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A highly enantioselective chemoenzymatic synthesis of *syn*-3-amino-2-hydroxy esters: key intermediates for taxol side chain and phenylnorstatine

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Abstract—Starting from the bromination of α-ketoesters to obtain 3-bromo-2-oxoalkanoates and bioreduction with *Saccharomyces cerevisiae* entrapped in calcium alginate pellets with double gel layers, *syn*-(2*R*,3*S*)-β-bromo-α-hydroxy esters were obtained regioselectively in high yields and high ee. These chiral bromohydrins were cyclized to epoxides that were transformed into oxazolidines and finally opened by acidic hydrolysis to give *syn*-(2*S*,3*S*)-β-amino-α-hydroxy esters in high overall yields and high ee. The enantiomeric excesses of all the intermediates were maintained during the reaction sequence.

1. Introduction

In recent years, the enantioselective syntheses of β-amino-α-hydroxy acids, amides and esters have attracted much attention not only because of the synthetic interest but mainly due to their presence in various medicinally important molecules.[1] The importance of Taxol,[2] a complex diterpene, in cancer therapy is well established.[3] Initially, its only source was from the bark of the pacific yew tree, *Taxus brevifolia*, which cannot be considered a renewable resource because of its slow growth and, therefore, the supply of Taxol was quite limited. On the other hand, the key terpenoid fragment 10-deacetylbaccatin III (10-DAB) is readily obtained from a rapidly renewable resource, the yew bush: *Taxus baccata*.[4] Since the initial work by Potier,[5] a number of methods have been developed to convert 10-DAB to Taxol, all of which rely on the coupling of a protected phenylisoserinate to a 7-protected baccatin derivative.[6] As the side chain is not readily available from natural sources, its sole supply is from chemical synthesis. While several approaches have been published, only a few examples are enzyme-resolution-based syntheses.[7] β-Amino-α-hydroxy acid derivatives are also found in a renin inhibitor for hypertension, as a transition state mimics, including KRI 1314,[8] and some inhibitors of FIV and HIV proteases.[9] Herein, we report the preparation of 3-bromo-2-ketoalkanoates and their bioreduction with *Saccharomyces cerevisiae* to obtain the corresponding (2*S*,3*S*)-3-bromo-2-hydroxyalkanoates with high ee and yields, followed by a highly efficient transformation to *syn*-(2*R*,3*S*)-3-acylamino-2-hydroxyalkanoates. Earlier, two groups have reported yeast catalyzed reductions of α-ketoesters to produce chiral α-hydroxy esters to use in a sequence route to obtain the Taxol side chain.[10] However, the overall yields were both inferior to these from the procedure described herein and they are not of general applicability to allow the preparation of other analogues, such as phenylnorstatine.

2. Results and discussion

Bromination of ethyl 2-oxophenylbutanoate **1b** was carried out with a solution of bromine in chloroform at room temperature for 3 h to give ethyl 3-bromo-2-oxobutanoate **2b** as a yellow oil in 97% yield, after purification by silica gel column chromatography. The bromination procedure was extended to α-ketoesters **1a**, **1c**, and **1d** to obtain the bromo derivatives in high yields (Scheme 1). Bioreduction of 3-bromo-2-oxoalkanoates **2a**–**d** was carried out by *S. cerevisiae* entrapped in calcium alginate pellets with double gel layers under

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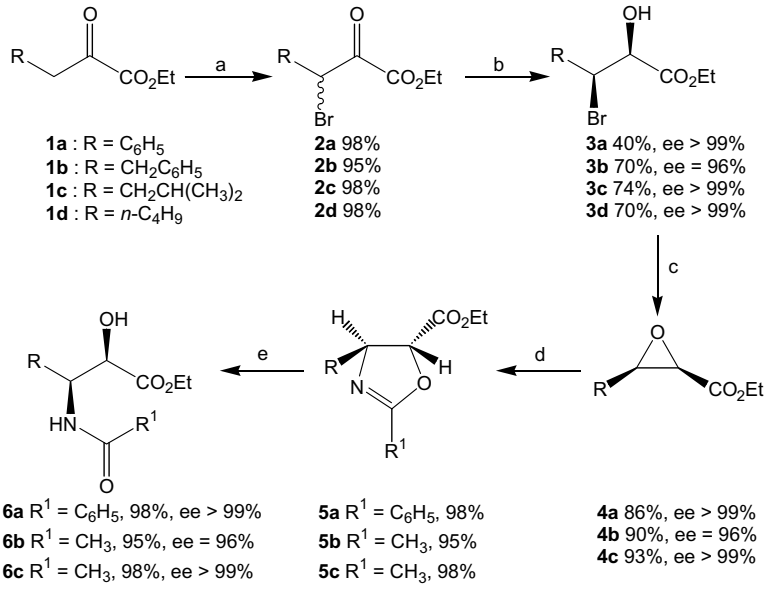


Scheme 1. Reagents and conditions: (a) Br_2, $CHCl_3$, room temp, 1 h; (b) *S. cerevisiae* entrapped in Ca-alginate pellets with double gel layers, pH 4, 30 °C, 24 h; (c) K_2CO_3, EtOH, 12 h; (d) $BF_3{\cdot}Et_2O$, R^1CN ($R^1 = C_6H_5$ or CH_3), room temp, 3 h; (e) (i) HCl–MeOH, 1.5 h; (ii) $NaHCO_3$, 16 h.

