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Synthesis of functionalized analogs of pyochelin, a siderophore of *Pseudomonas aeruginosa* and *Burkholderia cepacia*

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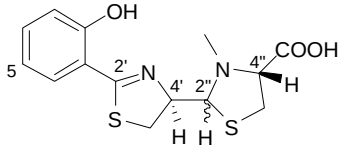
Abstract—Using an improved synthesis of pyochelin, a siderophore common to several pathogenic *Pseudomonas* species, three functionalized pyochelin analogs were efficiently synthesized starting from appropriate 2-hydroxybenzonitriles.

1. Introduction

Iron is a crucial element for aerobic life, unfortunately its bioavailability is limited by the low solubility of iron(III) at physiological pHs. To overcome this problem, microorganisms have developed very efficient iron uptake systems mediated by low molecular weight molecules called siderophores.[1] Under iron limited conditions, microorganisms synthesize and excrete these molecules into the extracellular medium in order to chelate iron(III). In Gram-negative bacteria, the siderophore–iron(III) complex is recognized and transported by a specific outer membrane receptor. The uptake process is driven by the proton motive force of the inner membrane via an inner membrane complex composed of TonB, ExbB and ExbD proteins.[2,3] *Pseudomonas aeruginosa* and *Burkholderia cepacia*, are two opportunistic Gram-negative bacteria, causes of severe and often lethal lung infections especially for cystic fibrosis and aids affected patients.[4] The low permeability of the outer membrane of these bacteria and the increasing antibiotic mediated selective pressure raised emerging multiresistant strains. During infection, these bacteria are in the host in an iron limited environment: higher eucaryotes contain substantial amount of this metal but tightly associated with transport and storage proteins and not freely available for pathogens. Consequently, the level of free iron in biological fluids is usually estimated to be only 10^{-18} M and *P. aeruginosa* and *B. cepacia* use siderophores to compete for iron with the host.

One way to increase the efficiency of antibiotics targeting these bacteria is the Trojan horse strategy where antibiotics are coupled to siderophores and transported across the bacterial membranes via the iron uptake pathways.[5] Such an approach has been already developed giving promising results with the pyoverdine mediated iron uptake system.[6] A disavantage of the pyoverdine iron uptake pathway is that each *P. aeruginosa* strain produces its own pyoverdine along with a corresponding specific transporter.[7] Very few crossfeeding have been observed between these different pyoverdines and their corresponding transporters. For the pyochelin **1** pathway, this siderophore is produced by all *P. aeruginosa* and *B. cepacia* strains.[8] Therefore, pyochelin is a more interesting candidate for such a prodrug strategy and the bactericidial activity of pyochelin–antibiotic conjugate should be more extended compared with pyoverdine based prodrugs (Fig. 1).



Pyochelin **1**

Figure 1. Structure of pyochelin **1**.

In view of its use as a versatile antibiotic vector, pyochelin **1** was functionalized in order to be further connected to the selected antibiotics. Taking into account the distance

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between the heteroatoms involved in iron chelation and the easiness of synthetic access, the fact that bulky C5-substituted analogs of pyochelin were shown to transport iron at reasonable rates,[9] position 5 on the aromatic ring was selected in a first approach to host an amine function. The synthesis of such pyochelin analogs was thus planned using the improved protocol adapted from a total synthesis of pyochelin **1** previously published.[10] According to this procedure, pyochelin analogs **2**, **3** and **4** were thus synthesized starting, respectively, from amino substituted 2-hydroxybenzonitriles **5**, **6** and **7** (Fig. 2).

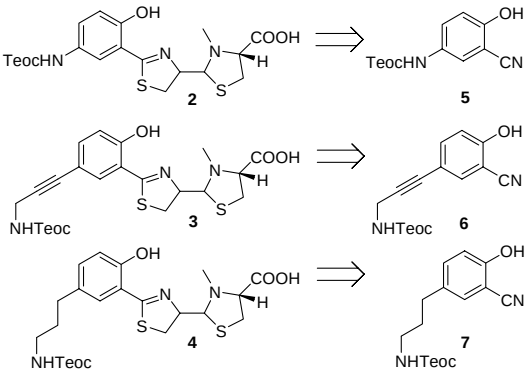
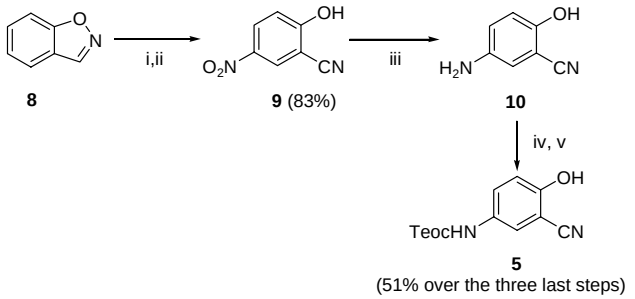


Figure 2. Retrosynthetic routes to functionalized pyochelins **2**, **3** and **4**.

In analog **2** the functionality is directly grafted on pyochelin whereas analogs **3** and **4** offer some alternative in terms of distance and flexibility towards the siderophore. All along the synthesis, the amine was protected with a trimethylsilylethoxycarbonyl (Teoc) group,[11] in order to facilitate purifications and to avoid side reactions. This protecting group was chosen for its good stability during the synthetic process and for the easiness and mildness of the deprotection conditions. In this paper, we describe the synthesis of functionalized 2-hydroxybenzonitriles **5**, **6** and **7** and their efficient conversions into the three unprecedented pyochelin analogs **2**, **3** and **4**.

