mp 246–247 °C; IR (KBr) 3400, 3307, 3193, 2207, 1653, 1617, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (m, 4 H, 2 CH_2), 3.67 (m, 2 H, CH_2), 4.31 (m, 2 H, CH_2), 6.47 (s, 1 H, H-10), 7.60 (m, 5 H, ArH), 8.70 (br s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6) δ 22.35 (t, CH_2), 22.81 (t, CH_2), 45.77 (t, CH_2), 51.16 (t, CH_2), 81.26 (sd, ^3J = 7.9 Hz, C-8), 100.97 (d, ^1J = 173 Hz, C-10), 115.96 (s, CN), 127.88, 129.09, 130.63, 135.59 (ArC, o, m, p, ipso), 155.46 (sm, C-7), 155.68 (sdd, ^2J and ^3J = 2.5 Hz, C-9), 158.17 (sm, C-10a). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.52; H, 5.95; N, 21.13.

2-(Phenylimino)-3,4-diphenylthiazoline (12). To a warm solution (50 °C) of *N,N'*-diphenylthiourea (Aldrich; 4 mmol, 0.912 g) in dry ethanol (30 mL) was added in one portion a solution of 1 (4 mmol, 1 g). The yellow reaction mixture was stirred at this temperature for 10 min and cooled to 25 °C, and triethylamine (4 mmol, 0.7 mL) in ethanol (3 mL) was added. The dark solution was refluxed for 45 min and then kept at room temperature for a few hours. The separated needles were filtered off and washed with water and ether to give 0.36 g (28%) of **12**, mp 191–196 °C. An analytical sample was obtained by recrystallization from ethanol; mp 195–196 °C (lit.[12] mp 192 °C).

2-Hydrazino-4-phenylthiazole. To a warm solution (50 °C) of thiosemicarbazide in DMF (10 mL) was added at once a solution of 1 (4 mmol, 1 g) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at this temperature for 5 min and cooled to 25 °C, and triethylamine (4.0 mmol, 0.7 mL) in ethanol (3 mL) was added dropwise over 5 min. After being heated at 50 °C for 45 min, the dark solution was poured into ice water (150 mL). The white crystalline material was filtered off by suction, washed with ether, and dried to afford 0.45 g (57%) of 2-hydrazino-4-phenylthiazole, mp 167–168 °C (ethanol) (lit.[11] mp 169 °C). The spectral data of our product were in good agreement with those of an authentic sample prepared according to ref 11.

A General Approach to the Synthesis of 1,6-, 1,7-, and 1,8-Naphthyridines[1]

James A. Turner

Discovery Research, DowElanco, 2800 Mitchell Drive, Walnut Creek, California 94598

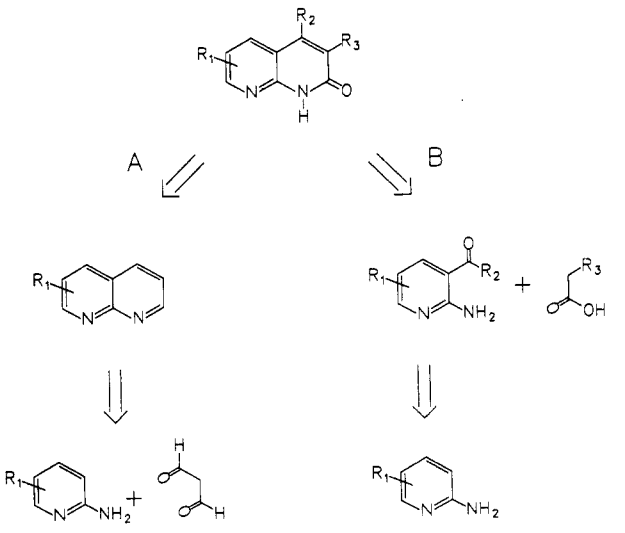
Received December 27, 1989

A new three-step procedure for pyridine annulation is described and illustrated with efficient syntheses of various 1,6-, 1,7-, and 1,8-naphthyridin-2-ones as well as 6-chloroquinolin-2-one. The regiospecific ortho metalation and subsequent formylation of 2-, 3-, or 4-(pivaloylamino)pyridines provides the corresponding protected ortho aminopyridinecarboxaldehydes as key intermediates in this procedure. After condensation of these aldehydes with *tert*-butyl lithioacetate the resulting β-hydroxy esters are treated with refluxing aqueous HCl to generate the naphthyridine system in excellent yield. Naphthyridines with diverse substitution patterns in either of the pyridine rings are available by appropriate modification of the overall pyridine annulation sequence.

The 1,*X*-naphthyridines (pyridopyridines) are deceptively simple members of the diazanaphthalene series.[2] In contrast to other heterocycles in this group (e.g., quinazolines and quinoxalines), the naphthyridines have attracted relatively little synthetic attention and, perhaps as a consequence, have only occasionally been used as substrates for biologically active molecules.[3] As part of continuing studies in our laboratory[4] we recently required a series of specifically substituted, yet previously unknown, 2-chloro-1,*X*-naphthyridines. We envisioned that our targeted materials would be readily available by dehydrative chlorination of the corresponding 1,*X*-naphthyridin-2-ones and thus set as our goal the development of methodology which would be widely applicable to the synthesis of the latter.

Retrosynthetic analysis of a 1,*X*-naphthyridin-2-one (Scheme I) suggested two approaches from readily available aminopyridines. Each route has parallels in quinoline chemistry[5] and both methods have been applied to the synthesis of various naphthyridines. In the first (route A),

Scheme I



a variant of which is directly analogous to the Skraup reaction, an electrophilic aromatic substitution is employed to elaborate the second ring. The well-known difficulty of pyridines to undergo such a reaction has limited this approach to those systems in which the starting pyridine is either unsubstituted or functionalized with electron-donating substituents.[2a,6]

(1) Presented in part at the 10th International Congress of Heterocyclic Chemistry; August, 1985; Waterloo, Ontario.

(2) For recent reviews see: (a) Paudler, W. W.; Sheets, R. M. *Adv. Heterocycl. Chem.* **1983**, *33*, 147. (b) Wozniak, M.; van der Plas, H. C. *Heterocycles* **1982**, *61*, 318.

(3) A notable exception is the series of pyridonecarboxylic acid antibiotics related to nalidixic acid. For leading references see: (a) Parikh, V. D.; Fray, A. H.; Kleinman, E. F. *J. Heterocycl. Chem.* **1988**, *25*, 1567. (b) Miyamoto, T.; Egawa, H.; Shibamori, K.; Matsumoto, J. *J. Heterocycl. Chem.* **1987**, *24*, 1333.

(4) Turner, J. A. U. S. Patent 4,472,193, 1984; U. S. Patent 4,533,381, 1985; U. S. Patent 4,536,208, 1985.

(5) Jones, G. In *Quinolines*; Jones, G., Ed.; John Wiley: New York, 1977; Part I, Chapter 2.

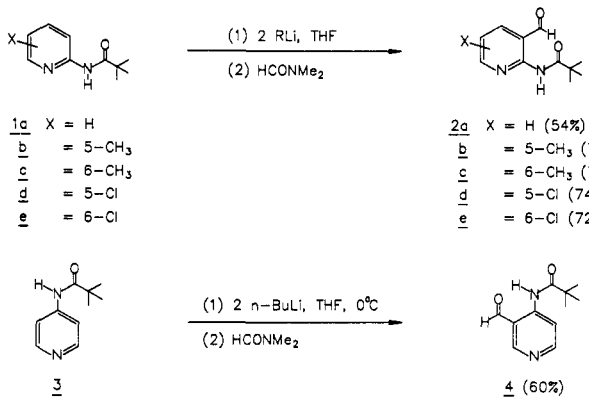
(6) For a successful example of the use of this approach for preparation of 1,5-naphthyridine see: Hamada, Y.; Takeuchi, I. *Chem. Pharm. Bull.* **1971**, *19*, 1857.

