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Enantio- and chemoselective bioreduction of β-keto nitriles by the fungus *Curvularia lunata*

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Abstract

The use of methanol as cosolvent allows the chemoselective reduction of aromatic β-keto nitriles by the fungus *Curvularia lunata* CECT 2130, yielding the corresponding (*S*)-β-hydroxy nitriles in a highly enantioselective way.

1. Introduction

The importance of optically active β-hydroxy acid derivatives as versatile building blocks in asymmetric synthesis is well established.[1,2] Among the many existing methods to prepare them, microbial enantioselective reduction of β-keto esters has proved to be one of the most effective processes.[3] Their nitrogenated analogous, β-keto amides, have also been subjected to bioreduction, but to a more limited extent.[4] From the resultant β-hydroxy amides, optically active β- and γ-amino alcohols have been easily obtained.[5] This gives the process a high added value, due to the importance of amino alcohols in both asymmetric synthesis[6] and medicinal chemistry.[7]

Another suitable way to obtain amino alcohols by this strategy would be from β-hydroxy nitriles. For instance, the antidepressant fluoxetine[8] can be readily prepared from 3-hydroxy-3-phenylpropanenitrile.[9] However, one of the most characteristic features of the bioreduction of α-non substituted β-keto nitriles by bakers' yeast is the existence of a competing α-ethylation reaction,[10,11] resulting in low chemical yields of the desired products, the corresponding α-non substituted β-hydroxy nitriles.

We have recently communicated that when an ethanolic solution of 3-oxo-3-phenylpropanenitrile, **1a**, was incubated with the fungus *Curvularia lunata* CECT 2130, an almost equimolar mixture of (*S*)-3-hydroxy-3-phenylpropanenitrile, **2a** (88% ee), and (2*R*,1′*R*)-2-(1-hydroxy-1-phenylmethyl)butanenitrile, **3a**, was obtained (see Scheme 1).[12]

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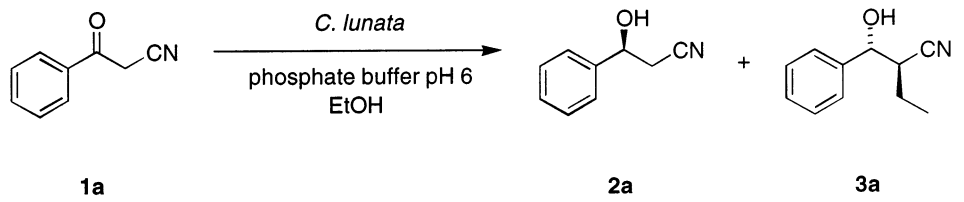


1a 2a 3a

Scheme 1.

In the course of our work, an attempt to minimize this ethylation reaction by decreasing the temperature appeared in the literature.[13] However, this methodology led to low conversion values when applied to substituted aromatic β-keto nitriles.

Therefore, the chemoselective bioreduction of β-keto nitriles has remained until now an unsolved problem. Here we present an alternative and general methodology to carry out this biotransformation, in most cases in a highly enantioselective fashion.

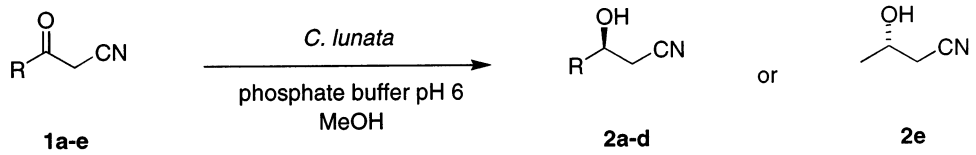
2. Results and discussion

Since the origin of the ethyl group incorporated in the α position during the incubation of **1a** with *C. lunata* seemed to be the ethanol used as cosolvent, we decided to substitute it for *N*,*N*-dimethylformamide (DMF) to prevent the synthesis of product **3a** and, therefore, optimize the yield in **2a**. However, a significant amount of **3a** (ca. 20%) was still obtained. This result suggests that the ethyl group does not only come from the cosolvent, but also from the ethanol produced by the fungal metabolism.

