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Exploitation of Intramolecular Glaser–Eglinton–Hay Macrocyclization for the Synthesis of New Classes of Optically Active Aza-Oxo-Thia Polyether Macrocycles from Amino Alcohol Building Blocks

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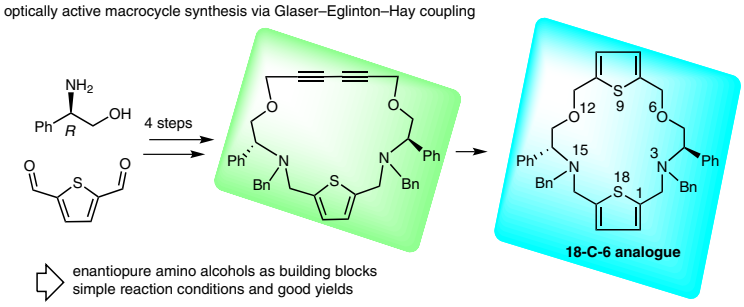

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Abstract We report an intramolecular Glaser–Eglinton–Hay coupling as an unprecedented route for assembling optically active aza-oxo polyether macrocycles containing a 1,3-diyne unit from enantiopure amino alcohol building blocks and suitable linkers. Furthermore, the conversion of the 1,3-diyne unit of the aza-oxo polyether macrocycles into a thiophene ring led to the assembly of new classes of optically active aza-oxa-thia (heterotopic) polyether macrocycle analogues of classical 18-C-6 and 18-C-5 systems.

Key words alkynes, amino alcohols, cross-coupling, crown compounds, macrocycles, Glaser–Eglinton–Hay reaction

Macrocycles are structurally attractive molecular frameworks, and there exist several naturally occurring and biologically active macrocycles.[1] Since the development of polyether macrocycles/crown ethers in 1967, the research field pertaining to polyether macrocycles has been actively pursued.[1,2] Alongside classical polyether macrocycles, aza, aza-oxo and thia-oxo polyether macrocycles have attracted significant attention due to their attractive molecular structures and enhanced complexing abilities.[1–3]

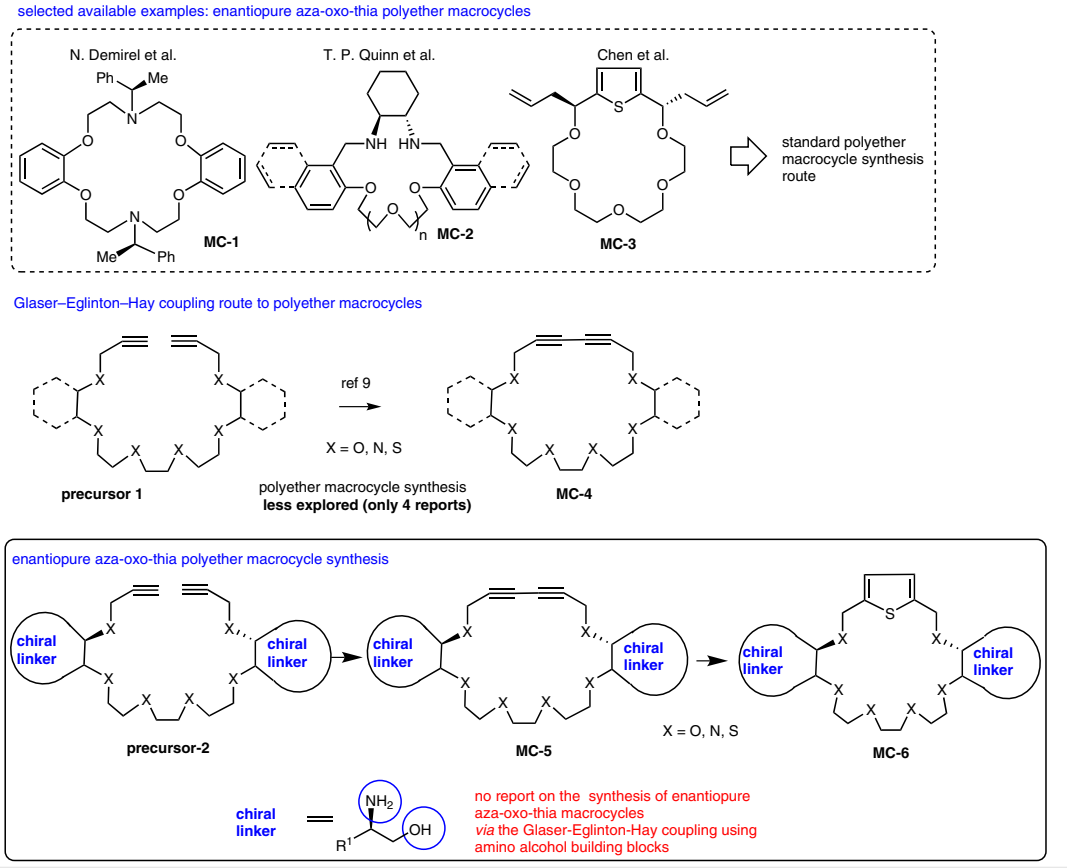
A variety of linkers and building blocks have been used in synthesizing a wide range of polyether macrocycles.[1–3] Accordingly, the synthesis of classical and aza-oxo polyether macrocycles is relatively well explored in comparison to the synthesis of aza-oxa-thia (heterotopic-type) polyether macrocycles.[1–5] Apart from numerous linkers and building blocks, several enantiopure synthetic building blocks (e.g., amino acids, sugars, BINOL, amines or amino alcohols) and a number of asymmetric synthesis routes have been exploited in synthesizing optically active polyether macrocycles.[4,5] Optically active polyether macrocycles have found various applications in organic synthesis.[5]

