An Enantioselective Ketene−Imine Cycloaddition Method for Synthesis of Substituted Ring-Fused 2-Pyridinones

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Previously, a method for the stereoselective synthesis of β-lactams, starting from 2*H*-Δ^2-thiazolines and Meldrum's acid derivatives, has been reported from our laboratory. We now report a new method for the synthesis of optically active, highly substituted ring-fused 2-pyridinones. This was discovered when 2-alkyl-Δ^2-thiazolines and Meldrum's acid derivatives were treated with HCl(g) in benzene at 5 → 78 °C. Further refinement of the synthetic protocol revealed that use of 1,2-dichloroethane as solvent at 0 → 64 °C led to the desired 2-pyridinones in good yields and with excellent enantioselectivity. Use of these conditions allowed preparation of 2-pyridinones from several different Δ^2-thiazolines and Meldrum's acid derivatives and may be a general route to 2-pyridinones.

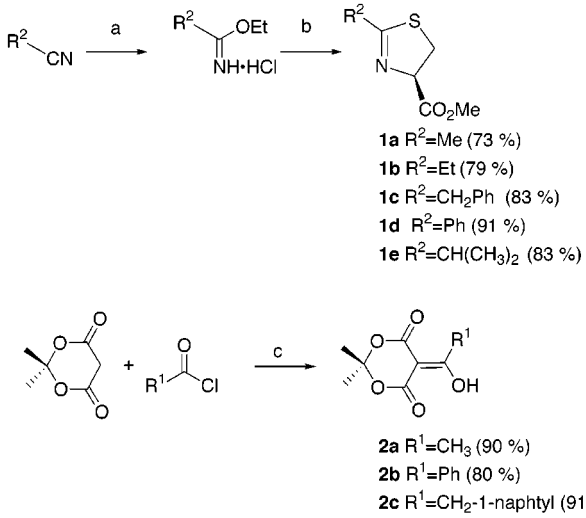
Introduction

Recently, we reported the stereoselective synthesis of optically active β-lactams.[1] This rigid framework, with different stereochemistry than that of penicillin, was designed to be a suitable scaffold for the development of compounds (termed pilicides) that inhibit pilus formation in uropathogenic *E. coli*. The synthesis took use of acyl Meldrum's acids and Δ^2-thiazolines as key intermediates, which gave the desired β-lactams in yields as high as 93% in the best cases. In our design work, however, we saw a possibility to obtain more potent pilicides if we could introduce an additional substituent in the β-lactam ring. To do so, the most direct approach would be to use 2-alkyl- or 2-aryl-substituted Δ^2-thiazolines and perform the same ketene−imine cycloaddition. Although the steric hindrance in the β-lactam-forming step would be substantial with a substituent in the Δ^2-thiazoline, others have shown that this approach can be successful.[2,3]

Therefore, substituted Δ^2-thiazolines were synthesized by the method described by Myers.[4,5] This methodology is very attractive since commercially available nitriles, via their corresponding imino ethers, can be condensed with (*R*)-cysteine methyl ester hydrochloride. Thus, a set of different substituted Δ^2-thiazolines was prepared (Scheme 1). The other building block, i.e., the Meldrum's acid derivatives, was easily made from an activated carboxylic acid and Meldrum's acid[6] (Scheme 1).

Surprisingly, when the benzyl-substituted Δ^2-thiazoline **1c** was used, the previously so successful approach did not give the desired benzyl-substituted β-lactam. Instead, a ring-fused 2-pyridinone framework was formed (Figure 1).

Scheme 1[a]



[a] Key: (a) HCl(g), EtOH, 0 °C, 4 h; (b) (*R*)-cysteine methyl ester hydrochloride, TEA, CH_2Cl_2, 0 °C → rt, 17 h; (c) DMAP, CH_2Cl_2, −12 °C → rt, 4 h.

