6-[(Benzyloxycarbonyl)amino]-2(*S*)-[3(*R*)-((*tert*-butyloxycarbonyl)amino)-3-(indol-3-ylmethyl)-2-oxo-1-pyrrolidinyl]hexanoic Acid Methyl Ester (2a). The compound was prepared from **5a** according to the method described for **2b**. Spectral data is as follows: IR ($CHCl_3$) 3400, 2900, 1700 cm^{-1}; ^1H NMR (CD_3OD) δ 1.30, 1.54, and 1.75 (m, 6 H), 1.39 (s, 9 H), 2.39 (br t, 2 H, J = 8 Hz), 2.79 (m, 1 H), 3.05 (d, 1 H, J = 14 Hz), 3.15 (d, 1 H, J = 14 Hz), 3.05–3.3 (m, 3 H), 3.50 (s, 3 H), 4.64 (d of d, 1 H, J_1 = 6 Hz, J_2 = 11 Hz), 5.07 (s, 2 H), 7.03 (t, 1 H, J = 8 Hz), 7.13 (t, 1 H, J = 8 Hz), 7.14 (s, 1 H), 7.36 (m, 5 H), 7.61 (d, 1 H, J = 8 Hz); FAB mass spectrum, m/e 607 (M + H); $[\alpha]^{24}_D$ −1.69° (c 0.4, MeOH).

Isolated as a minor product from this reaction was **7a**: IR ($CHCl_3$) 1700, 1510, 1430 cm^{-1}; ^1H NMR (CD_3OD) δ 1.25–1.55 (m, 8 H), 1.73 (m, 4 H), 2.29 (m, 2 H), 2.43 (m, 2 H), 2.82 (m, 2 H), 3.05 (d, 2 H, J = 14 Hz), 3.15 (d, 2 H, J = 8 Hz), 3–3.2 (m, 6 H), 3.52 (s, 6 H), 4.62 (m, 2 H), 4.99 (s, 4 H), 7.00 (t, 2 H, J = 7 Hz), 7.09 (t, 2 H, J = 8 Hz), 7.15 (s, 2 H), 7.2–7.35 (m, 10 H), 7.56 (d, 2 H, J = 8 Hz); FAB mass spectrum, m/e 1039 (M + H); $[\alpha]^{24}_D$ −11.74° (c 0.28, MeOH).

Acknowledgment. I thank Dr. B. Arison, Dr. D. Cochran, and J. Murphy for NMR spectra, J. Smith for FAB mass spectra, C. Homnick for HPLC support, Y. Lee for optical rotations, and C. Colton for technical assistance. I also thank M. Banker for typing the manuscript and Drs. D. Veber and P. Anderson for their support of this work.

Registry No. **2a**, 97569-97-6; **2b**, 97569-98-7; **3**, 27894-50-4; **4**, 5617-70-9; **5** (isomer 1), 97551-29-6; **5** (isomer 2), 97551-30-9; **6a**, 97569-99-8; **6b**, 97551-31-0; **7a**, 97570-00-8; **7b**, 97643-01-1; N^{ϵ}-(benzyloxycarbonyl)-N^2-formyllysine methyl ester, 53917-46-7; gramine methiodide, 5457-31-8.

Enantioselective Synthesis of the Depsipeptide Unsaturated Acid Portion of Madumycin II

