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# New Synthesis of Chiral 1,3-Oxazinan-2-ones from Carbohydrate Derivatives

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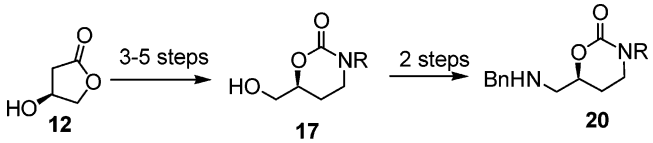


Chiral 1,3-oxazinan-2-ones are useful intermediates in synthesizing pharmaceutical compounds and amino alcohols. In this paper, we report a new synthetic method to chiral 6-hydroxymethyl 1,3-oxazinan-2-ones and their analogues from carbohydrate derivatives. The synthesis was accomplished by the reaction of optically pure 3-hydroxy-$\gamma$-butyrolactone with a primary amine to give an amide, which was reduced and carbonylated to give the desired compound class.

## Introduction

Small chiral molecules are very important building blocks for pharmaceutical compounds. Chiral 5-substituted 2-oxazolidinones (**1** and **2**; Chart 1) and the analogous 6-substituted 1,3-oxazinan-2-ones (**3** and **4**) are important core structures in many drug molecules and useful intermediates in the synthesis of chiral amino alcohols. The 5-(hydroxymethyl)- and 5-(aminomethyl)-2-oxazolidinones **1** and **2** are important in the preparation of oxazolidinone antibacterial agents.[1] Representative oxazolidinone antibiotics include linezolid (**5**; Zyvox) and eperezolid (**6**). Oxazolidinones have been used in the synthesis of chiral amino alcohols such as the beta-blocker carvedilol.[2] There has been great interest in developing efficient syntheses toward 2-oxazolidinones.[3,4] We and others have developed several efficient synthetic methods toward the synthesis of chiral 5-substituted 2-oxazolidinones.[5−7] The homologous six-membered cyclic carbamate 1,3-oxazinan-2-ones are also useful intermediates in synthesizing natural products and 1,3-amino alcohols.[8−10] 1,3-Oxazinan-2-ones **5** and **6** are important heterocycles that are present in several biologically active natural products such as maytansine and its analogues.[11−13] 1,3-Oxazinan-2-one derivatives exhibit a variety of biological activities, and they are being explored as antiinflammatory agents and as agents for treating ulcers, allergies, asthma, arthritis, and diabetes.[13] Some 6-phenyl-1,3-oxazinan-2-ones (**7**) have phosphodiesterase IV inhibitory effects and have been shown to be remedies for inflammatory diseases and antiasthmatics.[14] 1,3-Oxazinan-2-ones have been used as key intermediates in Woodward's total synthesis of erythromycin A,[9] in the synthesis of thrombolytics (**8**),[15] and in the synthesis of liquid crystal devices.[16] The six-membered 1,3-oxazinan-2-one ring systems have also been used as chiral auxiliaries or other chiral control elements,[17,18] although they are not used as extensively as

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(1) 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.

(2) Pittelkow, T.; Fischer, E.; Treppendahl, S. P. PCT Int. Appl. WO 2001087837, 2001; *Chem. Abstr*. **2001**, *136*, 5898.

(3) Brickner, S. J. *Curr. Pharm. Design* **1996**, *2*, 175−194.

(4) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010−2023.

(5) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; et al. *Org. Process Res. Dev.* **2003**, *7*, 533−546.

(6) Wang, G.; Hollingsworth, R. I. *Tetrahedron: Asymmetry* **2000**, *11*, 4429−4432.

(7) Hollingsworth, R. I.; Wang, G. *Chem. Rev.* **2000**, *100*, 4267−4282.

(8) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P., *Can. J. Chem*. **1985**, *63*, 2818−2820.

(9) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; et al. *J. Am. Chem. Soc.* **1981,** *103***,** 3213−3215.

(10) Baenteli, R.; Bauer, W.; Cottens, S.; Ehrhardt, C.; Hommel, U.; Kallen, J.; Meingassner, J. G.; Nuninger, F.; Weitz-Schmidt, G. PCT Int. Appl. WO 0048989, 2000; *Chem. Abstr.* **2000**, *133*, 177065.

(11) Gormley, G., Jr.; Chan, Y. Y.; Fried, J. *J. Org. Chem.* **1980**, *45*, 1447−1454.

(12) Larson, G. M.; Schaneberg, B. T.; Sneden, A. T. *J. Nat. Prod*. **1999**, *62*, 361−363.

(13) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1−26.

(14) Yamana, K.; Suzuki, N.; Takahama, A.; Ine, S. Jpn. Kokai Tokkyo Koho JP 2002179572, 2002; *Chem. Abstr*. **2002**, *137*, 57555.

(15) Jin, F.; Confalone, P. N. PCT Int. Appl. (119 pp) WO 2000000481, 2000; *Chem. Abstr*. **2000**, *132*, 78560.

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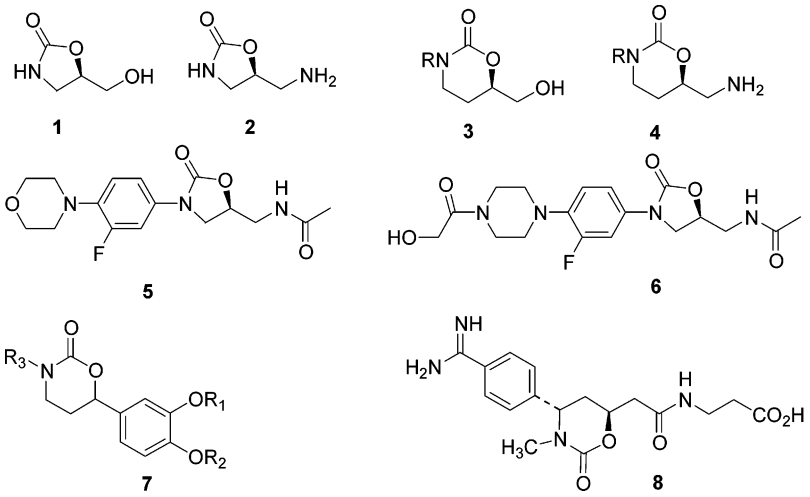
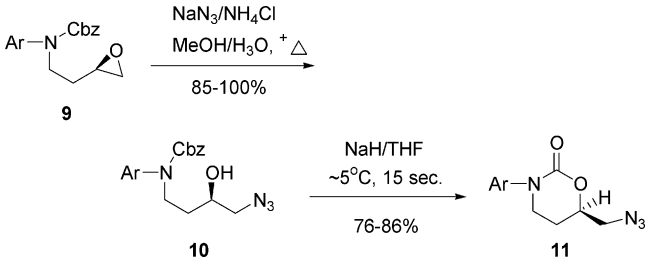
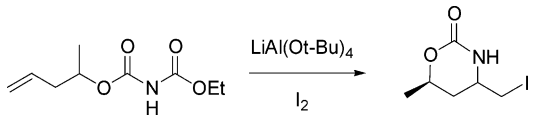
**CHART 1**