The core structure of these heterocycles can be found in numerous biologically active compounds with diverse medicinal properties. These range from antibacterial[7−9] and antifungal[10] agents to free-radical scavengers[11,12] and angiotensin converting enzyme (ACE) inhibitors (Figure

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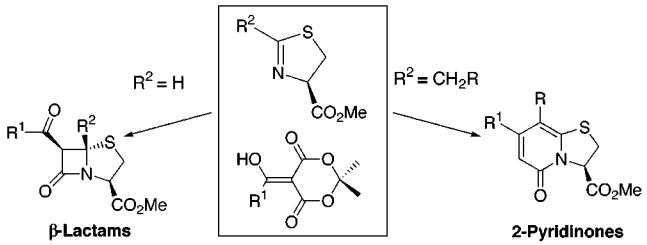

Figure 1. β-Lactams or 2-pyridinones can be selectively prepared by choosing a 2-H-substituted or a 2-alkyl-substituted Δ^2-thiazoline.

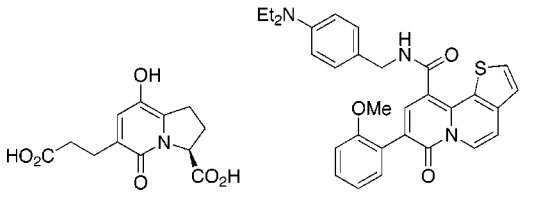

Figure 2. Examples of a natural product and a synthetic compound of medicinal interest that possess a 2-pyridinone framework.

2).[13−15] 2-Pyridinones also serve as inhibitors of Aβ-peptide aggregation,[16,17] which is believed to play an important role in amyloid formation in Alzheimer's disease (Figure 2).

N-Substituted 2-pyridinones have also been used as active ingredients for the therapy of fibrotic disease,[18] and they have been evaluated as inhibitors of human leukocyte elastase.[19] Moreover, this framework can be transformed to piperidine, pyridine, quinolizidine, and indolizidine alkaloids,[20,21] which, together with their potential as conformationally constrained amino acids,[22−24] make them into important intermediates in natural product synthesis and versatile scaffolds for preparation of peptide mimetics.

Due to the importance of substituted 2-pyridinones, many preparative methods have been reported in the literature.[25−38] In recent years, attractive cycloaddition procedures have been reported separately by Padwa[39,40] and Liebeskind[41,42] that cover the preparation of ring-fused 2-pyridinones.

Results and Discussion

Although a variety of methods for the synthesis of substituted 2-pyridinones are available, new direct approaches that are regioselective and mild enough to allow preparation of optically active products are continuously attracting interest. Therefore, we decided to investigate this novel enantioselective route from acyl Meldrum's acids and substituted Δ^2-thiazolines further. Sets of 2-alkyl- and 2-aryl-substituted Δ^2-thiazolines **1a**−**e** and Meldrum's acid derivatives **2a**−**c** (Scheme 1) were therefore synthesized. Using the conditions applied in our previous β-lactam synthesis, i.e., HCl(g) in benzene at 5 → 78 °C, a small library of substituted ring-fused 2-pyridinones **3a**−**e** was then prepared (Table 1). The yields were moderate to good, and all the products were optically active. Moreover, the synthesis could easily be performed on a gram scale without any decrease in the isolated yields; 2.3 g of 2-pyridinone **3a** was prepared corresponding to an isolated yield of 69% (83% based upon recovered Δ^2-thiazoline **1c**).

A tentative mechanistic explanation to the formation of substituted 2-pyridinones could be as follows (Scheme 2). Instead of an attack back at the activated imine **A**, which would give a β-lactam, a [1,5] sigmatropic rearrangement results in enamide **B**. Then, an intramolecular attack at the β carbonyl group closes the six-membered ring to give **C**. After consecutive removal of a proton and water, the final 2-pyridinone **D** is thus formed. According to this mechanism, a Δ^2-thiazoline lacking a methylene group in the R^2-substituent adjacent to the imine carbon would not be able to form a 2-pyridinone. Therefore, attempts to use 2-phenyl- or 2-isopropyl-substituted Δ^2-thiazolines (**1d** and **1e**) should not result in any 2-pyridinones. Indeed, performing the reaction with these substrates resulted in undefined products. In these cases, one could expect the β-lactam "pathway" to be dominating but no substituted β-lactams could be isolated.