Generally, macrocycles/polyether macrocycles are assembled by such techniques as peptide coupling, Yamaguchi lactonization, ring-closing metathesis, Williamson ether synthesis, or other methods.[1–6] The intramolecular Glaser–Eglinton–Hay reaction has also been used for synthesizing macrocycles.[7,8] Although this method has been used to synthesize several 1,3-diyne-based shape-persistent linear and macrocyclic molecules,[7,8] to the best of our knowledge there are only two reports by other groups and two reports by our group that describe syntheses of 1,3-diyne unit-containing polyether macrocycles.[9] Furthermore, to the best of our knowledge, there are no reports on the synthesis of optically active polyether macrocycles by an intramolecular Glaser–Eglinton–Hay-type cross-coupling reaction (Scheme 1).[9]

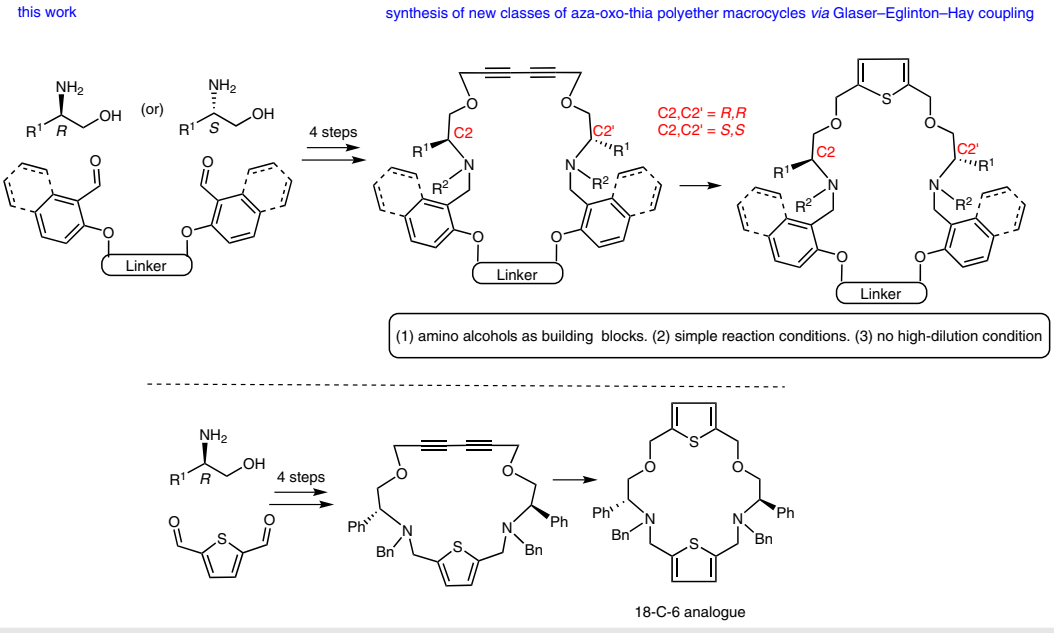
In this Letter, we report our preliminary work on the synthesis of optically active aza-oxo polyether macrocycles containing 1,3-diyne units from amino alcohol building blocks and suitable linkers by exploiting an intramolecular Glaser–Eglinton–Hay macrocyclization as the key step (Scheme 2).