**SCHEME 1. Synthesis of *N*-Aryl-1,3-oxazinan-2-ones from Aspartic Acid**




**SCHEME 2. Synthesis of 1,3-Oxazinan-2-one by Iodoaminocyclization**




the homologous 2-oxazolidinones. This is probably due to the difficulties in synthesizing chiral 1,3-oxazinan-2-ones. Besides inducing chirality, the 1,3-oxazinan-2-ones were also used as aminopropylation agents[19] and as intermediates for the preparation of amino alcohols.[20]

Chiral versions of the homologous 6-substituted 1,3-oxazinan-2-ones are difficult to synthesize. There are not many available syntheses for chiral 1,3-oxazinan-2-ones in the literature. One chiral pool approach method utilizes aspartic acid as the starting material (Scheme 1); an epoxide containing Cbz-protected arylamine was obtained as an intermediate (**9**), and then the epoxide ring was opened by sodium azide and cyclization of the hydroxyl group with the Cbz group gave the desired 1,3-oxazinan-2-one **11**.[21] A short synthesis for 1,3-oxazinan-2-ones was accomplished by reductive amination of 2-deoxy-D-ribose followed by cyclization of the aryl chloroformate derivatized amine.[22] Other methods to synthesize 1,3-oxazinan-2-ones include halogen-mediated cyclization reactions,[23−25] a trans-sulfamoylation through sulfamide intermediates,[26] selenium-mediated cyclization of amino alcohol with carbon monoxide,[27] rearrangement from cyclic sulfates,[28] intramolecular Michael additions,[29] asymmetric dihydroxylation of homoallylic amines,[30] and a Hoffmann rearrangement of a primary amide to form the carbamate.[31] The iodoaminocyclization reaction is highly stereoselective when using a homoallyl carbamate with a chiral center at the homoallylic position (Scheme 2).[23]

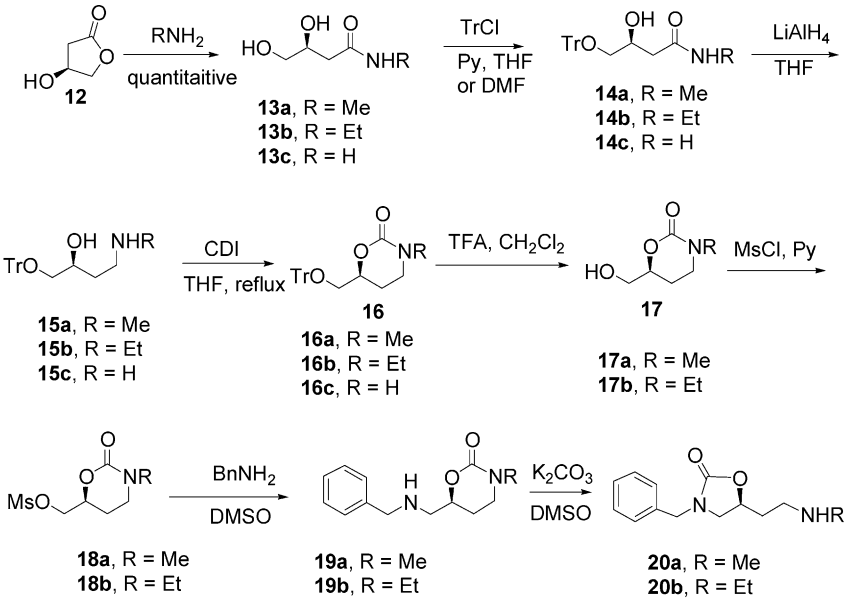
The chiral 1,3-oxazinan-2-ones **3** and **4** are useful in drug development toward new therapeutic agents. They are also useful in organic syntheses as chiral auxiliaries or as intermediates for synthesizing 1,3-amino alcohols. Because of these potential applications and as part of our interest in synthesizing new chiral heterocyclic derivatives as therapeutic agents, we developed a novel method to synthesize these chiral six-membered-ring carbamates from carbohydrate derivatives.

## Results and Discussions

We have designed and carried out the syntheses of these important chiral compounds from the carbohydrate

(16) Takiguchi, T.; Iwaki, T.; Tokanou, G.; Kosaka, Y.; Nakamura, S. JP9151179, 1997; *Chem. Abstr*. **1997**, *127*, 42427.
(17) Abbas, T. R.; Cadogan, J. I. G.; Doyle, A. A.; Gosney, I.; Hodgson, P. K. G.; Howells, G. E.; Hulme, A. N.; Parsons, S.; Sadler, I. H. *Tetrahedron Lett.* **1997**, *38*, 4917−4920.
(18) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Gould, R. O.; Hodgson, K. G.; McDougall, D. *Tetrahedron* **1998**, *54*, 9765−9784.
(19) Poindexter, G. S.; Strauss, K. M. *Synth. Commun.* **1993**, *23*, 1329−1338.
(20) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chem. Lett.* **1988**, 87−90.
(21) Lohray, B. B.; Baskaran, S.; Reddy, B. Y.; Rao, K. S. *Tetrahedron Lett.* **1998**, *39*, 6555−6556.
(22) Ross, B. C. U.S. Patent 4107435, 1977; *Chem. Abstr*. **1977**, *88*, 7304.
(23) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330−7335.
(24) Jorda-Gregori, J. M.; Gonzalez-Rosende, M. E.; Cava-Montesinos, P.; Sepulveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3769−3777.
(25) Muehlstaedt, M.; Meusinger, R.; Olk, B.; Weber, L.; Widera, R. *J. Prakt. Chem*. **1986**, *328*, 309−313.
(26) Dewynter, G.; Abdaoui, M.; Regainia, Z.; Montero, J.-L. *Tetrahedron* **1996**, *52*, 14217−14224.
(27) Sonoda, N.; Yamamoto, G.; Natsukawa, K.; Kondo, K.; Murai, S. *Tetrahedron Lett.* **1975**, *16*, 1969−1972.
(28) Kemp, S. J.; Bao, J. G.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 7162−7167.
(29) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* **1986**, 393−394.
(30) Walsh, P. J.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5545−5548.
(31) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919−8921.