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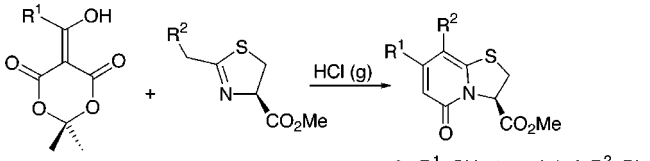
Table 1. Influence of Different Conditions for the Synthesis of 2-Pyridinones Regarding Yield and Enantiomeric Excess

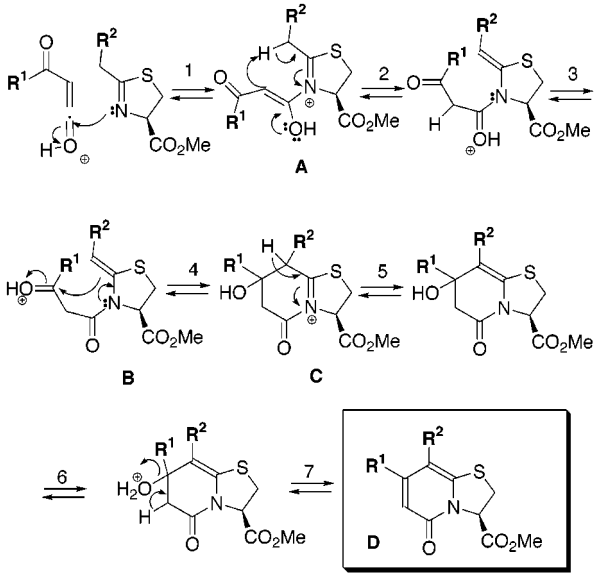


3a R^1=CH_2-1-naphthyl, R^2=Ph
3b R^1=CH_2-1-naphthyl, R^2=H
3c R^1=CH_3, R^2=Ph
3d R^1=CH_3, R^2=CH_3
3e R^1=Ph, R^2=H

compd	*T* (°C)	time (h)	yield[a] (%)	ee 2-pyridinone (%)	ee Δ^2-thiazoline (%)	Δ ee[b] (%)
Reactions with Benzene as Solvent						
3a	78	3	69	77	92	15
3b	78	3	29	97	100	3
3c	78	3	69	73	92	19
3d	78	3	66	64	75	11
3e	78	3	36	84	100	16
3a	69	4	63	86	92	6
Reactions with 1,2-Dichloroethane as Solvent						
3a	64	14	85	89	92	3
3b	64	14	86	97	100	3
3c	64	14	66	92	92	0
3d	64	14	77	75	75	0
3e	64	14	63	97	100	3
3a	64	1	32	92	92	0

[a] Yields were determined after purification by flash column chromatography. [b] The difference in enantiomeric excesses between the Δ^2-thiazolines and the 2-pyridinones.

Scheme 2. Tentative Mechanism for the Formation of 2-Pyridinones from Δ^2-Thiazolines and Ketenes Generated from Acyl Meldrum's Acids



Measurement of Optical Purity and Optimization of the 2-Pyridinone Synthesis. To establish the enantioselectivity in formation of the 2-pyridinones, the enantiomeric excess of the Δ^2-thiazolines was first measured by chiral HPLC using a Chiralcel OD-H column.[43] The enantiomers were detected by UV spectroscopy and had identical spectra. The 2-pyridinones were also subjected to a chiral HPLC measurement and the (*S*,*S*) Whelk-O1 column gave excellent separation. In this case, the enantiomers were detected with both UV spectroscopy and mass spectrometry (Figure 3). Racemic 2-pyridinone (±)-**3a** was also prepared to verify that the peaks from the UV and MS detection corresponded to the enantiomers. The reproducibility of the ee determinations was confirmed by five separate HPLC measurements on different batches of 2-pyridinone **3b**. The major enantiomer ((−)-**3b**) was thus obtained with an enantiomer ratio of 98.5 ± 0.3% corresponding to 97% ee.

