Highly efficient and enantioselective biotransformations of β-lactam carbonitriles and carboxamides and their synthetic applications†‡

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Catalyzed by *Rhodococcus erythropolis* AJ270, a nitrile hydratase and amidase containing microbial whole cell catalyst, a number of racemic 1-arylmethyl- and 1-allyl-4-oxoazetidine-2-carbonitriles and carboxamides underwent efficient transformations under very mild conditions to produce enantiopure functionalized *S*-amide and *R*-acid products in excellent yields. While the nitrile hydratase showed good enzyme activity but virtually no enantioselectivity, the amidase displayed high *R*-enantioselectivity against almost all amide substrates tested. The synthetic applications of the resulting functionalized chiral β-lactam derivatives were demonstrated by the facile preparation of β-lactam-fused heterocyclic compounds.

Introduction

Chiral β-lactam constitutes the core structure of β-lactam antibiotics that are extensively used in a clinical setting.[1] Amoxicillin, for example, remained one of the most prescribed antibiotics in the United States, with approximately 49.5 million prescriptions filled in 2009.[2] Chiral β-lactam compounds are also very useful intermediates in organic synthesis, and they provide a versatile platform for the preparation of various chiral organic compounds.[1,3] Enantiomerically pure β-lactam compounds are synthesized mainly from various intramolecular cyclizations of chiral starting materials and 2+2 cycloaddition reactions employing the chiral auxiliary.[4] While the lipase-catalyzed hydrolysis of *cis*-3-acetyloxy-4-*t*-butyl-2-azetidinone gives enantiopure 3*R*-*cis*-3-acetyloxy-4-*t*-butyl-2-azetidinone in a good yield,[5] biocatalytic reductions of α-keto-β-lactams with yeast reductases produce α-hydroxy-β-lactams with *re*- and *si*-face selectivity.[6] Recently, the *N*-heterocyclic carbene catalyzed asymmetric Staudinger reaction has provided another attractive approach to the preparation of chiral β-lactam derivatives.[7] Because of the paramount importance of β-lactams in chemistry, biology and medicine, it is highly desirable to establish general and efficient methods for the synthesis of diverse β-lactam compounds of excellent enantiopurity.

One of the biocatalytic nitrile degradation pathways involves the nitrile hydratase-catalyzed hydration of a nitrile followed by the amide hydrolysis catalyzed by the amidase.[8] A large number of the microorganisms containing nitrile hydratases and amidases have been isolated,[9] and the microbial transformation of nitriles has become the most effective and environmentally benign method for the production of carboxamides and carboxylic acids.[10] One of the best-known examples is the industrial production of acrylamide from the biocatalytic hydration of acrylonitrile.[11] More remarkably, owing to the enantioselectivity of the enzymes, the biotransformation of nitriles has been demonstrated to complement the existing asymmetric chemical and enzymatic methods for the synthesis of chiral carboxylic acids and their amide derivatives.[10,12] One of the distinct advantages of enzymatic transformation of nitriles is the straightforward generation of enantiopure amides, valuable organo-nitrogen compounds in synthetic chemistry, in addition to the formation of enantiopure carboxylic acids. For example, we have shown that *Rhodococcus erythropolis* AJ270,[13] a nitrile hydratase/amidase-containing whole cell catalyst, is able to efficiently and enantioselectively transform a variety of racemic nitriles into highly enantiopure carboxylic acids and amides.[12] Using the highly enantioselective nitrile biotransformation approach, many structurally diverse acids and amides that contain a three-membered ring such as cyclopropane,[14] epoxide[15] and aziridine[16] have been synthesized. Very recently, we[17] have discovered that the simple four-membered heterocyclic nitriles, azetidine-2-carbonitriles, are converted efficiently into enantiopure azetidine-2-carboxylic acids and azetidine-2-carboxamides *via* biocatalysis. Our interests in functionalized β-lactam compounds and in exploration of nitrile biotransformation in organic synthesis led us to undertake the current study. Herein, we report the biotransformation of 1-alkyl-4-oxoazetidine-2-carbonitriles and 2-carboxamimdes, a highly efficient method for the preparation of enantiopure β-lactam derivatives. Preliminary applications of the resulting β-lactam products in synthesis are also demonstrated.

Results and discussion

We initiated our study by examining the biotransformations of racemic 1-benzyl-4-oxoazetidin-2-carbonitrile **1a**.[18] The reaction was conducted in neutral aqueous potassium phosphate buffer at 30 °C. Since the substrate **1a** is highly viscous and does not disperse well in the aqueous buffer, a very small amount of acetone was used as a co-solvent. To facilitate the isolation of product, acid **3a** was

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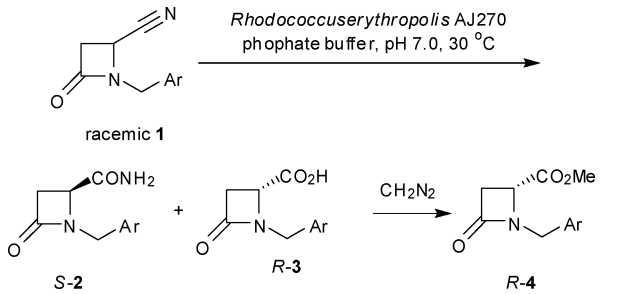
‡ Electronic supplementary information (ESI) available: Synthesis and characterization of all racemic nitrile, amide and ester compounds, characterization and ^{1}H and ^{13}C spectra of all products, and X-ray structures of *S*-**2e** and **17**. CCDC reference numbers 779903 and 779904. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00198h

Table 1 Enantioselective biotransformations of racemic nitriles **1**[a]

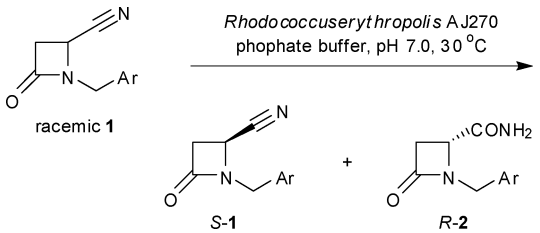


Entry	1	Ar	*t*/h	*S*-**2** (%)[b]	*S*-**2** (ee)[c]	*R*-**4** (%)[b]	*R*-**4** (ee)[c]	*E*[d]
1	**1a**	C_6H_5	3.5	45	>99.5	49	>99.5	>200
2[e]	**1a**	C_6H_5	8.75	45	97.6	48	>99.5	>200
3	**1b**	4-F-C_6H_4	10	39	>99.5	47	>99.5	>200
4	**1c**	4-Me-C_6H_4	17.5	50	>99.5	40	>99.5	>200
5[f]	**1d**	4-Br-C_6H_4	72	23	>99.5	21	>99.5	>200
6	**1e**	3-Br-C_6H_4	13	45	>99.5	47	>99.5	>200
7[g]	**1f**	2-Br-C_6H_4	192	30	>99.5	29	>99.5	>200
8[h]	**1g**	4-MeO-C_6H_4	192	—	—	—	—	—

