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# Microwave-Assisted Synthesis of Highly Substituted Aminomethylated 2-Pyridones

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By employing microwave-assisted organic synthesis (MAOS) efficient conditions to introduce aminomethylene substituents in highly substituted bicyclic 2-pyridones have been established. Primary amino methylene substituents were introduced via a cyanodehalogenation followed by a borane dimethyl sulfide reduction of the afforded nitrile. In both of these transformations, microwave irradiation proved to be superior to traditional conditions and the primary amines were obtained in good overall yields (55−58% over three steps). To incorporate tertiary aminomethylene substituents in the 2-pyridone framework, a microwave-assisted Mannich reaction using preformed iminium salts proved to be effective. Thus highly substituted 2-pyridones were obtained in 48−93% yields.

## Introduction

The core structure of 2-pyridinones, or more commonly referred to as 2-pyridones, is present in a wide range of compounds with diverse biological application areas (Figure 1). Besides showing, e.g., antibacterial,[1] antifungal,[2] and antitumor activity,[3,4] members of these heterocycles also act as inhibitors of A$\beta$-peptide aggregation thought to play an important role in Alzheimers' disease.[5,6]

An enantioselective acyl-ketene imine cycloaddition reaction to synthesize ring-fused substituted 2-pyridones has previously been reported from our laboratory (Figure 2).[7,8] Starting from commercially available nitriles and carboxylic acids, this synthetic pathway rendered a first generation of 2-pyridones that were designed to target periplasmic escort proteins, chaperones, in uropathogenic *Escherichia coli*. Recently, efficient improvements of the original synthetic procedure were reported (Figure 2).[9] This alternative microwave-assisted method allows simple and fast preparation of highly substituted 2-pyridones in good yields and with limited racemization.

Chaperones are essential for the assembly of adhesive protein organelles known as pili or fimbriae present on the surface of the bacteria. In the absence of these organelles the bacteria become noninfectious.[10] Thus, compounds interfering with pili/fimbriae formation, *pilicides*, would represent a novel class of antibacterial agents directed against bacterial virulence.[11] Encouraging affinity predictions of substituted 2-pyridones binding to the chaperones PapD and FimC have previously been confirmed in vitro by direct binding assays using both surface plasmon resonance techniques and NMR spectroscopy, where the corresponding acid of **4a** (Scheme 1) was found to be a potent binder.[12] Still, position six (Figure 2) is available for further substitution and thus provides an opportunity to introduce hydrophilic functionalities targeting increased bioavailability and enhanced chaperone affinity in the pilicide project. For example, in the case of ampicillin and amoxycillin, the introduction of an amine substituent led to a broad spectrum antibiotic also affecting Gram-negatives.[13] In addition, introducing amine substituents in the 2-pyridone framework would result in highly substituted rigid amino acids, which could serve as versatile scaffolds and peptide mimetics (compare with compound **3** in Figure 1).[14]

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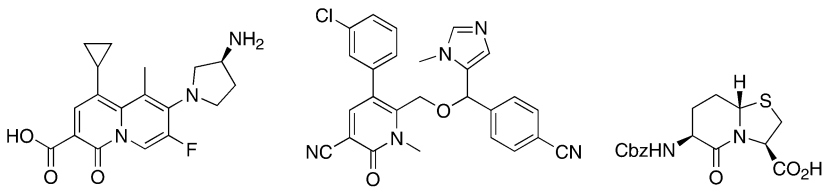


**FIGURE 1.** Examples of 2-pyridones (**1** and **2**) and a tetrahydro derivative **3** with different biological effects.[1,4,14]

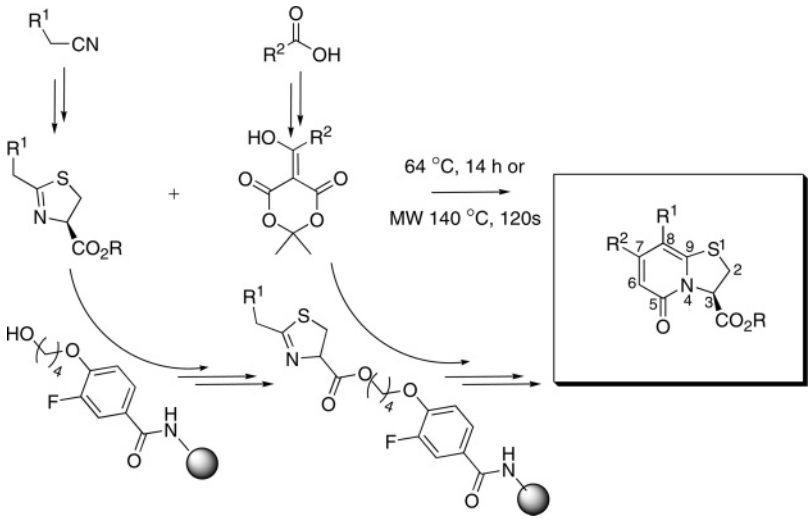


**FIGURE 2.** Synthetic methods toward substituted bicyclic 2-pyridones based upon the acyl-ketene imine cycloaddition.[7−9]

