Synthesis of Chiral Five-, Six-, and Seven-Membered Heterocycles from (*S*)-3-Hydroxy-γ-butyrolactone

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Abstract: Chiral small molecules such as amino alcohols and their heterocyclic derivatives are useful building blocks for asymmetric synthesis and the preparation of biologically active compounds. Using a common starting material derived from carbohydrate, the (*S*)-3-hydroxy-γ-butyrolactone, we have synthesized several five-, six-, and seven-membered nitrogen-containing chiral heterocycles. These include (*S*)-3-benzyloxypyrrolidine, a protected 6-substituted morpholin-3-one and its homologous 1,4-oxazepan-3-one, and 6-trityloxymethyl tetrahydro-1,3-oxazine-2-thiones. These chiral small heterocycles were synthesized from the lactone via efficient cyclization reactions. Their syntheses and characterization are reported here.

Key words: amino alcohols, heterocycles, cyclization, lactones, chiral pool, asymmetric synthesis

Chiral nitrogen and oxygen-containing heterocycles are important intermediates for the preparation of many biologically active compounds including natural products and medicinally relevant molecules. Among these, five- and six-membered-ring heterocycles are especially useful either as core structures for biologically active molecules[1]or as ligands for asymmetric synthesis.[2,3] Among five-membered-ring heterocycles, functionalized 3-hydroxypyrrolidines are very useful moieties found in many biologically interesting compounds.[4,5] Figure 1 shows several examples of medicinally active compounds containing various heterocyclic structures. Compounds **1** and **2** contain the 3-hydroxypyrrolidine core structure. The cyclohexylpyrrolidinol **1** and its analogues are ion channel modulating compounds and are also useful for the treatment of arrhythmia.[4] Compound **2** is a human 5-HT_{1D} receptor antagonist, which has significance in neurological disorder treatment.[5] Several other disubstituted pyrrolidines also exhibit both serotonergic activity[6] and phosphodiesterase 10A inhibition.[7] The six-membered-ring morpholinones or morpholines contained in compounds **3**–**6** are heterocyclic compounds that are of medicinal importance as well; they are present in many drug classes either as core structures or as functional groups that improve pharmacokinetic properties.[8] Compound **3** is a selective rat 5-hydroxytryptamine$_{1B}$ (5-HT_{1B}) receptor antagonist.[9] The aminomethyl morpholine **4** has shown activity against checkpoint kinase 1 (CHK1),[10] and may have applications in anticancer therapies. Another important class of nitrogen containing heterocycles is the cyclic carbamates. These functional groups are also found in several drug molecules, for instance, 5-aminomethyl oxazolidinone is the core structure of the orally available factor Xa inhibitor rivaroxaban (**5**)[11] and antibacterial agent linezolid (**6**).[12] We have previously demonstrated that the 6-aminomethyloxazinan-2-one derivatives also have important antibacterial activities.[1,13] Other oxazinan-2-one compounds have been explored as inhibitors of the 11-β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which may have implications in the treatment of obesity and insulin resistance. Compound **7** is an example of this class of compounds.[14] The analogous thiocarbamate functional group also has shown interesting biological relevance. Compound **8** is a nonsteroidal progesterone receptor agonist; its fluorinated analogues have been applied in breast tumor imaging.[15,16]

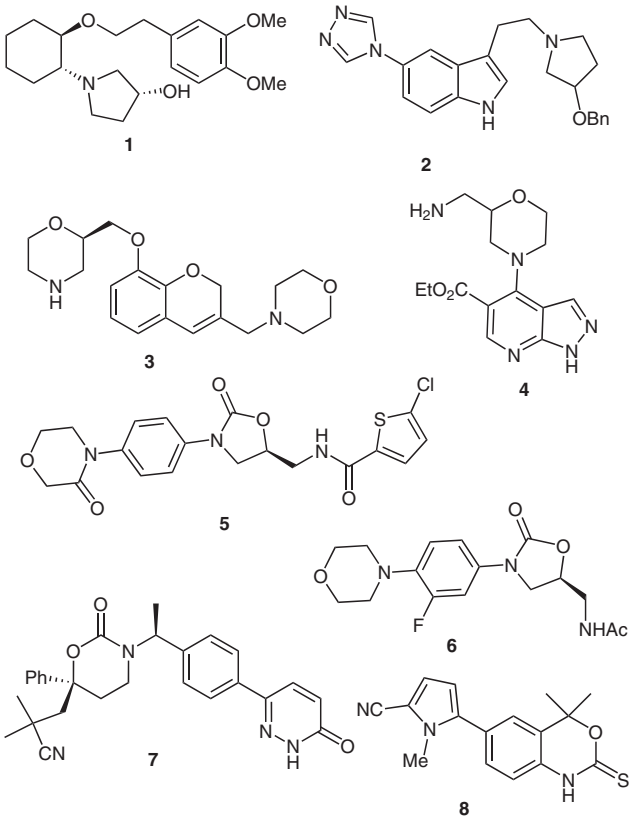

Figure 1 Structures of biological active compounds containing small chiral heterocycles derived from amino alcohols

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Because of their importance in the preparation of biologically active compounds, there have been many studies for the synthesis of these heterocycles and their derivatives.[17–32] Chiral amino alcohols are often used for the synthesis of heterocycles that are of biological relevance or that are used as ligands for asymmetric synthesis. In recent years, a versatile building block, (*S*)-3-hydroxy-γ-butyrolactone, has found many applications in organic synthesis. It is a commercially available compound that can be synthesized readily in large scale from carbohydrate feed stock such as starch or lactose.[33] The lactone has been converted into 1,2- and 1,3-amino alcohols and their derivatives via very efficient methods.[34,35] Using the (*S*)-3-hydroxy-γ-butyrolactone (**9**) as the starting material, we report here new and efficient synthetic routes to several protected small molecule heterocycles including the protected five-membered-ring pyrrolidine **10**, 6-hydroxymethylmorpholin-3-one **11**, 7-hydroxymethyl-1,4-oxazepan-3-one **12**, and the six-membered-ring oxazinan-2-thione **13** (Figure 2).