[a] Nitrile (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (0.1 M, pH 7.0, 50 mL) at 30 °C. Acetone (0.5 mL) was used as a co-solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Calculated following a literature method.[20] [e] Nitrile (2 mmol) was used. [f] Nitrile *S*-**1d** (41%, ee 5.2%) was recovered. [g] Nitrile *S*-**1f** (41%, ee 13.2%) was recovered. [h] Nitrile **1g** (99%) was recovered.

converted into its methyl ester using CH_2N_2 (Table 1). It was found that, hydrolysis of **1**, catalyzed by *Rhodococcus erythropolis* AJ270 whole cell catalyst,[19] proceeded very efficiently and enantioselectively. Enantiopure 1-benzyl-4-oxoazetidine-2-carboxamide *S*-**2a** and methyl 1-benzyl-4-oxoazetidine-2-carboxylate *R*-**4a** were obtained in good yield within a short period of time (entries 1 and 2, Table 1). To study the effect of the substituent of benzyl on the reaction, racemic nitrile analogs **1b–g** were prepared according to a literature procedure[18] and subjected to biotransformations. As summarized in Table 1, the efficiency of biotransformations was strongly governed by the nature of the substituent and its substitution pattern. While 4-fluoro (**1b**) and 4-methyl (**1c**) substituted nitrile substrates underwent efficient reactions to afford high yields of amide and acid products in 10 h and 17.5 h, respectively (entries 3 and 4), slow nitrile hydration reaction was observed for 4-bromo substituted analog **1d**. Along with the isolation of amide *S*-**2d** (23% yield) and ester *R*-**4d** (21% yield), for example, nearly 50% of the starting nitrile **1d** was recovered after 3 days' incubation with *Rhodococcus erythropolis* AJ270 whole cells (entry 5, Table 1). The presence of a methoxy group at the *para*-position caused complete inhibition of nitrile hydration reaction of **1g**. After 8 days, intact starting substrate was recovered almost quantitatively (entry 8, Table 1). Interestingly, moving the bromo substituent from the *para*- to the *meta*-position led to the acceleration of biotransformations, as substrate **1e** was biocatalytically transformed into enantiopure *S*-amide *S*-**2e** and *R*-acid *R*-**3e** in excellent yields in 13 h (entry 6, Table 1). However, further moving the bromo substituent to the *ortho*-position had a detrimental effect. This was exemplified by the isolation of 41% of **1f** after 8 days' interaction with the biocatalyst (entry 7, Table 1). It is important to note that, except for nitrile **1g**, which was inert to the whole cell biocatalyst, biotransformations

Table 2 Biocatalytic kinetic resolution of racemic β-cyano-β-lactams **1**[a]



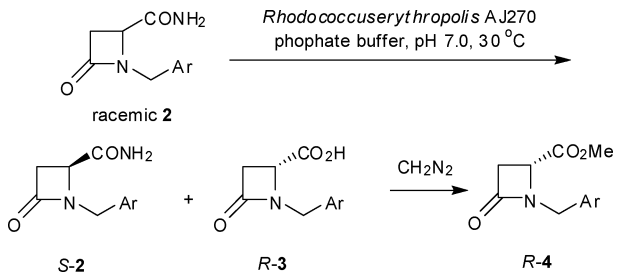
Entry	1	Ar	*t*/min	*S*-**1** (%)[b]	*S*-**1** (ee)[c]	*R*-**2** (%)[b]	*R*-**2** (ee)[c]
1	**1a**	C_6H_5	120	34	ND[d]	61	4.3
2	**1b**	4-F-C_6H_4	70	59	ND[d]	40	11.4
3	**1c**	4-Me-C_6H_4	120	45	ND[d]	53	12.6
4	**1d**	4-Br-C_6H_4	180	59	1.2	39	2.2
5	**1e**	3-Br-C_6H_4	70	44	ND[d]	56	19.2
6	**1f**	2-Br-C_6H_4	1 d	89	ND[d]	10	9.8
7	**1g**	4-MeO-C_6H_4	7 d	99	ND[d]	—	—

[a] Nitrile (2 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (0.1 M, pH 7.0) at 30 °C. Acetone (1 mL) was used as a co-solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Not determined.

of all racemic nitrile substrates **1a–f** produced enantiomerically pure *S*-amide and *R*-acid products with an enantiomeric ratio *E*[20] being higher than 200 (entries 1 to 7, Table 1). This suggested that the formation of enantiopure amide and acid products from nitrile biotransformations was not affected by the nature of the substituent on the benzene ring or its substitution pattern. On the other hand, however, recovered nitriles after 50% conversion gave very low enantiomeric excess values, with ee of *S*-**1d** and *S*-**1f** being only 5.2% and 13.2%, respectively (entries 5 and 7), indicating low enantioselectivity of the nitrile hydratase against these nitrile substrates. It might be worth noting that the microbial cell catalyst did not effect the hydrolytic ring opening reaction of β-lactam even with a very long incubation time (entries 7 and 8, Table 1). The amidase within *Rhodococcus erythropolis* AJ270 therefore acted specifically on a carbamoyl group rather than a β-lactam moiety.

To gain a deep insight into the catalytic efficiency and stereochemistry of the nitrile hydratase and the amidase of *Rhodococcus erythropolis* AJ270, kinetic resolution of nitrile hydration and of amide hydrolysis was investigated. As demonstrated by the results in Table 2, except for **1f** and **1g**, all racemic nitriles tested underwent rapid biocatalytic hydration reaction, with 50% conversion being completed within 3 h. In all cases, the enantiomeric excess values of *S*-nitriles and *R*-amides isolated were extremely low, ranging from 1.2% to 19.2%. This indicated clearly that the nitrile hydratase in *Rhodococcus erythropolis* AJ270 shows extremely low *R*-enantioselectivity against 1-arylmethyl-4-oxoazetidin-2-carbonitrile substrates. The results are consistent with previous observations[12] that the nitrile hydratases are generally a type of highly active but less enantioselective enzymes against a variety of nitrile substrates. These characteristics of the nitrile hydrates, such as having a broad substrate spectrum and possessing low or no enantioselectivity, are intrinsically determined by the enzyme structure[21] in which there is a spacious pocket around active site. In other words, a pair of enantiomers of 1-arylmethyl-4-oxoazetidin-2-carbonitriles were hardly differentiated by the nitrile hydratase, leading almost identical biocatalytic hydration reactions.