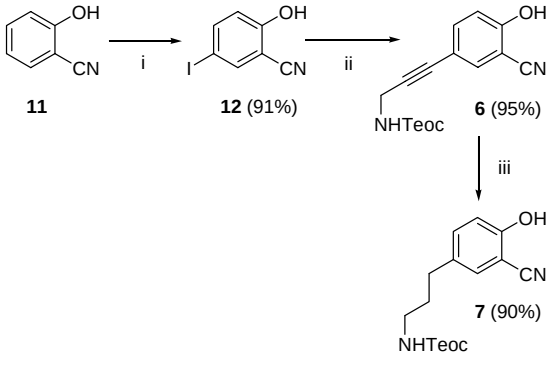
2. Results and discussion

The 2-hydroxybenzonitrile derivative **5** was prepared starting from 1,2-benzisoxazole **8**. The regioselective nitration of **8** with a sulfonitric mixture,[12] and the subsequent hydrolysis in basic conditions of the oxazole moiety led to the expected 5-nitro-2-benzonitrile **9** isolated in 83% overall yield.[13] The nitro function was then reduced into an amine. Using $TiCl_3$ in MeOH the expected amine **10** was isolated in an average yield after a tedious purification protocol.[14] A quite quantitative yield was obtained by catalytic hydrogenation using palladium on charcoal: the resulting amine **10** was quite unstable and had either to be stored at $-20\,^{\circ}C$ in the dark and under argon or immediately used as such for the next step. Since, the phenol function of compound **10** appeared to be more reactive than the amine function, amine **10** was treated with more than a two fold excess of *p*-nitrophenyl-trimethylsilylethyl-carbonate[15] and yielded a Teoc bisprotected compound. Further treatment of the crude mixture with sodium carbonate in refluxing wet acetone induced the selective deprotection of phenol and gave carbamate **5** isolated in an overall 51% yield over the three last steps (Scheme 1).



Scheme 1. Synthesis of functionalized 2-hydroxybenzonitrile **5**. (i) HNO_3, H_2SO_4, 0 °C. (ii) NaOH, H_2O/EtOH, 20 °C. (iii) H_2, Pd/C 10%, EtOH, 20 °C. (iv) *p*-$NO_2(C_6H_4)OCOCH_2CH_2Si(CH_3)_3$, pyridine, DMAP, CH_2Cl_2 reflux. (v) Na_2CO_3, H_2O/acetone reflux.

Cyanophenols **6** and **7** were both prepared starting from commercially available 2-hydroxybenzonitrile **11**. In a first step, compound **11** was converted in excellent yield into the iodinated derivative **12** using *N*-iodosuccinimide in presence of HBF_4 at low temperature.[16] Iodo compound **12** was then coupled to Teoc protected propargylamine **13**[17] via a Sonogashira coupling reaction, using a catalytic amount of $Pd(PPh_3)_4$, copper(I)iodide and DIPEA in DMF.[18] Thus, the expected substituted 2-hydroxybenzonitrile **6** was isolated in excellent yield and catalytically reduced in compound **7** with hydrogen over palladium adsorbed on charcoal. In this step, an extended hydrogenation cause the reduction of both the alkyne triple bond and the nitrile group. However, when the course of the reaction was carefully checked, the expected carbamate **7** was isolated usually in 90% yield (Scheme 2).



Scheme 2. Synthesis of functionalized 2-hydroxybenzonitriles **6** and **7**. (i) NIS, $HBF_4 \cdot Et_2O$, CH_3CN, $-10\,^{\circ}C$. (ii) **13**, $Pd(PPh_3)_4$, CuI, DIPEA, DMF, 20 °C. (iii) H_2, Pd/C 10%, EtOH, 20 °C.

Having in hand the different 2-hydroxybenzonitriles, the synthesis of the pyochelin analogs was then investigated. In natural pyochelin, the absolute configurations are $4'R$ and $4''R$ while configuration at C2″ is wobble and C2″:can readily be epimerized. During the synthesis of pyochelin, partial racemization occurs at C4′ while the absolute configuration at C4″ remains unaffected thus affording a mixture of pyochelin **a** ($4'R$,$2''R$,$4''R$), **b** ($4'R$,$2''S$,$4''R$), and

neopyochelin **c** (4′*S*,2″*R*,4″*R*) and **d** (4′*S*,2″*S*,4″*R*) (Fig. 3).[19,10a,d]

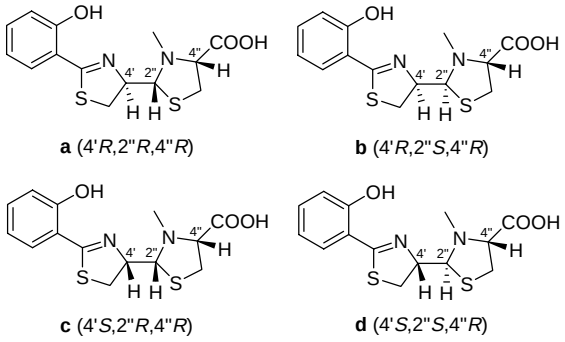
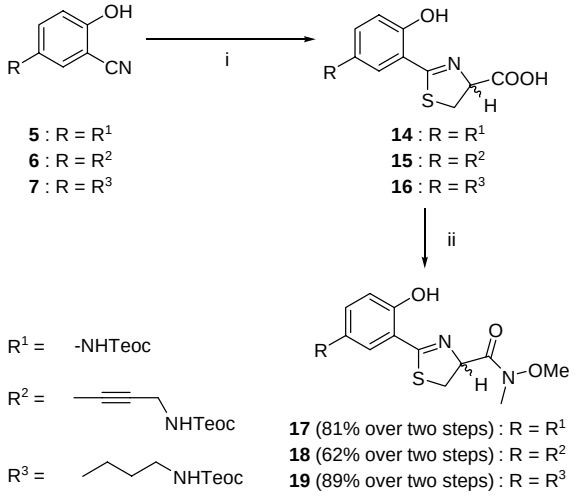