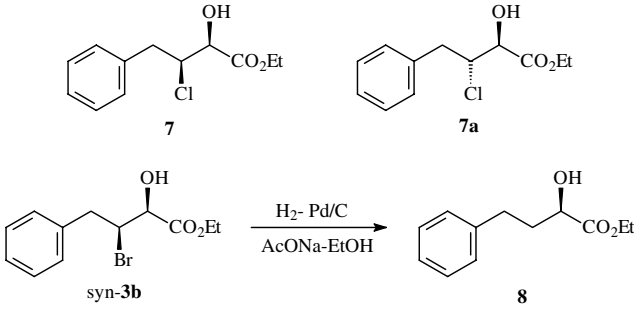
Table 1. Bioreduction of ethyl 3-bromo-2-oxoalkanoates mediated by *Saccharomyces cerevisiae* entrapped in calcium alginate pellets with double gel layers

Compound	Yield (%)	Ratio	ee%		$[\alpha]_D^{20}$	
		syn/*anti*	*syn*	*anti*	*syn*	*anti*
2a[a]	40	100/0	>99	—	+42.0	
2b[b]	82	85/15	96	99	−16.8	−18.8
2c[b]	87	90/10	>99	>99	+3.8	+6.4
2d[b]	93	75/25	>99	>99	−18.1	+3.6

Reagents and conditions: (a) *S. cerevisiae* (30 g), buffer citrate, pH 4 (400 mL, 0.5 mol L^{-1}), substrate (2.2 mmol), glucose (30 g), agitated for 24 h; after each 6 h more glucose (6 g) was added; (b) *S. cerevisiae* (5 g), buffer citrate, pH 4 (400 mL, 0.5 mol L^{-1}), substrate (2.2 mmol), glucose (8 g); after every 6 h more glucose (1.6 g) was added.

optimized conditions to give the *syn*-bromo alcohols as major compounds in excellent ee (Table 1).

Screenings of several fungi and bacteria were carried out in order to find an ideal biocatalyst for the bioreduction. From them, we chose *S. cerevisiae* due to the ease of use and the high regio- and diastereoselectivity of the desired *syn*-product. The relative configuration of *syn*-**2b** was established by comparison with the known ethyl (2*S*,3*S*)-3-chloro-2-hydroxy-4-phenylbutanoate[11] while the absolute configuration was determined by hydrogenolysis with H_2 in the presence of Pd/C 5% of the *syn*-**3b** to give the known ethyl (−)-(2*R*)-2-hydroxy-4-phenylbutanoate **8** in 95% yield {$[\alpha]^{20} = -32.5$ (*c* 2.0, $CHCl_3$)} (Scheme 2).[12] Bioreduction of ethyl 3-chloro-2-oxobutanoate by *S. cerevisiae* entrapped in alginate pellets with double gel layers gave ethyl (2*S*,3*S*)-3-chloro-hydroxybutanoate **7** (85% ee) and its epimer, the (2*S*,3*R*)-derivative **7a** (>99% ee; ratio **7**/**7a** = 30:70) in 85% yield. ^1H NMR coupling constants for 2-H and 3-H for *syn*-**7** (δ 4.44, $J_{2,3} = 1.8$ Hz) and *anti*-**7a** (δ 4.24, $J_{2,3} = 2.6$ Hz) have the same H as for *syn*-**3b** (δ 4.50, $J_{2,3} = 1.8$ Hz) and *anti*-**3b** (δ 4.46, $J_{2,3} = 2.6$ Hz), confirming the proposed absolute configuration for **3b** (^1H NMR and ^{13}C NMR values matched those reported in the literature[11]) and by extension for **3a**, **3c**, and **3d**.

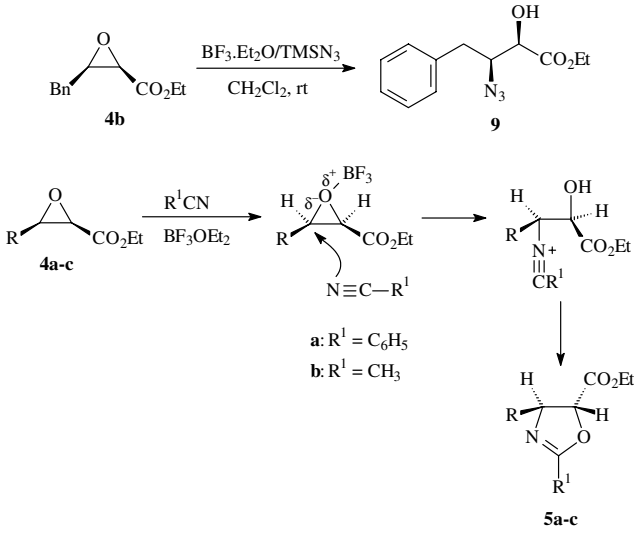


Scheme 2.