Furthermore, the conversion of the 1,3-diyne unit of these aza-oxo polyether macrocycles into a thiophene ring led to the assembly of optically active aza-oxa-thia heterotopic polyether macrocycles analogous to classical 18-C-6 and 18-C-5 systems.

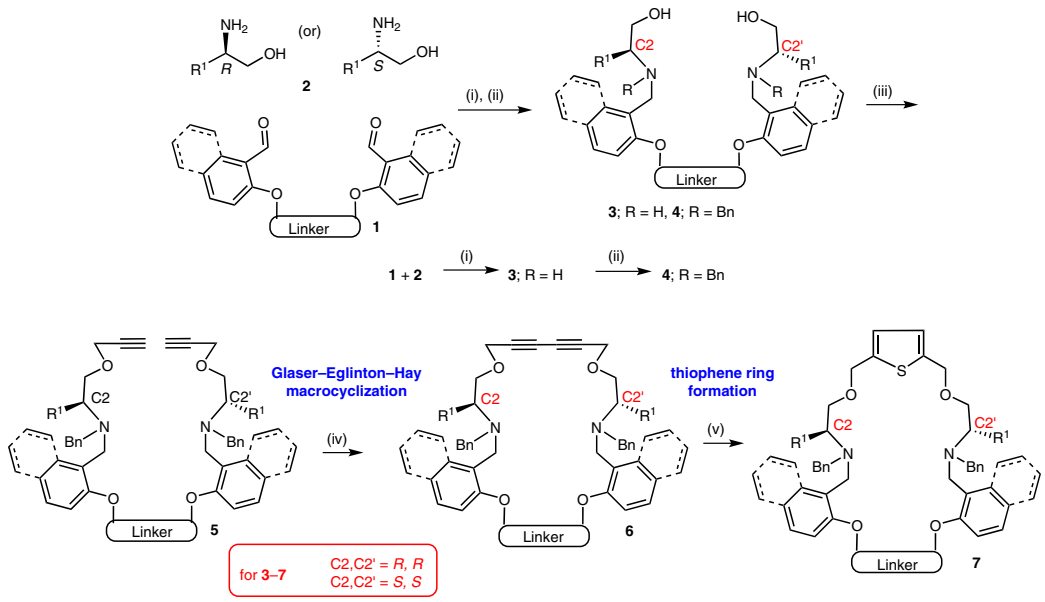
Our general strategy for executing the intramolecular Glaser–Eglinton–Hay macrocyclization-based synthesis of optically active aza-oxo-thia polyether macrocycles from amino alcohols is shown in Scheme 3.



