reaction of β-keto nitriles by growing cells of *Curvularia lunata* CECT 2130 has been explored. The reaction conditions for the ethylation of benzoylacetonitrile have been optimized in terms of both yield and stereoselectivity and the mechanism of this biotransformation was studied. The scope of this reaction has been extended to other alkylations (R = Et, Pr, Bu, *iso*-Bu) and to a series of aromatic and heteroaromatic substrates, yielding the corresponding optically active α-alkyl β-hydroxy nitriles. The yield (directly related to competing carbonyl reduction reaction) depends on the substrate bulk, whereas the enantiomeric and diastereomeric excesses (both up to 98%) seem to be dependent on several factors.

1. Introduction

Optically active α-alkyl β-hydroxy acid derivatives are nowadays recognized as highly valuable chiral synthons. Traditionally, most popular chemical[1] and enzymatic[2,3] methods to obtain them consisted of the stereoselective reduction of the corresponding α-alkyl β-keto acid derivatives. In particular, a couple of examples concerning the bioreduction of acyclic[4] and cyclic[5] α-substituted β-keto nitriles have been reported.

Several years ago, Itoh et al. described that during the incubation of 3-oxobutyronitrile with baker's yeast, an ethyl group was incorporated at the α-position, together with the carbonyl reduction.[6] Unfortunately, the process showed only very low diastereoselection, although both epimers were virtually enantiopure.

Despite this elegant (and somewhat curious) means of stereoselective C–C bond formation, no further examples of stereoselective alkylation–reduction (AR) reactions with baker's yeast have appeared in the literature. Fuganti et al. proposed a mechanism for this reaction, but they could not extend it to the structurally related β-keto esters.[7] Smallridge et al. showed that in the presence of an excess of acetaldehyde, baker's yeast was able to mediate the non-stereoselective introduction of an ethyl group in some aromatic β-keto nitriles (without reduction of the ketone), due to the racemization of the product in the reaction medium.[8]

In a preliminary communication, we have described that the fungus *Curvularia lunata* CECT 2130 is able to introduce short alkyl chains and reduce the carbonyl group of benzoylacetonitrile, **1**.[9] Herein, continuing our studies on the preparation of optically active amino alcohols through chemoenzymatic transformations, using isolated enzymes[10,11] or microorganisms[12] as biocatalysts, we provide full details of the AR process and a study of its scope and limitations, by subjecting a series of aliphatic, aromatic and heteroaromatic substrates to the action of this fungal strain. The corresponding α-alkyl β-hydroxy nitriles obtained are useful precursors of new amino alcohols with potential applications in asymmetric synthesis[13] and medicinal chemistry.[14]

2. Results and discussion

2.1. Optimization of the AR of benzoylacetonitrile

During our screening for a suitable strain to enantioselectively reduce benzoylacetonitrile, **1**, we observed that the fungus *C. lunata* produced an almost equimolar mixture of the expected 3-hydroxy-3-phenylpropanenitrile, **2**, and 2-(1-hydroxy-1-phenylmethyl)butanenitrile, **3a**, in 22% yield, whose chiral chromatographic analysis gave the promising values of 78% e.e. and 97% d.e. (see Scheme 1).

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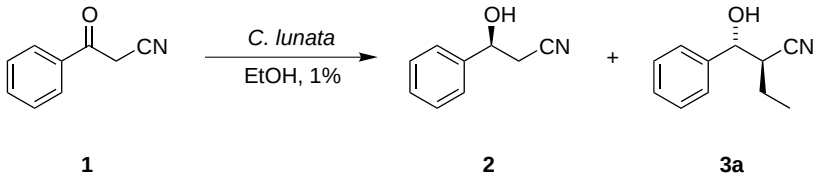


1 2 3a

Scheme 1.

The mechanism for this quite unusual biotransformation was confirmed to be that proposed by Fuganti et al.,[7] and several clues for this have been already presented (biotransformation of a supposed intermediate, modified pH conditions and isotopic labeling of the co-solvent).[9] The fact that AR does not occur with similar β-keto esters (although extensively studied) seems to be a consequence of their lower acidity,[15] which might prevent the non-enzymatic condensation with the acetaldehyde generated in the medium.

Our first interest was to minimize the competing simple reduction, in order to obtain **3a** in a synthetically useful yield. The use of resting cells instead of growing cells did not lead to considerable modifications in the proportion of the two products. However, the use of growing cells of different ages did produce a significant change (see Fig. 1).

A plausible hypothesis for this behavior could be that 'young' cells use glucose (together with the ethanol added as co-solvent) as the energy source. After 3 days, we observed that no more glucose was left in the culture medium and, therefore, the co-factor regenerating system oxidizes ethanol to acetaldehyde faster. Afterwards, the enoate–reductase activity (responsible of the irreversibility of the AR process) might decrease faster than the alcohol deshydrogenase which yields **2**. Furthermore, the stereoselectivity of the process using 4-day-old growing cells increased to 96% d.e. and 98% e.e. Therefore, these optimized conditions were adopted as standard for the remaining experiments.

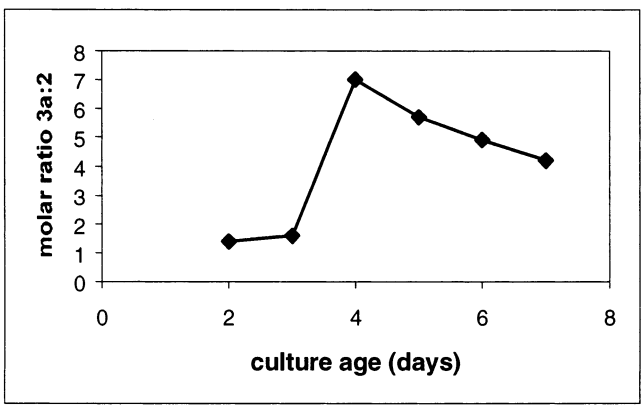
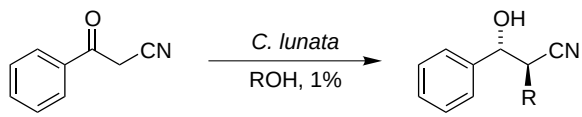


Figure 1. Molar ratio between products **3a** and **2** obtained in the biotransformation of **1** with growing cells of *C. lunata* of different ages.