Attempts to substitute the bromide of bromohydrin **3b** by azide to obtain the corresponding azido alcohol to be reduced in the sequence to the amino alcohol were unproductive. The isolated product was always the 2,3-epoxyester **4b**, independent of the azide, solvent, and temperature (10–50 °C) used. Also unsuccessful

was the substitution of the bromo with an azide in alcohol **3b** protected with ethyl chloroformate. To overcome these difficulties in preparing the azidoalcohol, we decided to study a route via the epoxide. After many attempts with different bases, such as KOH, KOH/tetrabutylammonium chloride, NaOEt in EtOH and NaH, the most successful procedure was with ethanol in K_2CO_3 at room temperature for 12 h, which gave the 2,3-epoxide **4** in high yield (Scheme 1). The configuration of *cis*-**4b** was established by comparison of the coupling constant $J_{2,3} = 4.8$ Hz for H-2 at δ 3.58 ppm with similar data reported by Hoffman et al. for the racemic compound.[13]

Two methodologies were evaluated to obtain β-amino-α-hydroxy ester. Initially, we opened the epoxyester **4b** by employing a procedure developed by Behrens and Sharpless[14] using NaN_3/NH_4Cl, with a modification of the solvent mixture changing from dimethoxyethane to reflux for 5 h in ethanol–water, which has a lower bp in order to preserve the azide integrity. Azido alcohol **9** was obtained in 80% yield with a minor isomer, ethyl 2-azido-3-hydroxy-4-phenylbutanoate (identified by GC–MS), which we were unable to purify. Considering that Lewis acids have been used to open epoxyamides[14] and epoxyalcohols,[15] we employed $TMSN_3$ in the presence of boron trifluoride–diethyl etherate in dichloromethane at room temperature for 3 h to give **9** in 90% yield. The *cis*-configuration of **9** was established by comparison of the coupling constant $J_{2,3} = 1.8$ Hz for H-2 at δ 4.10 ppm, which is consistent with the data reported by Hoffman et al. for the racemic compound.[13] Pearson and Hines reduced the azido with H_2 in the presence of Pd/C to obtain the corresponding amino alcohol in 86% yield after 48 h. This product is an advanced intermediate for the synthesis of (−)-bestatin.[16] For the synthesis of aliphatic β-amino-α-hydroxy carboxylic esters such as **6c**, the pathway via azido alcohols, obtained by reaction of oxiranecarboxylic esters with azide ions, cannot be used because of a lack of regioselectivity of this epoxide opening.[17] In the search for an alternative approach, we employed the procedure developed by Zwanenburg, which converted the oxiranecarboxylic esters into oxazoline-5-carboxylic esters by a Ritter-type reaction with acetonitrile or benzonitrile.[18] Treatment of **4b** with acetonitrile in the presence of 2 equiv of boron trifluoride etherate at room temperature for 3 h produced oxazoline **5b** in 95% yield. The same reaction with **4c** gave oxazoline **5c** in 98% yield. Changing acetonitrile for benzonitrile, and employing the same conditions, we isolated oxazoline **5a** in 98% yield from epoxide **4a**. The structures of oxazolines **5** were established on the basis of their ^{1}H NMR spectra. The coupling constants of C4-H and C5-H of 6.6 Hz are reliable evidence for the *trans* relationships of these hydrogens as demonstrated by Botta[19] and Tasic.[20] No trace of *cis*-oxazoline could be detected. The spectra revealed that the nitrile had reacted regioselectively at C3 of the epoxide. The mechanistic pathway to the ring expanded products has been proposed by Zwanenburg[18] and also by Wohl.[21] Initial opening of the epoxide by the nitrile at C3 in an S_N2 fashion produced a nitrilium ion that undergoes an intramolecular ring closure reaction (Scheme 3).



Scheme 3.

Successful ring opening of the oxazolines was obtained using oxalic acid in boiling ethanol[22] and HCl in refluxing methanol.[19] To avoid loss of stereochemical integrity, we used less harsh conditions avoiding high temperatures. Treatment of oxazolines with HCl in methanol at 25 °C for 1.5 h gave the amino alcohols **6** in good yields (>95%) and excellent ee (>96%). The ring opening is an easy process since chloroform solutions of the oxazolines spontaneously evolved into the *N*-acetyl-aminohydroxy derivatives in one week at 25 °C. The structures of **6** were established on the basis of their ^{1}H NMR spectra. The coupling constants of C2-H and C3-H of ca. 2 Hz are reliable evidence for the *cis*-relationships of these hydrogens. It should be noted that the enantiomeric excesses of **6a–c** were maintained during the reaction sequence from bromohydrins, since they are identical to **3a–c**.

The easy accessibility of both masked *syn*-β-amino-α-hydroxy esters **5a–c** and the *N*-acetyl protected *syn*-β-amino-α-hydroxy ester **6a–c**, formed by the present enantioselective α-amination methodology, shows the applicability of this sequence. These *syn*-β-amino-α-hydroxy ester fragments are present in many different important compounds of pharmaceutical interest, such as the renin inhibitor KRI 1314, inhibitors of FIV and HIV proteases, and the side chain of Taxol analogues.[23] Other reports[24] have used oxazoline intermediate **5a** to prepare the Taxol side chain, but most did not prepare it directly by the epoxide intermediate **4a**, which makes these routes longer. Others have employed the epoxide **4a**, but did not transform it directly to **6a** via oxazoline **5a**,[25] which also increases the number of steps, when compared with the sequence described herein.

3. Conclusion

In conclusion, we have developed a highly enantioselective route to 3-amino-2-keto esters by a biocatalytic

asymmetric reduction of 3-bromo-2-keto esters. The reaction gives an easy entry to optically active masked *syn*-(2*R*,3*S*)-3-amino-2-hydroxy esters in high overall yield and excellent ee.

