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A short synthesis of chiral peraza-macrocycles through opening of cyclic sulfamidates

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Abstract

Efficient and general synthetic methods for novel chiral peraza-macrocycles have been developed. Sequential reactions of the known cyclic sulfamidate **4** derived from *N*-benzyl-L-serine methyl ester with *p*-methoxybenzylamine provided a symmetric triamine **3**, which served as a building block for the construction of various chiral peraza-macrocycles. Reaction of the triamine with a proper connecting unit provided [18]-N_6 or [10]-N_3 chiral peraza-macrocycles. © 1999 Elsevier Science Ltd. All rights reserved.

Aza-crown macrocycles[1] had been known even before the advent of crown ethers.[2] Peraza-crown macrocycles containing transition metals have been utilized as artificial enzymes.[3] Therefore, development of efficient synthesis for the peraza-macrocycles has received much attention.[1] However, few general synthetic methods have been reported for the construction of chiral peraza-macrocycles. There are only a handful of chiral aza-macrocycles reported to date,[4] most of which have been derived from naturally occurring oxygen-containing optically active starting materials such as amino alcohols and carbohydrates. Considering the potential of the chiral peraza-macrocycles as a catalyst,[3] the development of an efficient and general synthetic methodology for chiral peraza-macrocycles is of increasing importance. In this note, we report on the development of very short and efficient synthesis for chiral [10]-N_3 and [18]-N_6 peraza-macrocycles.

In the design of our chiral peraza-macrocycles, two requirements have been set: (1) positioning of stereogenic centers close to the metal center(s), preferably being embedded in the ring; and (2) presence of a connecting point for tethering the macrocycle to a stationary phase such as polymers for later immobilization of the macrocycle. Compounds **1** and **2** in Fig. 1 have been selected as suitable target molecules meeting these requirements and we envisioned that these aza-macrocycles could be constructed from triamine unit **3** prepared from the known cyclic sulfamidate **4** as depicted in Fig. 1.[5]

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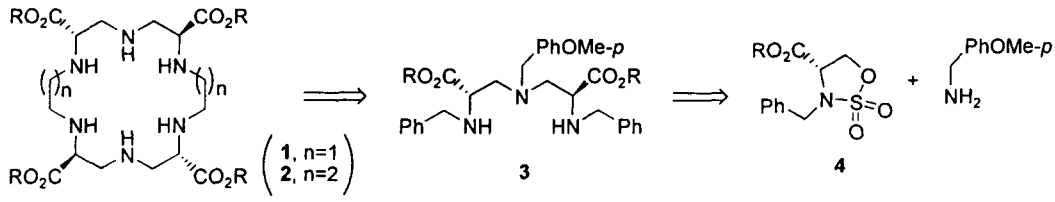
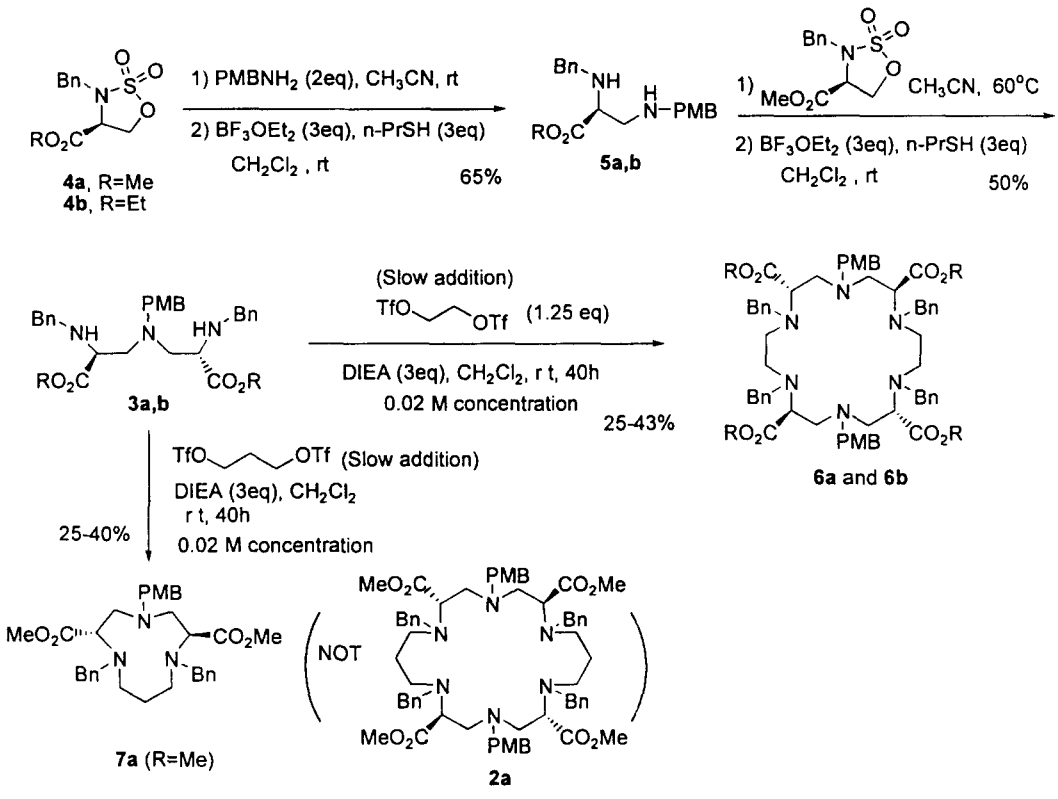