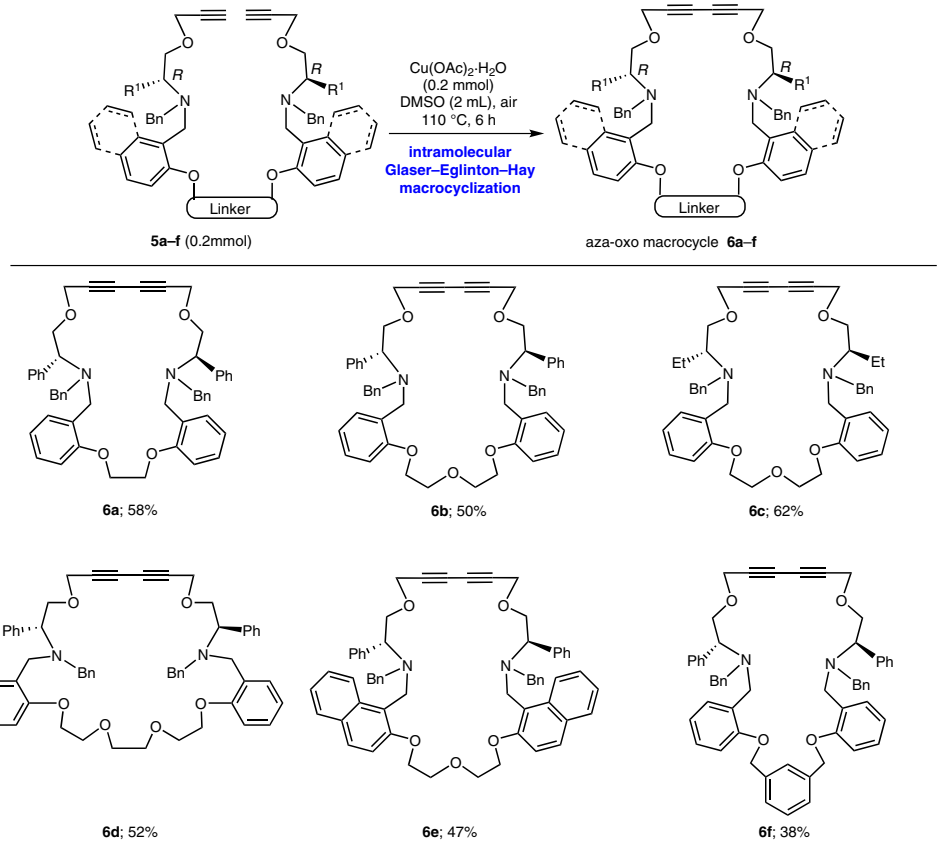
Scheme 1 Enantiopure aza/oxo/thia polyether macrocycles



Scheme 2



Scheme 3 *Reagents and conditions*: (i) EtOH, reflux, 12 h, then $NaBH_4$, reflux, 12 h; (ii) BnCl, K_2CO_3, MeCN, reflux, 72 h; (iii) propargyl bromide, NaH, THF, r.t.; (iv) $Cu(OAc)_2·H_2O$, DMSO, 110 °C, air, 6 h; (v) $Na_2S·xH_2O$, CuI, 1,10-phenanthroline, DMF, 90 °C, air, 9 h.



Scheme 4 Synthesis of aza-oxo macrocycles **6a–f**[10]

First, several dialdehydes **1** were prepared from the corresponding 2-hydroxybenzaldehydes and a variety of linkers. Next, the treatment of the (*R*)- or (*S*)-amino alcohol **2** with dialdehyde **1**, followed by addition of $NaBH_4$, afforded the corresponding diol precursors **3**. Subsequent N-benzylation followed by O-propargylation of the amino alcohol moieties of **3** gave the corresponding substrates containing two terminal alkyne units **5** and various aliphatic, polyether, or aromatic linkers (Scheme 3).

