First Total Synthesis of Phenylpyridine Analogues of the Antimitotic Rhazinilam

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The first synthesis of phenylpyridine analogues of rhazinilam and evaluation of these new structures as inhibitors of microtubule disassembly by interaction with tubulin are described. The synthesis is based on such key steps as picolinic metalation, hetero-ring cross-coupling and reduction of an acetyl group to an ethyl group. Elaboration of a quaternary picolinic carbon is one of the challenges of the synthesis. Biological evaluation of compounds bearing a quaternary picolinic carbon showed interactions with tubulin similar to (−)-rhazinilam but at a lower level.

Introduction

(−)-Rhazinilam **1** (Figure 1) is an axially chiral phenylpyrrole compound which has been isolated from various Apocynaceae species.[1−3] Biological studies showed that rhazinilam exhibited the same behavior as paclitaxel (Taxol) on mammalian cells.[4] It induces both microtubule bundling in interphase and blocks mitotic cells in aster-like structures. In vitro, this antimitotic compound induces spiralization of tubulin (vinblastine effect) and inhibits the cold-induced disassembly of microtubules (paclitaxel effect). The naturally occurring (−)-rhazinilam **1** is found as a sole enantiomer, and it should be noted that the nonnatural enantiomer is inactive.[2] Structurally, the dihedral angle characterizing the phenylpyrrolic linkage of **1** is 95°, and the amide conformation is cis.[5]

Despite its biological interest, (−)-rhazinilam **1** suffers from lack of activity in vivo. This prompted synthetic chemists to prepare structural analogues of **1**. Thus, a number of phenylpyrroles **2** were obtained, by total synthesis,[6] biosynthetic-like schemes[7−10] or modification[7] of **1**. Recently, the team of Françoise Guéritte and Daniel Guénard focused on the synthesis of biphenyls[11] **3** mimicking the structure of (−)-rhazinilam and studied the replacement of the lactam moiety by a lactone, urea, or best, by a carbamate group.[12] These biphenyl compounds showed an activity on microtubule disassembly very close to that of (−)-rhazinilam, and carbamate (−)**-4** was even twice as active as **1**.[11,12] This work established the first features needed for maximum antitubulin activity. Thus, the presence of a biaryl unit sustaining a nine-membered ring is crucial, as well as a quaternary center at the 13 position, mimicking the stereogenic carbon of **1**. Moreover, only one atropoisomer retains the activity of a racemate.

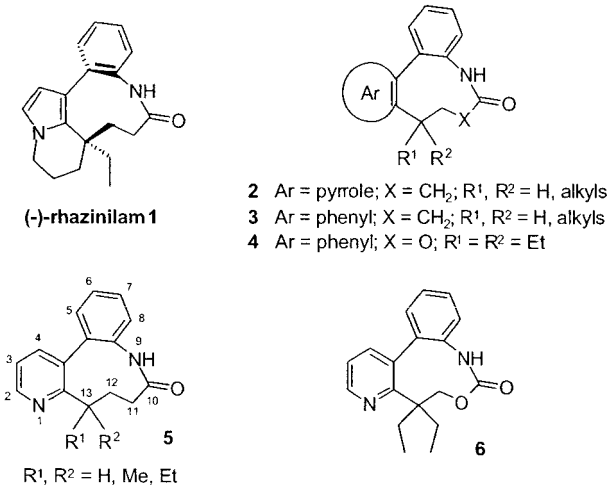

Figure 1.

As part of the studies in this series, we considered the synthesis of phenylpyridine analogues **5** and **6**. This choice was confirmed by molecular modeling studies showing that compounds **5** and **6** fitted well the confor-

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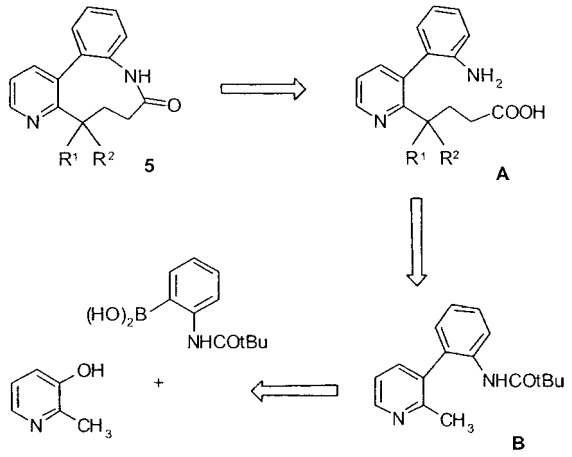
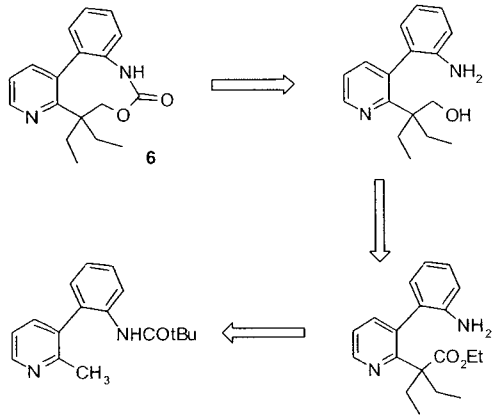
Scheme 1



Scheme 2



mation of **1**. Previously, we reported synthetic methodologies toward simple pyridinic models bearing a quaternary picolinic carbon.[13] Here, we wish to report the first total synthesis of phenylpyridine analogues **5** and **6** of rhazinilam, their antitubulin activity, and discuss interesting features of some atropoisomeric structures encountered during this work (Figure 1).

Retrosynthesis

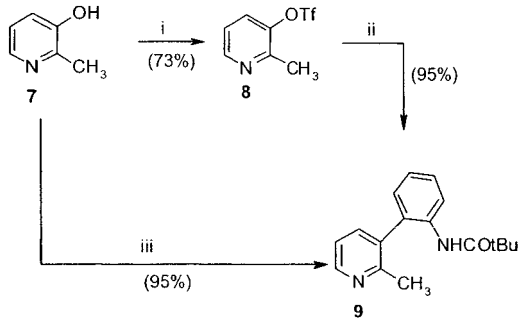
A retrosynthetic analysis suggests that phenylpyridine analogues **5** could be prepared by cyclization of amino acid **A**. The latter could be obtained from key compound **B**, using a previously described route[13] mainly consisting of dialkylation and cyanoethylation. Biaryl **B** would arise from a cross-coupling reaction[14] between the required benzene and pyridine building blocks (Scheme 1).

Our approach is based on installing the biaryl unit early in the synthesis, followed by elaboration of the quaternary picolinic carbon. Indeed, Guéritte et al. showed the sensitivity of cross-coupling toward steric hindrance in biphenyl series.[11] Concerning carbamate **6**, our retrosynthetic approach is quite similar, as outlined in Scheme 2.

Results and Discussion

Analogues with a secondary and tertiary picolinic carbon. Commercially available 3-hydroxy-2-methylpyridine **7** was used as starting material to synthesize biaryl **9**. Treatment of **7** with triflic anhydride in pyridine[15] at room temperature led to the corresponding triflate **8** in a 73% yield. A cross-coupling reaction, using Suzuki conditions,[14] was then carried out between triflate **8** and 2-pivaloylaminophenylboronic acid[16] to afford biaryl **9** in very good yield. However, a better synthesis of **9** was designed by using a "one-pot" procedure, thus avoiding the tedious isolation of triflate **8** (Scheme 3).

Scheme 3[a]



[a] (i) Tf_2O, pyridine, 20 °C, 75 min. (ii) 1.3 equiv of 2-pivaloylaminophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 M, toluene, EtOH, 6 h reflux (N_2). (iii) Tf_2O, pyridine, 20 °C, 45 min; then 1.2 equiv of 2-pivaloylaminophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 M, toluene, EtOH, 80 °C, 3 h (N_2).

