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ITERATIVE ONE POT REACTIONS OF A CHIRAL SULFAMIDATE WITH 2,4,6-TRICHLOROPYRIDINE: REGIOCONTROLLED SYNTHESIS OF LINEAR AND ANGULAR CHIRAL DIPYRROLIDINO PYRIDINES

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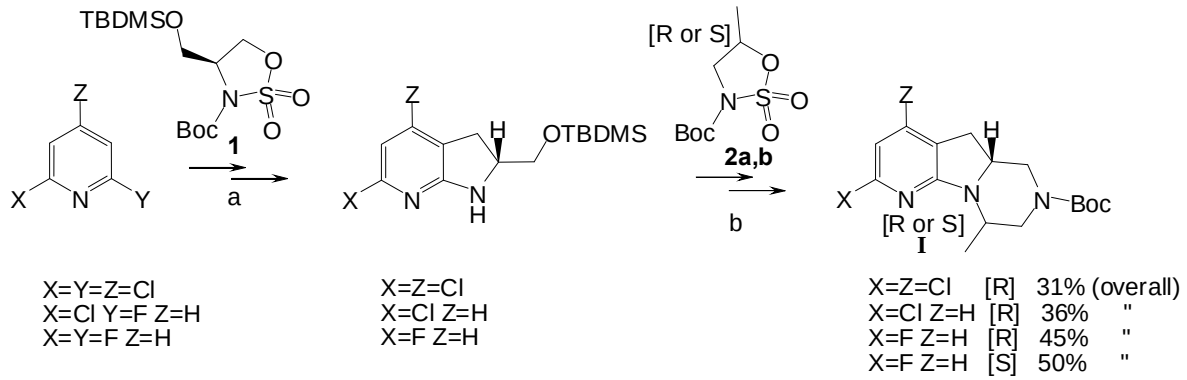
Abstract - The product of the ring opening of a chiral sulfamidate with the 3-lithiopyridine species obtained by deprotonation of 2,4,6-trichloropyridine with *n*-BuLi can be deprotonated again in situ with *n*-BuLi and reacted with a second equivalent of the sulfamidate furnishing a bis β-aminoethyl pyridine derivative which can be cyclized regioselectively to linear or angular chiral dipyrrolidino pyridines.

INTRODUCTION

Ring opening of cyclic sulfamidates with appropriate nucleophilic components has become recognized as a valuable strategy for the construction of a wide variety of *N*-heterocycles as demonstrated in a perspective by Bower *et al*.[1]

Recently we contributed to the topic with a concise stereocotrolled synthesis[2] of pharmacologically interesting hexahydro-pyrido[3',2':4,5]pyrrolo[1,2-*a*]pyrazines **I**[3a,3b] which was based on two consecutive ring opening reactions of chiral sulfamidates easily obtainable from the chiral pool. The first ring opening involved reactions of silyloxymethyl substituted sulfamidate **1**, derived from serine, with 2-halo-3-lithiopyridines and allowed the rapid construction of azaindolines. A second ring opening of sulfamidates **2a** or **2b**, derived from *R* or *S* 1-amino-2-propanols, involving the 7-azaindoline *NH* as the nucleophile permitted rapid construction of the pyrazine part of the target structure **I** (Scheme 1).