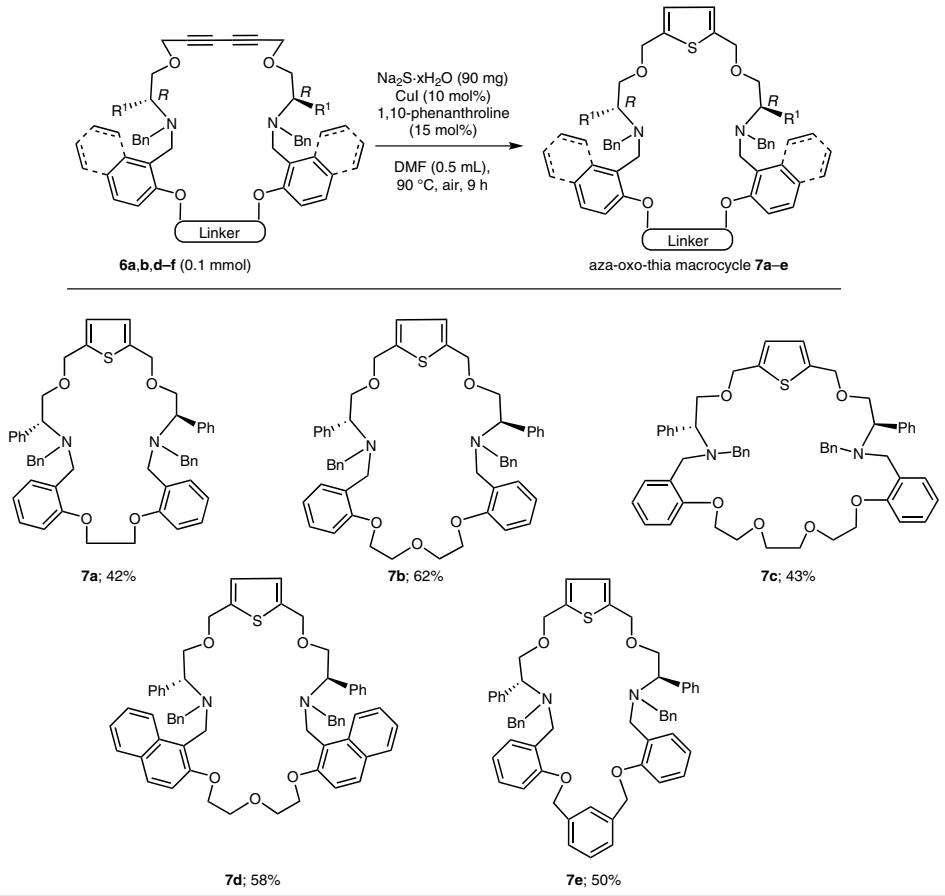
We then investigated the intramolecular sp–sp C–C bond-forming Glaser–Eglinton–Hay-type macrocyclization of the diynes **5**. Initially, we examined the Glaser–Eglinton–Hay macrocyclization of diyne **5a**, derived from the corresponding (*R*)-amino alcohol (Scheme 4). The reaction of substrate **5a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in DMSO at 110 °C under aerobic conditions gave a 58% yield of the aza-oxo polyether macrocycle **6a** containing a 1,3-diyne unit.[10]

To investigate the substrate scope of this reaction, we carried out the macrocyclization of the starting materials **5b–f** containing various polyether-based linkers. The Cu-promoted Glaser–Eglinton–Hay macrocyclization of substrates **5b–f** gave the corresponding optically active aza-oxo polyether macrocycles **6b–f** in 38–62% yield (Scheme 4).[10]

