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Syntheses of chiral nopinane-annelated pyridines of C_2 and D_2-symmetry: X-ray structures of the fused derivatives of 4,5-diazafluorene, 4,5-diaza-9*H*-fluoren-9-one, and 9,9′-bi-4,5-diazafluorenylidene

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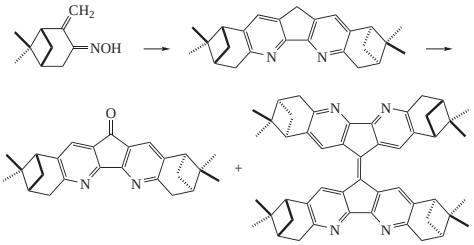
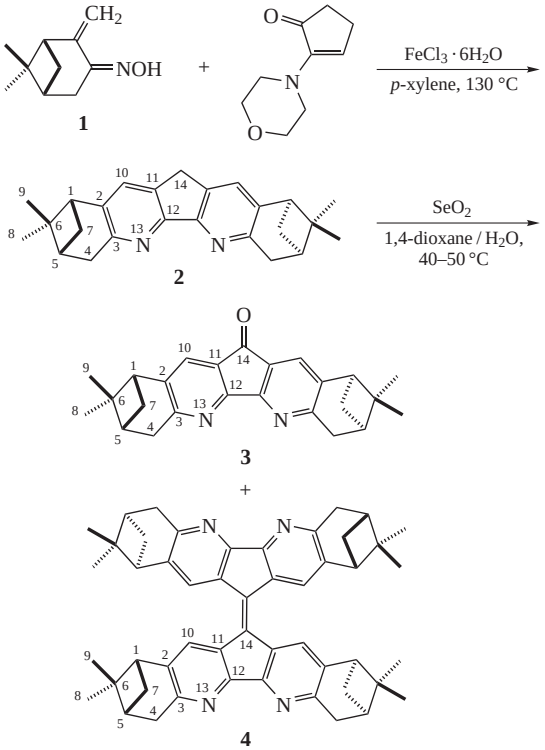
Reaction of (+)-pinocarvone oxime with 2-morpholinocyclopent-2-enone and $FeCl_3 \cdot 6H_2O$ affords chiral C_2-symmetric fused derivative of 4,5-diazafluorene, whose oxidation with SeO_2 gives nopinane-annelated derivatives of 4,5-diaza-9*H*-fluoren-9-one (C_2-symmetry) and of 9,9′-bi-4,5-diazafluorenylidene (D_2-symmetry). Structures of the compounds synthesized were proved by X-ray crystallography.



Chiral pyridine derivatives attract much attention as ligands for coordination chemistry.[1] Chiral fused pyridine-pinane hybrids are among the most prospective chiral auxiliaries.[2] Recently we have developed new synthetic route to chiral nopinane-annelated pyridines by microwave assisted condensation of pinocarvone oxime **1** with enamines promoted by transition metal salts.[3] The method was applied for the preparation of C_2-symmetric chiral derivative of dihydrophenanthroline type which is a prospective ligand for coordination chemistry.[4] The good coordination properties of this ligand are provided by the 2,2′-bipyridine moiety having additional linker in the form of bis-methylene group. This additional linker retains the ligand conformationally flexible, which is manifested in the existence of two conformations of the central cyclohexadienyl fragment.[4] To obtain similar ligands with a rigid central bipyridyl moiety we have developed a scheme providing an additional linker as a single methylene group. Here we report a simple method for synthesis of chiral rigid bis-nopinane-annelated bipyridine **2** and preparation of its oxidation products **3** and **4** (Scheme 1).

Treatment of (+)-pinocarvone oxime **1**[5] with 2-morpholinocyclopent-2-enone[6] and $FeCl_3 \cdot 6H_2O$ brought about the desired compound **2** (see Scheme 1) as white crystals.† The C_2-symmetric bipyridine derivative **2** was found to be easily oxidized at the bis-benzylic position (–CH_2– linkage between pyridine nuclei). For example, treatment of compound **2** with SeO_2 results in a mixture of keto derivative **3** and tetrapyridine derivative **4** as a product of oxidative dimerization.‡ NMR spectra of these compounds contain 13 signals each proving formation of symmetric molecules, structures of C_2-symmetry in case of compounds **2** and **3**, and structure of D_2-symmetry for compound **4**. Chemical shifts and spin–spin couplings of the compounds **2**–**4** are similar to those found for



Scheme 1 The atom numbering is given for NMR assignment.