2.2. Introduction of different alkyl groups

An obvious challenge that would give this AR reaction a higher value was to extend it to other alkyl groups other than ethyl. Bearing this in mind, we carried out the biotransformation of **1** using other primary aliphatic alcohols (linear or not) as co-solvents. Although MeOH clearly inhibited the AR,[16] other short chain alcohols behaved as ethanol and the corresponding alkyl groups were incorporated at the α position (see Scheme 2).



1 3a-3d

Scheme 2.

As shown in Table 1, the longer the alkyl chain, the lower the yield of the corresponding α-alkyl β-hydroxy nitrile **3**. The diastereomeric ratio (d.r.), as well as the e.e. of the products were high to excellent, which makes this AR reaction very attractive for the synthesis of optically active compounds with two contiguous stereogenic centers.

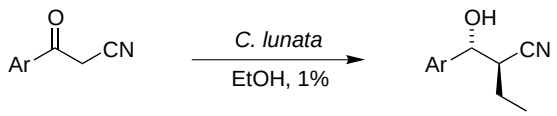
Table 1. Biotransformations of benzoylacetonitrile with *C. lunata* in the presence of different alcohols

Alcohol	Product	R	Yield (%)[a]	D.r.[b]	E.e. (%)[b,c]
EtOH	**3a**	Et	69	98:2	98
PrOH	**3b**	Pr	38	99:1	98
BuOH	**3c**	Bu	13	93:7	86
^{i}BuOH	**3d**	^{i}Bu	14	97:3	97

[a] Isolated yield, after flash chromatography.
[b] Determined by GC analysis of their MTPA derivatives.
[c] E.e. of the major diastereomer.

2.3. AR reactions of other aromatic β-keto nitriles

As shown above, BY was only able to perform the AR with one substrate.[6] When bulkier substrates, such as **1**, were used, only alkylation, without reduction and the introduction of chirality, occurred.[8] In order to study the scope and limitations of our AR reaction, and taking into account this high substrate specificity shown by BY, we subjected a series of benzoylacetonitrile derivatives to the action of *C. lunata*, using EtOH as co-solvent, due to the higher yield (as well as the very satisfactory stereochemical outcome) obtained in the case of product **3a** (see Scheme 3).



1 **3a-8a**

Scheme 3.

As shown in Table 2, the AR reactions took place with high chemoselectivities except in the case of *m*-methylbenzoylacetonitrile, where the competing reduction decreased the chemical yield slightly down to 42%, probably due to steric hindrance. In the case of *para* substituted compounds, the yields were similar to that obtained with **3a**, but both diastereo- and enantiodiscrimination were lower.

Table 2. Biotransformations of aromatic β-keto nitriles with *C. lunata* in the presence of EtOH

Ar	Product	Yield (%)[a]	D.r.	E.e. (%)[b]
C_6H_5	**3a**	69	98:2[c]	98[c]
m-CH_3-C_6H_4	**4a**	42	89:11[d]	70[d]
p-CH_3-C_6H_4	**5a**	64	96:4[d]	83[d]
p-CH_3O-C_6H_4	**6a**	58	94:6[d]	75[d]

[a] Isolated yield, after flash chromatography.
[b] E.e. of the major diastereomer.
[c] Determined by GC analysis of its MTPA derivatives.
[d] Determined by chiral GC.

2.4. AR of heteroaromatic β-keto nitriles

We also wanted to study the effect of having an heteroatom in the aromatic ring in the AR reaction. As substrates, we chose 2-thenoylacetonitrile, due to the well-known similarity between thienyl and phenyl derivatives,[17] and its oxygenated analogue, 2-furoylacetonitrile.

Interestingly enough, the sulfurated α-ethyl β-hydroxy nitrile **7a** obtained had very high e.e. and d.e. However, the furyl derivative **8a** showed modest diastereodiscrimination, although the e.e. of the major diastereomer was quite high (see Table 3).

Table 3. Biotransformations of heteroaromatic β-keto nitriles with *C. lunata* in the presence of EtOH

Ar	Product	Yield (%)[a]	D.r.[b]	E.e. (%)[b,c]
2-Thienyl	**7a**	63	97:3	93
2-Furyl	**8a**	59	86:14	87

[a] Isolated yield, after flash chromatography.
[b] Determined by chiral GC.
[c] E.e. of the major diastereomer.

2.5. Biotransformations of aliphatic β-keto nitriles under AR conditions

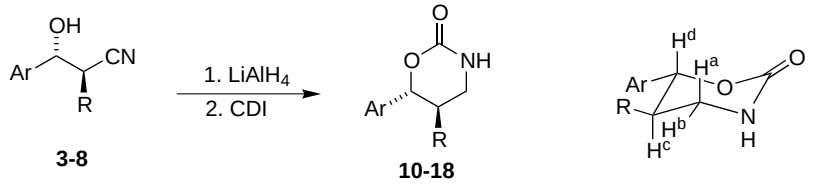
To complete our study, we also analyzed the 'behavior' of *C. lunata* towards aliphatic substrates. The results obtained were, however, quite disappointing. The first substrate tested, 3-oxobutyronitrile, had already been subjected to AR with baker's yeast.[6] With *C. lunata*, also a diastereomeric mixture (ca. 1:1) of *syn* and *anti* 2-ethyl-3-hydroxybutyronitrile, was obtained. But contrary to that example, low e.e. values were obtained (ca. 75% for the *syn* and 25% for the *anti*). In the reactions of 4,4-dimethyl-3-oxopentanenitrile and 3-cyclohexyl-3-oxopropanenitrile no appreciable amounts of the corresponding α-ethyl β-hydroxy nitriles were observed. In the first case, steric hindrance may be invoked, but the cause for the failed reaction in the latter case is not clear. At this time, we do not have a conclusive explanation for this. In both cases, only carbonyl reduction took place, but the e.e. values of the products were lower than those previously reported using methanol as co-solvent.[16]

2.6. Assignment of the absolute configuration. Synthesis of γ-amino alcohols

The absolute configuration of the carbinol atom in the products **3a–d** and **4a–8a** was assigned by a comparative study of the ^{1}H NMR of their MTPA esters.[18] In all cases, the $\Delta\delta$ values ($\delta_{S\text{-ester}}-\delta_{R\text{-ester}}$) were positive for the aliphatic protons (both in the alcohol[19] and in the MTPA moiety[20]), and negative for the aromatic ones (see Section 4), thus allowing us to tentatively assign the absolute configuration for the C(1′) as (*R*).

