CH); ^{13}C NMR (D_2O, dioxane = 66.5 MHz) δ 22.67 (2), 26.51 (2), 26.90 (2), 27.13 (2), 30.35 (2), 47.46 (2, NCH_2), 56.23 (1), 59.48 (1), 70.01 (2, OCH_2), 134.72 (0, C-2), 143.21 (1, 3 C, C-3 and C=C), 166.22 (C(O)N), 171.43 (C(O)O). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.6; H, 6.6; N, 8.2.

The hydrogen fumarate of (1*R*)-anatoxinal *O*-methyloxime (**9**) was prepared from crude **53**: 72% yield; mp 197-199 °C; ^1H NMR (D_2O/DMSO-d_6, 2.49 ppm) δ 1.65-1.79 (m, 2 H), 1.84-2.13 (m, 3 H), 2.22-2.47 (m, 3 H), 3.72 (s, 3 H, OCH_3), 4.08-4.15 (m, 1 H, H-6), 4.75 (d, 1 H, *J* = 9.2, H-1), 6.24 (dd, 1 H, *J* = 4.0, 8.1, H-3), 6.46 (s, 2 H, HC=CH), 7.64 (s, 1 H, H-10); ^{13}C NMR (D_2O/DMSO-d_6 = 39.50 ppm) δ 24.32, 27.73, 28.70, 31.01, 53.97, 60.04, 62.92, 136.32, 137.12, 144.03, 152.27, 171.15. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.7; H, 6.8; N, 9.4. Found: C, 56.7; H, 6.9; N, 9.2.

The hydrogen fumarate of (1*R*)-2-(Hydroxymethyl)-9-azabicyclo[4.2.1]non-2-ene (**10**) was prepared from **52**: mp 139-141 °C; ^1H NMR (D_2O) δ 1.63-1.70 (m, 2 H), 1.86-2.07 (m, 4 H), 2.10-2.33 (m, 4 H), 3.85 (s, 2 H, H-10a,b), 4.03 (d, 1 H, *J* = 9.2, H-6), 4.07-4.13 (m, 1 H, H-1), 5.82 (dd, 1 H, *J* = 1.8, 8.4, H-3), 6.55 (s, 2 H, HC=CH); ^{13}C NMR (D_2O, dioxane = 66.5 ppm) δ 21.91 (2), 26.31 (2), 27.89 (2), 30.30 (2), 56.91 (1), 59.33 (1), 65.82 (2, C-10), 131.62 (1, C-3), 134.43 (1, 2C, C=C), 140.58 (0, C-2), 170.45 (2 C, fumarate CO_2). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1; N, 5.2. Found: C, 58.1; H, 7.2; N, 5.1.

The hydrogen fumarate of (1*R*)-2-(Hydroxyacetyl)-9-azabicyclo[4.2.1]non-2-ene (**11**) was prepared from hydroxy ketone **45**: 58% yield; mp 193-195 °C; ^1H NMR (D_2O) δ 1.58-2.10 (m, 5 H), 2.21-2.32 (m, 1 H), 2.37-2.57 (m, 2 H), 4.07-4.15 (m, 1 H, H-6), 4.50 (s, 2 H, H-10a,b), 4.85 (d, 1 H, *J* = 9.3, H-1), 6.52 (s, 2 H, HC=CH), 7.11 (d, 1 H, *J* = 8.5, H-3); ^{13}C NMR (D_2O, dioxane = 66.5 ppm) δ 23.23 (2), 26.56 (2), 27.05 (2), 29.58 (2), 52.76 (1), 59.13 (1), 63.51 (2), 134.54 (1, 2 C), 139.76 (0, C-2), 149.18 (1, C-3), 170.76 (CO_2). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.4; N, 4.7. Found: C, 57.0; H, 6.6; N, 5.2.

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Registry No. **2**, 125736-21-2; **4**·fumarate, 125736-23-4; **5**, 125736-24-5; **5**·fumarate, 125826-61-1; **6**·fumarate, 125736-26-7; **7**·fumarate, 125736-28-9; **8**·fumarate, 125736-30-3; **9**·fumarate, 125736-32-5; **10**·fumarate, 125736-34-7; **11**·fumarate, 125736-36-9; (*S*)-**14**, 90741-31-4; **15**, 53856-93-2; (*R*)-**16**, 125736-40-5; (*S*)-**16**, 125736-39-2; **17**, 125736-41-6; **18**, 125736-42-7; **23**, 125736-43-8; **24**, 125736-44-9; (*E*)-**25**, 125736-45-0; (*Z*)-**25**, 125762-84-7; **26**, 125736-46-1; **27**, 125736-47-2; **28**, 125736-48-3; **29**, 125736-49-4; **30**, 125736-50-7; **33** (α epimer), 112020-12-9; **33** (β epimer), 112020-13-0; **35**α, 125736-01-8; **35**β, 125736-00-7; **36**, 125736-02-9; **37**α, 125736-05-2; **37**α (α-TBDMS ester), 125736-04-1; **37**β, 125736-03-0; **38**α, 125736-07-4; **38**β, 125736-06-3; **39a**, 125736-08-5; **39b**, 125736-09-6; **40a**, 125736-37-0; **40b**, 125736-38-1; (±)-**41**, 125736-10-9; **41**, 125826-58-6; **42**, 90741-53-0; **43**, 125736-11-0; **44**, 125736-12-1; **45**, 125736-13-2; **46**, 125736-14-3; **47**, 125736-15-4; **48**, 125736-16-5; **49**, 125736-17-6; **50**, 125736-18-7; **51**, 125826-59-7; **52**, 125736-20-1; (*E*)-**53**, 125736-19-8; (*Z*)-**53**, 125826-60-0.

