JOC The Journal of Organic Chemistry

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Synthesis of the β_3-Adrenergic Receptor Agonist Solabegron and Analogous *N*-(2-Ethylamino)-β-amino Alcohols from *O*-Acylated Cyanohydrins – Expanding the Scope of Minor Enantiomer Recycling

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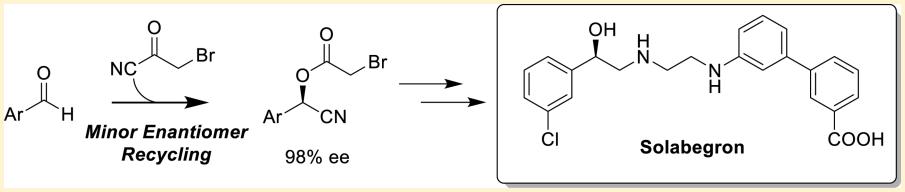
Supporting Information



ABSTRACT: A novel methodology to produce highly enantioenriched *N*-(2-ethylamino)-β-amino alcohols was developed. These compounds were obtained from *O*-(α-bromoacyl) cyanohydrins, which were synthesized by the minor enantiomer methodology employing a Lewis acid and a biocatalyst, followed by nucleophilic substitution with amines and reduction. The importance of the developed methodology was demonstrated by completing a highly enantioselective total synthesis of the β_3-adrenergic receptor agonist Solabegron.

The *N*-(2-ethylamino)-β-amino alcohol fragment (Figure 1) is an important structural element present in several

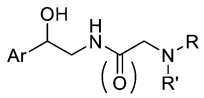
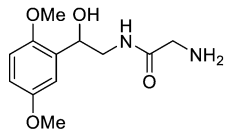
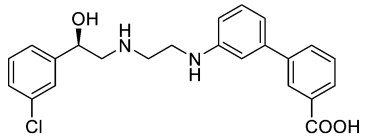


Figure 1. The *N*-(2-ethylamino)-β-amino alcohol fragment.

biologically active compounds. Examples comprise the α_1-adrenoreceptor agonist Midodrine[1] (**1**) and the β_3-adrenergic receptor agonist Solabegron[2,3] (**2**), as well as analogues of the latter compound.[4,5] Solabegron (**2**) is currently in clinical trials for both overactive bladder (OAB) and irritable bowel syndrome (IBS) with promising results.[6,7]



Midodrine (**1**)

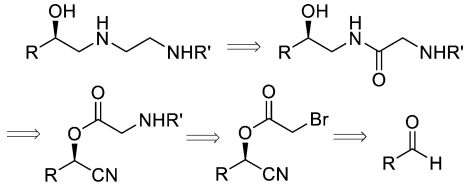


Solabegron (**2**)

Solabegron (**2**) has in previous syntheses been obtained starting from (*R*)-3-chlorostyrene oxide[2,8] or (*R*)-3-chloromandelic acid,[3,9,10] which are both commercially available in enantiopure form.

We envisioned an alternative strategy to obtain these types of structures starting from *O*-(α-bromoacyl) cyanohydrins. Substitution of the bromide with nitrogen nucleophiles, followed by reduction of the nitrile group to the amine, accompanied by intramolecular acyl transfer,[11] would result in a range of highly interesting *N*-acylated β-amino alcohols (Scheme 1). A special advantage is that this reaction sequence has a high atom economy since the acyl group becomes a vital part of the desired target molecule.

Scheme 1. Retrosynthetic Plan for Formation of *N*-(2-Ethylamino)-β-amino Alcohols