Aromatic cyanodehalogenation and subsequent reduction of the cyano functionality was considered a well investigated and straightforward pathway toward primary aminomethylated 2-pyridones.[15,16] As a complement to the primary amines, and to expand the chemical diversity of these structures, tertiary amines were also desired. A few scattered examples where 2-pyridones react with imines in a Mannich reaction in the corresponding position have previously been described,[17,18] and recently, microwave-mediated Mannich reactions performed with electron-rich aromatic substrates have also been published.[19,20] Nevertheless, applications on more complex structures such as functionalized 2-pyridones with a challenging substitution pattern have previously not been reported. In this paper, we describe two efficient microwave-assisted synthetic pathways to primary and tertiary aminomethylated 2-pyridones. Primary amines were obtained via a cyanodehalogenation followed by reduction of the resulting nitrile, and a modified Mannich reaction furnished the corresponding tertiary amines.

## Results and Discussion

To obtain the nitriles to be used as amine precursors, brominated 2-pyridones **5a**−**c** were prepared in excellent yields using bromine in acetic acid (Scheme 1).[21] Various cyanodehalogenation procedures employing transition-metal catalysts, e.g., palladium-catalyzed reactions utilizing zinc cyanide as the cyanide source, have worked well with aryl halides.[22,23] Unfortunately, the brominated 2-pyridone **5a** was not consumed in these reactions, a fact that might be due to poisoning of the catalyst by the sulfur containing starting material. As a consequence, the attention was turned to the original Rosenmund von Braun cyanation employing CuCN in refluxing DMF, and this time the desired cyanosubstituted 2-pyridones were obtained. Still, the long reaction times and the rather harsh workup procedure were not ideal resulting in low and irreproducible yields. Recent reports of alternative cyanodehalogenation reactions performed on aryl halides have shown that microwave-assisted organic synthesis, MAOS, can improve this reaction significantly.[23−26] Therefore, it was investigated if this technology would be

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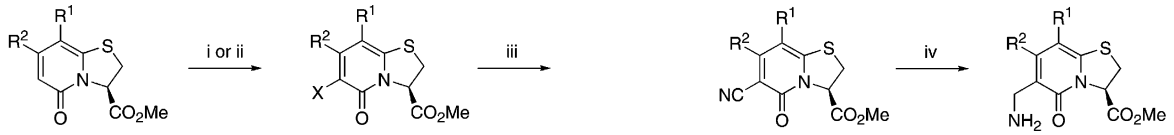
**SCHEME 1**[a]




**4a**: $R^1$=Ph, $R^2$=$CH_2$-1-naphthyl
**4b**: $R^1$=cyclopropyl, $R^2$=$CH_2$-1-naphthyl (79% ee)
**4c**: $R^1$=Ph, $R^2$=Me

**5a**: X=Br, 93%
**5b**: X=Br, 90% (79% ee)
**5c**: X=Br, 98%
**5d**: $R^1$=Ph, $R^2$=$CH_2$-1-naphthyl, X=I, 78%

**6a**: 82%
**6b**: 88% (36% ee)
**6c**: 86%

**7a**: 72%
**7b**: 73% (8% ee)
**7c**: 67%

[a] Reagents and conditions: (i) $Br_2$, AcOH, rt gave **5a**−**c**; (ii) *N*-iodosuccinimide, AcOH/TFA, rt gave **5d**; (iii) CuCN, NMP, MW 220 °C, 20 min; (iv) $BH_3$·$Me_2S$, THF, MW 100 °C, 1 min.

beneficial also for the Rosenmund von Braun cyanodehalogenation. In the first attempts, 2-pyridone **5a** and CuCN were heated in DMF at 200 °C for 10 min using microwave irradiation. Although product was formed, the yields were still low (<30%) and a lot of unconsumed starting material remained. Extending the reaction time to 20 min gave more product but also significant amounts of byproducts. Fortunately by increasing the temperature to 220 °C and switching the solvent to *N*-methyl-2-pyrrolidinone, NMP, the cyano-substituted 2-pyridone **6a** was obtained without detecting any competing side reaction. However, the isolated yields did not reflect the encouraging TLC and LC−MS data. The commonly applied workup procedures for the Rosenmund von Braun reaction are often harsh, e.g., heating with HCl and $FeCl_3$,[15] which clearly affected the total yield and also was a concern regarding the risk of racemization. Therefore, after trying different extraction procedures with unsatisfactory outcomes, most of the NMP was lyophilized from water. This was followed by thorough extraction of the remaining solid with $CH_2Cl_2$, which proved critical to obtain good overall yields. Final purification with column chromatography resulted in cyano-substituted 2-pyridones **6a**−**c** (Scheme 1) in very good yields taking into account the presence of the sterically demanding naphthyl substituent in **5a** and **5b**. Although still optically active, a substantial loss in enantiomeric purity was observed in the cyanation step, and the enantiomeric excess (ee) went down from 79% for **4b** and **5b**, respectively, to a moderate ee of 36% for the cyanated derivative **6b**.

