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Triazolopyridines. Part 25: Synthesis of new chiral ligands from [1,2,3]triazolo[1,5-*a*]pyridines☆

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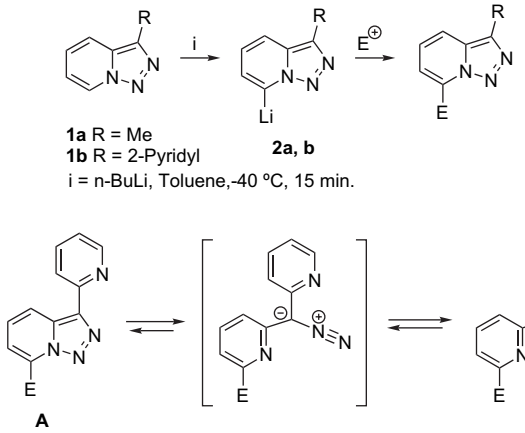
Abstract—The synthesis of new chiral triazolopyridine ligands possessing fluorescent properties is described. The triazolo ring opening was studied in order to obtain new chiral 2,6-disubstituted pyridines. A preliminary coordination assay with Zn(II) is also presented.

1. Introduction

The pyridine ring can be found as structural motif in a large number of chiral ligands used in asymmetric catalysis,[2] and molecular recognition chemistry.[3] Pyridines and 2,2′-bipyridines are common donor ligands.[4] Jones and some of us have reported on the synthesis of interesting 2,6-disubstituted pyridines[5] and bipyridines,[6] using [1,2,3]triazolo[1,5-*a*]pyridines as synthons. We have also reported many aspects of the chemistry of [1,2,3]triazolo[1,5-*a*]pyridines,[7] their fluorescent behaviour,[8] application in the field of magnetic materials[9,10] and in the preparation of fluorescent sensors.[11] However, there are no studies dealing with the preparation of chiral triazolopyridines. Due to our interest in the chemistry of triazolopyridines, we have now prepared new chiral compounds possessing fluorescent properties. The triazolo ring opening reaction affording chiral 2,6-disubstituted pyridines has also been studied as well as a preliminary coordination assay with Zn(II).

2. Results and discussion

We had reported that the regioselective metalation of [1,2,3]triazolo[1,5-*a*]pyridines (**1a** and **b**) with *n*-BuLi in toluene at −40 °C gives the 7-lithioderivatives **2a** and **b**, which react subsequently with a number of electrophiles to give 7-substituted triazolopyridines from **2a**.[5,6b] However, starting with **2b** the unexpected reaction products reveal an interesting structural feature. By an experimental (^{1}H NMR) and theoretical (DFT) studies,[1,12] we have demonstrated that there is a ring–chain–ring isomerization of 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl derivatives (**A**) into 6-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-2-pyridyl derivatives (**B**). The **A**/**B** ratio depends on the electronic properties of the substituent in the 7-position (Scheme 1). Electron-donating substituents favour the **A** form, electron-withdrawing substituents the **B** form, and only in the case where the substituent is a methyl group both forms are present (75% of **A** and 25% of **B**).



Scheme 1.

Using this methodology and with chiral electrophiles such as (−)-fenchone or (*R*)-(+)-menthyl-*p*-toluenesulfinate, we

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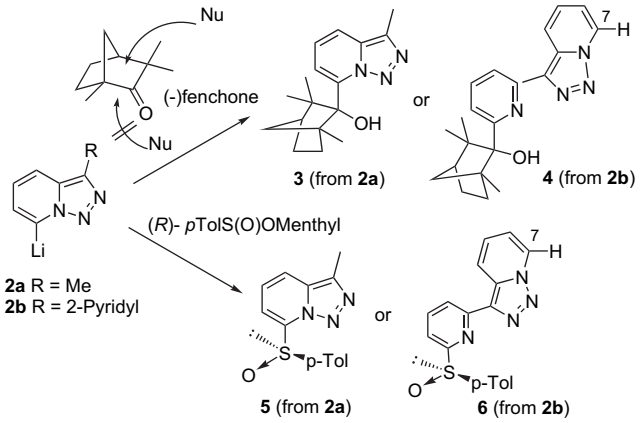
have now obtained the corresponding chiral alcohols **3** (80%) and **4** (in **B** form, evidenced by ^{1}H, ^{13}C NMR and COSY experiments) (88%) as well as the chiral sulfoxides **5** and **6** (also in **B** form) (Scheme 2).



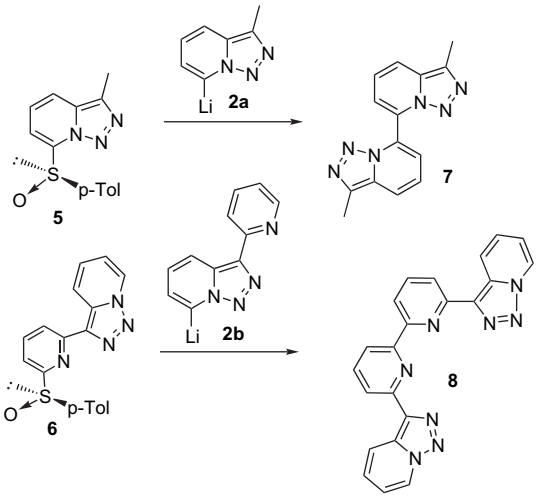
Scheme 2.

