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A C_2-SYMMETRIC CHIRAL 2,2'-BIPYRIDINE DERIVED FROM TARTARIC ACID

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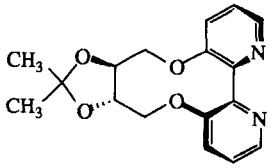
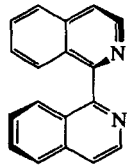
ABSTRACT: The synthesis of the C_2-symmetric, homochiral bipyridine **1**, whose atropisomeric stereochemistry is imposed by a side-chain derived from tartaric acid, is reported.

2,2'-Bipyridines are of interest in coordination chemistry, as ligands for catalysts, as herbicides, as red-ox systems, etc.[2] The atropisomeric nature of the 2,2'-bipyridine skeleton makes this molecule intrinsically chiral, though of difficult resolution into its antipods because the interconvertion between the two chiral forms is a low-energy process. If properly stabilized, however, this chirality feature could be utilized especially in asymmetric synthesis because it may impart elipticity to the many catalysts in which 2,2'-bipyridines can be used as ligands.[3] We report here the preparation of the optically pure and optically stable bipyridine **1** where the labile atropisomerim of the system is expected to be fixed by the chirality of a side-chain derived from tartaric acid.



1



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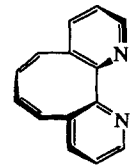


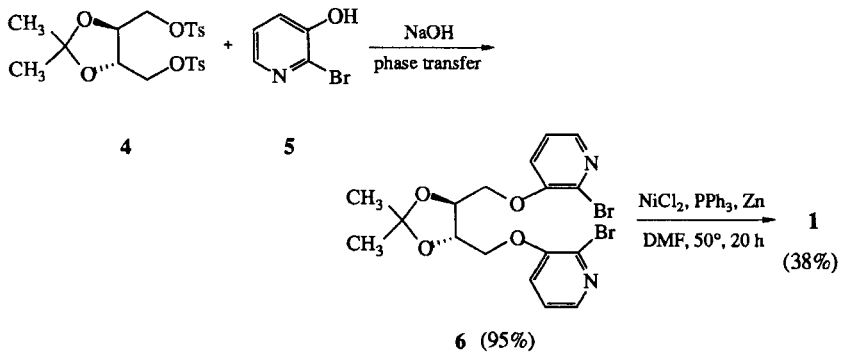
3

Molecule possessing similar geometric features are, for example, the 1,1'-bi-isoquinoline **2**[4] and the bipyridine **3**,[5] but the former racemizes with ease and the latter is of unpractical resolution.

The atropisomeric chirality of **1** is imparted by the ring chain at the 3 and 3' positions which is derived from the inexpensive tartaric acid. The chiral ring was planned to give elipticity without sterically interfeering with the binding sites for metals (*i.e.* the pyridine nitrogens). Consequently, it is expected that any asymmetric induction associated with **1** will be due solely to the chiral twisting of the aromatic rings. In other words, the chiral lock should effect only the conformation of the bipyridine system without introducing extra chiral informations to the system..With what the absolute stereochemistry is concern, starting from L-tartaric acid, *i.e.* with the chiral carbon atoms of **1** with *S*-absolute configuration, an M-atropisomeric elipticity of the bipyridine system is expected on the basis of conformational preferences.

Another feature which was taken into accounts in the planning of **1** is the size of the ring, which was considered sufficient to impart chirality without affecting flexibility for a proper bidentate metal-ligand interaction. Furthermore care was paid not to introduce possible extra reactive sites into the ring chain.

The synthesis of **1** is illustrated in the equation and made use of the coupling procedure described by Tiecco and collaborators as the key step.[6]



Nucleophilic substitution of the pyridine **5** on the readily available or commercial ditosylate **4**, affonded the intermediate **6**, which was cyclized with nickel-triphenylphosphine complex to **1**.[7] It should be noted that several attempts to cyclize directly 2,2'-bipyridines-6,6'-diol under a variety of reaction conditions were so far unsuccessful.