4. Experimental

All reagents and solvents were obtained from commercial sources. Ethyl acetate, hexane, and chloroform were distilled under argon before use. The solvents, dichloromethane and methanol, were distilled under argon from suspensions over calcium hydride and calcium oxide, respectively. Acetonitrile was distilled from calcium hydride and benzonitrile was dried over molecular sieves. Thin layer chromatographic (TLC) analyses were performed with precoated aluminum sheets (silica gel 60 Merck), while flash column chromatography was carried out on silica (200–400 mesh, Merck). IR spectra were recorded on a FT-IR BOMEM MB-100 from Hartmann and Braun. ^{1}H NMR spectra were determined at 300 (Varian Gemini 300) or 500 MHz (INOVA-500), and ^{13}C NMR spectra were determined at 75.5 MHz (Varian Gemini 300) or 125.7 MHz (INOVA 500). Chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) in $CDCl_3$. Gas chromatographic analyses and mass spectra were obtained on a QP 5000-SHIMADZU or an AGILENT GC 6890/HEWLETT PACKARD 5973, equipped with a J&W Scientific HP-5 (5% phenylmethylpolysiloxane, 30.0 m × 250 μm × 0.25 μm) column. Gas chromatographic analyses of reaction mixture samples were made after evaporation and dilution with ethyl acetate. High-resolution mass spectra were determined on a VG AUTO SPEC from Micromass. Optical rotations were measured with a Perkin Elmer Polarimeter 341. Melting points were measured on a Microquimica MQ APF-301 apparatus.

4.1. Bromination of 2-ketoesters

A solution of 2-oxoketoesters **1a**–**c** (24.2 mmol) in chloroform (7 mL) was added slowly to a solution of bromine in carbon tetrachloride (1.06 mol L^{-1}) until the color of the solution became red-orange. The excess of bromine was destroyed with a saturated sodium thiosulfate solution and the reaction mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, then filtered, and evaporated. The crude material was purified by flash chromatography and eluted with 20% ethyl acetate in hexane.

4.1.1. Ethyl 3-bromo-2-oxophenylbutanoate 2a. Pale yellow oil, 97% yield; ^{1}H NMR values matched those reported in the literature.[26]

4.1.2. Ethyl 3-bromo-2-oxophenylpropanoate 2b. Pale yellow oil, 95% yield; ^{1}H NMR values matched those reported in the literature.[27]

4.1.3. Ethyl 3-bromo-5-methyl-2-oxohexanoate 2c. Pale yellow oil, 95% yield; ^{1}H NMR values matched those reported in the literature.[27]

4.1.4. Ethyl 3-bromo-2-oxoheptanoate 2d. Pale yellow oil, 95% yield; ^{1}H NMR values matched those reported in the literature.[27]

4.2. General procedure for the reduction mediated by *S. cerevisiae* entrapped in calcium alginate pellets of double gel layers

To a suspension of *S. cerevisiae* (5 g) in distilled water (50 mL) was added a 3% solution of sodium alginate and the mixture extruded using syringe nozzles with inner diameters of 1.0 mm to a solution of $CaCl_2$ (0.2 mol L^{-1}) to give beads with 3 mm diameter. After 20 min, the beads were filtered and surface dried, using filter papers. Afterwards, the calcium alginate beads were transferred into 400 mL of stirred 1.5% sodium alginate. After 20 min, the beads were sieved, washed with water, and hardened for 2 h in a solution of $CaCl_2$ (0.2 mol L^{-1}). The beads with double gel layers were washed with water to remove excess $CaCl_2$. In a 500 mL bioreactor, the beads were suspended in citrate–phosphate buffer (300 mL, pH 4.0) containing glucose (8 g) and stirred at 300 rpm at 30 °C. After activation of the yeast for 2 h, the pH of the medium was adjusted with a 10% solution of NH_4OH and the substrates **2a**–**d** (2.2 mmol in 5.0 mL of ethanol), then slowly added over 10 h, with stirring. Every 6 h, glucose (1.6 g) was added. The reaction was monitored by GC–MS and, at the end of the reaction (24 h), the beads were filtered, washed with ethyl acetate, and the reaction mixture extracted with ethyl acetate, dried over anhydrous $MgSO_4$, then filtered, and evaporated. The crude material was purified by flash chromatography and eluted with 20% of ethyl acetate in hexane.

4.2.1. Ethyl (2*S*,3*S*)-3-bromo-2-hydroxyphenylpropanoate 3a. White solid, mp 84–87 °C. $[\alpha]_D^{20} = +42.0$ (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3503, 2946, 2919, 2890, 1717, 1450, 1361, 1284, 1250, 1025 cm^{-1}; MS *m*/*z* (%): 272 (1), 254 (10), 228 (1), 201 (3), 193 (30), 169 (52), 119 (48), 103 (10), 91 (100), 77 (8), 65 (11), 51 (8); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, *J* 7.3 Hz), 4.33 (2H, m), 4.46 (1H, dd, *J* 2.2 and 7.3 Hz, H-3), 5.37 (1H, d, *J* 2.3 Hz, H-2), 7.32 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8 (CH_3), 56.3 (CH, C-3), 63.2 (CH_2), 74.8 (CH, C-2), 128.9 (CH, aromatic), 130.0 (2CH, aromatic), 130.1 (CH, aromatic), 133.5 (C, C-4), 160.3 (C=O); HRMS: calcd for $C_{11}H_{13}BrO_3$: 272.00481; found: 271.99918.