The alcohols **3** and **4** were formed as optically pure diastereomers, as was evidenced by ^{1}H NMR analysis. The preferential nucleophilic attack of 7-lithiotriazolopyridine to the carbonyl group of fenchone from the sterically less hindered side occurs according to the Felkin–Ahn model.[13]

Although chiral sulfoxides are very important compounds for asymmetric synthesis[14] and asymmetric catalysis,[15] the synthesis of enantiomerically pure triazolopyridine sulfoxides was so far unknown. Quéguiner et al.[16] had shown that sulfoxides of π-deficient heterocycles can be obtained with excellent enantiomeric excesses by the Andersen method,[17] using organometallic intermediates and chiral menthyl-*p*-toluenesulfinates as electrophiles. We have studied the reaction of 7-lithio-triazolopyridines **2a** and **b** with (*R*)-(+)-menthyl-*p*-toluenesulfinate, employing either normal or reverse addition at −40 °C under different concentrations using toluene or tetrahydrofuran as solvent. The best conditions (see Experimental 3), afforded **5** and **6** in a low yield of 20% and 16%, respectively, with 97% ee (determined by HPLC). Concomitant formation of the dimerized compounds **7** (56%) and **8** (26%) was observed. Previously **7**[6a] and **8**[1] were obtained in lower yields as secondary compounds in lithiation reactions. In our opinion the higher yield of dimerized side-products is due to a higher reactivity of in situ generated sulfoxide, which reacts with the lithiated intermediates **2a** and **b** by nucleophilic substitution. This reactivity pattern is well established in pyridine chemistry (Scheme 3).[18]

We had demonstrated that the conjugation of a triazolopyridine group with an aryl or heteroaryl group gives highly efficient fluorescent compounds.[8] Derivatives **4** and **6** are new examples of fluorescent triazolopyridines. The alcohol **4** emitted at 409 nm and sulfoxide **6** at 387 nm and 404 nm when excited at 331 nm in $CHCl_3$ solution.

Another interesting application of triazolopyridines is their capacity to coordinate with metals, and behave as chemosensors for metal ions or anionic species.[11] The Zn^{2+} ion is an essential component of many enzymes, and plays an important role in maintaining the key structural features of gene



Scheme 3.

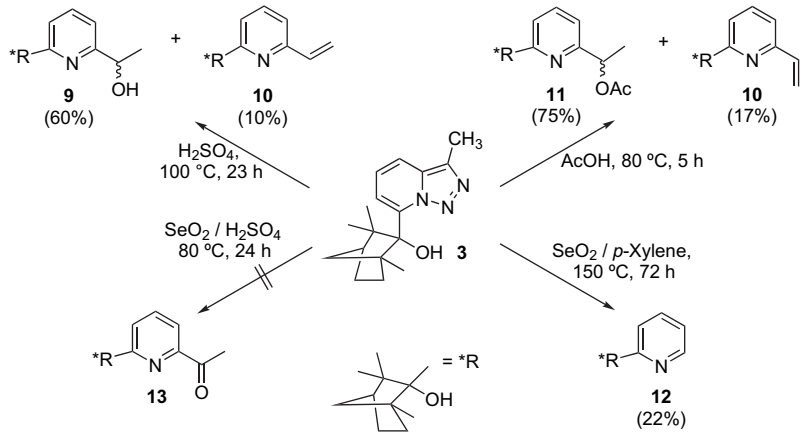
transcription proteins.[19] Also, the role of Zn^{2+} in neurobiology has received significant attention.[20] In this regard, we are interested to develop chemosensors for Zn^{2+} ions. In a preliminary study, we have used the alcohol **4** to obtain a Zn(II) complex by reaction with zinc chloride. FABMS supports the formation of 1:1 $[Zn(\mathbf{4})]^{2}$+–Cl_2 aggregate. The emissive property of the complex presents a bathochromic shift of the fluorescence emission at 392 nm and 398 nm (λ^{exc} 331 nm), which appears at 409 nm. Encouraged by our preliminary results, we presently investigate the optical properties of these new chiral ligands.

3-Substituted-[1,2,3]triazolo[1,5-*a*]pyridines react with electrophiles by a triazol ring opening reaction with loss of nitrogen yielding 2,6-disubstituted pyridines.[21] We have studied now the triazole ring opening reaction of the chiral alcohols **3** and **4** with the aim to obtain chiral 2,6-disubstituted pyridines. The reactions were performed with acetic acid, 2.5 M sulfuric acid and selenium dioxide as electrophiles.

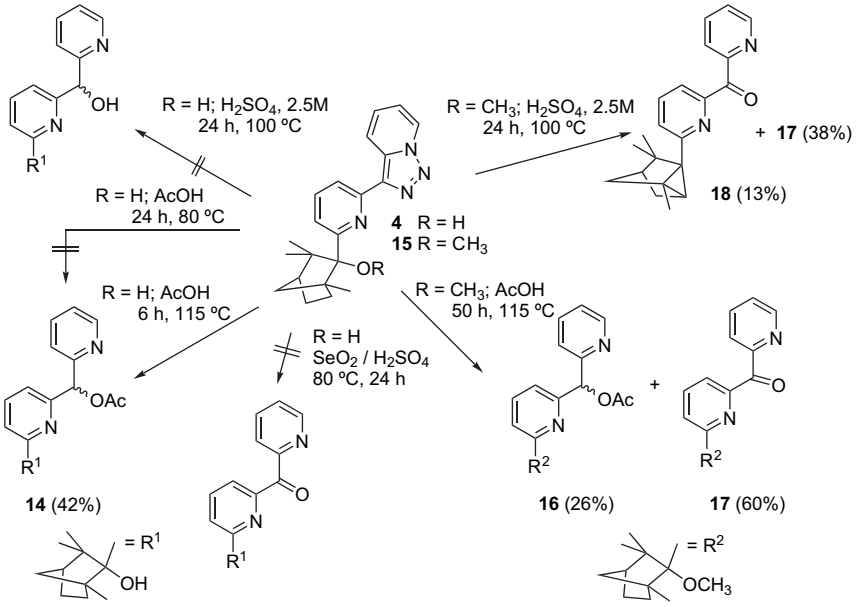
Treatment of compound **3** with aqueous sulfuric acid gave the alcohol **9** (60%) as a diastereoisomeric mixture, de 5% (determined by NMR), and with acetic acid, the acetate **11** (75%, de 5%) was obtained. The chiral fenchyl group is too far from the triazolopyridine 3-position for chiral induction. In both cases small quantities of the elimination product, the vinylpyridine **10**, was formed. Under the usual conditions for treatment with selenium dioxide (i.e., 2.5 M sulfuric acid, 80 °C, 24 h)[21b] no reaction was observed. However, in *p*-xylene at reflux temperature, the known pyridine **12**[22] was obtained, probably due to a total oxidation followed by decarboxylation of compound **13** (Scheme 4).

