Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 10034–10041
Tetrahedron

Synthesis of chiral 2-oxazolidinones, 2-oxazolines, and their analogs

Jean-Rene Ella-Menye and Guijun Wang*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

Received 19 March 2007; revised 8 July 2007; accepted 13 July 2007
Available online 19 July 2007

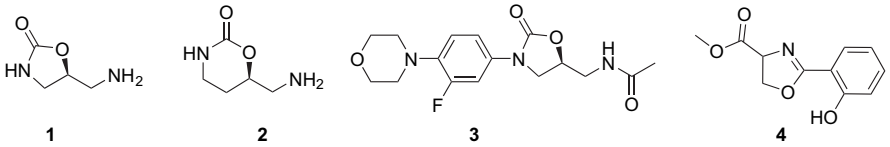
Abstract—Chiral five-membered ring 2-oxazolidinones and six-membered ring 1,3-oxazinan-2-ones are synthesized from the corresponding amino alcohols with complete inversion or retention of stereochemistry. Chiral 5-substituted 2-oxazolines and 6-substituted 2-oxazines are also synthesized from the same starting materials with inversion of stereochemistry through an intramolecular S_N2 reaction. These compounds are useful intermediates in organic synthesis and crucial building blocks for many pharmaceutical compounds.

1. Introduction

Nitrogen and oxygen containing heterocycles, such as cyclic carbamates and oxazolines, are important intermediates in organic synthesis and useful building blocks for biologically active compounds. For example, the (*S*)-5-aminomethyl 2-oxazolidinone (**1**) is the core structure in antibacterial agent linezolid (**3**),[1,2] which is the first member of the synthetic oxazolidinone antibiotics[3–7] effective against resistant Gram-positive bacterial infection. The six-membered ring 1,3-oxazinan-2-one (**2**) derivatives also exhibit biological activities, such as anti-inflammatory,[8] anti-thrombotic,[9] and antibacterial activities.[10] These heterocycles can be synthesized from amino alcohols or related starting materials. Another class of heterocyclic compounds that can be interconverted from amino alcohols is the oxazolines.[11,12] They are also important pharmacophores in many drug molecules including the natural product **4**, which has antibiotic activity.[13] Besides being important building blocks for the preparation of biologically active compounds, the 1,3-oxazinan-2-ones, 2-oxazolidinones, and 2-oxazolines are also used as chiral auxiliaries or as protected forms of amino alcohols in the synthesis of complex molecules.

Because of the importance of these heterocycles as pharmaceutical core structures in asymmetric synthesis, there have been great interests in developing their effective syntheses. The preparations of optically pure cyclic carbamates include the conversion of a chiral hydroxyl amide by Hofmann rearrangement[14] and the carbonylation reaction of chiral 1,3-amino alcohols.[15] Many examples are available for the synthesis of cyclic carbamates from chiral amino alcohols with retention of stereochemistry.[16–29] There are fewer methods for the preparation of cyclic carbamates with opposite stereochemistry to the starting amino alcohol derivatives.[19,30–33] For the preparation of the opposite stereoisomers, the hydroxyl group is usually converted to a better leaving group through mesylation or Mitsunobu reaction, and the nitrogen is derivatized with Boc_2O or CbzCl. The S_N2 cyclization from the displacement of the activated hydroxyl group affords the cyclic carbamate with opposite stereochemistry.

A general precursor for oxazoline synthesis is a β-hydroxy amide. The hydroxyl group is usually converted to a better leaving group such as a sulfonate or halide, then an intramolecular S_N2 cyclization reaction gives the corresponding oxazoline. Many chiral 1,2-amino alcohols can be prepared from naturally occurring α-amino acids, and the oxazolines formed from these amino alcohols are 2,4-disubstituted oxazolines. Relatively fewer 5-substituted 2-oxazolines have been synthesized because of the lack of accessibility of the



* Corresponding author. Tel.: +1 504 280 1258; fax: +1 504 280 6860; e-mail: gwang2@uno.edu

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.044

corresponding amino alcohols. There are also fewer six-membered ring 2-oxazines comparing to five-membered ring oxazolines, for the same reason as above, 1,3-amino alcohols are less accessible than the amino acid derived 1,2-amino alcohols, which are used often in the synthesis of 2-oxazolines.

(*S*)-3-Hydroxy-γ-butyrolactone is a commercially available compound that can be synthesized readily from starch or lactose.[34] The lactone has been converted to chiral (*S*)-1,2-amino alcohols, (*S*)-1,3-amino alcohols, and their derivatives via efficient methods.[14,35] These chiral amino alcohols have structures that are complementary to those of natural amino acids derived amino alcohols. As part of our effort in synthesizing chiral building blocks that are useful in drug discovery, we devised new routes for several chiral heterocycles from intermediates generated from (*S*)-3-hydroxy-γ-butyrolactone. These chiral heterocycles include 5-substituted 2-oxazolines, 6-substituted 2-oxazines, and both enantiomers of 5-trityloxymethyl-2-oxazolidinones and 6-trityloxymethyl-1,3-oxazinan-2-ones.

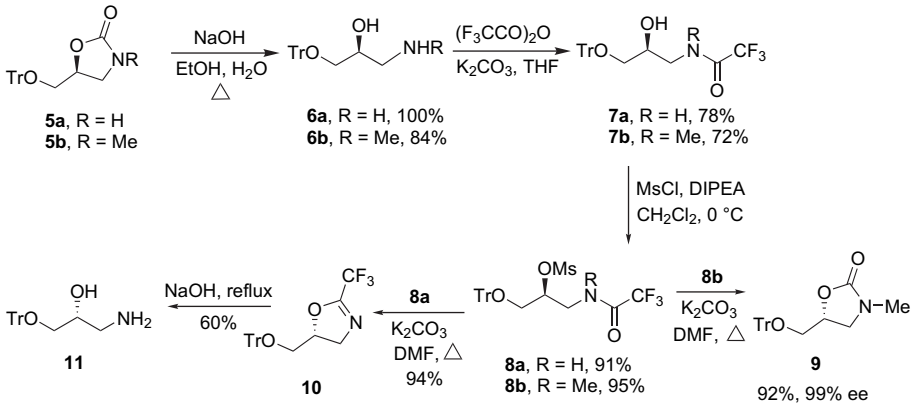
2. Results and discussions

For the preparation of the five-membered ring compounds, we started from the trityloxymethyl oxazolidinones **5a** and **5b**. These can be prepared from (*S*)-3-hydroxyl-γ-butyrolactone according to literature procedures.[9,14] Compound **5** was decarbonylated by refluxing with NaOH in a mixture of THF, ethanol, and water to give the trityl protected amino alcohol **6** in excellent yield. The amino alcohol **6** was then treated with trifluoroacetic anhydride at low temperature to give the corresponding amide **7**, followed by mesylation of the free hydroxyl group in **7** to give the intermediate **8**. The mesylate **8b** (R=Me) was cyclized to *N*-methyl-oxazolidinone **9** ($[\alpha]_D^{25}$ −41.0, EtOAc, *c* 1.00) under basic condition using potassium carbonate in DMF. Compound **9** has a stereochemistry opposite to that of the starting material **5b** ($[\alpha]_D^{25}$ +40.9, EtOAc, *c* 1.00). The cyclization to the oxazolidinone occurred through intramolecular S_N2 displacement of the mesylate and subsequent rearrangement. The yield for the transformation is excellent with complete inversion of stereochemistry.[36] In this four-step sequence, the chirality of the oxazolidinone starting material is inverted.