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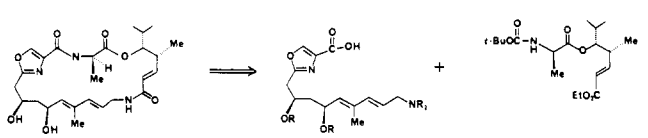
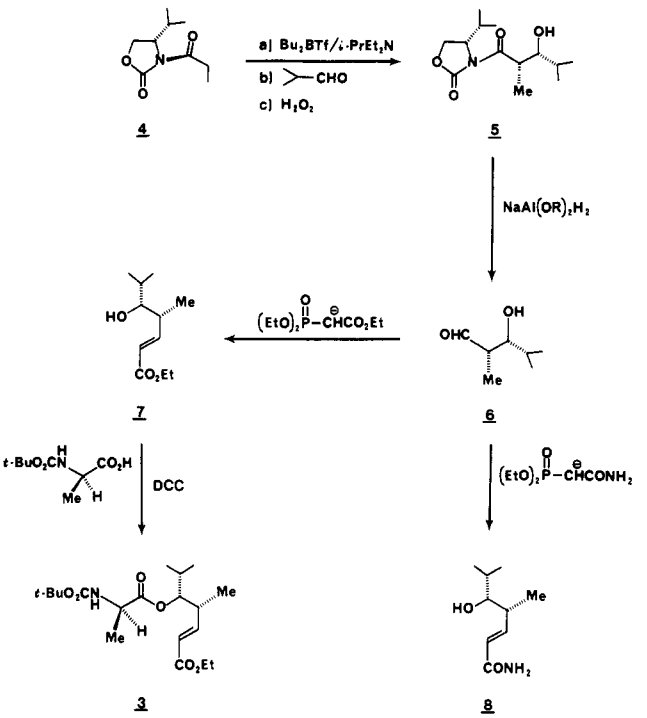
In our efforts directed toward the synthesis of the group A streptogramin antibiotics,[1] griseoviridin,[2] and madumycin II (1), we required an enantioselective route to the depsipeptide unsaturated ester **3**. Our strategy called for coupling **3** to the oxazole moiety **2**[3] to reach madumycin II.



(+)1 (+)2 (+)-3

We describe herein an efficient approach to (+)-**3** which further demonstrates the utility of the oxazolidone-mediated asymmetric synthesis developed by Evans.[4]

Treatment of the *N*-propionyl imide **4** with di-*n*-butyl boron triflate in the presence of Hunig's base produced the *Z*-enolate and addition of isobutyraldehyde at −78 °C gave the β-hydroxy imide **5**, in 71% yield, after oxidative



4 5 7 6 3 8

workup. The diastereomeric ratio of **5** (523:1) was determined via gas chromatography on the *O*-silyl ether with the syn diastereomer predominating. Methanolysis of **5** to its methyl ester and comparison of the optical rotation with the known material indicated that the enantioselectivity was greater than 99%. A single recrystallization gave **5** free of any epimeric material. Reduction with sodium bis(methoxyethoxy) aluminum hydride (Red-Al) produced the β-hydroxy aldehyde **6** which proved to be unstable when isolation was attempted (distillation or chromatography). Therefore, **6** was treated in crude form directly with the potassium salt of triethyl phosphonoacetate at −78 °C and, after workup and purification via chromatography, gave the unsaturated ester **7** in 45% overall yield from **5**. Similarly, reaction of the hydroxy aldehyde **6** with the potassium salt of diethyl phosphonoacetamide gave the unsaturated amide **8** in 32% purified yield.

Ganem[5] has reported an enantioselective synthesis of **7** starting with (*Z*)-β-isopropylallyl alcohol and, after a Sharpless asymmetric epoxidation, followed by seven synthetic steps, furnished the product in 66% ee. More significant in the Ganem work, however, was the confirmation of the absolute stereochemistry in these antibiotics (e.g., virginiamycin M and madumycin) by conversion of **7** into the known lactone degradation product [(2*R*,3*R*)-**9**].

9 10

Our analytical determination of **7** (HPLC) indicated it was now a 96:4 mixture of syn and anti material, with a trace (~2%) of (*Z*)-olefin. Apparently a small amount of epimerization took place at the α-carbon during the Red-Al

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(2) For synthetic studies; see: Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.

(3) Meyers, A. I.; Lawson, J.; Amos, R. A.; Walker, D. G.; Spohn, R. F. *Pure Appl. Chem.* **1982**, *54*, 2537.

(4) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *Ibid.* **1982**, *104*, 1737. Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(5) Wood, R. D.; Ganem, G. *Tetrahedron Lett.* **1982**, *23*, 707.

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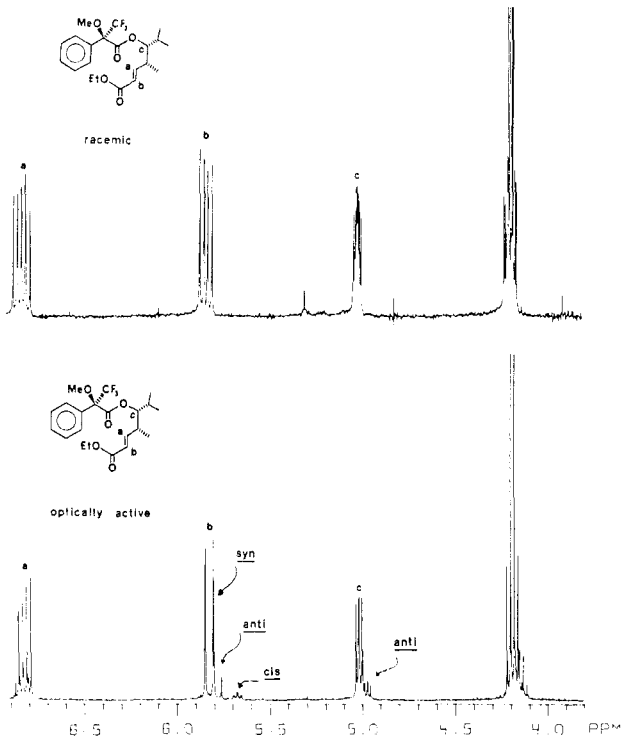