The alcohol **4** is more stable and does not react with sulfuric acid, acetic acid or selenium dioxide under the conditions described for reaction with **3**. When **4** was treated with acetic acid at reflux a diastereoisomeric mixture (de 3.5%) of acetates **14** was obtained in 42% yield (Scheme 5).

According to our hypothesis, the unusual stability of the alcohol **4** can be explained by an intramolecular hydrogen bond between the hydroxyl group and the lone pairs of the pyridine and N3-triazole nitrogen atoms (in analogy to a



Scheme 4.



Scheme 5.

proton sponge).[23] This hypothesis was supported by the treatment of ether **15** with acetic acid at reflux. In this case, the corresponding diastereoisomeric mixture (de 4%) of acetates **16** (26%) and ketones **17** (60%) was obtained. Thermal decomposition of diarylmethyl acetates to form ketones has been reported.[24] Reaction with sulfuric acid gave two ketone products, **17** (38%) as major product (probably obtained by oxidation of the initial alcohol intermediate) and the amazing cyclofenchone **18** (13%). The formation of **18** can be explained by the formation, in acid media, of a norbornyl cation as has been reported by Vonwiller[25] in fenchyl chemistry. The new chiral dipyridyl ketones **17** and **18** could be very interesting compounds as building block in cluster chemistry.[26] This possibility is currently under investigation.

3. Experimental

3.1. General

Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300 MHz in $CDCl_3$ as solvent. COSY experiments were done for all compounds. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). Ultraviolet spectra were recorded on a Shimadzu UV-2101 instrument. Fluorescence spectra were recorded on a Spectrofluorimeter P.T.I. (Photon Technology International) instrument. Optical rotation measurements were determined on a Perkin–Elmer 241 polarimeter at room temperature in $CHCl_3$ solution. HPLC determinations were done in a Waters HPLC system with Mallinkrodt–Baker Chiralcel OD-H column. All the lithiation reactions were done under inert atmosphere and dry solvents.[27]

3-Methyl-[1,2,3]triazolo[1,5-a]pyridine ***1a*** *and 3-(2-pyridyl)-[1,2,3]triazolo[1,5-a] pyridine* ***1b*** were prepared as described elsewhere.[28–30,6b]

3.2. General procedure for lithiation of [1,2,3]triazolo[1,5-*a*]pyridines 1a and b

To a solution of the corresponding [1,2,3]triazolo[1,5-*a*]pyridines **1a** and **b** (1 equiv) in anhydrous toluene at −40 °C,

a solution of *n*-butyllithium in hexane (2.5 M) (1.1 equiv) was added with stirring. A deep red colour developed. The mixture was kept at −40 °C (15 min).

3.3. Reaction with (–)-fenchone

The corresponding mixture was treated with a dry toluene solution (10 mL) of (−)-fenchone (excess) recently distilled. Then was left at −40 C° (2 h) and allowed at room temperature overnight, a colour change to yellow was observed. Then was treated with a saturated solution of ammonium chloride (15 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3×20 mL). After drying over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained. The crude product was washed with hexane and filtered. Purification by recrystallization from ethyl acetate/hexane gave compounds **3** or **4** as white solids. The amount of reactants and yields are given for each compound.

3.3.1. (1*R*,2*S*,4*S*)-1,3,3-Trimethyl-2-[7′-(3′-methyl[1,2,3]-triazolo[1,5-*a*]pyridyl)]bicyclo[2.2.1]hept-2-ol 3. Compound **1a** (2 g, 15.03 mmol), toluene (120 mL), *n*-BuLi (6.6 mL), (−)-fenchone (5 g). Compound **3** (3.8 g, 88%) was obtained as a white solid. Mp 113 °C (AcOEt/Hex 1:7). $[\alpha]_D^{20}$ −144.6 (*c* 1.2, $CHCl_3$). HRMS found for M^+ 285.1824; $C_{17}H_{23}N_3O$ requires 285.1841. ^{1}H NMR δ 7.44 (dd, J_1=7.8 Hz, J_2=1.8 Hz, 1H), 7.14 (dd, J_1=7.8 Hz, J_2=7.2 Hz, 1H), 7.10 (dd, J_1=7.2 Hz, J_2=1.8 Hz, 1H), 6.67 (s, 1OH), 2.53–2.50 (m, 1H), 2.18 (dd, J_1=10.5 Hz, J_2=2.1 Hz, 1H), 1.78–1.67 (m, 2H), 1.45–1.29 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H), 1.15 (ddd, J_1=12.6 Hz, J_2=12.6 Hz, J_3=3.9 Hz, 1H), 0.24 (s, 3H). ^{13}C NMR δ 141.16 (C), 133.83 (C), 132.74 (C), 123.60 (CH), 115.02 (C), 114.26 (CH), 83.62 (C), 51.86 (C), 48.87 (CH), 45.97 (C), 42.00 (CH_2), 35.52 (CH_2), 26.94 (CH_2), 24.64 (CH_3), 22.82 (CH_3), 18.14 (CH_3), 10.27 (CH_3). UV λ_{max} (log ε) ($CHCl_3$) 294 (4.89), 312 (4.72). EM (EI) *m*/*z* (%) 285 (50), 257 (58), 242 (23), 229 (50), 214 (28), 174 (41), 160 (55), 105 (62), 104 (100).