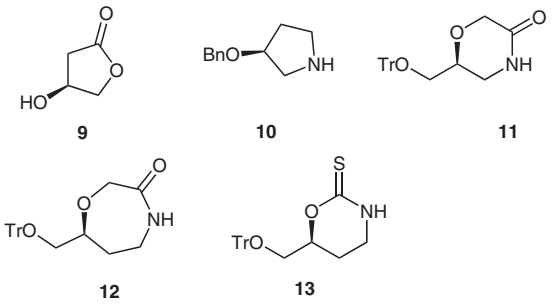
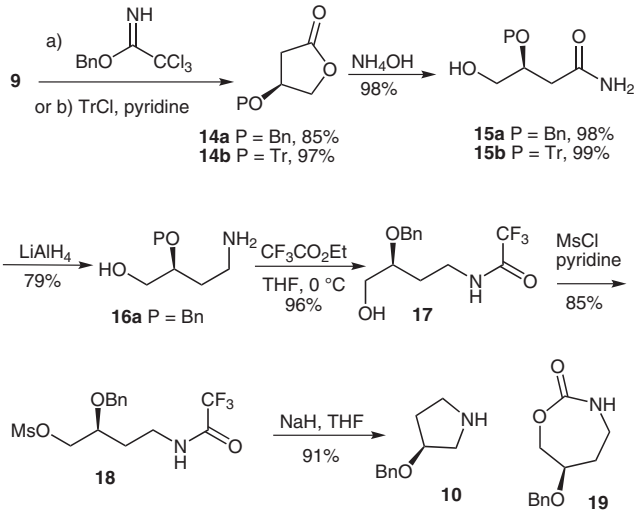


Figure 2 Structures of the heterocycles

The protected 3-hydroxypyrrolidine **10** can be synthesized from the lactone in a few steps. As shown in Scheme 1, the lactone was protected with a benzyl group under slightly acidic conditions to give compound **14a**, ring-opening with ammonia in water afforded the amide **15a** in nearly quantitative yield. Subsequent reduction of the amide afforded the key intermediate 1,4-amino alcohol **16a**. Protection of the primary amino group in **16a** gave trifluoroacetamide **17**, which was then converted into the mesylate **18**. Treating **18** with sodium hydride in THF directly produced the desired protected product (*S*)-3-benzyloxypyrrolidine (**10**). The trifluoromethyl group was released during the workup procedure. This procedure of converting the lactone into the protected pyrrolidine is very efficient and nearly all steps gave good to excellent yields. Therefore, this is a new and convenient route for the synthesis of pyrrolidine derivatives from carbohydrate raw materials.

During the synthesis, we also attempted to prepare a seven-membered-ring cyclic carbamate **19**. We had hoped that direct treatment of the 1,4-amino alcohol **16** with 1,1′-carbonyldiimidazole (CDI) would afford compound **19**, similarly to our previous synthesis of the six-membered-ring oxazinan-2-one by cyclization of the corresponding 1,3-

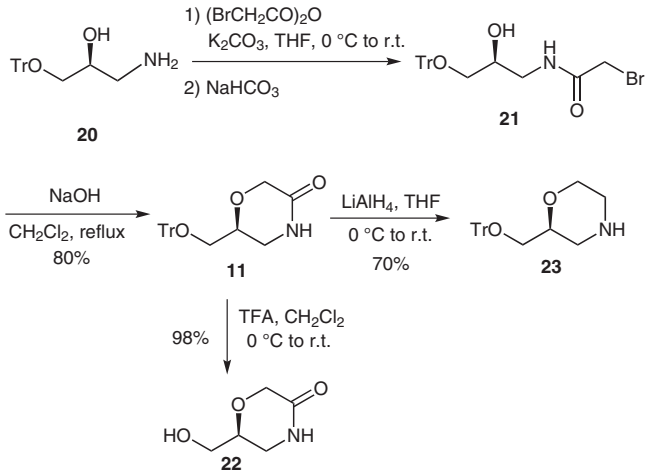


Scheme 1 Synthesis of five-membered-ring pyrrolidine **10**

amino alcohol.[27] However, this cyclization reaction did not work for the 1,4-amino alcohol **16**. Other methods of forming the cyclic carbamate were then tried in several attempts, including the conversion of the amino group into the corresponding open-chain carbamate using benzyl chloroformate or Boc anhydride, followed by base treatment to afford the cyclization product. However, none of these conditions were able to produce the seven-membered-ring carbamate **19**.

The benzyl protecting group was optimal for the scheme. The hydroxy group of the lactone could be protected using trityl chloride to afford compound **14b**, and the subsequent ammonia ring-opening gave compound **15b** in excellent yield. However, reduction of amide **15b** using $LiAlH_4$ did not afford the desired amino alcohol product **16b**, instead, the amide decomposed rapidly under $LiAlH_4$ treatment, mostly leading to eliminated intermediates and intractable mixture of by-products. We speculate that the trityl group is too bulky for the reaction to proceed as planned; under even mild basic conditions, elimination is favored over reduction. The benzyl group, on the other hand, causes much less steric hindrance and the amide reduction could be carried out successfully.

From amino alcohol **20**,[26] which was synthesized from the lactone **9**, 3,6-disubstituted 3-morpholinones can be synthesized (Scheme 2). Treating compound **20** with a slight excess of bromoacetic anhydride afforded the O- and N-acylated product, and the ester was selectively hydrolyzed using sodium bicarbonate at room temperature to give β-hydroxyamide **21** quantitatively. It was then cyclized using sodium hydroxide in dichloromethane under refluxing condition to afford the trityl-protected morpholinone **11**. Other conditions were tried for the cyclization of **21** such as using K_2CO_3, Na_2CO_3, and NaOH in THF, which all failed to give the desired product in good yield. The trityl group can be removed to afford the free 6-hydroxymethylmorpholin-3-one (**22**) in excellent yield, giving us a free hydroxy group that can be further functionalized. The nitrogen in **11** can be functionalized as well by N-alkylation,

