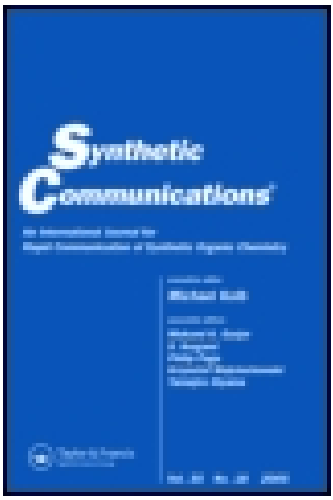

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SYNTHETIC COMMUNICATIONS, 23(13), 1897-1903 (1993)

OPTICALLY ACTIVE 2,2':6',2"-TERPYRIDINE: SYNTHESIS OF 6-[6,6-DIMETHYLNORPYNAN-2-YL]- AND 6,6"-BIS-[6,6-DIMETHYLNORPYNAN-2-YL]- 2,2':6',2"-TERPYRIDINE

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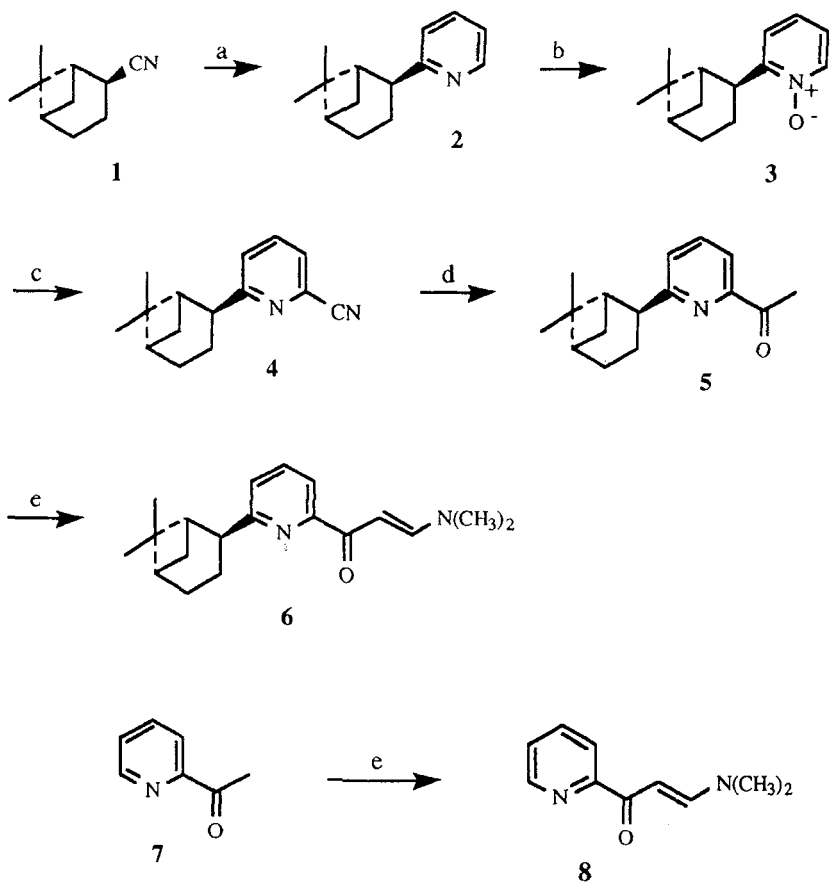
ABSTRACT: A procedure for the preparation of the title compounds from the parent 2-alkylpyridine is reported.

2,2':6',2"-Terpyridines have been extensively employed as tridentate chelating ligands in both preparative and analytical coordination chemistry.[1] Although interest in substituted terpyridines continues unabated,[2] no optically active 2,2':6',2"-terpyridine has been reported in the literature so far.

With the aim of making a new class of chiral complexes available and of investigating their effectiveness in asymmetric homogeneous catalysis, we undertook a study on a generalizable procedure to obtain optically active terpyridines.