† *(1*R,3R,*8*R,*10*R*)-2,2,9,9-Tetramethyl-2,3,4,7,8,9,10,12-octahydro-1*H*-1,3:8,10-dimethanocyclopenta[1,2-b:5,4-b′]diquinoline* **2**. A mixture of (+)-pinocarvone oxime (6.60 g, 40 mmol), $FeCl_3 \cdot 6H_2O$ (3.00 g, 11 mmol) and *p*-xylene (5 ml) was added in 20 min portionwise at vigorous stirring to a hot (130 °C) solution of 2-morpholinocyclopent-2-enone (3.34 g, 20 mmol) in *p*-xylene (5 ml). After stirring for 10 min at 130 °C, the mixture was cooled down to room temperature and diluted with EtOH (15 ml). A mixture of EtOAc (40 ml) and 1 M aq. HCl (70 ml) was added, and the resulting mixture was stirred for 20 min at room temperature. The aqueous phase was separated; the organic layer was extracted with 1 M aq. HCl (3×70 ml). Tartaric acid (3 g) was dissolved in the combined aqueous extract, the resulting solution was treated with aqueous ammonia to pH > 9 and extracted with $CHCl_3$ (4×100 ml). The combined $CHCl_3$ extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product which was purified by column chromatography (SiO_2, $CHCl_3$–EtOAc, 15:1 → 7:1, v/v) to afford

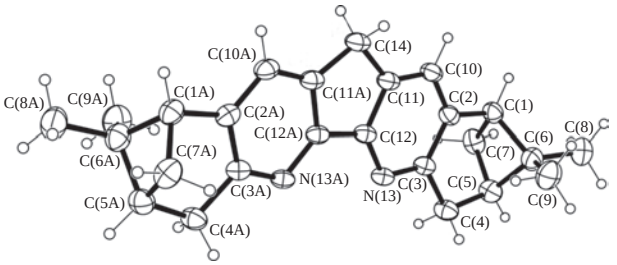


Figure 1 Crystal structure for compound **2** (the solvent molecules are not shown).

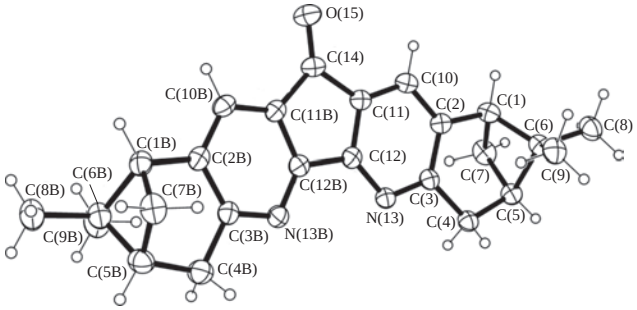


Figure 2 Crystal structure for compound **3**.

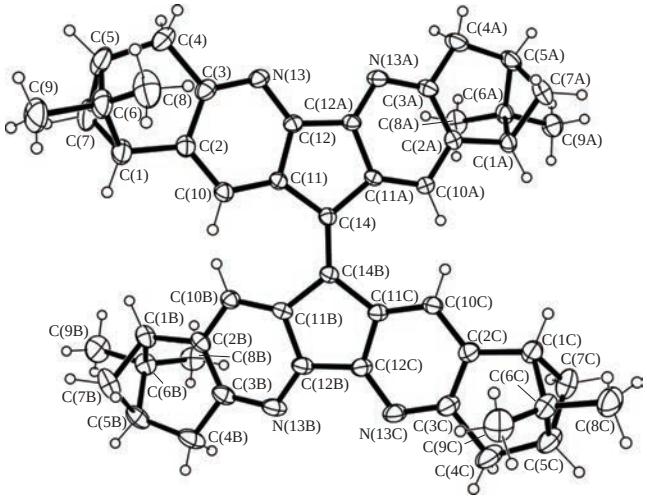


Figure 3 Crystal structure for compound **4** (the solvent molecules are not shown).