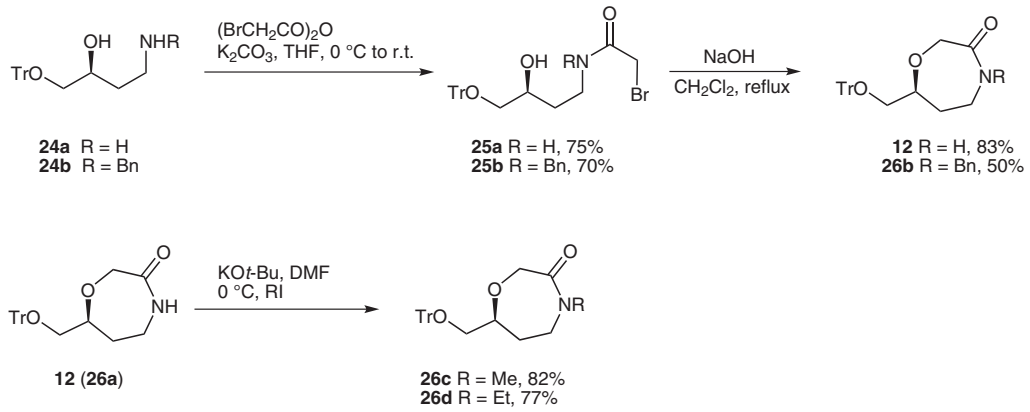


Scheme 2 Preparation of 3-morpholinones

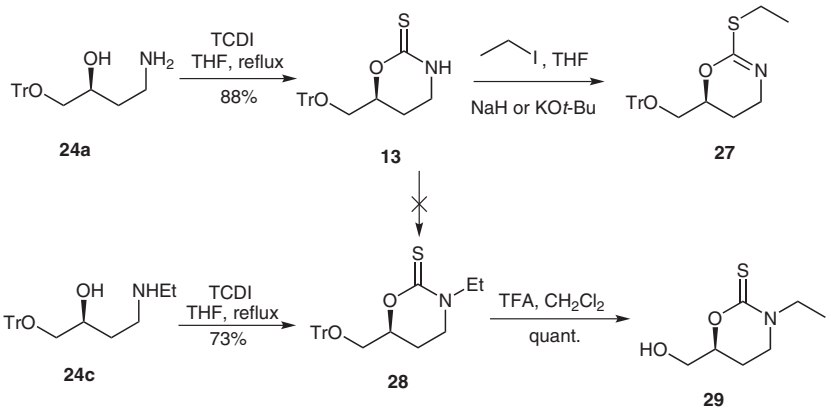
reductive amination, or N-arylation reactions to synthesize thrombin inhibitor analogous to compound **1**. The morpholinone can also be reduced to give the corresponding 6-trityl-protected hydroxymethylmorpholine **23**, another useful moiety in the synthesis of biologically active compounds.

Seven-membered homologues of **11** were also synthesized using a similar method. As shown in Scheme 3, amino alcohol **24** was converted into the corresponding bromoacetamide **25**, followed by an intramolecular SN_2 reaction to afford the 7-trityl-protected hydroxymethyl-1,4-oxazepan-3-ones **12** (≡ **26a**) and **26b**. When R = H, the cyclization reaction worked well, however, when R = Bn, the cyclization from the bromo compound gave a poorer yield of **26b**, probably due to steric hindrance of the benzylamide. However, this issue can be circumvented by alkylating the already cyclized oxazepan-3-one **12** (≡ **26a**) to obtain substituted products such as **26c** and **26d** in good yields. These novel seven-membered-ring heterocycles are expected to be valuable building blocks in the synthesis of biologically active compounds.

Besides the cyclic amides, several sulfur-containing cyclic carbamate derivatives were also synthesized using amino alcohols derived from the lactone **9**. As shown in Scheme 4, treating amino alcohol **24a** with thiocarbonyldiimidazole (TCDI) afforded the trityl-protected 6-trityloxymethyltetrahydro-1,3-oxazine-2-thione **13** smoothly in 88% yield. From this compound, we attempted alkylation on the nitrogen to obtain the *N*-ethyl-alkylated compound **28**, however, the reaction only led to the sulfur-alkylated product **27** as the main product. An alternative route was then used for the preparation of N-alkylated analogues. Starting from the amino alcohol **24c**, cyclization with TCDI afforded the ethyl-substituted product **28**.



Scheme 3 Preparation of trityl-protected oxazepan-3-one



Scheme 4 Synthesis of thiazinan-3-one and derivatives

Deprotection of the trityl group led to compound **29**, which can be converted into the corresponding mesylate and then alkylated with various halides to generate a small molecule library for the screening of biological activities.

In conclusion, using amino alcohols derived from (*S*)-3-hydroxy-γ-butyrolactone, we have synthesized several nitrogen-containing heterocycles. These include the (*S*)-3-benzyloxypyrrolidine, which was obtained from the corresponding 1,4-amino alcohol. Starting from 1,3-amino alcohol derivatives obtained from the lactone, 6-hydroxymethylthiaoxazinanone, 6-hydroxymethylmorpholin-3-one, and 7-hydroxymethyl[1,4]oxazepan-3-one were synthesized efficiently. Since the lactone **9** can be prepared from readily available starch or lactose in a one-pot reaction, the methods reported here represent access to important chiral molecules using affordable and renewable carbohydrates as starting materials. These compounds are expected to be useful in the preparation of medicinally important compounds.

General chemicals and reagents were purchased from Sigma-Aldrich or VWR International and used directly. The optically pure lactone was provided by Afid Therapeutics. NMR spectra were recorded using a 400 MHz Varian NMR spectrometer and a Bruker 250 MHz NMR spectrometer. High-resolution mass spectrometry data were measured on the Q-Tof UE521 of the Mass Spectrometry lab at the University of Illinois at Urbana Champaign after the low-resolution masses were confirmed. The ionization technique used was ESI (electrospray ionization) in ES+ mode. Melting points were measured using a Fisher-Jones melting point apparatus. Optical rotations were measured using a Rudolph Autopol III 6768MFG 1991 polarimeter; the concentrations reported here are in g/100 mL.

(*S*)-3-Benzyloxy-γ-butyrolactone (14a)

(*S*)-3-Hydroxy-γ-butyrolactone (**9**; 0.400 g, 4.90 mmol) was dissolved in 1,4-dioxane (5 mL) in a round-bottomed flask. Then, benzyl 2,2,2-trichloroacetimidate (1.48 g, 5.88 mmol) and trifluoroacetic acid (0.056 g, 0.49 mmol) were added to the flask. The reaction mixture was stirred at r.t. for 16 h, and then partitioned between EtOAc (150 mL) and H_2O (100 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with brine (200 mL) and dried (Na_2SO_4). The solvent was removed on a rotovap and the residue was purified by silica gel flash column chromatography (hexane–EtOAc, 4:1). The pure product was obtained as a colorless oil; yield: 0.64 g (85%, 3.33 mmol); $[\alpha]_D^{25}$ –27.6 (*c* = 1.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.38, (m, 5 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.34–4.40 (m, 3 H), 2.60–2.72 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 136.9, 128.6, 128.2, 127.7, 73.8, 73.1, 71.2, 35.0.