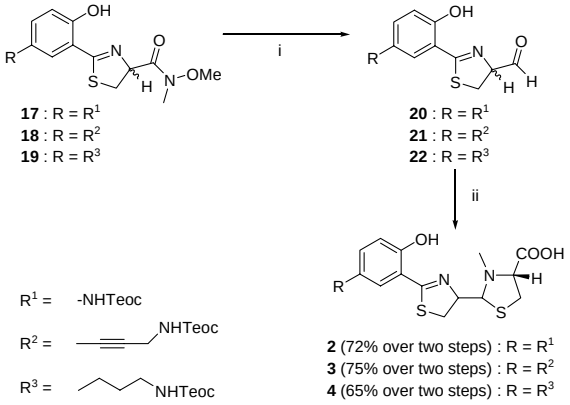
Figure 3. The four diastereoisomers of synthetic pyochelin.

On the other hand, pyochelin and neopyochelin were tested in iron uptake experiments and proved to transport iron with almost the same rate.[9] Our data indicate clearly that the configuration at C4′ is not determining in the recognition by the receptor FptA and in the iron transport process. We thus chose to use the inexpensive (*R*)-cysteine, as starting material for the condensation with the functionalized 2-hydroxybenzonitriles. The three hydroxybenzonitriles **5**, **6** and **7** were converted into the thiazolines **14**, **15** and **16** when treated with (*R*)-cysteine in a refluxing mixture of MeOH and phosphate buffer (0.1 M, pH 6.4). Thiazolines **14**, **15** and **16** were used without further purification to synthesize the corresponding Weinreb amides **17**, **18** and **19**. For this purpose, we modified the procedure we described previously by reacting **14**, **15** and **16** with *N*,*O*-dimethylhydroxylamine and *N*,*N*-dimethylaminopropyl-ethylcarbodiimide hydrochloride (EDCI). Under these conditions, hydroxamic esters **17**, **18** and **19** were easily isolated in good to excellent yield after two steps using a very simple work-up. (Scheme 3).



Scheme 3. Conversion of 2-hydroxybenzonitriles **5**, **6** and **7** into the hydroxamic esters **17**, **18** and **19**. (i) (*R*)-cysteine, phosphate buffer 0.1 M, pH 6.4, MeOH, 60 °C. (ii) $CH_3NHOCH_3 \cdot HCl$, DIPEA, EDCI, CH_2Cl_2, 0–20 °C.

The Weinreb amides **17**, **18** and **19** were then reduced to the corresponding aldehydes **20**, **21** and **22** using $LiAlH_4$.[20] The resulting aldehydes were very sensitive and thus were used straightforward without further purification. Condensation with *N*-methylcysteine,[21] in presence of potassium acetate in hydroethanolic medium furnished the expected functionalized pyochelins **2**, **3** and **4** in 65–75% yield over two steps (Scheme 4).



Scheme 4. Conversion of the hydroxamic esters **17**, **18** and **19** into the pyochelin analogs **2**, **3** and **4**. (i) $LiAlH_4$, THF, −40 to −10 °C. (ii) (*R*)-*N*-Methylcysteine·HCl, AcOK, $EtOH/H_2O$, 20 °C.

The ratios between the four stereoisomers **a**, **b**, **c** and **d** of each analog were the following: **2** (5/10/60/25), **3** (15/15/45/25) and **4** (20/10/50/20). These diastereoisomeric ratios were determined using ^1H NMR and comparing integration of the characteristic *N*-methyl signals. In addition, using COSY and ^1H–^{13}C correlation it was then possible to assign the chemical shifts of each the four diastereoisomers. The relative configurations of the stereocenters were unambiguously assigned by NOESY experiments. When proton H2″ was saturated, a marked Overhauser effect with H4″ proton was observed for **a** (4′*R*,2″*R*,4″*R*) and **c** (4′*S*,2″*R*,4″*R*) isomers whereas no nuclear Overhauser effect was observed for **b** (4′*R*,2″*S*,4″*R*) and **d** (4′*S*,2″*S*,4″*R*).

3. Conclusion

In summary, we report in this article very efficient synthetic ways to three unprecedented functionalized pyochelins: analog **2** was obtained in nine steps (30% overall yield) starting from the commercially available 1,2-benzisoxazole whereas analogs **3** and **4** were prepared starting from 2-hydroxybenzonitrile in six steps (40% overall yield) and seven steps (45% overall yield), respectively. These analogs will be used to build Trojan horse type antibiotic conjugates, which will be tested on different pathogenic clinical strains of *Pseudomonas aeruginosa* and *Burkholderia cepacia*.

4. Experimental

4.1. General procedures

All the reactions were carried out in glassware under inert argon atmosphere. Solvents used were of analytical grade

purity. DMF was distilled prior to use and was stored over activated 4 Å molecular sieves. Pyridine and *N*,*N*-diisopropylethylamine (DIPEA) were distilled and stored over KOH. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica gel $60F^{254}$ (0.25 mm). Column chromatographies were performed using Merck kieselgel 60 (63–200 μm). Melting points were determined with a Stuart Scientific Bibby SMP3 apparatus and were uncorrected. IR spectra were scanned neat using a Perkin Elmer Spectrum One spectrophotometer. NMR spectra were recorded either on a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) or a Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Elemental analyses were performed in the Service d'Analyses de l'Institut de Chimie at the Université Louis Pasteur of Strasbourg. Mass spectra were recorded in the Service de Spectrométrie de Masse de l'Institut de Chimie at the Université Louis Pasteur of Strasbourg and were measured after calibration in ES-TOF experiments performed on a Bruker Daltonic MicroTOF mass spectrometer.