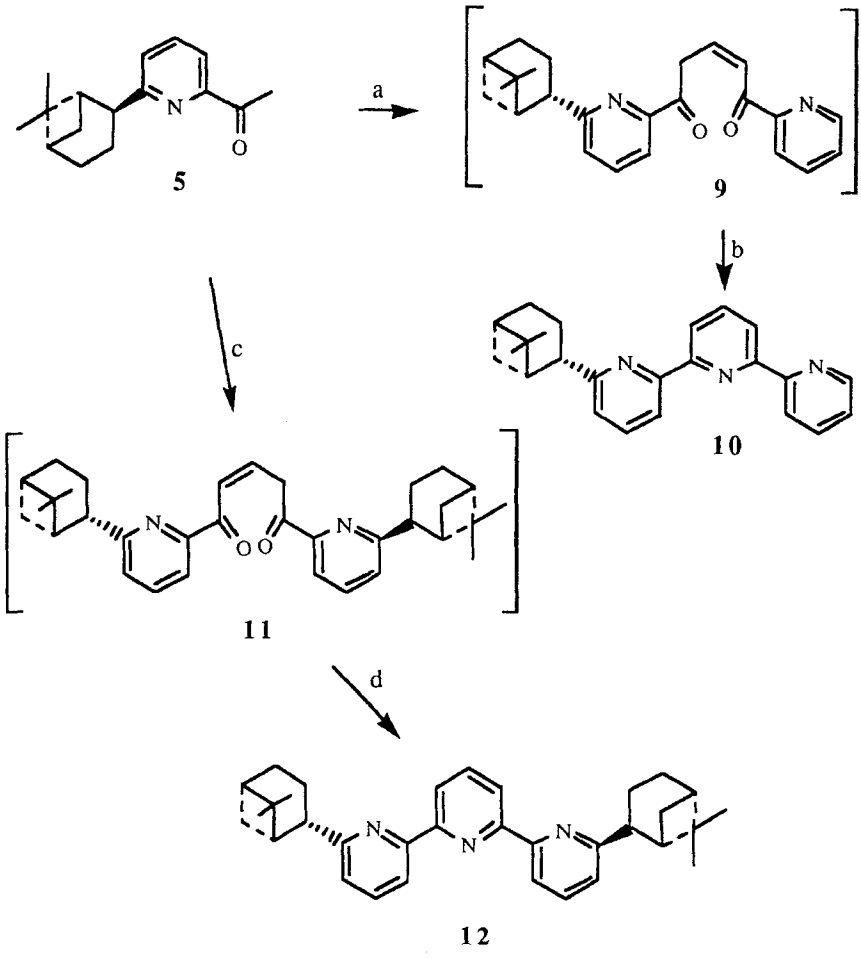
In this paper the results obtained in the synthesis of 6-[6,6-dimethylnorpynan-2-yl]-2,2':6',2"-terpyridine (**10**) and the corresponding C_2-symmetric 6,6"-bis-[6,6-dimethylnorpynan-2-yl]-2,2':6',2"-terpyridine (**12**) are reported.

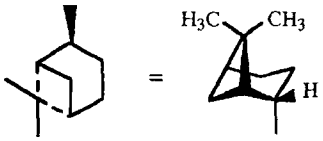
The synthesis of terpyridines **10** and **12** was achieved following the sequences reported in Schemes 1 and 2. The former sequence (Scheme 1) reports the synthesis of intermediates and the latter (Scheme 2) the final steps.



a: CpCo(COD), acetylene, 8 atm., 140 °C, 95%; b: MCPA, CH_2Cl_2, >95%; c: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2, r.t., 5 d, 95%; d: CH_3MgBr, Et_2O, 32%; e: $(CH_3)_2NCH(OCH_3)_2$, toluene, reflux, 24 h, 86%.

Scheme 1





a: *t*-BuOK, r.t., 2 h; then, **8**, r.t., 15 h; b: NH_4OAc,AcOH, 5 h, 45%; c: *t*-BuOK, r.t., 2 h; then, **6**, r.t., 15 h; d: NH_4OAc, AcOH, 5 h, 47%