The remaining step to the desired primary amines was the reduction of the nitrile. To accomplish this transformation, some constrains had to be considered. First, sulfur-assisted $NaBH_4$ reduction of carboxylic acid esters has been reported[27] indicating that one might experience selectivity problems and over-reduction to the corresponding alcohol. Second, Padwa and co-workers have shown that transition-metal-catalyzed hydrogenation reactions at high pressure (90 psi) saturates the 2-pyridone skeleton.[21] Encouraged by previous successful use of PdO in a selective dehalogenation of iodopyridone **5d** at atmospheric pressure, hydrogenation was utilized in the initial attempts to reduce the nitrile. Unfortunately, hydrogenations at atmospheric pressure using various catalysts, e.g., PdO, Pd/C,[28] and $PtO_2$,[29] as well as different sources of hydrogen (hydrogen gas or ammonium formate) or elevated pressure at 50 psi all proved unsuccessful. Pd−S/C[30] and Rh/C were also applied to investigate whether the low reactivity could be explained by poisoning of the catalyst, but without success. Several electrophilic reducing agents that had been reported as suitable reducing agents for nitriles such as *N*-ethyl-*N*-isopropylaniline−borane (BACH-EI),[31,32] $AlH_3$·$NMe_2Et$,[33] and $BH_3$·$Me_2S$ (BMS)[34] were tested. Again, the cyano group remained intact using both BACH-EI and $AlH_3$·$NMe_2Et$, yet in the latter case the methyl ester was reduced to the corresponding alcohol according to LC−MS. The most promising result was achieved with the BMS complex in THF, where traces of the desired amine could be detected after several hours at room temperature. Refluxing overnight gave a substantial increase of product formation, although this also yielded considerable amounts of byproducts. With the intention to improve the unsatisfactory yields and reaction times, microwave irradiation was studied as an alternative heating source. This gave complete conversion of the hitherto almost inert cyano functionality in 60 s at 100 °C, and primary amines **7a**−**c** were obtained in good yields (Scheme 1). The optical purity, however, continued to deteriorate also during this transformation and the enantiomeric excess for primary amine **7b** was only 8%.

To introduce symmetrical dialkylamines, the renowned Mannich reaction was employed; a classical method known since the early 1900s,[35] often mentioned as one of the most important C−C bond-forming reactions in organic chemistry.[36] Initial efforts using aqueous formaldehyde and protic solvents proved unfruitful as no aminomethylated product could be detected. However, switching to paraformaldehyde and dried aprotic solvents gave some product; still, the yields were poor and a lot of unidentified byproducts were formed. These well-known limitations of the Mannich reaction could possibly

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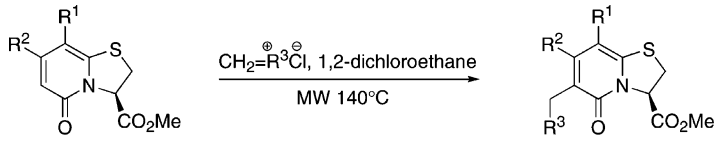
**TABLE 1. Microwave-Assisted Mannich Reaction on Substituted 2-Pyridones**




**4a-c** **8a-f**

| entry | $R^1$ | $R^2$ | $R^3$ | time (s) | product | yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | phenyl | methyl | $NMe_2$ | 400 | **8a** | 92 |
| 2 | phenyl | methyl | morpholine | 400 | **8b** | 93 |
| 3 | phenyl | $CH_2$-1-naphthyl | $NMe_2$ | 400 × 2[b] | **8c** | 48 |
| 4 | phenyl | $CH_2$-1-naphthyl | morpholine | 400 × 2[b] | **8d** | 64 |
| 5 | cyclopropyl | $CH_2$-1-naphthyl | $NMe_2$ | 400 × 2[b] | **8e** | 55 |
| 6 | cyclopropyl | $CH_2$-1-naphthyl | morpholine | 400 × 2[b] | **8f**[c] | 66 |

[a] Yield of the purified product. [b] An additional amount of 1.1 equiv of iminium salt was added. [c] The enantiomeric excess was 75% (compared to 79% ee for the starting material **4b**) as determined by chiral HPLC.

be diminished by shortening the reaction times, and encouraged by the results from both the cyanodehalogenation and the BMS reduction of the nitriles, microwave irradiation was applied also in this reaction. Initial studies resulted in poor yields, at the best 28%. This could be due to slow formation of the in situ generated iminium salt, allowing competing side reactions to occur. To avoid these problems, preformed methylene iminium salts were used, giving a higher concentration of the reactive species. Thus, commercially available Eschenmoser's salt ($I^- Me_2N^+ = CH_2$) and pyridone **4c** were irradiated for 9 min in 1,2-dichloroethane at 160 °C. This improved the result substantially as **8a** could be isolated in 78% yield. The use of preformed iminiumsalts is a well-proven strategy in the Mannich reaction often known to shorten reaction times and increase yields.[36] Several methods for their preparation are available,[37] and *N,N*-morpholine- and *N,N*-dimethylmethyleneammonium chloride were prepared according to published procedures by cleavage of aminals with acetyl chloride.[38] The aminals were conveniently synthesized by condensing the amine of choice with formaldehyde under aqueous conditions.[39] The methyleneammonium chloride salts proved effective and compounds **8a** and **8b** were isolated in 92 and 93%, respectively (Table 1, entries 1 and 2). With these excellent results in hand, the microwave-assisted Mannich reaction was now applied on the sterically more challenging 2-pyridones **4a** and **4b**, which required another portion of reactant and heating for an additional 400s to be completed. Bearing in mind the pronounced steric impact of the $CH_2$-naphthyl substituent $R^2$ in **4a** and **4b** (Table 1), the isolated yields for **8c**−**f** (48−66%) were satisfying. It has previously been observed that the dimethylmethyleneammonium salt is less reactive than the corresponding morpholineammonium salt.[37] This was also confirmed by the results obtained in this study (Table 1, entries 3 and 4). Besides resulting in good to excellent yields, this microwave-assisted method offers a much faster reaction, 7−14 min compared to >22 h for earlier published procedures.[17,18] Moreover, in contradiction to what was observed for the previously described microwave-assisted cyanation and reduction step, the optical purity was not affected as much during this transformation and tertiary amine **8f** was obtained with an ee of 75% (compared to 79% ee for the starting material **4b**).