4.2. Protocols, analytical and spectral data

4.2.1. (3-Cyano-4-hydroxy-phenyl)-carbamic acid 2-trimethylsilyl-ethyl ester (5). To a solution of nitro compound **9**[11,12] (500 mg, 3.05 mmol) in EtOH (100 mL) was added Pd/C 10% (158 mg, 0.15 mmol). The suspension was degassed under reduced pressure and then stirred under a hydrogen atmosphere. When all the starting material had been consumed, the mixture was degassed with argon before being filtered over Celite 545. The filtrate was evaporated under reduced pressure and the dark solid residue consisting predominantly of amine **10** was used without further purification for the next synthetic step. The crude amine **10** was dissolved in pyridine (7 mL) then *p*-nitrophenyl-trimethylsilylethylcarbonate (2.39 g, 8.44 mmol) and DMAP (233 mg, 1.91 mmol) were added. This solution was kept at 50 °C during 48 h before being evaporated under reduced pressure. The crude oil was dissolved in a mixture of acetone (20 mL) and water (20 mL) and Na_2CO_3 (2.00 g, 18.87 mmol) was added. This suspension was refluxed (60 °C) during 24 h before being cooled down to room temperature. The mixture was diluted with water (30 mL) and extracted with Et_2O (3×20 mL). The collected organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The yellow deliquescent crude mixture was chromatographed on a silica gel column (30 g of SiO_2, CH_2Cl_2/MeOH: 95:5) leading to the expected substituted carbamate **5** (432 mg, 1.56 mmol, overall yield starting from nitro compound **9**: 51%) isolated as a pale yellow solid. Mp 133–136 °C; IR (neat) 3351, 3216, 2958, 2901, 2245, 1765, 1703, 1605, 1548, 1506, 1427, 1365, 1251, 1227, 1205, 1169, 1115, 1060, 1041, 975, 931, 885, 825, 766, 730, 697. ^{1}H NMR $CDCl_3$, 300 MHz) δ 0.09 (s, 9H), 1.05 (m, 2H), 4.27 (m, 2H), 6.53 (br s, 1H), 6.91 (d, J=8.8 Hz, 1H), 7.41 (dd, J=2.5, 8.8 Hz, 1H), 7.56 (d, J=2.5 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 0.0 (3C), 19.7, 64.9, 101.9, 118.5, 118.9, 124.0, 127.5, 134.6, 156.2, 157.5. ESI-TOF *m*/*z* 579 ($2M+Na^+$), 857 ($3M+Na^+$). Anal. Calcd for $C_{13}H_{18}N_2O_3Si$: C, 56.09; H, 6.52; N, 10.06. Found C, 55.83; H, 6.55; N, 9.79.

4.2.2. 2-Hydroxy-5-iodobenzonitrile (12). To a solution of 2-hydroxybenzonitrile **11** (1.00 g, 8.30 mmol) in dry acetonitrile (7.5 mL), HBF_4 (1.8 mL of 54% solution in Et_2O) was added dropwise at −20 °C. *N*-Iodosuccinimide (2.00 g, 9.13 mmol) was then added portionwise as such a rate that the reaction temperature does not exceed −10 °C. The mixture was then warmed up to room temperature, vigorously stirred during 4 h, treated with an aqueous solution of $NaHSO_3$ 38% (20 mL) and extracted with *t*-butylmethylether (2×30 mL). The collected organic layers were then washed with brine (30 mL) and dried over Na_2SO_4. After filtration, the orange-brown solid was adsorbed on silica before being filtered on a silica gel column (30 g of SiO_2, CH_2Cl_2) leading to compound **12** (1.85 g, 7.55 mmol, yield: 91%) isolated as a white powder. Mp 169–172 °C; IR (neat) 3165, 2245, 1589, 1489, 1400, 1354, 1294, 1263, 1231, 1170, 1118, 1072, 950, 892, 873, 852, 815, 755, 730, 682. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 6.92 (d, J=9.0 Hz, 1H), 7.79 (dd, J=2.0, 9.0 Hz, 1H), 7.90 (d, J=2.0 Hz, 1H), 10.08 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 80.4, 103.2, 115.5, 119.3, 141.8, 143.8, 160.4. SM-EI *m*/*z* 245. Anal. Calcd for C_7H_4INO: C, 34.31; H, 1.65; N, 5.72. Found C, 34.35; H, 1.70; N, 5.68.

4.2.3. Prop-2-ynyl-carbamic acid 2-trimethylsilylethyl-ester (13). Solid *p*-nitrophenyl-trimethylsilylethylcarbonate[15] (1150 mg, 4.07 mmol) was added to a solution of propargylamine (515 μL, 7.51 mmol), DIPEA (800 μL, 4.59 mmol), DMAP (10 mg) in CH_2Cl_2 (14 mL), and the solution was refluxed for 48 h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 and washed twice with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/Et_2O: 9:1 then hexane/Et_2O: 8:2), to give carbamic ester **13** as a colorless oil (740 mg, 3.71 mmol, yield: 81%);[17] IR (neat) 3312, 2954, 1697, 1517, 1424, 1349, 1324, 1248, 1178, 1139, 1043, 973, 946, 857, 834, 767, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.96 (t, J=8.6 Hz, 2H), 2.21 (t, J=2.3 Hz, 1H), 3.94 (dd, J=2.3, 5.6 Hz, 2H), 4.16 (t, J=8.6 Hz, 2H), 4.86 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ −1.5 (3C), 17.7, 30.6, 53.4, 71.3, 79.9, 156.3.