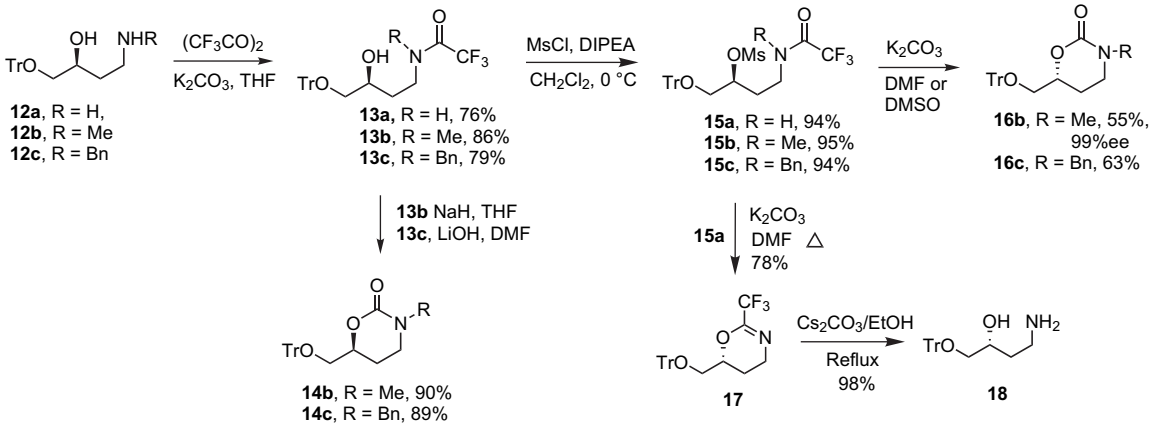
When the amide contains a hydrogen atom such as in compound **8a** (R=H), under the same mild basic conditions, the 2,5-disubstituted oxazoline **10** with inverted stereochemistry was obtained. The oxazoline was then hydrolyzed to give the amino alcohol **11** ($[\alpha]_D^{25}$ +15.3, EtOH, *c* 1.10), which has inverted stereochemistry compared to compound **6a** ($[\alpha]_D^{25}$ −15.9, EtOH, *c* 1.00). Because the oxazoline **10** is formed through an intramolecular reaction, it is expected to have high integrity of stereochemistry. Therefore, the stereochemistry of the amino alcohol **6a** can be inverted through a four-step sequence as shown in Scheme 1.

In the preparation of the six-membered ring analogs, the trityl protected amino alcohols **12b** and **12c** were used as starting materials. These compounds are synthesized by reacting (*S*)-3-hydroxy-γ-butyrolactone with amines to produce the corresponding dihydroxyl butyramides followed by the reduction of the trityl protected amides with lithium aluminum hydride.[15] As shown in Scheme 2, by a similar method as for the five-membered ring oxazolidinone synthesis, the amino alcohols **12** were converted to the trifluoroacetamide **13**. From compounds **13b** and **13c**, direct acyl transfer cyclization under anhydrous basic conditions led to the formation of (*S*)-1,3-oxazinan-2-ones **14b** ($[\alpha]_D^{25}$ +32.5, EtOAc, *c* 1.03), and **14c** ($[\alpha]_D^{25}$ +29.0, EtOAc, *c* 1.01) in excellent yields. This demonstrated the feasibility of converting the amino alcohols into cyclic carbamates using trifluoroacetamide intermediate through elimination of the trifluoromethyl group. To prepare the carbamates with opposite stereochemistry, the mesylates **15b** and **15c** were treated with potassium carbonate to afford the cyclization products **16b** ($[\alpha]_D^{25}$ −31.9, EtOAc, *c* 1.03) and **16c** ($[\alpha]_D^{25}$ −28.6, EtOAc, *c* 1.00) in moderate yields. Although the reaction suffered from lower yields, the optical purities of the oxazinanones with inverted stereochemistry are over 99% ee.[37]

The six-membered ring 2-oxazine homolog **17** can be synthesized by a similar method as the synthesis of 2-oxazoline **10**. The mesylate **15a** was converted to the 2-oxazine **17** and the hydrolysis of **17** using cesium carbonate gave the amino alcohol **18** with excellent yield. The isolated product amino alcohol **18** ($[\alpha]_D^{25}$ +15.0, EtOH, *c* 1.00) has reasonable good optical purity as compared to the optical rotation data of compound **12a** ($[\alpha]_D^{25}$ −15.7, EtOH, *c* 1.01).



Scheme 1. Synthesis of trityl protected 2-oxazoline **10** and the oxazolidinone **9**.



Scheme 2. Synthesis of both enantiomers of trityl protected 1,3-oxazinan-2-ones (**14** and **16**) and oxazine **17**.

The intramolecular S_N2 cyclizations in the six-membered ring formation suffered lower yields than the five-membered ring system. Several attempts using different bases, solvents, and lengths of reaction time failed to improve the yield of the 1,3-oxazinan-2-ones. The *N*-benzyl derivative **16c** was obtained in 63% yield from the corresponding mesylate **15c**, then we synthesized the *N*-methyl derivatives considering that the substituents on the nitrogen might affect the reaction outcome. The reaction of *N*-methyl derivative afforded poorer yield than the *N*-benzyl derivative. Compound **15b** in DMF treated with potassium carbonate and other bases only gave a small amount (20%) of the desired product **16b** with a large percentage of decomposition. When the reaction was done in DMSO with K_2CO_3 as the base, the desired product was obtained with a 55% yield. Therefore, this rearrangement reaction is perhaps more effective for the formation of five-membered ring system.

In the direct acyl transfer reaction leading to the cyclic carbamate with the same stereochemistry as the starting material, the cyclization occurred presumably by nucleophilic addition to the carbonyl group followed by elimination. Similar reactions are commonly used in the formation of cyclic carbamates, these include using a *t*-Boc or Cbz derivative of the amines. For the S_N2 cyclization reaction leading to heterocycles with opposite stereochemistry, a possible mechanism is shown in Scheme 3 using the oxazolidinone as an example. The first step here is the displacement of the mesylate and maybe through the formation of an unstable intermediate **19**. The second step involves the attack of a base to the intermediate **19**, a hydroxide ion or other base present in the reaction attacks the carbon-2 and gives the tetrahedral intermediate **20**, which then undergoes elimination to afford the 2-oxazolidinone **9**.