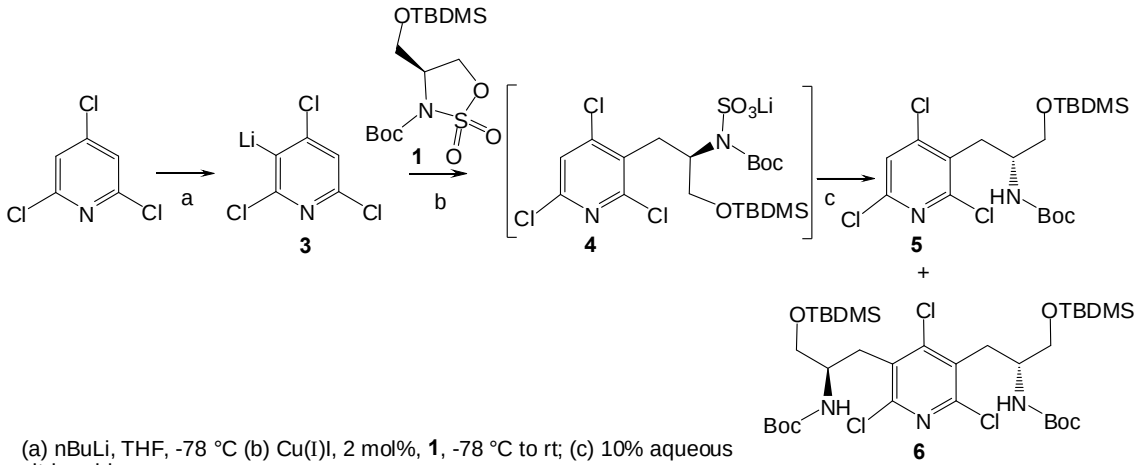
(a) 1.) nBuLi or LiTMP, THF, -78 °C, 2.) **1** -78 °C to rt, then aqueous citric acid, 3.) TBDMS triflate, CH_2Cl_2, rt.
(b) 1.) NaH, THF, rt, then **2a** or **2b**, 2.) NH_4F, methanol reflux, 3.) MsCl, DIPEA, CH_2Cl_2, rt, 4.) NaH, THF, rt.

Scheme 1. Synthesis of hexahydro-pyrido[3',2':4,5]pyrrolo[1,2-*a*]pyrazines

Especially the facile deprotonation of 2,4,6-trichloropyridine[4] with *n*-BuLi in THF at -78 °C and the stability of the resulting lithio complex motivated us to further explore its reactions with chiral substituted sulfamidates as a strategy to access heterocycles bearing aromatic substituents amenable to late stage derivatisations such as halo substituted azaindolines.[5]

RESULTS AND DISCUSSION

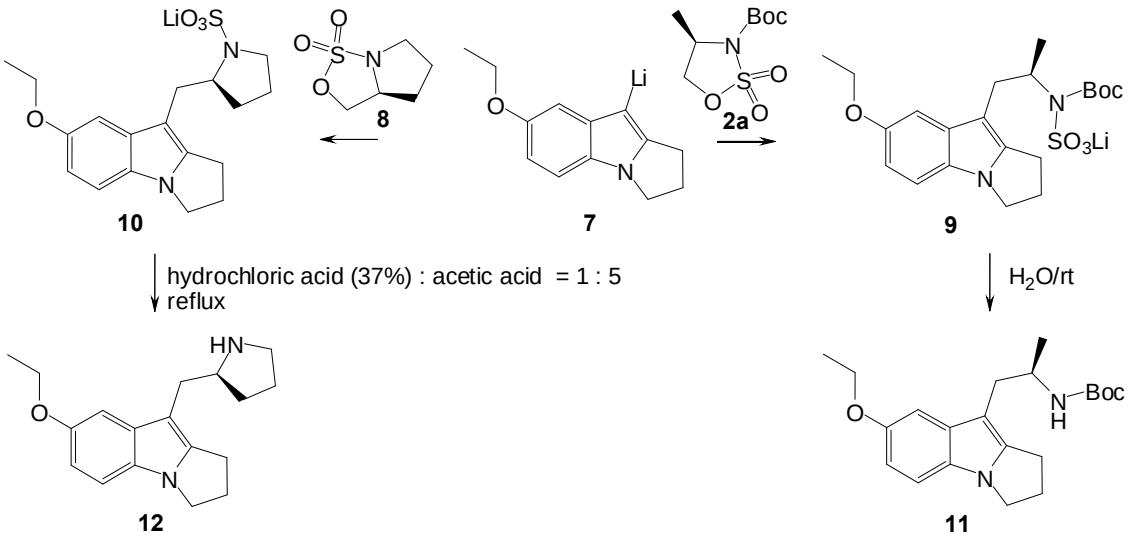
Careful analysis of the reaction of sulfamidate **1** with 3-lithio-2,4,6-trichloropyridine **3** revealed the formation of small amounts (ca 4-8%) of bis-alkylated pyridine **6**, the formal product of a double deprotonation while the mono adduct **5** was obtained in up to 81% yield. However when 2,4,6-trichloropyridine was treated with a twofold excess *n*-BuLi in THF at -78 °C followed by addition of 2 mol % of copper(I) iodide and 2 equivalents of sulfamidate **1** the mono-alkylated product **5** was still favored (31.3%) over the bis-alkylated product **6** (8.8%) following the established protocol, thus ruling out direct double lithiation at the pyridine (scheme 2).