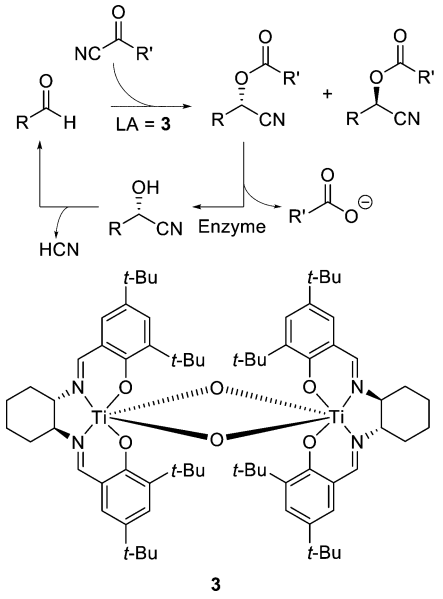


We have earlier developed a highly efficient and selective Lewis acid/Lewis base catalyzed method for the preparation of enantioenriched *O*-acylated cyanohydrins from a variety of acyl cyanides and aldehydes.[12,13] The *O*-(α-bromoacyl) cyanohydrins are, however, not readily available by direct acylcyanation using our dual activation methodology since the highly reactive α-bromoacyl cyanides are incompatible with the Lewis base present in the reaction mixture, resulting in low yields of the product. However, the desired compounds can be synthesized using a combination of chiral metal Lewis acid catalysis and biocatalysis (Scheme 2), conditions which do not require the presence of a Lewis base.[14,15] The role of the biocatalyst is to selectively hydrolyze the minor, undesired, enantiomer obtained in the product-forming step to the free cyanohydrin, which is in equilibrium with the starting aldehyde. The required

Received: February 11, 2015
Published: February 17, 2015

DOI: 10.1021/acs.joc.5b00322
J. Org. Chem. 2015, 80, 2937–2941

Scheme 2. Minor Enantiomer Recycling



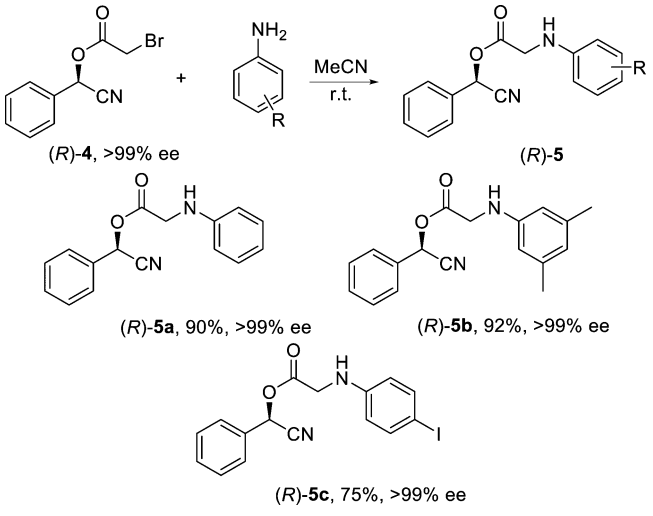
coupled exergonic process to generate chemical energy is provided by the irreversible release of carboxylate ions into the aqueous phase during the hydrolysis of the minor product enantiomer.[14,16]

O-(α-Bromoacyl) cyanohydrin (*R*)-**4**, derived from benzaldehyde, was used as a model substrate for our initial studies. This compound has previously been obtained with high enantiomeric purity using the minor enantiomer recycling methodology with (*S*,*S*)-titanium salen dimer **3**[17] as Lewis acid and *Candida antarctica* lipase B (CALB) as biocatalyst.[18]

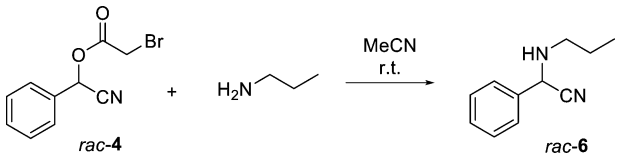
To our disappointment, substitution of (*R*)-**4** with aniline in the presence of DIPEA as a base resulted in depletion of the product ee. Fortunately, replacement of the base with an excess of the nucleophile afforded product (*R*)-**5a** in high yield without any racemization. The reaction was successful with anilines substituted with both electron-donating and electron-withdrawing groups (Scheme 3), but was, as expected, more efficient and required fewer equivalents of the nucleophile when the electron-rich nucleophile 3,5-dimethylaniline was used. Acetonitrile was superior as solvent to THF and DCM, which both resulted in no or little product formation.

Primary aliphatic amines, such as propylamine, did not lead to the desired product. Instead, the amine attacked the harder carbonyl carbon with formation of the free cyanohydrin, which decomposed to aldehyde and HCN. The aldehyde then reacted with another equivivalent of propylamine to form the imine, which was attacked by cyanide to give compound **6** (Scheme 4). Some secondary amines were also tested in the reaction but resulted in products with reduced ee.[19]