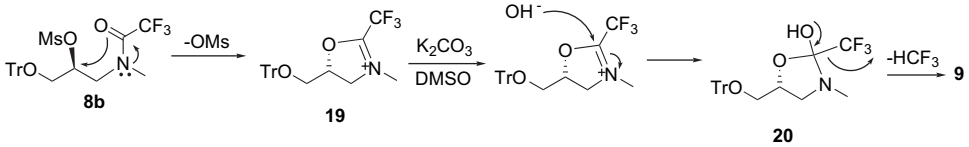
3. Conclusions

We have developed an efficient method to convert chiral trityl protected 3-amino-1,2-propane diol and 4-amino-1,2-butane diol to the corresponding optically pure cyclic carbamate derivatives. Direct acyl transfer reactions under basic conditions led to cyclic carbamates with retention of stereochemistry; while intramolecular S_N2 cyclization yielded 2-oxazolidinones or 1,3-oxazinan-2-ones with inversion of stereochemistry. The direct acyl transfer cyclization using trifluoroacetamide intermediate can be used as a complementary method to cyclizations using *t*-Boc or Cbz carbamates as intermediates to synthesize cyclic carbamates. The intramolecular S_N2 cyclization methods can be used to synthesize oxazolidinones with inverted stereochemistry. Chiral 2,5-disubstituted oxazolines and 2,6-disubstituted oxazines were also synthesized from the corresponding amino alcohols. Hydrolysis of these heterocycles yielded amino alcohols with opposite configuration to that of the starting materials. The effective synthesis of these chiral heterocycles allows feasible access to a variety of biologically active compounds including antibacterial agents.

4. Experimental section

4.1. General

4.1.1. (*S*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one 5b. (*S*)-5-(Trityloxymethyl)oxazolidin-2-one **5a** (118 mg, 0.328 mmol) was dissolved in anhydrous THF (5 mL). The reaction flask was cooled to 0 °C and potassium *tert*-butoxide (74.0 mg, 0.660 mmol) was added to the solution, which was stirred for 1 h. Iodomethane (0.051 mL, 0.819 mmol) was added to the mixture and the reaction was stirred at



Scheme 3. A possible mechanism for the formation of oxazolidinone.

room temperature for 2 h after which NMR of the crude mixture showed that all starting material had been transformed. The reaction flask was cooled to 0 °C and the reaction was quenched with cold methanol. The solvents were evaporated and the crude residue was taken up in dichloromethane. The solid residue was filtered out and the solvent was evaporated to afford a crude residue that was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 8:1:1. The pure product was isolated as a white solid (108 mg, 0.290 mmol). Yield: 88%. Mp 157–158 °C, $[\alpha]_D^{25}$ +40.9 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49–7.22 (m, 15H), 4.56 (m, 1H), 3.49 (t, 1H, *J*=8.7 Hz), 3.34 (m, 2H), 3.22 (dd, 1H, *J*=10.2, 4.5 Hz), 2.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 158.1, 143.4, 128.5, 127.9, 127.2, 86.8, 71.7, 64.3, 48.8. 30.9. HRMS calcd for $C_{24}H_{23}NO_3$ $[M+H]^+$ 374.1756, found 374.1748.

4.1.2. (*S*)-1-Amino-3-trityloxy-2-propanol 6a. (*S*)-5-Trityloxymethyl-2-oxazolidinone **5a** (2.00 g, 5.56 mmol) was dissolved in a (1:1) mixture of ethanol and THF (40 mL). Sodium hydroxide (1.35 g, 33.8 mmol) in distilled water (10 mL) was added dropwise to the solution. The mixture was refluxed overnight. The solvents were evaporated and the residue taken up in THF. A precipitate was formed and filtered out. The solution was concentrated to dryness under vacuum and the crude was dried on the vacuum pump without further purification to afford a white semi-solid (1.85 g, 5.55 mmol). Yield: 100%. $[\alpha]_D^{25}$ −15.9 (EtOH, *c* 1.00). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.47–7.21 (m, 15H), 3.75 (m, 1H), 3.15 (d, 2H, *J*=5.0 Hz), 2.77 (m, 2H), 2.09 (br s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 143.8, 128.6, 127.8, 127.1, 86.6, 71.3, 65.6, 44.4. HRMS calcd for $C_{22}H_{23}NO_2$ $[M+Na]^+$ 356.1651, found 356.1626.

4.1.3. (*S*)-1-(Methylamino)-3-(trityloxy)propan-2-ol 6b. (*S*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one **5b** (154 mg, 0.412 mmol) was dissolved in a mixture of THF and ethanol (2 mL each). Lithium hydroxide (100 mg, 4.18 mmol) and sodium hydroxide (85.0 mg, 2.12 mmol) were dissolved in water (4 mL) and added to the solution. The mixture was refluxed for 48 h and the solvents were evaporated. The crude residue was taken up in THF and the insoluble salts were filtered out; the THF was evaporated and the crude product was purified on silica gel with a gradient of hexane/CH_2Cl_2 1/9 to CH_2Cl_2/methanol 9:1. The product was obtained as a light brown semi-solid (120 mg, 0.345 mmol). Yield: 84%. $[\alpha]_D^{25}$ −14.2 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47–7.19 (m, 15H), 3.90 (m, 1H), 3.17 (m, 2H), 2.67 (m, 2H), 2.42 (s, 3H), 2.34 (br s, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 143.8, 128.6, 127.7, 126.9, 86.6, 68.6, 66.2, 54.3, 35.9. HRMS calcd for $C_{23}H_{25}NO_2$ $[M+H]^+$ 348.1964, found 348.1961.

4.1.4. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)acetamide 7a. (*S*)-1-Amino-3-(trityloxy)propan-2-ol **6a** (1.00 g, 3.00 mmol) was dissolved in anhydrous THF (25 mL). The mixture was stirred at 0 °C for about 5 min then potassium carbonate (2.5 g, 18.1 mmol) was added to the solution. After another 5 min, trifluoroacetic anhydride (0.50 mL, 3.54 mmol) was added and the mixture was stirred for 30 min at 0 °C. The solution was diluted with CH_2Cl_2 and K_2CO_3 was filtered out. The organic solvents were evaporated on the rotovap, the crude mixture taken up in CH_2Cl_2 and washed with water twice. The dichloromethane was then evaporated and the crude mixture purified on SiO_2 gel using a gradient of solvent of pure hexane to hexane/CH_2Cl_2/THF 6:3:1. The pure product was obtained as an off-white solid (1.01 g, 2.33 mmol). Yield: 78%. Mp 98–100 °C, $[\alpha]_D^{25}$ −19.2 (EtOH, *c* 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.41–7.12 (m, 15H), 7.04 (br s, 1H), 3.82 (m, 1H), 3.49 (m, 1H), 3.23 (dd, 1H, *J*=12.8, 5.9 Hz), 3.17 (dd, 1H, *J*=9.1, 4.1 Hz), 3.08 (dd, 1H, *J*=9.1, 5.4 Hz), 3.00 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 157.5 (q, C=O, ^2J=36.5 Hz), 143.2, 128.4, 127.9, 127.2, 115.7 (q, CF_3, ^1J=287.9), 87.0, 68.8, 64.9, 42.7. HRMS calcd for $C_{24}H_{22}F_3NO_3$ $[M+Na]^+$ 452.1449, found 452.1440.