(a) nBuLi, THF, -78 °C (b) Cu(I)I, 2 mol%, **1**, -78 °C to rt; (c) 10% aqueous citric acid

Scheme 2. Ring opening of *N*-Boc sulfamidate with 3-lithiopyridine

Next we considered sequential double alkylation. The primary product of the ring opening of a sulfamidate with an arylmetal species is a sulfamic acid salt such as **4**.[6] The nature of the substituents on the amine part of sulfamic acids greatly influences their stability. The hydrolysis of sulfamic acids has been reviewed and an A2 mechanism has been proposed.[7] During a program directed towards selective $5HT_{2C}$ agonists we had the opportunity to directly compare the hydrolysis of the two closely related sulfamic acids **9** and **10** which were isolated as salts form the reaction of an aryllithium species **7** with *N*-Boc sulfamidate **2a** and proline derived sulfamidate **8** (scheme 3).[8] The *N*-Boc sulfamic acid lithium salt **9** hydrolyzed spontaneously upon dissolution in water whereby the initial pH dropped from ca 9 to 1 indicating liberation of sulfuric acid during the process. Hydrolysis of sulfamic acid **10** required refluxing in a 1 : 5 mixture of fuming hydrochloric acid (37%) in acetic acid for 8 h. The presence of the *N*-Boc group thus greatly facilitates hydrolysis of a corresponding sulfamic acid derivative thus allowing sensitive functionality such as silyl ethers to survive.



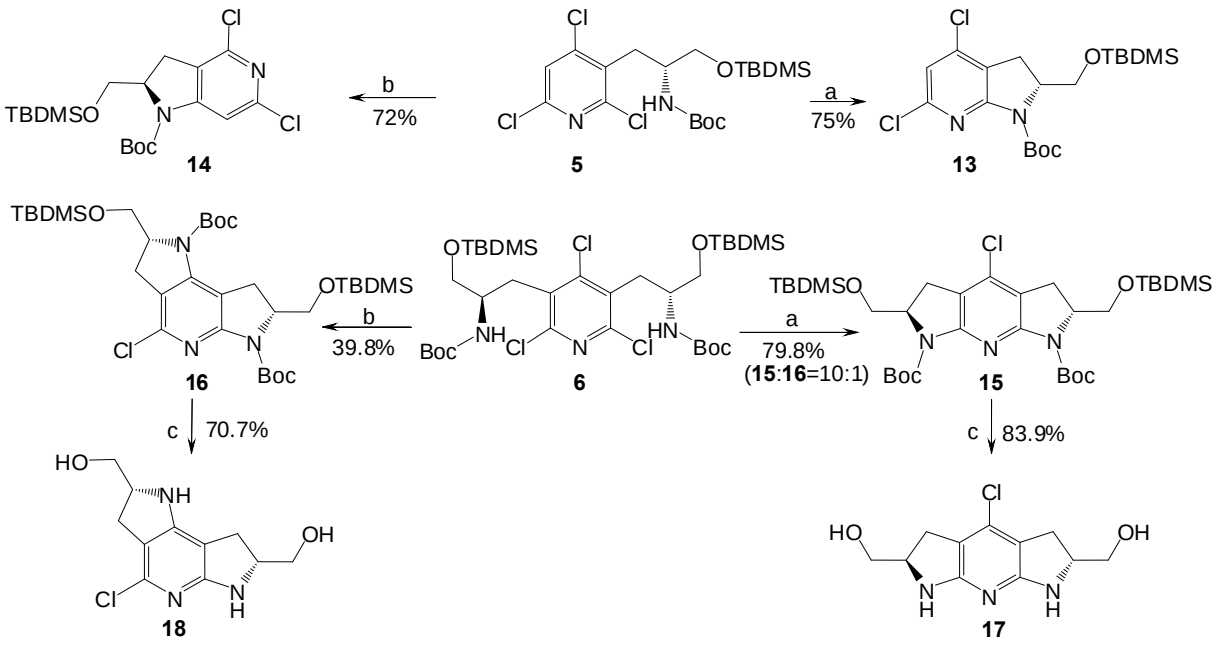
Scheme 3. Preparation and hydrolytic stability of sulfamic acids **9** and **10**