The next step of the work consisted in introducing the desired alkyl chains at the picolinic position. Thus, treatment of **9** with *n*-BuLi at low temperature followed by quenching with ethyl iodide yielded 75% of propyl product **10**, together with a small amount of pentyl derivative **11**. Compound **12** was obtained similarly in good yield, after metalation of **10** by using the superbasic mixture *n*-BuLi/*t*-BuOK/diisopropylamine ("KDA").[13,17−18] It should be noted that 3−3.5 equiv of base were needed in each case for complete deprotonation (Scheme 4).

To introduce the future carbon chain of the lactam ring, we considered the reaction of alkylpyridines **9**, **10**, and **12** with 4-bromobutene.[13] Compounds **9** and **10** were thus successfully metalated by *n*-BuLi and afforded the corresponding alkenes **13** in good yields (Scheme 5). However, the more hindered compound **12** was found to be inert toward metalation with strongly basic agents, even when treated by the superbasic KDA. Whatever the conditions used, the characteristic deep red color of picolinic anions could not be observed. The same unsuccessful results were obtained with the parent compound bearing an isopropyl moiety at the 2-position. Direct quaternization of the picolinic carbon, a successful process on 2-isopropylpyridine[19] and even more hindered alkylpyridines,[13] was therefore not applicable to our compounds arylated at the 3-position.

Nevertheless, we were still able to carry out the quick total synthesis of C-13 secondary and tertiary analogues of rhazinilam. Thus, oxidative cleavage of the double bond of compounds **13** by potassium permanganate in weekly acidic medium[20] led to the hard-to-extract corresponding

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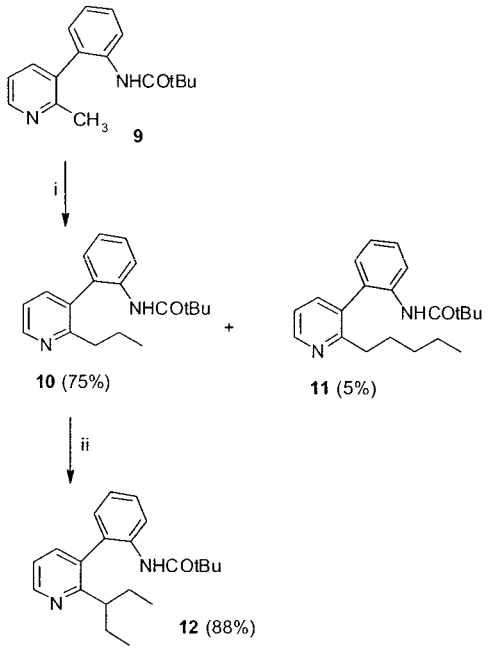
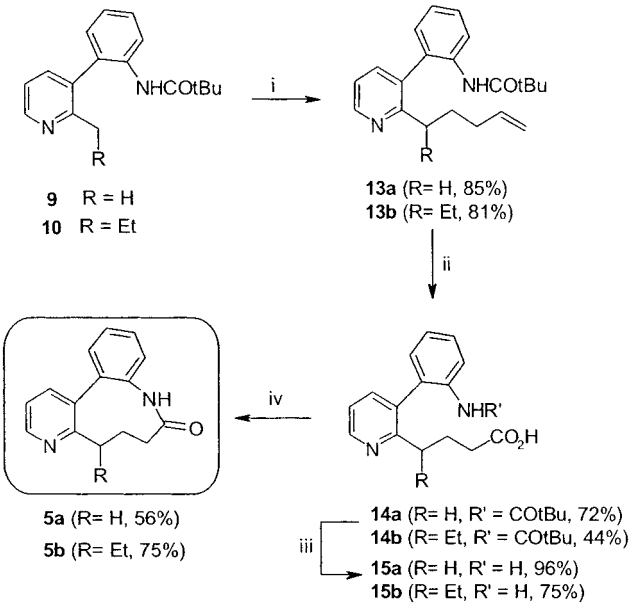
Scheme 4[a]



[a] (i) (1) 3.1 equiv of *n*-BuLi, THF, −20 °C, 1 h; (2) EtI, −50 °C, 30 min. (ii) 1) 3.5 equiv of KDA, THF, −50 °C, 30 min; (2) EtI, −70 °C, 15 min.

Scheme 5[a]



[a] (i) (R = H) 1) 3.1 equiv of *n*-BuLi, THF, −20 °C, 1 h; (2) 4-bromobutene, −50 °C → 0 °C, 1 h. (R= Et) (1) 3.5 equiv equiv KDA, −50 °C, 30 min; (2) 4-bromobutene, −40 °C, 40 min. (ii) $KMnO_4$, AcOH, H_2O, 20 °C, 1 h (R = H) or 5h (R = Et). (iii) H_2SO_4 30%, 160 °C, 2h then NH_4OH 25%. (iv) HOBT, EDCI, NEt_3, CH_2Cl_2, 40 °C/24 h (R = H) or 20 °C/48 h (R = Et).

acids **15** in moderate to good yields. Other systems such as O_3[21] and $KIO_4/RuCl_3$[22] did not provide better results. Cleavage of the pivaloyl moiety with hot aqueous sulfuric acid afforded amino acids **15**. Finally, highly diluted cyclization[11] of the latter compounds, **15**, led to the desired analogues **5a**,**b** (Scheme 5).

It should be noted that lactam **5b**, bearing a stereogenic carbon besides its axial chirality, is seen as a single diastereoisomer by NMR and HPLC analysis (even at 5 °C). This means that either rotation around the biarylic linkage is not restricted enough (the signals would then be found at a weighted average value for the two conformers), or there is only indeed one diastereoisomer, the other one being disfavored on steric considerations.[11,23]

Analogues with a Quaternary Picolinic Carbon. Treatment of **9** with *n*-BuLi at low temperature followed by action of dimethylacetamide[13,24] led to the corresponding pyridylacetone **16** with a good conversion factor (7% of unreacted starting material remained and was inseparable from the product). Compound **16** was isolated as a mixture of tautomers, as expected from previous work[24−27] with the ketone **16A**/enol **16B** ratio being 9:1 in $CDCl_3$. Action of 1 equiv of *n*-BuLi on **16**, followed by alkylation, afforded compounds **17** in good yields (Scheme 6). These conditions avoided dialkylation, except for methylation with methyl iodide. Quaternization of the picolinic carbon and introduction of the desired cyanoethyl moiety were best achieved by treatment of ketones **17** with acrylonitrile in the presence of benzyltrimethylammonium hydroxide[28] to give derivatives **18**. In the case of **17b** (R = Et), reactivity was low at the picolinic carbon, and tricyanoethylated compound **19** was obtained as a byproduct. Interestingly, the wanted Michael-adduct **18b** was not protonated by HCl on the pyridinic nitrogen, which allowed an easy separation of **18b** and recovery of starting ketone **17b** (Scheme 6).

Atropisomeric Phenomenon. Compounds **18** have bulky substituents in the ortho-position, thus inducing a restricted rotation around the biaryl bond. Since these compounds possess already a stereogenic picolinic carbon, two diastereoisomers are expected. This phenomenon was observed by ^{1}H NMR analysis where most of the spectra were doubled. We particularly studied the behavior of **18a** and **18b** in solution, where the two diastereoisomers were found to be in thermodynamic equilibrium, due to slow rotation around the biaryl bond. We were able to isolate the major isomer by precipitation from a mixture of ethyl acetate and light petroleum. The ^{1}H NMR spectrum of the freshly dissolved solid showed only a single set of signals, whereas that of the mother liquor exhibited the two types of signals previously observed. Conversion of this pure diastereoisomer to the thermodynamic mixture was monitored by ^{1}H NMR and was found to be much faster in DMSO-d_6 than in $CDCl_3$. At higher temperature, the interconversion rate was increased markedly (Table 1). The diastereoisomeric ratios at equilibrium were about the same for the two products, i.e., ca. 3:1 in $CDCl_3$ and ca. 2:1 in DMSO.