4.1.5. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)-*N*-methylacetamide 7b. (*S*)-1-(Methylamino)-3-(trityloxy)propan-2-ol **6b** (172 mg, 0.495 mmol) was dissolved in anhydrous THF (4 mL) and the reaction was cooled to −20 °C. DIPEA (0.431 mL, 2.47 mmol) was added and the reaction was stirred for 5 min. Trifluoroacetic anhydride (0.077 mL, 0.545 mmol) was then added and the reaction was stirred for about 40 min at −20 °C. The solvent was evaporated to dryness and the crude residue was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 20:1:1. The clean product was isolated as a brown oil (158 mg, 0.356 mmol). Yield: 72%, $[\alpha]_D^{25}$ −17.7 (EtOAc, *c* 1.01). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49–7.23 (m, 15H), 4.08 (m, 1H), 3.61 (dd, 1H, *J*=13.9, 3.6 Hz), 3.51 (dd, 1H, *J*=13.6, 7.9 Hz), 3.30 (dd, 1H, *J*=9.5, 4.8 Hz), 3.17 (m, 1H), 3.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.9 (q, C=O, ^2J=35.9 Hz), 143.4, 128.5, 127.9, 127.2, 116.4 (q, CF_3, ^1J=287.6 Hz), 87.0, 69.3, 65.2, 53.1, 36.7 (q, CH_3, ^4J=3.7 Hz); (minor tautomer) 157.8 (q, C=O, ^2J=35.9 Hz), 143.3, 128.5, 127.9, 127.3, 116.5 (q, CF_3, ^1J=287.9 Hz), 87.1, 69.7, 65.4, 53.2 (q, CH_2N, ^4J=2.1 Hz), 35.9. HRMS calcd for $C_{25}H_{24}F_3NO_3$ $[M+Na]^+$ 466.1606, found 466.1614.

4.1.6. (*S*)-1-(2,2,2-Trifluoroacetamido)-3-(trityloxy)propan-2-yl-methanesulfonate 8a. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)acetamide **7a** (880 mg, 2.05 mmol) was dissolved in anhydrous dichloromethane (20 mL). The solution was cooled to 0 °C and methanesulfonate chloride (0.24 mL, 3.09 mmol) was added. After 1 min, diisopropylethylamine (1.00 mL, 5.74 mmol) was added and the mixture was stirred for 40 min. Ice-water (2–3 mL) was added to quench the reaction and the organic phase was separated. Dichloromethane was evaporated and the crude mixture purified on SiO_2 gel using a gradient of pure hexane to hexane/CH_2Cl_2/THF 8:1:1. The pure product was obtained as a white solid (948 mg, 1.87 mmol). Yield: 91%. Mp 118–119 °C, $[\alpha]_D^{25}$ −10.1 (EtOAc, *c* 1.04). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.37–7.18 (m, 15H), 6.83 (br s, 1H), 4.75 (m, 1H), 3.71 (m, 1H), 3.47 (m, 1H), 3.39 (dd, 1H, *J*=11.3, 4.4 Hz), 3.27 (dd, 1H, *J*=10.9, 5.5 Hz), 2.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 157.6 (q, C=O, ^2J=38.4 Hz), 142.9, 128.4, 128.1, 127.5, 115.6 (q, CF_3, ^1J=287.9 Hz), 87.5, 78.2, 63.3, 40.9, 38.4. HRMS calcd for $C_{25}H_{24}F_3NO_5S$ $[M+Na]^+$ 530.1225, found 530.1219.

4.1.7. (*S*)-1-(2,2,2-Trifluoro-*N*-methylacetamido)-3-(trityloxy)propan-2-yl-methanesulfonate 8b. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)-*N*-methylacetamide

7b (336 mg, 0.758 mmol) was dissolved in anhydrous dichloromethane (10.0 mL). The solution was stirred at 0 °C for 5 min and methanesulfonyl chloride (0.100 mL, 1.29 mmol) followed by DIPEA (0.400 mL, 2.29 mmol) was added to the mixture and the reaction was stirred at 0 °C for 30 min. The solvent was evaporated to dryness and the crude residue purified on silica gel with a solvent system of hexane/dichloromethane/THF 10:1:1 to afford a white solid (375 mg, 0.720 mmol). Yield: 95%. Mp 47–48 °C, $[\alpha]_D^{25}$ −8.4 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.97–7.26 (m, 15H), 7.25 (br s,1H), 5.00 (m, 1H), 3.75 (dd, 1H, *J*=14.2, 4.0 Hz), 3.63 (dd, 1H, *J*=14.2, 8.2 Hz), 3.47 (dd, 1H, *J*=11.1, 3.5 Hz), 3.31 (dd, 1H, *J*=11.1, 5.6 Hz), 3.20 (s, 3H), 3.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.7 (q, C=O, ^2J=36.5 Hz), 143.0, 128.5, 128.0, 127.9, 116.1 (q, CF_3, ^1J=287.7 Hz), 87.5, 78.0, 63.4, 51.2, 38.4, 36.9 (q, CH_3, ^4J=3.8 Hz); (minor tautomer) 157.8 (q, C=O, ^2J=38.4 Hz), 142.9, 128.4, 128.1, 127.5, 116.2 (q, CF_3, ^1J=288.7 Hz), 87.6, 77.9, 63.3, 50.2, 38.7, 35.6. HRMS calcd for $C_{26}H_{26}F_3NO_5S$ $[M+Na]^+$ 544.1381, found 544.1392.

4.1.8. (*R*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one 9. (*S*)-1-(2,2,2-Trifluoro-*N*-methylacetamido)-3-(trityloxy)-propan-2-yl-methanesulfonate **8b** (87.0 mg, 0.167 mmol) was dissolved in DMF (4.00 mL). Potassium carbonate (92.0 mg, 0.667 mmol) was added and the solution was stirred at 120 °C for 45 min. K_2CO_3 was filtered out and the solvent was evaporated to dryness under nitrogen and then under vacuum. The pure product was obtained as a white solid (57.0 mg, 0.153 mmol). Yield: 92%. Mp 154–155 °C, $[\alpha]_D^{25}$ −41.0 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.46–7.22 (m, 15H), 4.60 (m, 1H), 3.55 (t, 1H, *J*=8.7 Hz), 3.35 (m, 2H), 3.22 (dd, 1H, *J*=10.2, 4.6 Hz), 2.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 158.1, 143.4, 128.5, 127.9, 127.2, 86.7, 71.7, 48.8, 30.9. HRMS calcd for $C_{24}H_{23}NO_3$ $[M+H]^+$ 374.1756, found 374.1764.