Table 3 Biocatalytic kinetic resolution of racemic β-carbamoyl-β-lactams **2**[a]



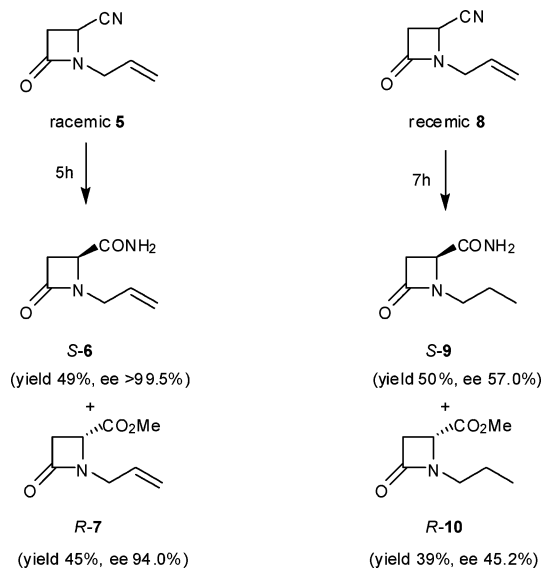
Entry	2	Ar	t/h	S-2 (%)[b]	S-2 (ee)[c]	R-4 (%)[b]	R-4 (ee)[c]	E[d]
1	**2d**	4-Br-C_6H_4	22	49	>99.5	49	>99.5	>200
2	**2f**	2-Br-C_6H_4	28	45	>99.5	46	>99.5	>200
3	**2g**	4-MeO-C_6H_4	20	46	>99.5	45	92.0	125

[a] Amide (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (0.1 M, pH 7.0) at 30 °C. Methanol (3 mL) was used as a co-solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Calculated following a literature method.[20]

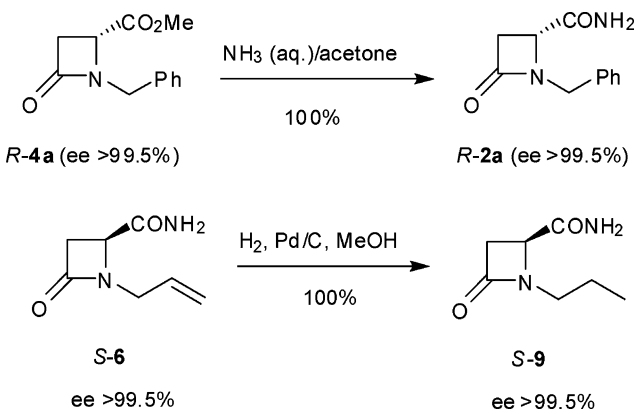
In stark contrast to the nitrile hydratase which catalyzed a virtually non-enantioselective nitrile hydration reaction, the amidase within *Rhodococcus erythropolis* AJ270 displayed excellent enantioselection. Biocatalytic kinetic resolution of racemic amides **2d**, **2f** and **2g** afforded excellent yields of the corresponding *S*-amides and *R*-acids with ee values ranging from 92.0% to >99.5% (Table 3). The outcomes are also in agreement with the previous observations[12] that the amidase within the *Rhodococcus erythropolis* AJ270 microbial cell is a highly enantioselective enzyme. It can be concluded that the overall enantioselectivity of the sequential nitrile biotransformations tabulated in Table 1 stems from the combined effect of a virtually non-enantioselective nitrile hydratase and a high *R*-enantioselective amidase.

The previous studies[12] have revealed that the amidase is a more demanding enzyme than the nitrile hydratase in terms of the steric effect of the substrates. If the nitrile with a sterically bulky substituent does not act as a good substrate of the nitrile hydratase, the corresponding amide is hardly accepted by the amidase. For instance, while 2,6-dichlorobenzonitrile is a fairly good substrate for the nitrile hydratase within *Rhodococcus erythropolis* AJ270, the amidase does not at all catalyze the hydrolysis of 2,6-dichlorobenzamide.[9] In the current study, however, the amidase efficiently transformed amides bearing a 4-bromo- (**2d**), 2-bromo- (**2f**) or 4-methoxy- (**2g**) substituent on the benzene ring of the substrate, whereas their nitrile counterparts **1d**, **1f** and **1g** were difficult substrates for the nitrile hydratase. Although the mechanism of interaction between the amidase and substrate awaits further investigation, enantioselective biotransformations of β-lactam carbonitriles and the corresponding amides ensure efficient preparation of functionalized β-lactam derivatives of high enantiomeric purity.

Encouraged by the efficient and highly enantioselective biotransformations of 1-arylmethyl-4-oxoazetidien-2-carbonitriles (±)-**1** and -carboxamides (±)-**2**, we then investigated the reaction of racemic 1-allyl-4-oxoazetidine-2-carbonitrile (±)-**5** and its carboxamide (±)-**6**, for the synthesis of enantiopure polyfunctionalized β-lactam derivatives. To understand the effect of the carbon–carbon double bond on the biocatalysis, biotransformation of 1-propyl-oxoazetidine-2-carbonitrile was also examined. To our delight, under the identical biocatalytic conditions, nitrile (±)-**5** underwent very rapid hydration reaction to form amide (±)-**6**, which was efficiently resolved into enantioenriched *R*-1-allyl-4-oxoazetidine-2-carboxamide *S*-**6** (ee > 99.5%) and, after esterification, methyl *S*-1-allyl-4-oxoazetidine-2-carboxylate *R*-**7** (ee 94.0%) in excellent yields (Scheme 2 and ESI‡). When the carbon–carbon double bond was reduced, a slightly slow biotransformation of racemic substrate **8** was observed. Noticeably, however, the enantiomeric excess values of the amide *S*-**9** and ester *R*-**10** were only moderate (Scheme 1), indicating a dramatic decrease of enantioselectivity of the amidase against racemic 1-propyl-4-oxoazetidine-2-carboxamide. The intriguing effect of a carbon–carbon unsaturated bond on the increase of reaction rate and the enhancement of the enantioselectivity of the amidase has been noted in our previous study.[22] This somewhat general and interesting feature of the amidase can serve as a guideline in the design of substrates in order to achieve efficient and enantioselective biocatalysis.



Scheme 1 Enantioselective biotransformations of racemic nitriles **5** and **8**.



Scheme 2 Chemical transformation of *R*-**4a** into *R*-**2a** and of *S*-**6** into *S*-**9**.

The structures of all products were established on the basis of their spectroscopic data and microanalysis results. To determine the absolute configurations of the products, a single crystal of biotransformed amide product **2e** (entry 6, Table 1), a heavy atom-containing compound, was cultivated from the slow evaporation of its solution in a mixture of petroleum ether and ethyl acetate (3 : 1). As illustrated in Fig. 1, X-ray diffraction analysis revealed unambiguously that the chiral center of the β-lactam ring of **2e** is *S*-configured. The absolute configuration of esters **4** was obtained by the comparison of the optical rotation of biotransformed amide *S*-**2a** ($[\alpha]_D^{25}$ −24° (*c* 0.5, $CHCl_3$)) with that of *R*-**2a** ($[\alpha]_D^{25}$ +28° (*c* 0.5, $CHCl_3$)), which was obtained from the chemical aminolysis of *R*-**4a** (Scheme 2). Catalytic hydrogenation of the double bond of amide *S*-**6** (ee >99.5%) gave 1-propyl-4-oxoazetidien-2-carboxamide *S*-**9** (ee >99.5%, $[\alpha]_D^{25}$ −80° (*c* 0.75, H_2O)) (Scheme 2) that has the same direction of the optical rotation as that of amide *S*-**9** (ee 57.0%, $[\alpha]_D^{25}$ −32° (*c* 0.75, H_2O)) obtained directly from biotransformations of nitrile, showing clearly that **9** has the same absolute configuration as **6** (Scheme 1). The amidase therefore exhibited the same enantio-preference for both 1-allyl- and 1-propyl-4-oxoazetidine-2-carboxamides. The absolute *R*-configuration of product **7** was then determined by the X-ray crystallography of its derivative (*vide infra*).