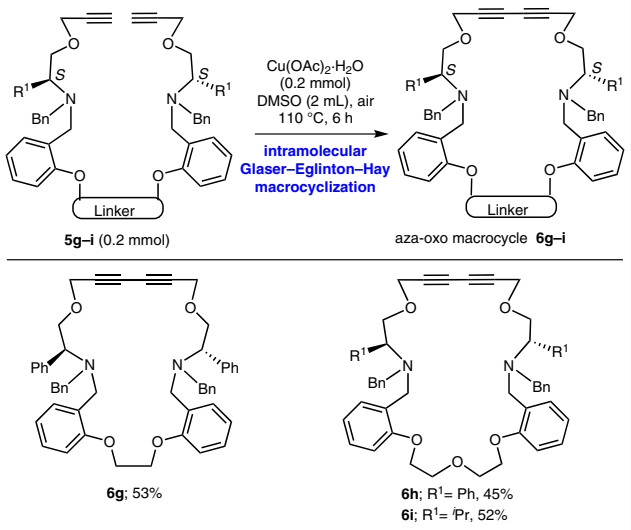
Next, we attempted to prepare optically active aza-oxa-thia polyether macrocycles by converting the 1,3-diyne units of the aza-oxo polyether macrocycles **6a–f** into thiophene rings. Initially we treated macrocycle **6a** with $Na_2S{\cdot}xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 °C to give the thiophene-containing aza-oxa-thia (heterotopic-type) polyether macrocycle **7a** in 42% yield (Scheme 5).[11,12]

Similarly, the reactions of diyne macrocycles **6b** and **6d–f** with $Na_2S{\cdot}xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 °C gave thiophene-containing aza-oxa-thia (heterotopic-type) polyether macrocycles **7b–e**, respectively, in 43–58% yield (Scheme 5).[11,12]

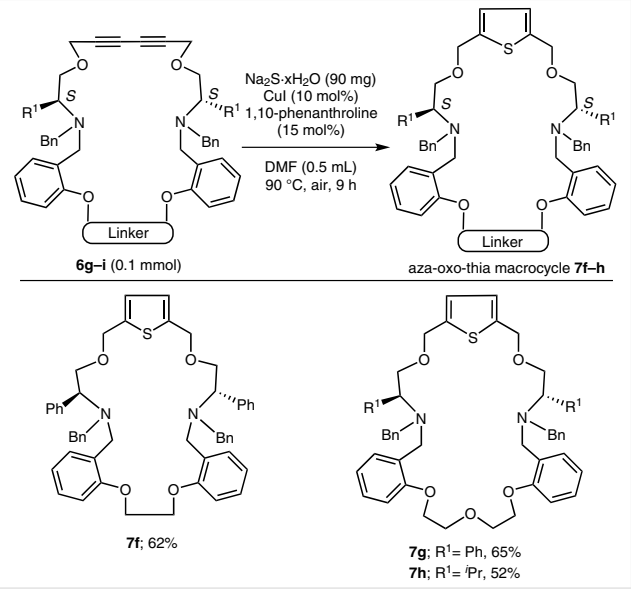
Next, to demonstrate the generality of this approach, we also carried out the Cu-promoted macrocyclization of diynes **5g–i** derived from the corresponding (*S*)-amino alcohols (Scheme 3). Accordingly, the Cu-promoted macrocyclization of **5g–i** gave the corresponding optically active aza-oxo polyether macrocycles **6g–i** in 45–53% yield (Scheme 6).[10]



Scheme 5 Synthesis of aza-oxo-thia macrocycles **7a–e**



Scheme 6 Synthesis of aza-oxo macrocycles **6g–i**



Scheme 7 Synthesis of aza-oxo-thia macrocycles **7f–h**

Subsequently, the reaction of macrocycles **6g–i** with $Na_2S{\cdot}xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 °C gave the thiophene-containing aza-oxa-thia (heterotopic-type) polyether macrocycles **7f–h**, respectively, in 52–65% yield (Scheme 7).[11,12]