Supplementary Material Available: Analytical data for compounds **15**, **18**, **23-30** and full experimental procedures and analytical data for compounds **16** and **17** (4 pages). Ordering information is given on any current masthead page.

Functionalization of 2-Methyl- and 2,7-Dimethyl-1,8-naphthyridine[1a]

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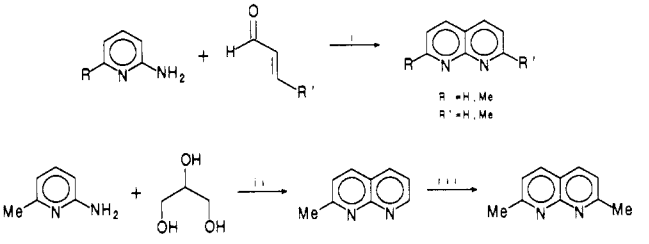
A new synthesis of 2,7-dimethyl-1,8-naphthyridine (dmnap) from 2-methyl-1,8-naphthyridine (mnap) upon treatment with 3 equiv of methyllithium is described. Oxidation of dmnap with 8 equiv of *N*-chlorosuccinimide gave (98%) 2,7-bis(trichloromethyl)-1,8-naphthyridine (**2**), while oxidation with 4 equiv gave (97%) 2,7-bis(dichloromethyl)-1,8-naphthyridine (**1**). Hydrolysis of **2** with phosphoric acid followed by esterification gave the corresponding diester **3** in 80% overall yield. Reduction of **3** with $NaBH(OMe)_3$ afforded (55%) diol **4**. Similar functionalization of mnap afforded 2-(trichloromethyl)-1,8-naphthyridine (**6**) in 85-94% yield along with 6-chloro-2-(trichloromethyl)-1,8-naphthyridine (**7**). Methanolysis of **6** gave (78%) 2-(methoxycarbonyl)-1,8-naphthyridine (**8**), which upon reduction with $NaBH(OMe)_3$ afforded (59%) the alcohol **9**. Treatment of **6** with KOH caused a displacement of the trichloromethyl moiety, generating 1,8-naphthyridin-2-one (**10**) as the sole product. Similarly, **2** gave 7-(trichloromethyl)-1,8-naphthyridin-2-one (**11**) under mild conditions or 7-(ethoxycarbonyl)-1,8-naphthyridin-2-one (**12**) when refluxed.

In 1967, Paudler and Kress first reported a feasible one-step synthesis of 2,7-dimethyl-1,8-naphthyridine [dmnap(s)],[2] 2-methyl-1,8-naphthyridine [mnap(s)],[2] and 1,8-naphthyridine [nap(s)][2,3] from commercially available starting materials. Since then, a plethora of novel inorganic complexes have been reported (Figure 1) using these potentially bidentate ligands, ranging from dodecahedral transition-metal complexes, to dinuclear complexes containing bridging naps, to 12-coordinate icosahedral lanthanide complexes. Despite this profusion of complexes, very few derivatives of 1,8-naphthyridine have been pre-

Scheme I.[a]



[a] (i) H_2SO_4, [O]; (ii) H_2SO_4, H_3BO_3, $Fe(SO_4)$, sodium *m*-nitrobenzenesulfonate; (iii) 3 equiv of MeLi, then $KMnO_4$, Me_2CO.

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0022-3263/90/1955-2838$02.50/0

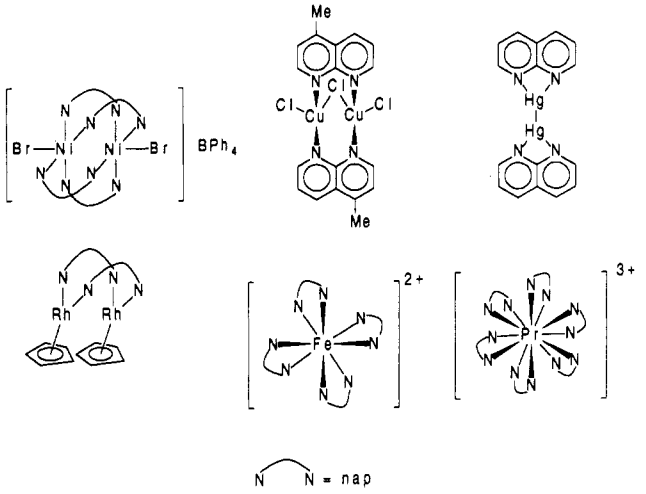


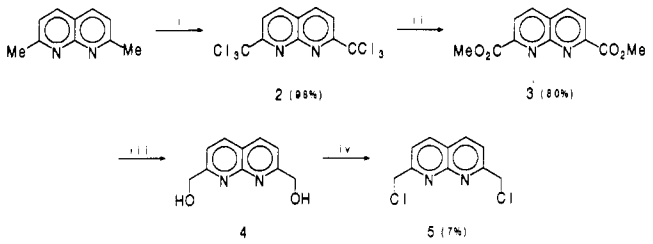
Figure 1. Interesting examples of 1,8-naphthyridine complexes.

pared that exploit the unique complexation properties of these ligands. For this reason, coupled with the decreased complexing ability of macrocyclic naphthyridine ligands possessing heteroatoms at the 2-position,[1b,4] we devised a method for the α-carbon functionalization of 2-methyl- and 2,7-dimethyl-1,8-naphthyridines.