Figure 1.

reduction of **5** to **6**. Furthermore, the Mosher ester[6] **10** was prepared and 360-MHz ^1H spectra (Figure 1) showed that *syn*-(*E*)-**7** was >99% enantiomercally pure with 4–5% anti-(*E*)-**7** present. The ee determination of **10** was made by comparison with racemic **10** (Figure 1). Esterification of **7** to the appropriate alanine ester suitably protected for further use in the synthesis of **1** was accomplished by using *N*-*t*-BOC-alanine in the presence of dicyclohexylcarbodiimide–(dimethylamino)pyridine. The depsipeptide unsaturated ester **3** was thus formed in 63% yield after chromatography.

In summary, we have provided an efficient route to our target compound and also shown an efficient method for the direct conversion of the β-hydroxy imide **5** to the corresponding aldehyde **6** required for the purpose at hand.

Experimental Section

***N*-(2(*S*)-Methyl-3(*R*)-hydroxy-4-methylpentanoyl)-4-(*S*)-isopropyloxazolidone (5).** To 125 mL of dry distilled CH_2Cl_2 (from P_2O_5) at 0 °C were added 9.35 g (49.93 mmol) of oxazolidone **4**, 15.08 g (13.0 mL, 1.1 equiv, 55 mmol) of Bu_2BTf, and 10.45 mL (1.2 equiv) of Hunig's base (diisopropylethylamine, distilled from CaH_2). The mixture was stirred for 30 min at 0 °C followed by stirring at −78 °C for 30 min, and then 1.1 equiv (10.45 mL) of distilled isobutyraldehyde was added neat, stirred at −78 °C for 30 min and then 1.5 h at room temperature. After cooling to 0 °C, the reaction was quenched with a mixture of 250 mL of absolute methanol and 120 mL of pH 7.0 buffered water at 0 °C. The borate was oxidized by adding 120 mL of 30% H_2O_2 and stirring at 0 °C for 1 h. Ether extraction followed by a brine wash, drying (Na_2SO_4), and concentration in vacuo gave 11 g (85%), mp 59–64 °C. The material was recrystallized from diethyl ether to give colorless needles: mp 84–85 °C $[\alpha]_D$ −8.22° (*c* 4.7, $CHCl_3$) [lit.[4] $[\alpha]_D$ −7.9° (*c* 5.7, $CHCl_3$)].

2(*S*)-Methyl-3(*R*)-hydroxy-4-methylpentanal (6). To a 50-mL flask under argon charged with 25 mL of dry THF was added 1.1 equiv (1.44 mL, 2.7 mmol, 1.88 M benzene) of sodium bis(2-methoxyethoxy) aluminum hydride. Following cooling to −78 °C, 0.640 g (2.47 mmol) of the β-hydroxy imide **5** in 10 mL of THF was added slowly. The evolution of gas can be seen as the solution was stirred for 10–15 min at −78 °C. This was then warmed ca. −50 °C ($CaCl_2$ (aqueous)/dry ice) and stirred between −55 °C and −40 °C for 1 h. The reaction was quenched at −50 °C with 4 mL of EtOAc and 1 mL of MeOH and then poured into a mixture of 14 mL of 5% HCl and 30 mL of Et_2O at −20 °C and stirred for 10–15 min. The aqueous layer froze out as a gel. The organic layer was decanted, and the gel was quickly rinsed twice (15 mL, Et_2O). The combined organic extracts were dried (K_2CO_3) and concentrated in vacuo to an oil, 0.634 g (200%). Attempts to purify the aldehyde led to complete decomposition: ^1H NMR ($CDCl_3$) δ 0.70–1.32 (m, 15), 1.32–21(m, 2), 2.33–2.8 (m, 1), 3.2–3.9 (m, 3), 3.9–4.57 (m, 1), 6.9 (s, 1), 9.66 (s, 1); IR 1700–1740 cm^{-1} br. The aldehyde was carried on immediately to the olefination step.