The enantiomeric excess of the key intermediates **1a**−**c** were 75−100%, and the resulting 2-pyridinones **3a**−**e** had ee's of 64−97% (Table 1). Thus, one could conclude that some racemization occurred on formation of 2-pyridinones when the synthesis was performed in refluxing benzene for 3 h. In the worst case, for the 2-pyridinone **3c**, the ee had decreased as much as 19%. The temperature was an obvious parameter that could affect the racemization rate, and a decrease in temperature to 69 °C in the synthesis of 2-pyridinone **3a** gave an increase in ee from 77 to 86% without any substantial decrease in isolated yield.

However, although previously the solvent of choice in the β-lactam synthesis based upon acyl Meldrum's acids,[1,6] there are drawbacks with using benzene as a solvent. Apart from being carcinogenic it also freezes at 4 °C. Since HCl(g) is led through the reaction mixture just above the freezing point of benzene, precipitation and thus a stop in the gas flow was occasionally experienced. Another problem is that the protonated Δ^2-thiazolines easily precipitate if the HCl(g) is passed through the solution too vigorously or under a prolonged time. Even though the temperature is raised during the synthesis, the precipitated Δ^2-thiazoline does not dissolve properly, giving a decrease in yield of the desired 2-pyridinones. It turned out that 1,2-dichloroethane is superior to benzene as solvent in this reaction in many aspects. One does not encounter any problems when introducing the HCl(g) into the solution, no back flow of HCl(g) and no precipitation *of* Δ^2-thiazoline occur. The reaction can also be heated to the temperatures required to get the 2-pyridinones. Moreover, when the synthesis was performed at 64 °C overnight only limited racemization (1.5%) could be detected for **3a**, **3b**, and **3e** while the other two 2-pyridinones, **3c** and **3d**, could be synthesized without any racemization at all (Table 1). Also a significant increase in isolated yield was observed with 1,2-dichloroethane as solvent and the most striking example was **3b** for which the yield increased from 29% (using benzene) to 86%. It should be noted that also **3a** could be prepared without any racemization, although at a lower yield, if the synthesis was conducted for only 1 h at 64 °C.

Conclusions

A new enantioselective synthesis of highly substituted 2-pyridinones has been developed. The method is mild and convergent, which indicates a high potential for future parallel synthesis of diverse 2-pyridinone libraries. The methodology is also easy to scale-up, which makes synthesis of potential leads for further biological testing in gram quantities straightforward. The synthetic protocol has been refined to a highly enantioselective 2-pyridinone forming step giving the desired 2-pyridinones in good to excellent yields. Therefore, by choosing the

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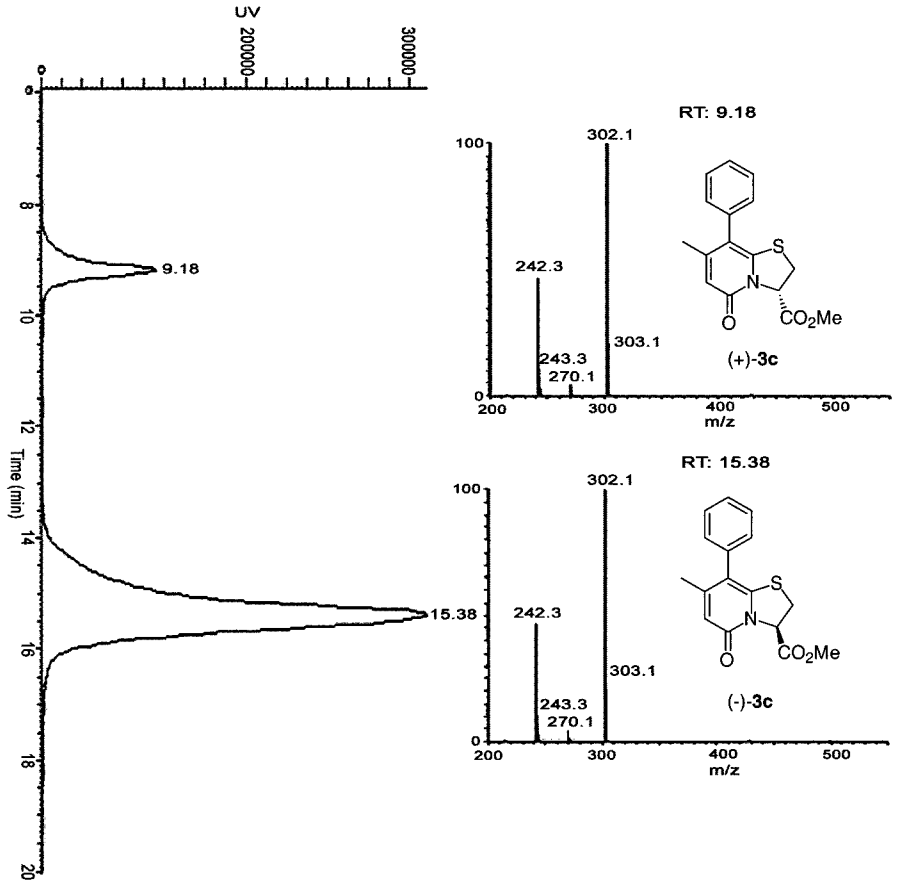