Since the first reported synthesis of 1,8-naphthyridines,[2] several modifications have been described[5] (Scheme I) that make these ligands readily available. Although most syntheses of dmnap have focused on a Skraup synthesis in which 2-amino-6-picoline is combined with crotonaldehyde,[6,7] this procedure is difficult due to the extreme ease and exothermicity of polymerization of crotonaldehyde. Attempts to improve the synthesis of dmnap were aided by three facts: (1) mnap can be prepared in very good yields[2,5b] by the reaction of 2-amino-6-picoline with acrolein (generated in situ from glycerol); (2) nap reacts[8,9] with excess PhLi to give (after oxidation) initially 2-phenyl-1,8-naphthyridine and finally 2,7-diphenyl-1,8-naphthyridine;[9] and (3) 2,2'-dipyridine reacts[10] with MeLi to give 6,6'-dimethyl-2,2'-dipyridine. Thus, we herein report a new synthesis of dmnap by treatment of mnap with 3 equiv of MeLi followed by oxidation of the resultant dihydronaphthyridine with $KMnO_4$–acetone to give dmnap in 43% overall yield from 2-amino-6-picoline.

To the best of our knowledge, the only reports of α-carbon functionalization at the 2- and 7-positions of methyl naps utilized SeO_2. Weissenfels and Ulrici described[11] the oxidation of one methyl group of mnap and dmnap to give the monoaldehydes in 24% and 15% yields, respectively. A later report[12] used SeO_2 to oxidize 2,4-dimethyl-7-hydroxy-1,8-naphthyridine to the 2,4-dialdehyde in 49%

Scheme II.[a]



[a] (i) 8 equiv of NCS, CCl_4; (ii) H_3PO_4, 170 °C, then MeOH, reflux; (iii) $NaBH(OMe)_3$, CH_2Cl_2–THF; (iv) PCl_3, $CHCl_3$.

yield. The most recent account of this oxidation was by Chandler et al.[5d] where dmnap was oxidized to the 2,7-dialdehyde, which was incorporated into macrocycles;[5d,13] despite these reports, this oxidation was not easily reproduced.

We herein report the application of *N*-chlorosuccinimide (NCS) oxidation[14] toward methyl functionalization of 2-methyl- and 2,7-dimethyl-1,8-naphthyridines.

Results

Functionalization of 2,7-Dimethyl-1,8-naphthyridine. Attempts to bis-monofunctionalize dmnap with 2 equiv of NCS[15] gave a mixture of at least seven products, which were isolated, with difficulty, by column chromatography; none of these products were formed in greater than 10% yield. On the basis of preliminary product analysis, reaction of dmnap with 4 equiv of NCS gave 2,7-bis(dichloromethyl)-1,8-naphthyridine (**1**) in 97% yield. However, when **1** was treated with either H_2SO_4 or Bu_3SnH,[16] no reaction occurred. Thus, the sequence reported for 2,9-dimethyl-1,10-phenanthroline was utilized on dmnap (Scheme II). The bis(trichloromethyl) derivative **2** was readily obtained in 98% yield via reaction of dmnap with 8 equiv of NCS. Methanolysis of **2** with H_2SO_4 at 110 °C gave **3** in 42% yield along with **2** and 2-(trichloromethyl)-7-(methoxycarbonyl)-1,8-naphthyridine; higher temperatures (140 °C) gave no discernible organic soluble products. Ring sulfonation probably occurred under these conditions and was easily circumvented by the use of H_3PO_4; thus, treatment of **2** with H_3PO_4 at ca. 170 °C followed by MeOH gave diester **3** in 80% yield.

Although $NaBH_4$ is not generally used to reduce esters, Brown and Rapoport reported[17] that in a large excess (10 molar equiv) it can be used to reduce aromatic esters in high yields. But when **3** was treated with an excess of $NaBH_4$, diverse products were formed presumably due to ring reduction. The ^1H NMR spectrum of the mixture showed peaks ranging from the aromatic to alkenyl to aliphatic regions. Similar results were obtained with the addition of only 1 equiv of $NaBH_4$; lower temperatures (−40 and −25 °C) gave less ring reduction, but also less ester reduction. Above 0 °C, borane reduces nap to 1,2,3,4-tetrahydro-1,8-naphthyridine in 44% yield;[18] thus, a monohydride source was selected that would not produce a

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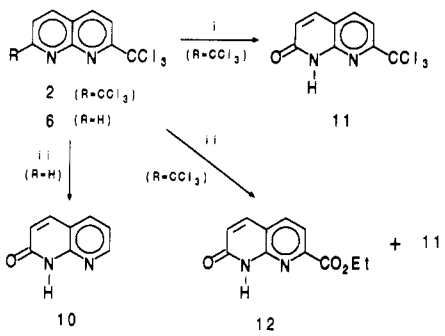
Scheme III.[a]

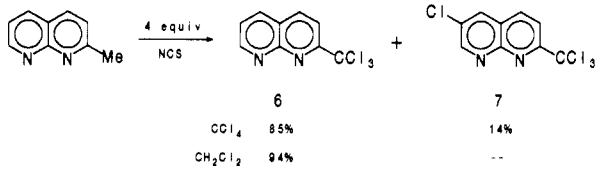


[a] (i) EtOH, KOH, 25 °C; (ii) EtOH, KOH, reflux.