In order to establish the absolute configuration of the C(2) stereogenic center, it was necessary to perform the transformation outlined in Scheme 4: nitrile reduction[21] with $LiAlH_4$ of compounds **3–8**, yielded the corresponding γ-amino alcohols which were directly[†] cyclized using *N*,*N*′-carbonyldiimidazole (CDI) to obtain the oxazinan-2-ones **10–18**, six-membered rings which allowed us to determine the relative configuration of C(2) and C(1′) atoms by means of the coupling constants (*J*) between the different protons (see Section 4).

[†] The aminoalcohols **9a–c** were purified and fully characterized (see Section 4). The others were used for the in situ preparation of the corresponding oxazinan-2-ones.



3-8 10-18

Scheme 4.

In all cases (and after irradiation of the NH signal, in order to simplify the spin system), we obtained a small coupling constant (J) value between H^c and H^b (ca. 5 Hz) which corresponds to axial–equatorial coupling and two large J values for the H^a–H^c (ca. 10 Hz) and H^c–H^d (ca. 9 Hz) couplings, in accordance with axial–axial arrangement, therefore leaving the Ar and the R groups in the equatorial positions. This, in conjunction with the Mosher analysis described above, corresponds to (*R*,*R*) absolute configuration for the β-hydroxy nitriles **3**–**8**.

3. Conclusions

C. lunata has shown its ability to α-alkylate and concomitantly reduce aromatic and heteroaromatic β-keto nitriles. After optimization of the conditions, in order to minimize the competing simple reduction process, this AR has allowed the creation of a C–C bond and two stereogenic centers in moderate yields of up to 69% and high stereoselectivities of up to 98% e.e. and d.e. in most cases. Further work making use of these interesting building blocks, as well as an extension of this methodology to other substrates is currently in progress in our laboratory.

4. Experimental

4.1. General

Reagents were obtained from Aldrich Chemie or Avocado. Solvents were distilled over an appropriate desiccant and stored under nitrogen. Precoated TLC plates of silica gel 60 F254 from Merck were used, while for column chromatography, Merck silica gel 60/230–400 mesh was applied. Melting points were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer 343 polarimeter. IR spectra were recorded on a Mattson Genesis FT Infrared spectrometer. ^{1}H and ^{13}C NMR spectra were carried out in $CDCl_3$ using a Bruker AC-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) spectrometer or AC-200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) using TMS as internal standard. Mass spectra were recorded on a Hewlett–Packard 5987 A spectrometer using electronic impact procedures (75 eV) or on a ESI-MSD (40 V). E.e. and d.r. values were determined by GC analysis on a Hewlett–Packard 6890 Series II chromatograph or by HPLC on a Shimadzu liquid chromatograph.

4.2. General procedures for cultures and biotransformations

The fungus *C. lunata* was obtained from CECT (Colección Española de Cultivos Tipo). It was precultured and cultured as previously described.[9] Afterwards, the substrate (1 g L^{-1}) and the alcohol used as co-solvent (1% v/v) were added and the biotransformation continued until disappearance of the substrate (6–12 h, TLC monitoring). The mycelium was then filtered off and the fungal cake washed several times with aqueous NaCl 0.8% until no further product was recovered. The filtrate was continuously extracted with AcOEt for 12 h. After drying with Na_2SO_4, the solvent was evaporated and the product purified by flash chromatography (eluent: hexane–AcOEt, 5:1) as a mixture of diastereomers. The spectroscopic data given below correspond to the major diastereomer.

4.2.1. (2*R*,1′*R*)-2-(1-Hydroxy-1-phenylmethyl)butanenitrile 3a. White solid; yield 69%; mp 68–69°C; $[\alpha]_D^{20}=+16.8$ (*c* 1.1, EtOH; e.e. 98%, d.r. 98:2); ^{1}H NMR: δ (ppm) 1.05 (t, $J=7.4$, 3H, CH_3), 1.4–1.7 (m, 2H, CH_2), 2.65–2.75 (m, 1H, C*H*-Et), 3.34 (br s, 1H, OH), 4.73 (d, $J=6.4$, 1H, CH-O), 7.36 (br s, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.3 (CH_3), 22.0 (CH_2), 42.3 (*C*H-Et), 73.0 (CH-O), 120.0 (CN), 125.9, 128.1, 128.3 ($CH_{arom.}$), 140.3 ($C_{arom.}$); IR (Nujol, cm^{-1}): 2242, 3458; EI-MS: m/z (relative intensity) 175 (M^+, <1%), 107 (100%); HRMS calcd for $C_{11}H_{13}NO$ 175.0997, found 175.0999. Anal. calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.26; H, 7.54; N, 7.92%. GC conditions for the (*R*)-MTPA ester: column hp 19091s-436, 1 mL min^{-1} He, 125°C, 0.1 min; 6.0°C min^{-1} until 280°C, t_R (min): 23.49 (two peaks), 23.72, 23.92 (major). Representative $\Delta\delta$ (Hz) of its MTPA esters: +8 (Me), +5 (CH-CN), −45 (arom.), +49 (MeO).