0022-3263/90/1955-4744$02.50/0

In the second approach (route B), the starting aminopyridine is functionalized in the ortho position with an electrophilic carbon atom, and the remaining atoms are appended via one of a variety of carbon–carbon bond forming reactions.[7] The naphthyridine nucleus is formed in a subsequent cyclization, often in a one-pot procedure. From a synthetic standpoint this latter approach is particularly attractive since, in principle, it should be applicable to a wide variety of substituted 1,*X*-naphthyridines by judicious choice of starting materials (R_1, R_2, and R_3 in Scheme I). In reality, the difficulty of preparing aminopyridines with the requisite electrophilic carbon atom ortho to the amino group has limited the application of this route to those systems obtainable from unsubstituted 2- and 4-aminonicotinaldehydes.[8,9] We previously described conditions for regiospecific electrophilic substitution of aminopyridines which offers a potential solution to this problem.[10] We have now used this methodology, along with a remarkably successful pyridine annulation procedure, for a unified approach to the preparation of a variety of 1,6-, 1,7-, and 1,8-naphthyridines. In addition, preliminary studies suggest that this synthetic approach may be equally applicable for preparation of substituted quinolines.

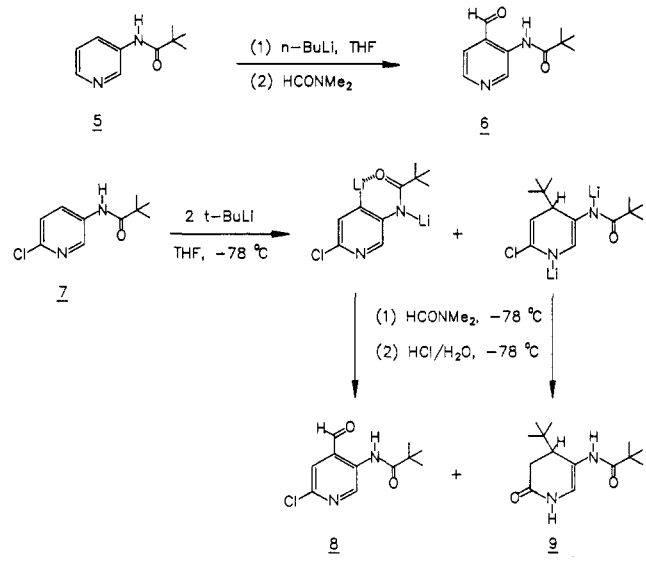
Results

Regiospecific ortho metalation of (pivaloylamino)-pyridines and subsequent treatment of the metalated pyridines with electrophiles results in ready access to a variety of ortho-substituted aminopyridines.[10] Thus, treatment of 2- or 4-(pivaloylamino)pyridine (**1a** or **3**) with excess *n*-butyllithium in THF results in exclusive formation of the corresponding 3-lithiopyridine. Subsequent



reaction of the metalation mixture with dimethylformamide, to give **2a** and **4** as previously described, serves to install the electrophilic carbon atom necessary for subsequent pyridine annulation to 1,8- and 1,6-naphthyridines, respectively (Scheme I). More highly substituted 2-(pivaloylamino)nicotinaldehydes (**2b–e**), which would ultimately lead to substituted 1,8-naphthyridines, were similarly prepared from the appropriate 2-(pivaloylamino)-pyridines (**1b–e**) by employing the previously described modifications[10] of the general metalation procedure.

While ortho lithiation of most 2- and 4-(pivaloylamino)pyridines proceeds cleanly, similar treatment of 3-(pivaloylamino)pyridine (**5**) is complicated by competitive nucleophilic attack of the metalating agent at the C-4 position of the pyridine.[10,11] Thus, treatment of the metalation mixture obtained from **5** with DMF resulted in only 22% of isonicotinaldehyde **6**, precursor to 1,7-naphthyridin-2-one. Ortho lithiation and aromatic sub-



stitution of the even more electrophilic 6-chloro-3-(pivaloylamino)pyridine (**7**) required very carefully controlled conditions. A solution of **7** in THF was first treated with *tert*-butyllithium (<-80 °C) and, after 1.5 h at −78 °C, DMF was added. Allowing this mixture to warm to room temperature, as in the usual procedure, resulted in considerable decomposition as evidenced by VPC analysis and darkening of the reaction mixture. This decomposition could be circumvented by quenching the reaction mixture at −78 °C with aqueous HCl and, under these conditions, two major products were isolated: the desired aldehyde (**8**, 29%), and a new dihydropyridine (**9**, 50%) the structure of which was established on the basis of its ^1H and ^{13}C NMR spectra (see Experimental Section). The latter must have arisen from a nucleophilic attack by *tert*-butyllithium on the pyridine nucleus of **7** followed by hydrolysis of the resulting intermediate α-chloroenamine.

Pyridine Annulation. Conversion of an *o*-aminopyridinecarboxaldehyde to the corresponding naphthyridine requires the addition of an acetic acid moiety and subsequent dehydrative cyclization to the aromatic bicyclic heterocycle (Scheme I). Such a transformation could be effected, after removal of the pivaloyl directing group from **4**, by the previously described based-catalyzed condensation of 4-aminonicotinaldehyde with acetonitrile[8b] and diazotive hydrolysis of the resulting 2-aminonaphthyridine to the corresponding naphthyridinone (**11a**).[12] However, we saw no need to deprotect the amino group of the pyridinecarboxaldehyde at this point and, instead, developed a simpler pyridine annulation procedure (Scheme II).

An initial condensation between 2-(pivaloylamino)-nicotinaldehyde (**2a**) and excess *tert*-butyl lithioacetate (2.1 mol equiv)[13] in ether (−78 °C to room temperature) cleanly installed the remaining atoms of the naphthyridine nu-

(7) This approach is technically equivalent to the Friedlander synthesis of quinolines. For a recent review see: Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.

(8) (a) Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc. (C)* **1966**, 316. (b) Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc. (C)* **1967**, 1564.

(9) (a) Hawes, E. M.; Gorecki, D. K. *J. J. Heterocycl. Chem.* **1971**, *9*, 703. (b) Hawes, E. M.; Gorecki, D. K. *J. Heterocycl. Chem.* **1974**, *11*, 151.

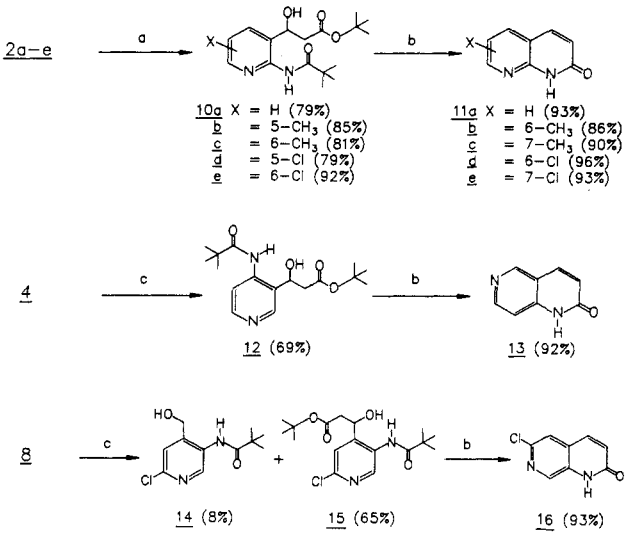
(10) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.

(11) An apparently improved procedure for ortho lithiation of 3-(pivaloylamino)pyridine has recently been reported: Estel, L.; Linard, F.; Marsais, F.; Godard, A.; Queguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 105.

(12) Eichler, E.; Rooney, C. S.; Williams, H. W. R. *J. Heterocycl. Chem.* **1976**, *13*, 841.

(13) Similar treatment of nicotinaldehyde **2a** with 1 mol equiv of *tert*-butyl lithioacetate gave a 3:2 mixture of β-hydroxy ester **10a** and starting aldehyde (NMR analysis).