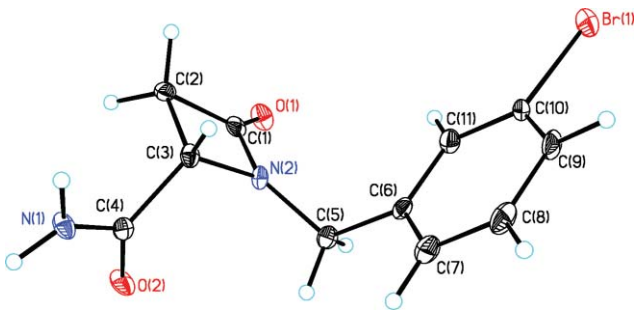
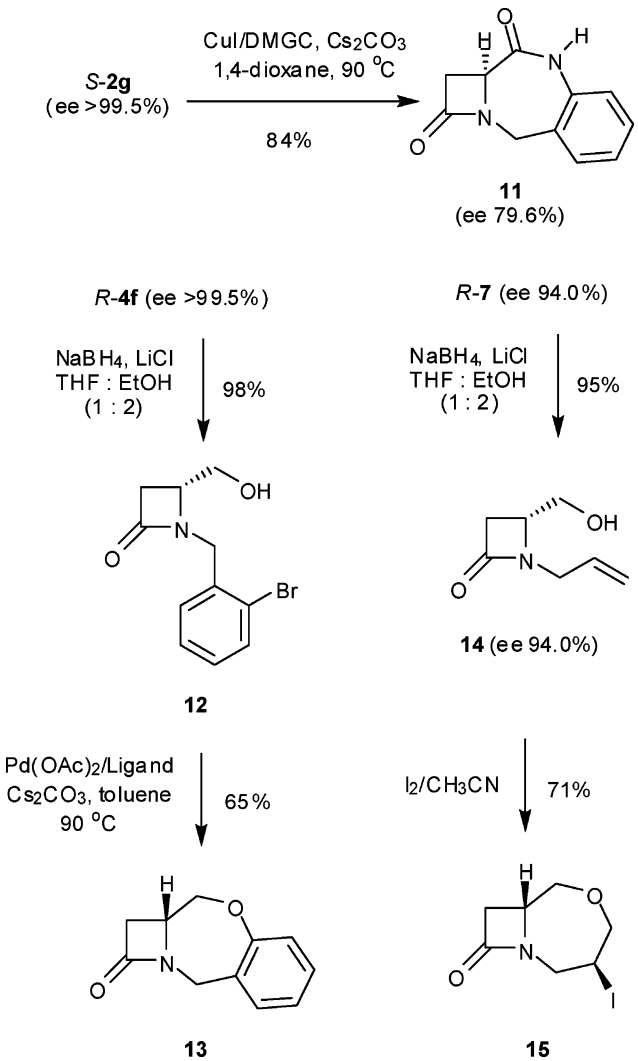


Fig. 1 X-Ray structure of *S*-**2e**.

β-Lactam products obtained from enantioselective nitrile and amide biotransformations are valuable chiral intermediates in organic synthesis. Their transformations into a wide variety of chiral compounds are conceivable according to previous studies.[1b,3,4] To demonstrate their synthetic usefulness, we attempted the synthesis of β-lactam-fused heterocycles that have potential pharmaceutical applications. As depicted in Scheme 3, CuI-catalyzed intramolecular cross coupling reaction[23] of *S*-1-(2-bromophenyl)methyl)-4-oxoazetidine-2-carboxamide *S*-**2g** produced *S*-1,10a-dihydroazeto[1,2-*a*]benzo[*e*][1,4]diazepine-2,10(4*H*,9*H*)-dione **11** in a good yield, albeit with partial racemization. Reduction of the ester group of *R*-**4f** and *R*-**7** with $NaBH_4$ led to the formation of alcohols **12** and **14** in almost quantitative yields. Catalyzed by $Pd(OAc)_2$ with a di-*tert*-butylphosphinobinaphthyl ligand under basic condition,[24] carbon–oxygen bond forming reaction was effected through intramolecular cross coupling reaction of **12** to furnish *R*-10,10a-dihydro-1*H*-azeto[2,1-*c*]benzo[*f*][1,4]oxazepin-2(4*H*)-one **13** in 65% yield. Intramolecular iodoetherification[25] of **14** afforded 3*S*,7*R*-3-iodo-5-oxo-1-azabicyclo[5.2.0]nonan-9-one **15** in 71% yield (Scheme 3). The structure of **15** was determined with X-ray crystallography (Fig. 2). Absolute *S*-configuration at 3-position



Scheme 3 Synthesis of β-lactam-fused heterocyclic compounds.

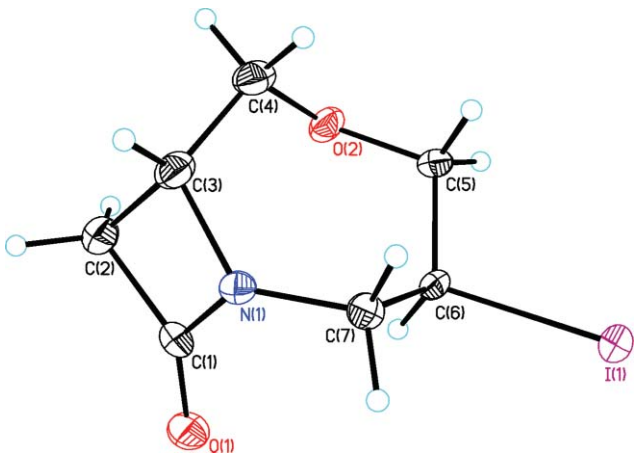


Fig. 2 X-Ray structure of **15**.

of the lactam ring revealed the *R*-enantioselectivity of the amidase against 1-allyl-4-oxoazetidine-2-carboxamide (Scheme 1). To the best of our knowledge, the types of β-lactam-fused seven-membered heterocyclic compounds **11**, **13** and **15** have not been reported. Not only do they stand as appealing scaffolds for

medicinal chemistry, they are also amenable to further chemical manipulations.