Scheme 2

According to Scheme 1 the pyridine **2**,[3] which is readily accessible in good yield by Co(I)-catalyzed co-cyclotrimerization of (1S,2S)-2-cyano-6,6-dimethylbicyclo[3.1.1]heptan[4] (**1**) with acetylene,[3,5] was converted in almost quantitative yield to the corresponding N-oxide **3** by oxidation with 3-chloroperbenzoic acid. The key intermediate nitrile **4** was obtained by treatment of **3** with trimethylsilylcyanide and dimethylcarbamoyl chloride at room temperature for 5 days (95% yield).[6] Compound **4** was converted into the ketone **5** by reaction with methyl magnesium iodide (32%). Both enaminones **6** and **8** were obtained in high yield (86%) by reaction of N,N-dimethylformamide dimethylacetal[7] with the pyridylketone **5** and 2-acetylpyridine **7**, respectively.
In the final step of this synthesis the potassium enolate of **5** was condensed[7] with the enaminones **6** or **8** to give the unisolated 1,5-enedione **9** and **11**, respectively. Cyclization with ammonium acetate[7] of unisolated **9** and **11** gave the terpyridines **10** and **12** in about 46% overall yield in the two steps.

In summary, in this paper we report the synthesis of two new related homochiral nitrogen ligands, outlining a generalizable procedure for the preparation of optically active 6- and 6,6''-substituted terpyridines from chiral 2-substituted pyridines.

Current work will cover the use of these ligands in enantioselective reactions.

EXPERIMENTAL

Boiling and melting points are uncorrected. ^1H (300 MHz) NMR Fourier transform spectra were performed on a Varian VXR-300 spectrometer with TMS as internal standard. The optical rotations were measured by a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube. Gas chromatographic analyses were performed by a Perkin-Elmer 8600 chromatograph using N_2 as a carrier gas on a 15 m DBWAX widebore capillary column (J&W).

Material: Methylmagnesium iodide (3M solution in Et_2O) was purchased from Aldrich. (1S,2S)-2-{6,6-dimethylbicyclo[3.1.1]hept-2yl}-pyridine (**2**) ($[\alpha]^{20}_D$ -17.69°; *c* 2.0, benzene) was prepared by co-cyclotrimerization (1S,2S)-2-cyano-6,6-dimethylbicyclo[3.1.1] heptane[3] ($[\alpha]^{20}_D$ -7.1°; *c* 3.0, benzene) (**1**) with acetylene in the presence of (π-cyclopentadienyl)cobalt 1,5-cycloottadiene.[3,5] The N-

oxide of (1S,2S)-2-{6,6-dimethylbicyclo [3.1.1]hept-2yl}-pyridine (**3**)[3] was obtained in almost quantitative yield by addition of 3-chloroperbenzoic acid (20% excess) to a CH_2Cl_2 solution of **2**. 2-[3-(Dimethylamino)-propenoyl]-pyridine (**8**) was prepared according to Jameson *et al.*[7]

(1S,2S)-2-Cyano-6,6-dimethylbicyclo[3.1.1] heptane (**4**).[3]

Dimethylcarbamyl chloride (5.35 g, 0.05 mol) was added dropwise to a solution of N-oxide of (1S,2S)-2-{6,6-dimethylbicyclo[3.1.1] hept-2yl}-pyridine (**3**) (10.85 g, 0.05 mol) and trimethylsilylcyanide (5.5 g, 0.055 mol) in CH_2Cl_2 (100 mL). The solution was stirred at room temperature for 5 days, then 10% K_2CO_3 was added and stirring continued for 15 minutes. The organic phase was separated, dried (Na_2SO_4), evaporated of the solvent and distilled to give **4** (10.73 g, 95%): bp 60 °C (0.01 mm); $[\alpha]^{25}_D$ -3.36° (*c* 2.0, benzene). Analytical and spectral data were identical with an authentic sample.

2-Etanoyl-6-{(1S,2S)-6,6-dimethylbicyclo [3.1.1] hept-2-yl}-pyridine (**5**).

A 3M solution in Et_2O of methylmagnesium iodide (14 ml, 42 mmol) was added dropwise to a solution of **4** (9.5 g, 42 mmol) in anhydrous Et_2O (60 mL). The reaction mixture was stirred for one night. After hydrolysis with 5N HCl, the mixture was stirred for 12h and then alkalized with 10% NaOH. The organic layer was separated and the aqueous phase extracted with Et_2O. The ethereal solution was dried (Na_2SO_4), the solvent evaporated and the residue chromatographed on silica gel using benzene as the eluant to give pure **5** (3.3 g, 32%): bp 120 °C (0.01 mm); $[\alpha]^{25}_D$ +7.00° (*c* 2.3, ethanol); ^1H NMR ($CDCl_3$) δ, ppm: 7.81 (d, 1H); 7.66 (t, 1H), 7.26 (d, 1H), 3.39 (m, 1H), 2.71 (s, 3H), 2.25-2.88 (m, 8H), 1.25 (s, 3H), 0.98 (s, 3H); Elemental Analysis (Calcd. for $C_{16}H_{21}NO$): C, 78.73 (78.96); H, 8.75 (8.70); N, 5.82 (5.76).