4.1.9. (*R*)-2-(Trifluoromethyl)-5-(trityloxymethyl)-oxazoline 10. (*S*)-1-(2,2,2-Trifluoroacetamido)-3-(trityloxy)-propan-2-yl-methanesulfonate **8a** (106 mg, 0.210 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (10.0 mL). Potassium carbonate (60.0 mg, 0.434 mmol) was added and the solution was stirred at 85 °C for 1 h. K_2CO_3 was then filtered out and DMF evaporated. The crude mixture was clean enough after drying under vacuum and did not require purification. The product was obtained as a white solid (81.6 mg, 0.198 mmol). Yield: 94%. Mp 180–182 °C, $[\alpha]_D^{25}$ −43.5 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.50–7.26 (m, 15H), 4.99 (m, 1H), 4.07 (m, 1H), 3.93 (dd, 1H, *J*=14.3, 6.6 Hz), 3.21 (dd, 1H, *J*=10.7, 4.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 155.2 (q, C=N, ^2J=39.9 Hz), 143.3, 128.5, 127.9, 127.2, 116.4 (q, CF_3, ^1J=274.4 Hz), 86.7, 81.3, 64.3, 56.4. HRMS calcd for $C_{24}H_{20}F_3NO_2$ $[M+Na]^+$ 412.1524, found 412.1542.

4.1.10. (*R*)-1-Amino-3-(trityloxy)propan-2-ol 11. (*R*)-2-(Trifluoromethyl)-5-(trityloxymethyl)-oxazoline **10** (88.9 mg, 0.216 mmol) was dissolved in a mixture of THF and EtOH (5.00 mL each). Sodium hydroxide (94.0 mg, 2.35 mmol) was dissolved in 2 mL of H_2O and added to the solution. The reaction was refluxed for 14 h then the solvents were evaporated. The crude residue was taken up in CH_2Cl_2 and the solid salts were filtered out. The solvent was evaporated and the crude product was purified on SiO_2 gel using a solvent system of CH_2Cl_2/MeOH 95:5. After drying under vacuum a colorless semi-solid was obtained (43.0 mg, 0.129 mmol). Yield: 60%. $[\alpha]_D^{25}$ +15.3 (EtOH, *c* 1.10). ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.48–7.19 (m, 15H), 3.79 (m, 1H), 3.17 (m, 5H), 2.84 (m, 1H), 2.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 143.7, 128.6, 127.8, 126.9, 86.6, 70.6, 65.6, 44.2.

4.1.11. (*S*)-4-(Benzylamino)butane-1,2-diol 12c. (*S*)-*N*-Benzyl-3-hydroxy-4-(trityloxy)butanamide (160 mg, 0.354 mmol) was dissolved in anhydrous THF (4 mL). Lithium aluminum hydride (41.0 mg, 1.08 mmol) was added at 0 °C and the mixture was stirred for 48 h. The mixture was cooled to 0 °C and the reaction was quenched by addition of cold methanol and water. The aluminum salts formed were filtered out, and after concentration, the crude product was purified on silica gel with a gradient of CH_2Cl_2/hexane 9:1 to CH_2Cl_2/MeOH 20:1. The pure product was dried on vacuum pump and obtained as a white solid (109 mg, 0.249 mmol). Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.49–7.22 (m, 20H), 4.05 (m, 1H), 3.77 (dd, 2H, *J*=19.4, 13.1 Hz), 3.22 (dd, 1H, *J*=9.0, 5.7 Hz), 3.06 (dd, 1H, *J*=9.0, 5.8 Hz), 2.94 (m, 1H), 2.81 (m, 1H), 1.81 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 144.0, 139.3, 128.6, 128.4, 128.1, 127.7, 127.1, 126.9, 86.3, 71.9, 67.4, 53.7, 47.4, 32.2. HRMS calcd for $C_{30}H_{31}NO_2$ $[M+H]^+$ 438.2433, found 438.2418.

4.1.12. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)-butyl)-acetamide 13a. (*S*)-4-Amino-1-(trityloxy)butan-2-ol **12a** (583 mg, 1.68 mmol) was dissolved in anhydrous THF (10.0 mL). Pyridine (0.405 mL, 5.03 mmol) was added to the solution, which was stirred for 30 min. Trifluoroacetic anhydride (0.475 mL, 3.36 mmol) was added to the mixture and after stirring for another 30 min, the reaction was quenched with ice-water (2 mL). The solvent was then evaporated and the crude residue was dissolved in CH_2Cl_2 and washed twice with water and once with brine. The organic phase was then evaporated and the crude residue was purified on SiO_2 gel using a gradient of pure hexane to hexane/CH_2Cl_2/THF 9:1:1. The pure product was obtained as a white solid (565 mg, 1.27 mmol). Yield: 76%. Mp 80–82 °C, $[\alpha]_D^{25}$ +16.3 (CH_2Cl_2, *c* 1.04). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.60 (br s, 1H), 7.48–7.24 (m, 15H), 3.93 (m, 1H), 3.65 (m, 1H), 3.32 (m, 1H), 3.21 (dd, 1H, *J*=9.5, 3.8 Hz), 3.13 (m, 1H), 2.93 (br s, 1H), 1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 157.1 (q, C=O, ^2J=36.5 Hz), 143.5, 128.5, 127.9, 127.2, 115.9 (q, CF_3, ^1J=287.9 Hz), 86.9, 70.7, 67.3, 37.9, 30.9. HRMS calcd for $C_{25}H_{24}F_3NO_3$ $[M+Na]^+$ 466.1606, found 466.1598.

4.1.13. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-*N*-methylacetamide 13b. This compound was prepared via a similar method as the one used for the synthesis of **13a**. Compound **12b** (300 mg, 0.830 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 15:1:1. The pure product was obtained as a white solid (318 mg, 0.700 mmol). Yield: 86%. Mp 106–107 °C, $[\alpha]_D^{25}$ −14.0 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52–7.23 (m, 15H), 3.73 (m, 2H), 3.43 (m, 1H), 3.20 (m, 2H), 3.10

(s, 2H), 2.98 (s, 1H), 2.84 (br s, 1H), 1.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 156.9 (q, C=O, ^2J=35.7 Hz), 143.6, 128.5, 127.7, 126.9, 116.3 (q, CF_3, ^1J=287.7 Hz), 86.6, 67.9, 67.4, 46.5, 35.0 (q, CH_3, ^4J=3.8 Hz), 30.2; (minor tautomer) 156.7 (q, C=O, ^2J=35.7 Hz), 143.5, 128.4, 127.8, 127.0, 116.4 (q, CF_3, ^1J=287.6 Hz), 86.7, 68.2, 67.3, 46.4, 34.5, 32.0. HRMS calcd for $C_{26}H_{26}F_3NO_3$ $[M+Na]^+$ 480.1762, found 480.1764.