3.3.2. (1*R*,2*S*,4*S*)-1,3,3-Trimethyl-2-(6-[1,2,3]triazolo-[1,5-*a*]pyridin-3-yl-pyridin-2-yl)-bicyclo[2.2.1]hept-2-ol 4. Compound **1b** (1.07 g, 8.7 mmol), toluene (80 mL), *n*-BuLi (4 mL), (−)-fenchone (4 g). Compound **4** (2.46 g, 80%) was obtained as a white solid. Mp 144–146 °C (AcOEt/Hex 1:7). $[\alpha]_D^{20}$ −69 (*c* 0.66, $CHCl_3$). HRMS found for M^+ 348.1915; $C_{21}H_{24}N_4O$ requires 348.1950. ^{1}H NMR δ 8.70 (d, *J*=6.9 Hz, 1H), 8.34 (d, *J*=7.9 Hz, 1H), 8.16 (d, *J*=8.3 Hz, 1H), 7.72 (dd, J_1=J_2=7.9 Hz, 1H), 7.40 (d, *J*=7.9 Hz, 1H), 7.32 (dd, J_1=6.9 Hz, J_2=8.3 Hz, 1H), 6.99 (dd, J_1=J_2=6.9 Hz, 1H), 5.89 (br s, 1OH), 2.35–2.15 (m, 2H), 1.90–1.75 (m, 1H), 1.50–1.41 (m, 1H), 1.33 (d, *J*=10.5 Hz, 1H), 1.20–1.18 (m, 1H), 1.00 (s, 6H), 0.82 (m, 1H), 0.45 (s, 3H). ^{13}C NMR δ 161.55 (C), 149.09 (C), 136.98 (C), 136.16 (CH), 131.56 (C), 126.80 (CH), 125.47 (CH), 121.56 (CH), 120.09 (CH), 118.54 (CH), 115.77 (CH), 84.07 (C), 55.77 (C), 48.81 (CH), 46.02 (C), 41.89 (CH_2), 32.61 (CH_2), 26.28 (CH_3), 24.27 (CH_2), 21.64 (CH_3), 17.14 (CH_3). UV λ_{max} (log ε) ($CHCl_3$) 290 (4.75), 313 (4.93), 324 (4.92). EM (EI): *m*/*z* (%) 348 (25), 320 (30), 292 (100), 169 (80).

3.4. Reaction with (*R*)-(+)-menthyl-*p*-toluenesulfinate

The lithiated triazolopyridines **2a** and **b** were poured by double-needle over a solution of (*R*)-(+)-menthyl-*p*-toluenesulfinate (1.5 equiv) in dry toluene (1.5 mL). The mixture was left at −40 C° (2 h) and allowed at room temperature overnight, a colour change to yellow was observed. Then it was treated with a saturated solution of ammonium chloride (15 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3×20 mL). After drying over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained. The residue was purified by chromatotron using hexane/ethyl acetate as eluent, starting material and menthol were obtained in the first fractions. The amount of reactants and yields are given for each compound.

3.4.1. (*R*)-3-Methyl-7-(toluene-4-sulfinyl)-[1,2,3]triazolo-[1,5-*a*]pyridine 5. Compound **1a** (153 mg, 1.15 mmol), toluene (10 mL), *n*-BuLi (0.5 mL) and (*R*)-(+)-menthyl-*p*-toluenesulfinate (490 mg). Compound **5** (60.5 mg, 20%) was obtained as a white solid. Mp 145 °C (AcOEt/Hex 1:7). $[\alpha]_D^{20}$ +281.6 (*c* 0.39, $CHCl_3$). HRMS found for M^+ 271.0778; $C_{14}H_{13}N_3OS$ requires 271.0779. ^{1}H NMR δ 7.89 (d, *J*=8.2 Hz, 2H), 7.71 (dd, J_1=6.9 Hz, J_2=1 Hz, 1H), 7.65 (dd, J_1=8.9 Hz, J_2=1 Hz, 1H), 7.38 (dd, J_1=8.9 Hz, J_2=6.9 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 2.58 (s, 3H), 2.30 (s, 3H). ^{13}C NMR δ 143.04 (C), 141.29 (C), 137.84 (C), 135.19 (C), 132.08 (CH), 129.92 (C), 126.28 (CH), 123.88 (CH), 118.88 (CH), 111.68 (CH), 21.47 (CH_3), 10.35 (CH_3). EM (EI) *m*/*z* (%) 273 (3), 271 (40), 243 (63), 226 (35), 195 (30), 139 (100), 120 (36), 104 (60), 91 (42), 77 (67). *7,7′-Bis(3-methyl[1,2,3]triazolo[1,5-a]pyridine)* ***7*** (81 mg, 56%) was obtained as a fluorescent yellow solid mp 238–240 °C.[6a]