Figure 3. Optical purity of the 2-pyridinones was measured by chiral HPLC ((*S*,*S*) Whelk-O1). The enantiomers showed identical mass spectra as exemplified for **3c** synthesized by the original conditions (HCl(g) in benzene, 5 → 78 °C, 3 h, 73% ee).

correct Δ^2-thiazolines (substituted or unsubstituted) we are now allowed to enantioselectively synthesize either β-lactams or 2-pyridinones (Figure 1).

Experimental Section

General Methods. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. 1,2-Dichloroethane and CH_2Cl_2 were distilled from calcium hydride immediately before use. THF was distilled from potassium, and toluene was distilled from sodium. HCl(g) was passed through concentrated sulfuric acid before use. TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light and staining with a solution of anisaldehyde (26 mL), glacial acetic acid (11 mL), and concentrated sulfuric acid (35 mL) in 95% ethanol (960 mL). Flash column chromatography (eluents given in brackets) was performed on silica gel (Matrex, 60 Å, 35−70 μm, Grace Amicon). Centrifugal preparative TLC was performed using rotors coated with silica gel 60 PF_{254} containing $CaSO_4$ (Merck). The moving bands were visualized using UV light. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 for solutions in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm), as internal standard] at 298 K. First-order chemical shifts and coupling constants were obtained from one-dimensional spectra, and proton resonances were assigned from COSY experiments. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. Optical rotations were measured with a Perkin-Elmer 343 polarimeter at 20 °C. High-resolution mass spectra [EI or FAB] were recorded on a JEOL JMS-SX 102 spectrometer. Analyses of enantiomeric excess were performed with a HPLC equipped with a Chiralcel OD-H column with hexane/2-propanol 70:30 as mobile phase for the Δ^2-thiazolines and a (*S*,*S*) Whelk-O 1 column with hexane/dichloromethane/2-propanol 48:48:4 as mobile phase for the 2-pyridinones.

(4*R*)-2-Methyl-4,5-dihydrothiazole-4-carboxylic Acid Methyl Ester (1a). Prepared as described for **1c** from acetonitrile to give Δ^2-thiazoline **1a** as an oil (3.06 g, 73%). Data in agreement with published procedures:[44,45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98−5.07 (m, 1H), 3.77 (s, 3H), 3.46−3.62 (m, 2H), 2.23 (d, J = 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.0, 78.0, 52.6, 36.1, 20.2; HRMS (EI+) calcd for $C_6H_9NO_2S$ 159.0354, obsd 159.0355.