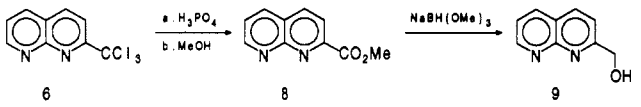
Lewis acid hydride product. Brown et al. reported[19] that $NaBH(OMe)_3$ reduces aldehydes and acyl chlorides effectively (66–79%) but is a poor reducing agent for ethyl benzoate (33%). However, reaction of **3** with 6 equiv of $NaBH(OMe)_3$ in CH_2Cl_2–THF gave diol **4** in 55% yield.

Although diol **4** has great potential for ligand modification and is in itself a tetradentate ligand, the bis(chloromethyl) derivative **5** was also a desired starting material. Reaction of **4** with PCl_3 in $CHCl_3$ did give **5**, but in only 7% yield with much decomposition. Even though pure **5** is relatively stable and can be stored for long periods, it appears that the acidic reaction conditions cause decomposition of the diol before the chlorination can occur;[20] $SOCl_2$ and concentrated HCl both gave decomposition. Several neutral chlorinating reagents were tried (PPh_3–CCl_4,[21] NCS–SEt_2,[22] treatment of the unquenched reduction mixture with PCl_3 or phenylsulfonyl chloride), with no success.

Functionalization of 2-Methyl-1,8-naphthyridine. Since the reaction of mnap with 1 equiv of NCS gave a mixture of products, treatment of mnap with 4 equiv of NCS in refluxing CCl_4 gave (85%) the desired 2-(trichloromethyl)-1,8-naphthyridine (**6**) along with 6-chloro-2-(trichloromethyl)-1,8-naphthyridine (**7**) as determined from ^1H NMR specta. Using a more selective solvent (CH_2Cl_2) for the reaction increased the yield of **6** to 94% with the formation of only a trace of **7**.



Treatment of **6** with H_3PO_4 at 140 °C followed by refluxing in MeOH gave (78%) 2-(methoxycarbonyl)-1,8-naphthyridine (**8**). Although attempts to reduce **8** with $NaBH_4$ again gave ring reduction, the use of $NaBH(OMe)_3$ afforded 2-(hydroxymethyl)-1,8-naphthyridine (**9**) in 59% yield. Attempts to chlorinate **9** under acidic conditions, as in the case of **4**, also gave decomposition of the alcohol.



Before the hydrolysis of **2** and **6** with H_3PO_4 was discovered, basic hydrolysis with KOH–EtOH was attempted. However, under these conditions, the first reaction that takes place is the displacement of the entire trichloromethyl group via nucleophilic heteroaromatic substitution to give a 2-hydroxy group (Scheme III). Thus, 1,8-naphthyridin-2-one (**10**) was obtained as the sole product from **6**, and, depending on the reaction conditions, either 7-(trichloromethyl)-1,8-naphthyridin-2-one (**11**) (25 °C) or its hydrolysis product 7-(ethoxycarbonyl)-1,8-naphthyridin-2-one (**12**) (reflux) was formed from **2**. The remaining heteroaromatic rings in **11** and **12** are not as electron deficient as in **2**; thus the second CCl_3 group is not displaced. This type of reaction has been reported for 1,3,5-triazines[23] and for quinazolines[24] but this is the first example in which a trichloromethyl group acts as a leaving group in a heterocyclic ring possessing only one heteroatom and no additional electron-withdrawing groups.[25] This reaction is not totally unexpected and is analogous to the haloform reaction for α,α,α-trihalo ketones.

NMR Spectroscopy. Both **2** and **3** exhibited downfield shifts of the aromatic resonances due to the electron-withdrawing CCl_3 and CO_2Me moieties, respectively. Diol **4** showed a resonance at 5.01 ppm due to the CH_2 group, which shifted slightly upfield in **5** to 4.9 ppm. The monosubstituted derivatives displayed similar shifts. For the naphthyridin-2-one derivatives **11** and **12**, the 3-nap*H* shifts were both shifted upfield to 6.79 ppm, due to the predominance of the lactam form, which causes a shift of the 3-nap*H* into the vinyl region.

Most of the ^{13}C NMR spectral resonances were easily assigned by comparison to the spectrum of 1,8-naphthyridine;[26] however, for **11** and **12**, the assignments for C3 and C6 were not straightforward. Shift constants for these carbons were calculated based on those derivatives (both mono- and disubstituted) that could be unequivocally assigned. Important to note is that, in 2-pyridone, the greatest shift difference in comparison to pyridine is in the 5-pyr*C* (para), which is shifted upfield by 16.9 ppm.[27] On the basis of this fact, in the spectrum of 1,8-naphthyridin-2-one (**10**), the signal at 118.6 ppm was assigned to C6. This led to an assignment of the resonances at 113.4 and 118.8 ppm in **11** and **12**, respectively, to C6.

IR Spectroscopy. The most important absorptions in the IR spectra are those of the NH and C=O stretches in **11** (3434 and 1663 cm^{-1}) and **12** (3425 and 1659 cm^{-1}) which indicate their "lactam" character.