Figure 1. Synthetic plan for the chiral peraza-macrocycles from cyclic sulfamidate **4**

Synthetic approaches towards the macrocycles are shown in Scheme 1. Recently, we have reported an efficient and stereospecific synthesis of optically pure 2,3-diaminopropanoate derivatives through opening of cyclic sulfamidates prepared from serine ester with amine nucleophiles.[5] Opening of the cyclic sulfamidate **4** with *p*-methoxybenzylamine (PMB–NH_2) according to the literature[5] provided 2,3-diaminopropanoate derivatives (**5a** or **5b**) in reasonable yields. The diamine **5** was utilized as yet another nucleophile for the preparation of a symmetric triamine **3**.[6] This triamine **3** could be used as a common building block for the synthesis of a variety of chiral peraza-macrocycles. Construction of macrocycle **6a**[7] from the triamine **3** according to the Richman–Atkins protocol[8] using ethyleneglycol bistrifluoromethanesulfonate (bistriflate) as a doubly electrophilic two-carbon connector was accomplished smoothly by slow addition of a dichloromethane solution of the bistriflate via syringe pump to a dichloromethane solution of **3** in the presence of diisopropylethylamine (DIEA) resulting in 0.016 M overall concentration. The presence of the desired cyclic structure was identified through matrix assisted laser desorption and ionization time-of-flight (MALDI–TOF) Mass spectroscopic analysis showing a peak at 1092.06 corresponding to the peraza-macrocycle **6a**. Upon different runs ranging from 100 mg to ca. 1 g of **3a** or **3b**, the macrocycle **6a** or **6b**, respectively, were obtained in 25–43% yields. It is of particular note that *the employment of the bistriflate was critical* for the success of macrocyclization since reactions using other two-carbon connectors[8] such as 1,2-dibromoethane, ethylene glycol bis(*p*-toluenesulfonate) or bismethanesulfonate have not been successful at all. In order to obtain the [20]-N_6 macrocycle, the same approach as in the preparation of **6** was applied except that **3a** and 1,3-propanediol bistriflate were used. However, instead of the 20-membered structure **2a**, the major product was identified as the 10-membered ring structure **7a**.[9] Efforts to identify 20-membered- or larger rings in the coupling reaction through extensive chromatography have not been successful so far. Again, 1,3-dielectrophiles other than the bistriflate have not been useful in fulfilling the cyclization. In order to examine the stereochemical integrity of the compounds **3**, **6** and **7a**,[10] they have been examined under various HPLC conditions using a number of achiral and chiral, and reverse and normal phase columns[11] and all of the chromatograms indicated >95% purity. Based upon these results it is most likely that the chiral peraza-macrocycles maintain high enantiomeric and diastereomeric purity.