The NMR data matched with the values reported in the literature.[36]

(*S*)-3-Trityloxy-γ-butyrolactone (14b)

To a stirred solution of **9** (1.00 g, 9.8 mmol) in THF (20 mL) were added trityl chloride (3.00 g, 10.8 mmol) and pyridine (1.74 mL, 19.6 mmol). The reaction mixture was stirred at 50 °C for 48 h, after which the reaction mixture was partitioned between EtOAc (200 mL) and H_2O (150 mL). The aqueous phase was extracted with EtOAc (2 × 200 mL). The organic phases were combined, washed with brine (100 mL), and dried (Na_2SO_4). After filtration and concentration of the solution on the rotavap, the crude residue was purified by silica gel flash column chromatography using a gradient of hexane–EtOAc (16:1 to 6:1) to give the final compound as a white solid; yield: 3.27 g (97%, 9.49 mmol); mp 92–93 °C; $[\alpha]_D^{25}$ –10.1 (*c* = 10, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.43 (m, 6 H), 7.40–7.28 (m, 9 H), 4.51 (m, 1 H), 3.86 (dd, *J* = 5.9, 9.9 Hz, 1 H), 3.80 (dd, *J* = 4.4, 9.9 Hz, 1 H), 2.34 (dd, *J* = 5.5, 17.9 Hz, 1 H), 2.29 (dd, *J* = 7.0, 17.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.3, 143.6, 128.4, 128.1, 127.5, 87.8, 73.3, 69.4, 35.6.

HRMS: *m*/*z* calcd for $C_{23}H_{20}O_3$ + Na $[M + Na]^+$: 367.1310; found: 367.1310.

(*S*)-3-Benzyloxy-4-hydroxybutanamide (15a)

To a solution of **14a** (600 mg, 3.12 mmol) in THF (5 mL) was added NH_4OH (218 mg, 6.24 mmol) and the reaction mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (25 mL) and the solvent phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). After filtration, the solution was concentrated on a rotovap. The obtained residue was purified using silica gel flash chromatography (hexane–EtOAc, 3:1) to afford the pure product as a semi-solid; yield: 1.06 g (98%, 5.06 mmol); $[\alpha]_D^{25}$ –23.4 (*c* = 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.37 (m, 5 H), 4.61 (s, 2 H), 3.93–3.98 (m, 1 H), 3.78 (dd, *J* = 4.0, 11.7 Hz, 1 H), 3.62 (dd, *J* = 4.3, 11.7 Hz, 1 H), 2.48–2.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 137.7, 128.6, 128.0, 127.9, 76.6, 72.2, 63.5, 38.2.

HRMS: *m*/*z* calcd for $C_{11}H_{15}NO_3$ + Na $[M + Na]^+$: 232.0950; found: 232.0948.

(*S*)-4-Hydroxy-3-(trityloxy)butanamide (15b)

To a stirred solution of **14b** (1.00 g, 2.80 mmol) in THF (10 mL) was added NH_4OH (0.969 mL, 27.7 mmol). The reaction mixture was stirred at r.t. overnight, then diluted with CH_2Cl_2 (100 mL), and the organic layer was washed with H_2O (70 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic phases were combined, washed with brine (50 mL), and dried (Na_2SO_4). After filtration and concentration on the rotovap, the crude mixture was purified by silica gel flash chromatography using a gradient of hexane–CH_2Cl_2–acetone (8:1:1 to 2:1:1) to give the pure product as a semi-solid; yield: 1.03 g (99%, 2.84 mmol); mp 135.0–136.0 °C; $[\alpha]_D^{25}$ +14.2 (*c* = 1.7, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.3 Hz, 6 H), 7.30 (m, 9 H), 5.52 (s, 2 H, NH_2), 4.00 (m, 1 H), 3.52 (m, 2 H), 2.91 (m, 1 H, OH), 2.02 (dd, *J* = 3.7, 14.7 Hz, 1 H), 1.94 (dd, *J* = 7.0, 14.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 144.3, 128.7, 128.1, 127.4, 87.4, 70.8, 64.3, 38.4.

HRMS: *m*/*z* calcd for $C_{23}H_{24}NO_3$ $[M + H]^+$: 362.1756; found: 362.1769.

(*S*)-4-Amino-2-(benzyloxy)butan-1-ol (16a)

To a stirred suspension of $LiAlH_4$ (0.0597 g, 11.9 mmol) in anhyd THF (10 mL) at 0 °C was added slowly the amide **15a** (0.500 g, 2.39 mmol). The solution was brought to r.t. and refluxed for 6 h under anhydrous conditions. The reaction was quenched with cold MeOH (10 mL) and diluted with CH_2Cl_2 (20 mL). The solution was filtered through a pad of Celite and concentrated on the rotovap. The crude product was purified by silica gel flash chromatography (2% MeOH in CH_2Cl_2) to afford pure amino alcohol **16a** as a semi-solid; yield: 0.370 g (79%, 1.88 mmol); $[\alpha]_D^{25}$ –18.7 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.34 (m, 5 H), 4.54–4.62 (m, 2 H), 3.65 (dd, *J* = 5.4, 11.7 Hz, 1 H), 3.62 (dd, *J* = 4.0, 11.7 Hz, 1 H), 3.56 (q, *J* = 5.1 Hz, 1 H), 2.89–2.96 (m, 1 H), 2.72–2.78 (m, 1 H), 1.68–1.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 128.4, 127.7, 127.6, 78.0, 71.1, 63.6, 37.6, 35.3.

HRMS: *m*/*z* calcd for $C_{11}H_{18}NO_2$ [M + H]$^+$: 196.1338; found: 196.3333.