Finally, we attempted to apply our synthetic method to the synthesis of the heterotopic aza-oxa-thia polyether macrocycles **13** and **19**, which are analogous to classical 18-C-5 and 18-C-6 systems (Scheme 8). Accordingly, treatment of the (*R*)-amino alcohol **2a** with isophthalaldehyde (**8**) or thiophene-2,5-dicarbaldehyde (**14**), followed by addition of $NaBH_4$, gave the corresponding diol precursors **9** and **15**, respectively (Scheme 8). Sequential *N*-benzylation and *O*-propargylation of the amino alcohol moieties of **9** and **15** gave the corresponding substrates **11** and **17** possessing two terminal alkyne units. Substrates **11** and **17** were then subjected to Cu-promoted macrocyclization to afford the corresponding optically active aza-oxo polyether macrocycles **12** and **18** containing 1,3-diyne units in 50 and 44% yield, respectively. Treatment of **12** and **18** with $Na_2S{\cdot}xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 °C afforded the corresponding thiophene-containing aza-oxa-thia polyether macrocycles **13** and **19** in 45 and 50% yield, respectively. Notably, the conversion of the 1,3-diyne units of the aza-oxo polyether macrocycles **12** and **18** into thiophene rings led to the assembly of the 18-membered-ring optically active aza-oxa-thia polyether macrocycles **13** and **19**, analogous to classical 18-C-5 and 18-C-6 systems, respectively.

In summary, we have described our preliminary work on exploiting the intramolecular Glaser–Eglinton–Hay macrocyclization reaction to synthesize optically active aza-oxo polyether macrocycles containing a 1,3-diyne unit. Conversion of the 1,3-diyne units of these aza-oxo polyether macrocycles into thiophene rings led to the assembly of novel optically active aza-oxa-thia polyether macrocycles. We also prepared some examples analogous to classical 18-C-6 and 18-C-5 systems.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588329.

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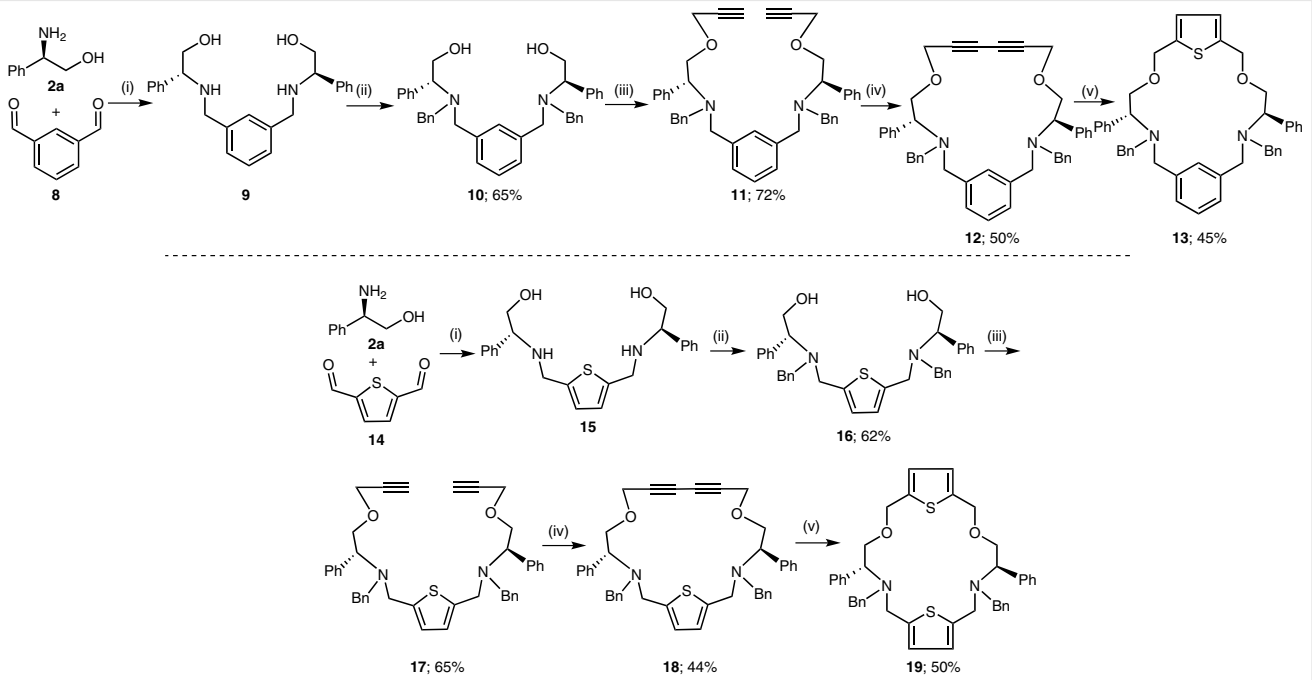