Conclusion

In summary, we have showed that biotransformations of racemic 1-arylmethyl- and 1-allyl-4-oxoazetidine-2-carbonitriles and carboxamides using *Rhodococcus erythropolis* AJ270, a nitrile hydratase and amidase containing microbial whole cell catalyst, under very mild conditions provided an efficient and high yielding method for the preparation of *S*-4-oxoazetidine-2-carboxamides and *R*-4-oxoazetidine-2-carboxylic acids with ee values up to >99.5%. The overall excellent enantioselectivity of nitrile biotransformations originated from a combined effect of a virtually non-enantioselective nitrile hydratase and a highly *R*-enantioselective amidase involved in *Rhodococcus erythropolis* AJ270. We have demonstrated that the resulting enantiopure β-lactam derivatives were useful chiral intermediates in organic synthesis, and they were readily converted into the β-lactam-fused heterocyclic compounds.

Experimental section

General procedure for the biotransformations of nitriles and amides

To an Erlenmeyer flask (150 mL) with a screw cap were added *Rhodococcus erythropolis* AJ270 cells[19] (2 g wet weight) and potassium phosphate buffer (0.1 M, pH 7.0, 50 mL), and the resting cells were activated at 30 °C for 0.5 h with orbital shaking. Racemic nitriles dissolved in acetone or racemic amide dissolved in methanol (see Tables 1–3) were added in one portion to the flask, and the mixture was incubated at 30 °C using an orbital shaker (200 rpm). The reaction, monitored by TLC or HPLC, was quenched after a specified period of time (see Tables 1–3) by removing the biomass through a Celite pad filtration. The resulting aqueous solution was extracted with ethyl acetate. After drying (Na_2SO_4) and removing the solvent under a vacuum, the residue of the organic phase was chromatographed on a silica gel column using a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure amide product **2** and recovered nitrile **1**. The aqueous phase was freeze-dried (–50 to –60 °C), and the residue was treated with CH_2N_2 in ether below –15 °C. When esterification was finished, the reaction was quenched by addition of some water and then extracted with ethyl acetate. After drying (Na_2SO_4) and removing the solvent under a vacuum, the pure methyl ester **4** was obtained. All new compounds were fully characterized as follows.

(*S*)-(–)-1-Benzyl-4-oxoazetidine-2-carboxamide (2a). Solid; mp 178.0–179.0 °C; IR (KBr) *ν* 3367, 3190, 1741, 1643 cm^{-1}; $[\alpha]_D^{25}$ –24° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.26–7.37 (m, 5H), 5.73 (s, 1H), 5.60 (s, 1H), 4.67 (d, *J* = 14.7 Hz, 1H), 4.21 (d, *J* = 15.0 Hz, 1H), 3.86 (dd, *J* = 2.4 Hz, 5.4 Hz, 1H), 3.27 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.01 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) *δ* 171.2, 166.1, 135.9, 128.6, 127.9, 127.4, 50.5, 44.7, 41.6; MS (ESI) *m*/*z* (%) 205 $[M+H]^+$, 227 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.46 H, 5.94; N, 13.73.

(*S*)-(–)-1-(4-Fluorobenzyl)-4-oxoazetidine-2-carboxamide (2b). Solid; mp 178.0–179.0 °C; IR (KBr) *ν* 3369, 3192, 1741, 1640 cm^{-1}; $[\alpha]_D^{25}$ –27° (*c* 0.15, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.23–7.28 (m, 2H), 7.02–7.08 (m, 2H), 5.70 (s, 1H), 5.56 (s, 1H), 4.66 (d, *J* = 14.7 Hz, 1H), 4.18 (d, *J* = 15.0 Hz, 1H), 3.84 (dd, *J* = 2.7 Hz, 5.7 Hz, 1H), 3.26 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.02 (dd, *J* = 2.4 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) *δ* 171.2, 166.1, 161.5 (d, *J* = 241.5 Hz, C-F), 132.2 (d, *J* = 3.0 Hz, C-F), 130.0 (d, *J* = 8.3 Hz, C-F), 115.3 (d, *J* = 21.0 Hz, C-F), 50.6, 44.1, 41.6; MS (ESI) *m*/*z* (%) 223 $[M+H]^+$ (10), 245 $[M+Na]^+$ (100). Anal. Calcd. for $C_{11}H_{11}FN_2O_2$: C, 59.45; H, 4.99; N, 12.61. Found: C, 59.11; H, 4.95; N, 12.50.

(*S*)-(–)-1-(4-Methylbenzyl)-4-oxoazetidine-2-carboxamide (2c). Solid; mp 197.0–198.0 °C; IR (KBr) *ν* 3365, 3189, 1741, 1662 cm^{-1}; $[\alpha]_D^{25}$ –32° (*c* 0.125, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.16 (s, 4H), 5.73 (s, 1H), 5.58 (s, 1H), 4.61 (d, *J* = 14.7 Hz, 1H), 4.18 (d, *J* = 15.0 Hz, 1H), 3.84 (dd, *J* = 2.4 Hz, 5.4 Hz, 1H), 3.25 (dd, *J* = 6.0 Hz, 14.7 Hz, 1H), 3.00 (dd, *J* = 1.8 Hz, 14.7 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) *δ* 171.2, 166.0, 136.5, 132.8, 129.1, 127.9, 50.3, 44.4, 41.6, 20.6; MS (ESI) *m*/*z* (%) 219 $[M+H]^+$ (5), 241 $[M+Na]^+$ (100). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.42; N, 13.00.

(*S*)-(–)-1-(4-Bromobenzyl)-4-oxoazetidine-2-carboxamide (2d). Solid; mp 179.0–180.0 °C; IR (KBr) *ν* 3367, 3188, 1741, 1662 cm^{-1}; $[\alpha]_D^{25}$ –53° (*c* 0.15, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.49 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.80 (s, 2H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.14 (d, *J* = 15.0 Hz, 1H), 3.84 (dd, *J* = 3.0 Hz, 5.1 Hz, 1H), 3.26 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.02 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) *δ* 171.1, 166.2, 135.4, 131.4, 130.2, 120.5, 50.7, 44.2, 41.6; MS (ESI) *m*/*z* (%) 305 $[M+Na]^+$, 307 $[M+2+Na]^+$. Anal. Calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.44; H, 3.97; N, 9.70.

(*S*)-(–)-1-(3-Bromobenzyl)-4-oxoazetidine-2-carboxamide (2e). Solid; mp 210.0–211.0 °C; IR (KBr) *ν* 3344, 3182, 1742, 1680 cm^{-1}; $[\alpha]_D^{25}$ –20° (*c* 0.2, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.43–7.47 (m, 2H), 7.20–7.26 (m, 2H), 5.65 (s, 1H), 5.48 (s, 1H), 4.69 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 15.3 Hz, 1H), 3.88 (dd, *J* = 2.4 Hz, 5.4 Hz, 1H), 3.29 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.04 (dd, *J* = 2.1 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) *δ* 171.1, 166.3, 138.9, 130.7, 130.5, 130.2, 126.9, 121.8, 50.8, 44.2, 41.7; MS (ESI) *m*/*z* (%) 283 $[M+H]^+$ (11), 285 $[M+H+2]^+$ (10), 305 $[M+Na]^+$ (100), 307 $[M+Na+2]^+$ (94). Anal. Calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.70; H, 3.96; N, 9.72. A single crystal of *S*-**2e** was obtained from slow evaporation of its solution in a mixture of petroleum ether and ethyl acetate (3 : 1).

