A Facile Synthesis of New Chiral [1 + 1] Macrocyclic Schiff Bases

Paulsamy Suresh, Sankareswaran Srimurugan, and Hari N. Pati*
Department of Process Chemistry, Advinus Therapeutics, Phase-II, Peenya Industrial Area, Bangalore-560058, India

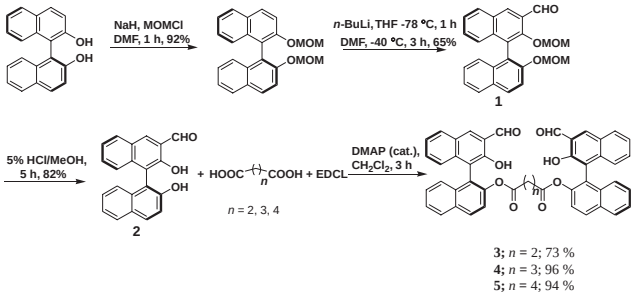
(Received July 12, 2007; CL-070739; E-mail: hari.pati@advinus.com)

A series of new chiral [1 + 1] macrocyclic Schiff bases have been synthesized in high yields and short reaction times from cyclocondensation of dialdehydes with long tethers and chiral diamines. The yields of the macrocycles were higher when the dialdehyde component is also chiral. The macrocyclisation was performed under microwave irradiation and aqueous reaction conditions employing salts of chiral diamines in contrast to free diamines normally employed.

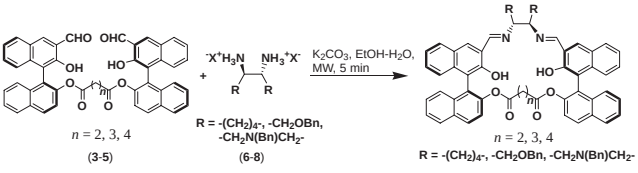
The design and study of new macrocyclic species is one of the most interesting areas in the field of supramolecular chemistry.[1] In particular, chiral macrocyclic compounds have been studied extensively for their applications in molecular recognition, host–guest chemistry, supramolecular structures, material chemistry, and catalysis. A variety of chiral macrocycles with different central cavity sizes and tunable functionalities were synthesized and explored in this regard.[2] Chiral macrocyclic Schiff bases derived from condensation of diamines and dialdehydes allows for easy tuning of the central cavities and they can be further functionalised.[3] These macrocyclic structures are generally formed under thermodynamic control depending on the type of dialdehydes employed and hence this method can be applied for the synthesis of macrocycles with desired central cavities. Though there are many examples that describe the synthesis of [2 + 2] and [3 + 3][4,5] chiral macrocyclic Schiff bases, there are only few papers involving [1 + 1] macrocycles. Li and co-workers[6] reported the synthesis of binol-based [1 + 1] macrocyclic Schiff bases and explored their possible application towards enantioselective fluorescence recognition. Martinez and co-workers[7] reported a series of chiral [1 + 1] macrocycles derived from achiral dialdehyde moieties and chiral diamines. However, the reported methods involve either a longer reaction time or moderate yields of macrocycle.

As an extension of our earlier works on the synthesis of chiral macrocyclic Schiff bases with moderate ([2 + 2] and [3 + 3])[8] and large ([6 + 6])[9] cavity sizes, macrocycles with small cavities ([1 + 1]) were explored. Both the chiral and achiral dialdehydes were employed for this purpose.

The conformational bias offered by the dialdehydes forms a key factor in deciding the major macrocycle formed during condensation with chiral diamines. On this basis, dialdehydes containing a long tether between the aldehyde moieties can facilitate [1 + 1] macrocyclisation with chiral diamines. As an initial effort, bisbinaphthyl aldehyde tethered using a diester group was used for the reaction. The bisbinaphthyl aldehyde **3** was synthesized from the corresponding optically pure (*S*)-[1,1′-binaphthyl]-2,2′-diol (BINOL) according to the Scheme 1. Condensation of **2** with succinic acid using EDC as a coupling agent afforded bisbinaphthyl aldehyde **3** in 73% yield. In order to study the effect of the tether length of dialdehyde on macrocyclisation, **4** and **5** were synthesized in an analogous manner using glutaric and adipic acid in place of succinic acid.



Scheme 1.



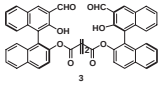
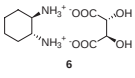
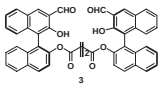
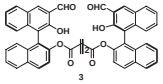
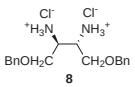
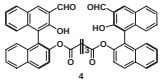
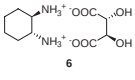
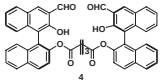
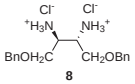
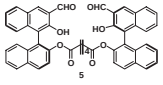
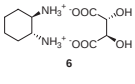
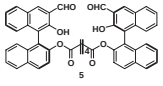
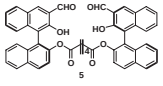
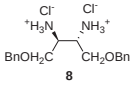
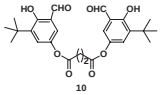
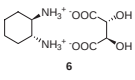
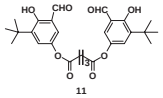
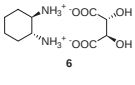
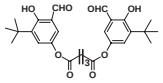
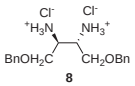
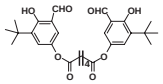
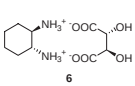
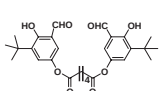
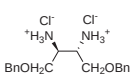
Scheme 2.