These experiments allowed us to calculate the rotation barriers[29] at 25 °C in $CDCl_3$: 22.6 and 23.7 kcal/mol,

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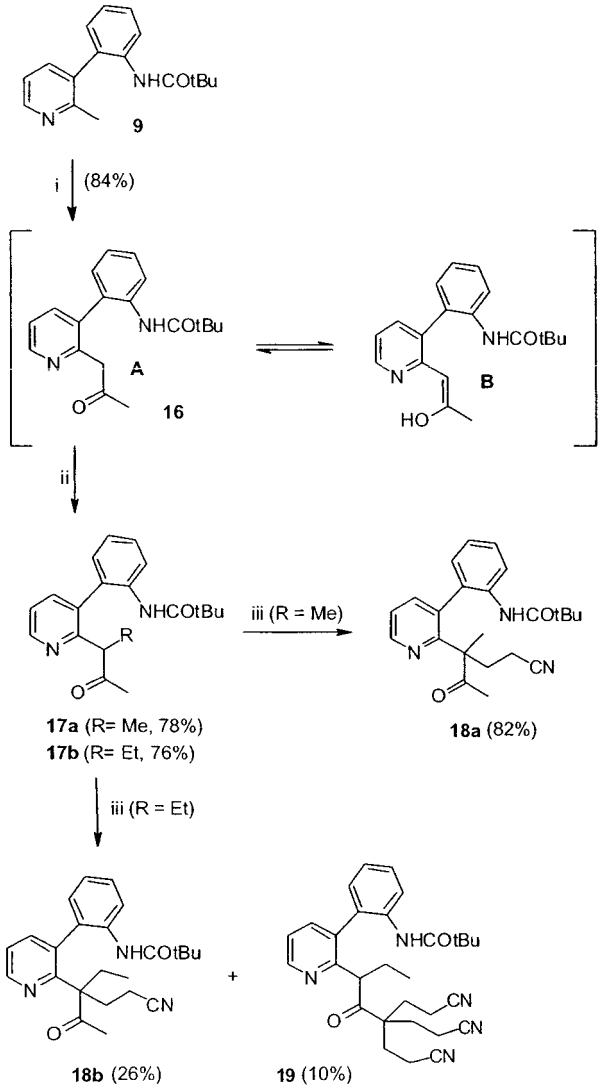
Scheme 6[a]



[a] (i) (1) 1.1 equiv of *n*-BuLi, THF, −20 °C, 1 h; (2) CH_3CONMe_2, −70 °C, 30 min then H_2O. (ii) (1) 1 equiv of *n*-BuLi, THF, −70 °C/10 min then −70 °C → 20 °C in 40 min; (2) 1−1.2 equiv RI, 20 °C/16 h (R= Me) or reflux/16 h (R = Et). (iii) acrylonitrile, $BnMe_3N^+OH^-$, *t*-BuOH, 25 °C, 16 h (R = Me) or 7 days (R = Et).

Table 1. Diastereoisomeric Ratio

product	solvent	temp (°C)	diastereoisomeric ratio (at equilibrium)	time (in hours) needed to reach equilibrium
18a	$CDCl_3$	25	3.1:1	25
		40	3.1:1	4
	DMSO-d_6	22	2:1	1.5
18b	$CDCl_3$	25	3.1:1	98
		40	3.1:1	10
	DMSO-d_6	25	2.2:1	2

respectively, for **18a** (R = Me) and **18b** (R = Et). These values, indicative of the presence of true atropoisomers, are quite unusual for biaryl compounds with only one substituent at each ortho-position. Contrary to this, tertiary compounds **17** showed a very quick interconversion at room temperature (NMR and HPLC), thus indicating the presence of conformers rather than diastereoisomers.[30] In the next part, all the compounds will be described as only one product, even if they exist as

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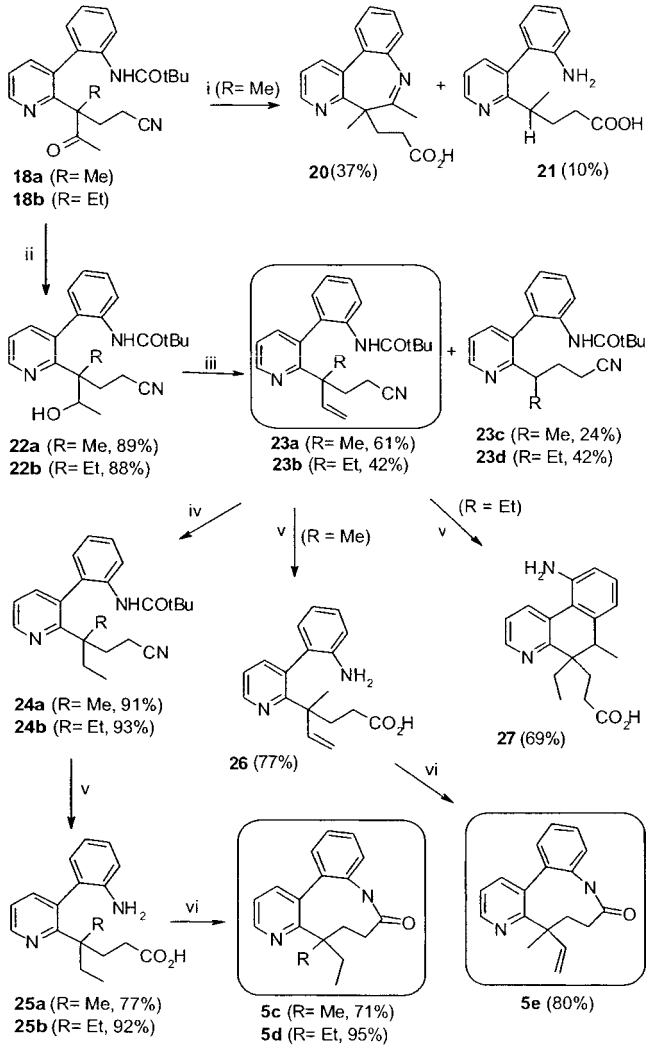
Scheme 7[a]



[a] (i) (R = Me) (1) $NH_2NH_2 \cdot H_2O$, ethylene glycol, 150−160 °C, 4 h, (2) KOH, 160 °C, 3 h then HCl. (ii) $NaBH_4$, EtOH, 20 °C, 4 h (R = Me) or 16 h (R = Et). (iii) HMPA, 1 equiv H_2SO_4, 215−220 °C/1 h (R = Me) or 220−225 °C/1.5 h (R = Et). (iv) H_2, Pd−C, MeOH, 1 atm, 20 °C, 1 h. (v) H_2SO_4 30%, 160 °C, 2 h then NH_4OH 25%. (vi) HOBT, EDCI, NEt_3, $CHCl_3$, 36 h, reflux (R = Me) or 50 °C (R = Et).

two or more diastereoisomers (see Experimental Section for diastereoisomeric ratios).

Reduction of Keto Derivatives 18 to Alkanes. The modified Wolff−Kishner conditions used with success for model studies[13] were inapplicable. Despite the formation—at least partially—of the hydrazone derived from **18a**, as evidenced by ^{1}H NMR, basic treatment of the latter did not afford the desired alkane. Instead, imine **20** was isolated, together with a small amount of the strong base-induced deacetylated product[31,32] **21** (Scheme 7). To avoid these unwanted reactions, ketones **18** were first reduced to the corresponding alcohols **22** with $NaBH_4$ and then dehydrated to **23** in hot HMPA.[33,34] Provided that a small amount of sulfuric acid was added, the latter key reaction was clean, but we could not totally avoid the formation of byproducts **23c**,**d** due to ethanolic chain cleavage. Vinyl compounds **23a**,**b** were then converted to alkanes

