Synthesis of chiral cyclic oligothiazolines: a novel structural motif for a macrocyclic molecule†

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The synthesis of chiral cyclic oligo(4-β-methyl)thiazolines is described; linear oligothiazolines were efficiently prepared by the iterative formation of a thiazoline ring and a two-directional block condensation, and construction of 24- to 36-membered cyclic oligothiazoline systems could be achieved by the head-to-tail cyclooligomerization of doubly deprotected linear fragments and subsequent thiazoline formation.

The rational design and construction of macromolecular architectures possessing defined structural motifs is one of the key subjects in the areas of molecular recognition,[1] supramolecular chemistry,[2] and drug design.[3] For the construction of structural motifs, repetitious assembly of heteroaromatic subunits has been adopted as one of the main strategies because heteroaromatic rings are known to take part in non-covalent interactions such as dipole–dipole interactions, hydrogen bonding, and π–π interactions.[1–3] One of the limitations of the use of heteroaromatic rings, however, is the difficulty in incorporating chiral centers into the framework.[4] In addition, due primarily to the lack of a general synthetic methodology, only limited types of heteroaromatic rings are amenable to the construction of macromolecules,[4] thereby preventing flexible design of molecules with structural diversity.

As a subunit for the construction of macromolecules, we have focused our attention on the thiazoline ring. A linear array of thiazoline rings coupled with a combination of (*R*) and (*S*) stereochemistry is found in a number of natural compounds such as mirabazole B (**1**),[5] tantazole B (**2**),[6] and thiangazole (**3**),[7] and these compounds have proven themselves to possess significant

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† Electronic supplementary information (ESI) available: Experimental procedure and spectra (IR, HRMS, ^{1}H- and ^{13}C-NMR) of macrocycles **22**, **23** and **25**. See DOI: 10.1039/b601628f

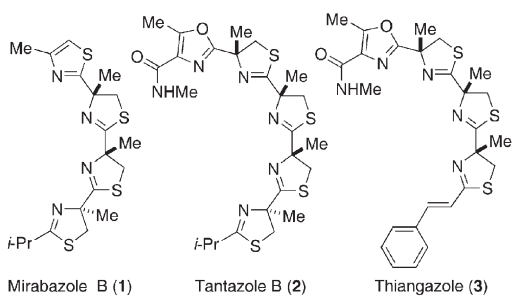


Fig. 1 Structures of natural compounds **1**, **2** and **3**.

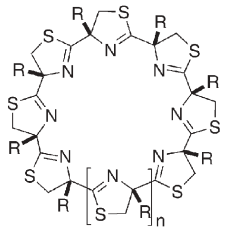
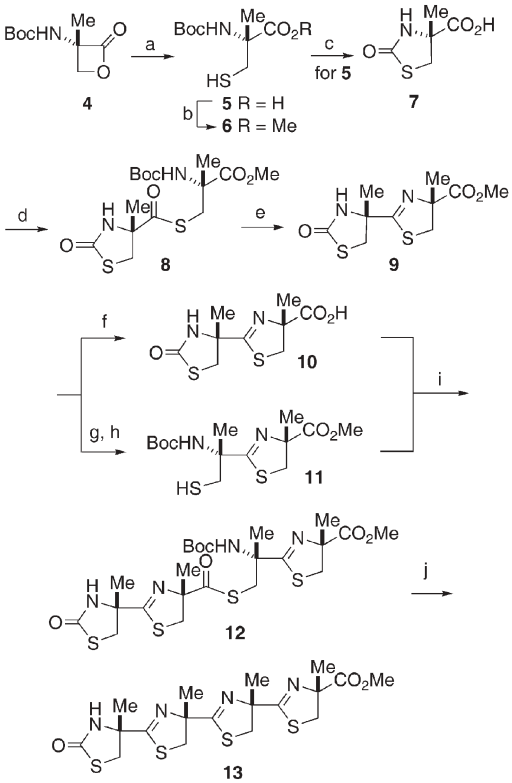
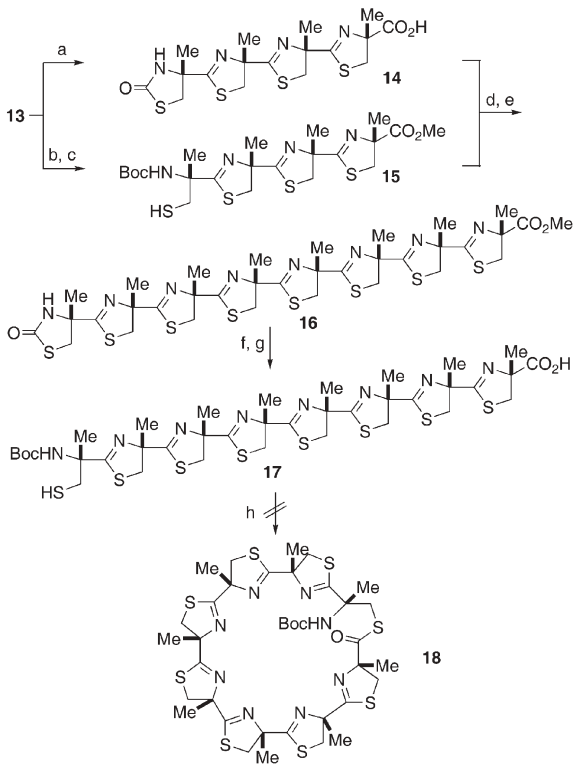