4.2.4. [3-(3-Cyano-4-hydroxy-phenyl)-prop-2-ynyl]-carbamic acid 2-trimethylsilylethyl ester (6). A solution of iodinated compound **12** (707 mg, 2.88 mmol), carbamic ester **13** (748 mg, 3.75 mmol) and DIPEA (2.40 mL, 1780 mg, 13.80 mmol) in freshly distilled DMF (13 mL) was cooled down to 0 °C and degassed under reduced pressure. $Pd(PPh_3)_4$ (172 mg, 0.15 mmol) and CuI (116 mg, 0.61 mmol) were then successively added under argon. The mixture was degassed again at 0 °C and then warmed up at room temperature and stirred 2 h. DMF was then removed by distillation under reduced pressure and the crude mixture was adsorbed on silica before being chromatographed on a silica gel column (40 g of SiO_2, hexane/Et_2O: 2:1 then hexane/Et_2O: 1:1). The acetylenic compound **6** (869 mg, 2.74 mmol, yield: 95%) was isolated as a yellow foamy solid. Mp 80–82 °C; IR (neat) 3400, 3130, 2954, 2230, 1668, 1605, 1537, 1508, 1412, 1376, 1355, 1305, 1261, 1250, 1217, 1176, 1142, 1111, 1069, 1043, 1006, 942, 890, 855, 836, 769, 726, 693, 662. ^{1}H NMR ($CDCl_3$, 300 MHz) δ

0.06 (s, 9H), 1.02 (t, $J=8.4$ Hz, 2H), 4.16 (d, $J=5.9$ Hz, 2H), 4.24 (t, $J=8.4$ Hz, 2H), 5.01 (br s, 1H), 6.93 (d, $J=8.7$ Hz, 1H), 7.27 (d, $J=8.7$ Hz, 1H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.4, 64.3, 84.9, 91.1, 100.0, 114.6, 115.9, 116.8, 136.2, 137.6, 157.2, 159.6; ESI-TOF *m/z* 655 ($2M+Na^+$), 971 ($3M+Na^+$). Anal. Calcd for $C_{16}H_{20}N_2O_3Si$: C, 60.73; H, 6.37; N, 8.85. Found C, 60.87; H, 6.25; N, 8.34.

4.2.5. [3-(3-Cyano-4-hydroxy-phenyl)-propyl]-carbamic acid 2-trimethylsilylethyl ester (7). To a solution of acetylenic carbamate **6** (700 mg, 2.22 mmol) in EtOH (40 mL) was added Pd/C 10% (260 mg, 0.22 mmol). The suspension was degassed under reduced pressure and then stirred under hydrogen atmosphere. When all the starting material had been consumed, the mixture was degassed with argon before being filtered on Celite. The filtrate was evaporated under reduced pressure and the oily residue was chromatographed on a silica gel column (30 g of SiO_2, hexane/Et_2O: 1:1) leading to the expected substituted 2-hydroxybenzonitrile **7** (640 mg, 2.00 mmol, yield: 90%) isolated as a thick colorless oil, which slowly crystallized upon storage in the refrigerator. Mp 89–91 °C; IR (neat) 3389, 3135, 2956, 2928, 2910, 2861, 2236, 1668, 1611, 1598, 1532, 1515, 1461, 1428, 1374, 1307, 1275, 1260, 1251, 1210, 1174, 1143, 1115, 1064, 1020, 980, 951, 934, 887, 837, 825, 782, 762, 694, 677. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 9H), 0.98 (t, $J=8.6$ Hz, 2H), 1.78 (p, $J=7.5$ Hz, 2H), 2.56 (t, $J=7.5$ Hz, 2H), 3.17 (q, $J=6.6$ Hz, 2H), 4.16 (t, $J=8.6$ Hz, 2H), 4.80 (br s, 1H), 6.90 (d, $J=8.3$ Hz, 1H), 7.21 (d, $J=8.3$ Hz, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.3, 31.5, 40.3, 63.6, 99.3, 116.5, 117.0, 132.2, 133.0, 134.1, 157.6, 158.0. ESI-TOF *m/z* 321 ($M+H^+$), 343 ($M+Na^+$), 359 ($M+K^+$), 663 ($2M+Na^+$). Anal. Calcd for $C_{16}H_{24}N_2O_3Si$: C, 59.97; H, 7.55; N, 8.74. Found C, 59.68; H, 7.70; N, 8.24.

4.3. General procedure for Weinreb amides (17), (18) and (19)

Substituted 2-hydroxybenzonitriles **5**, **6** or **7** (1.00 equiv) and (*R*)-cysteine (2.00 equiv) were dissolved in methanol (8 mL/mmol of substituted 2-hydroxybenzonitrile). The suspension was warmed up to 50 °C then 0.1 M phosphate buffer pH 6.4 (8 mL/mmol of substituted 2-hydroxybenzonitrile) was added. The mixture was vigorously stirred at 60 °C during 36 h. The resulting yellow solution was cooled down to room temperature before being diluted with water and acidified to pH 2.0 by addition of solid citric acid. After extraction with CH_2Cl_2, the collected organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude thiazolines **14**, **15** and **16** isolated as yellow powders were used without further purification for the next step. Thiazoline was dissolved in CH_2Cl_2 (25 mL/mmol of thiazoline), the solution was cooled down to 0 °C. EDCI (1.10 equiv) was then added, immediately followed by a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.20 equiv) and DIPEA (1.20 equiv) in CH_2Cl_2 (25 mL/mmol of *N*,*O*-dimethylhydroxylamine hydrochloride). The mixture was allowed to warm up to room temperature and was stirred during 2 h. The mixture was directly adsorbed on silica before being chromatographed on a silica gel column eluted with hexane/Et_2O: 1:1, leading to the expected Weinreb amides **17**, **18** or **19**.