(*S*)-(–)-1-(2-Bromobenzyl)-4-oxoazetidine-2-carboxamide (2f). Solid; mp 185.0–186.0 °C; IR(KBr) *ν* 3378, 3202, 1752, 1678 cm^{-1}; $[\alpha]_D^{25}$ –48° (*c* 0.125, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.58 (d, *J* = 8.1 Hz, 1H), 7.30–7.38 (m, 1H), 7.17–7.26 (m, 3H), 5.82 (s, 1H), 5.63 (s, 1H), 4.76 (d, *J* = 14.7 Hz, 1H), 4.42 (d, *J* = 15.0 Hz, 1H), 3.90 (dd, *J* = 2.4 Hz, 5.4 Hz, 1H), 3.28 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.02 (dd, *J* = 2.1 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.9, 166.7, 134.2, 133.3, 131.4, 130.2, 128.3, 124.1, 52.1, 46.4, 43.3; MS (ESI) *m*/*z* (%) 283 $[M+H]^+$ (11), 285 $[M+H+2]^+$ (10), 305 $[M+Na]^+$ (100), 307 $[M+Na]^+$ (94). Anal. Calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.64; H, 3.82; N, 9.52.

(*S*)-(−)-1-(4-Methoxybenzyl)-4-oxoazetidine-2-carboxamide (2g). Solid; mp 186.0–187.0 °C; IR(KBr) ν 3370, 3193, 1737, 1640 cm^{-1}; $[\alpha]_D^{25}$ −48° (*c* 0.125, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.78 (s, 1H), 5.67 (s, 1H), 4.59 (d, *J* = 14.7 Hz, 1H), 4.17 (d, *J* = 14.7 Hz, 1H), 3.82–3.84 (m, 1H), 3.80 (s, 3H), 3.24 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 2.99 (dd, *J* = 1.8 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 171.3, 166.0, 158.6, 129.3, 127.7, 114.0, 55.0, 50.1, 44.1, 41.5; MS (ESI) *m*/*z* (%) 235 $[M+H]^+$ (3), 257 $[M+Na]^+$ (100). Anal. Calcd. for $C_{12}H_{14}N_2O_3$:C, 61.53; H, 6.02; N, 11.96; Found: C, 61.57; H, 6.05; N, 11.90.

(*R*)-(+)-Methyl 1-benzyl-4-oxoazetidine-2-carboxylate (4a). Oil; IR (KBr) ν 1761 cm^{-1}; $[\alpha]_D^{25}$ +28° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.29 (m, 5H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 15.0 Hz, 1H), 3.86 (dd, *J* = 2.4 Hz, 5.7 Hz, 1H), 3.60 (s, 3H), 3.11 (dd, *J* = 5.7 Hz, 14.4 Hz, 1H), 2.94 (dd, *J* = 2.1 Hz, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.7, 134.8, 128.8, 128.5, 127.9, 52.4, 49.9, 45.7, 41.9; MS (EI) *m*/*z* (%) 219 $[M]^+$ (3), 191 (17), 160 (12), 132 (22), 91 (100). Anal. Calcd. for $C_{12}H_{13}NO_3$: 219.0895, Found: 219.0899.

(*R*)-(+)-Methyl 1-(4-fluorobenzyl)-4-oxoazetidine-2-carboxylate (4b). Oil; IR(KBr) ν 1760 cm^{-1}; $[\alpha]_D^{25}$ +28° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.27 (m, 2H), 7.00–7.06 (m, 2H), 4.69 (d, *J* = 15.0 Hz, 1H), 4.19 (d, *J* = 15.0 Hz, 1H), 3.94 (dd, *J* = 2.7 Hz, 5.7 Hz, 1H), 3.71 (s, 3H), 3.21 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.04 (dd, *J* = 2.4 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 165.7, 162.4 (d, *J* = 244.5 Hz, C-F), 130.7 (d, *J* = 3.8 Hz, C-F), 130.3 (d, *J* = 8.3 Hz, C-F), 115.7 (d, *J* = 21.8 Hz, C-F), 52.4, 50.0, 45.0, 41.9; MS (EI) *m*/*z* (%) 237 $[M]^+$ (3), 209 (17), 150 (19), 109 (100). Anal. Calcd. for $C_{12}H_{12}NO_3F$: 237.0801. Found: 237.0803.

(*R*)-(+)-Methyl 1-(4-methylbenzyl)-4-oxoazetidine-2-carboxylate (4c). Oil; IR (KBr) ν 1762 cm^{-1}; $[\alpha]_D^{25}$ +20° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.17 (m, 4H), 4.72 (d, *J* = 15.0 Hz, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.92 (dd, *J* = 2.7 Hz, 5.7 Hz, 1H), 3.70 (s, 3H), 3.19 (dd, *J* = 5.4 Hz, 14.4 Hz, 1H), 3.02 (dd, *J* = 1.8 Hz, 14.7 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.7, 137.7, 131.7, 129.5, 128.5, 52.4, 49.8, 45.4, 41.8, 21.1; MS (ESI) *m*/*z* (%) 233 $[M]^+$ (2), 205 (16), 190 (9), 174 (9), 146 (14), 105 (100). Anal. Calcd. for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1055.

(*R*)-(+)-Methyl 1-(4-bromobenzyl)-4-oxoazetidine-2-carboxylate (4d). Solid; mp 60.0–61.0 °C; IR (KBr) ν 1762 cm^{-1}; $[\alpha]_D^{25}$ +21° (*c* 0.3, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.67 (d, *J* = 15.3 Hz, 1H), 4.17 (d, *J* = 15.0 Hz, 1H), 3.94 (dd, *J* = 2.4 Hz, 5.4 Hz, 1H), 3.71 (s, 3H), 3.22 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.05 (dd, *J* = 2.1 Hz, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.7, 133.9, 132.0, 130.2, 122.0, 52.5, 50.0, 45.1, 42.0; MS (ESI) *m*/*z* (%) 298 $[M+H]^+$, 300 $[M+H+2]^+$. Anal. Calcd. for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.54; H, 4.19; N, 4.57.