On the other hand stability of sulfamic acids derived from **8** towards bases is controversially discussed.[9,6] However sulfamic acid lithium salts of type **9** appeared to be stable solids and we reasoned that the sulfamic acid group could act as an intermediary protective group[10] during a second deprotonation at the pyridine nucleus. We thus treated the hypothetical intermediate **4** obtained from reaction of 3-lithiopyridine **3** with sulfamidate **1** at -78 °C with a second equivalent *n*-BuLi and an extra equivalent sulfamidate **1**. Allowing the reaction mixture to warm to room temperature followed by mild acidic hydrolysis, extractive workup and chromatography indeed furnished crystalline bis alkylated pyridine **6** in an unexpected 91% yield (Scheme 4). The presence of the negatively charged sulfamic acid group in **4** appears to be no obstacle for a second deprotonation. The sulfamic acid group rather acts as an

intermediary protecting group for the *N*-Boc group which would otherwise not be inert to the strong base employed. The formation of small quantities of **6** during single deprotonation can be explained by in situ hydrogen lithium exchange between 3-lithiopyridine **3** and pimary adduct **4** which supposedly is of similar C-H acidity on the pyridine core as 2,4,6-trichloropyridine itself.

In our previous work we had established conditions for the regioselective ring closure of mono adduct **5** to chiral azaindolines **13** and **14** via an intramolecular S_NAr reaction (Scheme 4).[2] Reaction with sodium hydride which can coordinate to the pyridine nitrogen gave exclusively ring closure to the *ortho* position to yield azaindoline isomer **13** whereas reaction with the non coordinating cesium carbonate resulted in ring closure to the *para* position to furnish azaindoline isomer **14**.

In analogy treatment of bis-alkylated pyridine **6** with sodium hydride in THF resulted in a 79.8% yield of the linear double ring closed product **15** and its angular counterpart **16** in a ratio of 10 : 1 from which the major linear isomer was obtained in pure form by crystallization from methanol. Due to poor solubility of the bis alkylated pyridine **6** in DMSO at room temperature the reaction with cesium carbonate was carried out at 100 °C resulting in exclusive formation of angular tricycle **16** albeit in somewhat reduced yield (39.8%). Treatment of tricycles **15** and **16** with trifluoroacetic acid furnishing fully deprotected dipyrrolopyridine derivatives **17** and **18** respectively, providing a novel access to these tricyclic ring system.[11a,11b] The method tolerates divers functionality well suited for further modification and proceeds without loss of stereochemical integrity as evidenced by X-Ray single crystal analysis of compound **15** (figure 1).[12]



(a) sodium hydride, THF, rt, (b) Cs_2CO_3, DMSO, (c) TFA, rt.

Scheme 4. Regiochemistry in the double intramolecular S_NAr of 2,4,6-trichloropyridine derivatives