Fig. 2 Structure of cyclic oligothiazolines.



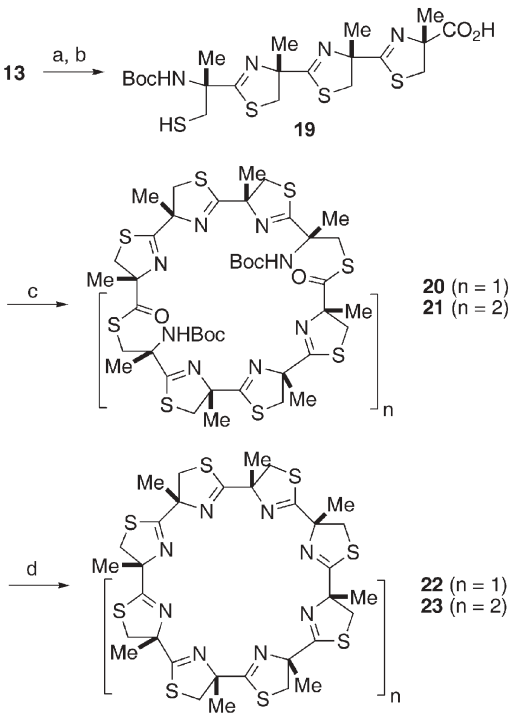
Scheme 1 *Reagents and conditions*: (a) H_2S, Et_3N (2.5 eq.), CH_2Cl_2, 0 °C; (b) CH_2N_2 in Et_2O (3.0 eq.), THF, 0 °C, (88%, 2 steps); (c) TFA, r.t., then evaporated to dryness; triphosgene, 20% aq. KOH, dioxane, 0 °C to r.t., (71%, 2 steps); (d) **6** (1.0 eq.), BOP-Cl (1.5 eq.), Et_3N (2.5 eq.), CH_2Cl_2, r.t., 79%; (e) TFA, r.t., evaporated to dryness; then benzene, reflux, 96%; (f) 10% aq. NaOH (1.2 eq.), dioxane–MeOH (4 : 1 v/v), r.t., 78%; (g) Boc_2O (1.2 eq.), Et_3N (2.5 eq.), DMAP (cat.), CH_2Cl_2, r.t. 91%; (h) NaOMe (1.0 M in MeOH) (1.2 eq.), THF, 0 °C, 81%; (i) BOP-Cl (1.5 eq.), Et_3N (2.5 eq.), CH_2Cl_2, r.t., 77%; (j) TFA, r.t., evaporated to dryness; then benzene, reflux, 4 h, 93%.



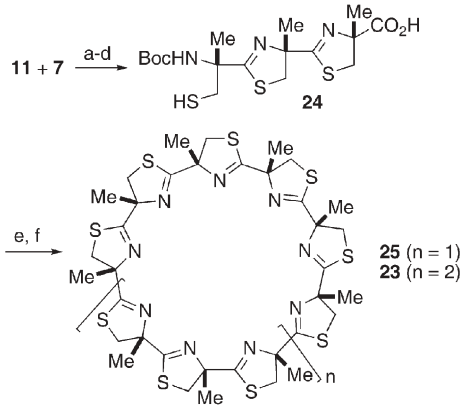
Scheme 2 *Reagents and conditions*: (a) 10% aq. NaOH (1.2 eq.), dioxane–MeOH (4 : 1 v/v), r.t., 84%; (b) Boc_2O (1.2 eq.), Et_3N (2.5 eq.), DMAP (cat.), CH_2Cl_2, r.t.; (c) NaOMe (1.0 M in MeOH) (1.2 eq.), THF, 0 °C, 73% (2 steps); (d) BOP-Cl (1.5 eq.), Et_3N (2.5 eq.), CH_2Cl_2, r.t.; (e) TFA, r.t., evaporated to dryness; benzene, reflux, 64% (2 steps); (f) Boc_2O (1.2 eq.), Et_3N (2.5 eq.), DMAP (cat.), CH_2Cl_2, r.t.; (g) 10% aq. NaOH (2.2 eq.), THF–MeOH (4 : 1 v/v), 0 °C to r.t., 81% (2 steps); (h) BOP-Cl (2.0 eq.), Et_3N (4.0 eq.), CH_2Cl_2 (2 mM), r.t.