Scheme II[a]



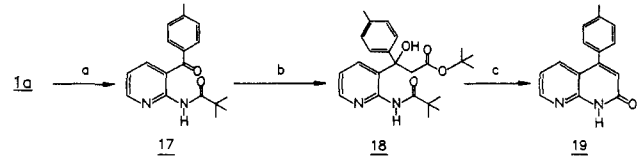
[a] Reagents: (a) 2.1 equiv $LiCH_2CO_2tBu$; (b) 3 N HCl/H_2O; (c) 1.0 equiv *t*-BuOAc, 2.1 equiv LDA.

cleus. The resulting β-hydroxy ester, **10a**, was then converted to 1,8-naphthyridin-2-one (**11a**) simply by refluxing this material in aqueous 3 N HCl for a period of 7 h. In this reaction a minimum of four separate transformations, (a) hydrolysis of the *tert*-butyl ester, (b) deprotection of the amine, (c) cyclodehydration to form the naphthyridine nucleus, and (d) dehydration of the β-hydroxy group, were accomplished in a single pot in exceptionally high yield (93%). It is unlikely that dehydration of the β-hydroxy ester (or acid) occurred before cyclization as this would presumably lead to a preponderance of the thermodynamically more stable trans geometry in the resulting unsaturated carbonyl derivative. Successful acid-mediated double-bond isomerization and subsequent cyclization of such trans unsaturated esters is reported[12] to require much more drastic conditions (6 N HCl, 6 days, reflux) than those described here.[14]

The two-step annulation procedure was readily extended to pyridinecarboxaldehydes **4**, **8**, and **2b–e** to provide 1,6- (**13**), 1,7-(**16**), and more highly substituted 1,8-naphthyridin-2-ones (**11b–e**), respectively. Treatment of aldehydes **2b–e** with 2.1 mol equiv of *tert*-butyl lithioacetate as described above furnished β-hydroxy esters **10b–e** without complication. Under slightly modified conditions (1.05 mol equiv of *tert*-butyl acetate and 2.10 mol equiv of LDA) nicotinaldehyde **4** was smoothly converted to ester **12** as the sole isolable product. However, similar reaction of isonicotinaldehyde **8** produced the expected β-hydroxy ester, **15** (65%), along with 8% of primary alcohol **14**, the latter presumably arising from reduction of the starting aldehyde by excess LDA.[15]

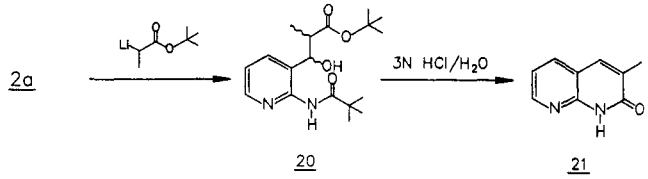
Acid-catalyzed cyclization of β-hydroxy esters **10b–e**, **12**, and **15**, using dioxane as a cosolvent in those cases where the starting pyridine was insoluble in aqueous HCl, furnished the corresponding 1,*X*-naphthyridinones shown in Scheme II in excellent yield. The reaction is maintained at reflux until the initially complex mixture (as judged by TLC analysis of a neutralized aliquot) is converted to a single, more polar product (usually 3–5 h). The cyclization reactions are remarkably clean, and the highly crystalline

Scheme III[a]

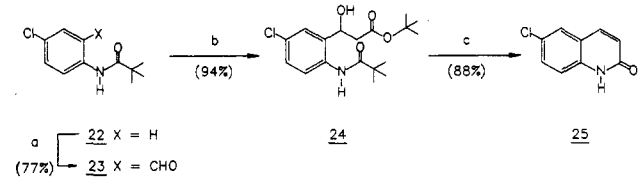


[a] Reagents: (a) 1. 2 *n*-BuLi, THF, 0 °C, 2. 4-$CH_3PhCON(CH_3)$-OCH_3; (b) $LiCH_2CO_2tBu$; (c) 3 N HCl/H_2O.

Scheme IV



Scheme V[a]



[a] Reagents: (a) 1. *n*-BuLi, 0 °C, 2. DMF; (b) $LiCH_2CO_2t$-Bu, Et_2O, −78 °C–RT; (c) 3 N HCl, dioxane, reflux.

naphthyridinone products are often isolated in analytically pure form directly from the reaction mixture.

The examples presented above illustrate that the substitution pattern of the C-5–C-8 positions in the product 1,*X*-naphthyridin-2-one is dictated by the location of substituents on the starting aminopyridine. Likewise, substitution at the C-3 and C-4 positions of the naphthyridine can be controlled by the nature of the reagents used in annulation of the second pyridine ring (see Scheme I). Thus, for preparation of a C-4-substituted 1,*X*-naphthyridine, the appended electrophilic carbon atom ortho to the amino group must be in the form of a ketone instead of a carboxaldehyde ($R_2 \neq H$). Such a ketone (**17**) was readily prepared by ortho metalation of 2-(pivaloylamino)pyridine (**1a**) and acylation of the intermediate lithiopyridine by using the methodology of Nahm and Weinreb[16] (Scheme III). Reaction of ketone **17** with *tert*-butyl lithioacetate followed by cyclization of the resulting β-hydroxy ester (**18**) in the usual fashion (3 N aqueous HCl, dioxane) cleanly provided substituted 1,8-naphthyridinone **19**. Unexpectedly, this latter transformation required 3 *days* at reflux, instead of the typical 3–5 h for the corresponding C-4-unsubstituted examples, to effect complete conversion.

Substitution at C-3 in the product naphthyridinone can be accomplished by reaction of a pyridinecarboxaldehyde (or ketone) with a *substituted* acetic acid equivalent. Thus, condensation of aldehyde **2a** with *tert*-butyl lithiopropionate resulted in formation of a diastereomeric mixture of α-methyl-β-hydroxy esters **20** (Scheme IV). This mixture of alcohols was treated directly (without further purification) with aqueous HCl in refluxing dioxane for a period of 24 h to produce 3-methyl-1,8-naphthyridin-2-one (**21**) in 79% overall yield.

This new pyridine annulation methodology was readily extended to the preparation of a substituted 2-quinolinone

(14) Under milder conditions (10% HCl, 1 h, reflux), a 1:1 cis/trans mixture of a similar unsaturated ester gave only 35% of the expected naphthyridinone. See: Tamura, Y.; Chen, L. C.; Fujita, M.; Kita, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1257.

(15) Majewski, M. *Tetrahedron Lett.* **1988**, *33*, 4057.

(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(Scheme V). Ortho lithiation of trimethylacetanilide **22** by the procedure of Gschwend[17] and subsequent treatment with dimethylformamide provided protected ortho aminobenzaldehyde **23** as a stable, colorless crystalline solid in 77% yield. Reaction of this aldehyde with *tert*-butyl lithioacetate in the usual fashion (to provide 94% of hydroxy ester **24**) followed by hydrolysis in refluxing 3 N aqueous HCl and dioxane (4 h, 88%) resulted in a remarkably efficient synthesis of 6-chloroquinolin-2-one (**25**).[18] This sequence is an attractive alternative to the Friedlander synthesis of quinolines since, in this case, there is no need to generate the relatively unstable unprotected ortho aminobenzaldehyde.[5,7]

Discussion

The simple pyridine annulation procedure described above represents the first unified approach to the synthesis of 1,6-, 1,7-, and 1,8-naphthyridines. The key to this methodology is the ability to effect a difficult electrophilic carbon–carbon bond formation ortho to the amino group of an aminopyridine by a directed metalation procedure. In addition to ensuring the regiochemical integrity of the substituents on the aromatic ring, the regiospecificity of this (pivaloylamino)-directed ortho lithiation defines the nature of the ultimate bicyclic heterocycle. Thus, since lithiation of the amides derived from 2- and 4-aminopyridine occurs exclusively at C-3, the sole products from this sequence are 1,8- and 1,6-naphthyridines, respectively. Likewise, since ortho lithiation of 3-(pivaloylamino)-pyridine occurs solely at C-4, and not C-2, then 3-aminopyridine is transformed into 1,7- and, consequently, not 1,5-naphthyridine.