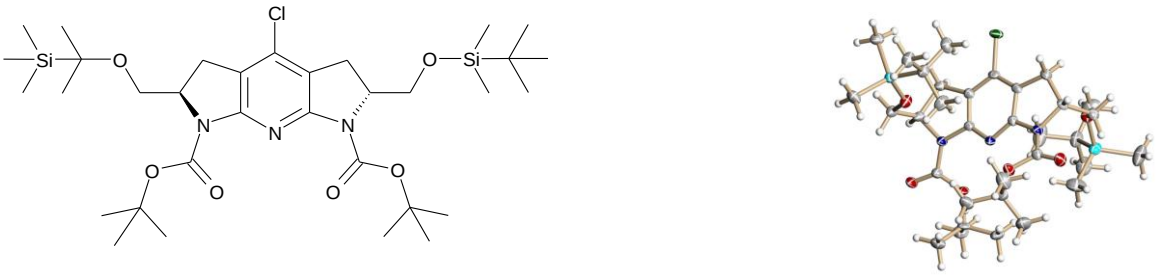


Figure 1. X-Ray crystal structure of linear tricycle **15**

CONCLUSION

We have shown that the intermediate from a reaction of a sulfamidate **1** with 3-lithio-2,4,6-trichloropyridine, a sulfamic acid salt of type **4**, can be deprotonated again with *n*-BuLi at the pyridine nucleus allowing an iterative reaction with sulfamidate **1**. The presence of a negatively charged sulfamic acid residue in **4** does not prevent further deprotonation and acts as an intermediary protective group for the *N*-Boc group which would otherwise be prone to intramolecular S_NAR reactions at the reactive halogens of the pyridine nucleus. Such intramolecular reactions indeed take place, after mild acidic hydrolysis of the sulfamic acids, upon exposure to bases. The regiochemistry of these intramolecular S_NAR reactions is determined by the potential of the base to coordinate with the pyridine nitrogen. Sodium hydride favors ring closure to the *ortho* positions resulting in a linear tricycle whereas cesium carbonate favors ring closure to the *para* position resulting in an angular tricycle. The method provides a rapid entry into linear and angular chiral dipyrrolidinopyridines carrying functional groups useful for further derivatisations.

EXPERIMENTAL

tert-Butyl (2*R*,2'*R*)-3,3'-(2,4,6-trichloropyridine-3,5-diyl)bis(1-(*tert*-butyldimethylsilyloxy)propane-3,2-diyl)dicarbamate **6**

A solution of freshly distilled 2,4,6-trichloropyridine (250 mg, 1.37 mmol, Eq: 1.00) in THF (2.00 mL) was added drop wise at -78 °C to a 1.6 M solution of *n*-BuLi in hexanes (1.03 mL, 1.65 mmol, Eq: 1.20) and the mixture was stirred at -78 °C for 30 min. To the resulting yellow solution was added copper(I) iodide (10.0 mg, 52.6 µmol, Eq: 0.038) and (*R*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)-3-(2,4,6-trichloropyridin-3-yl)propan-2-ylcarbamate **1** (0.505 g, 1.37 mmol, Eq: 1.00) and the mixture was stirred at -78 °C for 30 min. To the resulting slightly orange solution was added drop wise at -78 °C a 1.6 M solution of *n*-BuLi in hexanes (1.03 mL, 1.65 mmol, Eq: 1.20) and the mixture was stirred at -78 °C for 30 min. To the resulting solution was added (*R*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)-3-(2,4,6-trichloropyridin-3-yl)propan-2-ylcarbamate (0.505 g, 1.37 mmol, Eq: 1.00) and the mixture was stirred at

-78 °C for 30 min and then allowed to taw to room temperature. To the resulting mixture was added a 10% aqueous solution of potassium bisulfate (10mL) and EtOAc (ca 10mL) with stirring. The phases were separated and the organic phase was purified by chromatography on silica gel with a gradient of heptane to heptane : ethyl acetate = 9 : 1 to yield *tert*-butyl (2*R*,2'*R*)-3,3'-(2,4,6-trichloropyridine-3,5-diyl)bis(1-(*tert*-butyldimethylsilyloxy)propane-3,2-diyl)dicarbamate **6** (0.95 g, 1.25 mmol, 91.3 %).

For analytical purposes the material was rechromatographed on silica gel using a gradient of CH_2Cl_2 to CH_2Cl_2: EtOAc = 19 : 1 and the product was crystallized from methanol (mp 144-146 °C).

MS (m+1) $C_{33}H_{61}Cl_3N_3O_6Si_2$ calc 756.316452; found 758.3114.

^{1}H NMR (600 MHz, DMS*O*-d_6) δ ppm 6.49 (d, *J* = 6 Hz, 1 H), 3.77-3.70 (m, 1 H), 3.01-2.95 (m, 1 H), 2.80-2.71 (m, 1 H), 1.10 and 0.97 (s, 9 H, rotamers), 0.73 (s, 9 H), 0.09 (s, 6 H).