structurally related molecules.[3,7] Chemical structures of the products were established by X-ray single crystal diffractometry (Figures 1–3).[§]

The mechanism of the oxidative dimerisation is unclear but seems to be typical of compounds of this type because the simplest models demonstrate a tendency to dimerization under different conditions, *i.e.* both reductive transformation of 4,5-diaza-9*H*-fluoren-9-one and bromination of 4,5-diazafluorene resulted in dimeric products.[8] Oxidative dimerisation also occurs when alkylpyridines are oxidized with SeO_2.[9]

an analytical sample of compound **2** (1.2 g, 3.4 mmol, 17%, R_f 0.29 on SiO_2 plates with light petroleum–EtOAc, 1 : 1). White crystals, mp 264 °C (EtOAc–C_6H_6, 1 : 1, v/v). $[\alpha]_{589}^{20}$ −142 (*c* 0.071, EtOH). UV (EtOH, λ/nm): 269 (8600), 322 (20200), 329 (23700), 336 (27400). HRMS (EI, 70 eV), *m/z:* 356.2248 $[M]^+$ (calc. for $C_{25}H_{28}N_2$, *m/z:* 356.2247). Found (%): C, 83.9; H, 7.9; N, 7.9. Calc. for $C_{25}H_{28}N_2$ (%): C, 84.23; H, 7.92; N, 7.86.

‡ A solution of SeO_2 (55 mg, 0.5 mmol) in a mixture of 1,4-dioxane (8 ml) and water (0.5 ml) was added dropwise in 30 min at 40–50 °C to a stirred solution of bis-pinopyridine **2** (0.356 g, 1 mmol) in 1,4-dioxane (3 ml). After staying overnight at room temperature, a solution of the reaction products was separated by decantation and concentrated under reduced pressure. The residue was separated by column chromatography (SiO_2, $CHCl_3$–EtOAc, 20 : 1) to afford consistently bis-pinopyridine ketone **3** as yellow crystals (0.140 g, 0.38 mmol, 38% yield, R_f 0.4 on SiO_2 plates with $CHCl_3$) and tetrapyridine derivative **4** as orange crystals (0.123 g, 0.17 mmol, 35% yield, R_f 0.3 on SiO_2 plates with $CHCl_3$).

*(1*R,*3*R,*8*R,*10R)-2,2,9,9-Tetramethyl-3,4,7,8,9,10-hexahydro-1*H*-1,3 : 8,10-dimethanocyclopenta[1,2*-b*:*5,4*-b′*]diquinolin-12(2*H*)-one* **3**. Yellow crystals, mp 247 °C (benzene–EtOAc, 1 : 1), $[\alpha]_{589}^{20}$ −224 (*c* 0.59, $CHCl_3$). UV (EtOH, λ/nm): 258 (42500), 324 (15600), 339 (19500). HRMS (EI, 70 eV), *m/z*: 370.2049 $[M]^+$ (calc. for $C_{25}H_{26}N_2O$, *m/z:* 370.2040). Found (%): C, 81.1; H, 6.8; N, 7.4. Calc. for $C_{25}H_{26}N_2O$ (%): C, 81.05; H, 7.07; N, 7.56.

*(1*R,*3*R,*8*R,*10*R,*1′*R,*3′*R,*8′*R,*10′*R)-2,2,2′,2′,9,9,9′,9′-Octamethyl-1,1′,2,2′,3,3′,4,4′,7,7′,8,8′,9,9′,10,10′-hexadecahydro-1,3 : 1′,3′ : 8,10 : 8′,10′-tetramethano-12,12′-bi(cyclopenta[1,2-*b*:*5,4-*b′*]diquinolinylidene)* **4**. Orange crystals (from C_6H_6–$CHCl_3$) which quickly crack and become turbid, $[\alpha]_{589}^{31}$ −283 (*c* 0.72, $CHCl_3$). UV (EtOH, λ/nm): 257 (55600), 331 (28400), 430 (23100). HRMS (EI, 70 eV), *m/z:* 708.4193 $[M]^+$ (calc. for $C_{50}H_{52}N_4$, *m/z*: 708.4187). Found (%): C, 75.8; H, 6.3; N, 5.9. Calc. for $C_{50}H_{52}N_4 \cdot 2C_6H_6 \cdot CHCl_3$ (%): C, 76.85; H, 6.65; N, 5.69.

