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From 2,6-Dichloronicotinic Acid to Thiopeptide Cores

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The scope of 2,6-dichloronicotinic acid as a precursor of thiopeptide polyheterocylic cores has been extensively studied in a cross-coupling-based approach. Differentiation of the two chlorinated positions under S_NAr conditions and versatility of the carboxylic acid are key for the preparation of 2,3,6-trisubstituted pyridines with complete regiocontrol. With the present strategy, nine different azole-substituted pyridines were synthesized. Studies towards the selective deprotection of their functionalities resulted in a set of fully orthogonal protecting groups that permits the elongation of all three pyridine substituents.

Introduction

Polyheterocyclic scaffolds containing thiazole and oxazole rings are common to numerous biologically active natural products,[1] such as thiopeptide antibiotics,[2,3] which have garnered much attention during the past few years owing to their therapeutic utility and challenging synthesis.[2b,3] Thiopeptide antibiotics are classified according to structure,[2a] and those bearing a fully unsaturated 2,3,6-trisubstituted pyridine outnumber those with different polyheterocyclic cores (Figure 1).

Over the past few decades, various research groups have endeavored to synthesize the pyridine core of thiopeptides by developing two general procedures: modification of prefunctionalized pyridines, and late-stage construction of the pyridine ring.[2b] Current advances in cross-coupling methodologies have enabled the facile preparation of aryl-substituted thiazoles.[4] However, during our investigations towards the total synthesis of baringolin,[5] we found that more alternative cross-coupling methodologies and strategies are in demand to broaden the scope of starting materials and functionalities that can be used to assemble the polyheterocyclic cores of thiopeptides with the double aim to synthesize natural compounds as well as to develop analogue programs for structure-activity relationship studies.

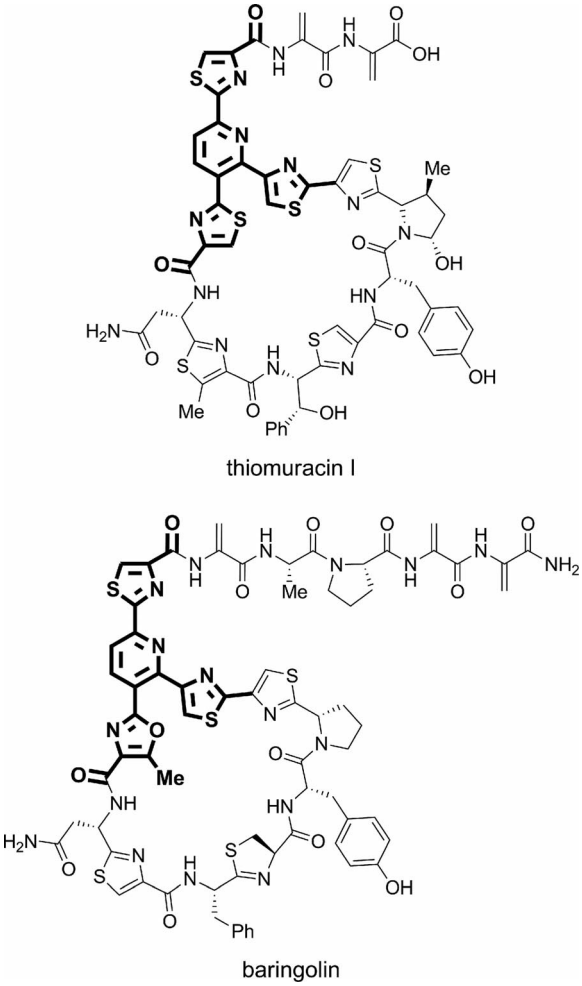

Figure 1. Examples of thiopeptides containing a 2,3,6-trisubstituted pyridine core (highlighted in bold).

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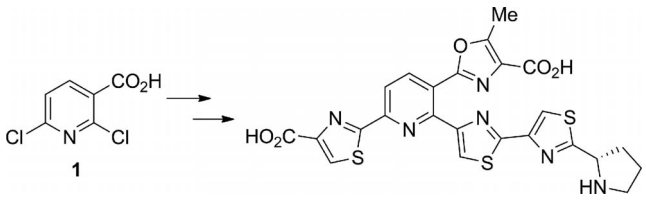
2,6-Dichloronicotinic acid (**1**) has been widely used as the starting material for the synthesis of many drugs.[6] Pyridine **1** already has the required substitution pattern, which should permit the formation of the oxazole ring in its position 3 and also serve for the subsequent cross-coupling reactions with the appropriate thiazole fragments in positions 2 and 6 (Scheme 1).

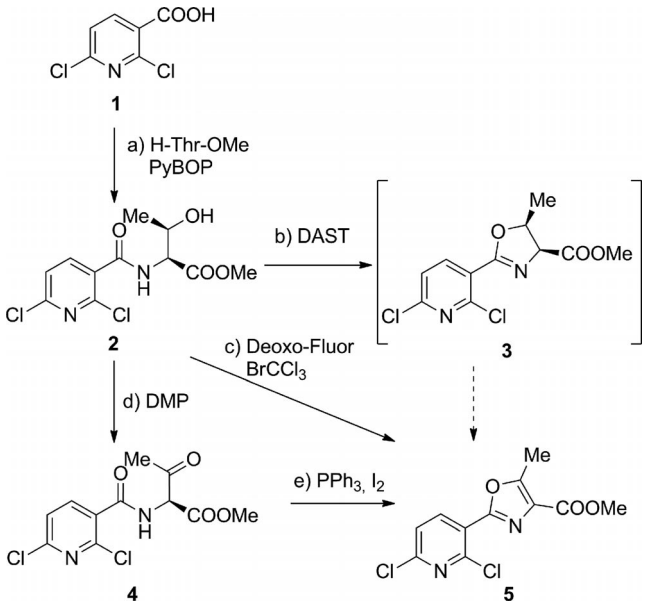


Scheme 1. Synthesis of baringolin's polyheterocyclic core from **1**.

The scope, limitations and applications of this strategy to the synthesis of the tri-azole-substituted pyridine core of thiopeptides are discussed in this paper. With the total synthesis of thiopeptides in mind, special attention was paid to the preparation of their central cores with a suitable set of protecting groups, which permits the elongation of the thiazole chains. This modular approach was applied for the syntheses of several core analogues.

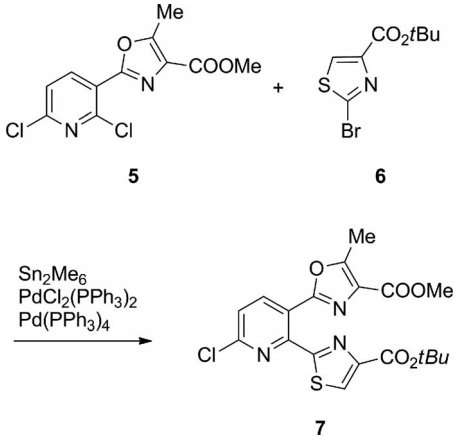
Results and Discussion

To study the required cross-coupling reactions on a suitable substrate, formation of the methyloxazole ring in position 3 of pyridine **1** was carried out first, following a biomimetic strategy (Scheme 2). After condensation of **1** with threonine methyl ester (H-Thr-OMe) to yield amide **2**, a two-step cyclization/oxidation approach was attempted. However, the resulting oxazoline **3** was never isolated as a pure substance, but always in combination with varying amounts of the starting material, pointing out the reversibility of the cyclization. Hence, an alternative one-step route by using deoxo-fluor and bromotrichloromethane was taken into consideration.[7] Despite the convenience of a one-step procedure, the low yield obtained thereby moved us to a third sequence based on a two-step oxidation/cyclization formation of the oxazole. Oxidation of the Thr residue to the corresponding methyl ketone **4** and cyclization in the presence of triphenylphosphane and iodine rendered the desired methyloxazole **5** in excellent overall yield.[8]



Scheme 2. Synthesis of oxazolylpyridine **5**. Reagents and conditions: (a) (L)-H-Thr-OMe, PyBOP, DIPEA, THF, 0 °C, 5 h, 94%. (b) Diethylaminosulfur trifluoride (DAST), K_2CO_3, CH_2Cl_2, –78 °C to 0 °C, 7 h, 61%. (c) Deoxo-Fluor, $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 3.5 h, 39%. (d) Dess–Martin periodinane, CH_2Cl_2, room temp., 6 h, 87%. (e) PPh_3, I_2, Et_3N, CH_2Cl_2, 0 °C to room temp., 16 h, 94%.

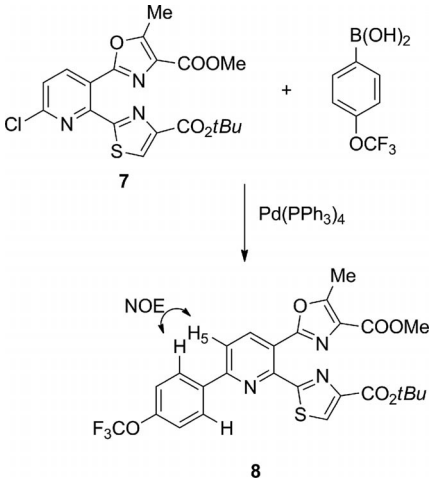
With **5** in hand, introduction of a thiazol-2-yl substituent was assessed first. Given the difficulty in preparing 2-stannylthiazole-4-carboxylate reagents,[9] alternatives to these reagents have been found through the use of a one-pot stannation-coupling protocols to obtain the desired cross-coupling product.[10] This methodology and its regioselectivity was assessed by using bromothiazole **6** as coupling partner and different distannanes (Scheme 3). After screening several variables, including the use of additives and different distannanes, the best conditions, as outlined in Scheme 3, only yielded small amounts of product **7**. NMR and MS spectroscopic data correspond to structure **7**; however with this data it was impossible to determine which regioisomer had been obtained.



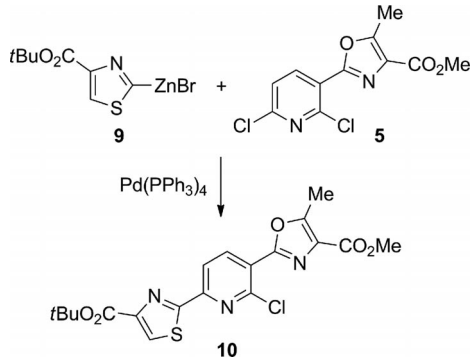
Scheme 3. One-pot stannation-coupling reaction between **5** and **6**. Reagents and conditions: Sn_2Me_6, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, 1,4-dioxane, 100 °C, 17%.

Despite the low yields obtained with the cross-coupling procedure, **7** was further converted into derivative **8** to determine the regioselectivity of the reaction. The NOE correlation observed between the proton in position 5 of the pyridine and the *ortho* protons of the phenyl substituent revealed that the thiazole was linked to position 2 of the pyridine (Scheme 4).

The next attempt focused on the use of thiazolezinc derivative **9**, which has been reported to selectively react with 3-substituted 2,6-dibromopyridines in position 6 under palladium(II) catalysis.[3f] Very small conversions were obtained with pyridine **5** and only when palladium(0) was used (Scheme 5). ^1H NMR spectroscopic analysis[11] of the



Scheme 4. Derivatization of **7**. Reagents and conditions: 4-(CF_3O)-C_6H_4-$B(OH)_2$, $Pd(PPh_3)_4$, 2 M $NaHCO_3$, *i*PrOH, 90 °C MW, 20 min, 65%.



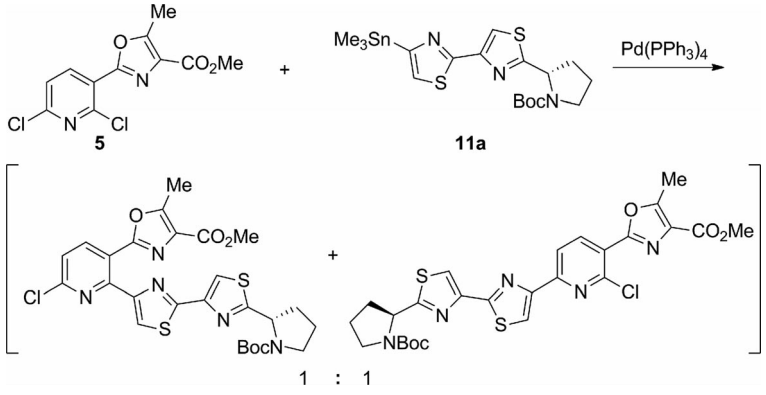
Scheme 5. Negishi cross-coupling between **9** and **5**. Reagents and conditions: $Pd(PPh_3)_4$, DMA, 60 °C, 5 d, 3%.

product obtained with this methodology showed a different regioisomer (**10**) to the one obtained with the previous stannation-coupling approach (see Supporting Information).