EXPERIMENTAL

*(+)(4S-*trans*)-[4,5-Dimethanol-2,2-dimethyl-1,3-dioxolane]-bis[3-(2-bromo)pyridine]* (**6**)- An aqueous solution (9 mL) of sodium hydroxyde (1.5 g, 37.9 mmol) and 2-bromo-3-hydroxypyridine **5** (3.3 g, 19.0 mmol) was stirred 1 h at room temperature. To the solution were added sequentially toluene (18 mL), (-)-2,3-*O*-isopropylidene-1,4-di-*O*-tosyl-L-threitol **4** (3.0 g, 6.3 mmol) and tetrabutylammonium bromide (2.0 g) as phase transfer reagent and the resulting heterogeneous mixture was heated into an oil bath at 85 °C for 48 h. The progress of the reaction was followed by TLC eluting with 1:1 *n*-hexane-ethyl acetate (UV detection). After cooling to room temperature, more water (50 mL) was added and the organic layer was separated and washed with brine (3 x 50 mL). After drying ($MgSO_4$) and roto-evaporating the solvent, the crude oil was purified by flash-chromatography (230-400 mesh silica gel - *ca.* 20:1 weight ratio adsorbant to substrate) eluting with a gradient of *n*-hexane-ethyl ether to give a colorles glass.(2.8 g, 95% yield): [α] = +28.4° (C_6H_6, c= 2.4). ^1H NMR (80 MHz, $CDCl_3$, TMS) δ, ppm: 1.52 (6 H, s),

4.3-4.6 (6 H, m), 7.22 (4 H, d, J = 3 Hz), 7.99 (2 H, t, J = 3 Hz). IR (KBr disk) ν: 3059, 2989, 2887, 1587, 1424, 1372, 1296, 1280, 1243, 1166, 1112, 1077, 1022, 862, 823, 807, 792, 750 cm^{-1}.

*(-)-3,3'-[(4S-*trans*)-1,3- Dioxolane-4,5-dimethanoyl-2,2-dimethyl]-2,2'-bipyridine* (**1**) - A solution of $NiCl_2$ hexahydrate (5.7 g, 24.2 mmol), triphenylphosphine (25.4 g, 96.6 mmol) and zinc powder (1.6 g, 24.2 mmol) in dimethylformamide (120 mL) was heated at 50 °C with efficient stirring under nitrogen for 1 h. To the resulting red-brown solution, the dibromide **6** (5.1 g, 12.1 mmol) was added in one portion and the reaction mixture was kept stirring at 50 °C for 20 h. The reaction mixture was poured into ammonium hydroxide (30%, 450 mL) and extracted with chloroform (3 x 100 mL), washed with water (x 3), dried ($MgSO_4$) and rotoevaporated to a brown solid. Silica gel chromatography (230-400 mesh, *ca.* 20:1 weight ratio adsorbant to substrate), eluting with a gradient of ethyl acetate in *n*-hexane, gave a white solid (1.2 g, 38% yield): mp 160-1 °C (*n*-heptane). [α] = -19.0° (C_6H_6, c= 1.5). ^1H NMR (200 MHz, $CDCl_3$, TMS) δ, ppm: 1.43 (6 H, s), 4.06 (4 H, m), 4.78 (2 H, d, J = 7.5 Hz), 7.33 (4 H, d, J = 3 Hz), 8.45 (2 H, t, J = 3 Hz). IR (KBr disk) ν: 3059, 2989, 2887, 1587, 1577, 1424, 1372, 1280, 1242, 1166, 1112, 1077, 1021, 862, 807 cm^{-1}. Elemental Analysis (Calcd. for $C_{17}H_{18}N_2O_4$): C, 64.64 (64.96); H, 5.59 (5.77); N, 8.78 (8.91).

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7. The ^{1}H NMR spectrum of **1** in $CDCl_3$ at room temperature exhibits somewhat broad lines suggesting the expected conformational mobility which should allow a facile metal binding.

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