Scheme 3. Substitution of (*R*)-4 with Different Anilines

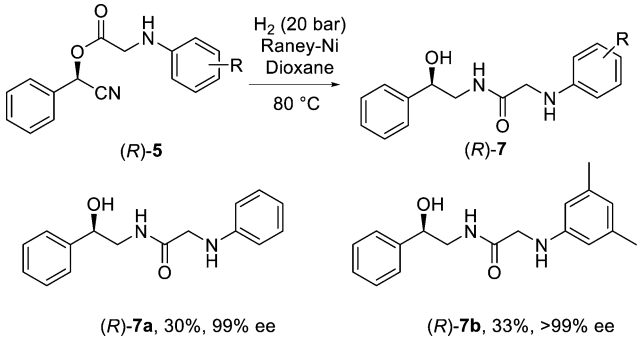


Scheme 4. Reaction of 4 with Propylamine



The subsequent reduction was achieved by catalytic hydrogenation using Raney nickel as catalyst and with 20 bar of H_2 in 1,4-dioxane at 80 °C. Whereas reduction of enantioenriched *O*-acetylated (*S*)-mandelonitrile at 120 °C has been shown to result in partial racemization (from 95% to 75% ee),[11] our modified conditions gave the desired products (*R*)-**7a**–**b** with practically no racemization, albeit in low yields (Scheme 5). Reduction of (*R*)-**5c** gave a product which we were not able to obtain in pure form.

Scheme 5. Catalytic Hydrogenation of (*R*)-5

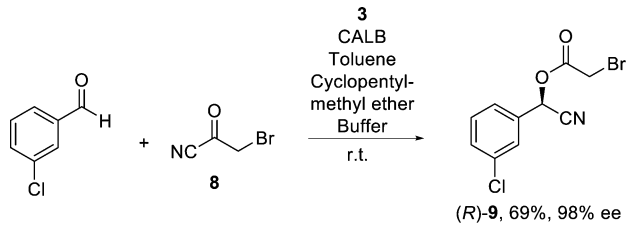


A more divergent approach to the desired products would be the direct reduction of the bromine-containing substrate **4** and nucleophilic substitution of the resulting product with the amine. However, attempts to perform the catalytic hydrogenation of **4** only led to reduction of the bromide to yield *O*-acetylated mandelonitrile.

To demonstrate the usefulness of the developed methodology, a total synthesis of Solabegron (**2**) was performed. The synthesis started with the minor enantiomer recycling with 3-chlorobenzaldehyde and acyl cyanide **8**, prepared from CuCN and bromoacetyl bromide (Scheme 6).[20] In the minor enantiomer recycling step, a decrease of ee during the addition of acyl cyanide **8** was observed. This annoyance was previously observed with a similar acyl cyanide and was attributed to inhibition of the enzyme *Candida antarctica* lipase B (CALB) by the acyl cyanide.[18] A comparison of kinetic resolutions with the present substrate, *rac*-**9**, with or without acyl cyanide **8** present showed a significant difference in the performance of the enzyme (see the Supporting Information). In order to

DOI: 10.1021/acs.joc.5b00322
J. Org. Chem. 2015, 80, 2937–2941

Scheme 6. Minor Enantiomer Recycling to Obtain (*R*)-9



counteract the effect of the inhibition, larger amounts of the enzyme were used, which indeed gave a higher final ee of the product. A reaction in preparative scale gave the product with a final ee of 86%. The addition of an additional portion of CALB to the reaction mixture, thereby allowing the enzyme to hydrolyze the remaining minor enantiomer, gave after purification the product (*R*)-**9** in 69% yield and with 98% ee.

The next step in the synthesis was the reaction of (*R*)-**9** with the aniline derivative **13**. This aniline was efficiently synthesized according to a slightly modified literature procedure consisting of a one-pot two-step reaction using Pd/C as a catalyst for both the Suzuki coupling between **10** and **11** and hydrogenation of the nitro group (Scheme 7).[21] The substitution gave product (*R*)-**14** in high yield and practically without any racemization. The drawback with this reaction is the need to use 3 equiv of the aniline derivative **13**; however, most of the remaining compound was possible to recover from the chromatographic purification. In the catalytic hydrogenation to obtain amino alcohol (*R*)-**15**, using conditions identical to those used for the other substrates, only a slight decrease in enantiomeric excess was observed (97% to 94%). In order to reduce the amide to an amine without reducing the ester functionality, we used a modified literature procedure employing borane dimethylsulfide complex;[22] this transformation gave the known compound (*R*)-**16** with an enantiomeric excess of 95%. Final hydrolysis of the ester function to the carboxylic acid was accomplished following a literature procedure using LiOH.[3] The absolute configuration of **2** was confirmed to be *R* by comparing the sign of the optical rotation with that previously reported.[9,23]

In conclusion, we have developed an efficient synthetic procedure for the synthesis of highly enantioenriched *N*-(2-ethylamino)-β-amino alcohols. The synthetic importance of the procedure was demonstrated by the synthesis of the β_3-adrenergic receptor agonist Solabegron.