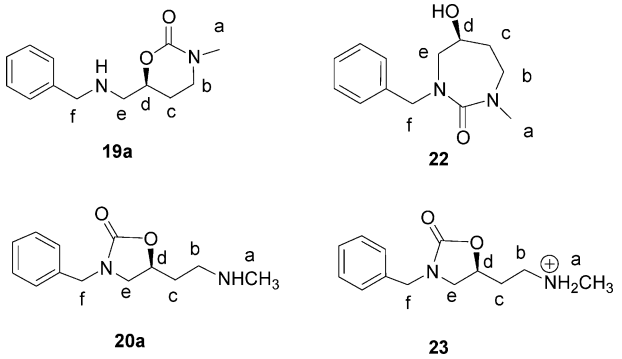
**SCHEME 3. Synthesis of Chiral 1,3-Oxazinan-2-ones from Lactone 12**




derivative (*S*)-3-hydroxy-$\gamma$-butyrolactone (**12**; Scheme 3). Starting from optically pure lactone **12**,[32] ring opening with amines led to the dihydroxybutyramide **13** quantitatively.[33] The diol was selectively protected with a trityl group to increase the hydrophobicity of the compound. This is necessary for the reduction step when the R group is a small alkyl group. Without a protecting group, the reduction product is too polar and it is hard to recover it from the reaction mixture. The trityl group showed excellent selectivity to the primary hydroxyl group, although some small amount of diprotected byproduct can be obtained after a prolonged period of stirring. Reduction of the protected amide **14** using $LiAlH_4$ in THF gave the corresponding intermediate amino alcohol **15** in excellent yield. Cyclization of the intermediate **15** using carbonyl diimidazole gave the protected 1,3-oxazinan-2-ones **16** in 70−93% yield. Attempts at using Cbz-protected amine and using the carbonyl group of the Cbz group to form the carbamate ring resulted in a lower yield. The trityl protecting group was removed quantitatively using TFA in dichloromethane. The primary hydroxyl group in **17** can then be converted to an amino group by converting it to the mesylate **18** and displacing the mesylate by benzylamine in DMSO at 60−80 °C. The benzyl protecting group in **19** can be removed by catalytic hydrogenation to give the corresponding 6-(aminomethyl)-1,3-oxazinan-2-ones.

The displacement product is mainly the direct $S_N2$ displacement product **19** when using DMSO as solvent and 2−2.5 equiv of benzylamine at 60−80 °C. However, we found that when the temperature is higher than 85 °C and in the presence of potassium carbonate, a significant quantity of compound **20** was obtained. This is presumably obtained from rearrangement of the 1,3-oxazinan-2-one **19**. To understand the requirement for the rearrangement, we monitored the compound **19b** (R = $CH_2CH_3$) in $d_6$-DMSO at >85 °C by $^1H$ NMR spectroscopy. The 1,3-oxazinan-2-ones are stable under neutral conditions. Heating at over 85 °C for 48 h resulted in almost no decomposition of pure compound **19b** in DMSO. Addition of benzylamine to the sample did not cause rearrangement of compound **19b** either. However, addition of potassium carbonate promoted the rearrangement in the presence of benzylamine. In the absence of benzylamine, $K_2CO_3$ promoted the rearrangement to completion after 18 h of heating at >85 °C. This indicated that participation of a nonbulky base is important to the reaction. We also carried out the rearrangement reaction for compound **19a** cleanly in DMSO using 2 equiv of potassium carbonate at 100 °C for 24 h. A possible mechanism of the formation of **20** is shown in Scheme 4. A base $B^-$ (such as hydroxide) molecule attacks the carbamate and opens up the six-membered ring, forming the tetrahedral intermediate **21**, and cyclization with the neighboring 6-benzylamino group leads to the formation of a five-membered-ring carbamate, the oxazolidinone **20**.

**CHART 2**




Besides the five-membered-ring oxazolidinone, another possible rearrangement product could be the seven-membered urea **22** (Chart 2) by cleavage of the C−O bond instead of the C−N bond. However, this possibility is ruled out for the above rearrangement reaction on the basis of both $^1H$ and $^{13}C$ NMR spectral data. The five-membered ring is also thermodynamically more stable than the seven-membered ring. The amine **20a** has a

(32) Hollingsworth, R. I. *Biotech. Annu. Rev.* **1996**, *2*, 281−287.
(33) Wang, G.; Hollingsworth, R. I. *J. Org. Chem.* **1999**, *64*, 1036−1038.