3.4.2. (*R*)-3-[6-(Toluene-4-sulfinyl)-pyridin-2-yl]-[1,2,3]-triazolo[1,5-*a*]pyridine 6. Compound **1b** (153 mg, 0.79 mmol), toluene (10 mL), *n*-BuLi (0.34 mL) and (*R*)-(+)-menthyl-*p*-toluenesulfinate (345 mg). Compound **6** (41 mg, 15%) was obtained as a white solid. Mp 167–170 °C (AcOEt/Hex 1:7). $[\alpha]_D^{20}$ +15.5 (*c* 1.2, $CHCl_3$). HRMS found for M^+ 334.0904; $C_{18}H_{14}N_4OS$ requires 334.0888. ^{1}H NMR δ 8.69 (d, *J*=7.0 Hz, 1H), 8.37 (d, *J*=8.9 Hz, 1H), 8.27 (dd, J_1=7.2 Hz, J_2=1.8 Hz, 1H), 7.91 (dd, J_1=7.1 Hz, J_2=7.8 Hz, 1H), 7.88 (dd, J_1=7.8 Hz, J_2=1.8 Hz, 1H), 7.65 (d, *J*=8.1 Hz, 2H), 7.33 (dd, J_1=7.0 Hz, J_2=8.9 Hz, 1H), 7.2 (d, *J*=8.1 Hz, 2H), 7.0 (dd, J_1=7.0 Hz, J_2=6.9 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR δ 165.00 (C), 152.40 (C), 141.90 (C), 141.26 (C), 138.67 (CH), 136.16 (C), 132.19 (C), 129.93 (CH), 126.96 (CH), 125.42 (CH), 125.35 (CH), 121.19 (CH), 120.84 (CH), 116.74 (CH), 116.05 (CH), 21.82 (CH_3). UV λ_{max} (log ε) ($CHCl_3$) 240 (4.45), 275 (4.42), 331 (4.46). EM (EI) *m*/*z* (%) 336 (3), 334 (40), 306 (75), 258 (65), 215 (10), 199 (5), 183 (86), 167 (100), 139 (80), 113 (20), 91 (44), 78 (47). *7,7′-Bis(3-(2-pyridyl)-[1,2,3]triazolo[1,5-a]pyridine)* ***8*** (80 mg, 26%) was obtained as a fluorescent yellow solid mp >300 °C.[1]

3.5. (1*R*,2*S*,4*S*)-3-[6-(2-Methoxy-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)pyridin-2-yl]-[1,2,3]triazolo-[1,5-*a*]pyridine 15

To a stirred solution of 2-[6-([1,2,3]triazolo[1,5-*a*]pyridin-3-yl)pyridin-2-yl]-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **4**

(348 mg, 1 mmol, 1 equiv) in THF (11 mL), NaH (100 mg, 4.10 mmol, 4.10 equiv) was added at 25 °C. After being stirred for 30 min, iodomethane (0.569 g, 4.00 mmol, 0.56 mL) was added, and the resulting mixture was stirred for 16 h at 25 °C, monitored by TLC. Then saturated aqueous NH_4Cl (5 mL) solution was added to quench the reaction, the resulting mixture was extracted with CH_2Cl_2 (3×50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. Column chromatography (silica, ethyl acetate/cyclohexane gradient) provided 0.343 mg (95%) of **15** as a white solid. Mp 127–130 °C. $[\alpha]_D^{20}$ 7.7 (*c* 1, $CHCl_3$). HRMS found for M^+ 362.2096; $C_{22}H_{26}N_4O$ requires 362.2107. ^1H NMR δ 8.81 (d, J=9.07 Hz, 1H), 8.76 (d, J=6.98 Hz, 1H), 8.26 (d, J=7.80 Hz, 1H), 7.75 (dd. J_1=J_2=7.90 Hz, 1H), 7.41 (d, J=7.93 Hz, 1H), 7.35 (dd. J_1=6.60 Hz, J_2=8.90 Hz, 1H), 7.03 (dd, J_1=J_2=6.64 Hz, 1H), 3.23 (s, 3H), 3.05 (d, J=8.61 Hz, 1H), 2.15 (m. 1H), 2.89 (m, 1H), 1.7 (d, J=4.21 Hz, 1H), 1.5 (m, 2H), 1.31 (m, 2H), 1.04 (s, 3H), 0.38 (s, 3H). ^{13}C NMR δ 162.4 (C), 149.8 (C), 138.2 (C), 136.1 (CH), 131.5 (C), 125.9 (CH), 125.3 (CH), 121.8 (CH), 121.0 (CH), 117.8 (CH), 115.6 (CH), 90.0 (C), 54.7 (OCH_3), 52.3 (C), 48.8 (CH), 48.5 (C), 44.4 (CH_2), 32,2 (CH_2), 29.1 (CH_3), 25.1 (CH_2), 21.6 (CH_3), 20.7 (CH_3). EM (EI) *m*/*z* (%) 362 (27), 347 (64), 319 (64), 281 (36), 221 (50), 195 (24), 168 (75), 167 (38), 81 (100), 78 (65).

3.6. General procedure for ring opening reactions of triazolopyridines 3, 4 and 15 with AcOH

A solution of the corresponding triazolopyridine in glacial acetic acid (10 mL) was heated (see conditions in Table 1). The solution was neutralized with saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The organic solvent was dried and evaporated. The residue was purified by silica column chromatography or chromatotron. The products, yields and conditions of purification are given for each compound.