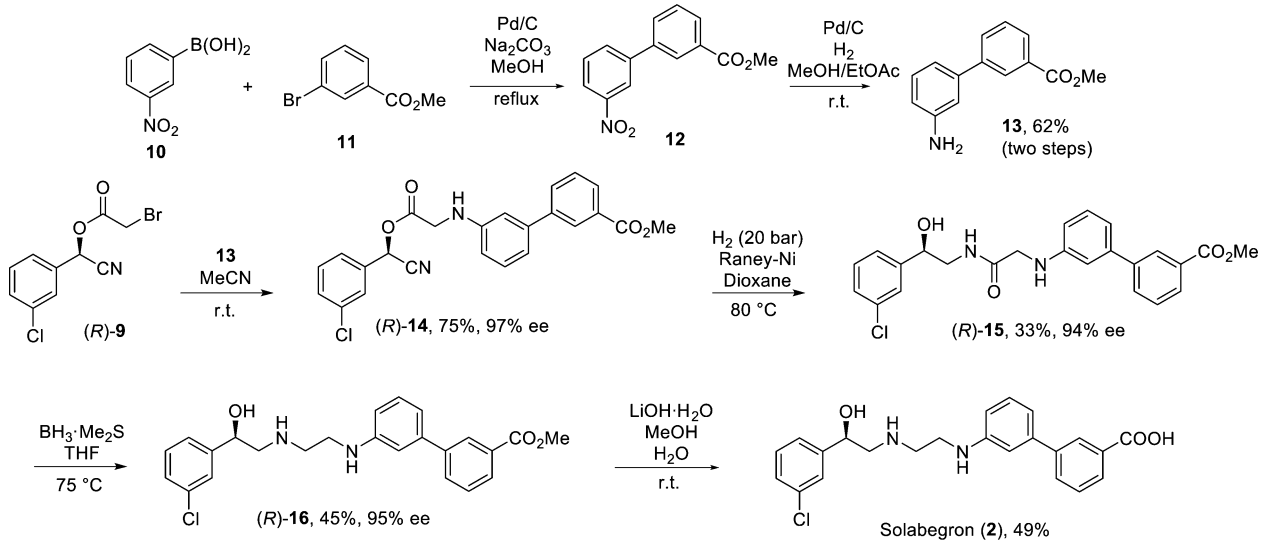
EXPERIMENTAL SECTION

General. Dry solvents were taken from a Glass Contour solvent dispensing system, except for 1,4-dioxane, which was distilled over $LiAlH_4$ prior to use. (*S*,*S*)-[(4,6-Bis(^{t}butyl)salen)Ti(μ-O)]$_2$ (**3**) was prepared according to a published procedure.[17] Immobilized (acrylic resin, >5000 U g^{-1}) *Candida antarctica* lipase B (CALB, expressed in *Aspergillus niger*) was purchased from Sigma-Aldrich. 3-Chlorobenzaldehyde was distilled prior to use. CuCN is highly toxic and should be handled with great care. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 400 MHz and 125 or 100 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to residual $CHCl_3$ or CD_2HOD in $CDCl_3$ and CD_3OD, respectively. GC analyses were conducted with an FID detector and a chiral column: CYCLOSIL B (30 m × 0.25 mm × 0.25 μm). HPLC analyses were conducted with a UV detector and a chiral column: Daicel Chiralpak IC (0.46 cm × 25 cm), Daicel Chiralpak IA, (0.46 cm × 25 cm) or Daicel Chiralcel OD-H (0.46 cm × 25 cm).