(4*R*)-2-Ethyl-4,5-dihydrothiazole-4-carboxylic Acid Methyl Ester (1b). Prepared as described for **1c** from ethyl cyanide to give Δ^2-thiazoline **1b** as an oil (4.19 g, 79%): $[\alpha]_D$ 93° (*c* 1.28, $CHCl_3$); IR 2976, 2953, 1739, 1620, 1437, 1200, 926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97−5.06 (m, 1H), 3.76 (s, 3H), 3.42−3.58 (m, 2H), 2.53 (dq, J = 7.6, 1.5 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 171.3, 77.8, 52.5, 35.2, 27.7, 11.9; HRMS (EI+) calcd for $C_7H_{11}NO_2S$ 173.0510, obsd 173.0510.

(4*R*)-2-Benzyl-4,5-dihydrothiazole-4-carboxylic Acid Methyl Ester (1c). Dry HCl(g) was passed through a solution of benzylcyanide (22.6 g, 193 mmol) in dry EtOH (15 mL) during 4 h at 0 °C. After standing overnight at room temperature, the mixture was concentrated to give ethyl benzylimidate hydrochloride as white crystals, which were used in the next step without further purification. Triethylamine (12 mL, 86.1 mmol) was slowly added to a suspension of (*R*)-cysteine methyl ester hydrochloride (15.0 g, 87.4 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C. After 20 min, a suspension of ethyl benzylimidate hydrochloride (13 g, 65.1 mmol) in CH_2Cl_2 (30

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mL) was added, and the mixture was allowed to attain room temperature overnight. Then, the mixture was diluted with CH_2Cl_2 and washed with water, saturated aqueous $NaHCO_3$, and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (heptane/ethyl acetate, 1:1) to give Δ^2-thiazoline **1c** as an oil (12.7 g, 83% from benzylcyanide): $[\alpha]_D$ −59° (*c* 2.40, $CHCl_3$); IR λ 3027, 2951, 1736, 1616, 1435, 1198, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.36 (m, 5H), 5.09 (m, 1H), 3.80−3.91 (m, 2H), 3.82 (s, 3H), 3.42−3.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 171.2, 135.6, 129.1, 128.7, 127.3, 77.9, 52.7, 40.8, 35.7; HRMS (EI+) calcd for $C_{12}H_{13}NO_2S$ 235.0667, obsd 235.0669.

4-(R)-2-Phenyl-4,5-dihydro-thiazole-4-carboxylic acid methyl ester, (1d). Prepared as described for **1c** from phenyl cyanide to give Δ^2-thiazoline **1d** as an oil (2.18 g, 91%). Data in agreement with published procedures.[43]

(4*R*)-2-Isopropyl-4,5-dihydrothiazole-4-carboxylic Acid Methyl Ester (1e). Prepared according to published procedures.[46]

5-(1-Hydroxyethylidene)-2,2-dimethyl[1,3]dioxane-4,6-dione (2a). Prepared according to published procedures.[6]

5-(Hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (2b). Prepared according to published procedures.[6]

5-(1-Hydroxy-2-naphthalen-1-ylethylidene)-2,2-dimethyl[1,3]dioxane-4,6-dione (2c). Oxalyl chloride (10 mL, 114 mmol) and DMF (0.1 mL) were added to a solution of 1-naphthylacetic acid (7.56 g, 40.6 mmol) in dry CH_2Cl_2 (80 mL). After being stirred for 30 min at room temperature, the solution was refluxed for 1.5 h, cooled to room temperature, and concentrated. The residue was co-concentrated three times from dry CH_2Cl_2 and dissolved in dry CH_2Cl_2 (40 mL). The solution was added slowly during 1 h to a stirred solution of Meldrum's acid (5.19 g, 36 mmol) and DMAP (8.62 g, 70.3 mmol) in dry CH_2Cl_2 (80 mL) at −10 °C. The resulting solution was allowed to attain room temperature and was then stirred for 3 h before being diluted with CH_2Cl_2 and washed with aqueous $KHSO_4$ (2%), water, and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was recrystallized from Et_2O to give **2c** as white crystals (10.2 g, 91%): mp 104 °C dec; IR λ 3060, 2995, 1728, 1645, 1568, 1201, 918, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 15.49 (s, 1H), 7.95−8.01 (m, 1H), 7.86−7.92 (m, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.41−7.58 (m, 4H), 4.96 (s, 2H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 170.5, 160.5, 133.8, 132.1, 130.5, 128.8, 128.3, 128.2, 126.5, 125.8, 125.4, 123.6, 105.0, 91.6, 38.4, 26.8; HRMS (EI+) calcd for $C_{18}H_{16}O_5$ 312.0998, obsd 312.0999. Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; N, 25.61. Found: C, 69.2; H, 5.2; N, 25.6.