2-[3-(Dimethylamino)-propenoyl]-6-{(1S,2S)-6,6-dimethylbicyclo [3.1.1] hept-2-yl}-pyridine (**6**).

A solution of **5** (1.08 g, 4.44 mmol) and N,N-dimethylformamide dimethyl acetal (1.12 g) in toluene (5 mL) was heated to reflux. Methanol was gradually removed by fractional distillation. The reaction was heated until no more methanol was distilled (ca. 12 h).

The toluene was removed on a rotary evaporator and the residue chromatographed on silica gel (eluent: benzene/ethyl acetate, 8/2) to give pure **6** (1.08 g, 86%): mp 95-96 °C; ^{1}H NMR ($CDCl_3$) δ, ppm: 7.91 (m, 2H), 7.67 (t, 1H), 7.19 (d, 1H), 6,57 (d broad, 1H), 3.42 (t, 3H), 3.13 (s broad, 3H), 2.98 (s broad, 3H), 2.26-1.85 (m, 8H), 1.27 (s, 3H), 0.98 (s, 3H). Elemental Analysis (Calcd. for $C_{19}H_{26}N_2O$): C, 76.63 (76.46); H, 8.59 (8.79); N, 7.82 (9.39).

6,6''-Bis-[6,6-dimethylnorpynan-2-yl]-2,2':6',2''-terpyridine (**12**).

Compound **5** (1.16 g, 4.77 mmol) was added to a solution of potassium *t*-butoxide (1.08 g) in anhydrous THF (25 mL). The solution was allowed to stir for 2 h at room temperature and then **6** (1.36 g, 4.77 mmol) was added in a single portion. After 14 h stirring at room temperature, the mixture (deep red) was treated successively with ammonium acetate (3.67g) and acetic acid (10 mL). The THF was removed by slow distillation over the course of 2 h and the remaining acetic acid was removed on a rotary evaporator. The residue was work up with CH_2Cl_2 and treaded with 10% K_2CO_3. The organic solution was dried (Na_2SO_4), the solvent evaporated and the residue chromatographed on neutral alumina using benzene as the eluant to give pure **12** (1.05 g, 46.5%): mp 165 °C; $[\alpha]^{25}_D$ +28.19° (*c* 2.0 cyclohexane); ^{1}H NMR ($CDCl_3$) δ, ppm: 8.50 (d, 2H), 8.41 (d, 2H), 7.92 (t, 1H), 7.71 (t, 2H), 7.14 (d, 2H), 3.45 (t, 2H), 2.35-1.90 (m, 16H), 1.28 (s, 6H), 1.05 (s, 6H). Elemental Analysis (Calcd. for $C_{33}H_{39}N_3$): C, 82.73 (82.96); H, 8.51 (8.23); N, 8.82 (8.80).

6-[6,6-Dimethylnorpynan-2-yl]-2,2':6',2''-terpyridine (**10**).

Following the above procedure, the potassium enolate of **5** (0.972 g, 4 mmol) by treatment with **8** (0.704 g, 4 mmol), gave **10** (0.61 g, 45%): mp 84-5 °C; $[\alpha]^{25}_D$ +14.42° (*c* 2.12 cyclohexane); ^{1}H NMR ($CDCl_3$) δ, ppm: 8.65 (d, 1H), 8.59 (d, 1H), 8.52 (d, 1H), 8.40 (dt, 2H), 7.90 (t, 1H), 7.77 (t, 1H), 7.67 (t, 1H), 7.23 (m, 1H), 7.10 (d, 1H), 3.43 (t, 1H), 2.35-1.88 (m, 8H), 1.27 (s, 3H), 0.99 (s, 3H). Elemental Analysis (Calcd. for $C_{24}H_{25}N_3$): C, 80.93 (81.08); H, 7.22 (7.09); N, 11.82 (11.83).

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