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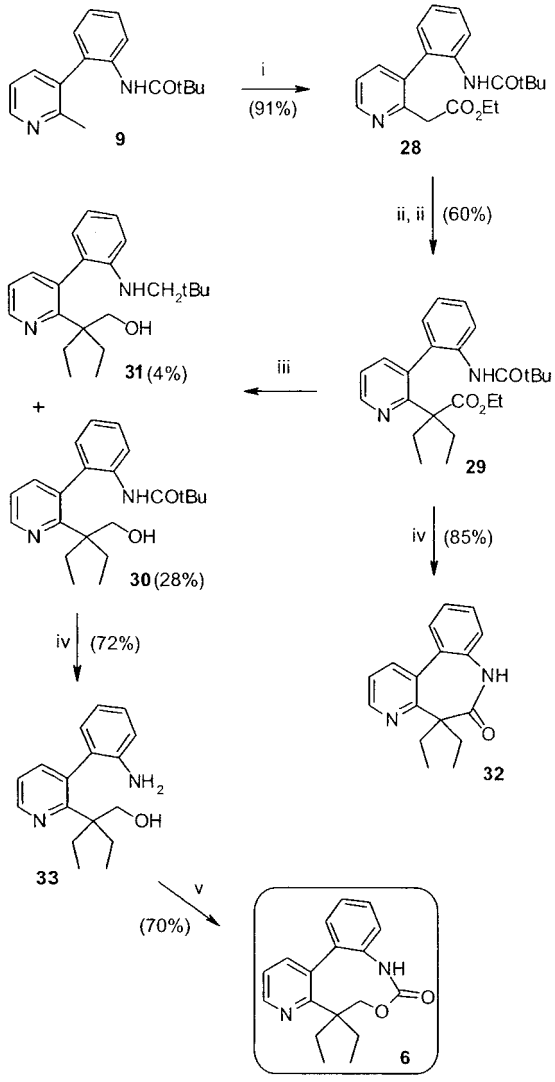
24a,**b** by a catalytic hydrogenation. The resulting amines were finally deprotected to the corresponding amino acids **25** by aqueous sulfuric acid treatment. ^{1}H NMR indicated that the latter adopted a zwitterionic-type structure in $CDCl_3$, it was not the case in DMSO. After cyclization, using the HOBT/EDCI system, target lactams **5c**,**d** were obtained in good yields (Scheme 7). Starting from **25a** (diastereoisomeric ratio 1:1), lactamization gave a diastereoisomeric ratio of 2.7:1 for **5c**, each of which could be separated by HPLC.

Following a similar strategy, an analogue with a vinyl appendage **5e** was prepared from **23a**. Interestingly, attempted amine deprotection of alkene **23b** led to a tricyclic product **27**, probably via a S_EAr2 process (Scheme 7).

Carbamate Analogue. Starting with our key intermediate **9**, we were able to synthesize an analogue with a cyclic carbamate functionality. Again, the strategy involves the introduction of an activating group at the picolinic position, namely an ester. Thus, treatment of **9** with *n*-BuLi/*t*-BuONa/diisopropylamine[35] ("NDA") at low temperature, followed by reaction of the resulting anion with diethyl carbonate yielded 91% of the corresponding ester **28**. Diethylation of the latter gave 60% of **29**. The $LiAlH_4$ reduction of **29** was quite difficult, and only 28% (best conditions) of the corresponding alcohol **30** were obtained. We recovered 64% of starting material together with 4% of product **31** arising from reduction of both ester and amide functionalities. The presence of the latter compound prevented us from using higher temperature and/or reaction times. To circumvent the problematic reduction of amidoester **29**, we considered its prior hydrolysis to the corresponding amino acid which could be reduced more easily. However, treatment of **29** with aqueous H_2SO_4 did not afford the target compound, but rather the seven-membered ring lactam **32**. Therefore, we had to carry on the synthesis from hydroxy amide **30**, which was hydrolyzed to the corresponding amino alcohol **33**. Treatment of the latter with triphosgen[12,36] ($Cl_3COCO_2CCl_3$) led to the desired analogue **6** possessing a carbamate function (Scheme 8) (AB-type signals were observed by ^{1}H NMR for CH_2 protons throughout this synthesis, again highlighting the asymmetry brought by the biaryl linkage).

Biological Results. Besides the synthesis of new tricyclic hindered phenylpyridine lactams, the aim of this study was to show if the phenylpyrrole moiety of rhazinilam **1** could be replaced by a phenylpyridine system without affecting the interaction with tubulin. The novel phenylpyridine compounds **5** and **6** were tested, under their racemic form, for their ability to inhibit the cold-disassembly of microtubules.[7] Each diastereoisomers **5c** and **5e** were assayed separately after separation by HPLC. Compounds **5a, 5b**, and **5c** were found inactive, whereas **5d**, **5e** (major diastereoisomer), and **6** interact with tubulin**.** This implies that the bulkiness of the substituents at the picolinic carbon is important for antitubulin activity. Compared to rhazinilam **1** (IC_{50} = 3 μM), compounds **5d**, **5e**, and **6** were, respectively, 9.5, 14, and 6 times less active. All three analogues possess similar activity to that of the biphenyl **3** (R = Et, IC_{50} = 24 μM),[11,12] and modification of the lactam to an urethane function increases the activity. Thus, compound **6** (IC_{50} = 18μM) is slightly more active than **5d** (IC_{50} = 28μM), but possesses a weaker activity as compared to racemic biphenyl **4** (IC_{50} = 3 μM). Knowing the acidic character of tubulin, the lower activity of **5d** and **6** may be due to the protonation of the pyridine ring leading to an unfavorable charge distribution[37] for the interaction with tubulin. It must be mentioned that the overall conformation and charge distribution[37] of **5d** and **6** is similar to that of the biphenyl compounds **3** (R = Et) and **4**, respectively. Regarding the cytotoxicity of the compounds on KB cells,[38] there is a good correlation with the microtubules disassembly assay, compound **6** being the most cytotoxic but 8 times less cytotoxic than rhazinilam (IC_{50} = 2 μM).

Scheme 8[a]



[a] (i) (1) 3.5 equiv of NDA, THF, −70 °C, 1 h; (2) 3.5 equiv of $(EtO)_2CO$, −70 °C, 40 min. (ii) (1) 3.1 equiv of LDA, THF, −70 °C, 10 min; (2) 3.1 equiv of EtI, −70 °C → 20 °C, 3 h, (3) idem. 1. (4) idem. 2. (iii) $LiAlH_4$, THF, 40 °C, 4 h. (iv) H_2SO_4 30%, 160 °C, 2 h then NH_4OH 25%. (v) $Cl_3COCO_2CCl_3$, DMAP, CH_2Cl_2, −70 °C, 15 min then −70 °C → 20 °C, 4 h.

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(37) Molecular modeling studies were performed on a Silicon Graphics Indigo II (R10000) workstation, using Sybyl from Tripos (force field: MMFF94) for the generation of conformers and MOPAC (AM1) for evaluation of charge distribution.

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Conclusion

For the first time, analogues of rhazinilam **1** possessing a phenylpyridine structure were prepared. Lactams bearing a secondary or tertiary picolinic carbon were first obtained, thanks to key steps such as lateral metalation and cross-coupling. The synthesis of lactams with a quaternary picolinic carbon was then achieved, the reduction of an acetyl group to an ethyl group being the crucial step. Compounds **5** were obtained in five to nine steps with overall yields of 5.1% to 31.3% depending on the structure. In this pyridine series, biological assays showed that a fully substituted picolinic carbon was needed for interaction of the lactams with tubulin, as evidenced in pyrrole or phenyl series. However, the best results were obtained for cyclic carbamate **6**, which was synthesized using a similar strategy. Racemic **6** is six times less active than the parent (−)-rhazinilam **1**, which means that the active enantiomer of the former would be only three times less active than **1**. The strategy is currently being extended to the preparation of other phenylpyridine analogues of rhazinilam.

Experimental Section

General Data. See refs 16 and 19. Organic layers were dried with $MgSO_4$. Silica gel was used for all flash chromatographies. $^1H-^1H$ NMR coupling constants for aromatic protons and ethyl moiety are consistent with those of the literature and are given in hertz.