4.2.2. Ethyl (2*S*,3*S*)-3-bromo-2-hydroxyphenylbutanoate 3b. Colorless oil, $[\alpha]_D^{20} = -16.8$ (*c* 2.1, $CHCl_3$); IR (film) ν_{max}: 3503, 3066, 3027, 2983, 2929, 1732, 1596, 1499, 1455, 1367, 1256, 1110, 1017, 740, 701 cm^{-1}; MS *m*/*z* (%): 206 (2), 189 (15), 177 (1), 161 (5), 143 (15), 133 (51), 115 (66), 91 (100), 77 (15), 55 (20), 51 (15); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* 7.1 Hz, H-12), 3.32 (2H, m, H-4), 4.14 (1H, d, *J* 1.8 Hz, H-2), 4.26 (2H, m, H-11), 4.50 (1H, dt, *J* 1.8 and 8.1 Hz, H-2), 7.26 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8 (CH_3), 42.4 (CH_2, C-4), 56.9 (CH, C-3), 62.9 (CH_2, OCH_2), 71.5 (CH, C-2), 127.6 (CH, aromatic), 129.1 (2CH, aromatic), 129.7 (2CH, aromatic), 138.0

(C, aromatic), 172.2 (C=O). HRMS: calcd for $C_{12}H_{15}BrO_3$: 286.02046; found: 286.02051.

4.2.3. (2*S*,3*S*)-3-Bromo-2-hydroxy-5-methylhexanoate 3c. Colorless oil, $[\alpha]_D^{20} = +3.8$ (*c* 1.5, $CHCl_3$); IR (film) ν_{max}: 3430, 2958, 2908, 2820, 1733, 1027 cm^{-1}; MS *m*/*z* (%): 181 (21), 173 (5), 163 (17), 155 (36), 99 (55), 81 (100), 69 (18), 57 (60); ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, d, *J* 7.3 Hz, H-6), 0.97 (3H, d, *J* 7.3 Hz, H-7), 1.33 (3H, m, H-9), 1.4–2.3 (3H, m, H-4 and H-5), 3.16 (1H, d, *J* 7.3 Hz, OH), 4.22 (2H, dd, *J* 1.8 and 7.3 Hz, H-2), 4.32 (2H, m, H-8), 4.42 (ddd, 1H, *J* 1.8, 5.2, and 10.1 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3, C-9), 21.4 (CH_3, C-7), 22.6 (CH_2, C6), 26.1 (CH_2, C-5), 44.1 (CH_2, C-4), 55.9 (CH, C-3), 62.4 (CH_2, C-8), 73.1 (CH, C-2), 171.8 (C=O). HRMS: calcd for $C_9H_{17}BrO_3$: 252.03611; found: 252.03605.

4.2.4. Ethyl (2*S*,3*S*)-3-bromo-2-hydroxyoctanoate 3d. Colorless oil, $[\alpha]_D^{20} = -18.1$ (*c* 1.6, $CHCl_3$); IR (film) ν_{max}: 3440, 2958, 2908, 2890, 2820, 1737, 1055 cm^{-1}; MS *m*/*z* (%): 207 (2), 181 (30), 163 (18), 155 (52), 127 (15), 99 (35), 81 (100), 75 (12), 57 (61); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* 7.3 Hz, H-7), 1.31 (7H, m, H-5, H-6, and H-9), 1.30–2.00 (4H, m, H-4 and H-6), 4.20–4.40 (2H, m, H-2 and H-3), 4.27 (2H, q, *J* 7.2 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3, C-9); 14.1 (CH_3, C-7), 22.1 (CH_2, C6), 29.9 (CH_2, C-5). 35.4 (CH_2, C-4); 57.5 (CH, C-3), 62.4 (CH_2, C-8), 72.8 (C-2), 171.9 (C=O). HRMS: calcd for $C_9H_{17}BrO_3$: 252.03611; found: 252.03604.

4.2.5. Ethyl 3-chloro-2-hydroxy-4-phenylbutanoates 7a and 7b. The reduction of 3-chloro-2-oxo-4-phenylbutanoate was carried out by the procedure described above for **2a**–**d**. The crude products were separated by flash chromatography and eluted with hexane/ethyl acetate (5:1). IR and ^1H NMR values matched those reported in the literature for **7a** and **7b**.[11]

4.3. General procedure to obtain the oxiranes 4a–c

To a 50 mL double-necked round bottomed flask with a $CaCl_2$ drying tube were added bromohydrin **3** (0.3 mmol), dry ethanol (10 mL), and potassium carbonate (0.58 g, 0.42 mmol). After 2.5 h, K_2CO_3 (30 mg) was added and the reaction kept at room temperature for 7 h. Water (100 mL) was then added and the reaction extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by flash chromatography and eluted with 20% ethyl acetate in hexane.

4.3.1. Ethyl (2*R*,3*R*)-3-phenyl-2,3-oxiranepropanoate 4a. Colorless oil, $[\alpha]_D^{20} = +15.0$ (*c* 1.8, $CHCl_3$); IR (film) ν_{max}: 3015, 2978, 2951, 2919, 2880, 1733, 1455, 1361, 1046 cm^{-1}; MS *m*/*z* (%): 192 (12), 176 (8), 146 (14), 135 (85), 118 (39), 107 (46), 91 (100), 79 (42), 65 (19), 55 (11); ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, t, *J* 7.3 Hz), 3.83 (1H, d, *J* 4.8 Hz, H-3), 4.11 (2H, m), 4.27 (1H, d, *J* 4.8 Hz, H-2), 7.24 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (CH_3, C-11), 57.2 (CH, C-3), 58.3 (CH, C-2), 62.2 (CH_2, aromatic), 126.3 (CH, aromatic), 129.1 (2CH, aromatic), 129.4 (CH, aromatic), 135.4 (C, aromatic), 168.6 (C=O).