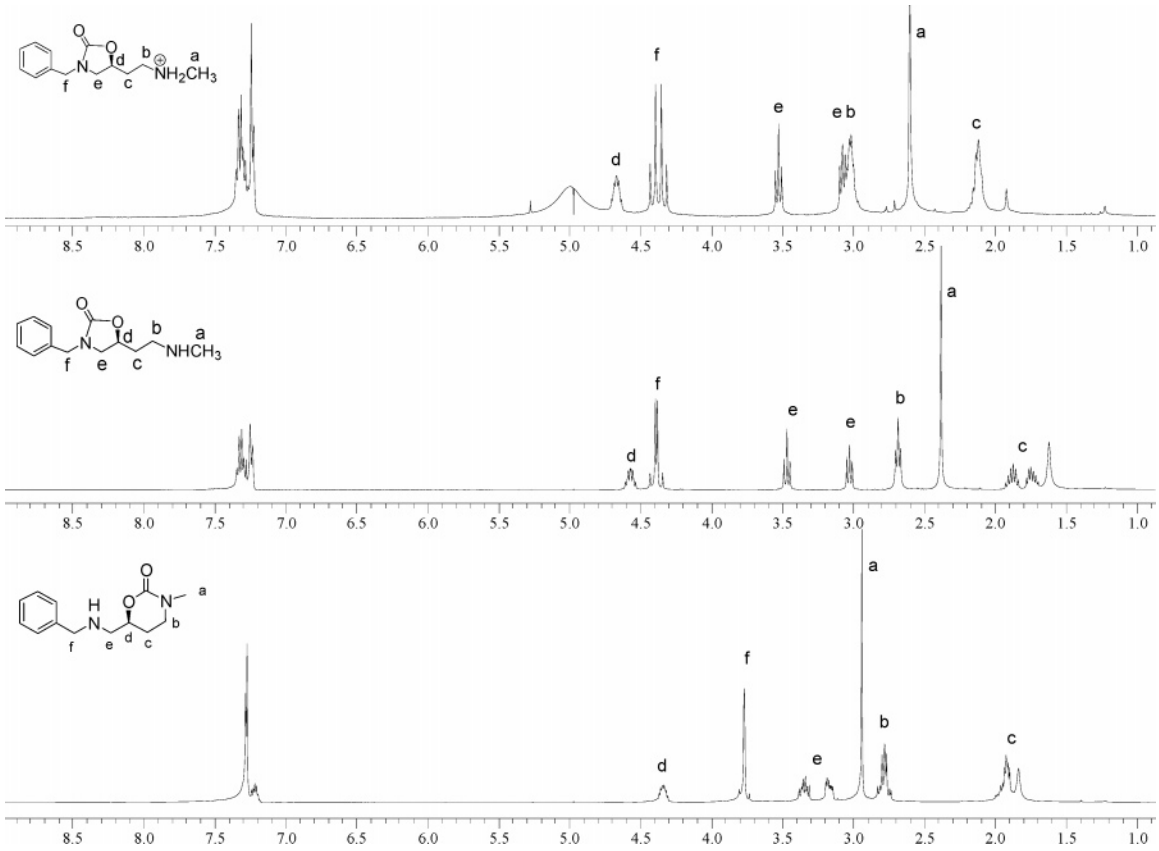
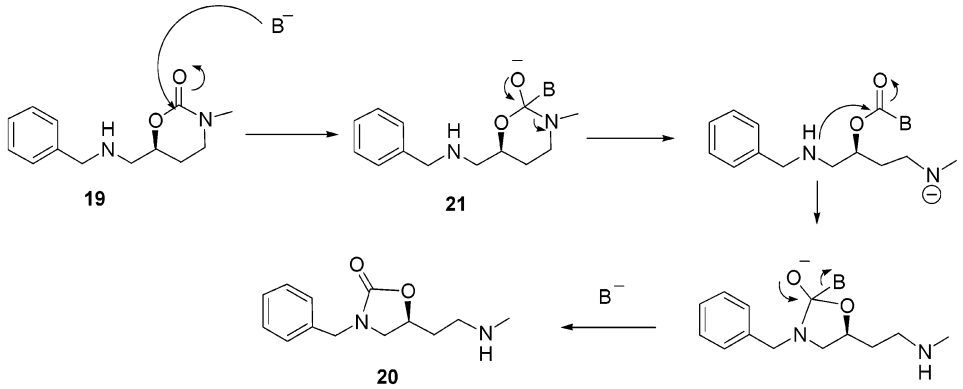


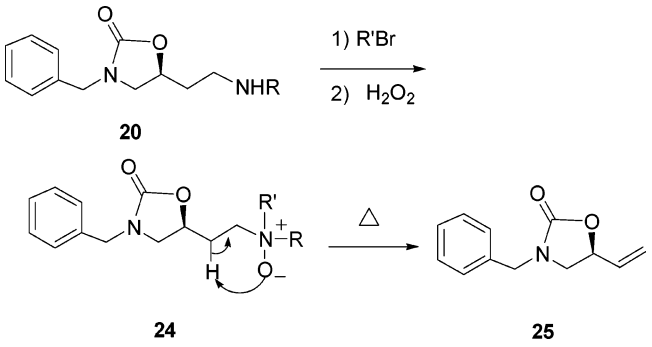

**FIGURE 1.** $^1$H NMR spectra of compounds **19a** (bottom), neutral amine **20a** (middle), and protonated amine **23** (top). All spectra were obtained in $CDCl_3$.

**SCHEME 4. Possible Mechanism of the Rearrangement from Six-Membered to Five-Membered Carbamates Promoted by Base**




certain solubility (~10 mg/mL) in water, and it is easily protonated. The protonated form **23** would exhibit changes of chemical shifts for the methyl a and methylenes b and c. The $^1$H NMR spectra of the three compounds are shown in Figure 1. If the seven-membered-ring urea **22** is the rearrangement product, the $^1$H NMR chemical shifts for the methyl a and methylene b should not change significantly, since the chemical environments for a and b are essentially the same in **19a** and **22**. However, if the rearrangement product is the amine **20a**, then the $^1$H NMR absorptions of a and b should change significantly. This is what we have observed, as shown in Figure 1. The chemical shift for methyl a moved upfield from 2.94 ppm in **19a** to 2.38 ppm, and the methylene group b also shifted upfield from 2.78 ppm in **19a** to 2.68 ppm. The methine proton d moved downfield from 4.34 ppm in **19a** to 4.68 ppm in the rearrangement product. This is strong evidence that the structure **22** is not the rearrangement product, in which the methine proton d is expected to have a chemical shift around 4.0 ppm. Furthermore, the absorptions for a and b in the ammonium salt **23** should move downfield in comparison to the signals for the neutral form **20a**. For the urea, addition of acid will not affect the chemical shifts of a and b significantly. As shown in Figure 1, the chemical shifts of the groups close to the nitrogen have significantly moved downfield after addition of acid: methyl a shifted from 2.38 to 2.60 ppm, and methylene b shifted from 2.68 to 3.01 ppm. We have also compared the $^1$H and $^{13}$C spectral data to those for existing 2-oxazolidinones,[6] and the similarities of the five-

**SCHEME 5. Proposed Synthesis of the New Oxazolidinone Building Block 25**




membered-ring absorption data confirmed that the structure **20a** is the correct product. The above results confirm our hypothesis that the rearrangement product is the five-membeed-ring 2-oxazolidinone **20**, not the seven-membered-ring urea **22**.

The formation of **20** is another method of synthesizing chiral oxazolidinones that have stereochemistry opposite to that of the Hoffmann rearrangement method from **13c**.[6] The rearrangement product **20** can be used to synthesize 2-oxazolidinones with an alkene functional group by oxidation of the amine (after converting to a tertiary amine and treatment with hydrogen peroxide) followed by Cope elimination (Scheme 5). The 2-oxazolidinone **25** after Cope elimination can be used as a general building block in the synthesis of 2-oxazolidinone derivatives. Substituted 2-oxazolidinones can be obtained by electrophilic addition to the double bonds.