(*R*)-(+)-Methyl 1-(3-bromobenzyl)-4-oxoazetidine-2-carboxylate (4e). Oil; IR (KBr) ν 1761 cm^{-1}; $[\alpha]_D^{25}$ +32° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.43 (m, 2H), 7.17–7.27 (m, 2H), 4.69 (d, *J* = 15.0 Hz, 1H), 4.18 (d, *J* = 15.0 Hz, 1H), 3.98 (dd, *J* = 2.7 Hz, 5.7 Hz, 1H), 3.72 (s, 3H), 3.25 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.07 (dd, *J* = 2.4 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.8, 137.2, 131.4, 131.1, 130.4, 127.1, 122.8, 52.5, 50.1, 45.1, 42.1; MS (EI) *m*/*z* (%) 297 $[M]^+$ (3), 299 $[M+2]^+$ (3), 238 (9), 240 (9), 210 (14), 212 (14), 169(100), 171(94). Anal. Calcd. for $C_{12}H_{12}BrNO_3$: 297.0001 $[M]^+$, 298.9980 $[M+2]^+$. Found: 297.0005 $[M]^+$, 298.9984 $[M+2]^+$.

(*R*)-(+)-Methyl 1-(2-bromobenzyl)-4-oxoazetidine-2-carboxylate (4f). Oil; IR (KBr) ν 1764 cm^{-1}; $[\alpha]_D^{25}$ +16° (*c* 0.5, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 1H), 7.28–7.31 (m, 2H), 7.15–7.21 (m, 1H), 4.79 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.00 (dd, *J* = 2.4 Hz, 5.7 Hz, 1H), 3.71 (s, 3H), 3.24 (dd, *J* = 5.7 Hz, 14.7 Hz, 1H), 3.02 (dd, *J* = 2.1 Hz, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.6, 134.3, 133.1, 131.1, 129.7, 127.9, 123.9, 52.4, 50.6, 45.9, 42.3; MS (ESI) *m*/*z* (%) 298 $[M+H]^+$, 300 $[M+H+2]^+$, 320 $[M+Na]^+$, 322 $[M+Na+2]^+$. Anal. Calcd. for $C_{12}H_{13}BrNO_3$: 298.0079 $[M+H]^+$, 300.0080 $[M+H+2]^+$, Found: 298.0090 $[M+H]^+$, 300.0071 $[M+H+2]^+$.

(*R*)-(+)-Methyl 1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxylate (4g). Oil; IR (KBr) ν 1759 cm^{-1}; $[\alpha]_D^{25}$ +24° (*c* 0.5, $CHCl_3$); ee 92.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.68 (d, *J* = 14.7 Hz, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.91 (dd, *J* = 2.7 Hz, 5.7 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.18 (dd, *J* = 5.7 Hz, 14.4 Hz, 1H), 3.01 (dd, *J* = 2.2 Hz, 14.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.6, 159.3, 129.9, 126.8, 114.2, 55.2, 52.3, 49.7, 45.0, 41.7; MS (EI) *m*/*z* (%) 249 $[M]^+$ (6), 221 (7), 190 (5), 162 (17), 121 (100). Anal. Calcd. for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1004.

(*S*)-(−)-1-Allyl-4-oxoazetidine-2-carboxamide (6). Solid; mp 100.0–101.0 °C; IR (KBr) ν 3351, 3181, 1742, 1679 cm^{-1}; $[\alpha]_D^{25}$ −28° (*c* 0.5, H_2O); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.69 (s, 1H), 7.26 (s, 1H), 5.70–5.83 (m, 1H), 5.13–5.21 (m, 2H), 3.92–3.97 (m, 2H), 3.50 (dd, *J* = 6.6 Hz, 15.9 Hz, 1H), 3.11 (dd, *J* = 5.4 Hz, 14.1 Hz, 1H), 2.70 (dd, *J* = 1.8 Hz, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 174.8, 170.2, 130.4, 119.3, 51.5, 44.6, 41.0; MS (ESI) *m*/*z* (%) 155 $[M+H]^+$. Anal. Calcd. for $C_7H_{10}N_2O_2$:C, 54.54; H, 6.54; N, 18.17; Found: C, 54.63; H, 6.30; N, 18.05.

(*R*)-(+)-Methyl 1-allyl-4-oxoazetidine-2-carboxylate (7). Oil; IR (KBr) ν 1762 cm^{-1}; $[\alpha]_D^{25}$ +34° (*c* 0.7, $CHCl_3$); ee 94.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.83 (m, 1H), 5.19–5.24 (m, 2H), 4.09–4.15 (m, 2H), 3.78 (s, 3H), 3.71 (dd, *J* = 6.9 Hz, 15.3 Hz, 1H), 3.23 (dd, *J* = 5.7 Hz, 14.4 Hz, 1H), 3.00 (dd, *J* = 2.1 Hz, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 165.7, 131.1, 119.2, 52.4, 50.2, 44.3, 41.9; MS (ESI) *m*/*z* (%) 170 $[M+H]^+$. Anal. Calcd. for $C_8H_{11}NO_3$: 192.06294 $[M+Na]^+$; Found: 192.06311 $[M+Na]^+$.

(*S*)-(−)-4-Oxo-1-propylazetidine-2-carboxamide (9). Solid; mp 85.0–86.0 °C; IR (KBr) ν 3359, 3183, 1741, 1678 cm^{-1}; $[\alpha]_D^{25}$ −80° (*c* 0.75, H_2O); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, D_2O) δ 4.17 (dd, *J* = 1.7, 5.0 Hz, 1H), 3.11–3.26 (m,

2H), 2.87–2.96 (m, 1H), 2.79 (d, J = 14.8 Hz, 1H), 1.33–1.50 (m, 2H), 0.75 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 174.8, 170.4, 51.5, 43.6, 40.7, 20.0, 10.7; MS (ESI) m/z (%) 157 $[M+H]^+$ (5), 179 $[M+Na]^+$ (100). Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94; Found: C, 53.65; H, 7.69; N, 17.72.

(*R*)-(+)-Methyl 4-oxo-1-propylazetidine-2-carboxylate (10). Oil; IR (KBr) ν 1759 cm^{-1}; $[\alpha]_D^{25}$ +96° (c 0.25, $CHCl_3$); ee 45.2% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (dd, J = 2.4, 5.4 Hz, 1H), 3.80 (s, 3H), 3.34–3.44 (m, 1H), 3.22 (dd, J = 5.4, 14.4 Hz, 1H), 3.03–3.13 (m, 1H), 2.99 (dd, J = 2.1 14.4 Hz, 1H), 1.48–1.69 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.0, 52.5, 50.6, 43.4, 41.8, 20.8, 11.5; MS (ESI) m/z (%) 172 $[M+H]^+$. Anal. Calcd. for $C_8H_{13}NO_3$: 171.0895 $[M]^+$; Found: 171.0897 $[M]^+$.