Experimental Section

General Comments. All melting points were taken in open capillary tubes and are uncorrected. The ^1H and ^{13}C nuclear magnetic resonance spectra were recorded at 80.06 and 20.08 MHz, respectively, in $CDCl_3$ solutions, except where noted. Deuterated solvent residues were used as internal standards [$CHCl_3$: 7.27 (^1H) and 77.0 (^{13}C) ppm; Me_2SO: 2.49 (^1H) and 39.5 (^{13}C) ppm],

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and chemical shift values (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Infrared spectra (IR) were recorded on an IBM IR/38 Fourier transform infrared spectrophotometer. Elemental analyses were conducted by either Galbraith Laboratories, Inc. (Knoxville, TN), or M-H-W Laboratories (Phoenix, AZ). "Dry column" flash chromatography was performed by the method of Harwood[28] using preparative grade silica gel (Brinkman PF-254-366) in a quartz funnel with the eluants specified.

Reagents. Unless otherwise noted, all reagents and solvents utilized were of reagent grade and no further purification was undertaken. 2-Methyl-1,8-naphthyridine was prepared by the method of Hamada et al.[5b]

2,7-Dimethyl-1,8-naphthyridine. A solution of 2-methyl-1,8-naphthyridine (7.87 g, 55.0 mmol) in anhydrous Et_2O was cooled to −60 °C via a dry ice–acetone bath. Methyllithium (102 mL, 1.55 M, 158 mmol) was added dropwise at a rate such that the temperature was maintained <−50 °C. After 2 h, the solution was warmed to 25 °C for an additional 2 h and then carefully quenched with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo.[29] The resulting orange solid was oxidized with a solution of $KMnO_4$ in acetone. The solution was filtered, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (84%) 2,7-dimethyl-1,8-naphthyridine as a pale yellow solid: 7.3 g; mp 193–195 °C (C_6H_{12}) (lit.[7] mp 194–195 °C).

2,7-Bis(dichloromethyl)-1,8-naphthyridine (1). A suspension of dmnap (500 mg, 3.16 mmol), *N*-chlorosuccinimide (NCS; 1.69 g, 13.0 mmol), and benzoyl peroxide (100 mg) in CCl_4 (75 mL) was refluxed for 2 h and then cooled, filtered, and concentrated in vacuo to give (97%) **1** as colorless crystals: 906 mg; mp 179–180 °C; ^{1}H NMR δ 6.98 (s, $CHCl_2$, 1 H), 8.15 (d, 3,6-nap*H*, $J_{3,4}$ = 8.0 Hz, 1 H), 8.28 (d, 4,5-nap*H*, $J_{3,4}$ = 8.0 Hz, 1 H); IR (KBr) 3000, 1590, 1490, 1245, 1020, 830, 770 cm^{-1}; MS *m/e* 268 (2), 231 (100). Anal. Calcd for $C_{10}H_6N_2Cl_4$: C, 40.58; H, 2.04; N, 9.46. Found: C, 40.26; H, 1.97; N, 9.28.

2,7-Bis(trichloromethyl)-1,8-naphthyridine (2) was prepared (89%) from dmnap (500 mg, 3.16 mmol) by oxidation with NCS (3.38 g, 26.0 mmol) using the above procedure: 6.69 g; mp 234–236 °C (C_6H_{12}); ^{1}H NMR δ 8.28 (d, 3-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H), 8.47 (d, 4-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H); ^{13}C NMR δ 95.3 (CCl_3), 118.8 (C3), 121.0 (C4a), 137.3 (C4), 149.9 (C8a), 160.4 (C2); MS *m/e* 364 (6), 333 (21), 331 (67), 329 (100), 327 (64), 294 (33), 292 (21), 222 (11); IR (KBr) 1605, 1549, 1495, 876, 826, 772 cm^{-1}. Anal. Calcd for $C_{10}H_4N_2Cl_6$: C, 32.92; H, 1.10; N, 7.68; Cl, 58.30. Found: C, 32.76; H, 1.16; N, 7.51; Cl, 57.97.

2,7-Bis(methoxycarbonyl)-1,8-naphthyridine (3). A solution of **2** (7.00 g, 19.1 mmol) in 85% H_3PO_4 (25 mL) was heated to 160–170 °C. After 3 h (all of **2** had dissolved) the solution was cooled to 25 °C and MeOH (150 mL) was carefully added. After 12 h of refluxing, most of the MeOH was removed in vacuo, and then $CHCl_3$ (150 mL) and saturated aqueous Na_2CO_3 were carefully added. The solution was stirred vigorously for 15 min, the organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the $CHCl_3$ was removed in vacuo to give (80%) diester **3**: 3.76 g; mp 215–217 °C dec; ^{1}H NMR δ 4.08 (s, CH_3, 3 H), 8.34 (d, 3-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 8.46 (d, 4-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H); ^{13}C NMR δ 52.9 (CH_3), 123.3 (C3), 125.3 (C4a), 138.4 (C4), 152.2 (C2), 154.3 (C8a), 165.4 (CO); MS *m/e* 246 (2), 216 (30), 215 (5), 188 (100), 187 (24), 157 (5), 156 (40), 128 (67); IR (KBr) 1709, 1381, 1136, 872, 772 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.66; H, 4.25; N, 11.09.