(*R*)-Cyano(phenyl)methyl Phenylglycinate ((*R*)-5a). (*R*)-**4** (92.7 mg, 0.361 mmol) was dissolved in acetonitrile (1.4 mL) and put under a N_2 atmosphere. Aniline (99.0 μL, 1.09 mmol) was added, and the solution was stirred at room temperature. After 17 h of stirring, additional aniline (33.0 μL, 0.362 mmol) was added. The solution was stirred another 24 h, after which the solvent was evaporated, and the residue was dissolved in EtOAc and washed three times with aq. HCl (0.1 M). The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1, R_f = 0.48) to give (*R*)-**5a** (87.9 mg, 0.330 mmol, 90%, >99% ee) as pale yellow crystals. mp = 105−111 °C. IR: 3389, 1757, 1604, 1184 cm^{-1}. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 95:5, 0.7 mL/min, detection at 254 nm): t_R (major) 40.6 min, t_R (minor) 56.8 min. $[\alpha]_D^{24}$ −4.7 (*c* 0.77, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.51 (m, 5H), 7.20 (t, *J* = 7.9 Hz, 2H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.49 (s, 1H), 4.08 (A part of AB, *J* = 18.2 Hz, 1H), 4.03 (B part of AB, *J* = 18.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 146.1, 131.4, 130.8, 129.6, 129.5, 128.1, 119.5, 115.8, 113.7, 63.7, 46.1. HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1124.

(*R*)-Cyano(phenyl)methyl (3,5-Dimethylphenyl)glycinate ((*R*)-5b). (*R*)-**4** (90.9 mg, 0.358 mmol) was dissolved in acetonitrile (1.4 mL) and put under a N_2 atmosphere. 3,5-Dimethylaniline (133

Scheme 7. Synthesis of Solabegron



DOI: 10.1021/acs.joc.5b00322
J. Org. Chem. 2015, 80, 2937−2941

μL, 1.06 mmol) was added, and the solution was stirred at room temperature. After 17 h, the solvent was evaporated, and the residue was dissolved in EtOAc and washed three times with aq. HCl (0.1 M). The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1, R_f = 0.62) to give (*R*)-**5b** (96.5 mg, 0.328 mmol, 92%, >99% ee) as a pale brown oil. IR: 3408, 2917, 1761, 1604, 1161 cm^{-1}. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 93:7, 1.0 mL/min, detection at 220 nm): t_R (major) 22.7 min, t_R (minor) 31.2 min. $[\alpha]_D^{25}$ −5.1 (*c* 1.9, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.52 (m, 5H), 6.49 (s, 1H), 6.47 (s, 1H), 6.27 (s, 2H), 4.06 (A part of AB, *J* = 18.1 Hz, 1H), 4.01 (B part of AB, *J* = 18.2 Hz, 1H), 2.22 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 146.0, 139.3, 131.4, 130.7, 129.5, 128.1, 121.7, 115.8, 111.9, 63.6, 46.3, 21.6. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1441, found 295.1434.

(*R*)-Cyano(phenyl)methyl (4-Iodophenyl)glycinate ((*R*)-5c). (*R*)-**4** (87.1 mg, 0.343 mmol) and 4-iodoaniline (297 mg, 1.36 mmol) were dissolved in acetonitrile (1.4 mL) and put under N_2. The mixture was stirred at room temperature for 4 days, after which the precipitate formed was filtered off on a pad of cotton. The solvent was evaporated, the residue was dissolved in EtOAc, and the solution was washed three times with aq. HCl (0.1 M). The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1, R_f = 0.63) to give (*R*)-**5c** (101 mg, 0.258 mmol, 75%, >99% ee) as white crystals. mp = 98−106 °C Decomp. IR: 3390, 1760, 1590, 1178 cm^{-1}. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 95:5, 0.7 mL/min, detection at 254 nm): t_R (major) 40.8 min, t_R (minor) 54.3 min. $[\alpha]_D^{25}$ +4.9 (*c* 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.51 (m, 7H), 6.48 (s, 1H), 6.38 (d, *J* = 8.8 Hz, 2H), 4.03 (A part of AB, *J* = 18.2 Hz, 1H), 3.98 (B part of AB, *J* = 18.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 146.1, 138.2, 131.3, 130.9, 129.5, 128.1, 115.7, 115.5, 80.2, 63.8, 45.6. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{14}IN_2O_2$ 393.0094, found 393.0084.

General Procedure for Hydrogenation Reactions. Raney-Nickel (4200, slurry in water) was activated prior to use by treatment with aq. NaOH (0.1 M), washing with water until neutral pH, and finally washing twice with MeOH.

The substrate dissolved in 1,4-dioxane was added to the activated catalyst in an autoclave. The autoclave was sealed and flushed once with H_2 before increasing the pressure to 20 bar. The mixture was stirred at 80 °C for 3 h, allowed to reach room temperature, and filtered through Celite using EtOAc as eluent, and the solvents were evaporated. The residue was purified by flash chromatography.