## Conclusions

To accomplish the incorporation of aminomethylene substituents in highly substituted and functionalized 2-pyridones, microwave-assisted chemistry has been utilized. New conditions to efficiently cyanodehalogenate 2-pyridones were established followed by a microwave-assisted borane dimethyl sulfide reduction of the afforded nitrile. Finally, microwave irradiation in combination with the use of preformed iminium salts proved to be effective for the synthesis of 2-pyridones substituted with tertiary amines. For all these reactions, the common theme was that, despite substantial steric hindrance, satisfying yields and short reaction times were achieved.

## Experimental Section

**2-Pyridonecarboxylic Acid Methyl Esters (4a−c).** Prepared according to previously published procedures.[7,9]

**(3*R*)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (5a).** $Br_2$ (110 μL, 2.1 mmol) was added dropwise to a stirred solution of **4a** (1.0 g, 2.3 mmol) in AcOH (40 mL) at rt. After being stirred for 10 min, the reaction mixture was concentrated. Purification by silica gel chromatography (heptane/EtOAc, 1:1) gave **5b** as a white foam (1.1 g, 93%): $[\alpha]_D$ −140 (*c* 1.0, $CHCl_3$); IR λ 2921, 2850, 1747, 1654, 1581, 1467, 1357, 1224 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.76−7.69 (m, 2H), 7.48−7.32 (m, 3H), 7.20−6.94 (m, 6H), 5.78 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.38−4.24 (m, 2H), 3.89 (s, 3H), 3.73 (dd, *J* = 11.8, 8.6 Hz, 1H), 3.50 (dd, *J* = 11.8, 2.6, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.1, 157.7, 152.2, 146.2, 136.1, 133.6, 132.5, 131.5, 129.7, 129.2, 128.7, 128.6 (broad and splitted), 128.5, 127.0, 125.9, 125.5, 125.4, 124.4, 122.8, 117.0, 114.4, 64.9, 53.5, 37.2, 31.7; HRMS (FAB) calcd for $[M + H]^+$ $C_{26}H_{21}BrNO_3S$ 506.0426, obsd 506.0427.

**6-Bromo-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (5b).** $Br_2$ (28 μL, 0.54 mmol) was added dropwise to a stirred solution of **4b** (200 mg, 0.51 mmol) in AcOH (6 mL) at rt. After being stirred for 30 min, the reaction was quenched with 10% aqueous $Na_2S_2O_5$ and the solution was extracted with $CH_2Cl_2$. The organic layers were washed with 10% aqueous $NaHCO_3$ and brine, and the resulting aqueous

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layers were combined and re-extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. Purification by silica gel chromatography (heptane/EtOAc, 1:4) gave **5b** as a white foam (217 mg, 90%): $[\alpha]_D$ −177 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2996, 2950, 2356, 1752, 1639, 1209, 790; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 8.2 Hz, 1H), 7.90 (d, $J$ = 8.1 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.64−7.51 (m, 2H), 7.31 (t, 1H), 6.86 (d, $J$ = 6.9 Hz, 1H), 5.72 (dd, $J$ = 8.7, 2.5 Hz, 1H), 4.88−4.74 (m, 2H), 3.85 (s, 3H), 3.72 (dd, $J$ = 11.8, 8.7 Hz, 1H), 3.57−3.51 (dd, $J$ = 11.8, 2.4 Hz, 1H), 1.44−1.36 (m, 1H), 0.73−0.63 (m, 2H); 0.59−0.50 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) 168.3, 157.6, 154.4, 146.6, 133.8, 132.4, 131.8, 128.9, 127.1, 126.2, 125.7, 125.6, 123.8, 122.9, 114.7, 114.4, 64.0, 53.4, 36.6, 31.6, 12.2, 7.7, 7.3; HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{21}BrNO_3S$ 470.0426, obsd 470.0439.