4.2.2. (2*R*,1′*R*)-2-(1-Hydroxy-1-phenylmethyl)pentanenitrile 3b. Oil; yield 38%; $[\alpha]_D^{20}=+12.8$ (*c* 1.7, EtOH; e.e. 98%, d.r. 99:1); ^{1}H NMR: δ (ppm) 0.92 (t, $J=6.8$, 3H, CH_3), 1.35–1.7 (m, 4H, CH_2CH_2), 2.58 (br s, 1H, OH), 2.8–2.9 (m, 1H, C*H*-Pr), 4.78 (d, $J=6.1$, 1H, CH-O), 7.3–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 13.4 (CH_3), 20.3 (CH_2-Me), 30.9 (CH_2-Et), 40.8 (*C*H-Pr), 74.0 (CH-O), 120.1 (CN), 126.1, 128.6, 128.7 ($CH_{arom.}$), 140.3 ($C_{arom.}$); IR (neat, cm^{-1}): 2247, 3421; EI-MS: m/z (relative intensity) 189 (M^+, 1%), 107 (100%); HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1161. Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.11; H, 8.02; N, 7.37%. GC conditions for the (*R*)-MTPA ester: column hp 19091s-436, 1 mL min^{-1} He, 125°C, 0.1 min; 6.0°C min^{-1} until

280°C, t_R (min): 23.73, 23.92, 24.71, 24.89 (major). Representative $\Delta\delta$ (Hz) of its MTPA esters: +3 (Me), +5 (CH-CN), −50 (arom.), +52 (MeO).

4.2.3. (2*R*,1′*R*)-2-(1-Hydroxy-1-phenylmethyl)hexanenitrile 3c. Oil; yield 13%; $[\alpha]_D^{20}$ +7.3 (*c* 2.8, EtOH; e.e. 86%, d.r. 93:7); ^{1}H NMR: δ (ppm) 0.90 (t, J=7.2, 3H, CH_3), 1.25–1.7 (m, 6H, $CH_2CH_2CH_2$), 2.50 (br s, 1H, OH), 2.75–2.9 (m, 1H, C*H*-Bu), 4.79 (d, J=6.1, 1H, CH-O), 7.35–7.45 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 13.6 (CH_3), 22.0 (CH_2-Me), 28.6 (CH_2-Et), 29.1 (CH_2-Pr), 41.0 (*C*H-Bu), 74.0 (CH-O), 120.2 (CN), 126.1, 128.6, 128.7 ($CH_{arom.}$), 140.3 ($C_{arom.}$); IR (neat, cm^{-1}): 2241, 3446; EI-MS: m/z (relative intensity) 203 (M^+, <1%), 107 (100%), 79 (80%); HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1296. Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.48; N, 6.71%. GC conditions for the (*R*)-MTPA ester: column hp 19091s-436, 1 mL min^{-1} He, 125°C, 0.1 min; 6.0°C min^{-1} until 280°C, t_R (min): 25.64, 25.67, 25.89, 26.07 (major). Representative $\Delta\delta$ (Hz) of its MTPA esters: +3 (Me), +5 (CH-CN), −50 (arom.), +52 (MeO).

4.2.4. (2*R*,1′*R*)-2-(1-Hydroxy-1-phenylmethyl)-4-methylpentanenitrile 3d. Oil; yield 14%; $[\alpha]_D^{20}$=+6.3 (*c* 1.4, EtOH; e.e. 97%, d.r. 97:3); ^{1}H NMR: δ (ppm) 0.89 (d, J=6.4, 3H, CH_3), 0.95 (d, J=6.4, 3H, CH_3), 1.2–1.4 (m, 1H, C*H*Me$_2$), 1.6–1.9 (m, 2H, CH_2), 2.52 (br s, 1H, OH), 2.85–2.95 (m, 1H, C*H*-^{i}Bu), 4.77 (d, J=5.9, 1H, CH-O), 7.35–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 21.0, 23.0 (CH_3), 26.0 (*C*HMe$_2$), 37.7 (CH_2), 39.1 (*C*H-^{i}Bu), 74.2 (CH-O), 120.1 (CN), 126.1, 128.6, 128.7 ($CH_{arom.}$), 140.3 ($C_{arom.}$); IR (neat, cm^{-1}): 2244, 3451; ESI-MS: m/z 226 (M+Na)$^+$. Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.79; H, 8.51; N, 6.71%; GC conditions for the (*R*)-MTPA ester: column hp 19091s-436, 1 mL min^{-1} He, 125°C, 0.1 min; 6.0°C min^{-1} until 280°C, t_R (min): 24.80, 24.88, 25.08, 25.28 (major). Representative $\Delta\delta$ (Hz) of its MTPA esters: +5 (CH-CN), −20 (arom.), +48 (MeO).

4.2.5. (2*R*,1′*R*)-2-[1-Hydroxy-1-(3-methylphenyl)methyl]-butanenitrile 4a. Oil; yield 42%; $[\alpha]_D^{20}$=+31.7 (*c* 0.7, $CHCl_3$; e.e. 70%, d.r. 89:11); ^{1}H NMR: δ (ppm) 1.09 (t, J=7.5, 3H, CH_3-CH$_2$), 1.35–1.7 (m, 2H, CH_2), 2.37 (s, 3H, CH_3-Ar), 2.47 (br s, 1H, OH), 2.7–2.8 (m, 1H, C*H*-Et), 4.74 (d, J=6.5, 1H, CH-O), 7.15–7.3 (m, 4H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.6 (*C*H$_3$-CH$_2$), 21.4 (CH_3-Ar), 22.5 (CH_2), 42.6 (*C*H-Et), 73.9 (CH-O), 120.1 (CN), 123.2, 126.7, 128.6, 129.5 ($CH_{arom.}$), 138.5, 140.2 ($C_{arom.}$); IR (neat): 2241, 3446 cm^{-1}; ESI-MS: m/z 212 (M+Na)$^+$. Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.27; H, 7.83; N, 7.28; GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 140°C, 5 min; 1.0°C min^{-1} until 200°C, t_R (min): 43.1, 43.3, 44.3 (major), 44.8. Representative $\Delta\delta$ (Hz) of its MTPA esters: +6 (CH_3-CH$_2$), −24 (CH_3-Ar), +61 (MeO).