(*S*)-*N*-[3-(Benzyloxy)-4-hydroxybutyl]-2,2,2-trifluoroacetamide (17)

Compound **16a** (0.100 g, 0.510 mmol) was dissolved in THF (2.50 mL) and cooled to 0 °C in an ice-bath. Ethyl trifluoroacetate (0.060 mL, 1.0 mmol) was added to the solution and the mixture was stirred at 0 °C for 10 min, by which time the reaction was complete. The reaction was quenched by the addition of ice-cold H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). After filtration and concentration on the rotovap, the crude residue was purified by silica gel flash chromatography using a gradient of hexane–EtOAc (12:1 to 6:1) to afford the pure product as a colorless liquid; yield: 0.143 g (96%, 0.49 mmol); $[\alpha]_D^{25}$ –22.5 (*c* = 1, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.50 (m, 5 H), 4.68 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 3.84 (dd, *J* = 7.3, 4.7 Hz, 1 H), 3.48–3.69 (m, 2 H), 3.29–3.45 (m, 1 H), 1.83–1.93 (m, 1 H), 1.65–1.82 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 157.3, 156.9, 156.5, 137.5, 128.7, 128.2, 128.0, 120.1, 117.2, 114.3, 111.5, 77.8, 71.8, 63.3, 37.0, 30.0.

HRMS: *m*/*z* calcd for $C_{13}H_{16}F_3NO_3$ + Na [M + Na]$^+$: 314.0980; found: 314.0986; *m*/*z* calcd for $C_{13}H_{17}F_3NO_3$ [M + H]$^+$: 292.1161; found: 292.1164.

(*S*)-2-Benzyloxy-4-(2,2,2-trifluoroacetamido)butyl Methanesulfonate (18)

Compound **17** (0.150 g, 0.51 mmol) was mixed with pyridine (0.41 mL, 5.1 mmol) in anhyd THF (2.00 mL). The solution was cooled to 0 °C and MsCl (0.120 mL, 1.53 mmol) was added and the mixture was stirred at r.t. overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4). After filtration and concentration on the rotovap, the crude residue was purified by silica gel flash chromatography with a gradient of hexane–EtOAc (12:1 to 6:1). The pure product was obtained as a colorless liquid; yield: 0.16 g (85%, 0.43 mmol); $[\alpha]_D^{25}$ –20.2 (*c* = 1.3, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 5 H), 6.70 (s, 1 H), 4.75 (d, *J* = 11.4 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.35 (dd, *J* = 4.4, 11.0 Hz, 1 H), 4.23 (dd, *J* = 4.7, 11.0 Hz, 1 H), 3.78 (td, *J* = 8.4, 4.2 Hz, 1 H), 3.52 (ddd~dt, *J* = 6.6, 13.2 Hz, 1 H), 3.35 (ddd~dt, *J* = 5.4, 6.6, 13.2 Hz, 1 H), 3.03 (s, 3 H), 1.76–1.94 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.3, 156.9, 136.9, 128.7, 128.5, 128.3, 117.1, 114.0, 74.9, 72.5, 69.5, 37.6, 36.8, 30.2.

HRMS: *m*/*z* calcd for $C_{14}H_{19}F_3NO_5S$ [M + H]$^+$: 370.0936; found: 370.0936.

(*S*)-3-(Benzyloxy)pyrrolidine (10)[37]

The mesylate **18** (0.050 g, 0.14 mmol) was dissolved in anhyd THF (1.5 mL). The mixture was cooled to 0 °C in an ice-bath, and then NaH (0.0071 g, 0.30 mmol) was added. The reaction mixture was stirred at r.t. for 6 h. The reaction was quenched with ice-cold H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (Na_2SO_4). After filtration, the solvent was removed on the rotovap and the crude residue was purified by silica gel flash chromatography using a gradient of hexane–EtOAc (12:1 to 6:1). The pure product was obtained as a yellow liquid; yield: 0.023 g (91%, 0.13 mmol); $[\alpha]_D^{25}$ +2.2 (*c* = 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.38 (m, 5 H), 4.48 (br s, 2 H), 4.11 (m, 1 H), 3.05–3.18 (m, 1 H), 2.78–2.91 (m, 1 H), 1.84–1.96 (m, 2 H), 1.75–2.07 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.4, 127.6, 127.6, 80.0, 70.9, 53.2, 45.8, 32.8.

HRMS: *m*/*z* calcd for $C_{11}H_{16}NO$ [M + H]$^+$: 178.1232; found: 178.1230.

(*S*)-2-Bromo-*N*-[2-hydroxy-3-(trityloxy)propyl]acetamide (21)

(*S*)-1-Amino-3-(trityloxy)propan-2-ol (**20**; 0.990 g, 2.97 mmol) was dissolved in anhyd THF (10.0 mL). The reaction mixture was kept at 0 °C and bromoacetic anhydride (0.926 g, 3.56 mmol) and K_2CO_3 (0.820 g, 5.94 mmol) were added to the solution. After stirring at 0 °C for 30 min and at r.t. for 2 to 3 h, the K_2CO_3 was filtered off and the THF evaporated on the rotovap. Ice-water (5–10 mL) was then added and the diacetylated product was extracted with EtOAc (3 × 25 mL). After evaporating the EtOAc, the product was directly stirred with $NaHCO_3$ in a mixture of EtOH, THF, and H_2O (1:1:1) at r.t. for 12 h. The EtOH and THF were removed by concentration on the rotovap and the monoacetylated product was extracted with CH_2Cl_2 (3 × 25 mL). After removing the CH_2Cl_2, the product was obtained as an off-white semi-solid; yield: 1.34 g (99%, 2.95 mmol), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.15 (m, 15 H), 6.77 (br s, 1 H), 3.91 (m, 1 H), 3.78 (s, 2 H), 3.54 (m, 1 H), 3.27 (m, 1 H), 3.17 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 143.5, 128.5, 127.9, 127.2, 86.9, 69.7, 64.9, 43.1, 28.9.

HRMS: *m*/*z* calcd for $C_{24}H_{24}BrNO_3$ + Na [M + Na]$^+$: 476.0837; found: 476.0839.