(*E*)-Ethyl 4(*R*)-Methyl-5(*R*)-hydroxy-6-methyl-2-heptenoate (7). The synthesis of either the amide **8** or the ester **7** differ only in the phosphonate reagent that was used. The ester synthesis is given here. To 125 mL of THF in a 250-mL flask under argon was added 2.78 mL (14.0 mmol, 1.15 equiv) of triethyl phosphonoacetate, followed by 1.49 g (1.1 equiv, 13.3 mmol) of potassium *tert*-butoxide. This mixture was stirred at room temperature for 5 min and then cooled to −78 °C. The crude hydroxy aldehyde **6** (3.02 g, 12.09 mmol, 1.0 equiv) in 25 mL of THF was then slowly added and stirred overnight while warming to room temperature. The mixture was poured into brine, extracted with (3 × 50 mL) Et_2O, dried (K_2CO_3), and concentrated in vacuo to 0.566 g. Flash chromatography (60% Et_2O/hexane) gave 1.091 g, 45% yield based on the starting oxazolidone **5**: ^1H NMR ($CDCl_3$) δ 0.85–1.45 (12, m), 1.45–1.95 (1, m), 2.13 (s, 1, OH, exchanges with D_2O), 2.16–2.74 (1, m), 3.2 (1, t, *J* = 5.5 Hz), 4.12 (2, q, *J* = 7 Hz), 5.75 (1, d of d, *J* = 1, 16 Hz), 6.84 (1, d of d, *J* = 8, 16 Hz); $[\alpha]_D$ +18.97° (*c* 5.83, $CHCl_3$). HPLC (60% H_2O/40% MeOH, reverse phase) shows 95.5% pure syn compound and 4.5% anti compound. The syn compound is 100% ee by analysis of the Mosher ester that follows.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.70; H, 10.11.

(*E*)-4(*R*)-Methyl-5(*R*)-hydroxy-6-methyl-2-heptenamide (8). Following the above reaction using the β-hydroxy aldehyde **6** (0.684 g, 2.66 mmol) from imide **5**, 1.56 g (3.0 equiv, 8.0 mmol) of diethyl phosphonoacetamide and 0.842 g (2.8 equiv, 7.5 mmol) of sublimed potassium *tert*-butoxide afforded 0.142 g (32%) of the α,β-unsaturated hydroxy amide **8**. Purification was accomplished by radial chromatography (EtOAc): ^1H NMR ($CDCl_3$) δ 0.85–1.35 (m, 9), 1.4–2.0(m, 1), 2.30–2.80 (m, 2, after D_2O, m, 1), 3.1–3.35 (m, 1), 5.82 (d, *J* = 16 Hz, 1), 6.15 (s, 2, after D_2O, 0), 6.75 (d of d, *J* = 7, 16 Hz, 1). The amide was very hygroscopic and water soluble, and suitable precautions were necessary.

Anal. Calcd for $C_9H_{17}O_2N$; C, 63.13; H, 10.01; Found: C, 62.76; H, 10.10.

(*E*)-Ethyl 4(*R*)-Methyl-5(*R*)-[(2*R*)-2-phenyl-2-methoxy-2-(trifluoromethyl)acetoxy]-6-methyl-2-heptenoate (10). To 0.100 mL of carbon tetrachloride and 0.200 mL or pyridine was added 0.060 g of hydroxy ester **7** and 0.111 g (1.5 equiv) of 2-(S)-phenyl-2-methoxy-2-(trifluoromethyl)acetyl chloride and stirred at ambient temperature overnight. The solution and precipitate were added to Et_2O (10 mL), washed with H_2O (5 mL), 5% HCl (5 mL), saturated $NaHCO_3$ (5 mL), and brine (2 × 5 mL), dried (K_2CO_3), filtered, and concentrated to 0.125 g (100%). HPLC (50% Et_2O/hexanes) afforded 0.100 g (80%): ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (d, *J* = 8.4 Hz, 3), 0.92 (d, *J* = 8.4 Hz, 3), 0.98 (d, *J* = 8.4 Hz, 3), 1.18 (t, *J* = 8.4 Hz, 3), 1.94 (m, 1), 2.70 (m, 1) 3.53 (s, 3), 4.18 (q, *J* = 8.4 Hz, 2), 5.02 (d of d, *J* = 1, 6 Hz, 1), 5.82 (d of d, *J* = 0.5, 16 Hz, 1), 6.32 (d of d, *J* = 8.4, 16 Hz, 1), 7.39 (m, 3), 7.56 (m, 2).