4.2.6. (2*R*,1′*R*)-2-[1-Hydroxy-1-(4-methylphenyl)methyl]-butanenitrile 5a. Oil; yield 64%; $[\alpha]_D^{20}$=+43.1 (*c* 1.3, $CHCl_3$; e.e. 83%, d.r. 96:4); ^{1}H NMR: δ (ppm) 1.07 (t, J=7.4, 3H, CH_3-CH$_2$), 1.45–1.65 (m, 2H, CH_2), 2.35 (s, 3H, CH_3-Ar), 2.58 (br s, 1H, OH), 2.7–2.8 (m, 1H, C*H*-Et), 4.73 (d, J=6.5, 1H, CH-O), 7.15–7.3 (m, 4H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.6 (*C*H$_3$-CH$_2$), 21.1 (*C*H$_3$-Ar), 22.4 (CH_2), 42.6 (*C*H-Et), 73.7 (CH-O), 120.1 (CN), 126.0, 129.4 ($CH_{arom.}$), 137.3, 138.5 ($C_{arom.}$); IR (neat): 2242, 3452 cm^{-1}; EI-MS: m/z (relative intensity) 189 (M^+, 23%), 121 (100%); HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1150. Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.12; H, 8.10; N, 7.29%; GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 130°C, 5 min; 1.0°C min^{-1} until 200°C, t_R (min): 51.5, 52.4, 52.9 (major), 53.8. Representative $\Delta\delta$ (Hz) of its MTPA esters: +7 (CH_3-CH$_2$), +5 (C*H*-Et), −6 (CH_3-Ar), −38 (arom.), +50 (MeO).

4.2.7. (2*R*,1′*R*)-2-[1-Hydroxy-1-(4-methoxyphenyl)-methyl]butanenitrile 6a. Oil; yield 58%; $[\alpha]_D^{20}$=+41.0 (*c* 1.0, $CHCl_3$; e.e. 75%, d.r. 94:6); ^{1}H NMR: δ (ppm) 1.06 (t, J=7.4, 3H, CH_3-CH$_2$), 1.4–1.65 (m, 2H, CH_2), 2.57 (br s, 1H, OH), 2.65–2.75 (m, 1H, C*H*-Et), 3.80 (s, 3H, CH_3O), 4.72 (d, J=6.8, 1H, CH-O), 6.90 (d, J=8.7, 2H, $H_{arom.}$), 7.29 (d, J=8.7, 2H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.6 (*C*H$_3$-CH$_2$), 22.4 (CH_2), 42.7 (*C*H-Et), 55.2 (CH_3-O), 73.5 (CH-O), 114.0 ($CH_{arom.}$), 120.2 (CN), 127.4, ($CH_{arom.}$), 132.4, 159.7 ($C_{arom.}$); IR (neat, cm^{-1}): 2246, 3441; EI-MS: m/z (relative intensity) 205 (M^+, 2%), 187 (3%), 137 (100%); HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1101. Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.01; H, 7.41; N, 6.69; GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 140°C, 5 min; 1.0°C min^{-1} until 200°C, t_R (min): 52.0, 52.6, 53.6 (major), 54.1. Representative $\Delta\delta$ (Hz) of its MTPA esters: +8 (CH_3-CH$_2$), +4 (C*H*-Et), −38, −22 (arom.), +54 (MeO).

4.2.8. (2*R*,1′*R*)-2-[1-Hydroxy-1-(2-thienyl)methyl]butanenitrile 7a. Oil; yield 63%; $[\alpha]_D^{20}$=+27.0 (*c* 2.0, $CHCl_3$; e.e. 93%, d.r. 97:3); ^{1}H NMR: δ (ppm) 1.09 (t, J=7.5, 3H, CH_3), 1.5–1.7 (m, 2H, CH_2), 2.75–2.9 (m, 1H, C*H*-Et), 3.07 (br s, 1H, OH), 5.03 (d, J=6.3, 1H, CH-O), 6.95–7.0 (m, 1H, $H_{arom.}$), 7.05–7.10 (m, 1H, $H_{arom.}$), 7.3–7.35 (m, 1H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.5 (CH_3), 22.3 (CH_2), 42.9 (*C*H-Et), 69.8 (CH-O), 119.8 (CN), 125.2, 125.7, 126.8 ($CH_{arom.}$), 143.6 ($C_{arom.}$); IR (neat, cm^{-1}): 2240, 3448; ESI-MS: m/z 204 (M+Na)$^+$. Anal. calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.48; H, 6.21; N, 6.55%; HPLC conditions: column Chiralcel OD, eluent hexane: propan-2-ol (95:5), 0.8 mL min^{-1}; t_R (min): 27.1, 28.9, 32.1, 33.9 (major). Representative $\Delta\delta$ (Hz) of its MTPA esters: +10 (CH_3-CH$_2$), +7 (C*H*-Et), +48 (MeO).

4.2.9. (2*R*,1′*R*)-2-[1-(2-Furyl)-1-hydroxymethyl]butanenitrile 8a. Oil; yield 59%; $[\alpha]_D^{20}$=+45.3 (*c* 1.0, $CHCl_3$; e.e. 87%, d.r. 86:14); ^{1}H NMR: δ (ppm) 1.09 (t, J=7.4, 3H, CH_3), 1.45–1.75 (m, 2H, CH_2), 2.86 (d, J=5.4, 1H, OH), 2.95–3.1 (m, 1H, CH-Et), 4.79 (dd, J=5.4, 6.6, 1H, CH-O), 6.3–6.5 (m, 1H, $H_{arom.}$), 7.35–7.45 (m, 2H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.5 (CH_3), 22.3 (CH_2), 40.1 (*C*H-Et), 67.5 (CH-O), 108.0, 110.4 ($CH_{arom.}$), 119.8 (CN), 142.7 ($CH_{arom.}$), 152.4 ($C_{arom.}$); IR (neat,

cm^{-1}): 2243, 3455; EI-MS: m/z (relative intensity) 165 (M^+, 3%), 147 (1%), 97 (100%); HRMS calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0788. Anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.59; H, 6.68; N, 8.58%; GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 125°C, 5 min, 1°C min^{-1} until 200°C, t_R (min): 28.6 (two peaks), 29.1 (major), 29.8. Representative $\Delta\delta$ (Hz) of its MTPA esters: +7 (CH_3-CH_2), +13 (CH-Et), −9, −16 (Fur), −20 (Ph), +52 (MeO).