§ X-ray crystallographic data for compounds **2** and **4** were obtained on a Bruker Kappa Apex II CCD diffractometer using φ,ω-scans of narrow 0.5°) frames with MoKα radiation (λ = 0.71073 Å) and a graphite monochromator, whereas a Bruker P4 diffractometer (monochromated MoKα radiation, $\theta/2\theta$ scans) was used to measure the unit cell dimensions and to collect data for compound **3**.

Crystal data for **2**: $C_{25}H_{28}N_2$, M = 356.49, cubic, space group $I23$, at 200 K: a = 18.9036(4) Å, V = 6755.1(2) Å^3, Z = 12, d_{calc} = 1.052 g cm^{-3}, μ(MoKα) = 0.061 mm^{-1}, a total of 15710 (θ_{max} = 27.07°), 2496 unique (R_{int} = 0.0600), 2049 [$F > 4\sigma(F)$], 125 parameters. GOOF = 1.01, R_1 = = 0.0486, wR_2 = 0.1301 [$I > 2\sigma(I)$], R_1 = 0.0571, wR_2 = 0.1361 (all data), max/min diff. peak 0.938/–0.296 eÅ^{-3}.

Crystal data for **3**: $C_{25}H_{26}N_2O$, M = 370.48, orthorhombic, space group $P2_12_12_1$, at 296 K: a = 10.182(3), b = 12.192(5) and c = 16.196(6) Å, V = 2010.6(13) Å^3, Z = 4, d_{calc} = 1.224 g cm^{-3}, μ(MoKα) = 0.075 mm^{-1}, a total of 2791 (θ_{max} = 25.52°), 2608 unique (R_{int} = 0.099), 2049 [$F > 4\sigma(F)$], 253 parameters. GOOF = 1.026, R_1 = 0.0677, wR_2 = 0.1650 [$I > 2\sigma(I)$], R_1 = 0.0757, wR_2 = 0.1686 (all data), max/min diff. peak 0.366/–0.281 eÅ^{-3}.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.03.006.

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Crystal data for **4**: $C_{50}H_{52}N_4 \cdot 2C_6H_6 \cdot CHCl_3$, M = 984.54, orthorhombic, space group $P2_12_12_1$, at 296 K: a = 12.6760(7), b = 14.5292(10) and c = = 29.433(2) Å, V = 5420.8(6) Å^3, Z = 4, d_{calc} = 1.206 g cm^{-3}, μ(MoKα) = = 0.212 mm^{-1}, a total of 52524 (θ_{max} = 25.94°), 10416 unique (R_{int} = 0.058), 8521 [$F > 4\sigma(F)$], 667 parameters. GOOF = 1.16, R_1 = 0.0683, wR_2 = 0.1690 [$I > 2\sigma(I)$], R_1 = 0.0970, wR_2 = 0.2153 (all data), max/min diff. peak 0.629/–0.903 eÅ^{-3}.

The structures were solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the SHELX-97 programs set.[10] The H atoms positions were calculated with the riding model. Molecules of compound **2** in the crystal are packed so that free solvent accessible volume derived from PLATON[11] routine analysis was found to be 4.5% (307.0 Å^3). This volume is occupied by highly disordered molecules that could not be modeled as a set of discrete atomic sites. We employed PLATON/SQUEEZE procedure to calculate the contribution to the diffraction from the solvent region and thereby produced a set of solvent-free diffraction intensities. Tetrapyridine derivative **4** gives the solvate which is formed by one crystallographically independent molecule of the substrate, two molecules of benzene and one molecule of $CHCl_3$ disordered by two positions with 0.55 : 0.45(1) occupation ratio.

CCDC 1491573, 1491574, and 1495211 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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