4.3.2. Ethyl (2*R*,3*R*)-4-phenyl-2,3-oxiranebutanoate 4b. Pale yellow oil, $[\alpha]_D^{20} = +4.2$ (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3458, 3062, 3028, 2930, 1733, 1603, 1496, 1455, 1379, 1253, 1197, 1094, 1031, 701, 697 cm^{-1}; MS *m*/*z* (%): 206 (2), 188 (1), 177 (5), 161 (3), 143 (15), 133 (100), 115 (33), 103 (33), 91 (40), 77 (35), 65 (20); ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* 7.3 Hz), 2.90 (1H, dd, *J* 6.6 and 14.6 Hz, H-4), 3.10 (1H, dd, *J* 6.5 and 14.3 Hz, H-4), 3.38 (1H, td, *J* 6.6 and 4.8 Hz, H-3), 3.58 (1H, d, *J* 4.8 Hz, H-2), 4.30 (2H, q, *J* 7.3 Hz, aromatic), 7.23 (5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 33.8 (CH_2, C-4), 52.8 (CH, C-3), 57.7 (CH, C-2), 61.6 (CH_2), 126.8 (CH, aromatic), 128.7 (2CH, aromatic), 128.9 (2CH, aromatic), 136.5 (C, aromatic), 168.2 (C=O).

4.3.3. Ethyl (2*R*,3*R*)-5-methyl-2,3-oxirane-hexanoate 4c. Colorless oil, $[\alpha]_D^{20} = -3.0$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2953, 2949, 2920, 1752, 1183, 1016 cm^{-1}; MS *m*/*z* (%): 157 (15), 144 (12), 139 (1), 129 (20), 115 (50), 99 (45), 85 (100), 81 (42), 69 (90), 55 (60); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, d, *J* 7.3 Hz, H-6), 0.99 (3H, d, *J* 7.3 Hz, H-7), 1.31 (3H, m, H-9), 1.33–1.87 (3H, m, H-4 and H-5), 3.19 (1H, m, H-3), 3.51 (2H, d, *J* 4.7 Hz, H-2), 4.27 (2H, q, *J* 7.2 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (CH_3, C-9), 22.6 (CH_3, C-7), 23.1 (CH_2, C6), 26.7 (CH_2, C-5), 36.2 (CH_2, C-4), 53.1 (CH, C-3), 53.1 (CH, C-2), 61.8 (CH_2, C-8), 168.8 (C=O). HRMS: calcd for $C_9H_{16}O_3$: 172.10995; found: 172.10975.

4.4. General procedure to obtain 4,5-dihydrooxazoles 5a–c

To a solution of oxiranes **4a**–**c** (0.3 mmol) in anhydrous acetonitrile or benzonitrile (1 mL) under argon was added $BF_3{\cdot}Et_2O$ (0.2 mL) and the reaction kept at room temperature for 4 h. The solvent was evaporated and the residue dissolved with ether (5 mL) and neutralized with a 10% solution of sodium bicarbonate. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by flash chromatography and eluted with 15% ethyl acetate in hexane.

4.4.1. Ethyl (4*S*,5*R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylate 5a. Brown oil, $[\alpha]_D^{20} = +20.0$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3017, 3005, 2958, 2923, 2222, 1752, 1654, 1455, 1361, 1016, 970 cm^{-1}; MS *m*/*z* (%): 222 (100), 194 (11), 193 (66), 166 (4), 165 (15), 145 (2), 132 (2), 119 (20), 105 (72), 89 (93), 91 (89), 77 (70), 65 (50), 51 (60); ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, t, *J* 7.3 Hz), 4.33 (2H, m), 4.88 (1H, d, *J* 6.6 Hz, H-4), 5.43 (1H, d, *J* 6.6 Hz, H-5), 7.24 (10H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (CH_3), 62.3 (CH_2), 73.9 (CH, C-4), 75.1 (CH, C-5), 126.9–133.1 (CH, aromatic), 141.0 (C, aromatic), 170.6 (C,

heterocyclic), 178.1 (C=O). HRMS: calcd for $C_{18}H_{17}NO_3$: 295.12084; found: 295.12071.

4.4.2. Ethyl (4*S*,5*R*)-4-benzyl-2-methyl-4,5-dihydrooxazole-5-carboxylate 5b. Brown oil, $[\alpha]_D^{20} = -14.5$ (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 2923, 1774, 1759, 1738, 1496, 1455, 1367, 1247, 1220, 701, 698 cm^{-1}; MS *m*/*z* (%): 247 (3), 206 (5), 188 (1), 174 (10), 156 (42), 144 (5), 133 (10), 112 (20), 103 (10), 84 (100), 77 (20), 65 (20), 43 (33); ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, *J* 7.3 Hz), 2.02 (3H, s, H-1), 2.84 (1H, dd, *J* 14.0 and 7.0 Hz), 3.05 (1H, dd, *J* 14.0 and 7.0 Hz), 4.11 (2H, q, *J* 7.0 Hz), 4.40 (1H, m, H-5), 4.51 (1H, d, *J* 6.6 Hz, H-5), 7.23 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 14.4 (CH_3, C-1), 42.0 (CH_2), 62.3 (CH_2), 72.9 (CH, C-4), 80.7 (CH, C-5), 129.7 (CH, C-11), 128.3 (2CH, aromatic), 130.1 (2CH, aromatic), 137.8 (C, heterocyclic), 171.4 (C=O). HRMS: calcd for $C_{14}H_{17}NO_3$: 247.12084; found: 247.12088.