4.1.14. (*S*)-*N*-Benzyl-2,2,2-trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-acetamide 13c. This compound was prepared via a similar method as the one used for the synthesis of **13a**. Compound **12c** (88.6 mg, 0.202 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 15:1:1. The pure product was obtained as a white solid (85.0 mg, 0.159 mmol). Yield: 79%. Mp 139–140 °C, $[\alpha]_D^{25}$ −16.8 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47–7.21 (m, 20H), 4.67 (m, 2H), 3.74 (m, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 3.17 (m, 1H), 3.10 (m, 1H), 1.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.3 (q, C=O, ^2J=35.7 Hz), 143.5, 134.8, 128.7, 128.5, 127.9, 127.8, 127.2, 127.1, 116.5 (q, CF_3, ^1J=287.9 Hz), 86.7, 68.1, 67.2, 49.4, 43.4, 30.3; (minor tautomer) 157.3 (q, C=O, ^2J=35.7 Hz), 143.7, 135.4, 128.9, 128.7, 128.1, 127.9, 127.2, 127.1, 116.6 (q, CF_3, ^1J=287.9 Hz), 86.8, 68.4, 67.3, 50.9 (q, CH_2Ph, ^4J=3.1 Hz), 43.7 (q, CH_2N, ^4J=2.9 Hz), 32.2. HRMS calcd for $C_{32}H_{30}F_3NO_3$ $[M+Na]^+$ 556.2075, found 556.2090.

4.1.15. (*S*)-3-Methyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 14b. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)-butyl)-*N*-methylacetamide **13b** (54.0 mg, 0.118 mmol) was dissolved in anhydrous DMF (5.00 mL). Lithium hydroxide (31.0 mg, 1.30 mmol) was added and the solution was stirred at 65 °C for 12 h. The organic solvent was evaporated and the crude mixture taken up in CH_2Cl_2. The solid LiOH was filtered out and the solvent evaporated under nitrogen. The crude residue was purified on silica gel with a solvent system of hexane/THF/CH_2Cl_2 15:1:1. The pure product was isolated as white crystals (41.2 mg, 0.106 mmol). Yield: 90%. Mp 160.5–161 °C, $[\alpha]_D^{25}$ +32.5 (EtOAc, *c* 1.03). ($CDCl_3$, 400 MHz); δ 7.45–7.19 (m, 15H), 4.34 (m, 1H), 3.35 (dd, 1H, *J*=9.8, 4.7 Hz), 3.31 (dd, 1H, *J*=11.5, 5.7 Hz), 3.21 (m, 2H), 2.97 (s, 3H), 2.08 (m, 1H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.6, 143.5, 128.6, 127.8, 127.1, 86.8, 75.7, 64.7, 46.1, 36.5, 24.6. HRMS calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 410.1732, found 410.1737.

4.1.16. (*S*)-3-Benzyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 14c. (*S*)-*N*-Benzyl-2,2,2-trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-acetamide **13c** (156 mg, 0.292 mmol) was dissolved in anhydrous THF (4.00 mL). The mixture was cooled to 0 °C and sodium hydride (14.0 mg, 0.583 mmol) was added. The solution was stirred for 20 min and quenched by addition of methanol. The solvent was evaporated and the crude mixture was taken up in CH_2Cl_2. The organic solvent was washed with H_2O three times, separated from the aqueous solvent and dried on Na_2SO_4. After filtration, the solvent was evaporated and the residue was dried under vacuum. The pure product (120 mg, 0.260 mmol) was obtained without further purification. Yield: 89%. Mp 167–168 °C, $[\alpha]_D^{25}$ +29.0 (EtOAc, *c* 1.01). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52–7.25 (m, 20H), 4.60 (dd, 2H, *J*=21.1, 14.9 Hz), 4.43 (m, 1H), 3.43 (dd, 1H, *J*=9.7, 4.7 Hz), 3.23 (m, 3H), 2.10 (m, 1H), 1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.5, 143.4, 136.5, 128.5, 128.4, 127.9, 127.7, 127.5, 127.0, 86.6, 75.7, 64.6, 52.4, 43.2, 24.5. HRMS calcd for $C_{31}H_{29}NO_3$ $[M+H]^+$ 464.2226, found 464.2222.

4.1.17. (*S*)-4-(2,2,2-Trifluoroacetamido)-1-(trityloxy)-butan-2-yl-methanesulfonate 15a. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-acetamide **13a** (486 mg, 1.10 mmol) was dissolved in anhydrous CH_2Cl_2 (10.0 mL). The solution was cooled to 0 °C. Methanesulfonyl chloride (0.130 mL, 1.67 mmol) was added, followed by diisopropylethylamine (0.570 mL, 3.30 mmol). The mixture was stirred at 0 °C for 30 min and some ice-water was added to quench the reaction. The solution was diluted with dichloromethane and washed twice with water. The organic solvent was evaporated and the crude residue purified on SiO_2 gel using a gradient of pure hexane to hexane/CH_2Cl_2/THF 8:1:1. The pure product was obtained as a colorless semi-solid (536 mg, 1.03 mmol). Yield: 94%. $[\alpha]_D^{25}$ −17.7 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.45–7.22 (m, 15H), 7.18 (br s, 1H), 4.61 (m, 1H), 3.59 (m, 1H), 3.38 (m, 2H), 3.27 (m, 1H), 3.02 (s, 3H), 1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 157.3 (q, C=O, ^2J=36.5 Hz), 143.0, 128.4, 128.0, 127.4, 115.7 (q, CF_3, ^1J=287.9 Hz), 87.6, 79.7, 65.4, 38.6, 35.4, 30.6. HRMS calcd for $C_{26}H_{26}F_3NO_5S$ $[M+Na]^+$ 544.1381, found 544.1368.