Madumycin Fragment (Depsipeptide Unsaturated Ester) 3. A mixture of hydroxy unsaturated ester **7** (74.5 mg, 0.4 mmol), 4-(dimethylamino)pyridine (97.7 mg, 0.8 mmol), *t*-BOC-D-alanine (78 mg, 0.44 mmol), and 5 mL of dry dichloromethane was cooled to 0 °C and treated with dicyclohexylcarbodiimide (99 mg, 0.48 mmol). The mixture was allowed to warm to room temperature while stirring overnight. The solvent was evaporated and the residue taken up in 75 mL of ether and filtered through Celite. The solution was washed with 5% HCl (2 × 20 mL), saturated bicarbonate (2 × 20 mL), and brine (1 × 20 mL). After drying ($MgSO_4$), filtration, and concentration, the residue was chromatographed (silica, 230–400 mesh, 60% ether/hexane), furnishing

(6) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

85.8 mg of a clear, colorless oil, 3, 58%. Also obtained was 5.1 mg of recovered hydroxy acid 7. The product 3 had the following data: $[\alpha]^{25}_D$ 21.37° (c 1.17, $CHCl_3$); IR ($CHCl_3$) 3440, 1730, 1710, 1655, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (d of d, J = 8, 16 Hz, 1), 5.83 (d, J = 16 Hz, 1), 5.1–4.5 (NH), 4.85 (d of d, J = 5, 6 Hz, 1), 4.28 (q, J = 7 Hz, 2), 2.55–2.38 (m, 1), 2.05–1.78 (m, 1), 1.47 (s, 9), 1.31 (d, J = 5 Hz, 3), 1.24 (d, J = 7 Hz, 3), 1.02 (t, J = 7 Hz, 3), 0.93 (d, J = 6 Hz, 6); ^{13}C NMR δ 172.81, 165.86, 154.77, 149.16, 121.61, 60.19, 49.38, 38.41, 29.88, 19.49, 18.73, 16.57, 14.64, 14.18.

Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.43. Found: C, 63.04; H, 6.33.

Acknowledgment. R.J.L. is grateful for a National Research Service Award Postdoctoral Fellowship (NIH); A.I.M. acknowledges an Alexander von Humboldt Senior Scientist Award (1984) and wishes to express his gratitude for generous hospitality and stimulating discussions with the faculty of the University of Wurzburg. Financial assistance from the National Institutes of Health to support his work is also gratefully acknowledged.

Registry No. 1, 58717-24-1; 3, 97522-37-7; 4, 77877-19-1; 5, 77877-21-5; 6, 97522-38-8; 7, 82290-72-0; 8, 97522-39-9; 10, 97522-40-2; isobutyraldehyde, 78-84-2; triethyl phosphonoacetate, 867-13-0; diethyl phosphonoacetamide, 5464-68-6; (S)-phenyl-2-methoxy-2-(trifluoromethyl)acetyl chloride, 20445-33-4; t-BOC-D-alanine, 7764-95-6.

N-Oxides of 2,2′:6′,2″-Terpyridine

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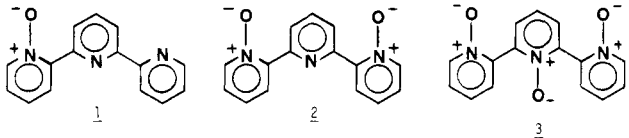
Received November 19, 1984

Whereas preparation of the tri-N-oxide of 2,2′:6′,2″-terpyridine (3) was described by Case in 1962,[1] the mono- and di-N-oxides (1 and 2) were previously unknown. We wish to report the preparation of these two systems and some conformational properties associated with this series of molecules.