3.6.1. 1-[6-(2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-pyridin-2-yl] ethyl acetate 11. Diastereomeric mixture, 5% de (1*R*,2*S*,4*S*,1′*S*) and (1*R*,2*S*,4*S*,1′*R*). Purified by chromatotron with ethyl acetate/hexane (132 mg, 75%, colourless oil). HRMS found for M^+ 317.1986; $C_{19}H_{27}N_3O$ requires 317.1990. ^1H NMR δ 7.62 (dd, J_1=7.8 Hz, J_2= 7.5 Hz, 2H), 7.40 (d, J=7.8 Hz, 1H), 7.41 (d, J=7.8 Hz, 1H), 7.17 (d, J=7.5 Hz, 1H), 7.16 (d, J=7.5 Hz, 1H), 5.92–5.84 (m, 2H), 2.35–2.20 (br m, 2H), 2.11 (s, 3H), 2.10 (s, 3H), 1.90–1.7 (m, 4H), 1.55 (d, J=6.6 Hz, 6H), 1.51–1.41 (m, 2H), 1.33 (d, J=10.2 Hz, 2H), 1.13 (ddd, J_1=J_2= 12.3 Hz, J_3=4.5 Hz, 2H), 0.99 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.38 (s, 3H), 0.35 (s, 3H). ^{13}C NMR δ 170.22/170.14 (C), 161.84/161.82 (C), 157.34/157.25 (C), 135.88/135.57 (CH), 121.75/121.63 (CH), 117.73/117.63 (CH), 83.56 (C), 72.55/72.49 (C), 51.62/51.57 (CH), 48.76 (CH), 45.92 (C), 41.84/41.73 (CH_3), 32.43/32.31 (CH_2), 29.09 (CH_2), 24.36/24.22 (CH_2), 22.13 (CH), 21.19/21.15 (CH_3), 20.84/20.48 (CH_3), 20.36/20.22 (CH_3), 17.11/17.08 (CH_3). EM (EI) *m*/*z* (%) 317 (10), 236 (85), 176 (20), 81 (100).

3.6.2. (1*R*,2*S*,4*S*)-1,3,3-Trimethyl-2-(6-vinylpyridin-2-yl)-bicyclo[2.2.1]hept-2-ol 10. Purified by chromatotron with ethyl acetate/hexane (15 mg, 17% oil colourless). HRMS found for M^+ 257.1779; $C_{17}H_{23}NO_2$ requires 257.1779. ^1H NMR δ 7.60 (dd, J_1=7.8 Hz, J_2=7.5 Hz, 1H), 7.39 (d, J=7.8 Hz, 1H), 7.16 (d, J=7.5 Hz, 1H), 6.76 (dd, J_1=17.4 Hz, J_2=12 Hz, 1H), 6.20 (dd, J_1=17.4 Hz, J_2=1.5 Hz, 1H), 5.45 (dd, J_1=12 Hz, J_2=14.5 Hz, 1H), 2.32–2.15 (m, 2H), 1.87–1.7(m, 2H), 1.5–1.37 (m, 1H), 1.29 (dd, J_1=1.5 Hz, J_2=12 Hz, 1H), 1.18 (br s, 1OH), 1.06 (ddd, J_1=J_2=12.6 Hz, J_3=4.8 Hz, 2H), 0.92 (s, 3H), 0.90 (s, 6H), 0.39 (s, 3H). ^{13}C NMR δ 152.56 (C), 152.41 (C), 136.30 (CH), 135.64 (CH), 122.01 (CH), 119.07 (CH), 118.00 (CH_2), 83.528 (C), 48.80 (CH), 45.96 (C), 42.01 (CH_2), 32.52 (CH_2), 29.69 (C), 29.29 (CH), 24.38 (CH_2), 24.41 (CH_3), 22.28 (CH_3), 17.17 (CH_3). EM (EI) *m*/*z* (%) 257 (15), 242 (15), 229 (35), 176 (100), 160 (82), 153 (12), 104 (45), 81 (60), 77 (18).

3.6.3. [6-(2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)pyridin-2-yl](pyridin-2-yl) methyl acetate 14. Diastereomeric mixture 3.5% de (1*R*,2*S*,4*S*,1′*S*) and (1*R*,2*S*,4*S*,1′*R*). Silica column chromatography eluted with ethyl acetate/cyclohexane (91.1 mg, 42%, colourless oil). HRMS found 380.2108 for M^+; $C_{23}H_{28}N_2O_3$ requires 380.2100. ^1H NMR δ 8.53 (m, 2H), 7.67 (m, 4H), 7.51 (dd, J_1=J_2=8.0 Hz, 2H), 7.40 (m, 4H), 7.18 (m, 2H), 6.87 (s, 1H), 6.85 (s, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 1.82–1.72 (m, 4H), 1.43 (m, 2H), 1.28 (m, 2H), 1.10 (m, 2H), 0.95 (s, 3H), 0.93 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.26 (s, 3H), 0.23 (s, 3H). ^{13}C NMR δ 169.9/169.9 (C), 157.9 (C), 155.0/154.9 (C), 149.3/149.2 (CH), 136.6 (CH), 136.1 (CH), 122.9/122.8 (CH), 122.5/122.2 (CH), 121.9/121.7 (CH), 119.8/119.2 (CH), 83.7 (C), 78.2 (CH), 48.1(CH), 46.0/45.9 (C), 41.8 (CH_3), 32.5/32.4 (CH_2), 28.8/28.7 (CH_3), 24.3 (CH_2), 22.0/21.9 (CH_3), 21.1/21.0 (CH_3), 17.1/17.0 (CH). EM (EI) *m*/*z* (%) 380 (7), 321 (27), 320 (100), 299 (30), 292 (31), 283 (30).