The availability of a wide variety of 2-aminopyridines makes this pyridine annulation sequence particularly attractive for the synthesis of functionalized 1,8-naphthyridines. While preparation of 1,7-naphthyridines is necessarily limited by the decreased yields of ortho metalation observed for 3-(pivaloylamino)pyridines, alternative routes[2b] to the 1,7-naphthyridine nucleus are often so cumbersome that our technique may still find considerable utility. In addition, this methodology should complement traditional methods for preparation of quinolines from anilines. In conclusion, naphthyridines and quinolines with diverse substitution patterns in either of the two rings should be available by appropriate modification of this new pyridine annulation sequence.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets with a Beckman Acculab 3 infrared spectrophotometer. Proton NMR spectra were recorded in $CDCl_3$ at either 90 MHz (unless otherwise stated) by using a Varian EM-390 spectrometer or at 200 MHz by using a Varian XL-200 spectrometer. The ^{13}C NMR spectrum was recorded at 50.3 MHz in $CDCl_3$ by using the Varian XL-200 instrument. Chemical shifts are reported in ppm downfield from internal tetramethylsilane, and coupling constants are in Hz. Preparative chromatographies were performed with a Waters PrepSystem 500A liquid chromatograph. Tetrahydrofuran and ether were distilled from sodium benzophenone immediately prior to use. Diisopropylamine was distilled from CaH_2 and stored over 4A molecular sieves. *n*-Butyllithium (1.55–1.65 M in hexane) and *tert*-butyllithium (2.1 M in pentane) were obtained from Aldrich Chemical Co. 5-Amino-2-chloropyridine was prepared from commercially available 2-chloro-5-nitropyridine by the procedure of Cragoe and Hamilton.[19] Other reagents were generally used as received. Microanalyses were performed by Mary Gade of the Dow Chemical Co., Walnut Creek, CA.

General Procedure for Metalation and Formylation of *N*-(Pivaloylamino)pyridines.[10] An oven-dried, three-necked, round-bottom flask was equipped with a thermometer, a nitrogen inlet, and a magnetic stirrer and flushed with nitrogen. The flask was charged with the (pivaloylamino)pyridine and stoppered with a rubber septum, and solvent (2–4 mL/mmol of substrate) was introduced. After the solution was cooled to −78 °C, *n*-butyllithium or *tert*-butyllithium solutions were added dropwise via syringe. The resulting mixture was stirred at the appropriate temperature for the specified period of time before quenching with a solution of 2 mol equiv of dimethylformamide in 2–4 mL of solvent at −78 °C. The mixture was allowed to warm to room temperature, poured into dilute aqueous HCl, stirred for 15 min, and then neutralized with K_2CO_3. The aqueous mixture was extracted with three portions of ether, and the combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated to dryness.

2,2-Dimethyl-*N*-(3-formyl-5-methyl-2-pyridinyl)propanamide (2b). A solution of 9.60 g (50 mmol) of **1b**[10] in 150 mL of THF was treated with 125 mmol of *n*-butyllithium at −78 °C and then stirred at 0 °C for 3 h. After addition of DMF and standard workup as described above, a solid was obtained which was recrystallized from toluene to give 8.05 g (73%) of **2b** as colorless crystals: mp 113–5 °C; NMR 10.14 (s, 1 H, CHO), 8.66 (d, J = 2.5, 1 H, H-6), 8.00 (d, J = 2.5, 1 H, H-4), 2.42 (s, 3 H, CH_3), 1.39 (s, 9 H, *tert*-butyl); IR 3300, 2978, 1707, 1678, 1588 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.36; H, 7.26; N, 12.67.

2,2-Dimethyl-*N*-(3-formyl-6-methyl-2-pyridinyl)propanamide (2c). A mixture of 1.92 g (10 mmol) of **1c**[10] in 40 mL of ether was treated with *tert*-butyllithium (22 mmol) and stirred at −78 °C for 3 h and then at 0 °C for 30 min. After addition of DMF the mixture was allowed to stir at room temperature overnight. Standard workup left a yellow solid which was recrystallized from ethyl acetate/hexane to give 1.70 g (77%) of **2c** as yellow crystals: mp 130–2 °C; NMR 10.11 (s, 1 H, CHO), 8.09 (d, J = 8, 1 H, H-4), 7.18 (d, J = 8, 1 H, H-5), 2.67 (s, 3 H, CH_3), 1.40 (s, 9 H, *tert*-butyl); IR 3280, 2975, 1690 (s), 1605 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.12; H, 7.21; N, 12.61.

***N*-(5-Chloro-3-formyl-2-pyridinyl)-2,2-dimethylpropanamide (2d).** A solution of 5.31 g (25 mmol) of **1d**[10] in 100 mL of THF was treated at −78 °C with *tert*-butyllithium (55 mmol) and the resulting mixture stirred at −78 °C for 3 h. After addition of DMF (30 mmol) and standard workup, a solid was obtained which recrystallized from ethyl acetate/hexane to give 4.43 g (74%) of **2d** as colorless plates: mp 168–71 °C; NMR 10.14 (s, 1 H, CHO), 8.78 (d, J = 3, 1 H, H-4), 8.20 (d, J = 3, 1 H, H-6), 1.39 (s, 9 H, *tert*-butyl); IR 3265, 3022, 2975, 1710, 1655 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; N, 11.64. Found: C, 54.74; H, 5.40; N, 11.64.

***N*-(6-Chloro-3-formyl-2-pyridinyl)-2,2-dimethylpropanamide (2e).** A solution of 10.63 g (50 mmol) of **1e**[10] in 100 mL of THF was treated with 125 mmol of *n*-butyllithium and the resulting mixture stirred at −20 °C for 3 h. Following addition of DMF, standard workup left a solid which was recrystallized from ethyl acetate/hexane to give 8.61 g (72%) of **2e** as colorless crystals: mp 137–9 °C; NMR 10.14 (s, 1 H, CHO), 8.19 (d, J = 8, 1 H, H-4), 7.33 (d, J = 8, 1 H, H-5), 1.39 (s, 9 H, *tert*-butyl); IR 3280, 2975, 1700, 1665 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.45; N, 11.64. Found: C, 54.82; H, 5.40; N, 11.61.

2,2-Dimethyl-*N*-(4-formyl-3-pyridinyl)propanamide (6). The mixture prepared from treatment of 3.56 g (20 mmol) of **5**[10] with *n*-butyllithium (50 mmol) was stirred at 0 °C for 3 h, DMF was added, and the mixture was worked up in the standard fashion. The residual oil was purified first by preparative HPLC, eluting with 1:1 hexane/ethyl acetate, and the resulting solid (0.92 g, 22%) was further purified by Kugelrohr distillation (100 °C, 0.03 mmHg) and then recrystallized from hexane/ethyl acetate to give colorless crystalline **6**: mp 76–8 °C; NMR 10.33 (s, 1 H,

(17) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.
(18) Johnston, K. M.; Luker, R. M.; Williams, G. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1648.
(19) Cragoe, E. J., Jr.; Hamilton, C. S. *J. Am. Chem. Soc.* **1945**, *67*, 536.

H-2 or CHO), 10.30 (s, 1 H, H-2 or CHO), 8.76 (d, J = 5, 1 H, H-6), 7.75 (d, J = 5, 1 H, H-5), 1.40 (s, 9 H, *tert*-butyl); IR 3315, 2975, 1685 (br) cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.54. Found: C, 63.49; H, 6.72; N, 13.41.