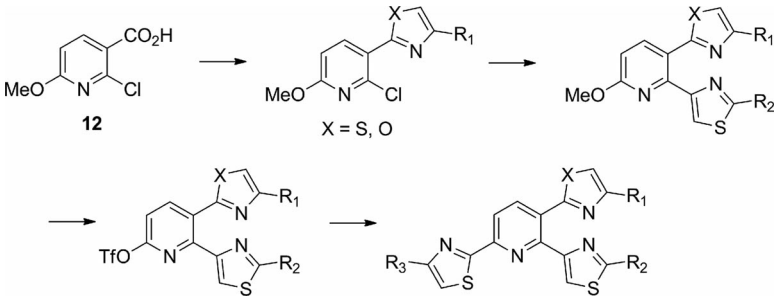
Although the desired isomer did form, the low conversion and complex crude mixtures obtained with this approach did not allow reliable development of a robust methodology. At this point, Stille cross-coupling with trimethyltinbithiazole **11a**[12] was attempted to evaluate whether higher yields and selectivity could be achieved (Scheme 6). However, although conversions were higher, no regioselectivity was observed and only a 1:1 mixture of both possible regioisomers was obtained.

To overcome the previous regioselectivity problems, early differentiation of the two alpha positions of 2,6-dichloronicotinc acid (**1**) might be the answer. Nucleophilic aromatic substitution (S_NAr) with in situ generated methoxide gives 2-chloro-6-methoxynicotinic acid (**12**) in good yield and regioselectivity.[6h]

Starting from **12**, a general strategy to construct an azole from a carboxylic acid moiety, in the same fashion as described for the synthesis of **5**, was envisioned. Next, cross coupling at the chlorinated position and subsequent conversion of the methoxy group into a triflate would render the required leaving group for a final cross-coupling step (Scheme 7). Such a sequential route would avoid any possible regioselectivity problems.

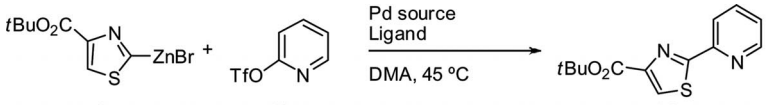


Scheme 6. Cross-coupling of **5** with bithiazole **11a**. Reagents and conditions: $Pd(PPh_3)_4$, 1,4-dioxane, 80 °C, 5 h, 51%.

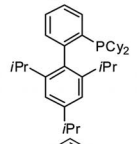
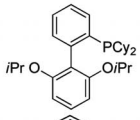
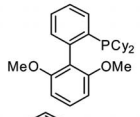
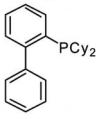


Scheme 7. Synthetic route towards polyazole-substituted pyridines from nicotinic acid **12**.

Table 1. Cross-coupling of thiazolylzinc bromide **9** with triflate **13.** Conditions: **9** (1.0 mmol, 2 equiv.), **13** (0.5 mmol, 1 equiv.), palladium source (20 mol-%), ligand (40 mol-%), DMA, 45 °C.



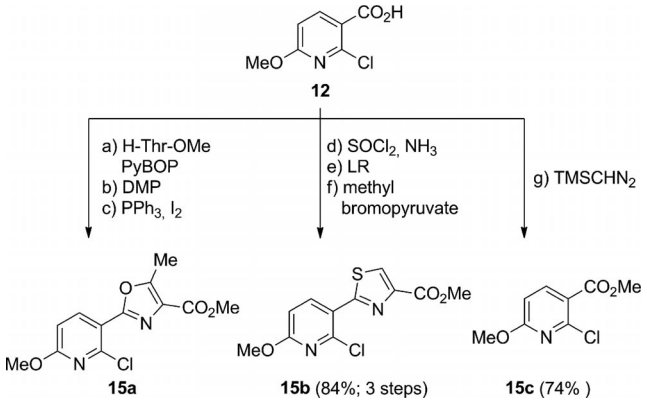
9 **13** **14**

Entry	Pd source	Ligand	Pd (mol-%)	Time (h)	Yield[a] (%)
1	$PdCl_2(PPh_3)_2$	-	20	1.5	0
2	$Pd(PPh_3)_4$	-	1	17	12
3	$Pd(PPh_3)_4$	-	5	3	76
4	$Pd(PPh_3)_4$	-	10	3	84
5	$Pd(PPh_3)_4$	-	20	1.5	100
6	$Pd(dba)_2$	PCy_3	20	24	20
7	$Pd(dba)_2$		20	17	46
8	$Pd(dba)_2$		20	17	33
9	$Pd(dba)_2$		20	17	44
10	$Pd(dba)_2$		20	17	67
11	$Pd(dba)_2$		20	17	63
12	$Pd(dba)_2$	PPh_3	20	1.5	80

[a] Yield determined by HPLC analysis of the reaction mixture.

The cornerstone of this synthetic route was the Negishi cross coupling between a triflate and a thiazolylzinc bromide. This last step was previously studied with compound **9** and pyridyl triflate **13** as model system (Table 1). Whereas $PdCl_2(PPh_3)_2$ did not work (Table 1, Entry 1), the use of increasing amounts of $Pd(PPh_3)_4$ did give progressively higher yields of **14** (Table 1, Entries 2–5). Because quantitative conversion was only observed when 20 mol-% of $Pd(PPh_3)_4$ was used, other ligands were tested to find one with a comparable outcome (Table 1, Entries 6–11). Interestingly, triphenylphosphane (Table 1, Entry 12) performed better than any of the other ligands (Table 1, Entries 6–11).

With a reliable methodology for cross coupling of thiazolylzinc bromide **9** with pyridin-2-yl triflates in hand, the construction of the desired fragments was addressed. Starting from 2-chloro-6-methoxynicotinc acid (**12**) it was easy to reproduce the construction of the oxazole ring by using the carboxylic acid in the same two-step oxidation/cyclization sequence to obtain **15a** (Scheme 8). In parallel, thiazolyl-pyridine **15b** was prepared in excellent yield through classical conversion of acid **12** into the corresponding thioamide, followed by Hantzsch thiazole formation

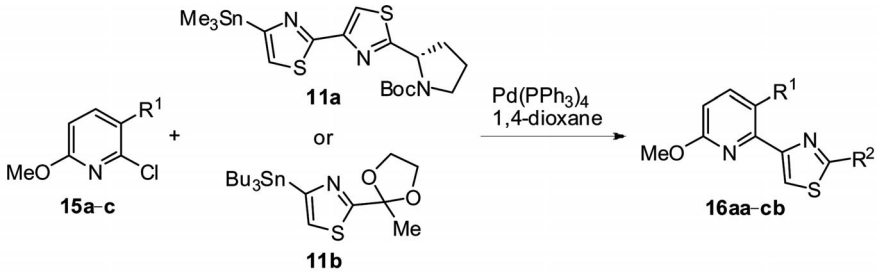


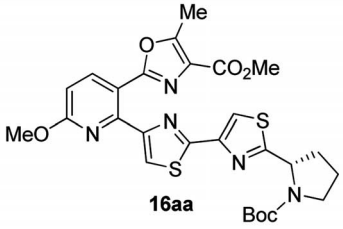
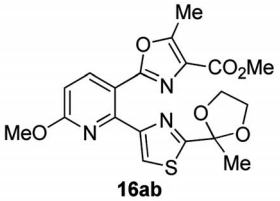
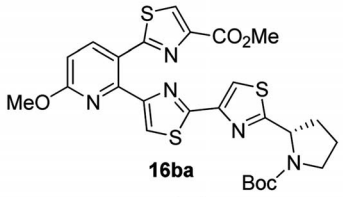
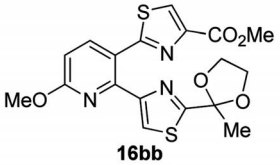
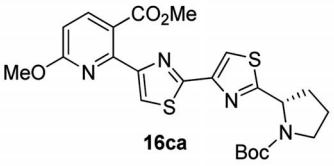
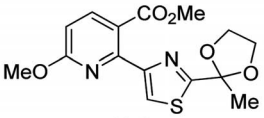
Scheme 8. Derivatization of 2-chloro-6-methoxynicotinic acid (**12**). Reagents and conditions: (a) H-Thr-OMe (1 equiv.), PyBOP (1.2 equiv.), DIPEA (3.5 equiv.), THF, 0 °C, 5 h, 82%. (b) Dess–Martin periodinane (1.2 equiv.), CH_2Cl_2, room temp., 7 h, 86%. (c) PPh_3 (2 equiv.), I_2 (2 equiv.), NEt_3 (4 equiv.), CH_2Cl_2, 0 °C to room temp., 15 h, 85% (d) (i) $SOCl_2$ (10 equiv.), reflux, 1 h; (ii) NH_4OH, THF, 0 °C, 1 h, 96% (2 steps). (e) Lawesson's Reagent (LR; 1 equiv.), THF, 70 °C, 2 h, 88%. (f) Methyl bromopyruvate (2 equiv.), pyridine (1.5 equiv.), EtOH, 80 °C, 3.5 h, quant. (g) $TMSCHN_2$ (1.8 equiv.), CH_2Cl_2/MeOH (1:1), 0 °C to room temp., 20 min, 74%.

with ethyl bromopyruvate. Esterification of **12** with (trimethylsilyl)diazomethane gave **15c**. With these different scaffolds **15a**–**15c** the scope of the strategy was tested.

First, cross coupling between 4-trialkyltinthiazoles **11a**–**11b** and 2-chloro-6-methoxypyridines **15a**–**15c** was evaluated (Table 2). Moderate to excellent yields of methoxypyridines **16aa**–**16cb** were obtained depending on the partner combination. The yields obtained with tributyltinthiazole **11b**[13] (Table 2, Entries 2, 4 and 6) were lower than those obtained with trimethyltinbithiazole **11a** (Table 2, Entries 1, 3 and 5). This discrimination caused either by the different bulkiness of alkyltin groups or the different electronic na-

Table 2. Cross-coupling between pyridines **15a**–**15c** and alkyltin thiazoles **11a** and **11b**. Conditions: Chloropyridine **15** (1 equiv.), alkyltinthiazole **11** (1.1 equiv.), $Pd(PPh_3)_4$ (10 mol-%), 1,4-dioxane, 80 °C.



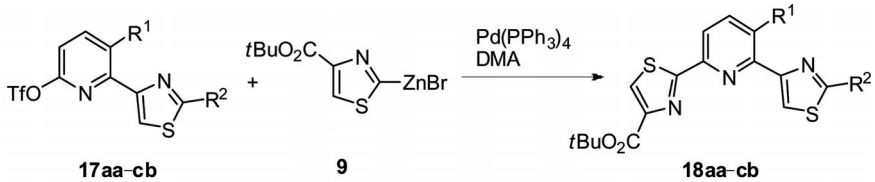
Entry	15	11	Product	Yield (%)[a]
1	**15a**	**11a**	 **16aa**	85
2		**11b**	 **16ab**	53
3	**15b**	**11a**	 **16ba**	56
4		**11b**	 **16bb**	44
5	**15c**	**11a**	 **16ca**	94
6		**11b**	 **16cb**	57

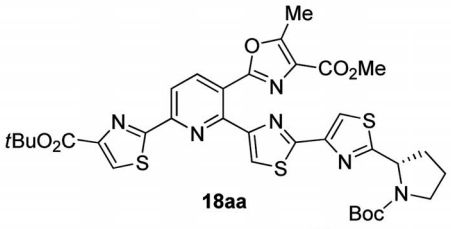
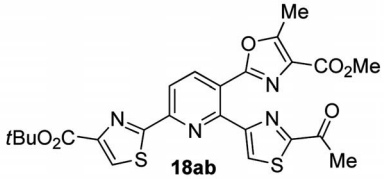
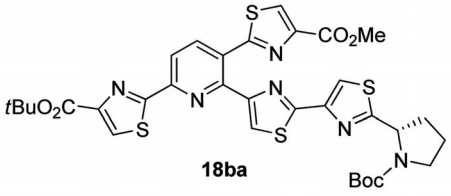
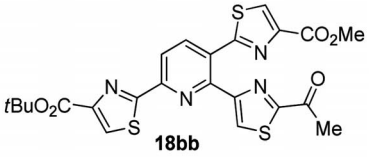
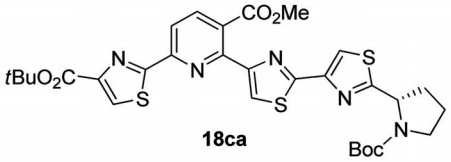
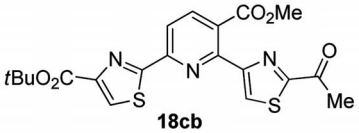
[a] Isolated yield.

ture of the substituents in position 2 of the thiazole ring. Nicotinate **15c** (Table 2, Entries 5 and 6) performed slightly better than the other pyridines, owing to the electro-withdrawing effect of the carboxylate. The yields obtained with oxazolylpyridine **15a** (Table 2, Entries 1 and 2) were higher than those obtained with thiazolylpyridine **15b** (Table 2, Entries 3 and 4).