Quite surprisingly, when we used methanol as cosolvent (in our aim to introduce a methyl group in the α position), we obtained compound **2a** as the only product in a moderate yield (55%). Furthermore, the ee value rose from 88 up to 96%. Methanol has been (although scarcely) used in biotransformations with whole cells[14] but, to the best of our knowledge, such a positive effect in both chemo- and enantioselectivity had not been previously observed. So far, we do not have a conclusive explanation for the different results obtained with DMF and MeOH, but some reasonable hypotheses could be: (a) MeOH is able to substitute the EtOH in the cofactor regenerating process. Therefore, no acetaldehyde is formed, and the ethylation mechanism cannot go further. (b) MeOH inhibits the bioreduction of the double bond of the unsaturated ketone by the enoate reductase. As the chemical aldol condensation is reversible under these aqueous conditions, **1a** would be regenerated and the carbonyl reduction would yield **2a** as the only product.

Encouraged by this result, we introduced some experimental modifications in order to improve the enantioselectivity of the process: we tested some other cosolvents (dimethylsulfoxide and acetonitrile); we added deshydrogenase inhibitors, such as methyl vinyl ketone, ethyl chloroacetate,[15] allylic alcohol and L-cysteine;[16] and we changed the concentration of both substrate **1a** and cosolvent (methanol). However, in no case did we reach a value higher than 96% ee.

In order to check the general applicability of this methodology, we decided to test a series of different α-non substituted β-keto nitriles bearing an aromatic, heteroaromatic or aliphatic moiety attached to the carbonyl group (see Scheme 2). Indeed, the corresponding β-hydroxy nitriles **2** were obtained as the only products (see Table 1) in moderate to good yields and high to excellent ee, except for 3-hydroxybutanenitrile, **2e**. This result can be explained considering the small difference in size between the methyl and the cyanomethyl groups in compound **1e** and, thus, the difficulty for the enzyme to distinguish between both enantiotopic faces of the carbonyl group. As a general trend, it seems that higher ee values are reached with aromatic compounds (**2a** and **2b**), whereas higher yields are obtained with aliphatic ones (**2c–e**).



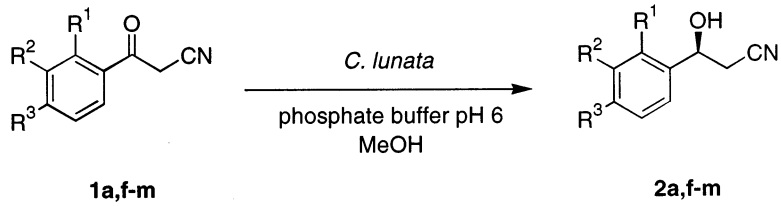
Scheme 2.

Table 1
Products obtained in the bioreduction of β-keto nitriles **1a–e** by *Curvularia lunata*

Product	R	Yield (%)[a]	ee (%)[b]	Abs. config.
2a	Ph	55	96	*S*
2b	2-Fur	55	92	*S*
2c	^{t}Bu	71	83	*S*
2d	Cy	77	88	*S*
2e	Me	65	40	*S*

[a] After column chromatography.
[b] Determined by chiral GC.

Considering that the best stereochemical result was obtained in the case of compound **2a**, we thought it would be of interest to continue our studies of bioreduction testing a series of aromatic keto nitriles bearing different substituents on the phenyl moiety, as shown on Scheme 3.



Scheme 3.

Once again, the corresponding β-hydroxy nitriles **2f–m** were obtained as the only products in moderate yield and high to very high enantiomeric excesses in most cases, as shown in Table 2. Although these results might not be extrapolated, some general tendencies in the enantioselectivity of the biotransformation were observed: (a) a substituent in the *para* position (compounds

2h, **2k** and **2m**) decreases the ee, whereas a substituent in the *ortho* (**2f**) or *meta* (**2g**, **2j** and **2l**) position does not produce significant changes, and sometimes results in even higher values than that obtained with **2a**; (b) considering the *para* position, a methyl (**2k**) or methoxy (**2m**) group results in a much higher ee value than a chlorine (**2h**); (c) the nature of the substituent when it is placed on a *meta* position (**2g**, **2j** and **2l**) is not so influential: ee values higher than 90% are always reached; (d) a double substitution in *meta* and *para* (**2i**) leads again to a high ee value, much closer to that obtained with **2g** than that with **2h**.