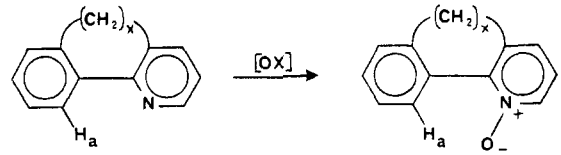


1 2 3

The tri-N-oxide 3 has been efficiently prepared (88%) by the reaction of 2,2′:6′2″-terpyridine with 30% hydrogen peroxide in acetic acid at 80 °C.[1] None of the lower N-oxides were observed in this reaction. On the other hand, the use of a stoichiometric amount of m-chloroperbenzoic acid as oxidant provides the mono-N-oxide 1 while excess of this reagent gives the di-N-oxide 2, both to the total exclusion of tri-N-oxide. Both 1 and 2 may be converted to 3 by treatment with 30% hydrogen peroxide. As expected, the increasing polarity of these substances leads to a monotonic increase in their melting points: 1 (134–135 °C), 2 (232–233 °C), and 3 (320–321 °C dec).

All three N-oxides showed a very intense and characteristic N–O stretching band at about 1250 cm^{-1} in their infrared spectra. Mass spectra were obtained by the thermospray ionization technique in which the positively charged protonated ions are observed. All three N-oxides showed a base peak equal to p + 1, giving values of m/z 250, 266, and 282 for the mono-, di-, and tri-N-oxides, respectively. Furthermore, the mono-N-oxide showed a significant peak at m/z 234, indicating the loss of one oxygen, the di-N-oxide showed peaks at m/z 250 and 234 indicating the successive loss of two oxygens, and the tri-N-oxide showed peaks at m/z 266, 250, and 234, indicating the successive loss of three oxygens. As the temperature of the thermospray nozzle was increased the proportion of deoxygenated species also increased.

Scheme I. Effect of N-Oxidation on the Bay-Region Proton of 2-Phenylpyridines



4a, X = 2; H_a = 8.28 ppm
b, X = 3; H_a = 7.71 ppm

5a, H_a = 9.38 ppm
b, H_a = 7.98 ppm

The aromatic proton resonances for terpyridine and its mono- and di-N-oxides are dispersed over almost 2 ppm making assignment of the 300-MHz NMR spectra fairly straightforward (Table I). This analysis was facilitated by comparison with the previously assigned NMR spectrum of 2,2′-bipyridine mono-N-oxide.[2] The tri-N-oxide 3 exhibits a coincidental overlap of four different resonances at about 7.85 ppm, so that complete assignment was not possible.

It is most likely that 1–3 all assume a somewhat transoid conformation such that the nitrogen lone pair electrons and the N–O moieties are oriented as far apart as possible. This geometry is substantiated by examination of the proton resonances on the central ring as one goes from terpyridine to 1 to 2 (Table I). The central $H_{4'}$ resonance is sterically and electronically unaffected by the addition of oxygen to the two neighboring pyridines and remains unchanged at 7.95–7.98 ppm. When N-1 is oxygenated, $H_{3'}$ becomes deshielded, and its resonance shifts about 0.54 ppm downfield, while $H_{5'}$ remains essentially unaffected. When N-1″ is oxygenated in 2, $H_{3'}$ is very little affected, while $H_{5'}$ moves downfield 0.47 ppm.

The degree of deshielding of $H_{3'}$ and $H_{5'}$ can also reveal information about the dihedral angle between the adjacent pyridine rings. To assist in examining this situation we considered the analogous change in chemical shift in the 3,2′-annelated 2-phenylpyridine system 4, where the dihedral angle between the two aromatic rings is controlled by the length of a polymethylene bridge (Scheme I). For system **5a**, where the bridge contains two methylene units, the dihedral angle between the phenyl and pyridyl rings as estimated from Dreiding models is about 20°. The change in chemical shift of the bay proton, H_a, upon N-oxidation is substantial (−1.1 ppm) due to its constrainment in the proximity of the deshielding N–O moiety. For **5b**, with a trimethylene bridge, the dihedral angle is estimated to be 55°, and the deshielding effect on H_a is only −0.27 ppm. Thus if we assume a proportional relationship between the changes in dihedral angle and chemical shift, for the terpyridine mono- and di-N-oxides 1 and 2, where the observed deshielding of $H_{3'}$ and $H_{5'}$ is about −0.5 ppm, we predict an intermediate dihedral angle of about 45°.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian Associates FT-80 or a Nicolet NT-300 WB spectrometer, and

(1) Case, F. H. *J. Org. Chem.* **1962**, *27*, 640.

(2) Wenkert, D.; Woodward, R. B. *J. Org. Chem.* **1983**, *48*, 283.

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