***N*-(6-Chloro-3-pyridinyl)-2,2-dimethylpropanamide (7).** A solution of 44.3 g (0.368 mol) of trimethylacetyl chloride and 60 mL of methylene chloride was added dropwise to an ice-cooled solution preparated from 45.0 g (0.35 mol) of 5-amino-2-chloropyridine, 42.4 g (0.42 mol) of triethylamine, and 300 mL of methylene chloride. The reaction mixture was stirred at room temperature for 2 h and then washed with water and 5% aqueous NaOH, dried over Na_2SO_4, and evaporated to dryness to leave a dark solid. The solid was taken up in hot ethyl acetate, treated with charcoal and filtered, diluted with hexane and allowed to cool to give 58.7 g (79%) of **7** as colorless crystals: mp 120–3 °C; NMR 8.60 (d, J = 3, 1 H, H-2), 8.17 (dd, J = 3, 9, 1 H, H-4), 7.41 (d, J = 9, 1 H, H-5), 1.34 (s, 9 H, *tert*-butyl); IR 3310, 1660, 1515 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.31; H, 6.14; N, 13.02.

***N*-(6-Chloro-4-formyl-3-pyridinyl)-2,2-dimethylpropanamide (8) and 2,2-Dimethyl-*N*-[4-(1,1-dimethylethyl)-6-oxo-1,4,5,6-tetrahydro-3-pyridinyl]propanamide (9).** A solution of 10.63 g (50 mmol) of **7** in 100 mL of THF was treated with 110 mmol of *tert*-butyllithium while maintaining the temperature below −80 °C. The resulting mixture was stirred at −78 °C for 1.5 h, and a solution of 10.95 g (150 mmol) of dimethylformamide in 5 mL of THF was then added. After the mixture was stirred at −78 °C for 30 min, 40 mL of 6 *N* HCl was added, and the resulting yellow mixture was allowed to warm to room temperature, and then it was stirred for 30 min. The mixture was then poured into water, neutralized with solid K_2CO_3, and extracted three times with ether. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and evaporated. Trituration of the resulting brown oil with ether gave a solid which was filtered, washed with ether, and reserved. The filtrates were concentrated and then separated into two fractions by preparative HPLC, eluting first with 4:1 hexane/ethyl acetate and then with acetone. The less polar fraction (3.5 g, 29%) was recrystallized from hexane to give **8** as pale yellow crystals: mp 105–6.5 °C; NMR 10.80 (br, 1 H, NH), 9.98 (s, 1 H, CHO or H-2), 9.91 (s, 1 H, H-2 or CHO), 7.57 (s, 1 H, H-5), 1.35 (s, 9 H, *tert*-butyl); IR 3300, 2955, 1685 (br), 1348 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; N, 11.64; Cl, 14.73. Found: C, 54.79; H, 5.38; N, 11.63; Cl, 14.74.

The more polar fraction was combined with the reserved solid and recrystallized from toluene to give 6.30 g (50%) of **9** as colorless crystals: mp 200–1 °C; NMR 7.16 (s, 1 H, H-2); 7.12 (br, 1 H, NH), 6.39 (br, 1 H, NH), 2.77 (dd, J = 7, 17, 1 H), 2.54 (dd, J = 3, 17, 1 H), 1.98 (dd, J = 3, 7, 1 H, H-4), 1.21 (s, 9 H, *tert*-butyl), 0.94 (s, 9 H, *tert*-butyl); ^{13}C NMR 176.0, 170.5, 118.1, 116.2, 46.6, 39.2, 35.6, 32.8, 27.6, 27.5; IR 3340, 3210, 3100, 2960, 1680, 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.66; H, 9.54; N, 11.04. Found: C, 66.63; H, 9.59; N, 11.10.

General Procedure for Reaction of Pyridinecarboxaldehydes with *tert*-Butyl Lithioacetate. An oven-dried, three-necked flask was equipped with a thermometer, a magnetic stirrer, and a N_2 inlet and flushed with N_2. The flask was stoppered with a rubber septum and charged with ether (3 mL/mmol of substrate) and diisopropylamine (2.1 mol equiv) and cooled to −78 °C. *n*-Butyllithium in hexane (2.1 mol equiv) was added, the solution stirred for 15 min and then a solution of *tert*-butyl acetate (2.1 mol equiv) in ether slowly added. After the mixture was stirred at −78 °C for 15–20 min, a solution of the appropriate pyridinecarboxaldehyde (1 mol equiv) in a minimum amount of THF was slowly added to give a thick, bright yellow precipitate. Upon completion of addition the mixture was stirred at −78 °C for 30 min and then allowed to warm to room temperature and poured into saturated aqueous NH_4Cl or water. The aqueous layer was separated and extracted twice with ether. The combined organic layers were washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and evaporated to dryness.

2-[(2,2-Dimethyl-1-oxopropyl)amino]-β-hydroxy-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (10a). This material was prepared from 2.06 g (10 mmol) of **2a** and *tert*-butyl lithioacetate by the procedure described above. The oil obtained after standard workup was recrystallized from hexane/acetone to yield 2.55 g (79%) of **10a** as colorless crystals: mp 127–9 °C; NMR 8.96 (br, exch with D_2O, 1 H, NH), 8.50 (dd, J = 1.7, 5, 1 H, H-6), 7.84 (dd, J = 1.7, 7.7, 1 H, H-4), 7.23 (dd, J = 5, 7.7, 1 H, H-5), 5.14 (dd, sharpens with D_2O, J = 6, 8, 1 H, *CH*OH), 4.56 (br, exch with D_2O, 1 H, OH), 2.90 (dd, J = 8, 16, 1 H), 2.67 (dd, J = 6, 16, 1 H), 1.41 (s, 9 H, *tert*-butyl), 1.35 (s, 9 H, *tert*-butyl); IR 3280, 2975, 1727, 1688 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.10; H, 8.08; N, 8.68.

2-[(2,2-Dimethyl-1-oxopropyl)amino]-β-hydroxy-5-methyl-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (10b). Treatment of 11.0 g (50 mmol) of **2b** with *tert*-butyl lithioacetate by the procedure described above and standard workup left a nearly colorless solid. This material was recrystallized from hexane/acetone to give 14.32 g (85%) of **10b** as colorless crystals: mp 122–4 °C; NMR 8.84 (br, exch with D_2O, 1 H, NH), 8.33 (d, J = 2, 1 H, H-6), 7.70 (d, J = 2, 1 H, H-4), 5.12 t, sharpens to dd, J = 6.5, 8 with D_2O, 1 H, *CH*OH), 4.52 (br, exch with D_2O, 1 H, OH), 2.88 (dd, J = 8, 16, 1 H), 2.67 (dd, J = 6.5, 16, 1 H), 2.37 (s, 3 H, CH_3), 1.40 (s, 9 H, *tert*-butyl), 1.34 (s, 9 H, *tert*-butyl); IR 3400, 3260, 2982, 1708, 1659 cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.23. Found: C, 63.97; H, 8.20; N, 8.24.

2-[(2,2-Dimethyl-1-oxopropyl)amino]-β-hydroxy-6-methyl-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (10c). Reaction of 7.70 g (35 mmol) of **2c** with *tert*-butyl lithioacetate by the procedure described above resulted in a colorless solid which was recrystallized from hexane/acetone. This gave 9.50 g (81%) of **10c** as colorless crystals: mp 136–8 °C; NMR 8.53 (br, exch with D_2O, 1 H, NH), 7.80 (d, J = 8, 1 H, H-4), 7.14 (d, J = 8, 1 H, H-5), 5.10 (t, sharpens to dd, J = 6.5, 8 with D_2O, 1 H, *CH*OH), 4.34 (br, exch with D_2O, 1 H, OH), 2.89 (dd, J = 8, 16, 1 H), 2.66 (dd, J = 6.5, 18, 1 H), 2.52 (s, 3 H, CH_3), 1.40 (s, 9 H, *tert*-butyl), 1.34 (s, 9 H, *tert*-butyl); IR 3300, 2990, 1728, 1705, 1620 cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.18; H, 8.37; N, 8.27.