4.3.1. {4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-carbamic acid 2-trimethylsilyl-ethylester (17). Isolated as a white powder (overall yield over two steps from **5**: 81%). Mp 119–122 °C; IR (neat) 3300, 2953, 1716, 1645, 1561, 1486, 1459, 1433, 1394, 1344, 1293, 1230, 1193, 1179, 1062, 994, 964, 947, 860, 834, 810, 767, 693, 664. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.98 (m, 2H), 3.24 (s, 3H), 3.42 (dd, $J=9.3$, 10.9 Hz, 1H), 3.70 (br t, $J=10.9$ Hz, 1H), 3.77 (s, 3H), 4.18 (m, 2H), 5.62 (br t, $J=9.3$ Hz, 1H), 6.65 (br s, 1H), 6.85 (d, $J=8.9$ Hz, 1H), 7.26 (br d, $J=8.9$ Hz, 1H), 7.44 (br s, 1H), 12.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.0 (3C), 19.2, 34.1, 34.5, 63.3, 65.0, 76.2, 117.2, 118.9, 122.6, 126.7, 131.0, 155.6, 156.7, 171.3, 175.4. ESI-TOF *m/z* 426 ($M+H^+$), 448 ($M+Na^+$), 851 ($2M+H^+$), 873 ($2M+Na^+$). Anal. Calcd for $C_{18}H_{27}N_3O_5SSi$: C, 50.80; H, 6.39; N, 9.87. Found C, 50.86; H, 6.13; N, 9.83.

4.3.2. (3-{4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-prop-2-ynyl)-carbamic acid 2-trimethylsilylethylester (18). Isolated as a yellow solid (overall yield over two steps from **6**: 62%). Mp 160–162 °C; IR (neat) 3316, 2952, 1711, 1668, 1619, 1561, 1520, 1486, 1425, 1391, 1355, 1323, 1292, 1248, 1201, 1178, 1130, 1044, 1002, 970, 943, 891, 858, 832, 768, 735, 695, 662. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 9H), 1.01 (t, $J=8.3$ Hz, 2H), 3.30 (s, 3H), 3.50 (dd, $J=9.4$, 10.5 Hz, 2H), 3.79 (t, $J=10.5$ Hz, 2H), 4.09 (d, $J=5.9$ Hz, 2H), 4.12 (t, $J=8.3$ Hz, 2H), 4.78 (br s, 1H), 5.69 (t, $J=9.4$ Hz, 1H), 6.92 (d, $J=8.5$ Hz, 1H), 7.39 (dd, $J=2.0$, 8.5 Hz, 1H), 7.50 (d, $J=2.0$ Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.5, 32.6, 33.0, 61.8, 63.5, 74.6, 82.2, 84.0, 113.2, 116.0, 117.4, 134.2, 136.5, 156.3, 159.2, 169.5, 173.6; ESI-TOF *m/z* 464 ($M+H^+$), 927 ($2M+H^+$). Anal. Calcd for $C_{21}H_{29}N_3O_5SSi$: C, 54.40; H, 6.30; N, 9.06. Found C, 54.76; H, 6.46; N, 8.82.

4.3.3. (3-{4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-propyl)-carbamic acid 2-trimethylsilanylethylester (19). Isolated as a white solid (overall yield over two steps from **7**: 89%). Mp 160–162 °C; IR (neat) 3347, 2926, 2854, 1715, 1672, 1628, 1597, 1567, 1521, 1491, 1388, 1248, 1176, 1138, 1043, 1007, 988, 966, 858, 834, 767, 735, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.94 (t, $J=8.6$ Hz, 2H), 1.74 (p, $J=7.5$ Hz, 2H), 2.54 (t, $J=7.5$ Hz, 2H), 3.15 (m, 2H), 3.25 (s, 3H), 3.43 (dd, $J=9.5$, 11.0 Hz, 2H), 3.73 (t, $J=9.5$ Hz, 1H), 3.79 (s, 3H), 4.41 (t, $J=8.6$ Hz, 2H), 4.71 (br s, 1H), 5.64 (t, $J=8.9$ Hz, 1H), 6.86 (d, $J=8.2$ Hz, 1H), 7.15 (m, 2H); 12.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 29.7, 31.9, 32.6, 32.9, 40.4, 61.8, 62.9, 76.6, 115.9, 117.7, 130.1, 131.9, 133.5, 156.8, 157.2, 169.7, 173.9. ESI-TOF *m/z* 468 ($M+H^+$); HRMS calcd for $C_{21}H_{34}N_3O_5SSi$ 468.1983, found 468.1981. Anal. Calcd for $C_{21}H_{34}N_3O_5SSi$: C, 53.93; H, 7.11; N, 8.99. Found C, 53.71; H, 7.25; N, 8.27.