4.4.3. Ethyl (4*S*,5*R*)-4-isopropyl-2-methyl-4,5-dihydrooxazole-5-carboxylate 5c. Brown oil, $[\alpha]_D^{20} = -3.2$ (*c* 1.6, $CHCl_3$); IR (film) ν_{max}: 2963, 2920, 2880, 1808, 1732, 1016 cm^{-1}; MS *m*/*z* (%): 213 (1), 198 (7), 184 (1), 170 (5), 156 (100), 140 (40), 129 (13), 115 (16), 98 (8), 84 (85), 68 (46), 55 (15); ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (6H, m, H-8 and H9), 1.30 (3H, t, *J* 7.0 Hz, H-12), 1.32–1.99 (3H, m, H-6 and H-7), 2.05 (3H, s, H-1), 4.1 (1H, m, H-4), 4.2 (2H, m, H-11), 4.42 (2H, d, *J* 6.6 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 14.5 (CH_3, C-8 and C-9), 22.8 (CH_3, C-1), 25.2 (CH_2, C-7), 46.2 (CH_2, C-6), 62.0 (CH_2), 70.3 (CH, C-4), 81.6 (CH, C-5), 164.1 (heterocyclic), 171.0 (C=O). HRMS: calcd for $C_{11}H_{19}NO_3$: 213.13649; found: 213.13632.

4.5. General procedure to obtain the (2*R*,3*S*)-3-amino-2-hydroxyalkanoates 6a–c

To a stirred solution of HCl (0.5 mol L^{-1}, 10 mL) were added 4,5-dihydrooxazole-5-carboxylate (0.84 mmol) **5a**–**c** and the solution was kept for 1.5 h at room temperature. Then, a saturated solution of $NaHCO_3$ was added to pH 9 and the solution stirred overnight. The reaction product was extracted with dichloromethane (3 × 20 mL) and the organic phase dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by recrystallization in hexane (3 mL) with 5% ethyl acetate to give white crystals.

4.5.1. Ethyl (2*R*,3*S*)-3-benzoylamino-2-hydroxy-3-phenylpropanoate 6a. White solid, mp 162–164 °C, $[\alpha]_D^{20} = -21.7$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3474, 3446, 3005, 2919, 2923, 2807, 1713, 1635, 1450, 1354 cm^{-1}; MS *m*/*z* (%): 222 (100), 194 (11), 193 (66), 166 (4), 165 (15), 145 (2), 132 (2), 119 (20), 105 (72), 89 (93), 91 (89), 89 (93), 77 (70), 65 (50), 51 (60); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, *J* 7.3 Hz), 3.26 (1H, s), 4.25 (2H, m), 4.62 (1H, d, *J* 1.9 Hz, H-2), 5.74 (1H, dd, *J* 2.0 and 9.0 Hz, H-3), 6.98 (1H, d, *J* 9.0 Hz), 7.24 (10H, m, H-5 aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (CH_3), 55.2 (CH, C-3), 63.3 (CH_2), 73.8 (CH, C-2), 127.3–132.1 (CH, aromatic), 134.6 (C, aromatic), 139.2 (C, aromatic), 167.1 (C, C=O), 173.3 (C, C=O). HRMS: calcd for: $C_{18}H_{19}NO_4$: 313.13141; found: 313.13139.

4.5.2. Ethyl (2*R*,3*S*)-3-acetylamino-2-hydroxy-4-phenylbutanoate 6b. White solid, mp 110–114 °C, $[\alpha]_D^{20} = -38.0$ (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3346, 2923, 1774, 1759, 1738, 1496, 1455, 1367, 1247, 1220, 701, 698 cm^{-1}; MS *m*/*z* (%): 247 (3), 206 (5), 188 (1), 174 (10), 156 (42), 144 (5), 133 (10), 112 (20), 103 (10), 84 (100), 77 (20), 65 (20), 43 (33); ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, *J* 7.1 Hz), 2.02 (3H, s), 2.93 (1H, m, H-4), 3.40 (1H, d, *J* 3.7 Hz, OH), 4.07 (br s, 1H, H-2), 4.37 (2H, m), 4.60 (1H, m, H-3), 5.84 (1H, d, *J* 9.2 Hz, NH), 7.30 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 14.4 (CH_3), 42.0 (CH_2, C-4), 62.3 (CH_2), 72.9 (CH, C-3), 80.7 (CHOH, C-2), 129.7 (CH, C-8), 128.3 (2CH, aromatic), 130.1 (2CH, aromatic), 137.8 (C, aromatic), 169.9 (C=O, C-13), 174.2 (C=O, C-1). HRMS: calcd for $C_{14}H_{19}NO_4$: 265.13141; found: 265.13242.