Scheme 8 Synthesis of aza-oxo-thia macrocycles **13** and **19**. *Reagents and conditions*: (i) **8**/**14** (3 mmol), **2a** (2 equiv), EtOH (10 mL), reflux, 12 h, then, $NaBH_4$ (4 equiv) reflux 12 h; (ii) **9**/**15** (crude from previous step), BnCl (4 equiv), K_2CO_3 (4 equiv), MeCN (10 mL), reflux, 72 h; (iii) **10**/**16** (1 mmol), NaH (4 equiv), propargyl bromide (5 equiv), THF (3 mL), 20 h, r.t.; (iv) **11**/**17** (0.25 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.25 mmol), DMSO (2 mL), 110 °C, air, 6 h; (v) **12**/**18** (0.1 mmol) $Na_2S{\cdot}xH_2O$ (90 mg), CuI (10 mol%), 1,10-phenanthroline (15 mol%), DMF (0.5 mL), 90 °C, air, 9 h.

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(10) **Cyclization of Diynes 5 to Macrocycles 6**; **General Procedure**
A mixture of the appropriate diyne **5** (0.2 mmol), $Cu(OAc)_2·H_2O$ (1 equiv), and DMSO (2 mL) was heated at 110 °C for 6 h in air. The mixture was then diluted with H_2O (4 mL) and the solution was filtered and washed with EtOAc (3 or 4 × 5 mL). Next, the combined layers were extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude residue was purified by column chromatography (Al_2O_3, EtOAc/hexane = 20:80).

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(12) **Conversion of Diyne-Containing Macrocycles 6 into Thiophene-Containing Macrocycles 7; General Procedure**
A mixture of the appropriate macrocyclic diyne **6** (0.10 mmol), $Na_2S·xH_2O$ (90 mg), CuI (10 mol%), and 1,10-phenanthroline (15 mol%) in DMF (0.5 mL) was heated at 90 °C for 9 h in air. Workup as described in Ref. 10 gave a crude residue that was purified by column chromatography (silica gel, EtOAc/hexane = 20:80).

Thiophene-Containing Macrocyclic Ether 7a
Pale-yellow liquid; yield: 33 mg (42%); $[\alpha]_D^{25}$ –29.08 (*c* 0.09, CH_2Cl_2); R_f = 0.55 (20% EtOAc–hexanes). IR (CH_2Cl_2): 2923, 1600, 1493, 1452, 1259 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, J_1 = 7.5, J_2 = 1.6 Hz, 2 H), 7.41–7.37 (m, 8 H), 7.31–7.27 (m, 8 H), 7.24–7.19 (m, 6 H), 7.00 (t, *J* = 7.4 Hz, 2 H), 6.85 (dd, J_1 = 8.2, J_2 = 0.7 Hz, 2 H), 6.77 (s, 2 H), 4.65 (d, *J* = 12.8 Hz, 2 H), 4.50 (d, *J* = 12.8 Hz, 2 H), 4.26–4.24 (m, 4 H), 4.07–3.89 (m, 8 H), 3.73 (d, *J* = 14.0 Hz, 2 H), 3.55 (dd, J_1 = 13.9, J_2 = 9.2 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 141.5, 140.4, 139.8, 130.3, 129.0, 128.7, 128.5, 128.2, 128.0, 127.6, 126.9, 126.7, 126.0, 120.8, 111.6, 69.4, 67.7, 66.4, 61.9, 55.1, 47.8. HRMS (ESI): $[M + H]^+$ calcd for $C_{52}H_{53}N_2O_4S$: 801.3726; found: 801.3734.