## Conclusions

We have developed a new efficient method to synthesize chiral 6-substituted 1,3-oxazinan-2-ones from (*S*)-3-hydroxy-$\gamma$-butyrolactone. The reaction scheme is straightforward and efficient and offers complete retention of stereochemistry. We also discovered that, under basic conditions, heat can promote the rearrangement of the six-membered-ring 1,3-oxazinan-2-ones to the more stable five-membered-ring 2-oxazolidinones. The product 2-oxazolidinone has stereochemistry opposite to that of the 2-oxazolidinone synthesized by a Hoffmann rearrangement. This method allows us to synthesize chiral core structures with complementary stereocenters, since the priority order is switched. The efficient syntheses of these chiral carbamates are important in the preparation of biologically active pharmaceutical compounds. The synthesis also provides intermediates for synthesizing chiral amino alcohol derivatives.

## Experimental Section

General procedure for the synthesis when R = Me is used as an illustration for the procedure. The compounds with R = Et, H are synthesized by a similar method. The characterization data for the *N*-ethyl analogues and R = H are given and the $^1$H and $^{13}$C NMR spectra are given in the supplementary section. Melting point (uncorrected) was measured using Fisher−Jones.

**(*S*)-3,4-Dihydroxy-*N*-methylbutyramide (13a).** Compounds **13a**−**c** were obtained by similar methods given in the literature.[21] The lactone (20.2 g, 0.20 mol) and methylamine (77.65 g, 1.0 mol, 40 wt % in water) were mixed at room temperature for 6−8 h. After concentrating on a rotavaporator, the excess methylamine can be removed by washing with hexane, and the last trace of solvent and methylamine can be removed on a vacuum pump. The crude product was obtained as a brown viscous liquid (26.6 g, 0.20 mol, 100%) and was used directly in the second step without further purification. $[\alpha]_D^{25} = -25.9°$ (*c* 1.08, EtOH). $^1$H NMR ($D_2O$, 400 MHz; $\delta$ (ppm)): 3.94 (m, 1H), 3.48 (dd, 1H, $J$ = 11.72, 3.9 Hz), 3.38 (dd, 1H, $J$ = 11.7, 6.8 Hz), 2.61 (s, 3H), 2.32 (dd, $J$ = 14.7, 3.9 Hz), 2.22 (dd, $J$ = 14.7, 8.8 Hz). $^{13}$C NMR ($CD_3OD$, $D_2O$, 100 MHz; $\delta$ (ppm)): 175.1, 70.1, 69.2, 40.8, 26.9.

**(*S*)-*N*-Ethyl-3,4-dihydroxybutyramide (13b).** Yield: 99%, yellow crystals. Mp: 59.0−61.0 °C. $[\alpha]_D^{25} = -26.7°$ (*c* 1.07, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 5.69 (bs, 1H), 4.07 (m, 1H), 2.41 (dd, 1H, $J$ = 15.6, 8.8 Hz), 2.31 (dd, 1H, $J$ = 15.6, 3.9 Hz), 3.67 (m, 1H), 3.51 (m, 1H), 3.29 (m, 2H), 1.14 (t, 3H, $J$ = 7.3 Hz). $^{13}$C NMR ($D_2O$, 5% $CD_3OD$, 100 MHz; $\delta$ (ppm)): 174.2, 70.1, 66.2, 40.9, 35.6, 14.6.

**(*S*)-3-Hydroxy-*N*-methyl-4-(trityloxy)butyramide (14a).** 3,4-Dihydroxy-*N*-methylbutyramide (**13a**; 19.41 g, 0.146 mol) was dissolved in 52 mL of anhydrous DMF under $N_2$. Trityl chloride (49 g, 0.175 mol) and pyridine (35 mL, 0.438 mol) were added to the solution, which was then stirred at room temperature for 24−36 h. The reaction was quenched by addition of ice water (100 mL) to the solution. The water was decanted, and the solid precipitate was dissolved in EtOAc (150 mL). The organic phase was washed several times with 30 mL of water and finally with 30 mL of brine. After drying with $Na_2SO_4$, the ethyl acetate was removed on a rotavaporator and 58 g of the crude product was obtained as an off-white solid. The crude product can be purified by flash chromatography on silica gel using a gradient of the solvent system hexane/ethyl acetate (3:1 to 1:1). The pure product was obtained as a white crystalline material. Mp: 107.0−108.0 °C. $[\alpha]_D^{25} = -18.3°$ (*c* 1.12, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): $\delta$ 7.40 (d, 6H, $J$ = 7.8 Hz), 7.19−7.34 (m, 9H), 5.98 (bs, 1H), 4.14 (m, 1 H), 3.55 (s, 1 H), 3.15 (dd, 1H, $J$ = 9.8, 5.9 Hz), 3.10 (m, 1H), 2.72 (d, 3 H, $J$ = 4.9 Hz), 2.40 (dd, 1H, $J$ = 15.6, 2.9 Hz), 2.31 (dd, 1H, $J$ = 15.6, 8.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 172.3, 143.5, 128.4, 127.6, 126.9, 86.4, 67.8, 66.6, 39.4, 25.9. HRMS (*m/z*): calcd for $C_{24}H_{25}NO_3Na^+$ $[M + Na]^+$, 398.1732; found, 398.1746. IR ($CHCl_3$; $cm^{-1}$): 3347, 3015, 1653, 1550, 1491, 1448, 1217, 1074, 758.

**(*S*)-*N*-Ethyl-3-hydroxy-4-(trityloxy)butyramide (14b).** Yield: 95% (0.05 mol scale) after purification using hexane/ethyl acetate (1:1). $R_f$ = 0.3. White solid. Mp: 119.0 °C. $[\alpha]_D^{25} = -19.1°$ (*c* 1.11, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.50−7.16 (m, 15H), 5.90 (bs, 1H), 4.16 (m, 1H), 3.52 (bs, 1H), 3.23 (m, 2H), 3.13 (m, 2H), 2.38 (dd, 1H, $J$ = 15.63, 2.93 Hz), 2.31 (dd, 1H, $J$ = 15.6, 7.8 Hz), 1.08 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 171.5, 143.7, 128.6, 127.8, 127.1, 86.7, 68.0, 66.6, 39.6, 34.2, 14.7. HRMS (*m/z*): calcd for $C_{25}H_{27}NO_3Na^+$ $[M + Na]^+$, 412.1889; found, 412.1909. IR ($CHCl_3$; $cm^{-1}$): 3444, 3372, 3062, 3017, 2934, 2878, 1651, 1533, 1448, 1217, 1074, 758 $cm^{-1}$.