All methoxypyridines **16aa**–**16cb** obtained were demethylated with HBr to yield the corresponding pyridones. This treatment also caused acetal hydrolysis or *tert*-butyloxycarbonyl (Boc) removal. In the latter case further pyrrolidine protection was required. All pyridone analogues were easily converted into corresponding triflates **17aa**–**17cb** by using triflic anhydride under 4-(dimethylamino)pyridine (DMAP) catalysis.[14] Lastly, palladium(0) catalyzed cross-coupling of **17aa**–**17cb** with thiazolezinc bromide **9** yielded expected polyazolepyridines **18aa**–**18cb** (Table 3). The presence of the methyl ketone (Table 3, Entries 2, 4 and 6) was detrimental for the reaction outcome. For the synthesis of baringolin's core **18aa**, the use of higher amounts of **9** rendered the desired polyheterocycle in excellent yield (Table 3, Entry 1).

Table 3. Cross-coupling between pyridines **17aa**–**17cb** and thiazole **9**. Conditions: triflate **17** (1 equiv.), thiazolezinc bromide **9** (2 equiv.), $Pd(PPh_3)_4$ (20 mol-%), DMA, 45 °C.



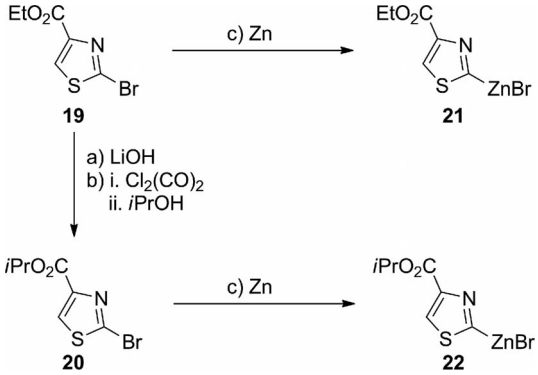
Entry	17	Product	Yield (%)[a]
1	**17aa**	 **18aa**	37 (92)[b]
2	**17ab**	 **18ab**	43
3	**17ba**	 **18ba**	54
4	**17bb**	 **18bb**	41
5	**17ca**	 **18ca**	66
6	**17cb**	 **18cb**	39

[a] Isolated yield. [b] Triflate **17aa** (1 equiv.), thiazolezinc bromide **9** (8 equiv.), $Pd(PPh_3)_4$ (20 mol-%), DMA, 45 °C.

After developing a useful strategy to synthesize azole-substituted pyridines, the next goal was selective removal of protecting groups to develop a reliable method for the total synthesis of thiopeptides. Compound **18aa** was the substrate of choice because it was part of our studies towards the total synthesis of baringolin.[5b] Our first attempts of Boc deprotection in **18aa** in the presence of a *tert*-butyl ester yielded the desired amine in excellent yield when literature protocols were used.[15] However, scaling up of this reaction resulted in reduced selectivities and therefore switching to alternative protecting groups patterns was required.

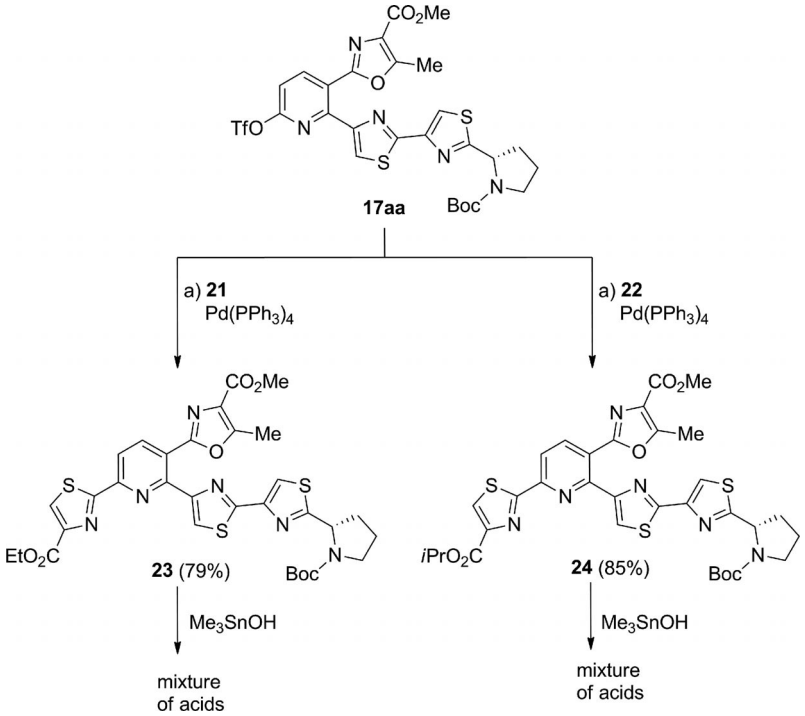
To circumvent the compatibility of protecting groups, the ester at the thiazole ring was changed. To do so, ethyl ester **19**[10] was converted into isopropyl ester **20** (Scheme 9). Both **19** and **20** could be used as precursors of organometallic thiazol-2-yl nucleophiles and appropriately converted into corresponding zinc bromides **21** and **22**, respectively, for subsequent use in the final cross coupling with pyridyl triflate **17aa** to yield **23** and **24** (Scheme 10). All our attempts to selectively deprotect the methyl ester in either **23** or **24** failed with trimethyltin hydroxide.[16] In both cases, mixtures of carboxylic acids were obtained even when equimolar amounts of reagent were used.

At this point, and given the previous bad results obtained for the selective removal of the esters, the need for a fully orthogonal pattern of protecting groups became evident. To this end, the polyheterocyclic core was synthesized again with a benzyl ester on the oxazole and an ethyl ester on the thiazole by using appropriately protected starting materials, giving rise to **25**.[5b]

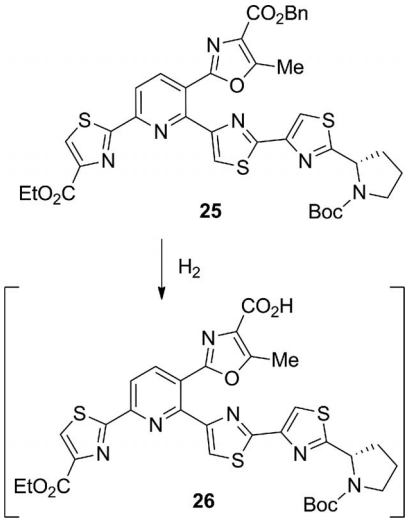


Scheme 9. Synthesis of bromothiazole **20** and preparation of organozinc reagents **21** and **22**. Reagents and conditions: (a) **19** (1 equiv.), LiOH (2 equiv.), THF/H_2O (10:1), room temp., 18 h, quant. (b) (i) Oxalyl chloride (2 equiv.), DMF (cat.); (ii) *i*PrOH/CH_2Cl_2 (10:1), 81%. (c) zinc dust, 1,2-dibromoethane, TMSCl, DMA, room temp.

Many attempts of benzyl ester hydrogenolysis of **25** with varying amounts of palladium on charcoal at different temperatures and increasing H_2 pressures only yielded traces of the acid. Only when palladium black was used, higher conversions were observed (Scheme 11). However, 100 wt.-% of this reagent was required for quantitative conversion to occur. Acid **26** was used in further transformations, which yielded the expected products.[5b] The use of palladium black with a similar substrate has also been described by Moody and co-workers,[3d] however, no details of previously performed tests are provided.



Scheme 10. Negishi cross-couplings of **17aa**. Reagents and conditions: (a) thiazolezinc bromide (8 equiv.), $Pd(PPh_3)_4$ (20 mol-%), DMA, 45 °C.



Scheme 11. Hydrogenolysis of **25**. Reagents and conditions: H_2 (1 atm), Pd black (100 wt.-%), CH_2Cl_2/EtOH (1:1), room temp., 4 h, quant.

Conclusions

In summary, studies towards the synthesis of various azole-substituted pyridines have been carried out by using 2,6-dicholoronicotinic acid (**1**) and 2-chloro-6-methoxynicotinic acid (**12**) as starting points. The best results were obtained with **12** owing to the differentiated α-positions and the higher reactivity of thiazolzinc bromides with pyridyl triflates. With the present strategy, a series of polyazole-substituted pyridines **18aa**–**18cb** were synthesized, which demonstrated the scope of the approach, which could also be used for the construction of various thiopeptides analogues (GE2270 A and T, thiomuracins, GE37468A, baringolin, etc.).[5a,17] This approach also permitted the synthesis of the polyheterocyclic core of baringolin, which has been synthesized with different combinations of protecting groups. Subsequent compatibility studies have facilitated the assessment of different chemistries. Finally, a set of orthogonal protecting groups was used to further modify baringolin's core in a fully selective and reliable manner. This combination of protecting groups could be useful for the total syntheses of other thiopeptides containing a fully unsaturated 2,3,6-trisubstituted pyridine core.

Experimental Section

See Supporting Information for general procedures.

(2*S*,3*R*)-*N*-[(2,6-Dichloropyridin-3-yl)carbonyl]threonine Methyl Ester (2): *N*,*N*-Diisopropylethylamine (DIPEA; 2.66 mL, 15.51 mmol) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP; 2.65 g, 5.09 mmol) were added to a solution of 2,6-dichloronicotinic acid (**1**; 850 mg, 4.43 mmol) and H-L-Thr-OMe (751 mg, 4.43 mmol) in dry tetrahydrofuran (THF; 22 mL) at 0 °C under argon. The mixture was then stirred at this temperature for 5 h. EtOAc and saturated aq. $NaHCO_3$ were added to the mixture and part of the solvent was evaporated under reduced pressure. More EtOAc (100 mL) was added and the organic layer was then washed with saturated aq. $NaHCO_3$ (50 mL) and saturated aq. NH_4Cl (2× 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 1:1) to yield the title compound as a pale solid (1.28 g, 94%), m.p. (EtOAc) 128–130 °C. $[\alpha]_D$ = 20.6 (c = 0.50, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3433, 3296, 3073, 2985, 2920, 1744, 1643, 1577, 844 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.4 Hz, 3 H), 3.82 (s, 3 H), 4.50 (dq, J = 6.4 and 2.3 Hz, 1 H), 4.80 (dd, J = 8.6 and 2.3 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (q), 53.1 (q), 58.2 (d), 68.1 (d), 123.7 (d), 129.5 (s), 142.3 (d), 146.8 (s), 152.3 (s), 164.5 (s), 171.0 (s) ppm. HRMS: calcd. for $C_{11}H_{13}Cl_2N_2O_4$ [M + H] 307.0247; found 307.0247.

Methyl (*S*)-2-(2,6-Dichloronicotamido)-3-oxobutanoate (4): Dess–Martin periodinane (1.91 g, 4.50 mmol) was added to a solution of pyridine **2** (1.15 g, 3.75 mmol) in dry CH_2Cl_2 (125 mL). The mixture was then stirred at room temp. under argon. After 7 h the reaction mixture was poured onto a mixture of saturated aq. $NaHCO_3$ (100 mL) and saturated aq. $Na_2S_2O_3$ (100 mL) and extracted with CH_2Cl_2 (2× 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 1:1) to yield the title compound as a white solid (0.99 g, 87%), m.p. (EtOAc) 112–113 °C. $[\alpha]_D$ = –0.3 (c = 1.01, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3290, 3072, 2958, 1740, 1721, 1642, 1578 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 3.89 (s, 3 H), 5.43 (d, J = 6.2 Hz, 1 H), 7.40 (d, J = 7.8 Hz, 1 H), 7.90 (d, J = 6.2 Hz, 1 H), 8.16 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 (q), 53.9 (q), 64.1 (d), 123.7 (d), 128.4 (s), 142.7 (d), 147.1 (s), 152.7 (s), 163.3 (s), 166.1 (s), 197.5 (s) ppm. HRMS: calcd. for $C_{11}H_{11}Cl_2N_2O_4$ [M + H] 305.0090; found 305.0090.

Synthesis of 2,6-Dichloro-3-[4-(methoxycarbonyl)-5-methyloxazole-2-yl]pyridine (5)

From Pyridine 2: Deoxo-Fluor 50% in THF (76 μL, 0.18 mmol) was added to a stirring solution of pyridine **2** (50 mg, 0.16 mmol) in dry CH_2Cl_2 (1.4 mL) at –20 °C under N_2. After 30 min, $BrCCl_3$ (58 μL, 0.58 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 87 μL, 0.58 mmol) were added dropwise and then the mixture stirred for 3.5 h at 0 °C. Saturated aq. $NaHCO_3$ (25 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3× 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica flash column chromatography (hex/EtOAc, 8:2) to yield the title compound as a white solid (24 mg, 50%).