4.4. General procedure for functionalized pyochelin derivatives (2), (3) and (4)

To a solution of Weinreb amide **17**, **18** or **19** in dry THF (16 mL/mmol of Weinreb amide), cooled down to −40 °C, $LiAlH_4$ (1.30 equiv of a 1 M solution in THF) was injected dropwise. The reaction temperature was allowed to rise

to −20 °C in 30 min. The reaction mixture was then hydrolyzed by successive additions of a saturated aqueous solution of NH_4Cl (12 mL/mmol of $LiAlH_4$) then a 1 M aqueous solution of $KHSO_4$ (5 mL/mmol of $LiAlH_4$). The mixture was warmed up to room temperature and vigourously stirring was applied until two phases were formed. After partition and extraction with Et_2O, the organic layers were collected, dried over Na_2SO_4, filtered before being evaporated. The crude aldehyde, very sensitive to oxidation, was used directly for subsequent reaction. It was dissolved into a mixture of ethanol (20 mL/mmol of Weinreb amide) and water (6 mL/mmol of Weinreb amide) and to this solution were successively added, potassium acetate (6.65 equiv) and (*R*)-*N*-methylcysteine hydrochloride (2.12 equiv). The mixture was then gently stirred in the dark during 14 h (overnight) before being diluted with water (30 mL) then washed with hexane (30 ml). The aqueous layer was then acidified to pH 4.0 by addition of solid citric acid before being extracted with CH_2Cl_2. The organic layers were collected, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The expected functionalized pyochelins **2**, **3** and **4** are isolated first as yellow foams then were dissolved in cyclohexane containing a minimun of CH_2Cl_2. After evaporation of the solvent under reduced pressure, the expected pyochelins were isolated as yellow powders.

4.4.1. 2′-[2-Hydroxy-5-(2-trimethylsilyl-ethoxycarbonyl-amino)-phenyl]-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]-bisthiazolyl-4-carboxylic acid (2). Isolated as a pale yellow powder (overall yield over two steps from **17**: 72%), proportions: **2a/2b/2c/2d**: 5/10/60/25. IR (neat) 3301, 2952, 2891, 1698, 1628, 1568, 1544, 1494, 1431, 1394, 1299, 1224, 1191, 1061, 996, 954, 928, 857, 834, 766, 693; HRMS calcd for $C_{20}H_{28}N_3O_5S_2Si$ 482.1245, found 482.1240.

4.4.2. (2c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.31 (dd, J=7.0–11.2 Hz, 1H, H5″), 3.45 (dd, J=7.0–11.2 Hz, 1H, H5″), 3.53 (dd, J=8.4–11.3 Hz, 1H, H5′), 3.63 (dd, J=8.4–11.3 Hz, 1H, H5′), 4.01 (dd, J=5.4–7.0 Hz, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.34 (d, J=8.4 Hz, 1H, H2″), 4.83 (q, J=8.4 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 33.5 (C5″), 34.9 (C5′), 44.8 (N–CH_3), 63.2 (CH_2–O), 73.9 (C4″), 79.4 (C2″), 83.4 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.3. (2d) (4′*S*, 2″*S*, 4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.70 (s, 3H, N–CH_3), 3.06 (dd, J=2.0–10.4 Hz, 1H, H5″), 3.18–3.27 (m, 1H, H5″), 3.38–3.50 (m, 2H, H5′), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.24 (dd, J=2.0–6.6 Hz, 1H, H4″), 5.05 (d, J=4.7 Hz, 1H, H2″), 5.28 (td, J=4.7–9.0 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.2 (C5′), 32.3 (C5″), 36.2 (N–CH_3), 63.2 (CH_2–O), 70.5 (C4″), 73.6 (C2″), 79.3 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.4. (2a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.64 (s, 3H, N–CH_3), 3.18–3.27 (m, 2H, H5″), 3.49 (d, J=9.0 Hz, 2H, H5′), 3.73 (dd, J=7.0–7.9 Hz, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.61 (d, J=5.4 Hz, 1H, H2″), 5.21 (td, J=5.4–9.0 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.8 (C5′), 33.1 (C5″), 41.3 (N–CH_3), 63.2 (CH_2–O), 73.3 (C4″), 77.1 (C2″), 80.3 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.5. (2b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.49 (s, 3H, N–CH_3), 3.18–3.27 (m, 2H, H5″), 3.43–3.49 (m, 1H, H5′), 3.63–3.68 (m, 1H, H5′), 4.18–4.28 (m, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.55 (d, J=8.2 Hz, 1H, H2″), 5.01 (q, J=8.2 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.1 (C5″), 35.1 (C5′), 37.8 (N–CH_3), 63.2 (CH_2–O), 71.0 (C4″), 77.9 (C2″), 81.2 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.6. 2′-{2-Hydroxy-5-[3-(2-trimethylsilyl-ethoxy-carbonylamino)-prop-1-ynyl]-phenyl}-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]bisthiazolyl-4-carboxylic acid (3). Isolated as a pale yellow powder (overall yield over two steps from **18**: 75%), proportions: **3a/3b/3c/3d**: 15/15/45/25. IR (neat) 3320, 2953, 1709, 1619, 1569, 1525, 1487, 1395, 1324, 1247, 1196, 1128, 1041, 939, 857, 833, 775, 694; HRMS calcd for $C_{23}H_{30}N_3O_5S_2Si$ 520.1402, found 520.1408.

4.4.7. (3c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.35 (dd, J=6.9–11.0 Hz, 1H, H5″), 3.44 (dd, J=5.2–11.0 Hz, 1H, H5″), 3.55 (dd, J=8.4–11.5 Hz, 1H, H5′), 3.66 (dd, J=8.4–11.5 Hz, 1H, H5′), 4.01 (dd, J=5.2–6.9 Hz, 1H, H4″), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.34 (d, J=8.4 Hz, 1H, H2″), 4.84 (q, J=8.4 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 31.5 (CH_2–N), 33.5 (C5″), 35.0 (C5′), 44.7 (N–CH_3), 63.0 (CH_2–O), 73.7 (C4″), 79.2 (C2″), 81.5 (C≡*C*–Ar), 83.1 (C4′), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (COOH).