Table 2
Products obtained in the bioreduction of aromatic β-keto nitriles by *Curvularia lunata*

Product	R^1	R^2	R^3	Yield (%)[a]	ee (%)[b]	Abs. config.
2a	H	H	H	55	96	*S*
2f	Cl	H	H	42	98	*S*
2g	H	Cl	H	57	97	*S*
2h	H	H	Cl	47	50	*S*
2i	H	Cl	Cl	43	92	*S*
2j	H	Me	H	59	94	*S*
2k	H	H	Me	54	82	*S*
2l	H	CF_3	H	41	98	*S*
2m	H	H	MeO	42	83	*S*

[a] After column chromatography.
[b] Determined by chiral GC.

All the β-hydroxy nitriles obtained in the bioreduction with *C. lunata* have *S* absolute configuration. For compounds **2a** and **2e**, it has been assigned by comparison of the sign of the specific rotation with the value published in the literature (see Section 4). Compound **2c** was hydrolyzed to 3-hydroxy-4,4-dimethylpentanoic acid, followed by treatment with diazomethane to give the corresponding methyl ester.[17] Compound **2d** was treated with acetic anhydride to give its *O*-acetylated derivative.[18] For the aromatic β-hydroxy nitriles, **2b**,**f**–**m**, the absolute configuration has been tentatively assigned on the basis of three convergent features: (a) the $\Delta\delta$ values measured in the ^{1}H NMR spectra of the MeO group of their MTPA esters,[19] using the modified Mosher's method[20] for secondary alcohols; (b) the Prelog's rule,[21] which *C. lunata* follows for the bioreduction of ketones,[12,22] considering the aromatic ring as the large substituent, and the cyanomethyl group as the small one; (c) the elution order on our chiral GC column: in all cases, the major enantiomer exhibits the longest retention time. As expected, all these aromatic compounds show the same absolute configuration, independently from the substituent on the phenyl ring.

3. Conclusion

In summary, a general methodology for the chemo- and enantioselective bioreduction of β-keto nitriles with the fungus *C. lunata* CECT 2130 has been accomplished using methanol as cosolvent. Coupled with our previous communication, we have shown that this fungal strain is a versatile biocatalyst, and depending on the experimental conditions, it is possible to selectively

obtain the alkylated product **3** or the reduced one **2**. Furthermore, the enantiomeric excesses of the corresponding β-hydroxy nitriles were very high in many cases, which could lead to a series of new derivatives of antidepressants in an optically active form by conventional methods.

4. Experimental

4.1. General

The fungus *C. lunata* was obtained from CECT (Colección Española de Cultivos Tipo). Reagents were purchased from Avocado, Aldrich Chemie or Lancaster. Solvents were distilled over an adequate 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 for ^{13}C) spectrometer, using TMS as internal standard. Mass spectra were recorded on a Hewlett–Packard 5987 A spectrometer, using electronic impact procedures (75 eV). The ee values were determined by GC on a Hewlett–Packard 5890 Series II chromatograph, using a Rt-βDEXse (30 m×0.25 mm, Restek) capillary column and nitrogen as carrier gas (15 psia).

4.2. General procedures for cultures and biotransformations

A loop of a solid culture of *C. lunata*, from an agar plate, was sown in a test tube containing 3 mL of sterilized Sabouraud's liquid medium (composed of bactopeptone (10 g), D-glucose (20 g) in distilled water (1.0 L); pH adjusted to 5.8). After growing over 72 h (rotatory shaker, 200 rpm, 28°C), 0.5 mL of this initial medium were used to inoculate another sterilized medium (75 mL, in a 250 mL Erlenmeyer flask), identical to that used for fungi in Ref. 23. After 72 h of cultivation (same conditions as above), cells were harvested by filtration (3.90 g wet weight), washed with aqueous 0.8% NaCl, and suspended in 75 mL of 0.2 M phosphate buffer, pH 6.0.

To this cell suspension, a solution of substrate (75 mg) in warm methanol (0.75 mL) was added. In some cases, a partial precipitation of the substrate was observed. However, as the reaction proceeded, this precipitate disappeared. Incubation was then carried out until disappearance of the substrate (6–12 h, TLC monitoring). Then, the mycelium was filtered out again, and the fungal cake was washed several times with aqueous 0.8% NaCl, until no more product was recovered. The combined aqueous phases were continuously extracted with AcOEt for 12 hours. After drying over anhydrous Na_2SO_4, the solvent was evaporated and the product purified by flash chromatography (eluent: hexane–AcOEt, 5:1).