From Pyridine 4: A solution of pyridine **4** (0.97 g, 3.16 mmol) in dry CH_2Cl_2 (38 mL) was added to a stirring solution of PPh_3 (1.65 g, 6.31 mmol) and I_2 (1.6 g, 6.31 mmol) in dry CH_2Cl_2 (58 mL) at 0 °C under an argon atmosphere. The resulting mixture was allowed to reach room temp. and stirred for 16 h. The solvent was removed under reduced pressure and the crude product purified by silica flash column chromatography (hexanes/EtOAc, 7:3) to yield the title compound as a white solid (0.85 g, 94%), m.p. (EtOAc) 135–136 °C. IR (KBr): $\tilde{\nu}$ = 3087, 2957, 1715, 1609, 1562, 1427, 1351 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.75 (s, 3 H), 3.96 (s, 3 H), 7.39 (d, J = 8.2 Hz, 1 H), 8.36 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5 (q), 52.4 (q), 121.8 (s), 123.3 (d), 129.2 (s), 141.9 (d), 148.2 (s), 151.9 (s), 155.5 (s), 157.9 (s), 162.5 (s) ppm. HRMS: calcd. for $C_{11}H_9Cl_2N_2O_3$ [M + H] 286.9985; found 286.9985.

2-[4-(*tert*-Butoxycarbonyl)thiazol-2-yl]-6-chloro-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (7): Hexamethyldistannane (195 μL, 0.95 mmol) was added to a stirring solution of bromothiazole **6**[3f] (166 mg, 0.63 mmol), dichloropyridine **5** (273 mg, 0.95 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.03 mmol) and $Pd(PPh_3)_4$ (37 mg, 0.03 mmol) in dry 1,4-dioxane (7.6 mL) under N_2 in a Schlenk tube. The tube was sealed with a glass stopper and the mixture stirred at 100 °C. After 4 h the mixture was allowed to reach room temp., filtered through a pad of Celite, washed with EtOAc, dried (Na_2SO_4) and concentrated in vacuo. The resulting crude was purified by silica flash column chromatography (hexane/EtOAc, 7:3) to yield the title product as a pale solid (46 mg, 17%), m.p. (EtOAc) 175–180 °C. IR (KBr): $\tilde{\nu}$ = 3111, 2978, 1707, 1620, 1437, 1352, 1163, 1102, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 2.67 (s, 3 H), 3.93 (s, 3 H), 7.46 (d, J = 8.0 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 8.20 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (q), 28.2 (q), 52.1 (q), 82.1 (s), 120.2 (s), 124.8 (d), 128.7 (s), 130.0 (d), 141.0 (s), 142.3 (d), 150.1 (s), 152.6 (s), 156.8 (s), 157.7 (s), 160.4 (s), 162.9 (s), 165.4 (s) ppm. HRMS: calcd. for $C_{19}H_{19}ClN_3O_5S$ [M + H] 436.0729; found 436.0727.

2-[4-(*tert*-Butoxycarbonyl)thiazol-2-yl]-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-[4-(trifluoromethoxy)phenyl]pyridine (8): A solution of pyridine **7** (30 mg, 0.07 mmol), 4-(trifluoromethoxy)-phenylboronic acid (17 mg, 0.08 mmol) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in *i*PrOH (0.35 mL) and $NaHCO_3$ (2 M, 0.1 mL) was stirred at 90 °C for 20 min under microwave irradiation. The reaction mixture was diluted with EtOAc, filtered through Celite, dried (Na_2SO_4) and concentrated in vacuo. Silica flash column chromatography (hexane/EtOAc, 7:3) yielded the title compound as a yellowish solid (25 mg, 65%), m.p. (EtOAc) 160–161 °C. IR (KBr): $\tilde{\nu}$ = 3123, 2974, 1724, 1699, 1254, 1169 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]acetone): δ = 1.52 (s, 9 H), 2.66 (s, 3 H), 3.88 (s, 3 H), 7.55 (m, 2 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.27 (d, J = 8.0 Hz, 1 H), 8.42 (m, 2 H), 8.46 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-acetone): δ = 11.6 (q), 27.5 (q), 51.1 (q), 81.2 (s), 120.3 (s), 121.0 (d), 121.5 (d), 128.7 (s), 129.3 (d), 130.3 (d), 136.3 (s), 141.4 (d), 148.9 (s), 149.8 (s), 150.8 (s), 156.6 (s), 157.2 (s), 157.3 (s), 160.2 (s), 162.7 (s), 167.2 (s) ppm. HRMS: calcd. for $C_{26}H_{23}F_3N_3O_6S$ [M + H] 562.1254; found 562.1251.

General Procedure for the Preparation of (Thiazol-2-yl)zinc Bromides: These reagents were prepared by using the method described by Bach and co-workers.[3f] Dry *N*,*N*-dimethylacetamide (DMA) and 1,2-dibromoethane (0.36 equiv.) were added to an oven-dried flask charged with zinc dust (3.12 equiv.) under an inert atmosphere. The mixture was heated with a heat gun until bubbling was observed and then cooled to room temp. This procedure was repeated twice and then chlorotrimethylsilane (0.66 equiv.) was added and the suspension stirred at room temp. After 5 min a solution of the alkyl 2-bromothiazole-4-carboxylate (1.00 equiv.) in dry DMA was added. After 30 min the suspension was allowed to settle for at least 30 min. The reagent solution was freshly prepared before each use.

[4-(*tert*-Butoxycarbonyl)thiazol-2-yl]zinc Bromide (9): This reaction was performed according to the general procedure for the preparation of (thiazol-2-yl)zinc bromides by using zinc dust (920 mg, 14.00 mmol), 1,2-dibromoethane (140 μL, 1.60 mmol) and chlorotrimethylsilane (380 μL, 3.00 mmol) in DMA (14.0 mL) and a solution of *tert*-butyl 2-bromothiazole-4-carboxylate[3f] (1.20 g, 4.50 mmol) in DMA (7.2 mL) This procedure gave a 0.21 M solution of the reagent.

[4-(Ethoxycarbonyl)thiazol-2-yl]zinc Bromide (21): This reaction was performed according to the general procedure for the preparation of (thiazol-2-yl)zinc bromides by using zinc dust (4.04 g, 61.77 mmol), 1,2-dibromoethane (615 μL, 7.13 mmol) and chlorotrimethylsilane (1.7 mL, 13.07 mmol) in DMA (62 mL) and a solution of ethyl 2-bromothiazole-4-carboxylate (**19**)[10] (4.67 g, 19.80 mmol) in DMA (32 mL) This procedure gave a 0.21 M solution of the reagent.

[4-(Isopropoxycarbonyl)thiazol-2-yl]zinc Bromide (22): This reaction was performed according to the general procedure for the preparation of (thiazol-2-yl)zinc bromides by using zinc dust (734 mg, 11.23 mmol), 1,2-dibromoethane (112 μL, 1.30 mmol) and chlorotrimethylsilane (300 μL, 2.38 mmol) in DMA (11.4 mL) and a solution of **20** (900 mg, 3.60 mmol) in DMA (5.7 mL) This procedure gave a 0.21 M solution of the reagent.

6-[4-(*tert*-Butoxycarbonyl)thiazol-2-yl]-2-chloro-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (10): A solution of thiazole **9** in dry DMA (0.21 M, 0.92 mL, 0.19 mmol) was slowly added to a solution of pyridine **5** (50 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in dry DMA (0.5 mL) under nitrogen in a Schlenk tube. The tube was sealed and the mixture stirred at 60 °C for 5 d. The mixture was filtered through a pad of Celite, dried ($MgSO_4$) and concentrated in vacuo. The resulting crude product was purified by using a C18 chromatography column. A gradient of H_2O (0.1% TFA)/MeCN (0.1% TFA) from 8:2 to 1:9 yielded the product as a white solid (2 mg, 3%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.77 (s, 3 H), 3.97 (s, 3 H), 8.21 (s, 1 H), 8.36 (d, J = 8.0 Hz, 1 H), 8.51 (d, J = 8.0 Hz, 1 H) ppm. HRMS: calcd. for $C_{19}H_{19}ClN_3O_5S$ [M + H] 436.0729; found 436.0738.

***tert*-Butyl 2-(Pyridin-2-yl)thiazole-4-carboxylate (14):** A solution of **9** (0.21 M, 4.8 mL, 1.0 mmol, 2 equiv.) was added to a Schlenk tube charged with the palladium species (20 mol-%) and the indicated phosphane (40 mol-%) under a nitrogen atmosphere. The mixture was pre-stirred at 45 °C and then treated with a solution of pyridin-2-yl trifluromethanesulfonate (**13**;[18] 114 mg, 0.5 mmol, 1 equiv.) in DMA (6 mL). The tube was sealed and the mixture stirred at 45 °C. The reaction mixture was analyzed by HPLC to determine the conversion of **13** to **14** according to previously prepared standards of these two compounds. Pure **14** was obtained after running the reaction with $Pd(PPh_3)_4$ (20 mol-%). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 8:2) to yield the title compound as a white solid (99 mg, 75%), m.p. (Et_2O) 89–93 °C. IR (KBr): $\tilde{\nu}$ = 2978, 2931, 1726, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 7.35 (ddd, J = 7.5, 4.8 and 1.2 Hz, 1 H), 7.82 (ddd, J = 8.0, 7.5 and 1.7 Hz, 1 H), 8.13 (s, 1 H), 8.34 (d, J = 8.0 Hz, 1 H), 8.61 (dm, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (q), 82.3 (s), 120.5 (d), 125.2 (d), 128.8 (d), 137.4 (d), 149.5 (d), 149.8 (s), 150.8 (s), 160.7 (s), 169.7 (s) ppm. HRMS: calcd. for $C_{13}H_{15}O_2N_2S$ [M + H] 263.0849; found 263.0852. The product obtained matched that described in the literature.[13]

Synthesis of 2-Chloro-6-methoxy-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (15a):

(2*S*,3*R*)-*N*-[(2-Chloro-6-methoxypyridin-3-yl)carbonyl]threonine Methyl Ester: DIPEA (3.2 mL, 18.66 mmol) and PyBOP (3.19 g, 6.13 mmol) were added to a solution of 2-chloro-6-methoxynicotinic acid **12**[6h] (1.00 g, 5.33 mmol) and H-L-Thr-OMe (904 mg, 5.33 mmol) in dry THF (27 mL) at 0 °C under argon, and the mixture was stirred for 5 h. EtOAc and saturated aq. $NaHCO_3$ were then added to the mixture, which was partially concentrated under reduced pressure. The resulting concentrate was poured onto saturated aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aq. NH_4Cl (2 × 50 mL), dried (Na_2SO_4) and then concen-

trated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc, 4:6) to yield the title compound as a white wax (1.33 g, 82%). $[\alpha]_D$ = +20.9 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3411, 2978, 2954, 1745, 1645, 1599, 1479, 1353, 1310 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.4 Hz, 3 H), 3.78 (s, 3 H), 3.96 (s, 3 H), 4.38 (qd, J = 6.4 and 3.2 Hz, 1 H), 4.64 (d, J = 3.2 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (q), 53.0 (q), 54.8 (q), 58.1 (d), 68.3 (d), 110.2 (d), 122.6 (s), 143.0 (d), 145.4 (s), 164.6 (s), 165.2 (s), 171.4 (s) ppm. HRMS: calcd. for $C_{12}H_{16}N_2O_5Cl$ [M + H] 303.0784; found 303.0742.

Methyl (*S*)-2-(2-Chloro-6-methoxynicotamido)-3-oxobutanoate: Dess–Martin periodinane (2.50 g, 5.90 mmol) was added to a solution of (2*S*,3*R*)-*N*-[(2-chloro-6-methoxypyridin-3-yl)carbonyl]threonine methyl ester (1.48 g, 4.92 mmol) in dry CH_2Cl_2 (80 mL). The mixture was then stirred at room temp. under argon. After 7 h the reaction mixture was poured onto a mixture of saturated aq. $NaHCO_3$ (100 mL) and saturated aq. $Na_2S_2O_3$ (100 mL) and then extracted with CH_2Cl_2 (2× 100 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc, 7:3) to yield the title compound as a white solid (1.27 g, 86%), m.p. (EtOAc) 92–96 °C. IR (KBr): $\tilde{\nu}$ = 3322, 2957, 1742, 1727, 1632, 1600, 1539, 1485, 1365, 1317, 1268 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 3.87 (s, 3 H), 3.99 (s, 3 H), 5.42 (d, J = 5.8 Hz, 1 H), 6.75 (d, J = 8.4 Hz, 1 H), 8.02 (d, J = 5.8 Hz, 1 H), 8.14 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 (q), 53.7 (q), 54.8 (q), 64.2 (d), 110.2 (d), 121.5 (s), 143.1 (d), 145.8 (s), 164.1 (s), 164.8 (s), 166.5 (s), 198.1 (s) ppm. HRMS: calcd. for $C_{12}H_{14}ClN_2O_5$ [M + H] 301.0586; found 301.0585.