**(*S*)-3-Hydroxy-4-(trityloxy)butyramide (14c).** Yield after purification: 90%. Mp: 107.5−108.5 °C. $[\alpha]_D^{25} = -18.4°$ (*c* 1.00, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.41 (d, 6H, $J$ = 7.8 Hz), 7.34−7.19 (m, 9H), 6.06 (bs, 1H), 5.64 (bs, 1H), 4.15 (m, 1H), 3.45 (bs, 1H), 3.16 (d, 2H, $J$ = 5.9 Hz), 2.37 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 174.1, 143.6, 128.5, 127.8, 127.1, 86.8, 67.7, 66.7, 39.2. IR ($CHCl_3$; $cm^{-1}$): 3494, 3408, 3019, 2929, 2878, 1675, 1594, 1492, 1448, 1217, 1075, 742.

**(*S*)-4-(Methylamino)-1-(trityloxy)butan-2-ol (15a).** 3-Hydroxy-*N*-methyl-4-(trityloxy)butyramide (**14a**; 55.0 g, 0.146 mol) was dissolved in anhydrous THF (240 mL), and the reaction flask was cooled to 0 °C in an ice−salt bath. $LiAlH_4$ (16.50 g, 0.434 mol) was added to the flask at 0 °C under dry $N_2$. The ice bath was removed after the generation of hydrogen settled down. The mixture was stirred at room temperature for 12−18 h, after which time the reaction is essentially

complete, on the basis of NMR spectroscopy. The reaction mixture was then cooled in an ice bath, and the reducing agent was quenched by adding 50 mL of a 1:1 mixture of MeOH and $H_2O$. The white precipitate that formed after addition of water and MeOH was removed by vacuum filtration, and the filtrate was extracted several times with $CHCl_3$. The combined organic phase was dried using $Na_2SO_4$ overnight. The solvent was removed on a rotavaporator, and the residue was dried on a vacuum pump. The crude product was obtained as an off-white solid (51.35 g, 0.142 mol, 97%) and was used directly in the next step without further purification. A small amount was purified by chromatography. Mp: 120.0 °C. $[\alpha]_D^{25} = -19.0°$ (*c* 1.02, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.45 (d, 6H, $J = 6.8$ Hz), 7.28 (t, 6H, $J = 7.8$ Hz), 7.21 (t, 3H, $J = 6.8$ Hz), 4.00 (m, 1H), 3.47 (bs, 2H), 3.17 (dd, 1H, $J = 9.8, 5.9$ Hz), 3.00 (dd, 1H, $J = 9.8, 5.9$ Hz), 2.83 (m, 1H), 2.73 (m, 1H), 2.36 (s, 3H), 1.75 (m, 1H), 1.59 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 144.0, 128.6, 127.6, 126.8, 86.2, 71.6, 67.4, 49.8, 85.9, 31.8. HRMS ES+ (*m/z*): calcd for $C_{24}H_{27}NO_2$ $[M + 1]^+$, 362.2120; found, 362.2127. IR ($CHCl_3$; cm$^{-1}$): 3318, 3061, 3011, 2929, 2872, 1598, 1491, 1448, 1217, 1075, 766.

**(*S*)-4-(Ethylamino)-1-(trityloxy)butan-2-ol (15b).** Yield: 73.0% (unoptimized yield). White crystals. Mp: 109.0−110.0 °C. $[\alpha]_D^{25} = -17.7°$ (*c* 1.07, EtOH), HRMS (*m/z*): calcd for $C_{25}H_{30}NO_2$ $[M + 1]^+$, 376.2277; found, 376.2281. $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.50−7.16 (m, 15H), 4.00 (m, 1H), 3.16 (dd, 1H, $J = 8.8, 5.9$ Hz), 2.98 (dd, 1H, $J = 8.8, 5.9$ Hz), 2.90 (m, 1H), 2.76 (m, 1H), 2.62 (m, 2H), 1.80−1.70 (m, 1H), 1.58 (m, 1H), 1.07 (t, 2H, $J = 7.3$ Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 144.1, 128.7, 127.7, 126.9, 86.4, 72.0, 67.5, 47.7, 43.8, 31.9, 14.8. IR ($CHCl_3$; cm$^{-1}$): 3062, 3019, 2972, 1491, 1448, 1216, 1075, 757.

**(*S*)-4-Amino-1-(trityloxy)butan-2-ol (15c).** Yield: 93% Mp: 104.0−106.0 °C. $[\alpha]_D^{25} = -16.0°$ (*c* 1.01, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.62−7.18 (m, 15H), 3.98 (m, 1H), 3.14 (dd, 1H, $J = 8.8, 5.9$ Hz), 3.04 (dd, 1H, $J = 8.8, 4.9$ Hz), 2.95 (m, 1H), 2.82 (m, 1H), 1.65 (m, 1H), 1.53 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 143.8, 128.4, 127.5, 126.7, 86.2, 70.3, 67.6, 39.3, 35.1. IR ($CHCl_3$; cm$^{-1}$): 3377, 3061, 3015, 2929, 2873, 1596, 1491, 1448, 1217, 1073, 767 cm$^{-1}$.

**(*S*)-3-Methyl-6-((trityloxy)methyl)-1,3-oxazinan-2-one (16a).** 4-(Methylamino)-1-(trityloxy)butan-2-ol (**15a;** 10.89 g, 0.030 mol) was dissolved in anhydrous THF or dioxane (50 mL). After the compound **15a** was completely dissolved, carbonyldiimidazole (9.98 g, 0.06 mol) was added to the flask and the solution was stirred with refluxing for 24 h. The solvent was evaporated on the rotavaporator, and the remaining solid was extracted in EtOAc. The organic phase was washed with about 10 mL of $H_2O$ several times and with 30 mL of brine. The EtOAc phase was concentrated on the rotavaporator to afford a brown solid that was purified by $SiO_2$ chromatography (hexane/ethyl acetate 5:1−3:1−1:1). The purified product was obtained as a white crystalline solid (10.87 g, 0.028 mol). Yield: 93%. Mp: 161.0−162.0 °C. $[\alpha]_D^{25} = +36.2$ (*c* 1.08, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.42 (d, 6H, $J = 6.8$ Hz), 7.32−7.20 (m, 9 H), 4.32 (m, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 2.96 (s, 3H), 2.07 (m, 1H), 1.96 (m. 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 153.3, 143.3, 128.3, 127.56, 126.9, 86.5, 75.4, 64.5, 45.8, 36.2, 24.3. HRMS ES+ (*m/z*): calcd for $C_{25}H_{26}NO_3$ $[M + 1]^+$, 388.1913; found, 388.1928. IR ($CHCl_3$; cm$^{-1}$): 3061, 3018, 2938, 2880, 1690, 1494, 1448, 1217, 1083, 760.