5-Chloro-2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxy-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (10d). The reaction of 12.03 g (50 mmol) of **2d** with 105 mmol of *tert*-butyl lithioacetate by the procedure described above and standard workup gave a thick white gum which was purified by preparative scale HPLC, eluting with 17:3 hexane/acetone. Recrystallization of the resulting solid from hexane/acetone gave 14.12 g (79%) of **10d** as colorless crystals: mp 142–4 °C; NMR 8.97 (br, exch with D_2O, 1 H, NH), 8.53 (d, J = 2.5, 1 H, H-6), 7.90 (d, J = 2.5, 1 H, H-4), 5.17 (ddd, collapses to dd, J = 6, 8 with D_2O, 1 H, *CH*OH), 4.54 (d, J = 3, exch with D_2O, 1 H, OH), 2.93 (dd, J = 8, 16.5, 1 H), 2.71 (dd, J = 6, 16.5, 1 H), 1.47 (s, 9 H, *tert*-butyl), 1.37 (s, 9 H, *tert*-butyl); IR 3270, 2970, 1729, 1692, 1163 cm^{-1}. Anal. Calcd for $C_{17}H_{25}ClN_2O_4$: C, 57.22; H, 7.06; N, 7.85. Found: C, 57.35; H, 6.98; N, 7.80.

6-Chloro-2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxy-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (10e). Reaction of 12.03 g (50 mmol) of **2e** with 105 mmol of *tert*-butyl lithioacetate by the procedure described above and standard workup gave a white solid. Recrystallization of this material from hexane/acetone gave 16.34 g (92%) of **10e** as colorless crystals: mp 128–30 °C; NMR 8.62 (br, 1 H, NH), 7.90 (d, J = 8, 1 H, H-4), 7.32 (d, J = 8, 1 H, H-5), 5.12 (ddd, collapses to dd, J = 6, 8 with D_2O, 1 H, *CH*OH), 4.28 (d, J = 3, exch with D_2O, 1 H, OH), 2.87 (dd, J = 8, 16, 1 H), 2.67 (dd, J = 6, 16, 1 H), 1.42 (s, 9 H, *tert*-butyl), 1.35 (s, 9 H, *tert*-butyl); IR 3400, 3230, 2985, 1738, 1665, 1437 cm^{-1}. Anal. Calcd for $C_{17}H_{25}ClN_2O_4$: C, 57.22; H, 7.06; N, 7.85. Found: C, 57.14; H, 7.04; N, 7.81.

4-[(2,2-Dimethyl-1-oxopropyl)amino]-β-hydroxy-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (12). This material was prepared from 10.3 g (50 mmol) of **4** by the procedure described above except that 52 mmol of *tert*-butyl acetate and 105 mmol of LDA were employed. After a standard workup the resulting oil was purified by preparative HPLC eluting with 1:1 hexane/ethyl acetate to give 11.13 g (69%) of **12** as a gum. The gum was crystallized from hexane containing a small amount of acetone to give colorless crystalline **12**: mp 106–7.5 °C; NMR 10.06 (br, exch with D_2O, 1 H, NH), 8.29 (s, 2 H, H-5, 6), 6.29 (br, exch with D_2O, 1 H, OH), 5.14 (dd, J = 5, 9, 1 H, *CH*OH), 2.86 (dd, J = 9, 16, 1 H), 2.54 (dd, J = 5, 16, 1 H), 1.43 (s, 9 H, *tert*-butyl), 1.30 (s, 9 H, *tert*-butyl); IR 3260, 2980, 2720, 1722, 1696, 1155 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.33; H, 8.01; N, 8.59.

2-Chloro-5-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxy-4-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (15) and *N*-[6-Chloro-4-(hydroxymethyl)-3-pyridinyl]-2,2-dimethylpropanamide (14). The mixture obtained from reaction of 6.50 g (27 mmol) of **8**, 29.7 mmol of *tert*-butyl acetate, and 56.7 mmol of LDA in the usual fashion was separated into two fractions by preparative HPLC, eluting with 7:3 hexane/ethyl acetate. The less polar material was recrystallized from hexane/acetone to give 6.24 g (65%) of **15** as colorless crystals: mp 123–5 °C; NMR 9.15 (br, 1 H, NH), 8.98 (s, 1 H, H-2), 7.05 (s, 1 H, H-5), 5.03 (dd, J = 5, 8, 1 H, C*H*OH), 4.74 (br, exch with D_2O, 1 H, OH), 2.83 (dd, J = 8, 17, 1 H), 2.57 (dd, J = 5.5, 17, 1 H), 1.44 (s, 9 H, *tert*-butyl), 1.29 (s, 9 H, *tert*-butyl); IR 3220, 2975, 1732, 1650 cm^{-1}. Anal. Calcd for $C_{17}H_{25}ClN_2O_4$: C, 57.21; H, 7.06; N, 7.85; Cl, 9.94. Found: C, 56.91; H, 7.03; N, 7.83; Cl, 10.19.

The more polar material was recrystallized from toluene/hexane to give 0.52 g (8%) of **14** as colorless crystals: mp 110–2.5 °C; NMR 9.04 (br, 1 H, NH), 8.97 (s, 1 H, H-2), 7.08 (s, 1 H, H-5), 4.65 (br, 2 H, CH_2), 4.10 (br, exch with D_2O, 1 H, OH), 1.29 (s, 9 H, *tert*-butyl); IR 3200, 2968, 1690 cm^{-1}. Anal. Calcd for $C_{11}H_{15}ClN_2O_2$: C, 54.43; H, 6.23; N, 11.54. Found: C, 55.04; H, 6.19; N, 11.18.

1,8-Naphthyridin-2-one (11a). A solution of 3.22 g (10 mmol) of **10a** in 25 mL of 3 N aqueous HCl was warmed at reflux for 7 h. After cooling to room temperature, the solution was extracted twice with ether and the aqueous layer was neutralized with solid K_2CO_3. The resulting precipitate was filtered, washed with water, and then recrystallized from water to give 1.36 g (93%) of **11a** as colorless crystals: mp 198–200.5 °C (lit.[8b] mp 197–8 °C). Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.89; H, 4.15; N, 19.08.

6-Methyl-1,8-naphthyridin-2-one (11b). A solution of 10.08 g (30 mmol) of **10b** in 60 mL of **3**N aqueous HCl was warmed at reflux for 5 h. After cooling to room temperature the solution was washed twice with ether and the aqueous phase neutralized with solid K_2CO_3 to give an off-white precipitate. The solid was filtered, washed with water, and recrystallized from 95% ethanol to give 4.14 g (86%) of **11b** as colorless crystals: mp 245–6 °C (lit.[20] mp 254–5 °C); NMR (DMSO-d_6) 8.34 (d, J = 2, 1 H, H-7), 7.87 (d, J = 2, 1 H, H-5), 7.83 (d, J = 9.5, 1 H, H-4), 6.52 (d, J = 9.5, 1 H, H-3), 2.32 (s, 3 H, CH_3); IR 2860 (br), 1670 (br) cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.17; H, 5.03; N, 17.41.

7-Methyl-1,8-naphthyridin-2-one (11c). A solution of 6.72 g (20 mmol) of **10c** in 40 mL of 3 N aqueous HCl was warmed at reflux for 3 h. The pale yellow solution was then cooled to room temperature and extracted twice with ether. The aqueous layer was neutralized with solid K_2CO_3 and the resulting yellow precipitate was filtered, washed with water, and reserved. The filtrates were extracted three times with chloroform and the combined organic layers dried over $MgSO_4$ and evaporated to give additional solid. The solids were combined and recrystallized from acetonitrile to give 2.87 g (90%) of **11c** as pale yellow crystals: mp 180–2 °C (lit.[21] mp 176–7 °C); NMR (DMSO-d_6) 7.96 (d, J = 7.5, 1 H, H-5), 7.85 (d, J = 9.5, 1 H, H-4), 7.08 (d, J = 7.5, 1 H, H-6), 6.46 (d, J = 9.5, 1 H, H-3), 2.51 (s, 3 H, CH_3); IR 3000 (br), 1650 (br) cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.25; H, 4.92; N, 17.49.