2,2-Dimethyl-*N*-(2-(2-(1-ethylprop-1-yl)-3-pyridyl)phenyl)propanamide (12). To a suspension of potassium *tert*-butoxide (363 mg, 3.2 mmol) in THF (4 mL) was added diisopropylamine (0.45 mL, 3.2 mmol). The mixture was cooled to −70 °C, and *n*-BuLi (1.3 mL, 3.2 mmol) was slowly added. The reaction mixture was then warmed to −50 °C over 15 min before adding a solution of propylpyridine **10** (274 mg, 0.92 mmol) in THF (2 mL). After 30 min of stirring and then cooling to −70 °C, iodoethane (0.28 mL, 3.5 mmol) was added dropwise. After 15 min of stirring at −70 °C the reaction mixture was hydrolyzed (3 mL of water), followed by extraction with CH_2Cl_2. The combined organic extracts were dried, and the solvent was evaporated. The residue was subjected to chromatography (1:9 EtOAc/cyclohexane) to yield **12** (263 mg, 88%), as a white solid, mp 137 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 0.62 (t, J = 7.3, 3H), 0.75 (t, J = 7.3, 3H), 1.00 (s, 9H), 1.61 (q, J = 7.3, 4H), 2.47 (q, J = 7.3, 1H), 6.96 (br s, 1H), 7.12 (m, 3H), 7.45 (m, 2H), 8.36 (d, J = 8.1, 1H), 8.69 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9, 12.2, 27.0, 27.9, 39.4, 45.4, 120.2, 120.9, 123.3, 128.6, 129.0, 129.7, 132.4, 135.4, 137.2, 149.5, 163.8, 175.7. IR (KBr) 3334, 1647 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O$ (324.47): C, 77.74; H, 8.70; N, 8.63. Found: C, 77.57; H, 8.65; N, 8.59.

2,2-Dimethyl-*N*-(2-(2-pent-4-enyl-3-pyridyl)phenyl)propanamide (13a). The same procedure as for the synthesis of **10** (see Supporting Information) was applied to picoline **9** (3.76 g, 14 mmol), reacting 4-bromobut-1-ene as electrophile over 1 h while raising the temperature from −50 °C to 0 °C. The residue was Kugelrohr distilled (180 °C/0.6 mbar) to yield **13a** (3.85 g, 85%), as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.64−1.96 (m, 4H), 2.60 (m, 2H), 4.86 (d, J = 10.4, 1H), 4.89 (d, J = 17.0, 1H), 5.65 (ddt, J = 17.0, 10.4, 6.5, 1H), 6.95 (br s, 1H), 7.16 (m, 2H), 7.26 (dd, J = 7.6 and 4.8, 1H), 7.44 (m, 1H), 7.51 (dd, J = 7.6 and 1.8, 1H), 8.37 (d, J = 8.2, 1H), 8.66 (dd, J = 4.8 and 1.8, 1H). IR (thin film) 3346, 1692 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O$ (322.45): C, 78.22; H, 8.13; N, 8.69. Found: C, 77.88; H, 8.11; N, 8.62. Refractive index: η^{20}_D = 1.5515.

2,2-Dimethyl-*N*-(2-(2-(1-ethylpent-4-enyl)-3-pyridyl)-phenyl)propanamide (13b). The same procedure as for the synthesis of **12** was applied to the propyl compound **10** (2.075 g, 7 mmol) reacting 4-bromobut-1-ene as electrophile at −40 °C for 40 min. The residue was Kugelrohr distilled (180 °C/0.6 mbar) to yield **13b** (1.99 g, 81%), as an orange viscous oil (1:1 mixture of diastereoisomers). ^1H NMR (200 MHz, $CDCl_3$) δ 0.65, 0.79 (2d, J = 7.4, 3H), 1.03 (s, 9H), 1.60−1.94 (m, 6H), 2.62 (m, 1H), 4.86 (m, 2H), 5.65 (m, 1H), 6.91 (br s, 1H), 7.18 (m, 3H), 7.42 (m, 1H), 7.48 (m, 1H), 8.39 (d, J = 8.2, 1H), 8.72 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 12.2, 27.1, 27.3, 28.0, 31.6, 31.9, 34.0, 34.2, 39.6, 43.5, 43.6, 114.2, 114.5, 120.5, 121.0, 123.4, 128.8, 128.9, 129.8, 129.9, 132.4, 132.5, 135.5, 137.5, 137.8, 138.5, 149.7, 163.8, 163.9, 176.0. IR (thin film) 3365, 1692, 1001, 916 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O$ (350.51): C, 78.82; H, 8.63; N, 7.99. Found: C, 78.98; H, 8.63; N, 8.11. Refractive index: η^{20}_D = 1.5508.

10,11,12,13-Tetrahydro-9*H*-benzo[*b*]pyrido[3,2-*d*]azonin-10-one (5a). This procedure is general for the lactamization of amino acids. To a suspension of HOBT (297 mg, 2.2 mmol), EDCI (422 mg, 2.2 mmol), and amino acid **15a** (564 mg, 2.2 mmol) in ethanol-free CH_2Cl_2 (1300 mL) was added triethylamine (306 μL). The mixture was stirred at 40 °C for 24 h, after which the solvent was evaporated. The residue was subjected to chromatography (95:5 CH_2Cl_2/MeOH) to yield **5a** (294 mg, 56%), as a yellow solid, mp 192 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.06 (m, 2H), 2.26 (m, 1H), 2.82 (m, 1H), 7.06 (dd, J = 7.6 and 4.8, 1H), 7.22 (dd, J = 7.6 and 1.8, 1H), 7.25 (m, 2H), 7.40 (m, 2H), 7.78 (br s, 1H), 8.51 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.9, 33.9, 36.9, 120.8, 128.6, 129.0, 129.1, 129.4, 133.7, 136.0, 140.6, 149.4, 158.9, 176.2. IR (KBr) 3168, 1654 cm^{-1}. MS (CI, *t*-BuH) *m*/*z* 239 $(M + H)^+$. Anal. Calcd for $C_{15}H_{14}N_2O$ (238.29): C, 75.60; H, 5.92; N, 11.76. Found: C, 75.39; H, 5.86; N, 11.78.

13-Ethyl-10,11,12,13-tetrahydro-9*H*-benzo[*b*]pyrido-[3,2-*d*]azonin-10-one (5b). The same procedure as above was applied to amino acid **15b** (142 mg, 0.5 mmol), the reaction mixture being stirred at room temperature for 48 h. The solvent was evaporated and the residue chromatographed (9:1 CH_2Cl_2/MeOH) to yield **5b** (100 mg, 75%), as a yellow solid, mp 186 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 0.60 (t, J = 7.2, 3H), 1.48 (m, 1H), 1.73−2.28 (m, 6H), 7.11 (dd, J = 7.6 and 4.8, 1H), 7.23 (br s, 1H), 7.30 (m, 3H), 7.46 (m, 2H), 8.65 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.3, 28.6, 32.8, 34.3, 47.2, 121.5, 129.0, 129.2, 129.4, 129.8, 135.4, 136.4, 137.2, 140.5, 148.9, 160.9, 176.2. IR (KBr) 3208, 1648 cm^{-1}. MS (CI, NH_3) *m*/*z* 267 $(M + H)^+$. Anal. Calcd for $C_{17}H_{18}N_2O$ (266.34): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.24; H, 6.88; N, 10.55.