Microwave irradiation (5 min)[10] of a mixture of bisbinaphthyl aldehyde **3**–**5** and chiral diamine **6**–**8** in presence of potassium carbonate afforded chiral [1 + 1] macrocyclic imines in good yields. The cyclocondensation does not require any anhydrous or dilute reaction conditions for the macrocycle synthesis. Moreover, salts of chiral diamines were employed instead of widely employed enantiopure diamines (Scheme 2).

The [1 + 1] macrocycle was formed exclusively in higher yield which was free from linear oligomers or higher macrocycles during the cyclocondensation of **3** with (1*R*,2*R*)-cyclohexanediammonium mono-(+)-tartrate (**6**) (Table 1, Entry 1). The tether length was found to exhibit little effect on the yield and the nature of macrocyclization. Accordingly, **4** and **5** gave [1 + 1] macrocycle in 94–96% with **6** (Table 1, Entries 4 and 6). Chiral diamines with different dihedral angles namely (3*R*,4*R*)-diamino-1-benzylpyrrolidine dihydrochloride (**7**) and (2*R*,3*R*)-1,4-bis(benzyloxy)butane-2,3-diamine dihydrochloride (**8**) displayed reactivity similar during the condensation with **6** forming [1 + 1] macrocycle in 78–91% yields (Table 1, Entries 2, 3, 5, 7, and 8). In all the cases MALDI-TOF mass spectra revealed a single peak corresponding to the molecular ion of the macrocycle. Similarly, all the macrocyclic imines displayed the predicted spectroscopic features, most importantly one set of NMR signals indicating a highly symmetric structure. The ^{1}H NMR of the [1 + 1] macrocycles derived from **5** and chiral diamines **6** and **8** displayed interesting features.

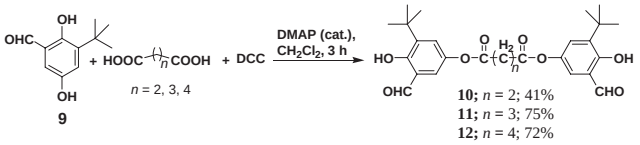
The influence of chirality at the aldehyde moiety on macrocyclisation was studied by synthesizing achiral dialdehydes possessing similar long diester tethers. Accordingly, dialdehydes **10**–**12** were synthesized by condensing 3-*tert*-butyl-2,5-dihy-

Table 1. [1 + 1] Cyclocondensation of chiral bisbinaphthyl and achiral aldehydes with chiral diamine salts

Entry	Bis(hydroxy aldehyde)	Chiral diamine	[n + n]	m/z	Yield /%
1	 3	 6	[1 + 1]	788	97
2	 3	 7	[1 + 1]	866	89
3	 3	 8	[1 + 1]	947	78
4	 4	 6	[1 + 1]	802	94
5	 4	 8	[1 + 1]	989	91
6	 5	 6	[1 + 1]	816	96
7	 5	 7	[1 + 1]	894	84
8	 5	 8	[1 + 1]	1003	89
9	 10	 6	[2 + 2]	1097	48
10	 11	 6	[1 + 1] + [2 + 2]	563, 1125	67
11	 11	 8	[1 + 1]	759	58
12	 12	 6	[1 + 1]	577	65
13	 12	 8	[1 + 1]	763	70

droxybenzaldehyde (**9**) with various diacids using DCC according to Scheme 3.

Cyclocondensation of dialdehydes **10**–**12** with chiral diamines **6** and **8** were performed under microwave irradiation in aqueous ethanol. The reactivity pattern was different in comparison to the chiral dialdehydes indicating the significance of rigid conformation in the process of macrocyclisation. In the case of dialdehyde **10** ($n = 2$), the cyclocondensation with **6** formed [2 + 2] macrocycle as the major product which was totally free



Scheme 3.

from the corresponding [1 + 1] macrocycle (Table 1, Entry 9). The reaction however produced little amounts of higher order macrocycles as observed in the MALDI-TOF mass spectrum.

Dialdehyde **11** ($n = 3$), on the other hand formed a mixture of [1 + 1] and [2 + 2] macrocycles with **6** under identical reaction conditions (Table 1, Entry 10). These macrocycles were analyzed as a mixture and the individual components were not isolated. Unusually cyclocondensation of **11** with acyclic diamine **8** afforded [1 + 1] macrocycle in 58% isolated yield (Table 1, Entry 11). Dialdehyde **12** with the long tether exclusively formed [1 + 1] macrocycle upon cyclocondensation with both cyclic and acyclic diamine **6** and **8** in 65–70% yields (Table 1, Entries 12 and 13) indicating the role of tether length in macrocyclisation.