For the spectral data of compounds **2a** and **2e**, see Ref. 24. For compound **2c**, see Ref. 25 and for compounds **2d**, **2f**, **2h** and **2m**, see Ref. 26. For new compounds (**2b**, **2g**, **2i**, **2j**, **2k** and **2l**) full characterization is given.

4.2.1. (S)-3-Hydroxy-3-phenylpropanenitrile, *2a*

Yield, 55%; $[\alpha]_D^{20}$ −57.7 (*c* 2.6, EtOH; ee 96%), lit. $[\alpha]_D^{20}$ +58.0 (*c* ca. 1, EtOH; ee 94% *R*);[24] GC conditions: 170°C, $t_R(R)$ 15.5 min and $t_R(S)$ 16.6 min.

4.2.2. (S)-3-(2-Furyl)-3-hydroxypropanenitrile, ***2b***

Oil; yield, 55%; $[\alpha]_D^{20}$ −38.6 (*c* 1.3, $CHCl_3$; ee 92%); ^1H NMR: δ (ppm) 2.88 (d, *J* 6.3 Hz, 2H, CH_2), 3.01 (br s, 1H, OH), 5.02 (t, *J* 6.1 Hz, 1H, CH–O), 6.35–6.40 (m, 2H, H_{arom}), 7.35–7.45 (m, 1H, H_{arom}); ^{13}C NMR: 24.8 (CH_2), 63.6 (CH–O), 107.3, 110.4 (CH_{arom}), 116.9 (CN), 142.7 (CH_{arom}), 152.7 (C_{arom}); IR (neat) 3410, 2255 cm^{-1}; MS: *m*/*z* (relative intensity) 137 (M^+, 15), 119 (9), 97 (100); HRMS calc. for $C_7H_7NO_2$ 137.047678, found 137.047651. GC conditions: 135°C, $t_R(R)$ 31.3 min and $t_R(S)$ 33.6 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: –42 Hz.

4.2.3. (S)-3-Hydroxy-4,4-dimethylpentanenitrile, ***2c***

Yield, 71%; $[\alpha]_D^{20}$ −32.2 (*c* 0.6, $CHCl_3$; ee 83%); GC conditions: 105°C, $t_R(S)$ 25.4 min and $t_R(R)$ 27.0 min.

4.2.4. (S)-3-Cyclohexyl-3-hydroxypropanenitrile, ***2d***

Yield, 77%; $[\alpha]_D^{20}$ −9.4 (*c* 0.9, $CHCl_3$; ee 88%); GC conditions for its *O*-acetylated derivative: 150°C, $t_R(S)$ 17.4 min and $t_R(R)$ 18.5 min.

4.2.5. (S)-3-Hydroxybutanenitrile, ***2e***

Yield, 65%; $[\alpha]_D^{20}$ −2.9 (*c* 0.8, EtOH; ee 40%), lit. $[\alpha]_D^{20}$ +4.1 (*c* 3.0, EtOH; ee 84% *R*);[24] GC conditions for its *O*-acetylated derivative: 115°C, $t_R(R)$ 7.0 min and $t_R(S)$ 8.2 min.

4.2.6. (S)-3-(2-Chlorophenyl)-3-hydroxypropanenitrile, ***2f***

Yield, 42%; $[\alpha]_D^{20}$ −95.1 (*c* 0.7, $CHCl_3$; ee 98%); GC conditions: 185°C, $t_R(R)$ 16.7 min and $t_R(S)$ 18.3 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: –42 Hz.