(*S*)-6-[(Trityloxy)methyl]morpholin-3-one (11)

The amide **21** (0.211 g, 0.464 mmol) was dissolved in anhyd CH_2Cl_2 (8 mL). NaOH (0.093 g, 2.33 mmol) was added to the solution, which was refluxed for 1.5 h. The solid residue was filtered off and washed with CH_2Cl_2 (~5 mL), and the organic phase was washed with sat. aq NH_4Cl (2 × 5 mL), H_2O (2 × 5 mL), and brine (5 mL). The aqueous phase was separated and the organic phase dried (Na_2SO_4). After filtration, the solvent was evaporated and the pure product was obtained as a white crystalline solid after drying under high vacuum and used without further purification; yield: 0.139 g (80%, 0.372 mmol); mp 187–187.5 °C; $[\alpha]_D^{25}$ –47.4 (*c* = 1.04, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.52–7.22 (m, 16 H), 4.29 (d, *J* = 16.9 Hz, 1 H), 4.17 (d, *J* = 16.9 Hz, 1 H), 3.87 (m, 1 H), 3.37 (m, 3 H), 3.15 (dd, *J* = 9.6, 5.9 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.4, 143.4, 128.5, 127.8, 127.1, 86.8, 72.0, 67.4, 63.8, 43.9.

HRMS: *m*/*z* calcd for $C_{24}H_{24}NO_3$ [M + H]$^+$: 374.1756; found: 374.1773.

(*S*)-6-(Hydroxymethyl)morpholin-3-one (22)

Compound **11** (0.090 g, 0.242 mmol) was dissolved in anhyd CH_2Cl_2 (4 mL). The solution was cooled to 0 °C for 5 min and trifluoroacetic acid (0.036 mL, 0.485 mmol) was added slowly. The mixture was stirred at r.t. for 4 h. The solvent was then evaporated and MeOH (4 × 1 mL) was successively added and evaporated. The crude mixture was taken up in H_2O (5 mL) and the precipitated trityl salts were filtered off. The aqueous phase was extracted with hexane (2 × 5 mL) and then dried under N_2 and subsequently under high vacuum. The pure product was obtained as a colorless semi-solid,

which was used without further purification; yield: 0.0311 g (98%; 0.237 mmol); $[\alpha]_D^{25}$ –42.9 (*c* = 1.04, EtOH).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.26 (br s, 1 H), 4.34 (d, *J* = 16.9 Hz, 1 H), 4.22 (d, *J* = 16.9 Hz, 1 H), 3.85 (m, 1 H), 3.78 (m, 1 H), 3.68 (dd, *J* = 11.7, 5.6 Hz, 1 H), 3.47 (m, 1 H), 3.30 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.3, 72.9, 66.7, 62.6, 42.5.

(*S*)-2-(Trityloxymethyl)morpholine (23)

Compound **11** (0.055 g, 0.15 mmol) was dissolved in anhyd THF (5 mL). The solution was cooled to 0 °C and stirred for 10 min. $LiAlH_4$ (0.017 g, 0.45 mmol) was added to the solution under N_2 and the reaction mixture was stirred for 2 h. Ice-water (10 mL) was added to quench the reaction, and the precipitated aluminum salts were filtered off. The THF was evaporated and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers was washed with H_2O (5 mL) and brine (5 mL), then evaporated and the product was dried under N_2 and under vacuum to afford a colorless semi-solid, which was used without further purification; yield: 0.037 g (70%, 0.103 mmol); $[\alpha]_D^{25}$ +13.0 (EtOH, *c* = 1.00).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49–7.19 (m, 16 H), 3.86 (m, 1 H), 3.69 (m, 1 H), 3.59 (dd, *J* = 11.2, 3.4 Hz, 1 H), 3.22 (dd, *J* = 9.3, 5.1 Hz, 1 H), 3.04 (m, 2 H), 2.81 (m, 2 H), 2.62 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 143.9, 128.6, 127.8, 127.0, 86.5, 75.9, 67.9, 65.1, 49.0, 45.9.

(*S*)-2-Bromo-*N*-[3-hydroxy-4-(trityloxy)butyl]acetamide (25a)

(*S*)-4-Amino-1-(trityloxy)butan-2-ol (**24a**; 3.85 g, 11.1 mmol) was dissolved in anhyd THF (60 mL). K_2CO_3 (3.06 g, 22.1 mmol), then bromoacetic anhydride (3.80 g, 14.6 mmol) were added and the solution was stirred at r.t. for 5–6 h. The K_2CO_3 was filtered off and the THF was evaporated on the rotovap. The solid residue was purified by silica gel flash chromatography (hexane–CH_2Cl_2–THF 6:3:1) and the pure product was isolated as a white solid; yield: 6.21 g (75%, 8.33 mmol); mp 79.0–80.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.23 (m, 15 H), 7.18 (s, 1 H), 3.87 (m, 1 H), 3.84 (s, 2 H), 3.58 (m, 1 H), 3.26 (m, 1 H), 3.14 (m, 2 H), 2.93 (br s, 1 H), 1.65 (m, 1 H), 1.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 143.6, 128.5, 127.8, 127.1, 86.8, 69.8, 67.4, 37.8, 32.0, 29.2.

(*S*)-*N*-Benzyl-2-bromo-*N*-[3-hydroxy-4-(trityloxy)butyl]acetamide (25b)

(*S*)-4-(Benzylamino)-1-(trityloxy)butan-2-ol (**24b**; 0.230 g, 0.530 mmol) was mixed with K_2CO_3 (0.218 g, 1.58 mmol) in THF (3.00 mL) and the mixture was cooled to 0 °C. Bromoacetic anhydride (0.205 g, 0.790 mmol) was added and the reaction mixture was stirred at r.t. The mixture was then diluted with CH_2Cl_2 (15 mL), the organic layer was washed with H_2O (3 × 5 mL), and dried (Na_2SO_4). After filtration, the solvent was removed in vacuo and the crude was purified by silica gel flash chromatography (hexane–EtOAc, 3:1). The pure product was obtained as a colorless liquid; yield: 0.207 g (70%, 0.370 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (major rotamer) = 7.17–7.51 (m, 20 H), 4.69 (d, *J* = 16.9 Hz, 1 H), 4.56 (d, *J* = 16.9 Hz, 1 H), 3.58–3.76 (m, 3 H), 3.31–3.54 (m, 2 H), 2.99–3.17 (m, 2 H), 2.41 (d, *J* = 3.3 Hz, 1 H, OH), 1.45–1.70 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major rotamer) = 168.1, 143.9, 136.8, 129.1, 128.7, 128.6, 128.0, 127.8, 127.5, 127.3, 127.0, 126.23, 86.6, 67.7, 67.4, 52.2, 48.1, 43.5, 31.3, 26.3.