2,7-Bis(hydroxymethyl)-1,8-naphthyridine (4). Method A. A solution of sodium trimethoxyborohydride (250 mg, 1.95 mmol) in THF (10 mL) was added to a stirred solution of diester **3** (78 mg, 317 μmol) in CH_2Cl_2 (10 mL). The solution was maintained at 25 °C for 1 h after which the solvents were removed in vacuo. The remaining solid was dissolved in saturated aqueous $NaHCO_3$ (10 mL), and the water was removed in vacuo. The resulting solid was extracted with hot EtOH (3 × 20 mL), and the EtOH was removed in vacuo; extraction of the resultant solid with CH_2Cl_2 and removal of the solvent in vacuo gave (55%)[30] diol **4**: 33 mg; mp 143–145 °C (CH_3CN); ^{1}H NMR δ 1.61 (br s, OH, 1 H), 5.01 (s, CH_2, 2 H), 7.48 (d, 3-nap*H*, $J_{3,4}$ = 8.3 Hz, 1 H), 8.21 (d, 4-nap*H*, $J_{3,4}$ = 8.3 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 66.2 (CH_2), 120.9 (C3), 122.5 (C4a), 139.6 (C4), 167.2 (C2) (C8a was not observed with a 20-s pulse delay); IR (KBr) 3322, 1609, 1433, 1071, 858, 804, 785 cm^{-1}; MS *m/e* 190 (51), 189 (100), 172 (58), 161 (49), 143 (73), 131 (20). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.20; H, 5.36; N, 14.72.

Method B. A solution of $NaBH_4$ (100 mg, 2.6 mmol) and diester **3** (440 mg, 1.8 mmol) in EtOH (25 mL) was stirred for 1 h at 25 °C. The EtOH was then removed and H_2O (25 mL) was added. Continuous extraction with $CHCl_3$ for 12 h afforded (12%) diol **4** after recrystallization from C_6H_6–$CHCl_3$.

2,7-Bis(chloromethyl)-1,8-naphthyridine (5). PCl_3 (75 μL, 8.6 mmol) was added dropwise to a stirred solution of diol **4** (102 mg, 0.54 mmol) in $CHCl_3$. After 30 min of refluxing, the $CHCl_3$ was removed in vacuo, and the resulting oil was neutralized with saturated aqueous Na_2CO_3 and then extracted with CH_2Cl_2. The solution was dried over anhyrous $MgSO_4$ and filtered, and the CH_2Cl_2 was removed to give traces of a white solid, which proved to be a mixture of **5** (85%) and diol **4** (15%) as determined by ^{1}H NMR. However, only 8 mg of solid was recovered (7% yield of **5**). A considerable amount of decomposition was noted in the reaction.

2-(Trichloromethyl)-1,8-naphthyridine (6). A stirred solution of 2-methyl-1,8-naphthyridine (3.0 g, 20.8 mmol) and NCS (11.10 g, 83.0 mmol) in CCl_4 (200 mL) was refluxed and benzoyl peroxide (1–3 mg) was added every 30 min for the first 2 h; the solution was refluxed for an additional 20 h. The solvent was removed in vacuo, and the solid residue was dissolved in $CHCl_3$ which was washed twice with saturated aqueous Na_2CO_3. The $CHCl_3$ solution was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to give a light yellow solid, which was purified by dry-flash chromatography ($CHCl_3$), collecting two fractions:

Fraction 1, 6-chloro-2-(trichloromethyl)-1,8-naphthyridine (7): 800 mg; 14%; mp 128–130 °C dec; ^{1}H NMR δ 8.25 (d, 5-nap*H*, $J_{5,7}$ = 2.6 Hz, 1 H), 8.26 (d, 3-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H), 8.35 (d, 4-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H), 9.11 (br s, 7-nap*H*, 1 H); ^{13}C NMR δ 97.0 (CCl_3), 119.8 (C3), 122.9 (C4a), 131.4 (C6), 134.5 (C4), 138.6 (C5), 151.8 (C8a), 154.3 (C7), 160.7 (C2); IR (KBr) 1595, 1549, 849, 829, 772 cm^{-1}; MS *m/e* 284 (7), 282 (14), 280 (10), 249 (32), 247 (100), 246 (96), 210 (15). Anal. Calcd for $C_9H_4N_2Cl_4$: C, 38.34; H, 1.43; N, 9.94; Cl, 50.30. Found: C, 38.24; H, 1.48; N, 9.77; Cl, 50.13.

Fraction 2, 2-(trichloromethyl)-1,8-naphthyridine (6): 4.38 g; 85%; mp 174–176 °C dec; ^{1}H NMR δ 7.61 (dd, 6-nap*H*, $J_{5,6}$ = 8.2, $J_{6,7}$ = 8.1 Hz, 1 H), 8.19 (d, 3-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H), 8.29 (dd, 5-nap*H*, $J_{5,6}$ = 8.2, $J_{5,7}$ = 2.0 Hz, 1 H), 8.40 (d, 4-nap*H*, $J_{3,4}$ = 8.7 Hz, 1 H), 9.23 (dd, 7-nap*H*, $J_{6,7}$ = 4.2, $J_{5,7}$ = 2.0 Hz, 1 H); ^{13}C NMR δ 97.3 (CCl_3), 118.7 (C3), 122.7 (C4a), 123.7 (C6), 136.7 (C4), 139.4 (C5), 153.7 (C8a), 154.9 (C7), 160.4 (C2); MS *m/e* 248 (18), 246 (19), 213 (68), 211 (100), 176 (21), 129 (14); IR (KBr) 1599, 1555, 824, 785, 768, 762 cm^{-1}. Anal. Calcd for $C_9H_5N_2Cl_3$: C, 43.67; H, 2.04; N, 11.32; Cl, 42.97. Found: C, 43.75; H, 1.88; N, 11.16; Cl, 42.84.