(3*R*)-7-(Naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (3a). Dry HCl(g) was passed through a solution of **1c** (501 mg, 2.13 mmol) and **2c** (970 mg, 3.11 mmol) in 1,2-dichloroethane (28 mL) during 15 min at 0 °C. The solution was stirred for 11 h at 64 °C, then more **2c** (480 mg, 1.53 mmol) was added. The mixture was then stirred for another 2 h before it was cooled to room temperature, diluted with CH_2Cl_2, and washed with water, saturated aqueous $NaHCO_3$, and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (heptane/ethyl acetate, 1:4) gave 2-pyridinone **3a** as a white foam (771 mg, 85% yield from Δ^2-thiazoline **1c**): $[\alpha]_D$ −152° (*c* 1.01, $CHCl_3$); IR λ 3041, 2953, 1753, 1655, 1581, 1485, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.2, 2.1 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.62 (dd, J = 7.2, 1.8 Hz, 1H), 7.45−7.34 (m, 8H), 7.21 (d, J = 6.8 Hz, 1H), 5.82 (s, 1H) 5.60 (dd, J = 8.5, 2.4 Hz, 1H), 3.89−4.06 (m, 2H), 3.80 (s, 3H), 3.65 (dd, J = 11.8, 8.6 Hz, 1H), 3.45 (dd, J = 11.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 161.2, 154.3, 146.4, 136.3, 133.9, 133.7, 131.7, 130.2, 129.7, 129.0 (splitted), 128.7, 128.4, 127.9, 127.6, 126.0, 125.6, 125.4, 123.7, 116.1, 115.2, 63.4, 53.2, 36.9, 31.6; HRMS (EI+) calcd for $C_{26}H_{21}NO_3S$ 427.1242, obsd 427.1228.

(3*R*)-7-(Naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (3b). By following the procedure described for the preparation of **3a** from **1c** and **2c**, **1a** (312 mg, 1.96 mmol) and **2c** (838 mg, 2.68 mmol) gave **3b** as a white foam (593 mg, 86%): $[\alpha]_D$ −184° (*c* 1.63, $CHCl_3$); IR λ 2920, 1747, 1647, 1572, 1504, 1211, 1018, 779 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.88−7.85 (m, 2H) 7.79 (d, J = 8.2 Hz, 1H) 7.48−7.410 (m, 3H) 7.34 (d, J = 6.8 Hz, 1H) 6.10 (d, J = 1.2 Hz, 1H) 5.97 (d, J = 1.3 Hz, 1H) 5.52 (dd, J = 8.3, 2.1 Hz, 1H) 4.20 (s, 2H) 3.78 (s, 3H) 3.67 (dd, J = 11.7, 8.3 Hz, 1H) 3.50 (dd, J = 11.7 Hz, 2.1 Hz, 1H), ^{13}C NMR (100 MHz, CDCl3) δ 168.4, 161.9, 155.2, 146.8, 133.9, 133.5, 131.9, 128.8, 127.9, 127.9, 126.3, 125.8, 125.5, 123.9, 114.1, 101.8, 62.5, 53.2, 38.9, 31.8; HRMS (FAB+) calcd for $C_{20}H_{18}NO_3S$ 352.1005, obsd 352.1007.