4.3. General procedure for the reduction of β-hydroxy nitriles with lithium aluminium hydride

To a solution of the corresponding α-alkyl β-hydroxy nitrile **3**–**8** (0.3 mmol) in anhydrous THF (2 mL) at 0°C, an excess of $LiAlH_4$ (3 mmol) was added and the suspension was allowed to reach rt with stirring. After 3 h, the reaction was quenched with water (2 mL) and extracted several times with Et_2O. The combined organic phases were dried and the solvent evaporated. Compounds **9a**–**c** were further purified by flash chromatography (eluent propan-2-ol:CH_2Cl_2:30% aq NH_3, 2:2:0.1). In the other cases, the product was neither isolated nor characterized, and the crude was directly used for the next step (see below).

4.3.1. (1*R*,2*R*)-2-(Aminomethyl)-1-phenylbutan-1-ol 9a. Oil; yield 90%; $[\alpha]_D^{20}$ = +17.9 (*c* 0.8, EtOH; e.e. 98%, d.r. 98:2); ^{1}H NMR: δ (ppm) 0.86 (t, J = 7.4, 3H, CH_3), 1.15–1.55 (m, 3H, $CHCH_2$), 2.77 (dd, J = 12.3, 7.0, 1H, C*H*HN), 3.00 (dd, J = 12.3, 2.8, 1H, CH*H*N), 3.28 (br s, 3H, OH, NH_2), 4.69 (d, J = 6.5, 1H, CH-O), 7.2–7.45 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 11.4 (CH_3), 21.9 (CH_2-Me), 43.0 (CH_2-N), 46.6 (CH-Et), 79.0 (CH-O), 126.3, 126.7, 127.9 ($CH_{arom.}$), 144.7 ($C_{arom.}$); IR (neat, cm^{-1}): 3300; EI-MS: m/z (relative intensity) 179 (M^+, 4%), 132 (80%), 117 (100%); HRMS calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1307. Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.48; H, 9.72; N, 7.63.

4.3.2. (1*R*,2*R*)-2-(Aminomethyl)-1-phenylpentan-1-ol 9b. Oil; yield 86%; $[\alpha]_D^{20}$ +10.6 (*c* 2.0, EtOH; e.e. 98%, d.r. 99:1); ^{1}H NMR: δ (ppm) 0.83 (t, J = 6.1, 3H, CH_3), 1.1–1.45 (m, 4H, CH_2CH_2), 1.6–1.7 (m, 1H, CH-Pr), 2.77 (dd, J = 12.2, 6.5, 1H, C*H*HN), 2.99 (m, 1H, CH*H*N), 3.47 (br s, 3H, OH, NH_2), 4.68 (d, J = 6.1, 1H, CH-O), 7.2–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 14.1 (CH_3), 20.0 (CH_2-Me), 31.3 (CH_2-Et), 43.3 (CH_2-N), 44.6 (CH-Pr), 79.3 (CH-O), 126.3, 126.7, 127.9 ($CH_{arom.}$), 144.7 ($C_{arom.}$); IR (neat, cm^{-1}): 3285; EI-MS: m/z (relative intensity) 193 (M^+, <1%), 176 (2%), 146 (14%), 77 (100%); HRMS calcd for $C_{12}H_{16}O$ 176.1171, found 176.1174. Anal. calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.41; H, 10.14; N, 7.11.

4.3.3. (1*R*,2*R*)-2-(Aminomethyl)-1-phenylhexan-1-ol 9c. Oil; yield 87%; $[\alpha]_D^{20}$ +14.5 (*c* 0.6, EtOH; e.e. 86%, d.r. 93:7); ^{1}H NMR: δ (ppm) 0.86 (t, J = 5.9, 3H, CH_3), 1.1–1.5 (m, 6H, $CH_2CH_2CH_2$), 1.55–1.75 (m, 1H, C*H*-Bu), 2.82 (dd, J = 12.6, 6.7, 1H, C*H*HN), 3.04 (dd, J = 12.6, 3.1, 1H, CH*H*N), 3.22 (br s, 3H, OH, NH_2), 4.73 (d, J = 6.1, 1H, CH-O), 7.2–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 13.9 (CH_3), 22.8 (CH_2-Me), 28.9 (CH_2-Et), 29.2 (CH_2-Pr), 43.5 (CH_2-N), 44.9 (*C*H-Bu), 79.5 (CH-O), 126.4, 126.8, 128.0 ($CH_{arom.}$), 144.9 ($C_{arom.}$); IR (neat, cm^{-1}): 3290 (br b); EI-MS: m/z (relative intensity) 207 (M^+, 8%), 190 (18%), 160 (37%), 77 (100%); HRMS calcd for $C_{13}H_{19}O$ 189.1474, found 189.1475. Anal. calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.19; H, 10.38; N, 6.61.

4.4. Synthesis of the 1,3-oxazinan-2-ones 10–18

N,*N*′-Carbonyldiimidazole (0.22 mmol) was added to a solution of the corresponding aminoalcohol (0.2 mmol) in CH_2Cl_2 at rt, and the resulting mixture was stirred for 12 h. Then, the solvent was evaporated and the residue solved in AcOEt and washed with aqueous HCl (0.1 N) and water. After drying and elimination of the solvent, the product was purified by flash chromatography (eluent: hexane–AcOEt, 1:2).