(*R*)-*N*-(2-Hydroxy-2-phenylethyl)-2-(phenylamino)acetamide ((*R*)-7a). The general procedure was followed using (*R*)-**5a** (65.1 mg, 0.245 mmol), Raney-Nickel (108 mg), and 1,4-dioxane (1.8 mL). Flash chromatography (petroleum ether/EtOAc 1:4 to 1:9, R_f = 0.41 (using 1:4 eluent) gave (*R*)-**7a** (20.1 mg, 0.0744 mmol, 30%, 99% ee) as a pale yellow solid. mp = 96−102 °C. IR: 3283, 1668, 1603 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 90:10, 0.7 mL/min, detection at 220 nm): t_R (major) 64.6 min, t_R (minor) 84.1 min. $[\alpha]_D^{25}$ −5.3 (*c* 1.1, MeOH). ^1H NMR (500 MHz, $CDCl_3$): δ 7.25−7.32 (m, 5H), 7.21 (dd, *J* = 7.6, 7.9 Hz, 2H), 7.13 (bs, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 2H), 4.82 (dd, *J* = 3.3, 7.7 Hz, 1H), 3.81 (s, 2H), 3.68 (ddd, *J* = 3.4, 6.7, 14.0 Hz, 1H), 3.40 (ddd, *J* = 5.9, 7.7, 13.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 146.9, 141.7, 129.7, 128.7, 128.0, 125.9, 119.6, 113.6, 73.8, 49.0, 47.4. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$ 271.1441, found 271.1436.

(*R*)-2-((3,5-Dimethylphenyl)amino)-*N*-(2-hydroxy-2-phenylethyl)acetamide ((*R*)-7b). The general procedure was followed using (*R*)-**5b** (76.1 mg, 0.259 mmol), Raney-Nickel (114 mg), and 1,4-dioxane (1.9 mL). Flash chromatography (petroleum ether/EtOAc 1:9, R_f = 0.47) gave (*R*)-**7a** (25.4 mg, 0.0851 mmol, 33%, >99% ee) as a pale brown gum. IR: 3371, 2918, 1657, 1604 cm^{-1}. HPLC (Daicel Chiralpak IA, hexanes/2-propanol 95:5, 0.5 mL/min, detection at 220 nm): t_R (major) 64.3 min, t_R (minor) 75.3 min. $[\alpha]_D^{25}$ −37 (*c* 1.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 7.28−7.33 (m, 4H), 7.24−7.28 (m, 1H), 7.16 (bs, 1H), 6.49 (s, 1H), 6.24 (s, 2H), 4.81 (dd, *J* = 3.3, 7.8 Hz, 1H), 3.78 (s, 2H), 3.66 (ddd, *J* = 3.4, 6.7, 14.0 Hz, 1H), 3.40 (ddd, *J* = 5.8, 7.8, 13.8 Hz, 1H), 2.25 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 147.1, 141.7, 139.5, 128.6, 128.0, 125.9, 121.5, 111.4, 73.8, 49.0, 47.4, 21.6. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{23}N_2O_2$ 299.1754, found 299.1749.

2-Bromoacetyl Cyanide (8).[24] Bromoacetyl bromide (5.4 mL, 62.0 mmol) was added to CuCN (6.7 g, 74.8 mmol) at room temperature under N_2. The mixture was stirred for 30 min at room temperature, after which it was heated to 65 °C for 16 h, then 75 °C for 6 h. The pure product was collected in a cold trap (−78 °C) by heating the mixture at 50 °C under vacuum (~5 mbar). This gave **8** (2.21 g, 15.0 mmol, 24%) as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$): δ 4.10 (s, 2H).

(*R*)-(3-Chlorophenyl)(cyano)methyl 2-Bromoacetate ((*R*)-9). 3-Chlorobenzaldehyde (140 μL, 1.24 mmol) and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (**3**) (75.5 mg, 0.0620 mmol) were dissolved in toluene (5 mL), and CALB (300 mg) and phosphate buffer pH 7 (2 M, 5 mL) were added to the solution. The mixture was stirred at room temperature while **8** (550 mg, 3.72 mmol) in cyclopentyl methyl ether (1.80 mL total volume) was added to the organic phase during 48 h using a syringe pump. When the addition was finished, CALB (100 mg) was added to the mixture, which was allowed to stir for 2 h 20 min. The phases were separated, the aqueous phase was extracted with diethyl ether, the combined organic phases were dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc 9:1, R_f = 0.44) to give (*R*)-**9** (246 mg, 0.852 mmol, 69%, 98% ee) as a yellow oil. IR: 1760, 1250, 1129 cm^{-1}. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 10 min, 20 °C/min to 100 °C, hold 5 min, 5 °C/min to 180 °C, hold 30 min): t_R (major) 54.1 min, t_R (minor) 57.0 min. $[\alpha]_D^{24}$ +1.7 (*c* 1.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.39−7.49 (m, 3H), 6.42 (s, 1H), 3.92 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 135.6, 132.8, 131.2, 130.9, 128.2, 126.2, 115.0, 63.7, 24.3. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_8BrClNO_2$ 287.9421, found 287.9410.