**(3*R*)-6-Bromo-7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (5c).** By following the procedure described for the preparation of **5a** from **4a**, **4c** (400 mg, 1.3 mmol) gave **5c** as a white foam (500 mg, 98%): $[\alpha]_D$ −213 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2998, 2950, 1745, 1639, 1579, 1471, 1429, 1211 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46−7.32 (m, 3H), 7.24−7.15 (m, 2H), 5.67 (dd, $J$ = 8.6, 2.4 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, $J$ = 11.7, 8.6 Hz, 1H), 3.42 (dd, $J$ = 11.8, 2.4 Hz, 1H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 157.2, 150.4, 145.1, 136.7, 129.9, 129.6, 128.9, 128.8, 128.4, 116.2, 112.5, 64.6, 53.3, 31.6, 22.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{16}H_{15}BrNO_3S$ 379.9956, obsd 379.9947.

**(3*R*)-6-Iodo-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (5d).** *N*-Iodosuccinimide (125 mg, 0.56 mmol) was added to a stirred solution of **4a** (100 mg, 0.23 mmol) in AcOH (1 mL) and TFA (50 $\mu$L) at rt. After being stirred for 24 h, the reaction mixture was poured on ice−water and neutralized with aqueous saturated $NaHCO_3$. The precipitate was filtered off and purified by silica gel chromatography (heptane/EtOAc, 1:1) giving **5d** as a pale orange solid (97 mg, 78%): $[\alpha]_D$ 176 (*c* 0.65, $CHCl_3$); IR $\lambda$ 2360, 2344, 1747, 1635, 1570, 1458, 1211, 1151, 993 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 7.8 Hz, 1H), 7.71 (m, 2H), 7.48−7.31 (m, 3H), 7.21−7.01 (m, 5H), 6.97 (d, $J$ = 7.5 Hz, 1H), 5.77 (dd, $J$ = 8.7, 2.4 Hz, 1H), 4.42−4.28 (m, 2H), 3.87 (s, 3H), 3.71 (dd, $J$ = 11.8, 8.7 Hz, 1H), 3.43 (dd, $J$ = 11.8, 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 158.7, 156.5, 147.6, 136.3, 133.5, 132.5, 131.5, 129.6, 129.1, 128.6, 128.5 (broad and splitted), 128.3, 127.0, 125.8, 125.5, 125.3, 124.5, 122.7, 117.1, 94.3, 65.2, 53.4, 42.0, 31.7; HRMS (FAB) calcd for $[M + H]^+$ $C_{26}H_{21}INO_3S$ 554.0287, obsd 554.0303.

**(3*R*)-6-Cyano-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (6a).** CuCN (120 mg, 1.3 mmol) was added to a stirred solution of **5a** (150 mg, 0.30 mmol) in NMP (1.0 mL) at rt. The reaction mixture was heated at 220 °C for 20 min using microwave irradiation, and the solvent was then removed by lyophilization from deionized water. The residue was thoroughly extracted with $CH_2Cl_2$, dried, and concentrated. Purification by silica gel chromatography (heptane/EtOAc, 1:1) gave **6a** as a white foam (110 mg, 82%): $[\alpha]_D$ −83 (*c* 1.0, $CHCl_3$); IR $\lambda$ 3012, 2956, 2217, 1751, 1654, 1486, 1442, 1369 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 7.8 Hz, 1H), 7.70 (d, $J$ = 8.1 Hz, 1H), 7.62 (d, $J$ = 8.2 Hz, 1H), 7.47−7.29 (m, 3H), 7.19−6.92 (m, 5H), 6.87 (d, $J$ = 7.3 Hz, 1H), 5.79 (dd, $J$ = 8.9, 2.3 Hz, 1H), 4.41−4.27 (m, 2H), 3.89 (s, 3H), 3.75 (dd, $J$ = 11.9, 8.9 Hz, 1H), 3.52 (dd, $J$ = 11.9, 2.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 160.7, 158.7, 155.2, 134.4, 133.6, 132.4, 131.4, 129.7, 129.2, 128.8 (broad and splitted), 128.6, 127.6, 126.1, 125.7, 125.3, 125.2, 122.7, 117.1, 115.2, 101.3, 64.4, 53.7, 35.3, 31.8; HRMS (EI) calcd for $[M]^+$ $C_{27}H_{20}N_2O_3S$ 452.1195, obsd 452.1193.

**6-Cyano-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (6b).** By following the procedure described for the preparation of **6a** from **5a**, **5b** (100 mg, 0.21 mmol) gave **6b** as a white foam (78 mg, 88%): $[\alpha]_D$ −44 (*c* 1.0, $CHCl_3$); IR $\lambda$ 3004, 2954, 2360, 2213, 1747, 1644, 1481, 1213, 1164, 792; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J$ = 8.2 Hz, 1H), 7.89 (d, $J$ = 7.9 Hz, 1H), 7.75 (d, $J$ = 8.7 Hz, 1H), 7.62−7.51 (m, 2H), 7.34 (t, 1H), 6,89 (d, $J$ = 7.1 Hz, 1H) 5.74 (dd, $J$ = 8.9, 2.2 Hz, 1H), 4.83−4.70 (m, 2H), 3.86 (s, 3H), 3.76 (dd, $J$ = 11.9, 9.0 Hz, 1H), 3.58 (dd, $J$ = 11.9, 2.2 Hz, 1H), 1.27−1.21 (m, 1H), 0.69−0.65 (m, 2H); 0.55−0.53 (m, 2H): $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.7, 162.9, 158.6, 155.6, 133.8, 132.4, 131.7, 128.9, 127.6, 126.4, 125.9, 125.5, 124.1, 122.8, 115.2, 114.5, 101.7, 63.5, 53.6, 34.8, 31.7, 11.3, 7.7, 7.2; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{21}N_2O_3S$ 417.1273, obsd 417.1289.