(*S*)-7-(Trityloxy)methyl-1,4-oxazepan-3-one (12 ≡ 26a)

(*S*)-2-Bromo-*N*-[3-hydroxy-4-(trityloxy)butyl]acetamide (**25a**; 156 mg, 0.333 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL). NaOH (66.6 mg, 1.67 mmol) was added to the solution and the mixture was stirred for 6 h. The solid residue was filtered off and the organic layer was washed with sat. aq NH_4Cl (2 × 5 mL), then with H_2O (5 mL) and brine (5 mL). After drying (Na_2SO_4) and filtration, the solvent was evaporated and the residue dried under vacuum to afford a fluffy white solid; yield: 107 mg (83%, 0.276 mmol); mp 88–90 °C; $[\alpha]_D^{25}$ –36.2 (*c* = 1.02, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.41–7.11 (m, 15 H), 6.42 (br s, 1 H), 4.32 (d, *J* = 15.9 Hz, 1 H), 4.05 (d, *J* = 15.9 Hz, 1 H), 3.70 (m, 1 H), 3.34 (m, 1 H), 3.20 (dd, *J* = 9.6, 5.9 Hz, 1 H), 2.94 (dd, *J* = 9.6, 5.0 Hz, 1 H), 1.92 (m, 1 H), 1.70 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.4, 143.8, 128.6, 127.8, 86.6, 79.9, 71.5, 65.8, 39.2, 32.5.

HRMS: *m*/*z* calcd for $C_{25}H_{25}NO_3$ + Na $[M + Na]^+$: 410.1732; found: 410.1734.

(*S*)-4-Benzyl-7-[(trityloxy)methyl]-1,4-oxazepan-3-one (26b)

Compound **25b** (0.070 g, 0.13 mmol) was mixed with NaOH (0.025 g, 0.60 mmol) in THF (1.50 mL) and the mixture was heated to reflux for 24 h. The crude was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with H_2O (3 × 5 mL). The organic phase was dried (Na_2SO_4) and after filtration, the solvent was removed in vacuo. The crude residue was purified by silica gel flash chromatography (hexane–EtOAc, 3:1). The pure product was obtained as a white solid; yield: 0.031 g (50%, 0.065 mmol); mp 145.0–146.5 °C; $[\alpha]_D^{25}$ –29.7 (*c* = 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.45 (m, 6 H), 7.20–7.36 (m, 14 H), 4.60 (s, 2 H), 4.54 (d, *J* = 15.7 Hz, 1 H), 4.26 (d, *J* = 15.7 Hz, 1 H), 3.73 (m 1 H), 3.46 (ddd, *J* = 14.6, 8.4, 2.2 Hz, 1 H), 3.30 (ddd, *J* = 14.6, 8.8, 2.2 Hz, 1 H), 3.24 (dd, *J* = 5.9, 9.5 Hz, 1 H), 2.98 (dd, *J* = 9.5, 5.1 Hz, 1 H), 1.82–1.92 (m, 1 H), 1.62–1.74 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 143.8, 137.1, 128.6, 128.1, 127.8, 127.5, 127.0, 86.6, 79.2, 71.8, 65.7, 51.6, 45.1, 31.6.

HRMS: *m*/*z* calcd for $C_{32}H_{31}NO_3$ + Na $[M + Na]^+$: 500.2202; found: 500.2206.

(*S*)-4-Methyl-7-[(trityloxy)methyl]-1,4-oxazepan-3-one (26c)

The oxazepanone **26a** (≡ **12**) (0.126 g, 0.325 mmol) was dissolved in anhyd DMF (1.50 mL) and cooled to 0 °C. KO*t*-Bu (0.077 g, 0.65 mmol) was added to the solution. After stirring at 0 °C for 5 min, the reaction mixture was allowed to warm to r.t. and stirred for an additional 50 min, at which point MeI (0.060 mL, 0.94 mmol) was added. The mixture was stirred under anhydrous atmosphere using $CaCl_2$ drying tube for about 2 h. The reaction mixture was quenched by the addition of dil HCl (~0.1 M; 5 mL). The product was extracted from the aqueous layer with CH_2Cl_2 (3 × 10 mL) and dried (Na_2SO_4). After filtration, the solvent was removed in vacuo and the crude residue was purified by silica gel flash chromatography (hexane–acetone, 9:1). The pure product was obtained as a light yellow liquid; yield: 0.106 g (82%, 0.265 mmol); $[\alpha]_D^{25}$ –38.0 (*c* = 3.9, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.40 (m, 6 H), 7.35–7.20 (m, 9 H), 4.44 (d, *J* = 15.7 Hz, 1 H), 4.18 (d, *J* = 15.7 Hz, 1 H), 3.77 (m, 1 H), 3.52 (ddd, *J* = 14.6, 8.6, 2.1 Hz, 1 H), 3.32–3.42 (m, 1 H), 3.27 (dd, *J* = 9.5, 5.9 Hz, 1 H), 3.01 (m, 1 H), 2.99 (s, 3 H), 1.98–2.07 (m, 1 H), 1.75–1.88 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 143.8, 128.6, 127.8, 127.0, 86.6, 78.8, 71.5, 65.6, 47.5, 36.4, 31.3.

HRMS: *m*/*z* calcd for $C_{26}H_{27}NO_3$ + Na $[M + Na]^+$: 424.1889; found: 424.1888.

(*S*)-4-Ethyl-7-[(trityloxy)methyl]-1,4-oxazepan-3-one (26d)

Compound **26d** was prepared from **26b** using EtI by a similar method as for the synthesis of compound **26c** and the pure product was

obtained as a colorless liquid; yield: 0.109 g (77%, 0.262 mmol); $[\alpha]_D^{25}$ –48.5 (*c* = 2.4, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.50 (m, 6 H), 7.21–7.35 (m, 9 H), 4.44 (d, *J* = 15.6 Hz, 1 H), 4.18 (d, *J* = 15.6 Hz, 1 H), 3.75 (m, 1 H), 3.48–3.57 (m, 1 H), 3.43 (m, 2 H), 3.31–3.40 (m, 1 H), 3.27 (dd, *J* = 9.5, 5.9 Hz, 1 H), 3.02 (dd, *J* = 9.5, 5.3 Hz, 1 H), 1.96–2.03 (m, 1 H), 1.71–1.83 (m, 1 H), 1.12 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 143.7, 128.5, 127.7, 126.9, 86.4, 79.0, 71.8, 65.6, 45.0, 43.3, 31.9, 12.7.