2,2-Dimethyl-*N*-(2-(2-(1-(2-oxopropyl)-1-methyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (18a). To a solution of ketone **17a** (1.46 g, 4.5 mmol) in *t*-BuOH (10 mL) were added dropwise $BnMe_3NOH$ (40% solution in methanol, 99 μL, 0.22 mmol) and then acrylonitrile (0.59 mL, 9 mmol). After 16 h of stirring at room temperature, the reaction mixture was hydrolyzed (10 mL of water), followed by extraction with CH_2Cl_2. The organic extract was dried, and the solvent was evaporated. The residue was subjected to chromatography (96:4 CH_2Cl_2/CH_3CN) to yield **18a** (1.39 g, 82%), as a colorless viscous oil (3:1 mixture of diastereoisomers). ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 2.2H), 1.06 (s, 6.8H), 1.35 (s, 2.3H), 1.38 (s, 0.7H), 1.69 (s, 0.7H), 1.76 (s, 2.3H), 2.09−2.67 (m, 4H), 6.89 (br s, 0.25H), 7.09 (br s, 0.75H), 7.16 (m, 2H), 7.30 (m, 1H), 7.40 (m, 2H), 8.05 (d, J = 8.0, 0.75H), 8.06 (d, J = 8.0, 0.25H), 8.61 (dd, J = 4.7 and 1.8, 0.75H), 8.64 (dd, J = 4.7 and 1.8, 0.25H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 13.6, 23.5, 24.9, 26.4, 26.9, 27.7, 34.6, 34.7, 39.9, 58.6, 119.9, 120.5, 122.4, 122.6, 123.9, 124.0, 124.3, 130.1, 130.2, 130.4, 130.6, 131.2. 133.5, 133.6, 136.3, 136.5, 140.6, 140.9, 148.8, 159.3, 159.7, 176.8, 210.3, 211.0. IR (thin film) 2246, 1713, 1689 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_2$ (377.49): C, 73.18; H, 7.21; N, 11.13. Found: C, 73.61; H, 7.25; N, 11.13.

2,2-Dimethyl-*N*-(2-(2-(1-(2-oxopropyl)-1-ethyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (18b). To a solution of ketone **17b** (2.465 g, 7.6 mmol) in *t*-BuOH (100 mL) was added dropwise $BnMe_3NOH$ (40% solution in methanol, 167 μL, 0.38 mmol) and then acrylonitrile (0.75 mL, 11.4 mmol). The mixture was stirred for 7 days, during which several portions of $BnMe_3NOH$ (0.167 mL, 0.38 mmol each portion) and acrylonitrile (0.25 mL, 3.8 mmol each portion)

were added. The solvent was evaporated and the residue taken up in THF (30 mL). 1 N aqueous HCl (20 mL) was added and the mixture stirred at room temperature for 1 h. After decantation and one extraction with Et_2O, the combined organic extracts were dried and concentrated. The residue was subjected to chromatography (9:1 CH_2Cl_2/CH_3CN) to yield **18b** (774 mg, 26%), as a waxy yellow solid (3:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (t, J = 7.5, 2.3H), 0.70 (t, J = 7.5, 0.7H), 0.99 (s, 9H), 1.49 (s, 0.7H), 1.65 (s, 2.3H), 1.67−2.41 (m, 4.5H), 2.58 (m, 1.5H), 6.88 (br s, 0.25H), 6.99 (br s, 0.75H), 7.08 (m, 2H), 7.20 (m, 1H), 7.36 (m, 2H), 7.89 (d, J = 7.7, 0.25H), 7.95 (d, J = 7.7, 0.75H), 8.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.14, 13.0, 13.5, 27.1, 27.6, 28.3, 28.7, 29.9, 31.0, 31.1, 39.8, 61.8, 62.7, 120.5, 122.2, 122.3, 124.2, 124.4, 124.9, 130.0, 130.2, 130.5, 131.3. 131.5, 133.9, 136.3, 136.6, 140.6, 140.8, 148.2, 148.4, 158.2, 158.9, 176.9, 177.0, 210.6, 211.6. IR (thin film) 2247, 1710, 1682 cm^{-1}. Anal. Calcd for $C_{24}H_{29}N_3O_2$ (391.52): C, 73.63; H, 7.47; N, 10.73. Found: C, 73.68; H, 7.54; N, 10.86. During purification, compound **19** was isolated in small amounts.

2,2-Dimethyl-*N*-(2-(2-(1-methyl-1-vinyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (23a). A solution of alcohol **22a** (171 mg, 0.45 mmol) in HMPA (1 mL) containing concd sulfuric acid (12.5 μL) was heated at 220 °C for 1 h. The solvent was removed by Kugelrohr distillation (130 °C/1 mbar) and the residue chromatographed (1:2 EtOAc/petroleum ether) to yield **23a** (99 mg, 61%) as an orange viscous oil (1:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92, 0.93 (2s, 9H), 1.18, 1.23 (2s, 3H), 2.04−2.40 (m, 4H), 4.65, 4.68 (2d, J = 17.4, 1H), 4.70, 4.71 (2d, J = 10.8, 1H), 5.60, 5.66 (2dd, J = 17.4, 10.8, 1H), 6.67, 6.71 (2br s, 1H), 7.03 (m, 2H), 7.26 (m, 1H), 7.33 (m, 2H), 8.13, 8.17 (2d, J = 8.2, 1H), 8.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ. 11.9, 22.2, 23.0, 26.9, 35.9, 38.6, 46.8, 46.9, 112.6, 119.1, 119.4, 120.0, 120.3, 120.5, 120.7, 122.2, 128.1, 128.2, 129.1, 129.6, 129.8. 131.6, 134.6, 139.4, 140.6, 142.0, 147.6, 147.8, 160.7, 161.1, 174.9, 175.0. IR (thin film) 2361, 1001, 919 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O$ (361.49): C, 76.42; H, 7.53; N, 11.62. Found: C, 76.20; H, 7.51; N, 11.54.

2,2-Dimethyl-*N*-(2-(2-(1-Ethyl-1-vinyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (23b). The same procedure as above was applied to alcohol **22b** (177 mg, 0.45 mmol), with a reaction time of 1.5 h to yield **23b** (71 mg, 42%) as a pale yellow viscous oil (1:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59, 0.65 (2t, J = 7.3, 3H), 0.92, 0.94 (2s, 9H), 1.50−2.48 (m, 6H), 4.56, 4.63 (2d, J = 17.6, 1H), 4.66, 4.71 (2d, J = 11.0, 1H), 5.49, 5.54 (2dd, J = 17.6 and 11.0, 1H), 6.67, 6.74 (2br s, 1H), 7.00 (m, 2H), 7.20 (m, 1H), 7.33 (m, 2H.), 8.11, 8.17 (2d, J = 8.0, 1H), 8.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 8.8, 12.6, 12.8, 27.4, 28.6, 29.0, 32.1, 32.2, 39.7, 39.8, 51.0, 51.2, 113.8, 114.8, 120.3, 120.7, 121.1, 121.3, 121.6, 121.8, 123.1, 129.3, 129.7, 130.3, 130.4, 130.7. 133.1, 133.5, 135.9, 139.4, 140.5, 140.6, 140.8, 141.3, 161.1, 161.2, 176.0, 176.1. IR (thin film) 2246, 1001, 919 cm^{-1}. Anal. Calcd for $C_{24}H_{29}N_3O$ (375.52): C, 76.77; H, 7.78; N, 11.19. Found: C, 76.95; H, 7.68; N, 11.21.

During purification of compounds **23a**,**b**, compounds **23c**,**d** were isolated in 24% and 42%, respectively.

2,2-Dimethyl-*N*-(2-(2-(1-ethyl-1-methyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (24a). To a solution of alkene **23a** (166 mg, 0.46 mmol) in methanol (5 mL) was added palladium on carbon (5%, 60 mg, 0.028 mmol). The mixture was stirred at room temperature for 1 h under 1 atm of hydrogen. After a N_2 flush, the mixture was filtered and the filtrate evaporated. The residue was subjected to chromatography (98:2 CH_2Cl_2/MeOH) to yield **24a** (152 mg, 91%) as a white solid (1:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61, 0.64 (2t, J = 7.3, 3H), 0.83, 0.87 (2s, 3H), 0.94 (s, 9H), 1.25−2.25, 2.75 (2m, 6H), 6.77, 6.80 (2br s, 1H), 7.04 (m, 2H), 7.18 (m, 1H), 7.33 (m, 2H), 8.27, 8.29 (2d, J = 8.4, 1H), 8.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 9.6, 13.3, 13.6, 23.3, 24.1, 27.7, 34.6, 36.0, 36.7, 38.3, 40.1, 46.2, 46.4, 112.6, 120.7, 120.9, 121.3, 121.5, 123.6, 123.7, 129.5, 129.9, 130.2, 131.3. 132.8, 133.2, 136.0, 140.9, 148.8, 149.0, 162.6, 162.7, 176.3, 176.4. IR (KBr) 2246, 1683 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_3O$ (363.51): C, 76.00; H, 8.04; N, 11.56. Found: C, 75.83; H, 8.08; N, 11.56.