Ring chlorination was diminished when the following procedure was used. A stirred solution of mnap (1.0 g, 6.9 mmol), NCS (3.7 g, 27.2 mmol), and a catalytic amount of 2,2′-dicyano-2,2′-azopropane (AIBN, ca. 5 mg) in CH_2Cl_2 (100 mL) was refluxed; additional AIBN (ca. 5 mg) was added every hour for 4 h. The solution was refluxed for an additional 12 h, cooled, washed twice with saturated aqueous Na_2CO_3, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo to give (94%) **6** as a light yellow solid. Only traces of ring-chlorinated product were detected (<5%).

2-(Methoxycarbonyl)-1,8-naphthyridine (8). A stirred mixture of **6** (1.6 g, 6.5 mmol) and 85% H_3PO_4 (10 mL) was heated to 140 °C for 3 h. After the mixture cooled, anhydrous MeOH (25 mL) was carefully added, and the mixture was refluxed for 12 h. Most of the MeOH was removed, and the remaining slurry

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(29) The product obtained at this point easily sublimes [25 °C (1 mm)] and so cannot be dried thoroughly under vacuum.

(30) A ^{1}H NMR (D_2O) spectrum of the unquenched reaction mixture showed only one naphthyridine derivative: δ 5.07 (s, CH_2OH, 2 H), 7.76 (d, 3-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 8.39 (d, 4-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H).

was treated with saturated aqueous Na_2CO_3. Extraction of the basified solution with CH_2Cl_2 followed by drying over anhydrous $MgSO_4$ and removal of the CH_2Cl_2 gave (78%) **8** as a tan solid: 950 mg; mp 146–150 °C; ^1H NMR δ 4.08 (s, CH_3, 3 H), 7.59 (dd, 6-nap*H*, $J_{5,6}$ = 8.2, $J_{6,7}$ = 4.2 Hz, 1 H), 8.26 (d, 3-nap*H*, $J_{3,4}$ = 9.8 Hz, 1 H), 8.27 (dd, 5-nap*H*, $J_{5,6}$ = 8.2, $J_{5,7}$ = 2.0 Hz, 1 H), 8.40 (d, 4-nap*H*, $J_{3,4}$ = 9.8 Hz, 1 H), 9.24 (dd, 7-nap*H*, $J_{6,7}$ = 4.2, $J_{5,7}$ = 2.0 Hz, 1 H); ^{13}C NMR δ 52.6 (CH_3), 121.6 (C6), 123.4 (C3), 124.0 (C4a), 136.6 (C5), 138.5 (C4), 150.6 (C8a), 154.6 (C7), 155.0 (C2), 165.4 (CO); MS *m/e* 158 (22), 130 (100), 129 (40); IR (KBr) 1709, 1601, 1451, 1318, 1235, 1140, 870, 801, 774 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.64; H, 4.41; N, 14.69.

2-(Hydroxymethyl)-1,8-naphthyridine (9). A solution of sodium trimethoxyborohydride (379 mg, 2.97 mmol) in THF (10 mL) was added to a stirred solution of ester **8** (184 mg, 979 μmol) in CH_2Cl_2 (10 mL). The solution was maintained at 25 °C for 1 h, and the solvents were removed in vacuo. The remaining solid was dissolved in saturated aqueous $NaHCO_3$ (10 mL), and the water was removed in vacuo. The resulting solid was then extracted with hot EtOH (3 × 20 mL), and the combined EtOH extract was concentrated in vacuo to give a solid, which was purified by dry-flash chromatography [EtOAc, then EtOAc–EtOH (3:2)] to give (59%) alcohol **9**: 93 mg; mp 99–100 °C (C_6H_6–$CHCl_3$); ^1H NMR δ 4.40 (br, OH, 1 H), 5.01 (s, CH_2, 2 H), 7.46 (d, 3-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 7.51 (dd, 6-nap*H*, $J_{5,6}$ = 8.1, $J_{6,7}$ = 4.3 Hz, 1 H), 8.20 (d, 4-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 8.22 (dd, 5-nap*H*, $J_{5,6}$ = 8.1, $J_{5,7}$ = 2.0 Hz, 1 H), 9.10 (dd, 7-nap*H*, $J_{6,7}$ = 4.3, $J_{5,7}$ = 2.0 Hz, 1 H); ^{13}C NMR δ 64.5 (CH_2), 119.7 (C3), 122.2 (C6), 137.2, 137.9 (C4, C5), 153.7 (C7), 163.9 (C2) (C4a and C8a were not observed with a 4-s delay); IR (KBr) 3412, 1607, 1499, 1080, 848, 808, 777 cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.25; H, 5.16; N, 17.30.