2-Chloro-6-methoxy-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-pyridine (15a): A solution of methyl (*S*)-2-(2-chloro-6-methoxynicotamido)-3-oxobutanoate (400 mg, 1.33 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirring solution of PPh_3 (700 mg, 2.67 mmol) and I_2 (675 mg, 2.67 mmol) in dry CH_2Cl_2 (17 mL) at 0 °C under argon. The resulting mixture was allowed to reach room temp. and stirred for 15 h. The solvent was removed under reduced pressure and the crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3) to yield the title compound as a white solid (318 mg, 85%), m.p. (EtOAc) 131–133 °C. IR (KBr): $\tilde{\nu}$ = 2990, 2957, 1716, 1618, 1603, 1473, 1354 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 3 H), 3.95 (s, 3 H), 4.01 (s, 3 H), 6.76 (d, J = 8.4 Hz, 1 H), 8.22 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (q), 52.3 (q), 54.7 (q), 109.9 (d), 115.6 (s), 128.7 (s), 142.1 (d), 157.1 (s), 162.9 (s), 164.3 (s) ppm. HRMS: calcd. for $C_{12}H_{12}ClN_2O_4$ [M + H] 283.0480; found 283.0479.

Synthesis of 2-Chloro-6-methoxy-3-[4-(methoxycarbonyl)thiazol-2-yl]pyridine (15b):

2-Chloro-6-methoxynicotinamide: A mixture of 2-chloro-6-methoxynicotinic acid **12**[6h] (1.00 g, 5.33 mmol) and thionyl chloride (3.9 mL, 53.31 mmol) was heated at reflux temperatures under nitrogen atmosphere for 5 h. After the mixture reached room temp., the excess thionyl chloride was removed under reduced pressure and the residue was dissolved in toluene. The volatiles were evaporated, more toluene was added and then the mixture was concentrated again. The resulting solid was dissolved in THF (10 mL) and cooled to 0 °C in an ice bath. An aq. solution of NH_3 (32%, 10 mL) was added and the mixture was stirred for 1 h. The THF was evaporated under reduced pressure and saturated aq. $NaHCO_3$ (40 mL) was added. The solution was extracted with CH_2Cl_2 (3× 50 mL), and the combined organic extracts were dried (Na_2SO_4) and then concentrated in vacuo. The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 98:2). The title product was obtained as a white solid (863 mg, 96%), m.p. (CH_2Cl_2) 172–173 °C. IR (KBr): $\tilde{\nu}$ = 3350, 3179, 1656, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.99 (s, 3 H), 6.14 (br. s, 1 H), 6.76 (d, J = 8.4 Hz, 1 H), 6.82 (br. s, 1 H), 8.22 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.8 (q), 110.3 (d), 121.9 (s), 143.5 (d), 145.5 (s), 164.7 (s), 166.2 (s) ppm. HRMS: calcd. for $C_7H_8ClN_2O_2$ [M + H] 187.0274; found 187.0262.

2-Chloro-6-methoxynicotinthioamide: A solution of 2-chloro-6-methoxynicotinamide (794 mg, 4.26 mmol) and Lawesson's reagent (860 mg, 2.13 mmol) in dry THF (85 mL) was stirred at reflux temperatures for 2 h and then allowed to reach room temp. The volatiles were evaporated under reduced pressure and saturated aq. $NaHCO_3$ (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3× 100 mL), and the combined organic extracts were dried (Na_2SO_4), and then concentrated in vacuo. The crude product was purified by silica flash column chromatography (CH_2Cl_2). The title product was obtained as a pale solid (760 mg, 88%), m.p. (CH_2Cl_2) 158–161 °C. IR (KBr): $\tilde{\nu}$ = 3310, 3143, 1642, 1593, 1477, 1299 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 6.71 (d, J = 8.4 Hz, 1 H), 7.52 (br. s, 1 H), 7.98 (br. s, 1 H), 8.22 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.8 (q), 110.1 (d), 128.4 (s), 142.0 (s), 144.1 (d), 164.3 (s), 199.3 (s) ppm. HRMS: calcd. for $C_7H_8ClN_2OS$ [M + H] 203.0046; found 203.0036.

2-Chloro-6-methoxy-3-[4-(methoxycarbonyl)thiazol-2-yl]pyridine (15b): Methyl bromopyruvate (750 μL, 7.05 mmol), and pyridine (430 μL, 5.28 mmol) were added to a solution of 2-chloro-6-methoxy-nicotinthioamide (714 mg, 3.52 mmol) in dry EtOH under a nitrogen atmosphere. The mixture was stirred at 80 °C for 3.5 h and then cooled down. Volatiles were evaporated under reduced pressure, and the resulting crude product was purified by silica flash column chromatography (CH_2Cl_2). The title product was obtained as a white solid (1.03 g, quant.), m.p. (CH_2Cl_2) 156–159 °C. IR (KBr): $\tilde{\nu}$ = 3120, 3021, 2955, 1749, 1600, 1351, 1268, 1218 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 4.01 (s, 3 H), 6.81 (d, J = 8.8 Hz, 1 H), 8.27 (s, 1 H), 8.62 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.7 (q), 54.7 (q), 110.5 (d), 121.3 (s), 128.5 (d), 142.3 (d), 146.0 (s), 146.6 (s), 162.1 (s), 163.1 (s), 164.0 (s) ppm. HRMS: calcd. for $C_{11}H_{10}ClN_2O_3S$ [M + H] 285.0107; found 285.0101.

Methyl 2-Chloro-6-methoxynicotinate (15c): A solution of trimethylsilyldiazomethane ($TMSCHN_2$) in diethyl ether (2.0 M, 2.2 mL, 4.32 mmol) was added to a stirring solution of 2-chloro-6-methoxynicotinic acid **12**[6h] (450 mg, 2.40 mmol) in CH_2Cl_2 (12 mL) and MeOH (12 mL) at 0 °C. After 20 min the reaction was allowed to reach room temp. and then stirred for another 20 min. Solvents were removed under reduced pressure and the crude product was purified by silica flash column chromatography (hexanes/EtOAc, 1:1). The title product was obtained as a white solid (359 mg, 74%), m.p. (EtOAc) 59–62 °C. IR (KBr): $\tilde{\nu}$ = 3087, 3006, 2953, 1725, 1594, 1480, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 4.00 (s, 3 H), 6.70 (d, J = 8.8 Hz, 1 H), 8.13 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.6 (q), 54.8 (q), 109.4 (d), 118.6 (s), 143.1 (d), 149.5 (s), 165.0 (s), 165.1 (s) ppm. HRMS: calcd. for $C_8H_9NO_3Cl$ [M + H] 202.0271; found 202.0269.

General Procedure for the Stille Cross-Coupling: A Schlenk tube was charged under argon with degassed dry 1,4-dioxane, pyridine **15** (1 equiv.), $Pd(PPh_3)_4$ (10 mol-%) and organotin **11** (1.1 equiv.). The tube was sealed and the mixture was stirred at 80 °C for 23 h,

except for the indicated reaction. After this time the mixture was allowed to reach room temp., filtered through Celite with EtOAc, dried (Na_2SO_4) and then concentrated in vacuo. The crude product was purified by silica flash column chromatography.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-methoxy-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (16aa): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15a** (771 mg, 2.73 mmol), $Pd(PPh_3)_4$ (315 mg, 0.27 mmol) and organotin **11a**[12] (1.50 g, 3.00) in 1,4-dioxane (55 mL) for 30 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3 to 1:1). The title product was obtained as a white wax (1.35 g, 85%). $[a]_D$ = –43.1 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2952, 2928, 1734, 1700, 1385 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.54 (m, 9 H), 1.92–2.08 (m, 2 H), 2.20–2.44 (m, 2 H), 2.54 (s, 3 H), 3.38–3.70 (m, 2 H), 3.95 (s, 3 H), 4.07 (s, 3 H), 5.10–5.30 (m, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 7.39 (s, 1 H), 7.94 (d, J = 8.4 Hz, 1 H), 8.07 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (q), 23.4 and 24.1 (t), 28.5 (q), 32.9 and 34.3 (t), 46.8 and 47.1 (t), 52.2 (q), 53.9 (q), 59.1 and 59.5 (d), 80.6 (s), 110.2 (d), 114.9 (d), 115.2 (s), 120.7 (d), 128.3 (s), 142.0 (d), 149.6 (s), 154.9 (s), 156.6 (s), 159.8 (s), 163.3 (s), 164.5 (s), 176.5 (s) ppm. HRMS: calcd. for $C_{27}H_{30}O_6N_5S_2$ [M + H] 584.1632; found 584.1628.

6-Methoxy-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-2-[2-(2-methyl-1,3-dioxolan-2-yl)thiazol-4-yl]pyridine (16ab): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15a** (100 mg, 0.35 mmol), $Pd(PPh_3)_4$ (40 mg, 0.04 mmol) and organotin **11b**[13] (174 mg, 0.38 mmol) in 1,4-dioxane (7 mL) for 47 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The title product was obtained as a white solid (77 mg, 53%), m.p. (Et_2O) 127–130 °C. IR (KBr): $\tilde{\nu}$ = 2991, 2952, 2893, 1732, 1716, 1615, 1470, 1386, 1326, 1197, 1104, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 2.60 (s, 3 H), 3.92 (s, 3 H), 3.97–4.07 (m, 7 H), 6.77 (d, J = 8.6 Hz, 1 H), 7.93 (d, J = 8.6 Hz, 1 H), 7.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 24.8 (q), 52.0 (q), 53.9 (q), 65.6 (t), 107.0 (s), 110.1 (d), 115.1 (s), 120.6 (d), 128.2 (s), 141.8 (d), 149.7 (s), 154.8 (s), 156.8 (s), 159.3 (s), 163.3 (s), 164.4 (s), 172.2 (s) ppm. HRMS: calcd. for $C_{19}H_{20}O_6N_3S$ [M + H] 418.1067; found 418.1065.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-methoxy-3-[4-(methoxycarbonyl)thiazole-2-yl]pyridine (16ba): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15b** (142 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and organotin **11a**[12] (275 mg, 0.55 mmol) in 1,4-dioxane (10 mL) for 23 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (164 mg, 56%), m.p. (CH_2Cl_2) 87–91 °C. $[a]_D$ = –73.8 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3111, 2975, 1739, 1696, 1596, 1381 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.57 (m, 9 H), 1.91–2.04 (m, 2 H), 2.21–2.45 (m, 2 H), 3.39–3.68 (m, 2 H), 3.95 (s, 3 H), 4.05 (s, 3 H), 5.11–5.28 (m, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 7.42 (s, 1 H), 7.88 (br. s, 1 H), 8.02 (d, J = 8.4 Hz, 1 H), 8.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 and 24.1 (t), 28.5 (q), 34.3 (t), 46.8 and 47.1 (t), 52.7 (q), 54.0 (q), 59.5 (d), 80.6 (s), 110.5 (d), 115.5 and 115.8 (d), 121.2 (d), 129.1 (d), 141.9 (d), 149.1 (s), 154.5 (s), 162.3 (s), 164.2 (s), 167.5 (s), 207.2 (s) ppm. HRMS: calcd. for $C_{26}H_{28}N_5O_5S_3$ [M + H] 586.1247; found 586.1243.

6-Methoxy-3-[4-(methoxycarbonyl)thiazol-2-yl]-2-[2-(2-methyl-1,3-dioxolan-2-yl)thiazol-4-yl]pyridine (16bb): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15b** (100 mg, 0.35 mmol), $Pd(PPh_3)_4$ (40 mg, 0.04 mmol) and organotin **11b**[13] (177 mg, 0.38 mmol) in 1,4-dioxane (7 mL) for 47 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The title product was obtained as a white solid (65 mg, 44%), m.p. (Et_2O) 114–118 °C. IR (KBr): $\tilde{\nu}$ = 3112, 2990, 2952, 2895, 2854, 1736, 1722, 1596, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 3 H), 3.93 (s, 3 H), 3.94–4.06 (m, 7 H), 6.80 (d, J = 8.6 Hz, 1 H), 7.84 (s, 1 H), 7.96 (d, J = 8.6 Hz, 1 H), 8.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (q), 52.6 (q), 54.0 (q), 65.5 (t), 107.0 (s), 110.3 (d), 121.3 (d), 121.4 (s), 129.0 (d), 141.8 (d), 146.5 (s), 149.2 (s), 154.5 (s), 162.3 (s), 164.2 (s), 167.2 (s), 171.5 (s) ppm. HRMS: calcd. for $C_{18}H_{18}O_5N_3S_2$ [M + H] 420.0682; found 420.0684.