4.4.1. (5*R*,6*R*)-5-Ethyl-6-phenyl-1,3-oxazinan-2-one 10. White solid; yield 75%; mp 137–138°C; $[\alpha]_D^{20}$ = −1.0 (*c* 1.0, EtOH; e.e. 98%, d.r. 98:2); ^{1}H NMR: δ (ppm) 0.84 (t, J = 7.4, 3H, CH_3), 1.0–1.45 (m, 2H, CH_2-Me), 1.9–2.1 (m, 1H, C*H*-Et), 3.11 (m, J = 9.5, 11.7, 1H, C*H*HN), 3.46 (m, J = 5.2, 11.7, 1H, CH*H*N), 4.97 (d, J = 8.7, 1H, CH-O), 6.46 (br s, 1H, NH), 7.2–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.9 (CH_3), 22.1 (CH_2), 38.6 (*C*H-Et), 43.6 (CH_2-N), 83.7 (CH-O), 126.8, 128.5, 128.6 ($CH_{arom.}$), 137.8 ($C_{arom.}$), 154.6 (CO); IR (Nujol, cm^{-1}): 1698; EI-MS: m/z (relative intensity) 205 (M^+, 5%), 107 (100%); HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1108. Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.15; H, 7.41; N, 6.71%.

4.4.2. (5*R*,6*R*)-6-Phenyl-5-propyl-1,3-oxazinan-2-one 11. White solid; yield 67%; mp 145–146°C; $[\alpha]_D^{20}$ = −17.2 (*c* 1.5, EtOH; e.e. 98%, d.r. 99:1); ^{1}H NMR: δ (ppm) 0.81 (t, J = 6.5, 3H, CH_3), 1.1–1.35 (m, 4H, CH_2CH_2), 2.05–2.2 (m, 1H, C*H*-Pr), 3.11 (m, J = 9.5, 11.5, 1H, C*H*HN), 3.45 (m, J = 5.1, 11.5, 1H, CH*H*N), 4.96 (d, J = 8.7, 1H, CH-O), 6.18 (br s, 1H, NH), 7.2–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 13.9 (CH_3), 19.6 (CH_2-Me), 31.2 (CH_2-Et), 36.9 (*C*H-Pr), 44.1 (CH_2-N), 83.8 (CH-O), 126.8, 128.5, 128.6 ($CH_{arom.}$), 137.8 ($C_{arom.}$), 154.3 (CO); IR (Nujol): 1692 cm^{-1}; EI-MS: m/z (relative intensity) 219 (M^+, 5%), 107 (100%); HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1262. Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.04; H, 7.91; N, 6.25%.

4.4.3. (5*R*,6*R*)-5-Butyl-6-phenyl-1,3-oxazinan-2-one 12. White solid; yield 63%; mp 111–112°C; $[\alpha]_D^{20}$ = −13.2 (*c* 0.5, EtOH; e.e. 86%, d.r. 93:7); ^{1}H NMR: δ (ppm) 0.81 (t, J = 6.3, 3H, CH_3), 1.1–1.35 (m, 6H, $CH_2CH_2CH_2$), 2.0–2.15 (m, 1H, C*H*-Bu), 3.10 (m, J = 9.4, 11.5, 1H, C*H*HN), 3.46 (m, J = 5.1, 11.5, 1H, CH*H*N), 4.97 (d, J = 8.7, 1H, CH-O), 6.15 (br s, 1H, NH), 7.2–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 13.7 (CH_3), 22.4 (CH_2-Me), 28.5 (CH_2-Et), 28.7 (CH_2-Pr), 37.0 (*C*H-Bu), 44.0

(CH_2-N), 83.0 (CH-O), 126.8, 128.5, 128.6 ($CH_{arom.}$), 137.8 ($C_{arom.}$), 154.4 (CO); IR (Nujol, cm^{-1}): 1697; EI-MS: m/z (relative intensity) 233 (M^+, 1%), 107 (100%); HRMS calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1420. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.91; H, 8.24; N, 6.05%.

4.4.4. (5*R*,6*R*)-5-(2-Methylpropyl)-6-phenyl-1,3-oxazinan-2-one 13. White solid; yield 58%; mp 125–126°C; $[\alpha]_D^{20}=-33.8$ (c 0.5, $CHCl_3$; e.e. 97%, d.r. 97:3); ^1H NMR: δ (ppm) 0.78 (d, $J=6.7$, 3H, CH_3), 0.84 (d, $J=6.4$, 3H, CH_3), 0.9–1.6 (m, 3H, $CHCH_2$), 2.1–2.3 (m, 1H, C*H*-^{i}Bu), 3.08 (m, $J=9.2$, 11.5, 1H, C*H*HN), 3.44 (m, $J=5.1$, 11.5, 1H, CH*H*N), 4.96 (d, $J=8.7$, 1H, CH-O), 6.22 (br s, 1H, NH), 7.3–7.5 (m, 5H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 21.2, 23.4 (CH_3), 24.8 ($CHMe_2$), 34.9 (*C*H-^{i}Bu), 38.1 (CH_2-^{i}Pr), 44.1 (CH_2-N), 84.0 (CH-O), 126.8, 128.5, 128.6 ($CH_{arom.}$), 137.7 ($C_{arom.}$), 154.4 (CO); IR (Nujol, cm^{-1}): 1695; EI-MS: m/z (relative intensity) 233 (M^+, 3%), 107 (100%); HRMS calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1411. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.98; H, 8.29; N, 5.83%.

4.4.5. (5*R*,6*R*)-5-Ethyl-6-(3-methylphenyl)-1,3-oxazinan-2-one 14. White solid; yield 62%; mp 95–96°C; $[\alpha]_D^{20}=+15.3$ (c 0.6, $CHCl_3$; e.e. 70%, d.r. 89:11); ^1H NMR: δ (ppm) 0.85 (t, $J=7.4$, 3H, C*H*$_3$-CH_2), 1.1–1.4 (m, 2H, C*H*$_2$-Me), 1.9–2.1 (m, 1H, C*H*-Et), 2.38 (s, 3H, C*H*$_3$-Ar), 3.11 (m, $J=9.5$, 11.5, 1H, C*H*HN), 3.47 (m, $J=5.1$, 11.5, 1H, CH*H*N), 4.94 (d, $J=8.7$, 1H, CH-O), 6.20 (br s, 1H, NH), 7.1–7.35 (m, 4H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.9 (*C*H$_3$-CH_2), 21.4 (*C*H$_3$-Ar), 22.1 (*C*H$_2$-Me), 38.6 (*C*H-Et), 43.7 (CH_2-N), 83.7 (CH-O), 123.9, 127.3, 128.3, 129.3 ($CH_{arom.}$), 137.7, 138.2 ($C_{arom.}$), 154.5 (CO); IR (Nujol, cm^{-1}): 1699; ESI-MS: m/z 242 $(M+Na)^+$. Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.04; H, 8.88; N, 6.15%.