Methyl 3′-Amino-[1,1′-biphenyl]-3-carboxylate (13).[9] **11**[25] (2.87 g, 13.4 mmol) and 3-nitrophenylboronic acid (**10**) (2.29 g, 13.7 mmol) were dissolved in MeOH (17 mL), and Na_2CO_3 (1.42 g, 13.4 mmol) and Pd/C (10 wt %) (710 mg) were added. The mixture was put under N_2 and stirred at reflux for 22 h. After allowing the mixture to reach room temperature, EtOAc (34 mL) and Pd/C (10 wt %) (710 mg) were added. The mixture was stirred at room temperature under a H_2 atmosphere for 22 h, whereafter it was filtered through Celite and eluted with EtOAc. The residue was purified by flash chromatography (petroleum ether/EtOAc 2:1, R_f = 0.48) to give **13** (1.88 g, 8.27 mmol, 62%) as a light brown solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.24−7.29 (m, 1H), 7.04−7.09 (m, 1H), 6.98−7.03 (m, 1H), 6.75−6.81 (m, 1H), 3.94 (s, 3H).

Methyl (*R*)-3′-((2-((3-Chlorophenyl)(cyano)methoxy)-2-oxoethyl)amino)-[1,1′-biphenyl]-3-carboxylate ((*R*)-14). (*R*)-**9** (182 mg, 0.632 mmol) and **13** (432 mg, 1.90 mmol) were dissolved in acetonitrile (2.5 mL) and put under N_2. The solution was stirred at room temperature for 40 h, and the solvent was evaporated. The residue was dissolved in EtOAc and washed with water, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc 3:1, R_f = 0.56) to give (*R*)-**14** (206 mg, 0.473 mmol, 75%, 97% ee) as a pale brown gum. IR: 3407, 1762, 1717, 1607 cm^{-1}. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 80:20, 0.7 mL/min, detection at 220 nm): t_R (major) 37.5 min, t_R (minor) 67.2 min. $[\alpha]_D^{25}$ −8.1 (*c* 1.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.40−7.45 (m, 1H), 7.34−7.39 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.47 (s, 1H), 4.18 (A part of AB, *J* = 18.2 Hz, 1H), 4.14 (B part of AB, *J* = 18.1 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 167.2, 146.6, 141.62, 141.56, 135.4, 133.1, 131.7, 131.0, 130.73, 130.71, 130.1,

DOI: 10.1021/acs.joc.5b00322
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128.9, 128.6, 128.4, 128.1, 126.1, 118.5, 115.3, 112.8, 112.3, 62.9, 52.3, 46.0. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{24}H_{20}ClN_2O_4$ 435.1106, found 435.1096.

Methyl (*R*)-3′-((2-((2-(3-Chlorophenyl)-2-hydroxyethyl)-amino)-2-oxoethyl)amino)-[1,1′-biphenyl]-3-carboxylate ((*R*)-15). The general procedure for hydrogenation was followed using (*R*)-**14** (177 mg, 0.407 mmol), Raney-Nickel (180 mg), and 1,4-dioxane (3.0 mL). Flash chromatography (petroleum ether/EtOAc 1:9, R_f = 0.52) gave (*R*)-**15** (59.3 mg, 0.135 mmol, 33%, 94% ee) as a pale yellow gum. IR: 3357, 1717, 1654, 1605 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, 1.0 mL/min, detection at 220 nm): t_R (minor) 44.9 min, t_R (major) 52.1 min. $[\alpha]_D^{26}$ −30 (*c* 0.79, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.27−7.36 (m, 3H), 7.15−7.22 (m, 3H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.97 (bs, 1H), 6.72 (bs, 1H), 4.86 (dd, *J* = 2.7, 7.8 Hz, 1H), 3.95 (bs, 2H), 3.91 (s, 3H), 3.68 (ddd, *J* = 3.0, 6.5, 14.0 Hz, 1H), 3.35 (ddd, 5.8, 7.9, 13.9 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 174.3, 168.6, 149.9, 146.2, 143.4, 142.3, 135.3, 132.7, 131.8, 130.9, 130.8, 130.0, 129.2, 128.9, 128.6, 127.2, 125.6, 117.9, 113.4, 112.6, 72.7, 52.7, 48.96, 47.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}ClN_2O_4$ 439.1419, found 439.1406.