2,2-Dimethyl-*N*-(2-(2-(1.1-diethyl-3-cyanopropyl)-3-pyridyl)phenyl)propanamide (24b). The same procedure as above was applied to alkene **23b** (173 mg, 0.46 mmol) to yield **24b** (161 mg, 93%) as a pale yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (t, J = 7.3, 3H), 0.61 (t, J = 7.3, 3H), 0.94 (s, 9H), 1.36−1.69 (m, 4H), 1.91−2.33 (m, 4H), 6.78 (br s, 1H), 7.05 (m, 2H), 7.18 (dd, J = 7.7 and 4.8, 1H), 7.33 (m, 2H), 8.28 (d, J = 8.1, 1H), 8.62 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 13.0, 27.6, 27.7, 29.2, 31.6, 40.1, 49.8, 120.7, 121.6, 121.8, 123.8, 129.6, 129.9, 131.5. 133.5, 136.0, 141.7, 148.4, 162.1, 176.5. IR (thin film) 2245, 1687 cm^{-1}. Anal. Calcd for $C_{24}H_{31}N_3O$ (377.53): C, 76.36; H, 8.28; N, 11.13. Found: C, 76.14; H, 8.26; N, 11.11.

4-(3-(2-Anilino)-2-pyridyl)-4-methylhexanoic acid (25a). The same procedure as for the synthesis of **15a** was applied to pivalamide **24a** (131 mg, 0.36 mmol). Chromatography (94:6 CH_2Cl_2/MeOH) yielded **25a** (83 mg, 77%) as a pale brown viscous oil (1:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (t, J = 7.4, 3H), 0.97, 1.04 (2s, 3H), 1.35−2.30, 2.50 (2m, 6H), 6.07 (br s, 3H), 6.67 (m, 2H), 6.88 (m, 1H), 7.12 (m, 2H), 7.31, 7.33 (2dd, J = 7.6 and 1.8, 1H), 8.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 9.6, 23.0, 24.2, 31.2, 35.1, 36.4, 37.1, 46.7, 115.6, 115.9, 118.1, 118.3, 121.6, 127.4, 127.5, 129.3, 130.6, 130.9, 134.7, 135.0, 141.6, 141.8, 143.8, 144.1, 147.7, 147.8, 163.8, 179.2. IR (thin film) 3377, 1617 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.39): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.78; H, 7.41; N, 9.38.

4-(3-(2-Anilino)-2-pyridyl)-4-ethylhexanoic Acid (25b). The same procedure as for the synthesis of **15a** was applied to pivalamide **24b** (136 mg, 0.36 mmol). Chromatography (97:3 CH_2Cl_2/MeOH) yielded **25b** (104 mg, 92%) as a pale brown solid, mp 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (t, J = 7.3, 6H), 1.48−1.68 (m, 4H), 1.95, 2.12 (2m, 4H), 5.50 (br s, 3H), 6.66 (m, 2H), 6.89 (dd, J = 7.4 and 1.5, 1H), 7.13 (m, 2H), 7.31 (dd, J = 7.7 and 2.2, 1H), 8.52 (dd, J = 4.6 and 2.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 8.8, 27.5, 28.9, 30.3, 30.8, 49.8, 115.7, 118.0, 121.5, 127.0, 129.2, 130.3, 134.9, 142.1, 143.6, 147.0, 163.5, 178.1. IR (KBr) 3364, 1625 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.42): C, 73.04; H, 7.77; N, 8.97. Found: C, 73.18; H, 7.78; N, 9.01.

4-(3-(2-Anilino)-2-pyridyl)-4-methylhex-5-enoic Acid (26). The same procedure as for the synthesis of **15a** (see Supporting Information) was applied to pivalamide **23a** (70 mg, 0.19 mmol). Chromatography (9:1 CH_2Cl_2/MeOH) yielded **26** (44 mg, 77%) as a yellow viscous oil (1:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11, 1.18 (2s, 3H), 1.81−2.23 (m, 4H), 4.50, 4.63 (2d, J = 10.2, 1H), 4.55, 4.64 (2d, J = 17.6, 1H), 5.45 (br s, 3H), 5.76, 5.83 (2dd, J = 17.6 and 10.2, 1H), 6.57 (m, 2H), 6.75, 6.80 (2dd, J = 7.5 and 1.1, 1H), 7.03 (m, 2H), 7.27 (m, 1H), 8.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 25.5, 31.8, 37.0, 37.3, 48.3, 48.5, 111.6, 111.8, 115.5, 117.5, 117.8, 121.7, 126.9, 127.2, 129.2, 129.3, 131.2, 131.5, 134.3, 141.2, 141.3, 144.3, 144.5, 144.5, 145.9, 148.1, 148.2, 163.7, 164.2, 180.6, 180.8. IR (thin film) 1616, 1000, 909 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.74; H, 6.84; N, 9.41.

13-Ethyl-13-methyl-10,11,12,13-tetrahydro-9*H*-benzo-[*b*]pyrido[3.2-*d*]azonin-10-one (5c). The same procedure as for the synthesis of **5a** was applied to amino acid **25a** (39 mg, 0.13 mmol), the reaction mixture (solvent: $CHCl_3$) being refluxed for 36 h with introduction of an additional 0.5 equiv of HOBT/EDCI/NEt_3 after 24 h. The solvent was evaporated and the residue chromatographed (93:7 CH_2Cl_2/MeOH) to yield **5c** (26 mg, 71%), as a white solid (2.7:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$, 40 °C) δ 0.50 (t, J = 7.3, 2.2H), 0.63 (t, J = 7.3, 0.8H), 0.72 (s, 0.8H), 1.12−1.70, 2.05−2.65 (2m, 8.2H), 5.80 (br s, 0.27H), 6.96 (dd, J = 7.6 and 4.7, 0.27H), 7.00 (dd, J = 7.6 and 4.7, 0.73H), 7.08 (m, 1H), 7.20 (m, 1H), 7.31 (m, 3H), 7.72 (br s, 0.73H), 8.51 (m, 1H). ^{13}C NMR (Problems of relaxation affect the NMR spectrum, and peaks are missing, especially in the aliphatic area.) (75 MHz, $CDCl_3$) δ 9.1, 46.2, 46.8, 120.5, 120.8, 128.3, 128.6, 129.5, 129.7, 128.5, 128.7, 129.4, 131.1, 133.4, 135.7, 136.4, 138.4,

143.1, 143.3, 148.7, 148.9. IR (KBr) 1659 cm^{-1}. MS (CI, *t*-BuH) *m*/*z* 281 $(M + H)^+$. Anal. Calcd for $C_{18}H_{20}N_2O$ (280.37): C, 77.11; H, 7.19; N, 9.99. Found: C, 76.68; H, 7.22; N, 10.00. Diastereoisomers were separated by semipreparative HPLC. mps: 164 °C (major diastereoisomer) and 198 °C (minor diastereoisomer).