(2*R*,6*R*)-Di-*tert*-butyl 2,6-bis((*tert*-butyldimethylsilyloxy)methyl)-4-chloro-2,3,5,6-tetrahydrodipyrrolo-[2,3-*b*:3',2'-*e*]pyridine-1,7-dicarboxylate **15**

To a solution of *tert*-butyl (2*R*,2'*R*)-3,3'-(2,4,6-trichloropyridine-3,5-diyl)bis(1-(*tert*-butyldimethyl-silyloxy)propane-3,2-diyl)dicarbamate **6** (0.14 g, 185 µmol, Eq: 1.00) in tetrahydrofuran (3 ml) was added NaH (64.5 mg, 1.48 mmol, Eq: 8) and the mixture was stirred with agitation in an ultrasound bath at ambient temperature for 3 h (temperature rises to 40 °C). The reaction mixture was partitioned between 10% aqueous sodium bisulfate and EtOAc. The phases were separated and the organic phase was washed with 10% aqueous $NaHCO_3$ and brine and purified by chromatography on silica gel with CH_2Cl_2 to CH_2Cl_2: EtOAc = 8:2. to yield a 10:1 mixture of isomers (2*R*,6*R*)-di-*tert*-butyl-2,6-bis((*tert*-butyl-dimethylsilyloxy)methyl)-4-chloro-2,3,5,6-tetrahydrodipyrrolo[2,3-*b*:3',2'-*e*]pyridine-1,7-dicarboxylate **15** and (2*R*,7*R*)-di-*tert*-butyl 2,7-bis[(*tert*-butyldimethylsilyloxy)methyl]-4-chloro-2,3,7,8-tetrahydro-dipyrrolo[2,3-*b*:2',3'-*d*]pyridine-1,6-dicarboxylate **16** (solid 0.101 g, 148 µmol, 79.8% yield). The material was crystallized from MeOH to yield pure **15**. Mp 138.2-139.3.

MS (m+1) $C_{33}H_{59}ClN_3O_6Si_2$ calc 684.363096; found 684.3638.

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.40-4.32 (m, 2 H), 3.76-3.72 (m, 2 H), 3.42-3.36 (m, 2 H), 2.96-2.86 (m, 4 H), 1.47 (s, 18 H), 0.75 (s, 18 H), 0.06 (s, 6 H), 0.02 (s, 6 H). X-Ray data deposited at the Cambridge CrystallographicData Centre under CCDC 823653 Unit cell parameters: a10.02490(10) b 11.6466(2) c 16.8618(2)beta 92.5640(10) space group P21.

(2*R*,7*R*)-Di-*tert*-butyl 2,7-bis[(*tert*-butyldimethylsilyloxy)methyl]-4-chloro-2,3,7,8-tetrahydrodipyrrolo-[2,3-*b*:2',3'-*d*]pyridine-1,6-dicarboxylate **16**

To a suspension of Cs_2CO_3 (300 mg, 921 µmol, Eq: 17.4) in DMSO (3 mL) was added at once at 100 °C *tert*-butyl (2*R*,2'*R*)-3,3'-(2,4,6-trichloropyridine-3,5-diyl)bis[1-(*tert*-butyldimethylsilyloxy)propane-3,2-

diyl]dicarbamate **6** (0.040 g, 52.8 µmol, Eq: 1.00) and the reaction mixture was stirred at this temperature for 0.5 h. The reaction mixture was partitioned between water and EtOAc. The phases were separated and the organic phase was washed with 10% aqueous citric acid, 10% aqueous $NaHCO_3$ and brine and purified by chromatography on silica gel with a gradient of heptane to heptane : EtOAc = 8 : 2 to yield (2*R*,7*R*)-di-*tert*-butyl 2,7-bis[(*tert*-butyldimethylsilyloxy)methyl]-4-chloro-2,3,7,8-tetrahydrodipyrrolo-[2,3-*b*:2',3'-*d*]pyridine-1,6-dicarboxylate **16** (white foam 0.0144 g, 21.0 µmol, 39.8%).