Synthesis of 11

Under argon protection, a mixture of *S*-**2g** (40 mg, 0.14 mmol), CuI (0.056 mmol, 11 mg), *N*,*N*-dimethylglycine hydrochloride (0.112 mmol, 16 mg), Cs_2CO_3 (0.28 mmol, 92 mg) and dry 1,4-dioxane (5 mL) was refluxed for 20 h. After cooling, ethyl acetate (15 mL) was added and the resulting mixture was filtered through a short silica gel (100–200 mesh) pad. The filtrate was concentrated and the residue was filtered with a silica gel column (100–200 mesh) and washed with ethyl acetate to give a crude product of **11**. The second silica gel (200–300 mesh) column chromatography eluted with a mixture of petroleum ether and ethyl acetate (1 : 1) gave pure product **11** (23 mg, 84%) as white solids; mp 166.0–167.0 °C; IR (KBr) ν 3203, 1762, 1660 cm^{-1}; $[\alpha]_D^{25}$ +241.5° (c 0.265, $CHCl_3$); ee 79.6% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.36–7.41 (m, 1H), 7.21–7.31 (m, 2H), 7.11–7.14 (m, 1H), 4.57 (d, J = 13.8 Hz, 1H), 4.47 (d, J = 13.8 Hz, 1H), 4.11 (dd, J = 1.8, 4.8 Hz, 1H), 3.43 (d, J = 15.0 Hz, 1H), 3.11 (dd, J = 4.8, 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 166.4, 136.6, 130.4, 129.6, 126.6, 126.4, 123.3, 50.6, 44.9, 39.1; MS (ESI) m/z (%) 203 $[M+H]^+$ (100), 225 $[M+Na]^+$ (99). Anal. Calcd. for $C_{11}H_{10}N_2O_2$:C, 65.34; H, 4.98; N, 13.85; Found: C, 65.00; H, 4.98; N, 13.57.

Synthesis of 13

To a solution of ester *R*-**4g** (104 mg, 0.35 mmol) in tetrahydrofuran (0.5 mL) was added anhydrous lithium chloride (30 mg, 0.7 mmol) and sodium borohydride (27 mg, 0.7 mmol). After addition of ethanol (1 mL), the mixture was stirred at room temperature for 1 h. The mixture was cooled with an ice-water bath, and water (1 mL) was then added. The mixture was extracted with ethyl acetate (3 × 5 mL). After drying (Na_2SO_4) and removing the solvent under vacuum, the residue of the organic phase was chromatographed on a silica gel (100–200 mesh) column using a mixture of petroleum ether and ethyl acetate (1 : 1) as the mobile phase to give pure product **12** (92 mg, 98%) as a white solid; mp 78.0–79.0 °C. IR(KBr) ν 3429, 1733 cm^{-1}; $[\alpha]_D^{25}$ +40° (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.9 Hz, 1H), 7.40 (dd, J = 1.4, 7.6 Hz, 1H), 7.30–7.35 (m, 1H), 7.15–7.18 (m, 1H), 4.66 (d, J = 15.4 Hz, 1H), 4.45 (d, J = 15.4 Hz, 1H), 3.76 (d, J = 11.6 Hz, 1H), 3.62–3.69 (m, 2H), 2.98 (dd, J = 4.8, 14.5 Hz, 1H), 2.87 (d, J = 13.7 Hz, 1H) 2.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 135.3, 133.1, 130.7, 129.6, 128.0, 123.5, 61.9, 52.7, 45.4, 38.9; MS (EI) m/z (%) 270 $[M+H]^+$ (8), 272 $[M+H+2]^+$ (7), 238 (9), 240 (6), 190 (100), 169 (39), 171 (35), 132 (60), 107 (54). Anal. Calcd. for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19; Found: C, 49.03; H, 4.48; N, 5.03.

Compound **13** was prepared from the Pd-catalyzed intramolecular coupling reaction of **12** following a literature procedure[24] Compound **13** was obtained as a white solid; mp 79.0–80.0 °C; IR(KBr) ν 1759 cm^{-1}; $[\alpha]_D^{25}$ +57° (c 1.4, $CHCl_3$); ee > 99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.23 (m, 2H), 7.05–7.09 (m, 2H), 4.73 (d, J = 15.8 Hz, 1H), 4.60 (dd, J = 3.6, 12.0 Hz, 1H), 4.20 (d, J = 15.8 Hz, 1H), 4.01–4.06 (m, 1H), 3.64 (dd, J = 9.6, 12.0 Hz, 1H), 3.10 (dd, J = 4.4, 14.7 Hz, 1H), 2.57 (dd, J = 1.8, 14.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 159.3, 130.3, 129.1, 129.0, 124.5, 122.5, 76.3, 51.7, 44.1, 40.0; MS (ESI) m/z (%) 190 $[M+H]^+$ (65), 212 $[M+Na]^+$ (100). Anal. Calcd. for $C_{11}H_{11}NO_2$: 189.0790; Found: 189.0793.

Synthesis of 15

Following the same procedure for the reduction of ester *R*-**4g**, *R*-**8** was converted to intermediate **14** (121 mg, 95%) as colourless oil; IR(KBr) ν 3402, 1734 cm^{-1}; $[\alpha]_D^{25}$ –44° (c 0.5, $CHCl_3$); ee 94.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76–5.89 (m, 1H), 5.20–5.29 (m, 2H), 3.96 (dd, J = 6.0, 15.9 Hz, 1H), 3.69–3.86 (m, 3H), 2.95 (dd, J = 4.8, 9.6 Hz, 1H), 2.77–2.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 132.4, 118.6, 62.2, 52.5, 43.9, 38.6; MS (ESI) m/z (%) 142 $[M+H]^+$ (78), 164 $[M+Na]^+$ (100). Anal. Calcd. for $C_7H_{11}NO_2$: 141.0790 $[M]^+$. Found: 141.0792 $[M]^+$.

A solution of **14** (70.5 mg, 0.5 mmol) in acetonitrile (1 mL) at 25 °C was treated with iodine (0.25 g, 1 mmol) and stirred overnight. The reaction mixture was diluted with ethyl acetate (5 ml), and then washed twice with a saturated solution of sodium bisulfite. The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. Chromatography on a silica gel (200–300 mesh) column eluting with a mixture of petroleum ether and ethyl acetate (3 : 1) gave product **15** (95 mg, 71%) as a while solid; mp 46.0–47.0 °C; IR(KBr) ν 1738 cm^{-1}; $[\alpha]_D^{25}$ –140° (c 1.0, $CHCl_3$); ee 94.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17–4.30 (m, 3H), 4.10 (d, J = 13.5 Hz, 1H), 3.84 (s, 1H), 3.73 (dd, J = 3.6, 13.5 Hz, 1H), 3.42–3.50 (m, 1H), 2.99–3.14 (m, 2H), 2.75 (dd, J = 2.1, 14.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 80.7, 72.9, 52.9, 49.8, 40.9, 23.4; MS (ESI) m/z (%) 268 $[M+H]^+$ (6), 290 $[M+Na]^+$ (100). Anal. Calcd. for $C_7H_{10}INO_2$: C, 31.48; H, 3.77; N, 5.24. Found: C, 31.85; H, 3.86; N, 5.23.

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