Methyl (*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-methoxynicotinate (16ca): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15c** (100 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and organotin **11a**[12] (275 mg, 0.55 mmol) in 1,4-dioxane (10 mL) for 23 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 8:2). The title product was obtained as a white solid (237 mg, 94%), m.p. (CH_2Cl_2) 69–73 °C. $[a]_D$ = –59.5 (c = 0.50, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3119, 2976, 1730, 1698, 1594, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.54 (m, 9 H), 1.92–2.10 (m, 2 H), 2.24–2.46 (m, 2 H), 3.40–3.70 (m, 2 H), 3.79 (s, 3 H), 4.03 (s, 3 H), 5.12–5.32 (m, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 7.80–7.85 (m, 2 H), 7.99 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 and 24.2 (t), 28.5 (q), 32.9 and 34.3 (t), 46.8 and 47.2 (t), 52.4 and 52.6 (q), 53.9 (q), 59.2 and 59.6 (d), 80.6 (s), 110.0 (d), 113.6 (s), 115.4 (d), 119.7 (d), 119.9 (s), 121.2 (s), 139.8 (d), 142.8 (s), 148.8 (s), 155.1 (s), 164.2 (s) ppm. HRMS: calcd. for $C_{23}H_{27}N_4O_5S_2$ [M + H] 503.1417; found 503.1415.

Methyl 6-Methoxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)thiazol-4-yl]-nicotinate (16cb): The reaction was performed according to the general procedure for the Stille cross-coupling by using pyridine **15c** (100 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and organotin **11b**[13] (253 mg, 0.55 mmol) in 1,4-dioxane (10 mL) for 17 h. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 8:2). The title product was obtained as a white solid (96 mg, 57%), m.p. (Et_2O) 95–99 °C. IR (KBr): $\tilde{\nu}$ = 2992, 2951, 2898, 1730, 1596, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3 H), 3.83 (s, 3 H), 4.01 (s, 3 H), 4.05–4.12 (m, 4 H), 6.72 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (q), 52.5 (q), 53.9 (q), 65.6 (t), 107.1 (s), 109.9 (d), 119.7 (d), 121.2 (s), 139.8 (d), 148.7 (s), 154.9 (s), 164.1 (s), 169.5 (s), 171.4 (s) ppm. HRMS: calcd. for $C_{15}H_{17}O_5N_2S$ [M + H] 337.0853; found 337.0854.

General Procedure for the Demethylation of Methoxypyridines: A solution of the starting methoxypyridine in HBr in AcOH (33%) was stirred at 90 °C under nitrogen for 30 min. The mixture was allowed to reach room temp., poured onto saturated aq. $NaHCO_3$, extracted with CH_2Cl_2 (×3), dried ($NaSO_4$) and then concentrated in vacuo. If required the crude product was purified by silica flash column chromatography.

General Procedure for Boc Protection of Bithiazolylpyrrolidines: *tert*-Butyl dicarbonate (1 equiv.) and NEt_3 (2 equiv.) were added to a flask charged with a solution of free bithiazolylpyrrolidine (1 equiv.) in dry CH_2Cl_2 at 0 °C for 4 h under nitrogen. The resulting mixture was stirred at 0 °C for the indicated time. The reaction mixture was poured into brine, extracted with CH_2Cl_2 (×3),

dried ($Na2SO_4$) and then concentrated in vacuo. The crude product was purified by silica flash column chromatography.

General Procedure for the Preparation of Pyridyl Triflates: 2,6-Lutidine (1.4 equiv.) and trifluoromethanesulfonic anhydride (1.2 equiv.) were added to a solution of the pyridone and DMAP (20 mol-%) in dry CH_2Cl_2 at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 2.5 h and then at room temp. for 2 h. The mixture was diluted with CH_2Cl_2, washed with water (× 2), dried (Na_2SO_4) and then concentrated in vacuo. The crude product was purified by silica flash column chromatography.

Synthesis of (*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-3-[-4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17aa):

(*S*)-5-[4-(Methoxycarbonyl)-5-methyloxazol-2-yl]-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16aa** (590 mg, 1.01 mmol). The title compound was obtained as a yellowish solid (420 mg, 89%), m.p. decomp. (CH_2Cl_2) 188 °C. $[a]_D$ = –64.3 (*c* = 1.00, CH_2Cl_2). IR (KBr): ṽ = 3420, 3088, 2955, 2918, 2849, 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.96 (m, 2 H), 2.00–2.10 (m, 1 H), 2.29–2.40 (m, 1 H), 2.63 (s, 3 H), 3.07–3.21 (m, 2 H), 3.94 (s, 3 H), 4.62 (dd, *J* = 8.2 and 5.4 Hz, 1 H), 6.61 (dd, *J* = 9.6 Hz, 1 H), 7.86 (dd, *J* = 9.6 Hz, 1 H), 7.89 (s, 1 H), 8.37 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 25.8 (t), 34.3 (t), 47.3 (t), 52.3 (q), 59.6 (d), 104.4 (s), 117.6 (d), 120.2 (d), 123.8 (d), 128.5 (s), 139.7 (s), 142.3 (d), 145.8 (s), 148.5 (s), 156.6 (s), 157.1 (s), 162.3 (s), 162.7 (s), 162.9 (s), 180.8 (s) ppm. HRMS: calcd. for $C_{21}H_{20}N_5O_4S_2$[M + H] 470.0957; found 470.0966.

(*S*)-6-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for the Boc protection of bithiazolylpyrrolidines by using (*S*)-5-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one (500 mg, 1.06 mmol) in CH_2Cl_2 (21 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 2:8). The title product was obtained as a yellowish solid (593 mg, 98%), m.p. (CH_2Cl_2) 143–147 °C. $[a]_D$ = –59.5 (*c* = 1.00, CH_2Cl_2). IR (KBr): ṽ = 3091, 2975, 1699, 1657, 1385, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.56 (m, 9 H), 1.93–2.10 (m, 2 H), 2.20–2.48 (m, 2 H), 2.66 (s, 3 H), 3.40–3.72 (m, 2 H), 3.96 (s, 3 H), 5.12–5.30 (m, 1 H), 6.62 (d, *J* = 9.6 Hz, 1 H), 7.86 (d, *J* = 9.6 Hz, 1 H), 7.94 (br. s, 1 H), 8.38–8.47 (m, 1 H), 10.92 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 23.5 and 24.2 (t), 28.5 (q), 33.0 and 34.3 (t), 46.8 and 47.2 (t), 52.3 (q), 59.1 and 59.5 (d), 80.7 (s), 104.5 (q), 117.0 (d), 120.2 (d), 124.0 (d), 128.5 (s), 139.6 (s), 142.3 (d), 145.9 (s), 148.1 (s), 154.4 and 154.9 (s), 156.6 (s), 157.0 (s), 162.4 (s), 162.7 (s), 176.9 (s) ppm. HRMS: calcd. for $C_{26}H_{28}O_6N_5S_2$ [M + H] 570.1476; found 570.1474.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-3-[-4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17aa): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using (*S*)-6-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridin-2(1*H*)-one (568 mg, 1.03 mmol), trifluoromethanesulfonic anhydride (207 µL, 1.23 mmol), 2,6-lutidine (168 µL, 1.44 mmol) and DMAP (27 mg, 0.21 mmol) in CH_2Cl_2 (10 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 1:1). The title product was obtained as a white solid (587 mg, 81%), m.p. (EtOAc) 77–81 °C. $[a]_D$ = –42.3 (*c* = 1.00, CH_2Cl_2). IR (KBr): ṽ = 3118, 2976, 1699, 1426, 1388, 1212 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.55 (m, 9 H), 1.92–2.05 (m, 2 H), 2.20–2.46 (m, 2 H), 2.57 (s, 3 H), 3.38–3.70 (m, 2 H), 3.97 (s, 3 H), 5.10–5.30 (m, 1 H), 7.21 (d, *J* = 8.2 Hz, 1 H), 7.34 (br. s, 1 H), 8.18 (s, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (q), 23.5 and 24.2 (t), 28.5 and 28.7 (q), 32.9 and 34.2 (t), 46.8 and 47.1 (t), 52.4 (q), 59.2 and 59.5 (d), 80.6 (s), 113.2 (d), 115.1 and 115.5 (d), 118.9 (q), 121.8 (s), 123.2 (d), 128.7 (s), 144.9 (d), 148.8 (s), 151.1 (s), 152.6 (s), 155.9 (s), 157.3 (s), 157.7 (s), 162.4 (s), 162.9 (s), 176.8 (s) ppm. HRMS: calcd. for $C_{27}H_{27}N_5O_8F_3S_3$ [M + H] 702.0974; found 702.0988.

Synthesis of 2-(2-Acetylthiazol-4-yl)-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17ab):

6-(2-Acetylthiazol-4-yl)-5-[4-(methoxycarbonyl)-5-methyloxazol-2-yl-]pyridine-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16ab** (70 mg, 0.17 mmol). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 96:4). The title product was obtained as a pale solid (41 mg, 67%), m.p. (Et_2O) 194–198 °C. IR (KBr): ṽ = 3083, 2921, 2851, 1719, 1674, 1441, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 2.65 (s, 3 H), 3.93 (s, 3 H), 6.66 (d, *J* = 9.6 Hz, 1 H), 7.90 (d, *J* = 9.6 Hz, 1 H), 8.81 (s, 1 H), 12.04 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 26.1 (q), 52.3 (q), 106.0 (s), 120.6 (d), 128.5 (s), 130.0 (d), 139.6 (s), 142.5 (d), 147.5 (s), 156.6 (s), 157.0 (s), 162.6 (s), 163.4 (s), 166.5 (s), 191.2 (s) ppm. HRMS: calcd. for C16H14O5N3S [M + H] 360.0649; found 360.0647.

2-(2-Acetylthiazol-4-yl)-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17ab): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using 6-(2-acetylthiazol-4-yl)-5-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine-2(1*H*)-one (38 mg, 0.11 mmol), trifluoromethanesulfonic anhydride (22 µL, 0.13 mmol), 2,6-lutidine (17 µL, 0.15 mmol) and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (1.1 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (54 mg, quant.). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 2.64 (s, 3 H), 3.96 (s, 3 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 8.48 (s, 1 H) ppm.

Synthesis of (*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-3-[4-(methoxycarbonyl)thiazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17ba):

(*S*)-5-[4-(Methoxycarbonyl)thiazole-2-yl]-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16ba** (149 mg, 0.25 mmol). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 95:5). The title product was obtained as a white solid (80 mg, 68%), m.p. (CH_2Cl_2) 119–123 °C. $[a]_D$ = –35.2 (*c* = 1.00, CH_2Cl_2). IR (KBr): ṽ = 2920, 1732, 1652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.96 (m, 2 H), 1.99–2.09 (m, 1 H), 2.27–2.39 (m, 1 H), 3.06–3.21 (m, 2 H), 3.99 (s, 3 H), 4.62 (dd, *J* = 8.4 and 5.4 Hz, 1 H), 6.62 (d, *J* = 9.4 Hz, 1 H), 7.41 (s, 1 H), 7.66 (d, *J* = 9.4 Hz, 1 H), 7.92 (s, 1 H), 8.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (t), 34.3 (t), 47.2 (t), 52.9 (q), 59.6 (d), 110.6 (s), 117.8 (d), 120.3 (d), 122.8 (d), 129.8 (d), 139.1 (s), 143.2 (d), 145.9 (s), 147.4 (s), 148.5 (s), 161.8 (s), 162.5 (s), 163.5 (s), 164.9 (s), 180.5 (s) ppm. HRMS: calcd. for $C_{20}H_{18}O_3N_5S_3$ [M + H] 472.0566; found 472.0564.