4.1.18. (*S*)-4-(2,2,2-Trifluoro-*N*-methylacetamido)-1-(trityloxy)butan-2-yl-methanesulfonate 15b. This compound was prepared via a similar method as the one used for the synthesis of **15a**. Compound **13b** (194 mg, 0.424 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 15:1:1. The pure product was obtained as a brown oil (215 mg, 0.401 mmol). Yield: 95%. $[\alpha]_D^{25}$ +5.8 (EtOAc, *c* 1.05). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47–7.24 (m, 15H), 4.77 (m, 1H), 3.42 (m, 4H), 3.10 (s, 2H), 3.04 (s, 2H), 3.03 (s, 1H), 2.99 (s, 1H), 1.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 156.9 (q, C=O, ^2J=35.7 Hz), 143.1, 128.5, 127.9, 127.3, 116.3 (q, CF_3, ^1J=287.7 Hz), 87.4, 79.6, 64.9, 46.0, 38.7, 35.2 (q, CH_3, ^4J=3.9 Hz), 28.7; (minor tautomer) 156.9 (q, C=O, ^2J=35.7 Hz), 143.0, 128.4, 128.0, 127.4, 116.4 (q, CF_3, ^1J=287.3 Hz), 87.5, 78.7, 64.5, 45.7 (q, CH_2N, ^4J=2.9 Hz), 38.6, 34.6, 30.7. HRMS calcd for $C_{27}H_{28}F_3NO_5S$ $[M+Na]^+$ 558.1538, found 558.1532.

4.1.19. (*S*)-4-(*N*-Benzyl-2,2,2-trifluoroacetamido)-1-(trityloxy)butan-2-yl-methanesulfonate 15c. This compound was prepared via a similar method as the one used for the synthesis of **15a**. Compound **13c** (1.03 g, 1.93 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 15:1:1. The pure product was obtained as a colorless semi-solid (1.11 g, 1.81 mmol). Yield: 94%. $[\alpha]_D^{25}$ +3.50 (EtOAc, *c* 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.43–7.14 (m, 20H), 4.67 (m, 1H), 4.60 (m, 2H), 3.33 (m, 2H), 3.26 (m, 2H), 2.98 (s, 3H), 1.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.1 (q, C=O, ^2J=35.1 Hz), 143.1, 134.4,

129.0, 128.9, 128.4, 127.9, 127.4, 127.3, 116.4 (q, CF_3, ^1J=287.9 Hz), 87.2, 78.5, 64.5, 49.6, 42.9, 38.7, 28.7; (minor tautomer) 157.7 (q, C=O, ^2J=35.1 Hz), 143.1, 135.1, 129.0, 128.9, 128.3, 128.1, 127.4, 127.3, 116.5 (q, CF_3, ^1J= 288 Hz), 87.4, 78.5, 64.6, 51.2, 42.8, 38.6, 30.8. HRMS calcd for $C_{33}H_{32}F_3NO_5S$ $[M+Na]^+$ 634.1851, found 634.1853.

4.1.20. (*R*)-3-Methyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 16b. (*S*)-4-(2,2,2-Trifluoro-*N*-methylacetamido)-1-(trityloxy)butan-2-yl-methanesulfonate **15b** (147 mg, 0.247 mmol) was dissolved in anhydrous DMSO (4.00 mL). Potassium carbonate (114 mg, 0.825 mmol) was added and the solution was stirred at 120 °C for 3 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2, and washed with cold water three to four times. The dichloromethane was evaporated and the crude mixture was purified on silica gel with a solvent system of hexane/CH_2Cl_2/THF 12:1:1. The pure product was isolated as a white solid (58.0 mg, 0.150 mmol). Yield: 55%. Mp 163–164 °C, $[\alpha]_D^{25}$ −31.9 (EtOAc, *c* 1.03). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.45–7.20 (m, 15H), 4.33 (m, 1H), 3.35 (dd, 1H, *J*=9.7, 4.7 Hz), 3.30 (dd, 1H, *J*=10.9, 5.5 Hz), 3.21 (m, 2H), 2.96 (s, 3H), 2.07 (m, 1H), 1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.6, 143.5, 128.6, 127.8, 127.1, 86.7, 75.7, 64.7, 46.0, 36.5, 24.6. HRMS calcd for $C_{25}H_{25}NO_3$ $[M+H]^+$ 388.1913, found 388.1897.

4.1.21. (*R*)-3-Benzyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 16c. (*S*)-4-(*N*-Benzyl-2,2,2-trifluoroacetamido)-1-(trityloxy)butan-2-yl-methanesulfonate **15c** (600 mg, 0.980 mmol) was dissolved in anhydrous DMF (5.00 mL) and potassium carbonate (0.542 g, 3.92 mmol) was added to the solution. The mixture was stirred at 120 °C for 20 h. The organic was evaporated under nitrogen overnight and the residue taken up in CH_2Cl_2. The solid K_2CO_3 was filtered out and the solution concentrated to dryness. The crude product was purified on silica gel with a gradient of hexane/THF 19:1 to hexane/CH_2Cl_2/THF 8:1:1. The pure product was dried under vacuum and obtained as a white solid (281 mg, 0.606 mmol). Yield: 63%. Mp 166–167 °C, $[\alpha]_D^{25}$ −28.6 (EtOAc, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52–7.23 (m, 20H), 4.58 (dd, 2H, *J*=21.9, 14.9 Hz), 4.39 (m, 1H), 3.42 (dd, 1H, *J*=9.7, 4.8 Hz), 3.23 (m, 1H), 3.15 (m, 2H), 1.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 153.5, 143.4, 136.5, 128.5, 128.4, 127.8, 127.7, 127.4, 127.0, 86.6, 75.7, 64.6, 52.3, 43.2, 24.4. HRMS calcd for $C_{31}H_{29}NO_3$ $[M+H]^+$ 464.2226, found 464.2232.

4.1.22. (*R*)-2-(Trifluoromethyl)-6-(trityloxymethyl)-5,6-dihydro-4*H*-1,3-oxazine 17. (*S*)-4-(2,2,2-Trifluoroacetamido)-1-(trityloxy)butan-2-yl-methanesulfonate **15a** (91.5 mg, 0.175 mmol) was dissolved in anhydrous dimethylformamide (5.00 mL). Potassium carbonate (97.0 mg, 0.702 mmol) was added and the solution stirred at 85 °C for 45 min. The solvent was then evaporated under nitrogen and the crude mixture purified on SiO_2 gel using a solvent system of hexane/CH_2Cl_2/THF 8:1:1. The pure product was obtained as an off-white solid (58.4 mg, 0.137 mmol). Yield: 78%. Mp 106–108 °C, $[\alpha]_D^{25}$ −46.1 (CH_2Cl_2, *c* 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49–7.21 (m, 15H), 4.42 (m, 1H), 3.54 (m, 2H), 3.27 (m, 2H), 1.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 148.4 (q, C=N, ^2J=38.4 Hz), 143.9, 129.0, 128.4, 127.6, 117.2 (q, CF_3, ^1J=276.4 Hz), 87.2, 75.9, 65.6, 42.2, 23.8. HRMS calcd for $C_{25}H_{22}F_3NO_2$ $[M+H]^+$ 426.1681, found 426.1672.