4.4.8. (3d) (4′*S*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.70 (s, 3H, N–CH_3), 3.05 (dd, J=2.4–10.4 Hz, 1H, H5″), 3.20–3.26 (m, 1H, H5″), 3.42–3.56 (m, 2H, H5′), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.24 (dd, J=2.4–6.6 Hz, 1H, H4″), 5.05 (d, J=

4.7 Hz, 1H, H2″), 5.30 (td, J=4.7–9.3 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.2 (C5′), 32.3 (C5″), 36.0 (N–CH_3), 63.0 (CH_2–O), 70.3 (C4″), 73.3 (C2″), 79.0 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.9. (3a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.20–3.24 (m, 2H, H5″), 3.52 (d, J=9.3 Hz, 2H, H5′), 3.71 (dd, J=6.8–8.0 Hz, 1H, H4″), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.61 (d, J=5.5 Hz, 1H, H2″), 5.21 (td, J=5.5–9.3 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.8 (C5′), 33.1 (C5″), 41.3 (N–CH_3), 63.0 (CH_2–O), 73.2 (C4″), 76.9 (C2″), 80.1 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.10. (3b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.50 (s, 3H, N–CH_3), 3.20–3.26 (m, 2H, H5″), 3.47–3.52 (m, 1H, H5′), 3.68–3.72 (m, 1H, H5′), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.23 (t, J=6.8 Hz, 1H, H4″), 4.55 (d, J=8.1 Hz, 1H, H2″), 5.02 (q, J=8.1 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.0 (C5″), 35.0 (C5′), 37.7 (N–CH_3), 63.0 (CH_2–O), 70.8 (C4″), 77.7 (C2″), 80.9 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.11. 2′-{2-Hydroxy-5-[3-(2-trimethylsilyl-ethoxy-carbonylamino)-propyl]-phenyl}-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]bisthiazolyl-4-carboxylic acid (4). Isolated as a yellow powder (overall yield over two steps from **19**: 65%), proportions: **4a/4b/4c/4d**: 20/10/50/20. IR (neat) 3326, 2950, 1695, 1626, 1569, 1528, 1492, 1248, 1100, 857, 834, 775, 693; HRMS calcd for $C_{23}H_{36}N_3O_5S_2Si$ 526.1860, found 526.1851.

4.4.12. (4c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.63 (s, 3H, N–CH_3), 3.11–3.17 (m, 2H, CH_2–N), 3.30 (dd, J=6.8–11.0 Hz, 1H, H5″), 3.44 (dd, J=5.2–11.0 Hz, 1H, H5″), 3.55 (dd, J=8.4–11.4 Hz, 1H, H5′), 3.62 (dd, J=8.4–11.4 Hz, 1H, H5′), 4.01 (dd, J=5.2–6.8 Hz, 1H, H4″), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.33 (d, J=8.4 Hz, 1H, H2″), 4.83 (q, J=8.4 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 34.4 (C5″), 34.7 (C5′), 40.7 (CH_2–N), 44.7 (N–CH_3), 62.4 (CH_2–O), 73.8 (C4″), 79.3 (C2″), 83.4 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.13. (4d) (4′*S*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.71 (s, 3H, N–CH_3), 3.06 (dd, J=2.4–9.7 Hz, 1H, H5″), 3.11–3.17 (m, 2H, CH_2–N), 3.18–3.24 (m, 1H, H5″), 3.40 (dd, J=9.1–11.0 Hz, 1H, H5′), 3.46 (dd, J=9.1–11.0 Hz, 1H, H5′), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.25 (dd, J=2.4–6.2 Hz, 1H, H4″), 5.05 (d, J=4.6 Hz, 1H, H2″), 5.27 (td, J=4.6–9.1 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.1 (C5′), 32.2 (C5″), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 36.1 (N–CH_3), 40.7 (CH_2–N), 62.4 (CH_2–O), 70.4 (C4″), 73.6 (C2″), 79.2 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.14. (4a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.64 (s, 3H, N–CH_3), 3.11–3.17 (m, 2H, CH_2–N), 3.18–3.20 (m, 2H, H5″), 3.48 (d, J=9.1 Hz, 2H, H5′), 3.71 (dd, J=6.7–8.2 Hz, 1H, H4″), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.62 (d, J=5.4 Hz, 1H, H2″), 5.19 (td, J=5.4–9.1 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 32.7 (C5′), 33.0 (C5″), 40.7 (CH_2–N), 41.4 (N–CH_3), 62.4 (CH_2–O), 73.2 (C4″), 77.1 (C2″), 80.2 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.15. (4b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.50 (s, 3H, N–CH_3), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 3.11–3.17 (m, 2H, CH_2–N), 3.21–3.24 (m, 2H, H5″), 3.45 (dd, J=9.0–11.5 Hz, 1H, H5′), 3.65 (dd, J=9.0–11.5 Hz, 1H, H5′), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.23 (t, J=6.8 Hz, 1H, H4″), 4.55 (d, J=8.2 Hz, 1H, H2″), 5.00 (q, J=8.2 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.0 (C5″), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 34.8 (C5′), 37.7 (N–CH_3), 40.7 (CH_2–N), 62.4 (CH_2–O), 70.9 (C4″), 77.8 (C2″), 81.1 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2), 173.1 (*C*OOH).

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