13,13-Diethyl-10,11,12,13-tetrahydro-9*H*-benzo[*b*]pyrido-[3,2-*d*]azonin-10-one (5d). The same procedure as for the synthesis of **5a** was applied to amino acid **25b** (69 mg, 0.22 mmol), the reaction mixture (solvent: $CHCl_3$) being heated at 50 °C for 36 h with introduction of an additional 0.5 equiv of HOBT/EDCI/NEt_3 after 24 h. The solvent was evaporated and the residue chromatographed (96:4 CH_2Cl_2/MeOH) to yield **5d** (62 mg, 95%), as a pale brown solid, mp 172 °C.^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 0.44 (t, J = 7.3, 3H), 0.69 (t, J = 7.3, 3H), 1.21 (m, 2H), 1.66 (m, 2H), 1.78, 2.07−2.57 (2m, 4H), 6.63 (br s, 1H), 6.99 (dd, J = 7.6 and 4.8, 1H), 7.08 (dd, J = 7.6 and 2.0, 1H), 7.17 (m, 1H), 7.32 (m, 3H), 8.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 7.3, 28.7 (this chemical shift corresponds to the midpoint of a very broad signal), 30.2, 47.6, 52.5, 119.2, 126.8, 127.0, 128.0, 128.4, 132.9, 134.5, 137.4, 141.8, 146.8, 161.1, 174.8. IR (KBr) 1653 cm^{-1}. MS (CI, *t*-BuH) *m*/*z* 295 $(M + H)^+$. Anal. Calcd for $C_{19}H_{22}N_2O$ (294.40): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.21; H, 7.50; N, 9.51.

13-Methyl-13-vinyl-10,11,12,13-tetrahydro-9*H*-benzo[*b*]-pyrido[3,2-*d*]azonin-10-one (5e). The same procedure as for the synthesis of **5a** was applied to amino acid **26** (36 mg, 0.12 mmol), the reaction mixture (solvent: $CHCl_3$) being refluxed for 40 h with introduction of an additional 0.5 equiv of HOBT/EDCI/NEt_3 after 24 h. The solvent was evaporated and the residue chromatographed (93:7 CH_2Cl_2/MeOH) to yield **5e** (27 mg, 80%), as a white solid (3:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$, 40 °C) δ 1. 00 (s, 0.75H), 1.48 (s, 2.25H), 1.62−2.51 (m, 4H), 4.50 (d, J = 17.6, 0.75H), 4.51 (d, J = 11.0, 0.75H), 4.96 (d, J = 17.6, 0.25H), 5.06 (d, J = 11.0, 0.25H), 5.72 (dd, J = 17.6 and 11.0, 0.75H), 6.59 (m, 0.25H), 6.78 (br s, 0.75H), 6.91 (br s, 0.25H), 7.04 (m, 1H), 7.11−7.39 (m, 5H), 8.54 (m, 1H). ^{13}C NMR (Problems of relaxation affect the signals and some of them are missing, even with a D1 parameter of several minutes.) (75 MHz, $CDCl_3$) δ 48.7, 110.5, 120.9, 127.8, 128.0, 128.5, 129.3, 134.1, 138.1, 138.4, 142.3, 148.6. IR (KBr) 1669 cm^{-1}. MS (CI, *t*-BuH) *m*/*z* 279 $(M + H)^+$. Anal. Calcd for $C_{18}H_{18}N_2O$ (278.36): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.85; H, 6.55; N, 10.05. Diastereoisomers were separated by semipreparative HPLC. mps: 168 °C (major diastereoisomer) and 210 °C (minor diastereoisomer).

Ethyl 2-Ethyl-2-(3-(2-pivalamidophenyl)-2-pyridyl)butanoate (29). To a solution of diisopropylamine (0.29 mL, 2.05 mmol) in THF (5 mL) was added *n*-BuLi (0.82 mL, 2.05 mmol) at −70 °C. The reaction mixture was stirred for 15 min at −70 °C before adding a solution of ester **28** (170 mg, 0.5 mmol) in THF (3 mL). After 30 min of stirring, iodoethane (0.39 mL, 2.5 mmol) was added. The reaction mixture was allowed to warm to room temperature over 3 h after which it was hydrolyzed (5 mL of water) and extracted with CH_2Cl_2. The combined organic extracts were dried, and the solvent was evaporated. The crude residue was eluted through a short plug of silica gel (1:3 EtOAc/petroleum ether) and then submitted to another sequence of metalation−ethylation, using the same conditions as above. After usual workup, the residue was subjected to chromatography (1:4 EtOAc/petroleum ether) to yield **29** (119 mg, 60%), as a white solid, mp 107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (t, J = 7.5, 3H), 0.72 (t, J = 7.5, 3H), 0.88 (t, J = 7.1, 3H), 0.96 (s, 9H), 1.86−2.12, 2.30 (2m, 4H), 3.40 (dq, J = 11.0 and 6.9, 1H), 3.70 (dq, J = 11.0 and 6.9, 1H), 7.08 (m, 2H), 7.12 (dd, J = 7.7 and 1.8, 1H), 7.19 (br s, 1H), 7.25 (dd, J = 7.7 and 4.8, 1H), 7.30 (m, 1H), 7.82 (d, J = 7.8, 1H), 8.56 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 8.8, 13.9, 26.6, 27.3, 28.2, 39.5, 58.0, 60.8, 121.3, 124.0, 124.5, 129.1, 130.7, 132.0, 133.5, 136.2, 140.2, 147.7, 159.6, 176.5, 177.0. IR (KBr) 3408, 1708, 1687 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_3$ (396.53): C, 72.70; H, 8.13; N, 7.04. Found: C, 72.54; H, 8.24; N, 6.98.

2-Ethyl-2-(3-(2-Aminophenyl)-2-pyridyl)butan-1-ol (33). The same procedure as for the synthesis of **15a** was applied to pivalamide **30** (168 mg, 0.47 mmol). Chromatography (1:2 EtOAc/petroleum ether) yielded **33** (91 mg, 72%) as a white solid, mp 139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, J = 7.3, 6H), 1.39−1.71 (m, 4H), 3.34 (br s, 2H), 3.70 (d, J = 11.7, 1H), 3.95 (d, J = 11.7, 1H), 4.25 (br s, 1H), 6.69 (m, 2H), 6.94 (dd, J = 7.7 and 1.5, 1H), 7.14 (m, 2H), 7.34 (dd, J = 7.7 and 1.8, 1H), 8.50 (dd, J = 4.8 and 1.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 9.6, 27.2, 28.5, 51.0, 67.0, 115.6, 117.9, 121.4, 126.5, 129.2, 130.1, 134.2, 141.7, 143.9, 147.4, 164.7. IR (KBr) 3476, 3337 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O$ (270.38): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.89; H, 8.19; N, 10.39.

13,13-Diethyl-10,11,12,13-tetrahydro-11-oxa-9*H*-benzo-[*b*]pyrido[3,2-*d*]azonin-10-one (6). Cooled (−70 °C), ethanol-free CH_2Cl_2 (2 mL) was added to a N_2-flushed flask containing amino alcohol **32** (25 mg, 0.094 mmol), 4-DMAP (105 mg. 0.94 mmol), and triphosgene (31 mg. 0.105 mmol). After 15 min of stirring at −70 °C, the reaction mixture was allowed to warm to room temperature over 4 h, after which it was hydrolyzed (2 mL of aqueous K_2CO_3) and extracted with EtOAc. The combined organic extracts were dried, and the solvent was evaporated. The residue was subjected to chromatography (99:1 CH_2Cl_2/MeOH) to yield **6** (20 mg, 70%), as an orange solid, mp 176 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (t, J = 7.3, 3H), 0.82 (t, J = 7.3, 3H), 1.20, 1.44−1.61, 1.80, 2.08 (4m, 4H), 3.78 (d, J = 11.0, 1H), 4.27 (d, J = 11.0, 1H), 6.05 (br s, 1H), 7.08 (m, 3H), 7.20 (m, 2H), 7.29 (m, 1H), 8.58 (dd, J = 4.1 and 2.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 23.4, 24.2, 52.1, 73.1, 120.9, 125.4, 126.0, 128.6, 129.9, 135.3, 136.6, 140.2, 141.7, 148.5, 156.6, 160.0. IR (KBr) 1714 cm^{-1}. MS (CI, *t*-BuH) *m*/*z* 297 $(M + H)^+$. Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.77; H, 6.82; N, 9.41.

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Supporting Information Available: Compounds **8**−**11**, **14**−**17**, **19**−**22**, **23c**,**d**, **27**, **28**, and **30**−**32** are described in this section. This material is available free of charge via the Internet at http://pubs.acs.org.

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