**(3*R*)-6-Cyano-7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (6c).** By following the procedure described for the preparation of **6a** from **5a**, **5c** (150 mg, 0.39 mmol) gave **6c** as a pale yellow foam (110 mg, 86%): $[\alpha]_D$ −161 (*c* 1.0, $CHCl_3$); IR $\lambda$ 3012, 2956, 2215, 1749, 1648, 1440, 1365, 1257, 1216 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50−7.39 (m, 3H), 7.25−7.18 (m, 2H), 5.72 (dd, $J$ = 8.8, 2.3 Hz, 1H), 3.85 (s, 3H), 3.72 (dd, $J$ = 11.9, 8.8 Hz, 1H), 3.51 (dd, $J$ = 11.9, 2.3 Hz, 1H), 2.21 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 158.8, 158.4, 154.3, 135.0, 129.7, 129.5, 129.1 (splitted), 128.9, 116.5, 115.4, 99.5, 64.1, 53.5, 31.7, 20.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{17}H_{15}N_2O_3S$ 327.0803, obsd 327.0805.

**(3*R*)-6-Aminomethyl-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (7a).** $BH_3$·$Me_2S$ (250 $\mu$L, 2 M in THF, 0.5 mmol) was added dropwise to a solution of **6a** (50 mg, 0.11 mmol) in dry THF (4 mL) at rt. The reaction vessel was sealed and heated for 60 s at 100 °C using microwave irradiation. The reaction mixture was cooled to room temperature, diluted with $CH_2Cl_2$, poured onto ice-cold aqueous HCl (1 M), and agitated. The pH was then adjusted to ∼10 with 2 M aqueous NaOH, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried and concentrated. The crude product was dissolved in MeOH and swirled with Amberlyst 15. The solid phase was transferred to a filtration funnel and washed with MeOH. The product was released by addition of 10% $NH_3$ in MeOH and eluted with MeOH. Concentration of the filtrate gave **7a** as a yellow oil (36 mg, 72%): $[\alpha]_D$ −44 (*c* 0.25, $CHCl_3$); IR $\lambda$ 2958, 2854, 1747, 1631, 1492, 1440, 1259, 1214 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, $J$ = 8.2 Hz, 1H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.71 (d, $J$ = 8.7 Hz, 1H), 7.54−7.00 (m, 9H), 5.74 (dd, $J$ = 8.6, 2.7 Hz, 1H), 4.25−4.11 (m, 2H), 3.96−3.51 (m, 8H), 3.48 (dd, $J$ = 11.8, 2.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 161.3, 153.5, 148.9, 135.8, 133.8, 133.6, 131.2, 129.7, 129.3, 128.7 (split), 128.5 (split), 127.3, 126.3, 125.9, 125.5, 124.4, 123.2, 118.4, 116.6, 64.2, 53.6, 38.0, 33.2, 31.7; HRMS (FAB) calcd for $[M + Na]^+$ $C_{27}H_{24}N_2NaO_3S$ 479.1405, obsd 479.1405.

**(3*R*)-6-Aminomethyl-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (7b).** By following the procedure described for the preparation of **7a** from **6a**, **6b** (46 mg, 0.11 mmol) gave **7b** as a yellow oil (33 mg, 73%): $[\alpha]_D$ −64 (*c* 0.25, $CHCl_3$); IR $\lambda$ 2952, 1747, 1631, 1569, 1504, 1259, 1214 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, $J$ = 8.2 Hz, 1H), 7.94−7.27 (m, 5H), 6.81 (d, $J$ = 6.8 Hz, 1H), 5.67 (d, $J$ = 7.3 Hz, 1H), 4.77−4.56 (m, 2H), 3.96−3.31 (m, 9H), 1.40 (m, 1H), 0.76−0.31 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.3, 161.1, 155.6 149.5, 133.7 (splitted), 131.6, 128.7, 127.3, 126.4, 126.0, 125.5, 123.8, 123.4, 116.9, 115.7, 63.4, 53.5, 37.6, 32.6, 31.6, 11.8, 7.2, 7.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{25}N_2O_3S$ 421.1586, obsd 421.1593.

**(3*R*)-6-Aminomethyl-7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (7c).** By following the procedure described for the preparation of **7a** from **6a**, **6c** (36 mg, 0.11 mmol) gave **7c** as a yellow oil (27 mg, 67%): $[\alpha]_D$ −110 (*c* 0.13, $CHCl_3$); IR $\lambda$ 2956, 1747, 1631, 1575, 1490, 1442, 1216 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49−7.30 (m, 3H), 7.25−7.15 (m, 2H), 5.64 (dd, $J$ =

8.5, 2.4, 1H), 3.92−3.69 (m, 7H), 3.62 (dd, $J$ = 11.5, 8.6, 1H), 3.41 (dd, $J$ = 11.6, 2.3, 1H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.8, 161.1, 152.0, 147.8, 136.4, 130.0, 129.9, 129.0, 128.9, 128.5, 118.0, 115.3, 64.0, 53.6, 37.9, 31.7, 18.0; MS (ESI) calcd $[M + H]^+$ for $C_{17}H_{19}N_2O_3S$ 331, obsd 331.