biological properties including antitumor and antifungal activities (Fig. 1). Stimulated by these unique structures, we have initiated studies on the design and synthesis of chiral oligothiazolines. In this report, we describe a general and facile method for the synthesis of linear chiral oligothiazolines[8] and an application of the protocol to the construction of unprecedented cyclic chiral oligothiazolines, which would provide a wheel-like architecture with a deep binding cavity (Fig. 2).

For the preparation of linear oligothiazolines, we have developed a facile iterative block condensation protocol. A solution of (−)-β-lactone **4** (Scheme 1), which was readily prepared from dimethyl *N*-Boc-amino malonate by a several-step sequence[8c] including enzymatic desymmetrization, was treated with hydrogen sulfide and the resultant *N*-Boc-methylcysteine **5** was methylated with diazomethane to obtain the corresponding methyl ester **6**. Removal of the Boc group in **5** with TFA, followed by treatment with triphosgene furnished thiazolidinone **7**. Subsequently, carboxylic acid **7** was condensed with thiol **6** using BOP-Cl to provide thioester **8**, which was treated with TFA to afford thiazoline **9**, a doubly protected dimer unit. Since the thiazolidinone and methyl ester functionalities are orthogonal, elongation of the thiazoline chain would be possible by block condensation after selective deprotections. Thus, carboxylic acid **10**, prepared by basic hydrolysis of **9**, and thiol **11**, prepared by the activation of the thiazolidinone ring with a Boc group and ring opening with



Scheme 3 *Reagents and conditions*: (a) Boc_2O (1.2 eq.), Et_3N (2.5 eq.), DMAP (cat.), CH_2Cl_2, r.t., 90%; (b) 10% aq. NaOH (2.2 eq.), THF–MeOH (4 : 1 v/v), 0 °C to r.t., 81%; (c) BOP-Cl (2.0 eq.), Et_3N (4.0 eq.), CH_2Cl_2 (4 mM), r.t., 63%. (d) TFA, r.t., evaporated to dryness; reflux in benzene, (79% for **22**, 77% for **23**).



Scheme 4 *Reagents and conditions*: (a) BOP-Cl (1.5 eq.), Et_3N (2.5 eq.), CH_2Cl_2, r.t., 77%; (b) TFA, r.t., evaporated to dryness; benzene, reflux, 93%; (c) Boc_2O (1.2 eq.), Et_3N (2.5 eq.), DMAP (cat.), CH_2Cl_2, r.t., 91%; (d) 10% aq. NaOH (2.2 eq.), THF–MeOH (4 : 1 v/v), 0 °C to r.t., 84%; (e) BOP-Cl (2.0 eq.), Et_3N (4.0 eq.), CH_2Cl_2 (4 mM), r.t., 58%; (f) TFA, r.t., evaporated to dryness; reflux in benzene, (74% for **25**, 71% for **23**).

NaOMe, were condensed and subsequent treatment of the resultant thioester **12** with TFA furnished tetramer **13**.

Having established an efficient protocol for the assembly of the chiral thiazolines, we then turned our attention to the construction of a macrocyclic system. First, the linear octamer chain **17** was prepared from the tetramer **13** by means of a block condensation protocol (Scheme 2). However, extensive efforts at cyclization of this linear compound proved futile, producing intractable mixtures. This is probably due to the limited conformational

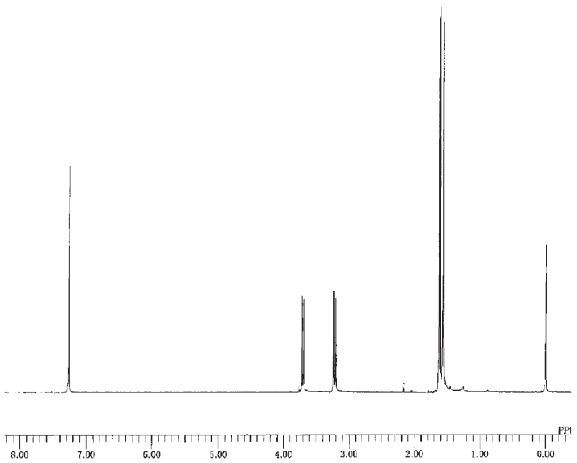


Fig. 3 ^{1}H-NMR spectrum of **22** in $CDCl_3$ (the peak at 1.56 ppm is due to H_2O in the sample).