MS (m+1) $C_{33}H_{59}ClN_3O_6Si_2$ calc 684.363096; found 684.3636.

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 4.56-4.50 (m, 1 H), 4.56-4.50 (m, 1 H), 4.42-4.36 (m, 1 H), 3.76-3.72 (m, 2 H), 3.70-3.66 (m, 1 H), 3.54-3.46 (m, 2 H), 3.29-3.23 (m, 1 H), 2.85-2.90 (m, 1 H), 2.81-2.76 (m,1 H) 1.43 (s, 9 H), 1.42 (s, 9 H), 0.06 (s, 12H).

((2*R*,6*R*)-4-Chloro-1,2,3,5,6,7-hexahydrodipyrrolo[2,3-*b*:3',2'-*e*]pyridine-2,6-diyl)dimethanol **17**

A solution of (2*R*,6*R*)-di-*tert*-butyl 2,6-bis((*tert*-butyldimethylsilyloxy)methyl)-4-chloro-2,3,5,6-tetrahydrodipyrrolo[2,3-*b*:3',2'-*e*]pyridine-1,7-dicarboxylate 1**5** (0.015 g, 21.9 µmol, Eq: 1.00) in trifluoroacetic acid (0.15 mL) was kept at ambient temperature for 3h. The solvent was evaporated and the residue was purified by chromatography on silica gel with CH_2Cl_2: MeOH : ammonia (25% in water) = 9 : 1 : 0.1. The product fractions were evaporated to yield a white solid which was triturated under $CDCl_3$. The solid was collected by filtration to yield ((2*R*,6*R*)-4-chloro-1,2,3,5,6,7-hexahydrodipyrrolo-[2,3-*b*:3',2'-*e*]pyridine-2,6-diyl)dimethanol **17** (0.0047 g, 18.4 µmol, 83.9%).

MS (m+1) $C_{11}H_{15}ClN_3O_2$ calc. 256.085280; found 256.0847.

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 6.04 (s, 2 H), 4.74 (t, *J* = 3 Hz, 2 H), 3.78-3.73 (m, 2 H), 3.38-3.34 (m, 2 H), 3.30-3.26 (m, 2 H) 2.87 (dd, *J* = 12 z, 4 Hz, 2 H), 2.57 (dd, *J* = 12 Hz, 3 Hz, 2 H).

((2*R*,7*R*)-4-Chloro-1,2,3,6,7,8-hexahydrodipyrrolo[2,3-*b*:2',3'-*d*]pyridine-2,7-diyl)dimethanol **18**

A solution of (2*R*,7*R*)-di-*tert*-butyl 2,7-bis((*tert*-butyldimethylsilyloxy)methyl)-4-chloro-2,3,7,8-tetrahydrodipyrrolo[2,3-*b*:2',3'-*d*]pyridine-1,6-dicarboxylate **16** (0.025 g, 36.5 µmol, Eq: 1.00) in trifluoroacetic acid (1 mL) was kept at ambient temperature for 72 h. The solvent was evaporated and the residue was purified by chromatography on silica gel with CH_2Cl_2: MeOH : ammonia (25% in water) = 9 : 1 : 0.1 to yield ((2*R*,7*R*)-4-chloro-1,2,3,6,7,8-hexahydrodipyrrolo[2,3-*b*:2',3'-*d*]pyridine-2,7-diyl)-dimethanol **18** (0.0066 g, 25.8 µmol, 70.7%) mp 181.2-182.4°C.

MS (m+1) $C_{11}H_{15}ClN_3O_2$ calc. 256.085280; found 256.0853.

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 6.51 (s, 1 H), 5.97 (s, 1 H), 4.82 (t, *J* = 3 Hz, 1 H), 4.72 (t, *J* = 3

Hz, 1 H), 3.87-3.83 (m, 1 H), 3.74-3.70 (m, 1 H), 3.4-3.2 (m, 4 H), 3.38-3.34 (m, 2H), 2.84 (dd, *J* = 12 Hz, 4 Hz, 2 H), 2.75 (dd, *J* =12 Hz, 4Hz, 2 H), 2.6-2.4 (m, 4 H).

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