**6-Dimethylamino-7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8a).** *N,N*-Dimethylmethyleneammonium chloride (140 mg, 1.50 mmol) was added to a stirred solution of **4c** (200 mg, 0.66 mmol) in dry 1,2-dichloroethane (3 mL) at rt. The reaction vessel was sealed and heated for 400 s at 140 °C using microwave irradiation. The reaction mixture was then diluted with $CH_2Cl_2$ and MeOH and concentrated. Purification by silica gel chromatography (EtOAc → EtOAc, 2.5% triethylamine) gave **8a** as a white foam (219 mg, 92%): $[\alpha]_D$ −163 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2939, 2817, 1747, 1631, 1490, 1209, 703; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.30 (m, 3H) 7.24−7.16 (m, 2H) 5.64 (dd, $J$ = 8.6, 2.5 Hz, 1H) 3.78 (s, 3H) 3.59 (dd, $J$ = 11.7, 8.7 Hz, 1H) 3.47 (d, $J$ = 12.2 Hz, 1H) 3.38 (dd, $J$ = 11.7, 2.5 Hz, 1H) 3.31 (d, $J$ = 12.2 Hz, 1H) 2.25 (s, 6H) 2.0 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.6, 161.5, 150.7, 144.2, 137.3 130.0, 129.7, 128.7, 128.6, 127.9, 122.2, 116.7, 64.0, 54.2, 53.1, 45.4, 31.3; 17.5; HRMS (FAB) calcd for $[M + H]^+$ $C_{19}H_{23}N_2O_3S$ 359.1429, obsd 359.1426.

**6-Morpholino-7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8b).** By following the procedure described for the preparation of **8a** from *N,N*-Dimethylmethyleneammonium chloride and **4c**, *N,N*-morpholinemethyleneammonium chloride and **4c** (200 mg, 0.66 mmol) gave **8b** as a white foam (249 mg, 93%): $[\alpha]_D$ −161 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2955, 2850, 2360, 1749, 1631, 1490, 1112, 703; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.34 (m, 3H), 7.26−7.20 (m, 2H), 5.67 (dd, $J$ = 8.6, 2.6 Hz, 1H), 3.82 (s, 3H), 3.70−3.64 (m, 4H), 3.63−3.53 (m, 2H), 3.46−3.38 (m, 2H), 2.53−2.48 (m, 4H), 2.07 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.6, 161.5, 151.3, 144.5, 137.2, 130.0, 129.8, 128.7, 128.6, 128.0, 121.0, 116.8, 67.1, 64.1, 53.4, 53.1, 31.2, 17.5; HRMS (FAB) calcd for $[M + H]^+$ $C_{21}H_{25}N_2O_4S$ 401.1535, obsd 401.1536.

**6-Dimethylamine-7-(naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8c).** *N,N*-Dimethylmethyleneammonium chloride (144 mg, 1.54 mmol) was added to a stirred solution of **4a** (300 mg, 0.70 mmol) in dry 1,2-dichloroethane (3 mL) at rt. The reaction vessel was sealed and heated for 140 °C for 400 s using microwave irradiation, more *N,N*-dimethylmethyleneammonium chloride (72 mg, 0.77 mmol) was added, and the reaction mixture was heated for another 400 s at 140 °C. The reaction mixture was then diluted with $CH_2Cl_2$ and MeOH and concentrated. Purification by silica gel chromatography (EtOAc → EtOAc 2.5% triethylamine) gave **8c** as a white foam (148 mg, 48%): $[\alpha]_D$ −151 (*c* 1.0, $CHCl_3$); IR $\lambda$ 3048, 2940, 2817, 2767, 1747, 1633, 1490, 790, 701; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83−7.77 (m, 2H), 7.67 (d, $J$ = 8.2 Hz, 1H), 7.45−7.30 (m, 3H), 7.12−6.99 (m, 6H), 5.76 (dd, $J$ = 8.6, 2.6 Hz, 1H), 4.44 (d, $J$ = 16 Hz, 1H), 4.32 (d, $J$ = 16 Hz, 1H), 3.85 (s, 3H), 3.66 (dd, $J$ = 11.8, 8.7 Hz, 1H), 3.44 (dd, $J$ = 11.8, 2.6 Hz, 1H), 3.30−3.20 (m, 2H), 2.21 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.5, 161.8 152.2, 145.5, 136.5, 134.5, 133.3, 131.6, 129.8, 129.2, 128.4, 128.3, 128.2, 127.9, 126.7, 125.8, 125.4, 125.3, 124.2, 123.4, 122.8, 117.2, 64.2, 53.9, 53.1, 45.6, 31.8, 31.3; HRMS (FAB) calcd for $[M + H]^+$ $C_{29}H_{29}N_2O_3S$ 485.1899, obsd 485.1866.