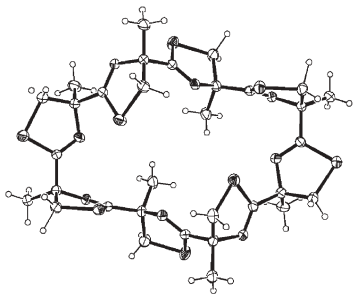


Fig. 4 X-Ray crystal structure of macrocycle **22**. Displacement ellipsoids represent 30% probability.

flexibility of **17**, which might preferentially be assuming extended conformations. We eventually found that doubly deprotected, shorter fragments tend to dimerize or trimerize easily in a head-to-tail fashion to give macrocyclic thioesters in remarkably high yields (Scheme 3). Thus, compound **13** was converted to thiolcarboxylic acid **19** and was subjected to a condensation reaction. The desired cyclization proceeded quite efficiently in a head-to-tail fashion to give a mixture of cyclic dimer **20** and trimer **21** in 63% combined yield (ratio of **20** : **21** = *ca.* 1.8 : 1) under the optimized conditions (BOP-Cl (2.0 eq.), Et_3N (4.0 eq.), CH_2Cl_2 (4 mM), r.t., 18 h). In this case, linking the precursor **13** together provides linear dimer or trimer intermediates having a very flexible thioester tether, which should facilitate the subsequent cyclizations. Finally, treatment of the mixture of cyclic thioesters **20** and **21** with TFA at room temperature, followed by heating in refluxing benzene after removal of TFA, furnished cyclic octathiazoline **22** and dodecathiazoline **23** in high yields. In a similar manner, cyclic nonathiazoline **25** and dodecathiazoline **23** were synthesized in 34% and 2.5% overall yields over 4 steps from trimer fragment **24** (Scheme 4).

The structures of these cyclic compounds were determined by standard spectroscopic techniques, including ^{1}H- and ^{13}C-NMR and high-resolution mass spectrometry. The observations of a simple single set of signals in its ^{1}H- (Fig. 3) and ^{13}C-NMR spectra in each case indicate that these macrocycles possess C_n symmetry (*n* corresponds to the number of the thiazoline unit). This behavior on ^{1}H-NMR did not change even at −60 °C, suggesting that conformation of the macrocycles is highly flexible in the solution state. The structure of octamer **22** was also confirmed by an X-ray crystallographic analysis (Fig. 4).[9]

In conclusion, we have developed an iterative protocol for the synthesis of linear and cyclic arrays of chiral oligothiazolines which are unprecedented molecular architectures. In particular, cyclic oligomers with various sizes were synthesized efficiently *via* the facile macrocyclization of the trimer and the tetramer fragments. As an application of this class of compounds, we have obtained preliminary results on chiral recognition of α-hydroxycarboxylic acids. The synthetic protocol established in this work is amenable in principle for divergent synthesis of both linear and cyclic oligothiazolines with limitless sequences of (*R*) and (*S*) thiazoline units,[8c] allowing us a general route to the design and construction of molecular architecture. Extensive studies on the application of chiral oligothiazolines to artificial receptors and biologically active compounds such as enzyme inhibitors and antitumor agents are currently under investigation in this laboratory.

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8 Selected other examples for synthesizing linear arrays of polythiazolines. For Mirabazole, see: (*a*) B. L. Kedrowski and C. H. Heathcock, *Heterocycles*, 2002, **56**, 601; (*b*) G. Pattenden and R. J. Boyce, *Tetrahedron*, 1995, **51**, 7313. For Tantazole, see: (*c*) T. Fukuyama and L. Xu, *J. Am. Chem. Soc.*, 1993, **115**, 8049; (*d*) R. L. Parsons and C. H. Heathcock, *Synlett*, 1996, 1168. For Thiangazole, see: (*e*) R. J. Boyce, G. C. Mulqueen and G. Pattenden, *Tetrahedron*, 1995, **51**, 7321; (*f*) P. Wipf and S. Vankatraman, *J. Org. Chem.*, 1995, **60**, 7224.

9 Crystal data for **22**·$(CHCl_3)_2$ at 153 K: $C_{34}H_{42}Cl_6N_8S_8$ (MW: 1031.99), 0.72 × 0.52 × 0.22 mm^3, colorless crystal, triclinic, space group *P*1, a = 8.8700(4) Å, b = 12.0090(9) Å, c = 12.7400(9) Å, α = 116.29(3)°, β = 88.97(5)°, γ = 101.44(5)°, V = 1189(13) Å^3, Z = 1; final $R1$ = 0.0472 for 3918 reflections of $I > 2\sigma(I)$, w$R2$ = 0.1262 for all 3918 reflections. CCDC 290621. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601628f.