Methyl (*R*)-3′-((2-((2-(3-Chlorophenyl)-2-hydroxyethyl)-amino)ethyl)amino)-[1,1′-biphenyl]-3-carboxylate ((*R*)-16).[9] (*R*)-**15** (36.4 mg, 0.0829 mmol) was dissolved in THF (0.70 mL) and put under N_2. The solution was cooled to 0 °C, $BH_3{\cdot}Me_2S$ (2 M in THF) (83 μL, 0.166 mmol) was added dropwise, and the reaction mixture was heated at 75 °C for 1.5 h. To quench the reaction, the solution was cooled to 0 °C and aq. HCl (0.5 M, 0.5 mL) was added. The mixture was stirred at room temperature for 1 h, after which aq. NaOH (0.2 M, 1.5 mL) was added. This was followed by extraction with EtOAc, drying over Na_2SO_4, and evaporation of the solvents. The residue was purified by flash chromatography (EtOAc/MeOH 9:1, R_f = 0.27), using base-washed SiO_2 (1% Et_3N in EtOAc/MeOH 9:1), to give (*R*)-**16** (15.9 mg, 0.0374 mmol, 45%, 95% ee) as a colorless oil. HPLC (Daicel Chiralpak IC, hexanes/2-propanol/Et_2NH 90:10:0.1, 0.8 mL/min, detection at 254 nm): t_R (minor) 47.9 min, t_R (major) 51.3 min. $[\alpha]_D^{24}$ −10 (*c* 1.6, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.17−7.29 (m, 4H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.65 (dd, *J* = 1.5, 8.0 Hz, 1H), 4.76 (dd, *J* = 3.2, 8.8 Hz, 1H), 3.94 (s, 3H), 3.34 (t, *J* = 5.7 Hz, 2H), 2.91−3.04 (m, 3H), 2.77 (dd, *J* = 9.0, 12.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ (Two carbons overlapped) 168.6, 150.6, 146.9, 143.6, 142.2, 135.4, 132.7, 131.7, 131.0, 130.8, 130.0, 129.1, 128.9, 128.6, 127.1, 125.4, 117.0, 113.5, 112.6, 72.5, 57.5, 52.7, 43.8.

(*R*)-3′-((2-((2-(3-Chlorophenyl)-2-hydroxyethyl)amino)ethyl)-amino)-[1,1′-biphenyl]-3-carboxylic Acid (2).[9] (*R*)-**16** (14.5 mg, 0.0341 mmol) was dissolved in MeOH (0.25 mL), and water (0.15 mL) and $LiOH{\cdot}H_2O$ (7.2 mg, 0.17 mmol) were added. The mixture was stirred at room temperature for 17 h; the pH was adjusted to ∼7 using aq. HCl (0.5 M), which resulted in a white precipitate. The mixture was extracted with EtOAc, the organic phase was dried over Na_2SO_4, and the solvents were evaporated. The crude material was triturated with DCM, discarding the soluble material, to give **2** (6.9 mg, 0.0168 mmol, 49%) as a white solid. $[\alpha]_D^{24}$ −11 (*c* 0.69, MeOH) [lit.[9] $[\alpha]_D^{20}$ −20 (*c* 0.075, MeOH)]. ^1H NMR (500 MHz, CD_3OD): δ 8.21 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.47 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.30−7.37 (m, 3H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.94−6.99 (m, 2H), 6.69 (d, *J* = 7.7 Hz, 1H), 5.00 (dd, *J* = 2.5, 10.1 Hz, 1H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.25−3.36 (m, 3H), 3.13 (dd, *J* = 10.5, 12.4 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

Characterization of compounds and graphs for enzymatic hydrolysis experiments are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Swedish Research Council (Grant 621-2012-3391) is gratefully acknowledged. We are grateful to Lorraine Cherrier for her skillful experimental work.

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DOI: 10.1021/acs.joc.5b00322
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