6-Chloro-1,8-naphthyridin-2-one (11d). A solution of 14.26 g (40 mmol) of **10d** in 80 mL of dioxane and 80 mL of 3 N aqueous HCl was warmed at reflux to give a pale yellow solution from which a solid soon began to precipitate. After 5 h at reflux, the mixture was cooled to room temperature and poured over ice. The resulting precipitate was filtered, washed well with water, and dried to give 6.94 g (96%) of **11d** as colorless crystals, mp 307–9 °C (with sublimation); NMR (DMSO-d_6) 8.46 (d, J = 2.5, 1 H, H-7), 8.22 (d, J = 2.5, 1 H, H-5), 7.86 (d, J = 10, 1 H, H-4), 6.59 (d, J = 10, 1 H, H-3); IR 2900 (br), 1673 (br) cm^{-1}. Anal. Calcd for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.52. Found: C, 52.89; H, 2.72; N, 15.57.

7-Chloro-1,8-naphthyridin-2-one (11e). A mixture of 12.48 g (35 mmol) of **10e**, 50 mL of dioxane, and 50 mL of 3 N aqueous HCl was warmed at reflux for a period of 5 h. The resulting pale yellow solution was cooled to room temperature and poured over ice. A precipitate formed which was filtered, washed with water, and then recrystallized from 95% ethanol to give 5.90 g (93%) of **11e** as colorless crystals: mp 255–7 °C with sublimation (lit.[22] mp 246–53 °C, sublimes); NMR (DMSO-d_6) 8.14 (d, J = 8, 1 H, H-5), 7.92 (d, J = 9.5, 1 H, H-4), 7.28 (d, J = 8, 1 H, H-6), 6.56 (d, J = 9.5, 1 H, H-3); IR 2900 (br), 1650 (br) cm^{-1}. Anal. Calcd for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.52. Found: C, 53.00; H, 2.71; N, 15.49.

1,6-Naphthyridin-2-one (13). A mixture of 16.1 g (50 mmol) of **12** and 75 mL of 3 N aqueous HCl was warmed at reflux for a period of 4 h. The resulting solution was cooled to room temperature, diluted with water, and washed twice with ether. The aqueous layer was neutralized with solid K_2CO_3, and the precipitate which formed was filtered, washed with water, and dried to give 6.73 g (92%) of **13** as colorless crystals which were pure by TLC and NMR criteria. An analytical sample was obtained by recrystallization from ethanol to give colorless crystalline **13**: mp 296–9 °C (lit.[23] mp 290–1 °C); NMR (DMSO-d_6) 8.82 (s, 1 H, H-5), 8.44 (d, J = 5.5, 1 H, H-7), 7.98 (d, J = 9.5, 1 H, H-4), 7.20 (d, J = 5.5, 1 H, H-8), 6.56 (d, J = 9.5, 1 H, H-3); IR 2980, 2840, 1677 (br) cm^{-1}. Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.56; H, 4.17; N, 19.15.

6-Chloro-1,7-naphthyridin-2-one (16). A solution of 4.63 g (13 mmol) of **15** in 70 mL of dioxane and 30 mL of 3 N aqueous HCl was warmed at reflux for a period of 4 h. The resulting light yellow solution was diluted with 100 mL of water and allowed to cool to give a white precipitate. The solid was filtered, washed with water, and dried to give 2.18 g (93%) of **16** as colorless crystals: mp 304–6 °C; NMR (DMSO-d_6) 8.42 (s, 1 H, H-8), 7.89 (d, J = 9.5, 1 H, H-4), 7.77 (s, 1 H, H-5), 6.79 (d, J = 9.5, 1 H, H-3); IR 3010, 2880, 1672, 1410 cm^{-1}. Anal. Calcd for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.52. Found: C, 53.55; H, 2.79; N, 15.47.

2,2-Dimethyl-*N*-[3-(4-methylbenzoyl)-2-pyridinyl]-propanamide (17). A solution of 5.34 g (30 mmol) of **1a** in 60 mL of THF was treated in the usual fashion with 63 mmol of *n*-butyllithium at −78 °C, and the resulting yellow solution was allowed to stir at 0 °C for 3 h. The mixture was cooled to −78 °C, and a solution of 5.91 g (33 mmol) of *N*,4-dimethyl-*N*-methoxybenzamide in 5 mL of THF was slowly added. After warming to room temperature, the mixture was stirred for 2 h, poured into water, and extracted with two portions of methylene chloride. The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated to dryness. The residual oil was purified by preparative HPLC, eluting with 85:15 hexane/acetone, to give 6.20 g (70%) of **17** as colorless crystals: mp 128–30 °C; NMR (200 MHz) 9.92 (br, 1 H, NH), 8.59 (dd, J = 2, 5, 1 H, H-4), 7.87 (dd, J = 2, 8, 1 H, H-6), 7.62 (d, J = 8, 2 H), 7.26 (d, J = 8, 2 H), 7.10 (dd, J = 5, 8, 1 H, H-5), 2.41 (s, 3 H, CH_3), 1.23 (s, 9 H, *tert*-butyl); IR 3210 (br) 2965, 1670 (br) cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.08; H, 6.83; N, 9.19.

2-[(2,2-Dimethyl-1-oxopropyl)amino]-β-hydroxy-β-(4-methylphenyl)-3-pyridinepropanoic Acid, 1,1-Dimethylethyl Ester (18). After treatment of 4.44 g (15 mmol) of ketone **17** with 31.5 mmol of *tert*-butyl lithioacetate as described above, the reaction mixture was stirred at room temperature overnight. Standard workup followed by purification of the product by preparative HPLC, eluting with 85:15 hexane/acetone gave 4.50 g (73%, 90% based on recovered starting material) of **18** which was recrystallized from hexane containing a trace of acetone to give colorless crystalline **18**: mp 171–3 °C dec; NMR (200 MHz) 9.70 (br, 1 H, NH), 8.49 (dd, J = 2, 6, 1 H, H-6), 7.50 (dd, J = 2, 8, 1 H, H-4), 7.13 (m, 2 H), 7.06 (m, 2 H), 7.00 (dd, J = 6, 8, 1 H, H-5), 6.12 (s, 1 H, OH), 3.15 (d, J = 18, 1 H), 2.87 (d, J = 18, 1 H), 2.27 (s, 3 H, CH_3), 1.41 (s, 9 H, *tert*-butyl), 1.03 (s, 9 H, *tert*-butyl); IR 3260, 2965, 1716, 1682 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.87; H, 7.82; N, 6.79. Found: C, 69.81; H, 7.75;

(20) Ferrarini, P. L. *Ann. Chim. (Rome)* **1971**, *61*, 318.
(21) Brown, E. V. *J. Org. Chem.* **1965**, *30*, 1607.
(22) Carboni, I. S.; Da Settimo, A.; Ferrarini, P. L.; Pirisino, G. *Gazz. Chim. Ital.* **1966**, *96*, 1456; *Chem. Abstr.* **1967**, *67*, 100084g.
(23) Kobayashi, Y.; Takeuchi, I.; Sayo, H. *Chem. Pharm. Bull.* **1969**, *17*, 1045.

N, 6.68.