**(*S*)-3-Ethyl-6-((trityloxy)methyl)-1,3-oxazinan-2-one (16b).** Yield: 79%. White crystals. Mp: 141.0−142.0 °C. $[\alpha]_D^{25} = +26.7°$ (*c* 1.07, EtOAc). HRMS (*m/z*): calcd for $C_{26}H_{28}NO_3$ $[M + 1]^+$, 402.2069; found, 402.2079. $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.52−7.16 (m, 15H), 4.32 (m, 1H), 3.42−3.26 (m, 4H), 3.24−3.14 (m, 2H), 2.10 (m, 1H), 1.93 (m, 1H), 1.12 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)):, 153.0, 143.5, 128.6, 127.8, 127.1, 86.7, 75.5, 64.7, 44.0, 43.4, 24.7, 12.1. IR ($CHCl_3$; cm$^{-1}$): 3062, 3019, 2982, 2938, 1685, 1491, 1450, 1280, 1217, 1094, 763.

**(*S*)-6-((Trityloxy)methyl)-1,3-oxazinan-2-one (16c).** Yield: 70%. Mp: 182.5−183.5 °C. $[\alpha]_D^{25} = +20.8°$ (*c* 1.01, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.60−7.18 (m, 15H), 7.42 (d, 6H, $J = 7.8$ Hz), 7.29 (t, 6H, $J = 7.8$ Hz), 7.21 (d, 3H, $J = 7.8$ Hz), 5.25 (bs, 1H), 4.38 (m, 1H), 3.34 (m, 3H), 3.23 (dd, 1H, $J = 9.8, 5.9$ Hz), 2.03 (dd, 1H, $J = 12.7, 2.9$ Hz), 1.92 (m, 1H), 1.55 (bs, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 154.46, 143.5, 128.5, 127.9, 127.1, 86.8, 76.1, 64.7, 38.7, 23.6. IR ($CHCl_3$; cm$^{-1}$): 3448, 3261, 3062, 3018, 2939, 2882, 1707, 1490, 1450, 1292, 1217, 1110, 1079, 750.

**(*S*)-6-(Hydroxymethyl)-3-methyl-1,3-oxazinan-2-one (17a).** The solution of 3-methyl-6-((trityloxy)methyl)-1,3-oxazinan-2-one (**16a**; 5 g, 0.013 mol) in a mixture of TFA and $CH_2Cl_2$ (20 mL, 1:1) was stirred for 12 h at room temperature. The TFA and the solvent were evaporated to dryness on a rotavaporator. Ice water was then added to the viscous liquid residue, and a solid precipitate formed. The solid was removed by vacuum filtration, and the water phase was extracted with hexane to remove a trace amount of trityl compound. The water phase was then evaporated on an oil pump, and MeOH was added to the product and then evaporated several times. The product was obtained as a light brown viscous liquid (1.9 g, 0.013 mol) and was used directly in the next step. Yield: 100%. $[\alpha]^{25}_D = +75.6°$ (*c* 1.09, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 4.29 (m, 1H), 3.74 (dd, 1H, $J = 11.7, 3.9$ Hz), 3.65 (dd, 1 H, $J = 11.7, 4.9$ Hz), 3.38 (m, 1H), 3.22 (m, 1H), 2.95 (s, 3H), 2.77 (bs, 1H), 1.97 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 154.0, 77.5, 63.7, 46.0, 36.3, 23.3. HRMS ES+ (*m/z*): calcd for $C_6H_{12}NO_3$ $[M + 1]^+$, 146.0817; found, 146.0820. IR ($CHCl_3$; cm$^{-1}$): 3381, 3009, 2939, 1677, 1499, 1450, 1256, 1079, 756.

**(*S*)-3-Ethyl-6-(hydroxymethyl)-1,3-oxazinan-2-one (17b).** Yield: quantitative. $[\alpha]_D^{25} = +64.1°$ (*c* 0.91, EtOH). HRMS ES+ (*m/z*): calcd for $C_7H_{14}NO_{23}$ $[M + 1]^+$, 160.0974; found, 160.0972. $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 4.28 (m, 1H), 3.79 (m, 1H), 3.66 (m, 1H), 3.38 (m, 3H), 3.26 (dd, 1H, $J = 5.9, 2.9$ Hz), 1.95 (m, 2H), 1.16 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 153.5, 77.5, 63.6, 43.8, 43.4, 23.3, 12.0. IR ($CHCl_3$; cm$^{-1}$): 3393, 3013, 2927, 1664, 755.

**(*S*)-Methanesulfonic Acid 3-Methyl-2-oxo-1,3-oxazinan-6-yl Methyl Ester (18a).** 6-(Hydroxymethyl)-3-methyl-1,3-oxazinan-2-one (**17a**; 1.87 g, 0.013 mol) was dissolved in dry dichloromethane (20 mL). Pyridine (12 mL, 0.156 mol) and methanesulfonyl chloride (5 mL, 0.065 mol) were added, and the solution was stirred at room temperature for 12 h. $NaHCO_3$ (5 g, 0.059 mol) was then added to the flask, and the mixture was stirred for 30 min, after which time the solvent was removed on a rotavaporator. The residue was cooled in an ice bath and water (30−40 mL) was added to quench the unreacted sulfonyl chloride. The water phase was extracted using EtOAc (30 mL, five times). The combined organic extracts were dried using $Na_2SO_4$, and the solvent was evaporated to give the crude product as a dark brown solid (2.38 g, 0.011 mol). Yield: 83%. Mp: 81.5−82.0 °C. $[\alpha]_D^{25} = +59.1°$ (*c* 1.14, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 4.49 (m, 1H), 4.34 (dd, 1H, $J = 11.7, 3.9$ Hz), 4.30 (dd, 1H, $J = 11.7, 3.9$ Hz), 3.42 (m, 1H), 3.27 (m, 1H), 3.08 (s, 3H), 2.98 (s, 3H), 2.04 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 152.5, 73.9, 69.6, 45.6, 37.5, 36.3, 23.2. HRMS (*m/z*): calcd for $C_7H_{13}NO_5S$ $[M + 1]^+$, 224.0593; found, 224.0583. IR ($CHCl_3$; cm$^{-1}$): 3019, 2942, 1693, 1496, 1448, 1356, 1177, 756 cm$^{-1}$.