4.2.7. (S)-3-(3-Chlorophenyl)-3-hydroxypropanenitrile, ***2g***

Oil; yield, 57%; $[\alpha]_D^{20}$ −56.8 (*c* 1.3, $CHCl_3$; ee 97%); ^1H NMR: δ (ppm) 2.72 (d, *J* 6.2 Hz, 2H, CH_2), 3.24 (br s, 1H, OH), 4.98 (t, *J* 6.0 Hz, 1H, CH–O), 7.2–7.4 (m, 4H, H_{arom}); ^{13}C NMR: 27.8 (CH_2), 69.1 (CH–O), 117.1 (CN), 123.6, 125.6, 128.7, 130.1 (CH_{arom}), 134.6, 142.9 (C_{arom}); IR (neat) 3431, 2257 cm^{-1}; MS: *m*/*z* (relative intensity) 181 (M^+, 6), 183 [$(M+2)^+$, 2], 163 (5), 141 (75), 77 (100); HRMS calc. for C_9H_8ClNO 181.029442, found 181.029264; GC conditions: 185°C, $t_R(R)$ 23.7 min and $t_R(S)$ 25.2 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: –42 Hz.

4.2.8. (S)-3-(4-Chlorophenyl)-3-hydroxypropanenitrile, ***2h***

Yield, 47%; $[\alpha]_D^{20}$ −52.1 (*c* 0.7, $CHCl_3$; ee 50%); GC conditions: 185°C, $t_R(R)$ 23.3 min and $t_R(S)$ 24.6 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: –49 Hz.

4.2.9. (S)-3-(3,4-Dichlorophenyl)-3-hydroxypropanenitrile, ***2i***

White solid; yield, 43%; mp 85–86°C; $[\alpha]_D^{20}$ −37.2 (*c* 0.8, $CHCl_3$; ee 92%); ^1H NMR: δ (ppm) 2.75 (d, *J* 6.0 Hz, 2H, CH_2), 2.0–3.2 (br s, 1H, OH), 5.03 (t, *J* 6.1 Hz, 1H, CH–O), 7.25 (dd, 1H, *J* 2.0, 8.3 Hz, H_{arom}), 7.48 (d, *J* 8.3 Hz, 1H, H_{arom}), 7.52 (d, *J* 2.0 Hz, 1H, H_{arom}); ^{13}C NMR: 27.9 (CH_2), 68.6 (CH–O), 116.8 (CN), 124.8, 127.5, 130.8 (CH_{arom}), 132.6, 132.9, 141.0 (C_{arom}); IR (KBr) 3425, 2255 cm^{-1}; MS *m*/*z* (relative intensity) 215 (M^+, 1), 217 [$(M+2)^+$, <1], 219 [$(M+4)^+$, <1], 197 (97), 162 (100); HRMS calc. for $C_9H_7Cl_2NO$ 214.990470, found 214.989396; GC conditions: 200°C, $t_R(R)$ 28.9 min and $t_R(S)$ 30.3 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: –55 Hz.

4.2.10. (S)-3-Hydroxy-3-(3-methylphenyl)propanenitrile, ***2j***

Oil; yield, 59%; $[\alpha]_D^{20}$ −59.3 (*c* 0.8, $CHCl_3$; ee 94%); ^1H NMR: δ (ppm) 2.37 (s, 3H, CH_3), 2.69 (br s, 1H, OH), 2.74 (d, *J* 6.2 Hz, 2H, CH_2), 4.98 (t, *J* 6.1 Hz, 1H, CH–O), 7.15–7.35 (m, 4H, H_{arom}); ^{13}C NMR: 21.3 (CH_3), 27.8 (CH_2), 70.0 (CH–O), 117.3 (CN), 122.5, 126.0, 128.7, 129.4 (CH_{arom}), 138.6, 140.9 (C_{arom}); IR (neat) 3447, 2254 cm^{-1}; MS: *m*/*z* (relative intensity) 161 (M^+, 12), 143.0 (10), 121 (100), 93 (83); HRMS calc. for $C_{10}H_{11}NO$ 161.084064, found 161.083587; GC conditions: 172°C, $t_R(R)$ 18.6 min and $t_R(S)$ 19.9 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: −56 Hz.