4-(4-Methylphenyl)-1,8-naphthyridin-2-one (19). A mixture of 2.06 g (5 mmol) of **18**, 10 mL of dioxane and 10 mL of 3 N HCl was warmed at reflux for 3 days. The mixture was then poured into water and neutralized with K_2CO_3, and the resulting solid was filtered, thoroughly washed with water, and recrystallized from acetonitrile to give 0.99 g (84%) of **19** as colorless needles: mp 233–5 °C; NMR (200 MHz) 8.51 (dd, J = 1.5, 5, 1 H, H-8), 7.78 (dd, J = 1.5, 8, 1 H, H-6), 7.33 (s, 4 H), 7.17 (dd, J = 5, 8, 1 H, H-7), 6.43 (s, 1 H, H-3), 2.36 (s, 3 H, CH_3); IR 1687 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.01; H, 5.38; N, 11.84.

3-Methyl-1,8-naphthyridin-2-one (21). To a solution of 18 mmol of LDA in 25 mL of THF prepared at −78 °C by the general procedure described above was slowly added a solution of 2.34 g (18 mmol) of *tert*-butyl propanoate in 3 mL of THF. After stirring at −78 °C for 15 min a solution of 1.75 g (8.5 mmol) of **2a** in 5 mL of THF was added, and the resulting bright yellow mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature. The mixture was poured into aqueous NH_4Cl and extracted twice with methylene chloride, and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness to leave a yellow gum. TLC of this material showed two materials, presumably a mixture of diastereomeric alcohols **20**.

The mixture of alcohols prepared above was warmed at reflux in a solution of 5 mL of dioxane and 20 mL of 3 N HCl for 24 h. The resulting solution was cooled, poured into water, and neutralized with K_2CO_3 to precipitate a tan solid. The solid was filtered, thoroughly washed with water, and dried to leave 1.08 g (79%) of **21** which was pure by TLC and NMR analysis. Recrystallization of a sample of this material from acetonitrile gave colorless crystalline **21**: mp 234–6 °C; NMR (200 MHz, DMSO-d_6) 8.42 (dd, J = 1.5, 5, 1 H, H-7), 7.98 (dd, J = 1.5, 8, 1 H, H-5), 7.74 (br s, 1 H, H-4), 7.18 (dd, J = 5, 8, 1 H, H-6), 2.07 (br s, 3 H, CH_3); IR 1663 cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.29; H, 4.96; N, 17.37.

2,2-Dimethyl-*N*-(4-chloro-2-formylphenyl)propanamide (23). A solution of 10.58 g (50 mmol) of **22**[17] in 100 mL of THF was treated at −78 °C with 125 mmol of *n*-butyllithium in the usual fashion. The resulting solution was stirred at 0 °C for 2 h when a solution of 7.3 g (100 mmol) of DMF in 10 mL of THF was slowly added. After stirring at 0 °C for 1 h, the mixture was poured into 1 N HCl, stirred for 15 min, and then extracted with two portions of ether. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The residue was purified by preparative HPLC, eluting with 9:1 hexane/ethyl acetate, to give 9.24 g (77%) of **23** as a colorless solid. The solid was recrystallized from hexane to give colorless needles of **23**: mp 92–4 °C; NMR 10.12 (s, 1 H, CHO), 8.99 (d, J = 9, 1 H, H-6), 7.84–7.63 (m, 2 H, H-3 and H-5), 1.37 (s, 9 H, *tert*-butyl); IR 3320 (br), 2985, 1680 (br, strong) cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.28; H, 6.06; N, 6.08.

5-Chloro-2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxybenzenepropanoic Acid, 1,1-Dimethylethyl Ester (24). Reaction of 7.19 g (30 mmol) of **23** and 63 mmol of *tert*-butyl lithioacetate as described above followed by a standard workup left a colorless oil which was crystallized from hexane to give 10.06 g (94%) of **24** as colorless crystals: mp 89–91 °C; NMR 9.67 (br, 1 H, NH), 8.29 (d, J = 9, 1 H, H-6), 7.49–7.23 (m, 2 H, H-4 and H-5), 5.17 (m, sharpens to dd, J = 5, 9 with D_2O, 1 H, C*H*OH), 4.44 (br, exch with D_2O, 1 H, OH), 2.93 (dd, J = 9, 17, 1 H), 2.63 (dd, J = 5, 17, 1 H), 1.49 (s, 9 H, *tert*-butyl), 1.33 (s, 9 H, *tert*-butyl); IR 3540, 3345, 2910, 1732, 1660 cm^{-1}. Anal. Calcd for $C_{18}H_{26}ClNO_4$: C, 60.75; H, 7.37; N, 3.94. Found: C, 61.06; H, 7.56; N, 3.94.

6-Chloroquinolin-2-one (25). A mixture of 5.33 g (15 mmol) of **24**, 25 mL of dioxane, and 25 mL of 3 N HCl was warmed at reflux for a period of 4 h. The mixture was cooled and poured into water, and the resulting precipitate was collected by filtration, dried, and then recrystallized from ethanol to give 2.36 g (88%) of **25** as colorless crystals: mp 265–7 °C (lit.[18] mp 265–6 °C); NMR (200 MHz, DMSO-d_6) 7.84 (d, J = 9, 1 H, H-4), 7.73 (d, J = 2, 1 H, H-5), 7.49 (dd, J = 2, 8.5, 1 H, H-7), 7.28 (d, J = 8.5, 1 H, H-8), 6.54 (d, J = 9, 1 H, H-3). Anal. Calcd for C_9H_6ClNO: C, 60.18; H, 3.37; N, 7.80. Found: C, 59.92; H, 3.49; N, 7.90.

Synthesis of (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic Acid: Bridging Effect of KF

A. Solladié-Cavallo* and N. Khiar

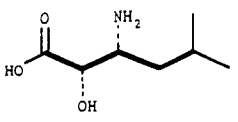
Laboratoire de stéréochimie organométallique, EHICS, 1, rue Blaise Pascal, 67008 Strasbourg, France

Received November 21, 1989

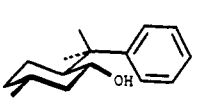
Natural (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid is synthesized in 53–55% yield (referred to (−)-8-phenylmenthol used as chiral auxiliary) by condensation of 1-nitro-3-methylbutane on (−)-8-phenylmenthol glyoxylate hydrate using KF as a mild base. With a large excess of KF in THF it has been possible to increase the diastereoselectivity of the nitro aldol condensation (up to **I**/**II**/**III**/**IV** = 77/13/10/0).

(2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic acid (**8a**) is the N-terminal amino acid of amastatine,[1] a tetrapeptide which has been found to inhibit leucine aminopeptidase and aminopeptidase A.[2] Recently it has been shown[3] that an antihypertensive drug, KRI 1230, containing the 2*R*,3*S* isomer of this acid is a human renin inhibitor as potent as the corresponding compound containing (3*S*,4*S*)-statine which drew new attention to this acid.

Amino hydroxy acid **8** has been synthesized from D-leucine[4,5] as a mixture of 2*S*,3*R* and 2*R*,3*R* diastereomers



(2S,3R)-8



(−)-8-phenylmenthol [29]

in a 70/30 ratio, respectively, and a total yield for the mixture of about 45% or from L-leucine[6] as a mixture of 2*R*,3*S* and 2*S* 3*S* in a 23/77 ratio, respectively, and a total yield for the mixture of about 45%.[7] Amino hydroxy acid,

(1) Tobe, H.; Morishima, H.; Naganawa, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Agr. Biol. Chem.* **1979**, *43*, 591.
(2) Aoyagi, T.; Tobe, H.; Kojma, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antiobiot.* **1978**, *31*, 221.
(3) Iizuka, K.; Kamijo, T.; Kubota, T.; Akahane, K.; Umeyama, H.; Kiso, Y. *J. Med. Chem.* **1988**, *31*, 701.
(4) Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.* **1977**, *20*, 510.
(5) Rich, D. H.; Moon, B. J.; Boparai, A. S. *J. Org. Chem.* **1980**, *45*, 2288.
(6) Johnson, R. L. *J. Med. Chem.* **1982**, *25*, 605.

0022-3263/90/1955-4750$02.50/0