**6-Morpholino-7-(naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8d).** *N,N*-Morpholinemethyleneammonium chloride (209 mg, 1.54 mmol) was added to a stirred solution of **4a** (300 mg, 0.70 mmol) in dry 1,2-dichloroethane (3.2 mL) at rt. The reaction vessel was sealed and heated for 400 s at 140 °C using microwave irradiation, more *N,N*-morpholinemethyleneammonium chloride (105 mg, 0.77 mmol) was added, and the reaction mixture was heated for another 400 s at 140 °C. The reaction mixture was then diluted with $CH_2Cl_2$ and MeOH and concentrated. Purification by silica gel chromatography (EtOAc → EtOAc, 2.5% triethylamine) gave **8d** as a yellow foam (237 mg, 64%): $[\alpha]_D$ −98 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2952, 2846, 1749, 1633, 1490, 1112, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.84−7.79 (m, 2H) 7.68 (d, $J$ = 8.2 Hz, 1H) 7.46−7.38 (m, 2H) 7.34 (t, 1H) 7.17−7.04 (m, 6H) 5.75 (dd, $J$ = 8.6, 2.7 Hz, 1H) 4.49 (d, $J$ = 15.9, 1H) 4.34 (d, $J$ = 15.9 Hz, 1H) 3.87 (s, 3H) 3.69 (dd, $J$ = 11.8, 8.7 Hz, 1H) 3.56−3.50 (m, 4H) 3.46 (dd, $J$ = 11.8, 2.7 Hz, 1H) 3.32 (m, 2H) 2.40−2.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.5, 161.9, 153.1, 145.7, 136.5, 134.8, 133.4, 131.7, 129.9, 129.3, 128.6, 128.4, 128.4, 128.0, 126.7, 125.8, 125.5, 125.4, 124.4, 122.8, 122.3 117.5, 66.9, 64.3, 53.5, 53.2, 53.2, 32.0, 31.3; HRMS (FAB) calcd for $[M + H]^+$ $C_{31}H_{31}N_2O_4S$ 527.2005, obsd 527.2008.

**6-Dimethylamino-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8e).** By following the procedure described for the preparation of **8c** from **4a**, **4b** (200 mg, 0.51 mmol) gave **8e** as a white foam (125 mg, 55%): $[\alpha]_D$ −177 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2939 2948, 2817, 2767, 1747, 1633, 1579, 1498, 1211, 792, 773; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.4 Hz, 1H), 7.86 (d, $J$ = 7.8 Hz, 1H) 7.69 (d, $J$ = 8.2 Hz, 1H) 7.60−7.48 (m, 2H) 7.31−27 (m, 1H) 6.82 (d, $J$ = 6.8 Hz, 1H) 5.69 (dd, $J$ = 8.7, 2.5 Hz, 1H) 4.83−4.80 (m, 2H) 3.81 (s, 3H) 3.67 (dd, $J$ = 11.8, 8.7 Hz, 1H) 3.48 (dd, $J$ = 11.7, 2.6 Hz, 1H) 3.30−3.19 (m, 2H) 2.19 (s, 6H) 1.34−1.24 (m, 1H) 0.63−0.53 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.8, 161.9, 155.1, 146.0, 134.6, 133.7, 132.1, 128.8, 126.8, 126.1, 125.7, 125.6, 123.7, 123.2, 114.4, 63.5, 53.8, 53.2, 45.6, 31.4 (split), 11.7, 7.4, 7.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{26}H_{29}N_2O_3S$ 449.1899, obsd 449.1887.

**6-Morpholino-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (8f).** By following the procedure described for the preparation of **8d** from **4a**, **4b** (400 mg, 1.02 mmol) gave **8f** as a yellow foam (331 mg, 66%): $[\alpha]_D$ −110 (*c* 1.0, $CHCl_3$); IR $\lambda$ 2956, 2844, 1749, 1631, 1496, 1110, 792, 773, 728; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.4 Hz, 1H), 7.87 (d, $J$ = 7.5 Hz, 1H) 7.70 (d, $J$ = 8.2 Hz, 1H) 7.61−7.48 (m, 2H) 7.29 (t, 1H) 6.84 (d, $J$ = 7.1 Hz, 1H) 5.68 (dd, $J$ = 8.7, 2.6 Hz, 1H) 4.87−4.78 (m, 2H) 3.82 (s, 3H) 3.69 (dd, $J$ = 11.8, 8.7 Hz, 1H) 3.52−3.45 (m, 5H) 3.32 (m, 2H) 2.34 (m, 4H) 1.40−1.32 (m, 1H) 0.68−0.53 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.6, 161.8, 155.5, 146.1, 134.7, 133.5, 131.9, 128.7, 126.6, 126.0, 125.6, 125.4, 123.6, 122.9, 122.4, 114.5, 66.9, 63.4 53.3, 53.1, 52.9, 31.4, 31.2, 11.5, 7.3, 7.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{28}H_{31}N_2O_4S$ 491.2005, obsd 491.1998.

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**Supporting Information Available:** $^{13}$C NMR spectra of **5a**−**d**, **6a**−**c**, **7a**−**c**, and **8a**−**f**. HPLC chromatogram for ee determinations of compounds **4b**, **5b**, **6b**, **7b**, and **8f**. General Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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