(*S*)-6-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-[4-(methoxycarbonyl)thiazole-2-yl]pyridin-2(1*H*)-one: The re-

action was performed according to the general procedure for Boc protection of bithiazolylpyrrolidines by using (*S*)-5-[4-(methoxycarbonyl)thiazole-2-yl]-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one (75 mg, 0.16 mmol) in CH_2Cl_2 (3 mL). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 95:5). The title product was obtained as a pale solid (91 mg, quant.), m.p. (CH_2Cl_2) 118–122 °C. $[\alpha]_D$ = –35.7 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3094, 2975, 1732, 1695, 1656, 1388 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.53 (m, 9 H), 1.92–2.06 (m, 2 H), 2.20–2.46 (m, 2 H), 3.40–3.70 (m, 2 H), 3.99 (s, 3 H), 5.11–5.28 (m, 1 H), 6.62 (d, *J* = 9.4 Hz, 1 H), 7.44 (br. s, 1 H), 7.65 (d, *J* = 9.4 Hz, 1 H), 7.95 (br. s, 1 H), 8.32 (s, 1 H), 10.77 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 and 24.2 (t), 28.5 (q), 33.0 and 34.3 (t), 46.8 and 47.2 (t), 52.9 (q), 59.2 and 59.5 (d), 80.7 (s), 110.5 (s), 117.2 and 117.5 (d), 120.3 (d), 123.0 (d), 129.9 (d), 139.0 (s), 143.3 (d), 145.9 (s), 147.4 (s), 148.1 (s), 161.8 (s), 162.4 (s), 164.8 (s), 176.9 (s) ppm. HRMS: calcd. for $C_{25}H_{26}N_5O_5S_3$ [M + H] 572.1091; found 572.1093.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-3-[4-(methoxycarbonyl)thiazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17ba): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using (*S*)-6-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-[4-(methoxycarbonyl)thiazole-2-yl]pyridin-2(1*H*)-one (65 mg, 0.11 mmol), trifluoromethanesulfonic anhydride (22 μL, 0.13 mmol), 2,6-lutidine (18 μL, 0.15 mmol) and DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (1.1 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The title product was obtained as a white solid (60 mg, 78%), m.p. (EtOAc) 153–157 °C. $[\alpha]_D$ = –37.6 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2976, 1733, 1696, 1426, 1386, 1212 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.52 (m, 9 H), 1.92–2.01 (m, 2 H), 2.19–2.43 (m, 2 H), 3.38–3.68 (m, 2 H), 3.97 (s, 3 H), 5.08–5.27 (m, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 7.28 (s, 1 H), 8.08 (br. s, 1 H), 8.26 (d, *J* = 8.4 Hz, 1 H), 8.37 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 and 24.2 (t), 28.5 (q), 33.0 and 34.2 (t), 46.8 and 47.2 (t), 52.8 (q), 59.1 and 59.5 (d), 80.6 (s), 113.5 (d), 115.7 and 116.1 (d), 117.3 (s), 120.5 (s), 123.5 (d), 127.9 (s), 129.7 (d), 144.9 (d), 146.9 (s), 150.5 (s), 152.5 (s), 155.6 (s), 162.0 (s), 165.2 (s), 176.6 (s) ppm. HRMS: calcd. for $C_{26}H_{25}O_7N_5F_3S_4$ [M + H] 704.0583; found 704.0593.

Synthesis of 2-(2-Acetylthiazol-4-yl)-3-[4-(methoxycarbonyl)thiazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17bb):

6-(2-Acetylthiazol-4-yl)-5-[4-(methoxycarbonyl)thiazol-2-yl]pyridine-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16bb** (111 mg, 0.26 mmol). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 96:4). The title product was obtained as a yellowish solid (68 mg, 72%), m.p. (Et_2O) 210–214 °C. IR (KBr): $\tilde{\nu}$ = 3093, 2921, 2850, 1731, 1660, 1239, 1214 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 3.98 (s, 3 H), 6.67 (d, *J* = 9.2 Hz, 1 H), 7.70 (d, *J* = 9.2 Hz, 1 H), 8.02 (s, 1 H), 8.30 (s, 1 H), 11.20 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3 (q), 52.9 (q), 111.3 (s), 121.1 (d), 129.5 (d), 129.7 (d), 138.2 (s), 143.3 (d), 147.1 (s), 147.5 (s), 161.6 (s), 162.4 (s), 164.5 (s), 167.0 (s), 191.1 (s) ppm. HRMS: calcd. for $C_{15}H_{12}O_4N_3S_2$ [M + H] 362.0264; found 362.0265.

2-(2-Acetylthiazol-4-yl)-3-[4-(methoxycarbonyl)thiazol-2-yl]-6-(trifluoromethylsulfonyloxy)pyridine (17bb): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using 6-(2-acetylthiazol-4-yl)-5-[4-(methoxycarbonyl)thiazol-2-yl]pyridine-2(1*H*)-one (25 mg, 0.07 mmol), trifluoromethanesulfonic anhydride (14 μL, 0.08 mmol), 2,6-lutidine (11 μL, 0.10 mmol) and DMAP (2 mg, 0.014 mmol) in CH_2Cl_2 (0.7 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (27 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 3.97 (s, 3 H), 7.27 (d, *J* = 8.2 Hz, 1 H), 8.18 (d, *J* = 8.2 Hz, 1 H), 8.38 (s, 1 H), 8.43 (s, 1 H) ppm.

Synthesis of methyl (*S*)-2-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-(trifluoromethylsulfonyloxy)nicotinate (17ca):

Methyl (*S*)-5-(methoxycarbonyl)-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16ca** (225 mg, 0.45 mmol). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 95:5). The title product was obtained as a white solid (152 mg, 87%), m.p. (CH_2Cl_2) 84–88 °C. $[\alpha]_D$ = –51.4 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2919, 1717, 1652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.96 (m, 2 H), 1.99–2.10 (m, 1 H), 2.28–2.40 (m, 1 H), 3.07–3.21 (m, 2 H), 3.86 (s, 3 H), 4.63 (dd, *J* = 8.2 and 5.4 Hz, 1 H), 6.53 (d, *J* = 9.6 Hz, 1 H), 7.94 (s, 1 H), 7.96 (d, *J* = 9.6 Hz, 1 H), 8.55 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (t), 34.3 (t), 47.2 (t), 52.5 (q), 59.6 (d), 108.4 (s), 117.5 (d), 119.3 (d), 125.4 (d), 142.5 (d), 142.9 (s), 145.6 (s), 148.5 (s), 162.4 (s), 162.7 (s), 166.0 (s), 180.6 (s) ppm. HRMS: calcd. for $C_{17}H_{17}O_3N_4S_2$ [M + H] 389.0737; found 389.0735.

Methyl (*S*)-6-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-(methoxycarbonyl)pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for Boc protection of bithiazolylpyrrolidines by using methyl (*S*)-5-(methoxycarbonyl)-6-[2′-(pyrrolidin-2-yl)-2,4′-bithiazol-4-yl]pyridin-2(1*H*)-one (140 mg, 0.36 mmol) in CH_2Cl_2 (7.2 mL). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 95:5). The title product was obtained as a pale solid (170 mg, 97%), m.p. (CH_2Cl_2) 96–100 °C. $[\alpha]_D$ = –55.7 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3088, 2975, 1699, 1653, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.55 (m, 9 H), 1.92–2.07 (m, 2 H), 2.23–2.46 (m, 2 H), 3.41–3.71 (m, 2 H), 3.87 (s, 3 H), 5.12–5.29 (m, 1 H), 6.53 (d, *J* = 9.6 Hz, 1 H), 7.94–8.00 (m, 2 H), 8.58 (s, 1 H), 10.96 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 and 24.2 (t), 28.5 (q), 33.0 and 34.3 (t), 46.8 and 47.2 (t), 52.6 (q), 59.1 and 59.5 (d), 80.7 (s), 108.4 (s), 116.9 and 117.3 (d), 119.3 (d), 125.7 (d), 140.6 (s), 142.5 (d), 142.8 (s), 145.6 (s), 148.1 (s), 154.3 (s), 162.6 (s), 166.0 (s), 176.9 (s) ppm. HRMS: calcd. for $C_{22}H_{25}N_4O_5S_2$ [M + H] 489.1261; found 489.1263.

Methyl (*S*)-2-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-(trifluoromethylsulfonyloxy)nicotinate (17ca): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using methyl (*S*)-6-{2′-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-5-(methoxycarbonyl)pyridin-2(1*H*)-one (137 mg, 0.28 mmol), trifluoromethanesulfonic anhydride (57 μL, 0.34 mmol), 2,6-lutidine (45 μL, 0.39 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (2.8 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (103 mg, 59%), m.p. (EtOAc) 59–62 °C. $[\alpha]_D$ = –48.1 (*c* = 0.50, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2977, 1734, 1699, 1427, 1388, 1216, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.56 (m, 9 H), 1.92–2.09 (m, 2 H), 2.22–2.46 (m, 2 H), 3.38–3.72 (m, 2 H), 3.88 (br. s, 3 H), 3.11–3.31 (m, 1 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 7.82 (s, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 8.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 and 24.2 (t), 28.5 (q), 32.9 and 34.3

(t), 46.8 and 47.2 (t), 53.2 (q), 59.1 and 59.3 (d), 80.6 (s), 113.3 (d), 115.8 and 116.2 (d), 117.3 (s), 120.5 (s), 122.2 (d), 128.1 (s), 141.9 (d), 149.0 (s), 149.5 (s), 152.6 (s), 155.3 (s), 168.3 (s), 176.8 (s) ppm. HRMS: calcd. for $C_{23}H_{24}O_7N_4F_3S_3$ [M + H] 621.0754; found 621.0756.

Synthesis of Methyl 2-(2-Acetylthiazol-4-yl)-6-(trifluoromethylsulfonyloxy)nicotinate (17cb):

6-(2-Acetylthiazol-4-yl)-5-(methoxycarbonyl)pyridin-2(1*H*)-one: The reaction was performed according to the general procedure for the demethylation of methoxypyridines by using **16cb** (89 mg, 0.26 mmol). The crude product was purified by silica flash column chromatography (CH_2Cl_2/MeOH, 98:2). The title product was obtained as a white solid (49 mg, 64%), m.p. (Et_2O) 184–188 °C. IR (KBr): $\tilde{\nu}$ = 3440, 3094, 1710, 1687, 1298 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.75 (s, 3 H), 3.83 (s, 3 H), 6.55 (d, J = 9.8 Hz, 1 H), 7.97 (d, J = 9.8 Hz, 1 H), 8.66 (s, 1 H), 11.58 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3 (q), 52.6 (q), 109.7 (s), 119.9 (d), 130.9 (d), 142.3 (d), 142.5 (s), 147.2 (s), 163.3 (s), 165.8 (s), 166.3 (s), 191.2 (s) ppm. HRMS: calcd. for $C_{12}H_{11}O_4N_2S$[M + H] 279.0434; found 279.0436.

Methyl 2-(2-Acetylthiazol-4-yl)-6-(trifluoromethylsulfonyloxy)nicotinate (17cb): The reaction was performed according to the general procedure for the preparation of pyridyl triflates by using 6-(2-acetylthiazol-4-yl)-5-(methoxycarbonyl)pyridin-2(1*H*)-one (45 mg, 0.15 mmol), trifluoromethanesulfonic anhydride (30 μL, 0.18 mmol), 2,6-lutidine (26 μL, 0.22 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (1.5 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (61 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.71 (s, 3 H), 3.93 (s, 3 H), 7.21 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 8.42 (s, 1 H) ppm.

General Procedure for Negishi Cross-Coupling: A solution of **9** in DMA (0.21 M, 2 equiv.) was added to a Schlenk tube charged with [$Pd(PPh_3)_4$] (20 mol-%) under nitrogen atmosphere. The mixture was stirred at 45 °C and then treated with a solution of pyridine-2-yl triflate (**3**; 1 equiv.) in DMA. The tube was sealed and the mixture was stirred at 45 °C for 18 h. After the indicated time the solution was allowed to reach room temp., filtered through Celite, washed with EtOAc, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica flash column chromatography.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (18aa): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (27 mL, 5.70 mmol), $Pd(PPh_3)_4$ (164 mg, 0.14 mmol) and **17aa** (500 mg, 0.71 mmol) in DMA (8.9 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The desired product was obtained as a yellowish solid (481 mg, 92%), m.p. (EtOAc) 186–190 °C. $[a]_D$ = –40.9 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3088, 2976, 1698, 1390, 1165, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.54 (m, 9 H), 1.65 (s, 9 H), 1.92–2.06 (m, 2 H), 2.21–2.46 (m, 2 H), 2.55 (s, 3 H), 3.38–3.70 (m, 2 H), 3.97 (s, 3 H), 5.10–5.30 (m, 1 H), 7.36–7.43 (m, 1 H), 8.21–8.23 (m, 2 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.38 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (q), 23.5 (t), 28.4 (q), 28.5 (q), 32.9 and 34.3 (t), 46.8 and 47.1 (t), 52.3 (q), 59.5 (d), 80.6 (s), 82.5 (s), 115.0 and 115.3 (d), 118.7 (d), 121.5 (d), 122.6 (s), 128.6 (s), 129.6 (d), 132.3 and 132.4 (s), 140.9 (d), 150.2 (s), 151.2 (s), 151.5 (s), 154.1 (s), 157.0 (s), 158.9 (s), 160.6 (s), 163.1 (s), 168.6 (s) ppm. HRMS: calcd. for $C_{34}H_{37}N_6O_7S_3$ [M + H] 737.1886; found 737.1894.