In conclusion, we have developed an efficient synthetic methodology for novel, ester-containing chiral peraza-macrocycles **6a**, **6b** and **7a** through sequential opening of cyclic sulfamidates with a primary amine and coupling of the resulting triamine units with α,ω-dielectrophiles. Preliminary complexation studies of the above peraza-macrocycles with copper salts showed no complexation at room temperature presumably due to an excessively crowded environment around the nitrogen atoms. Deprotection of the nitrogen blocking groups and subsequent investigation of stereodifferentiation using metal-complexed peraza-macrocycles as well as molecular recognition studies with chiral molecules such as amino acid derivatives are in progress and the results will be reported in due course.



Scheme 1. Synthesis of chiral peraza-macrocycles from cyclic sulfamidate **4**

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References

1. (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Aza-Crown Macrocycles*; John Wiley & Sons: New York, 1993; (b) Parker, D. In *Macrocycle Synthesis*; Parker, D., Ed.; Oxford University Press: Oxford, 1996.
2. Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
3. (a) Murakami, Y.; Kikuchi, J.-i.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (b) Koike, T.; Watanabe, T.; Aoki, S.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 12696. (c) Kimura, E.; Hashimoto, H.; Koike, T. *J. Am. Chem. Soc.* **1996**, *118*, 10963. (d) Kimura, E.; Kitamura, H.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1997**, *1198*, 10909. (e) Aoki, S.; Honda, Y.; Kimura, E. *J. Am. Chem. Soc.* **1998**, *120*, 10018. (f) Jang, B. B.; Lee, K. P.; Min, D. H.; Suh, J. H *J. Am. Chem. Soc.* **1998**, *120*, 12008. (g) You, J. S.; Yu, X. Q.; Li, X. S.; Yan, Q. S.; Xie, R. G. *Tetrahedron: Asymmetry* **1998**, *9*, 1197.
4. (a) Ranganathan, D.; Haridas, V.; Madhusudanan, K. P.; Roy, R.; Nagaraj, R.; John, G. B. *J. Am. Chem. Soc.* **1997**, *119*, 11578. (b) Alfonso, I.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 367. (c) Tripier, R.; Siri, O.; Rabiet, F.; Denat, F.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 79. (d) Choi, H. J.; Kwak, M. O.; Kim, J. M. *Tetrahedron Lett.* **1997**, *38*, 6217. (e) Grossel, M. C.; Hamilton, D. G.; Vine, T. A. *Tetrahedron Lett.* **1997**, *38*, 4639. (f) Joly, J. P.; Schroder, G. *Tetrahedron Lett.* **1997**, *38*, 8197. (g) Habata, Y.; Bradshaw, J. S.; Zhang, X. X.; Izatt, R. M. *J. Am. Chem. Soc.* **1997**, *119*. 7145. (h) Kim, B. H.; Jeong, E. J.; Jung, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 6390. (i) Hellier, P. C.; Bradshaw, J. S.;

Young, J. J.; Zhang, X. X.; Izatt, R. M. *J. Org. Chem.* **1996**, *61*, 7270. (j) Gryko, D. T.; Piatet, P.; Salanaki, P.; Jurczak, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1771.