4.1.23. (*R*)-4-Amino-1-(trityloxy)butan-2-ol 18. (*R*)-2-(Trifluoromethyl)-6-(trityloxymethyl)-5,6-dihydro-4*H*-1,3-oxazine **17** (65.6 mg, 0.154 mmol) was dissolved in absolute ethanol (6 mL). Cesium carbonate (0.500 g, 1.53 mmol) dissolved in 2.00 mL of water was added to the solution, which was refluxed for 36 h. The solvents were evaporated and the crude mixture was taken up in CH_2Cl_2. The insoluble salts were filtered out and the organic phase was washed once with water. After drying on Na_2SO_4, the solvent was evaporated and after drying under vacuum, the product was obtained as a colorless semi-solid (52.6 mg, 0.151 mmol). Yield: 98%. $[\alpha]_D^{25}$ +15.0 (EtOH, *c* 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.53–7.19 (m, 16H), 4.02 (m, 1H), 3.18 (dd, 1H, *J*=9.1, 6.1 Hz), 3.08 (dd, 1H, *J*=9.1, 5.4 Hz), 2.95 (m, 1H), 2.85 (m, 1H), 1.67 (m, 1H), 1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 143.9, 128.6, 127.8, 126.9, 86.4, 71.2, 67.6, 38.9, 35.1.

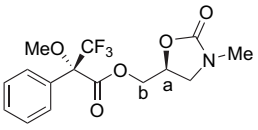
Acknowledgements

This work was supported in part by American Heart Association grant #0430285N.

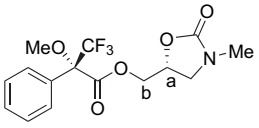
References and notes

1. Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010–2023.
2. Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175–194.
3. Gravestock, M. B. *Curr. Opin. Drug. Discov. Devel.* **2005**, *8*, 469–477.
4. Bush, K.; Macielag, M.; Weidner-Wells, M. *Curr. Opin. Microbiol.* **2004**, *7*, 466–476.
5. Renslo, A. R.; Luehr, G. W.; Gordeev, M. F. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 4227–4240.
6. Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021–1042.
7. Hollingsworth, R. I.; Wang, G.; Padmakumar, R.; Mao, J.; Zhang, H.; Dai, Z.; Puthuparampil, K. PCT Int. Appl. WO03106413 A, 2003; *Chem. Abstr.* **2003**, *140*, 59633.
8. Yamana, K.; Suzuki, N.; Takahama, A.; Ine, S. Jpn. Kokai Tokkyo Koho JP 179572, 2002; *Chem. Abstr.* **2002**, *137*, 57555.
9. Jin, F.; Confalone, P. N. PCT Int. Appl. WO0000481, 2000, 119 pp; *Chem. Abstr.* **2000**, *132*, 78560.
10. Wang, G.; Ella-Menye, J. R.; Sharma, V. *Bioorg. Med. Chem. Lett.* **2005**, *16*, 2177–2181.
11. Wong, G. S. K.; Wu, W. 2-Oxazolines. In *The Chemistry of Heterocyclic Compounds*; Palmer, D. C., Ed.; Oxazoles: Synthesis, Reactions, and Spectroscopy, Part B; John Wiley & Sons: Hoboken, NJ, 2004; Vol. 60, pp 331–528.
12. Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim Acta* **2003**, *36*, 39–50.
13. Sasaki, T.; Otani, T.; Yoshida, K.-I.; Unemi, N.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 881–883.
14. Wang, G.; Hollingsworth, R. I. *Tetrahedron: Asymmetry* **2000**, *11*, 4429–4432.
15. Ella-Menye, J. R.; Sharma, V.; Wang, G. *J. Org. Chem.* **2005**, *70*, 463–469.
16. Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12–13.

17. Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934–12935.
18. Crich, D.; Ranganathan, K.; Rumthao, S.; Shirai, M. *J. Org. Chem.* **2003**, *68*, 2034–2037.
19. Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 1983–1985.
20. Bergmeier, S. C.; Katz, S. J. *J. Comb. Chem.* **2002**, *4*, 162–166.
21. Kim, S. W.; Lee, J. G.; Lee, E. J.; Park Choo, H.-Y.; Yoo, C. Y.; Lee, D. Y.; Roh, K. R.; Kim, E. K. *J. Comb. Chem.* **2004**, *6*, 851–854.
22. Buchstaller, H.-P. *J. Comb. Chem.* **2003**, *5*, 789–793.
23. Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 5457–5460.
24. Miller, A. W.; Nguyen, S. T. *Org. Lett.* **2004**, *6*, 2301–2304.
25. Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J.-W.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 43–49.
26. Spino, C.; Tremblay, M.-C.; Gobdout, C. *Org. Lett.* **2004**, *6*, 2801–2804.
27. Osa, Y.; Hikima, Y.; Sato, Y.; Takino, K.; Ida, Y.; Hirono, S.; Nagase, H. *J. Org. Chem.* **2005**, *70*, 5737–5740.
28. Hein, J. E.; Geary, L. M.; Jaworski, A. A.; Hultin, P. G. *J. Org. Chem.* **2005**, *70*, 9940–9946.
29. ten Holte, P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **2001**, *3*, 1093–1095.
30. Dinsmore, C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885–2888.
31. Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2001**, *41*, 10071–10074.
32. Madhusudhan, G.; Om Reddy, G.; Ramanatham, J.; Dubey, P. K. *Tetrahedron Lett.* **2003**, *44*, 6323–6325.
33. Ghosh, A.; Shin, D.; Mathivanan, P. *Chem. Commun.* **1999**, 1025–1026.
34. Hollingsworth, R. I.; Wang, G. *Chem. Rev.* **2000**, *100*, 4267–4282.
35. Wang, G.; Hollingsworth, R. I. *J. Org. Chem.* **1999**, *64*, 1036–1038.
36. A small amount of compounds **5b** and **9** was deprotected using TFA to remove the trityl group and the free alcohol treated with Mosher's acid chloride to form the corresponding esters **24** and **25**. Integration of the signals on the ^{1}H NMR spectrum of the crude reaction products allowed us to confirm the optical purity with the optical rotation data. The crude 500 MHz ^{1}H NMR spectrum of compound **24** indicated no presence of diastereomer, the chemical shifts of protons a and b are: δ (ppm), 4.76 (br s, H*a*), 4.58 (d, 1H, H_b, J=0, 11.7 Hz), 4.41 (dd, H_b', J=3.9, 11.7 Hz), compound **25**: 4.78 (br s, H*a*), 4.58 (dd, 1H, H_b, J=2.9, 12.2 Hz), 4.37 (dd, H_b', J=3.9, 12.2 Hz), a small doublet impurity signal at 4.41 estimated less than 1% of the H_b' integration indicates that the purity of the enantiomer is 99%.



24



25

37. A small amount of compounds **14b**, **16b**, and their 1:1 mixture was converted to the corresponding hydroxyl trifluoromethyl ester derivatives by treating with TFA and trifluoroacetic anhydride. GC analysis of the derivatives using cyclodextrin column indicates that the optical purities of compounds **14b** and **16b** are both over 99% ee, there is no detectable presence of the opposite isomer.