Reaction of 2,7-Bis(trichloromethyl)-1,8-naphthyridine (2) with KOH in EtOH. A stirred solution of **2** (254 mg, 696 μmol) and KOH (474 mg, 8.46 mmol) in EtOH (35 mL) was refluxed for 3 h. The EtOH was then removed in vacuo, and aqueous saturated $NaHCO_3$ (10 mL) was added. The aqueous solution was extracted with $CHCl_3$ (3 × 15 mL), the combined organic solution was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to give a brown solid, which was purified by dry-flash chromatography [$CHCl_3$, then $CHCl_3$–EtOAc (1:1)] to give two fractions:

Fraction 1, 7-(trichloromethyl)-1,8-naphthyridin-2-one (11): 73 mg; 40%; mp 201–202 °C dec; ^1H NMR δ 6.79 (d, 3-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.74 (d, 4-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.86 (d, 6-nap*H*, $J_{5,6}$ = 8.2 Hz, 1 H), 8.03 (d, 5-napH, $J_{5,6}$ = 8.2 Hz, 1 H), 9.56 (br s, OH, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 96.8 (CCl_3), 113.4 (C6), 115.8 (C4a), 125.3 (C3), 138.2 (C4), 138.9 (C5), 148.9 (C8a), 157.1 (C7), 163.0 (C2); MS *m/e* 264 (11), 262 (10), 229 (71), 227 (100); IR (KBr) 3434, 1663, 1597, 1547, 870, 824, 762 cm^{-1}. Anal. Calcd for $C_9H_5N_2Cl_3O$: C, 41.02; H, 1.91; N, 10.63; Cl, 40.36. Found: C, 41.20; H, 1.87; N, 10.31; Cl, 40.41.

Fraction 2, 7-(ethoxycarbonyl)-1,8-naphthyridin-2-one (12): 26 mg; 17%; mp 207–208 °C dec; ^1H NMR δ 1.45 (t, CH_3, J = 7.1 Hz, 3 H), 4.50 (q, CH_2, J = 7.1 Hz, 2 H), 6.79 (d, 3-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.74 (d, 4-napH, $J_{3,4}$ = 9.6 Hz, 1 H), 7.99 (s, 5,6-nap*H*, 2 H), 9.48 (br s, OH, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 14.0 (CH_3), 61.4 (CH_2), 117.1 (C4a), 118.8 (C6), 125.4 (C3), 137.8 (C5), 138.4 (C4), 147.4 (C8a), 149.8 (C7), 163.0 (C2), 164.4 (CO); MS *m/e* 218 (30), 173 (7), 146 (100), 145 (30); IR (KBr) 3425, 1730, 1659, 1595, 1547, 1287, 1154, 764 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.74; N, 12.71.

When the reaction was conducted at 25 °C for 36 h, the formation of **11** was increased (79%) and very little **12** was formed.

Reaction of 2-(Trichloromethyl)-1,8-naphthyridine (6) with KOH in EtOH. A stirred solution of **6** (268 mg, 1.08 mmol) and KOH (623 mg, 11.1 mmol) in absolute EtOH (20 mL) was refluxed for 3 h and worked up as described above for **2** to give (61%) **1,8-naphthyridin-2-one (10)**: 96 mg; mp 198–201.5 °C (lit.[31] mp 198–199 °C); ^{13}C NMR δ 115.0 (C4a), 118.6 (C6), 123.8 (C3), 136.4 (C5), 138.8 (C4), 150.0 (C8a), 150.6 (C7), 164.0 (C2). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.59; H, 4.23; N, 19.10.

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Registry No. **1**, 125902-19-4; **2**, 125902-20-7; **3**, 125902-21-8; **4**, 125902-22-9; **5**, 125902-23-0; **6**, 125902-24-1; **7**, 125902-25-2; **8**, 125902-26-3; **9**, 125902-27-4; **10**, 15936-09-1; **11**, 125902-28-5; **12**, 125902-29-6; 2-methyl-1,8-naphthyridine, 1569-16-0; 2,7-dimethyl-1,8-naphthyridine, 14903-78-7.

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Regiochemistry of the Rearrangement of Cyclohexenyl and Cyclohexadienyl Phosphates to β-Keto Phosphonates

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Diethyl vinyl phosphates derived from substituted cyclohexanones are known to rearrange to β-keto phosphonates upon treatment with excess LDA. To develop strategies for the regiocontrol of this rearrangement, the effect of regiospecific preparation of the vinyl phosphate has been tested and the use of dienyl phosphates has been studied. With 3-methylcyclohexanone both phosphonate regioisomers are formed in a ratio independent of the regiochemistry of the vinyl phosphate. However, regiocontrol is observed in rearrangements of dienyl phosphates derived from methyl-substituted cyclohexenones. In this series, formation of the kinetic enolate, reaction with diethyl phosphorochloridate, and in situ treatment of the intermediate vinyl phosphate with LDA result in the phosphono ketone, with C–P bond formation at the site corresponding to the original kinetic enolate. Catalytic hydrogenation of the phosphono enone then can be used to obtain a phosphono ketone. In contrast to the course of this rearrangement with cyclohexenones, the diethyl vinyl phosphate derivative of cycloheptenone undergoes a 1,2-rearrangement yielding a hydroxy phosphonate.

We recently reported that dialkyl vinyl phosphate derivatives of five- and six-membered-ring ketones undergo rearrangement to β-keto phosphonates upon treatment with base.[2,3] This reaction represents a convenient method for the synthesis of some β-keto phosphonates that cannot

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