***(S)*-Methanesulfonic Acid 3-Ethyl-2-oxo-1,3-oxazinan-6-yl Methyl Ester (18b).** After purification by chromatography, white crystal. Yield: 92%. Mp: 68.0−70.0 °C. $[\alpha]^{25}_D = +52.2°$ (*c* 1.14, EtOAc). HRMS ES+ (*m/z*): calcd for $C_8H_{16}NO_5S$ $[M + 1]^+$, 238.0749; found, 238.0745. $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 4.47 (m, 1H), 4.34 (dd, 1H, $J = 11.7, 3.9$ Hz), 4.30 (dd, 1H, $J = 11.7, 4.9$ Hz), 3.38 (m, 3H), 2.29 (m, 1H), 3.08 (s, 3H), 2.10−1.92 (m, 2H), 1.15 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 152.1, 73.9, 69.5, 44.2, 43.2, 37.8, 23.6, 12.1. IR ($CHCl_3$; cm$^{-1}$): 3436, 3020, 1694, 1491, 1456, 1217, 758 cm$^{-1}$.

**(*S*)-6-((Benzylamino)methyl)-3-methyl-1,3-oxazinan-2-one (19a).** Methanesulfonic acid 3-methyl-2-oxo-1,3-oxazinan-6-yl methyl ester (**18a**; 0.81 g, 3.67 mmol) and benzylamine (0.8 mL, 8 mmol) were dissolved in anhydrous DMSO (10 mL). The mixture was stirred at 75−80 °C for 48 h under an anhydrous atmosphere. The reaction mixture was cooled to room temperature, and ice water (10−20 mL) was added to the flask. The water phase was extracted several times with dichloromethane. The combined organic phase was dried using $Na_2SO_4$ and concentrated on a rotavaporator to remove the solvent and give the crude product as a yellow viscous liquid. The crude compound was purified by silica gel chromatography using a gradient solvent system (hexane/THF, 9:1; hexane/$CH_2Cl_2$/THF, 6:3:1; $CH_2Cl_2$/MeOH, 9.9:0.1). The product was obtained as a light brown viscous liquid (0.77 g, 3.3 mmol). Yield: 91%. $[\alpha]^{25}_D = +68.2°$ (*c* 1.07, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.24−7.13 (m, 5H), 4.34 (m, 1H), 3.77 (m, 2H), 3.34 (m, 1H), 3.17 (m, 1H), 2.94 (s, 3H), 2.80 (dd, 1H, $J$ = 12.7, 6.8 Hz), 2.75 (dd, 1H, $J$ = 12.7, 3.9 Hz), 1.92 (m, 2H), 1.83 (bs, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 153.7, 139.4, 128.3, 128.0, 127.0, 76.3, 53.5, 52.3, 46.2, 36.3, 25.0. HRMS (*m/z*): calcd for $C_{13}H_{19}N_2O_2$ $[M + 1]^+$, 235.1447; found, 235.1447. IR ($CHCl_3$; $cm^{-1}$): 3330, 3009, 2938, 1690, 1496, 1449, 1409, 1354, 754.

**(*S*)-6-((Benzylamino)methyl)-3-ethyl-1,3-oxazinan-2-one (19b).** The reaction temperature was 65 °C, and the time was 36 h (crude yield 96%; $^1$H NMR spectroscopy indicated quantitative conversion). Isolated pure compound yield: 78% after column purification (solvent gradient hexane/$CH_2Cl_2$ 6:1 and then hexane/$CH_2Cl_2$/THF 6:3:1 to 3:5:2 to 0:6:1). $[\alpha]_D^{25} = +55.3°$ (*c* 0.64, EtOH). HRMS ES+ (*m/z*): calcd for $C_{14}H_{21}N_2O_2$ $[M + 1]^+$, 249.1603; found, 249.1597. $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.40−7.18 (m, 5H), 4.34 (m, 1H), 3.80 (d, 1H, $J$ = 12.7 Hz), 3.76 (d, 1H, $J$ = 12.7 Hz), 3.34 (m, 2H), 3.20 (m, 1H), 2.81 (dd, 1H, $J$ = 12.7, 6.8 Hz), 2.76 (dd, 1H, $J$ = 12.7, 4.9 Hz), 1.94 (m, 2H), 1.85 (s, 1H), 1.13 (t, 3H, $J$ = 6.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 153.2, 139.8, 128.4, 128.1, 127.0, 76.4, 53.7, 52.6, 44.0, 43.6, 25.3, 12.1. IR ($CHCl_3$; $cm^{-1}$): 3472, 2974, 2934, 1682, 1492, 1455, 1282, 1221, 1095, 755.

**(*S*)-3-Benzyl-5-(2-(methylamino)ethyl)oxazolidin-2-one (20a).** 6-((Benzylamino)methyl)-3-methyl-1,3-oxazinan-2-one (**19a**; 0.16 g, 0.0007 mol), anhydrous DMSO (5 mL), and $K_2CO_3$ (0.2 g, 0.0014 mol) were mixed and stirred at 95−100 °C for 24 h. The $^1$H NMR spectrum indicated complete conversion to the five-membered-ring product. The flask was cooled to room temperature, and ice water (5 mL) was added to the solution. The water phase was then extracted with $CH_2Cl_2$ several times. The combined organic phase was concentrated on a rotavaporator, and the yellow liquid obtained was purified by $SiO_2$ chromatography (hexane/THF, 9:1; hexane/$CH_2Cl_2$/THF, 6:3:1; $CH_2Cl_2$/MeOH, 9.9:0.1) to give the pure product as a light brown viscous liquid. Isolated yield: 0.13 g, 80%. $[\alpha]^{25}_D = +68.5°$ (*c* 1.00, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz; $\delta$ (ppm)): 7.36−7.21 (m, 5H), 4.57 (m, 1H), 4.41 (d, 1H, $J$ = 14.7 Hz), 4.36 (d, 1H, $J$ = 14.7 Hz), 3.47 (t, 1H, $J$ = 8.8 Hz), 3.03 (t, 1H, $J$ = 7.8 Hz), 2.69 (t, 2H, $J$ = 6.8 Hz), 2.38 (s, 3H), 1.88 (m, 1H), 1.74 (m, 1H), 1.62 (bs, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz; $\delta$ (ppm)): 158.0, 135.7, 128.8, 128.1, 127.9, 72.3, 49.4, 48.3, 47.5, 36.4, 35.1. HRMS (*m/z*): calcd for $C_{13}H_{19}N_2O_2$ $[M + 1]^+$, 235.1447; found, 235.1449. IR ($CHCl_3$; $cm^{-1}$): 3018, 2936, 1742, 1493, 1442, 1217, 756.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of compounds **13a**−**20a**, **13b**−**19b**, **14c**−**16c**, and protonated **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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