4.5.3. Ethyl (2*R*,3*S*)-3-acetylamino-2-hydroxy-5-methylhexanoate 6c. Colorless oil, $[\alpha]_D^{20} = +13.0$ (*c* 1.6, $CHCl_3$); IR (film) ν_{max}: 3335, 2991, 2924, 2820, 1810, 1728, 1203 cm^{-1}; EM *m*/*z* (%): 86 (100), 216 (1), 207 (1), 198 (1), 174 (3), 158 (10), 128 (60), 116 (9), 86 (100), 60 (10); ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (6H, d, *J* 6.7 Hz, H-6 and H7), 1.32 (3H, t, *J* 7.1 Hz, H-9), 1.33–2.21 (3H, m, H-4 and H-5), 1.97 (3H, s, H-11), 4.18 (1H, d, *J* 2.5 Hz, H-2), 4.22 (2H, q, *J* 7.1 Hz, H-8), 4.44 (2H, m, H-3), 5.63 (1H, d, *J* 6.8 Hz, H-12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3, C-9), 22.3 (CH_3, C-6 and C-7), 22.8 (CH_3, C-11), 24.8 (CH_2, C-5), 41.1 (CH_2, C-4), 49.6 (CH, C-3), 62.4 (CH_2, C-8), 72.2 (CH, C-2), 169.6 (C, C=O), 173.4 (C, C=O). HRMS: calcd for $C_{11}H_{21}NO_4$: 231.14706; found: 231.14700.

4.5.4. (−)-(2*R*)-2-Hydroxy-4-phenylbutanoate 8. To a solution of **3b** (182 mg, 0.7 mmol) in anhydrous ethanol (3 mL) were added under argon sodium acetate (57 mg, 0.7 mmol) and 5% palladium on carbon (16 mg). After stirring for 2 h at room temperature, the reaction mixture was filtered over Celite, extracted with ethyl acetate (3 × 50 mL), and washed with NaCl saturated solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography and eluted with hexane and ethyl acetate (15%) to give **8** (138 mg, 95%). Yellow oil, $[\alpha]_D^{20} = -32.5$ (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* 7.0 Hz, H-12), 1.90–2.18 (2H, m, H-4), 2.77 (2H, m, H-3), 4.20 (2H, q, *J* 7.0 Hz, H-11), 7.26 (5H, m, aromatic).[12]

4.5.5. Ethyl (2*R*,3*S*)-3-azido-2-hydroxyphenylbutanoate 9. To a solution of the oxirane **4b** (200 mg, 0.7 mmol) in anhydrous dichloromethane (2 mL) were added boron trifluoride–diethyl etherate (0.25 mL) and azidotrimethylsilane (0.08 g, 0.7 mmol) under argon. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane,

washed with sodium bicarbonate solution, dried over magnesium sulfate, and the solvent removed under reduced pressure. The residue was purified by column chromatography with silica gel and eluted with ethyl acetate to give **9** (156.9 mg, 90% yield, 96% ee) as a yellow oil. $[\alpha]_D^{20} = -12.0$ (c 1.8, $CHCl_3$); IR (film) ν_{max}: 3489, 3031, 2990, 2928, 2114, 1743, 1603, 1496, 1450, 1367, 1259, 1114, 1022, 748, 697 cm^{-1}; EM m/z (%): 91 (100), 221 (1), 206 (2), 189 (1), 177 (1), 161 (2), 148 (5), 133 (15), 118 (20), 104 (15), 91 (100), 76 (20), 65 (27), 51 (20); ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, J 7.1 Hz, H-12), 3.11 (2H, m, H-4), 3.75 (1H, td, J 1.8 and 7.7 Hz, H-3), 4.10 (1H, dd, J 1.8 and 5.1 Hz, H-2), 4.28 (2H, m), 7.31 (5H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3, C-12), 36.2 (CH_2, C-4), 62.5 (CH_2, C-11), 64.3 (CH, C-3), 71.4 (CHOH, C-2), 127.1 (CH, aromatic), 128.8 (2CH, aromatics), 129.4 (2CH, aromatics), 136.7 (aromatic), 172.7 (C=O).[13]

4.5.6. Ethyl 2-oxo-5-methylhexanoate. To a double-necked round bottomed flask with magnesium turnings (0.64 g, 0.027 mol) and iodine crystals in anhydrous THF under argon was added 1-bromo-2-methylpropane (4.03 g, 0.26 mol) dissolved in THF (15 mL) slowly over 45 min. This solution of Grignard reagent was added over 30 min to a stirred solution of diethyl oxalate (3.85 g, 0.026 mol) in anhydrous THF (30 mL) at −10 °C under argon. The reaction mixture was hydrolyzed with 2 M solution of HCl, extracted with ethyl acetate, and washed with saturated NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography and eluted with hexane and ethyl acetate (6%) to give ethyl 2-oxo-6-methylhexanoate in 85% yield. Pale green oil; IR (film) ν_{max}: 2953, 2934, 2880, 1727, 1723, 1469, 1245, 1070 cm^{-1}; MS m/z (%): 172 (2), 126 (14), 99 (100), 81 (92); ^1H NMR ($CDCl_3$): δ 0.95 (d, 6H, J 2.2 Hz, H-6 and H-7), 1.33 (t, 3H, J 7.3 Hz, H-9), 1.37 (m, 3H, H-4 and H-5), 2.83 (m, 1H, H-3), 4.35 (q, 2H, J 7.3 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (CH_3, C-9), 22.9 (2 CH_3, C6 and C-7), 28.1 (CH, C-5); 32.3 (CH_2, C-4), 37.9 (CH_2, C-8), 62.9 (CH_2, C-3), 161.7 (C=O); 195.2 (C=O).[28]

4.5.7. Ethyl 2-oxoheptanoate. Procedure as above for ethyl 2-oxo-6-methylhexanoate, giving IR and ^1H NMR values matching those reported in the literature.[29]

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