4.4.6. (5*R*,6*R*)-5-Ethyl-6-(4-methylphenyl)-1,3-oxazinan-2-one 15. White solid; yield 63%; mp 136–137°C; $[\alpha]_D^{20}=-3.3$ (c 0.5, $CHCl_3$; e.e. 83%, d.r. 96:4); ^1H NMR: δ (ppm) 0.83 (t, $J=7.4$, 3H, C*H*$_3$-CH_2), 1.1–1.4 (m, 2H, C*H*$_2$-Me), 1.9–2.1 (m, 1H, C*H*-Et), 2.36 (s, 3H, C*H*$_3$-Ar), 3.11 (m, $J=9.7$, 11.5, 1H, C*H*HN), 3.47 (m, $J=5.1$, 11.5, 1H, CH*H*N), 4.93 (d, $J=8.8$, 1H, CH-O), 5.77 (br s, 1H, NH), 7.1–7.2 (m, 4H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.9 (*C*H$_3$-CH_2), 21.6 (*C*H$_3$-Ar), 22.1 (*C*H$_2$-Me), 38.6 (*C*H-Et), 43.8 (CH_2-N), 83.6 (CH-O), 126.7, 129.1 ($CH_{arom.}$), 134.7, 138.4 ($C_{arom.}$), 154.3 (CO); IR (Nujol, cm^{-1}): 1694; ESI-MS: m/z 242 $(M+Na)^+$. Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.99; H, 8.89; N, 6.25%.

4.4.7. (5*R*,6*R*)-5-Ethyl-6-(4-methoxyphenyl)-1,3-oxazinan-2-one 16. White solid; yield 60%; mp 146–147°C; $[\alpha]_D^{20}=-1.8$ (c 0.6, $CHCl_3$; e.e. 75%, d.r. 94:6); ^1H NMR: δ (ppm) 0.83 (t, $J=7.4$, 3H, CH_3), 1.0–1.4 (m, 2H, C*H*$_2$-Me), 1.9–2.1 (m, 1H, C*H*-Et), 3.11 (m, $J=10.0$, 11.5, 1H, C*H*HN), 3.47 (m, $J=5.1$, 11.5, 1H, CH*H*N), 3.83 (s, 3H, CH_3O), 4.91 (d, $J=9.2$, 1H, CH-O), 6.05 (br s, 1H, NH), 6.91 (d, $J=8.6$, 2H, $H_{arom.}$), 7.25 (d, $J=8.6$, 2H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.9 (CH_3), 22.1 (*C*H$_2$-Me), 38.6 (*C*H-Et), 43.9 (CH_2-N), 55.2 (CH_3O), 83.5 (CH-O), 113.8, 128.2 ($CH_{arom.}$), 129.8 ($C_{arom.}$), 154.5 (CO) 159.7 ($C_{arom.}$-O); IR (Nujol): 1696 cm^{-1}; ESI-MS: m/z 258 $(M+Na)^+$. Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.19; H, 7.41; N, 5.82%.

4.4.8. (5*R*,6*R*)-5-Ethyl-6-(2-thienyl)-1,3-oxazinan-2-one 17. White solid; yield 58%; mp 137–138°C; $[\alpha]_D^{20}=-15.0$ (c 0.5, $CHCl_3$; e.e. 93%, d.r. 97:3); ^1H NMR: δ (ppm) 0.89 (t, $J=7.4$, 3H, CH_3), 1.1–1.6 (m, 2H, C*H*$_2$-Me), 1.95–2.2 (m, 1H, C*H*-Et), 3.11 (m, $J=9.5$, 11.8, 1H, C*H*HN), 3.51 (m, $J=5.1$, 11.8, 1H, CH*H*N), 5.27 (d, $J=9.0$, 1H, CH-O), 6.53 (br s, 1H, NH), 7.01 (m, 1H, $H_{arom.}$), 7.08 (m, 1H, $H_{arom.}$), 7.36 (m, 1H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.8 (CH_3), 22.3 (*C*H$_2$-Me), 39.1 (*C*H-Et), 43.5 (CH_2-N), 79.3 (CH-O), 126.1, 126.4, 126.5 ($CH_{arom.}$), 140.7 ($C_{arom.}$), 154.0 (CO); IR (Nujol): 1698 cm^{-1}; ESI-MS: m/z 234 $(M+Na)^+$. Anal. calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.97; H, 6.35; N, 6.50%.

4.4.9. (5*R*,6*R*)-5-Ethyl-6-(2-furyl)-1,3-oxazinan-2-one 18. White solid; yield 61%; mp 110–111°C; $[\alpha]_D^{20}=-32.7$ (c 0.5, $CHCl_3$; e.e. 87%, d.r. 86:14); ^1H NMR: δ (ppm) 0.87 (t, $J=7.5$, 3H, CH_3), 1.1–1.5 (m, 2H, C*H*$_2$-Me), 2.2–2.35 (m, 1H, C*H*-Et), 3.09 (m, $J=9.5$, 11.8, 1H, C*H*HN), 3.49 (m, $J=5.3$, 11.8, 1H, CH*H*N), 5.03 (d, $J=9.1$, 1H, CH-O), 6.24 (br s, 1H, NH), 6.35–6.4 (m, 2H, $H_{arom.}$), 7.4 (m, 1H, $H_{arom.}$); ^{13}C NMR: δ (ppm) 10.8 (CH_3), 22.1 (*C*H$_2$-Me), 35.7 (*C*H-Et), 43.5 (CH_2-N), 77.1 (CH-O), 109.6, 110.3, 142.9 ($CH_{arom.}$), 150.1 ($C_{arom.}$), 153.9 (CO); IR (Nujol): 1697 cm^{-1}; ESI-MS: m/z 218 $(M+Na)^+$. Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.42; H, 6.82; N, 7.09%.

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