In conclusion a facile method for synthesis of [1 + 1] chiral macrocyclic Schiff base is described. Chiral dialdehydes afforded [1 + 1] macrocycles in high yields with chiral diamines when compared to achiral dialdehydes.

References and Notes

1 D. Zhao, J. S. Moore, *Chem. Commun.* **2003**, 807; G. W. Gokel, W. M. Leevy, M. E. Weber, *Chem. Rev.* **2004**, *104*, 2723; F. C. J. M. van Veggel, W. Verboom, D. N. Reinhoudt, *Chem. Rev.* **1994**, *94*, 279; J. L. Atwood, L. J. Barbour, M. J. Hardie, C. L. Raston, *Coord. Chem. Rev.* **2001**, *222*, 3; V. Prautzsch, S. Ibach, *J. Inclusion Phenom. Macrocycl. Chem.* **1999**, *33*, 427.

2 S. Höger, *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2685.

3 P. Guerriero, S. Tarnburini, P. A. Vigato, *Coord. Chem. Rev.* **1995**, *139*, 17; P. A. Vigato, S. Tamburini, *Coord. Chem. Rev.* **2004**, *248*, 1717.

4 N. Kuhnert, A. Lopez-Periago, G. M. Rossignolo, *Org. Biomol. Chem.* **2005**, *3*, 524; N. Kuhnert, C. Patel, F. Jami, *Tetrahedron Lett.* **2005**, *46*, 7575; M. Kwit, P. Skowronek, H. Kolbon, J. Gawronski, *Chirality* **2005**, *17*, S93; M. Bru, I. Alfonso, M. I. Burguete, S. V. Luis, *Tetrahedron Lett.* **2005**, *46*, 7781; J. Gregoliński, J. Lisowski, T. Lis, *Org. Biomol. Chem.* **2005**, *3*, 3161.

5 C. Ma, A. Lo, A. Aldolmaleki, M. J. MacLachlan, *Org. Lett.* **2004**, *6*, 3841; J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687; J. Hodačová, M. Chadim, J. Závada, J. Aguilar, E. García-Espaňa, S. V. Luis, J. F. Miravet, *J. Org. Chem.* **2005**, *70*, 2042.

6 Z. Li, L. Pu, *Org. Lett.* **2004**, *6*, 1065; Z. Li, J. Lin, L. Pu, *Angew. Chem., Int. Ed.* **2005**, *44*, 1690; Z. Li, L. Pu, *J. Mater. Chem.* **2005**, *15*, 2860.

7 A. Martinez, C. Hemmert, H. Gornitzka, B. Meunier, *J. Organomet. Chem.* **2005**, *690*, 2163; A. Martinez, C. Hemmert, B. Meunier, *J. Catal.* **2005**, *234*, 250.

8 S. Srimurugan, B. Viswanathan, T. K. Varadarajan, B. Varghese, *Tetrahedron Lett.* **2005**, *46*, 3151.

9 S. Srimurugan, P. Suresh, H. N. Pati, *J. Inclusion. Phenom. Macrocycl. Chem.* **2007**, in press.

10 **Typical experimental procedure**: A mixture of dialdehyde **3** (1.0 equiv.), chiral diamine **6** (1.5 equiv.), and K_2CO_3 (2.0 equiv.) in water–ethanol (1:1) was irradiated in an unmodified domestic oven at low power settings for 5 min. The reaction mixture was cooled to room temperature and the solid materials were collected by filtration. It was redissolved in ethyl acetate and filtered. The filterate was dried over sodium sulfate and concentrated under reduced pressure to afford pure [1 + 1] macrocycle as a yellow solid in good yield. Yield: 94%; $[\alpha]_D^{28} = -110$ (c 0.1, CH_2Cl_2); ^{1}H NMR [400 MHz, $CDCl_3$] δ 12.92 (s, 2H), 8.54 (s, 2H), 7.92–7.86 (m, 6H), 7.77–7.75 (d, $J = 8.4$ Hz, 2H), 7.41–7.37 (t, $J = 7.6$ Hz, 2H), 7.33–7.13 (m, 10H), 6.90–6.88 (d, $J = 8.4$ Hz, 2H), 3.30–3.28 (d, $J = 9.6$ Hz, 2H), 1.83–1.80 (m, 4H), 1.40–1.38 (m, 2H), 1.22–1.18 (m, 4H), 1.16–1.13 (m, 2H); ^{13}C NMR [400 MHz, $CDCl_3$] δ 171.2, 164.9, 155.5, 151.5, 135.3, 134.7, 133.5, 130.0, 129.3, 129.2, 129.0, 128.3, 127.8, 126.5, 124.8, 124.6, 123.9, 123.3, 120.6, 117.7, 114.4, 113.5, 72.7, 60.4, 32.7, 24.1; MALDI-TOF-MS: m/z 789 ($[M + H]^+$).

Published on the web (Advance View) October 6, 2007; doi:10.1246/cl.2007.1332