(3*R*)-7-Methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (3c). By following the procedure described for the preparation of **3a** from **1c** and **2c**, **1c** (565 mg, 2.40 mmol) and **2a** (633 mg, 3.40 mmol) gave **3c** as a white foam (478 mg, 66% (95% based on recovered stmrl, Δ^2-thiazoline **1c**)): $[\alpha]_D$ −185° (*c* 1.47, $CHCl_3$); IR λ 3053, 2999, 2954, 1753, 1649, 1581, 1483, 1416, 1207, 991, 839, 748, 702, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45∠7.33 (m, 3H), 7.25−7.21 (m, 2H), 6.24 (d, J = 0.8 Hz, 1H), 5.65 (dd, J = 8.6, 2.5 Hz, 1H), 3.83 (s, 3H), 3.64 (dd, J = 11.6, 8.6 Hz, 1H), 3.45 (dd, J = 11.6, 2.5 Hz, 1H), 1.97 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.2, 151.9, 146.1, 136.6, 129.8, 128.8, 128.1, 116.6, 115.1, 63.5, 53.3, 31.8, 20.7; HRMS (EI+) calcd for $C_{16}H_{15}NO_3S$ 301.0773, obsd 301.0770.

(3*R*)-7,8-Dimethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]-pyridine-3-carboxylic Acid Methyl Ester (3d). By following the procedure described for the preparation of **3a** from **1c** and **2c**, **1b** (285 mg, 1.65 mmol) and **2a** (450 mg, 2.42 mmol) gave **3d** as a white foam (302 mg, 77% (97% based on recovered stmrl, Δ^2-thiazoline **1b**)): $[\alpha]_D$ −205° (*c* 3.92, $CHCl_3$); IR λ 2889, 2956, 1743, 1651, 1577, 1496, 1425, 1176, 985, 827, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.41 (d, J = 8.4 Hz, 1H), 3.65−3,53 (m, 4H), 3.36 (d, J = 11.8 Hz, 1H), 1.95 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 160.2, 152.2, 143.4, 114.3, 108.8, 62.8, 52.6, 31.3, 19.6, 15.3; HRMS (EI+) calcd for $C_{11}H_{13}NO_3S$ 239.0616, obsd 239.0616.

(3*R*)-5-Oxo-7-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (3e). By following the procedure described for the preparation of **3a** from **1c** and **2c**, **1a** (230 mg, 1.45 mmol) and **2b** (480 mg, 1.93 mmol) gave **3e** as a white foam (260 mg, 63%): $[\alpha]_D$ −68° (*c* 1.38, $CHCl_3$); IR λ 2950, 1743, 1645, 1562, 1495, 1207, 1174, 993, 843, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.55 (m, 2H), 7.34−7.44 (m, 3H), 6.45 (s, 1H), 6.36 (s, 1H), 5.60 (d, J = 8.8 Hz, 1H), 3.70−3.82 (m, 4H), 3.54 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 161.8, 153.2, 147.3, 137.3, 129.4, 128.8, 126.6, 111.9, 100.0, 62.5, 53.1, 31.8; HRMS (EI+) calcd for $C_{15}H_{13}NO_3S$ 287.0616, obsd 287.0611.

(3*RS*)-7-(Naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester ((±)-3a). To a solution of diisopropylamine (90 μL, 0.635 mmol) in dry THF (1.2 mL) was added *n*-butyllithium (330 μL 1.6 M in hexane, 0.529 mmol) at 0 °C. After being stirred for 1 h, the solution was cooled to −78 °C and **3a** (170 mg, 0.400 mmol) dissolved in dry THF (1.0 mL) was added dropwise. NH_4Cl(aq) (1 mL) was added after stirring at −78 °C for 1 h, and the mixture was allowed to attain room temperature before being diluted with CH_2Cl_2. The pH was adjusted to 4 with 6 N HCl, and the mixture was washed with water and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification by Centrifugal preparative TLC (heptane:ethyl acetate, 30:70) gave 2-pyridinone

(46) Pattenden, G.; Thom, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629−1636.

(±)-**3a** as a white foam (54 mg, 32%): $[\alpha]_D$ 0° (*c* 1.00, $CHCl_3$), NMR and IR data in agreement with **3a**.

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Supporting Information Available: ^{13}C NMR spectra of **1a**−**c**, **2c**, and **3a**−**e**. Chiral HPLC chromoatogram of **1a**−**c** and **3a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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