5. Kim, B. M.; So, S. M. *Tetrahedron Lett.* **1998**, *39*, 5381.
6. Procedure for the preparation of compound **3a**: To a solution of cyclic sulfamidate **4a** (350 mg, 1.3 mmol) in dry acetonitrile (4.3 mL) was added *p*-methoxyphenylmethylamine (0.25 mL, 1.9 mmol) and the mixture was stirred for 5–7 h at room temperature. Solvent was removed under reduced pressure and the mixture was dissolved in CH_2Cl_2 (4.3 mL). To the solution was slowly added $BF_3 \cdot OEt_2$ (0.65 mL, 5.2 mmol) under nitrogen at 0°C. After stirring for 30 min, the mixture was treated with *n*-PrSH (0.59 mL, 6.5 mmol). Then, the mixture was stirred for 1 h at room temperature and partitioned between EtOAc and sat. aq. $NaHCO_3$ solution. The organic layer was dried over anhyd $MgSO_4$, filtered, and concentrated. The crude product was purified on column chromatography to give 270 mg (63%) of compound **5a**: $[\alpha]_D^{19}$ −14.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (br, 2H), 2.76 (dd, J_{AB}=12.6, J_{AX}=7.7 Hz, 1H), 2.90 (dd, J_{AB}=12.6, J_{AX}=4.6 Hz, 1H), 3.49 (dd, *J*=7.7 and 4.6 Hz, 1H), 3.65–3.65–3.88 (m, 10H), 6.85–6.89 (m, 2H), 7.21–7.38 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.68, 51.85, 52.14, 52.65, 55.19, 60.15, 113.69, 127.06, 128.35, 129.23, 131.91, 139.69, 158.59, 174.65. Cyclic sulfamidate **4a** (1.30 g, 4.80 mmol) was treated with compound **5a** (1.90 g, 5.70 mmol) according to the same procedure as described above except that this time the reaction temperature was 60°C. Column chromatography of crude **3a** gave 1.40 g (55% yield) of a pale yellow oil: $[\alpha]^{19}_D$ −6.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.07 (br, 2H), 2.75–2.77 (m, 4H), 3.42–3.65 (m, 12H), 3.77–3.83 (m, 5H), 6.79–6.82 (m, 2H), 7.06–7.08 (m, 2H), 7.22–7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.66, 52.23, 55.14, 57.19, 58.55, 59.83, 113.54, 126.99, 128.28, 130.11, 130.91, 139.60, 158.66, 174.65; HRMS (FAB) *m/z*: calcd 520.2811 for $C_{30}H_{38}N_3O_5$ $[M+H]^+$; found: 520.2810.
7. Procedure for the preparation of compound **6a**: To a solution of compound **3a** (320 mg, 0.62 mmol) in dry CH_2Cl_2 (20 mL) was slowly added ethyleneglycol bisitriflate (300 mg, 0.92 mmol) in dry CH_2Cl_2 (20 mL) using a syringe pump over a period of 6 h at 0°C, then the reaction flask was warmed to room temperature. After stirring for 2 days, the mixture was partitioned between EtOAc (100 mL) and sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the filtrate concentrated under reduced pressure. Column chromatography of the crude product on silica gel gave a pale yellow oil (117 mg, 35%); ^1H NMR (300 MHz, $CDCl_3$): δ 2.48–2.50 (m, 4H), 2.53–2.58 (dd, *J*=3.2 and 12.4 Hz, 4H), 2.81–2.84 (m, 4H), 2.97–3.45 (m, 12H), 3.48–3.77 (m, 26H), 6.65–6.74 (m, 4H), 6.79–6.88 (m, 4H), 7.10–7.23 (m, 20H): MALDI-TOF MS (accelerating voltage: 26 kV): 1092.06; $[\alpha]_D^{21}$ −4.1 (*c* 1.0, $CHCl_3$); HRMS (FAB) *m/z*: calcd 1091.5858 for $C_{64}H_{79}N_6O_{10}$ $[M+H]^+$; found: 1091.5847.
8. Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268.
9. Procedure for the preparation of compound **7a**: Following the same procedure as in the preparation of compound **6a**, compound **3a** (180 mg, 0.35 mmol) was treated with 1,3-propanediol bistriflate (180 mg, 0.53 mmol) to afford macrocycle **7a** after purification on a silica gel chromatographic column (64 mg, 33%): $[\alpha]_D^{21}$ −67.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (m, 2H), 2.39–2.44 (m, 1H), 2.53–2.57 (m, 1H), 2.96–3.11 (m, 2H), 3.46–3.92 (m, 21H), 6.75–6.77 (m, 2H), 6.91–6.94 (m, 2H), 7.25–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.66, 45.37, 50.25, 50.68, 55.19, 56.81, 57.32, 60.73, 113.21, 127.13, 128.18, 129.61, 130.00, 138.64, 158.23, 172.91; HRMS (FAB) *m/z*: calcd 560.3125 for $C_{33}H_{42}N_3O_5$ $[M+H]^+$; found: 560.3130.
10. For the preservation of stereochemical integrity at the α-center under the reaction conditions involving cyclic sulfamidates of serine ester derivatives, see Ref. 5.
11. These include Vydac 218TP54 (4.6×250 mm), Phenomenex Chirex 00G-3005-E0 (4.6×250 mm), and Daicel Chiralcel OD-R (4.6×250 mm) columns for reverse phase analyses and Phenomenex Chirex 00G-3014-E0 (4.6×250 mm) and Daicel Chiralcel OD (4.6×250 mm) columns for normal phase ones.