HRMS: *m*/*z* calcd for $C_{27}H_{29}NO_3$ + Na $[M + Na]^+$: 438.2045; found: 438.2050.

(*S*)-6-[(Trityloxy)methyl]-1,3-oxazinane-2-thione (13)

(*S*)-4-Amino-1-(trityloxy)butan-2-ol (**24a**; 0.057g, 0.16 mmol) was mixed with thiocarbonyldiimidazole (TCDI) (0.059 g, 0.32 mmol) in 1,4-dioxane (6.0 mL) and the solution was heated to reflux at 120 °C for 24 h. The mixture was diluted with CH_2Cl_2 (10 mL), the organic layer washed with H_2O (2 × 5 mL), and dried (Na_2SO_4). The crude residue was purified by silica gel flash column chromatography using a gradient of hexane–EtOAc (6:1 to 2.5:1). The pure product was obtained as a light yellow solid; yield: 0.055 g (88%, 0.14 mmol); mp 155.0–156.0 °C; $[\alpha]_D^{25}$ +23.3 (*c* = 2.90, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (br s, 1 H), 7.38–7.48 (m, 6 H), 7.21–7.35 (m, 9 H), 4.40 (m, 1 H), 3.48 (dd, *J* = 9.9, 4.4 Hz, 1 H), 3.21–3.40 (m, 3 H), 2.12–2.24 (m, 1 H), 1.85–2.03 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.9, 143.3, 128.6, 128.0, 127.3, 87.1, 77.5, 64.3, 39.8, 22.5.

HRMS: *m*/*z* calcd for $C_{24}H_{23}NO_2S$ $[M]^+$: 389.1448; found: 389.1449.

(*S*)-2-(Ethylthio)-6-[(trityloxy)methyl]-5,6-dihydro-4*H*-1,3-oxazine (27)

The thione **13** (0.030 g, 0.077 mmol) was mixed with EtI (0.014 mL, 0.0800 mmol) in anhyd THF (1.00 mL). The reaction mixture was cooled in an ice-bath and KO*t*-Bu (0.013 g, 0.11 mmol) was added slowly. The mixture was stirred at r.t. for 80 min after which the reaction was complete. Dil HCl (4 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and after filtration and concentration, the crude residue was purified by silica gel flash chromatography using a gradient of hexane–EtOAc (10:1 to 5:1). The pure product was obtained as a colorless liquid; yield: 0.026 g (81%, 0.062 mmol); $[\alpha]_D^{25}$ +42.1 (*c* = 1.70, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 6 H), 7.21–7.36 (m, 9 H), 4.34 (m, 1 H), 3.56–3.35 (m, 2 H), 3.29 (dd, *J* = 9.9, 5.4 Hz, 1 H), 3.17 (dd, *J* = 9.9, 4.9 Hz, 1 H), 2.94–2.78 (m, 2 H), 1.97–1.77 (m, 2 H), 1.30 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 143.7, 128.7, 127.9, 127.1, 86.6, 75.8, 65.5, 43.5, 25.0, 24.7, 14.7.

HRMS: *m*/*z* calcd for $C_{26}H_{28}NO_2S$ $[M + H]^+$: 418.1841; found: 418.1840.

(*S*)-3-Ethyl-6-[(trityloxy)methyl]-1,3-oxazinane-2-thione (28)

(*S*)-4-(Ethylamino)-1-(trityloxy)butan-2-ol (**24c**; 0.218 g, 0.58 mmol) was mixed with TCDI (0.205 g, 1.16 mmol) in 1,4-dioxane (7.00 mL). The reaction mixture was heated to reflux for 24 h and the mixture was cooled to r.t., diluted with CH_2Cl_2 (20 mL), and the organic layer was washed with H_2O (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography using a gradient of hexane–EtOAc (4:1 to 1:1). The pure product was obtained as a white solid; yield: 0.177 g (73%, 0.42 mmol); mp 170.0–171.0 °C; $[\alpha]_D^{25}$ +25.6 (*c* = 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.46 (m, 6 H), 7.20–7.37 (m, 9 H), 4.37 (m, 1 H), 3.89 (m, 2 H), 3.50 (dd, *J* = 9.7, 4.4 Hz, 1 H), 3.41–3.29 (m, 2 H), 3.23 (dd, *J* = 9.6, 7.2 Hz, 1 H), 2.25–2.36 (m, 1 H), 1.95–2.08 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

NMR (101 MHz, $CDCl_3$): δ = 185.1, 143.4, 128.5, 127.9, 127.2, 87.0, 76.3, 64.2, 50.6, 44.6, 24.3, 10.9.

HRMS: *m*/*z* calcd for $C_{26}H_{27}NO_2S$ $[M]^+$: 417.1761; found: 417.1762.

(*S*)-3-Ethyl-6-(hydroxymethyl)-1,3-oxazinane-2-thione (29)

The thione **28** (0.100 g, 0.24 mmol) was dissolved in CH_2Cl_2 (3.00 mL) and the solution was cooled to 0 °C. Trifluoroacetic acid (0.070 mL, 2.4 mmol) was added and the mixture was stirred at r.t. overnight. The reaction was quenched by the addition of MeOH (3 mL) and the organic phase was washed with H_2O (3 × 3 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo on the rotovap. The crude residue was purified by silica gel flash chromatography (hexane–CH_2Cl_2–acetone 6:1:1). The pure product was obtained as a colorless liquid; yield: 0.042 g (~100%, 0.24 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.33 (m, 1 H), 3.81–4.03 (m, 3 H), 3.73 (dd, *J* = 12.5, 4.8 Hz, 1 H), 3.38–3.52 (m, 2 H), 2.02–2.24 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.1, 78.7, 63.4, 50.5, 44.9, 22.9, 10.9.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^{1}H and ^{13}C NMR spectra for compounds **10**–**18**, **21**–**23**, and **25**–**29**.

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