Table 1

Starting material (mg, mmol)	Reactant/solvent	*t* (h)/*T* (°C)	Product (mg, %)
3 (102, 0.35)	H_2SO_4/H_2O	23/100	**9** (52, 60); **10** (10, 10)
3 (160, 0.56)	AcOH	5/80	**11** (132, 75); **10** (15, 17)
3 (100, 0.35)	SeO_2/H_2SO_4	24/80	No reaction
3 (100, 0.35)	SeO_2/*p*-xylene	72/140	**12** (18, 22)
4 (109, 0.30)	H_2SO_4/H_2O	24/100	No reaction
4 (110, 0.31)	AcOH	24/80	No reaction
4 (197, 0.57)	AcOH	6/115	**14** (91, 42)
4 (100, 0.29)	SeO_2/H_2SO_4	24/100	No reaction
15 (150, 0.42)	H_2SO_4/H_2O	24/100	**18** (17, 13); **17** (55, 38)
15 (148, 0.40)	AcOH	50/115	**16** (40, 26); **17** (83, 60)

3.6.4. [6-(2-Methoxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)pyridin-2-yl](pyridin-2-yl) methyl acetate 16. Diastereomeric mixture, 4% de (1*R*,2*S*,4*S*,1′*S*) and (1*R*,2*S*,4*S*,1′*R*). Silica column chromatography eluted with ethyl acetate/cyclohexane (40 mg, 26%, yellow oil). HRMS found 394.2254 for M^+; $C_{24}H_{30}N_2O_3$ requires 394.2256. ^{1}H NMR δ 8.54 (m, 2H), 7.69 (ddd, J_1=J_2=7.71 Hz, J_3=1.75 Hz, 2H), 7.61 (dd, J_1=J_2=7.57 Hz, 2H), 7.57 (dd, J_1=J_2=8.80 Hz, 2H), 7.32 (dd, J_1=2.98 Hz, J_2=7.64 Hz, 2H), 7.28 (d, J=7.98 Hz, 2H), 7.17 (m, 2H), 6.91/6.89 (s, 2H), 3.12/3.11 (s, 6H), 2.51 (m, 2H), 2.21 (s, 6H), 2.05–1.96 (m, 2H), 1.83–1.73 (m, 2H), 1.54–1.36 (m, 4H), 1.18 (s, 3H), 1.15 (s, 3H), 1.12–1.07 (m, 2H), 1.00 (m, 2H), 0.92 (s, 6H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR δ 170/169 (C), 162.3/162.2 (C), 158.5 (C), 155.6/155.5 (C), 149.9/149.0 (CH), 136.4 (CH), 136.0 (CH), 122.8/122.7 (CH), 122.7/122.5 (CH), 122.0/121.9 (CH), 118.9/118.7 (CH), 89.9 (C), 78.7/78.6 (CH), 54.6 (CH_3), 52.4/52.3 (C), 48.4/48.3 (C), 48.4 (CH_3), 44.3/44.2 (CH_2), 31.7 (CH_2), 28.8/28.7 (CH_3), 25.3 (CH_2), 21.2/21.1 (CH_3), 20.0/19.8 (CH_3), 14.1 (CH). EM (EI) *m*/*z* (%) 394 (16), 380 (30), 379 (100), 319 (31), 314, (20), 313 (96).

3.6.5. (1*R*,2*S*,4*S*)-[6-(2-Methoxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)pyridin-2-yl](pyridin-2-yl) methanone 17. Silica column chromatography eluted with ethyl acetate/cyclohexane (83.1 mg, 60% colourless oil). HRMS found for M^+ 350.1995; $C_{22}H_{26}N_2O_2$ requires 350.1994. ^{1}H NMR δ 8.68 (m, 1H), 7.95 (dd, J_1=7.62 Hz, J_2=1.09 Hz, 1H), 7.94–7.79 (m, 3H), 7.06 (dd, J_1=7.99 Hz, J_2=1.10 Hz, 1H), 7.44–7.40 (m, 1H), 3.15 (s, 3H), 2.31 (m, 1H), 2.01 (m, 1H), 1.83–1.73 (m, 1H), 1.54–1.36 (m, 3H), 1.18 (s, 3H), 1.14–1.04 (m, 1H), 0.98 (s, 3H), 0.30 (s, 3H). ^{13}C NMR δ 194.4 (C=O), 162.2 (C), 155.8 (C), 152.5 (C), 148.9 (CH), 136.2 (CH), 136.1 (CH), 126.0 (CH), 125.3 (CH), 123.9 (CH), 121.6 (CH), 90.0 (C), 54.6 (CH_3), 52.2 (C), 48.5 (C), 48.4 (CH_3), 44.4 (CH_2), 31.6 (CH_2), 29.1 (CH_3), 24.4 (CH_2), 21.6 (CH_3), 19.9 (CH_3), 14.1 (CH). EM (EI) *m*/*z* (%) 350 (13), 335 (50), 269 (100), 78 (18).

3.7. General procedure for ring opening reactions of triazolopyridines 3, 4 and 15 with sulfuric acid

A solution of the corresponding triazolopyridine in aqueous sulfuric acid (10 mL, 2.5 M) was heated (see conditions in Table 1). The solution was neutralized with a saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The organic solvent was dried and evaporated. The residue was purified by silica column chromatography or chromatotron. With **4** no reaction was observed. The products, yields and conditions of purification are given for each compound.