4.2.11. (S)-3-Hydroxy-3-(4-methylphenyl)propanenitrile, ***2k***

Oil; yield, 54%; $[\alpha]_D^{20}$ −53.4 (*c* 1.5, $CHCl_3$; ee 82%); ^1H NMR: δ (ppm) 2.36 (s, 3H, CH_3), 2.68 (br s, 1H, OH), 2.72 (d, *J* 6.5 Hz, 2H, CH_2), 4.97 (t, *J* 6.1 Hz, 1H, CH–O), 7.20 (d, *J* 8.3 Hz, 2H, H_{arom}), 7.27 (d, *J* 8.5 Hz, 2H, H_{arom}); ^{13}C NMR: 21.0 (CH_3), 27.7 (CH_2), 69.8 (CH–O), 117.4 (CN), 125.3, 129.4 (CH_{arom}), 138.0, 138.5 (C_{arom}); IR (neat) 3433, 2257 cm^{-1}; MS: *m*/*z* (relative intensity) 161 (M^+, 6), 143.0 (10), 121 (100), 93 (83); HRMS calc. for $C_{10}H_{11}NO$ 161.084064, found 161.083519; GC conditions: 172°C, $t_R(R)$ 19.1 min and $t_R(S)$ 20.3 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: −45 Hz.

4.2.12. (S)-3-Hydroxy-3-(3-trifluoromethylphenyl)propanenitrile, ***2l***

Oil; yield, 41%; $[\alpha]_D^{20}$ −46.1 (*c* 1.5, $CHCl_3$; ee 98%); ^1H NMR: δ (ppm) 2.76 (d, *J* 6.5 Hz, CH_2), 3.29 (br s, 1H, OH), 5.10 (t, *J* 6.1 Hz, 1H, CH–O), 7.50–7.65 (m, 4H, H_{arom}); ^{13}C NMR: 27.9 (CH_2), 69.1 (CH–O), 117.0 (CN), 123.7 (q, *J* 273 Hz, CF_3), 122.3, 125.4, 128.9, 129.3 (CH_{arom}), 131.0 (q, *J* 32 Hz, C_{arom}–CF_3), 141.9 (C_{arom}); IR (neat) 3443, 2258 cm^{-1}; MS: *m*/*z* (relative intensity) 215 (M^+, <1), 197 (26), 175 (100), 127 (80); HRMS calc. for $C_{10}H_6F_3N$ (M^+–H_2O): 197.045233, found 197.045114; GC conditions: 180°C, $t_R(R)$ 14.1 min and $t_R(S)$ 15.4 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: −55 Hz.

4.2.13. (S)-3-Hydroxy-3-(4-methoxyphenyl)propanenitrile, ***2m***

Yield, 42%; $[\alpha]_D^{20}$ −59.7 (*c* 0.6, $CHCl_3$; ee 83%); GC conditions: 182°C, $t_R(R)$ 24.4 min and $t_R(S)$ 25.6 min. $\Delta\delta$ of the MeO group of its MTPA ester derivatives: −49 Hz.

4.2.14. Methyl (S)-3-hydroxy-4,4-dimethylpentanoate

A solution of **2c** (50 mg, 0.4 mmol) in 5 mL of conc. HCl was refluxed for 1 h. After cooling and diluting with 15 mL of AcOEt, the organic layer was washed with brine, dried and evaporated to give a white solid. It was solved in 1 mL THF and 0.2 mL MeOH, and treated with trimethylsilyldiazomethane (0.4 mL of a 2 M solution in hexane). After 5 hours, solvents were eliminated, the residue diluted in AcOEt, and washed again with brine. The organic phase was dried and the solvent eliminated. Purification by flash chromatography gave methyl (*S*)-3-hydroxy-4,4-dimethylpentanoate as a colourless oil (49 mg, 0.31 mmol, 77%). $[\alpha]_D^{20}$ −32.2 (*c* 0.6, EtOH), lit. $[\alpha]_D^{20}$ +38.4 (*c* 2.7, EtOH; ee 98% *R*).[17]

4.2.15. (S)-2-Cyano-1-cyclohexylethyl acetate

To a solution of **2d** (30 mg, 0.2 mmol) in CH_2Cl_2, 30 μL of Ac_2O (0.3 mmol) and 25 μL of pyridine (0.3 mmol) were added, and it was stirred for 3 hours. Then, water was added to quench the reaction, and after extraction with CH_2Cl_2, drying and evaporation of the solvent, the crude product was purified by flash chromatography (eluent, hexane:AcOEt, 10:1) to provide

(*S*)-2-cyano-1-cyclohexylethyl acetate (28 mg, 0.14 mmol, 72%). $[\alpha]_D^{20}$ +39.9 (*c* 1.5, $CHCl_3$), lit. $[\alpha]_D^{20}$ +33.3 (*c* 0.7, $CHCl_3$; ee 82% *S*).[18]

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