2-(2-Acetylthiazol-4-yl)-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]-3-[4-(methoxycarbonyl)-5-methyloxazol-2-yl]pyridine (18ab): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (1.0 mL, 0.22 mmol), $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) and **17ab** (54 mg, 0.11 mmol) in DMA (1.4 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (25 mg, 43%), m.p. (Et_2O) 178–182 °C. IR (KBr): $\tilde{\nu}$ = 3113, 2924, 2852, 1719, 1690, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.41 (s, 3 H), 2.62 (s, 3 H), 3.96 (s, 3 H), 8.22 (s, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.54 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 25.7 (q), 28.4 (q), 52.3 (q), 82.6 (s), 119.3 (d), 122.8 (s), 128.1 (d), 128.8 (s), 129.6 (d), 141.0 (d), 150.3 (s), 150.4 (s), 151.7 (s), 155.2 (s), 157.0 (s), 158.4 (s), 160.5 (s), 162.8 (s), 166.3 (s), 168.2 (s), 191.4 (s) ppm. HRMS: calcd. for $C_{24}H_{23}O_6N_4S_2$ [M + H] 527.1054; found 527.1059.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]-3-[4-(methoxycarbonyl)-thiazole-2-yl]pyridine (18ba): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (0.8 mL, 0.16 mmol), $Pd(PPh_3)_4$ (19 mg, 0.016 mmol) and **17ba** (58 mg, 0.08 mmol) in DMA (1.0 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The title product was obtained as a white solid (32 mg, 54%), m.p. (Et_2O) 110–114 °C. $[a]_D$ = –30.0 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2975, 1699, 1385, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.54 (m, 9 H), 1.65 (s, 9 H), 1.92–2.05 (m, 2 H), 2.21–2.45 (m, 2 H), 3.39–3.69 (m, 2 H), 3.97 (s, 3 H), 5.11–5.30 (m, 1 H), 7.44 (s, 1 H), 8.04 (br. s, 1 H), 8.20 (s, 1 H), 8.28–8.35 (m, 2 H), 8.41 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 and 24.2 (t), 28.4 (q), 28.5 (q), 33.0 and 34.2 (t), 46.8 (t), 52.8 (q), 59.2 and 59.5 (d), 80.6 (s), 82.5 (s), 115.8 and 116.2 (d), 119.2 (d), 122.0 (d), 129.1 (d), 129.5 (d), 140.5 (d), 146.8 (s), 149.0 (s), 150.1 (s), 150.9 (s), 151.1 (s), 153.8 (s), 160.6 (s), 162.1 (s), 166.3 (s), 168.7 (s), 176.5 (s) ppm. HRMS: calcd. for $C_{33}H_{35}O_6N_6S_4$ [M + H] 739.1495; found 739.1503.

2-(2-Acetylthiazol-4-yl)-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]-3-[4-(methoxycarbonyl)thiazol-2-yl]pyridine (18bb): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (0.44 mL, 0.09 mmol), $Pd(PPh_3)_4$ (11 mg, 0.009 mmol) and **17bb** (23 mg, 0.05 mmol) in DMA (0.6 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3). The title product was obtained as a white solid (10 mg, 41%), m.p. (Et_2O) 185–187 °C. IR (KBr): $\tilde{\nu}$ = 3111, 2928, 1724, 1690, 1213, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.33 (s, 3 H), 3.97 (s, 3 H), 8.19 (d, J = 8.2 Hz, 1 H), 8.21 (s, 1 H), 8.34 (s, 1 H), 8.43 (d, J = 8.2 Hz, 1 H), 8.46 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (q), 28.4 (q), 52.8 (q), 82.6 (s), 119.4 (d), 128.6 (d), 128.8 (s), 129.4 (d), 129.6 (d), 141.0 (d), 145.1 (s), 147.2 (s), 150.1 (s), 150.2 (s), 151.4 (s), 155.0 (s), 160.6 (s), 161.9 (s), 166.2 (s), 168.3 (s), 191.6 (s) ppm. HRMS: calcd. for $C_{23}H_{21}O_5N_4S_3$ [M + H] 529.0669; found 529.0676.

Methyl (*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]nicotinate (18ca): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (1.6 mL, 0.33 mmol), $Pd(PPh_3)_4$ (38 mg, 0.03 mmol) and **17ca** (101 mg, 0.16 mmol) in DMA (1.9 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 6:4). The title product was obtained as a white solid (69 mg, 66%), m.p. (Et_2O) 107–110 °C.

$[\alpha]_D$ = –38.3 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2975, 1732, 1699, 1385, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.56 (m, 9 H), 1.65 (s, 9 H), 1.92–2.11 (m, 2 H), 2.24–2.49 (m, 2 H), 3.41–3.71 (m, 2 H), 3.89 (br. s, 3 H), 5.13–5.33 (m, 1 H), 7.86 (s, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.18–8.21 (m, 2 H), 8.32 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 and 24.2 (t), 28.4 (q), 28.5 (q), 33.0 and 34.3 (t), 46.8 (t), 53.0 (q), 59.2 and 59.6 (d), 80.6 (s), 82.5 (s), 115.7 and 116.0 (d), 118.7 (d), 120.5 (d), 128.9 (s), 129.5 (d), 138.1 (d), 149.8 (s), 150.1 (s), 151.1 (s), 154.1 (s), 154.1 (s), 160.6 (s), 162.3 (s), 168.7 (s), 169.2 (s) ppm. HRMS: calcd. for $C_{30}H_{34}O_6N_5S_3$ [M + H] 656.1666; found 656.1666.

Methyl 2-(2-Acetylthiazol-4-yl)-6-[4-(*tert*-butoxycarbonyl)thiazol-2-yl]nicotinate (18cb): The reaction was performed according to the general procedure for Negishi cross-coupling by using **9** (1.4 mL, 0.30 mmol), $Pd(PPh_3)_4$ (34 mg, 0.03 mmol) and **17cb** (61 mg, 0.15 mmol) in DMA (1.9 mL). The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 8:2). The title product was obtained as a yellowish solid (26 mg, 39%), m.p. (Et_2O) 129–133 °C. IR (KBr): $\tilde{\nu}$ = 2977, 2929, 1730, 1690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.72 (s, 3 H), 3.92 (s, 3 H), 8.05 (d, *J* = 8.2 Hz, 1 H), 8.20 (s, 1 H), 8.37 (d, *J* = 8.2 Hz, 1 H), 8.50 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (q), 28.4 (q), 52.8 (q), 82.6 (s), 119.2 (d), 127.2 (d), 128.7 (s), 129.6 (d), 138.5 (d), 149.1 (s), 150.2 (s), 151.4 (s), 155.2 (s), 160.5 (s), 166.5 (s), 168.3 (s), 168.6 (s), 191.5 (s) ppm. HRMS: calcd. for $C_{20}H_{20}O_5N_3S_2$ [M + H] 446.0839; found 446.0843.

Isopropyl 2-Bromothiazole-4-carboxylate (20): A solution of lithium hydroxide (1.16 g, 27.62 mmol) in H_2O (13 mL) was added to a stirring solution of ethyl 2-bromothiazole-4-carboxylate[10] (3.26 g, 13.81 mmol) in THF (130 mL). The mixture was stirred at room temp. for 18 h and then concentrated under vacuum before aqueous HCl (2 M, 150 mL) was then added. The resulting mixture was extracted with EtOAc (3 × 200 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting white solid was dissolved in dry CH_2Cl_2 (28 mL) and cooled in an ice/water bath. Oxalyl chloride (2.3 mL, 27.68 mmol) and dimethylformamide (DMF; 3 drops) were added dropwise and the resulting mixture was stirred allowing it to reach room temp. After 1 h all volatiles were evaporated under reduced pressure. The residue was dissolved in *i*PrOH (100 mL) and stirred for 2 h. Volatiles were evaporated and the crude product purified by silica flash column chromatography (hexanes/EtOAc, 95:5). The title product was obtained as a white solid (2.80 g, 81%), m.p. (CH_2Cl_2) 58–59 °C. IR (KBr): $\tilde{\nu}$ = 3084, 2975, 1713, 1431, 1226, 1111, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.2 Hz, 6 H), 5.27 (h, *J* = 6.2 Hz, 1 H), 8.08 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (q), 69.6 (d), 130.5 (d), 136.6 (s), 147.7 (s), 159.7 (s) ppm. HRMS: calcd. for $C_7H_8BrNO_2S$ [M + H] 249.9531; found 249.9532.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-6-[4-(ethoxycarbonyl)thiazol-2-yl]-3-[5-methyl-4-(methoxycarbonyl)oxazol-2-yl]pyridine (23): A solution of **21** in DMA (0.21 M, 2.2 mL, 0.456 mmol) was added to a Schlenk tube charged with **17aa** (40 mg, 0.057 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol). The mixture was stirred at 45 °C. After 2 h EtOAc (20 mL) the mixture was added and washed with H_2O (2 × 5 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 9:1 to 1:1). The desired product was obtained as a yellowish solid (32 mg, 79%), m.p. (CH_2Cl_2) decomp. above 106 °C. $[\alpha]_D$ = –34.7 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3122, 2975, 2924, 1694, 1386, 1239, 1201, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.59 (m, 12 H), 1.91–2.07 (m, 2 H), 2.17–2.46 (m, 2 H), 2.53 (s, 3 H); 3.36–3.70 (m, 2 H), 3.96 (s, 3 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 5.09–5.29 (m, 1 H), 7.39 (br. s, 1 H), 8.20 (s, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 8.32 (s, 1 H), 8.37 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 14.7 (q), 23.6 and 24.3 (t), 28.6 and 28.8 (q), 33.1 and 34.4 (t), 46.9 and 47.3 (t), 52.4 (q), 59.3 and 59.6 (d), 62.0 (t), 80.7 (s), 115.1 and 115.5 (d), 118.9 (d), 121.6 (d), 122.8 (s), 128.7 (s), 130.5 (d), 141.0 (d), 149.0 (s), 149.1 (s) 151.4 and 151.5 (s), 154.2 (s) and 154.4 (s), 157.1 (s), 159.0 (s), 161.6 (s); 162.1 (s), 163.2 (s), 169.1 (s), 176.7 (s) ppm. HRMS: calcd. for $C_{32}H_{33}N_6O_7S_3$ [M + H] 709.1590; found 709.1567.

(*S*)-2-{2′-[*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-2,4′-bithiazol-4-yl}-3-[5-methyl-4-(methoxycarbonyl)oxazol-2-yl]-6-[4-(isopropoxycarbonyl)thiazol-2-yl]pyridine (24): A solution of **22** in DMA (0.21 M, 9.2 mL, 1.94 mmol) was added to a Schlenk tube charged with **17aa** (170 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (55 mg, 0.05 mmol). The mixture was stirred at 45 °C. After 16 h EtOAc (50 mL) the mixture was added and washed with H_2O (4 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica flash column chromatography (hexanes/EtOAc, 7:3 to 6:4). The desired product was obtained as a pale solid (148 mg, 85%), m.p. (CH_2Cl_2) decomp. above 130 °C. $[\alpha]_D$ = –37.2 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3122, 2975, 1700, 1386, 1239, 1214, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.53 (m, 15 H), 1.89–2.03 (m, 2 H), 2.18–2.45 (m, 2 H), 2.53 (s, 3 H), 3.36–3.68 (m, 2 H), 3.96 (s, 3 H), 5.10–5.36 (m, 2 H), 7.39 (br. s, 1 H), 8.20 (s, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 8.28 (s, 1 H), 8.38 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (q), 22.3 (q), 23.6 and 24.3 (t), 28.6 and 28.8 (q), 33.1 and 34.4 (t), 46.9 and 47.3 (t), 52.4 (q), 59.3 and 59.7 (d), 69.6 (d), 80.7 (s), 115.1 and 115.5 (d), 118.9 (d), 121.6 (d), 122.8 (s), 128.7 and 128.9 (s), 130.2 (d), 141.0 (d), 149.1 (s), 149.4 (s), 151.4 and 151.6 (s), 154.2 and 154.5 (s), 157.2 (s), 159.0 (s), 161.2 (s), 162.1 (s), 163.2 (s), 169.0 (s), 176.7 (s) ppm. HRMS: calcd. for $C_{33}H_{35}O_7N_6S_3$ [M + H] 723.1735; found 723.1724.

Supporting Information (see footnote on the first page of this article): General procedures and NMR spectra of compounds **2**, **4**, **5**, **7**, **8**, **10**, **14**, **15a**–**15c**, **16aa**–**16cb**, **17aa**–**17cb**, **18aa**–**18cb**, **20**, **23** and **24** as well as those of non-numbered intermediates.

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