3.7.1. 2-[6-(1-Hydroxy-ethyl)-pyridin-2-yl]-1,3,3-trimethylbicyclo[2.2.1]hept-2-ol 9. Diastereomeric mixture 5% de (1*R*,2*S*,4*S*,1′*S*) and (1*R*,2*S*,4*S*,1′*R*). Purified by chromatotron with ethyl acetate/hexane (52 mg, 60% colourless oil). HRMS found for M^+ 275.1889; $C_{17}H_{25}NO_2$ requires 275.1885. ^{1}H NMR δ 7.65 (dd, J_1=7.8 Hz, J_2=7.5 Hz, 2H), 7.43 (d, J=7.8 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 4.88 (d, J=6.6 Hz, 2H), 3.2 (br s, 2OH), 2.28 (m, 4H), 1.87–1.78 (m, 4H), 1.5 (d, J=6.6 Hz, 3H), 1.49 (d, J=6.6 Hz, 3H), 1.51–1.48 (m, 2H), 1.35 (d, J=9.3 Hz, 2H), 1.17 (ddd, J_1=J_2=12.9 Hz, J_3=4.8 Hz, 2H), 1.00 (s, 3H), 0.99 (s, 3H), 0.98 (s, 6H), 0.40 (s, 3H), 0.39 (s, 3H). ^{13}C NMR δ 162.11 (C), 161.19 (C), 136.62 (CH), 121.90/121.84 (CH), 117.71 (CH), 84.24 (C), 70.09/69.93 (CH), 52.45/52.36 (C), 49.24 (CH), 46.47 (C), 42.39 (CH_2), 32.92 (CH_2), 29.55/29.52 (CH), 24.80/24.68 (CH_2), 24.41 (CH_3), 22.55 (CH_3), 17.58 (CH_3). EM (EI) *m*/*z* (%) 275 (8), 260 (12), 194 (100), 178 (71). In the first fraction **10** (10 mg, 10%) was obtained.

3.7.2. Pyridin-2-yl [6-(2,7,7-trimethyltricyclo[2,2,1,0^{2,6}]hept-1-yl)pyridin-2-yl] methanone 18. Silica column chromatography with ethyl acetate/cyclohexane as eluent. Brown oil (17 mg, 13%). HRMS found for M^+ 318.1733; $C_{21}H_{22}N_2O$ requires 318.1732. ^{1}H NMR δ 8.73 (d, J=4.34 Hz, 1H), 8.06 (d, J=7.82 Hz, 1H), 7.90 (dd, J_1=7.67 Hz, J_2=0.98 Hz, 1H), 7.83 (ddd, J_1=J_2=7.71 Hz, J_3=1.7 Hz, 1H), 7.74 (dd, J_1=J_2=7.79 Hz, 1H), 7.43 (m, 1H), 7.35 (dd, J_1=7.86 Hz, J_2=1.00 Hz, 1H), 1.82 (m, 2H), 1.53 (m, 1H), 1.40 (s, 1H), 1.32 (m, 1H), 1.22 (m, 1H), 1.07 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H). ^{13}C NMR δ 193.4 (C=O), 159.0 (C), 154.7 (C), 153.5 (C), 149.1 (CH), 136.0 (CH), 127.3 (CH), 127.2 (CH), 125.7 (CH), 125.6 (CH), 121.3 (CH), 46.8 (C), 44.1 (CH), 42.0 (C), 38.6 (CH_2), 32.2 (CH_2), 29.4 (C), 27.1 (CH_3), 22.6 (CH_3), 21.7 (CH_3), 14.0 (CH). EM (EI) *m*/*z* (%) 318 (100), 303 (60), 277 (34), 212 (20), 78 (20). Further elution gave **17** (55.1 g, 38%).

3.8. Ring opening reaction of triazolopyridines 3 and 4 with SeO_2

Method A: a suspension of triazolopyridine **3** or **4** and selenium dioxide (2 equiv) in sulfuric acid (10 mL, 2.5 M) was heated (see conditions in Table 1). *Method B*: a suspension of **3** and selenium dioxide (2 equiv) in *p*-xylene was heated (see conditions in Table 1). Then the corresponding mixture was filtered and the filtrate neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with dichloromethane. The organic solvent was dried and evaporated. The residue was purified by chromatotron to obtain **12** (22%).

3.9. Synthesis of Zn(4)Cl_2

To a solution of (1*R*,2*S*,4*S*)-1,3,3-trimethyl-2-(6-[1,2,3]triazolo[1,5-*a*]pyridin-3-yl-pyridin-2-yl)-bicyclo[2.2.1]hept-2-ol **4** (50 mg, 0.14 mmol) in dichloromethane (20 mL), a solution of Cl_2Zn in ether (0.15 mL, 1 M) was added. A yellow solution was formed and was stirred (30 min) at room temperature. Evaporation of the solvent gives a yellow oil that was washed with hot ethyl acetate. The oil obtained has identical ^{1}H and ^{13}C NMR in DMSO-d_6 that the ligand **4**. HRMS (FAB) found for M^+ 447.093; $C_{21}H_{24}N_4OClZn$ requires 447.093. MS *m*/*e* (%) 454 (3), 453 (16), 452 (17), 451 (62), 450 (31), 449 (92), 448 (25), 447 (100). UV λ_{max} (log ε) (MeOH) 225 (2.5), 270 (2.47), 311 (2.56), 320 (2.57).

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