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Synthesis of novel chiral macrolides and their antifungal activity

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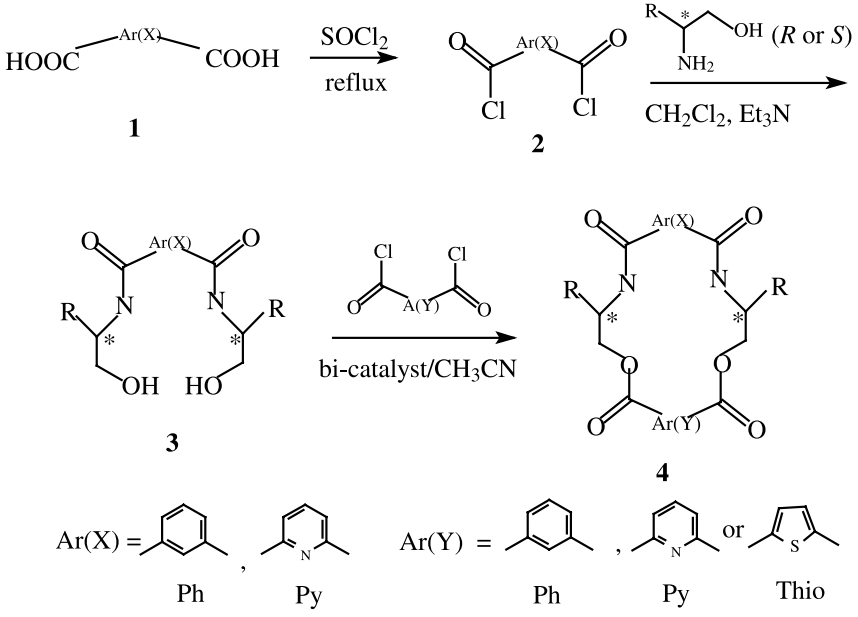
Abstract—Nineteen chiral macrocyclic diamide–diester ligands were synthesized using a three step reaction. The synthesis utilized the condensation of dicarbonyl dichlorides with chiral 2-aminoethanol derivatives. The reaction was catalyzed in a dual catalyst system. Some of the compounds were found to display antifungal activity. © 2002 Elsevier Science Ltd. All rights reserved.

Macrocyclic lactones and diamides are widely found in nature and constitute an extensive range of natural products with diverse biological activity.[1–3] As reported, macrocyclic lactones and macrolides, such as the erythromycins and cytochalasins, display antibiotic and antitumor activity.[4,5] All of these natural compounds are complex structures due to the presence of multi-functional groups and their chirality. A number of macrocyclic compounds containing diamide–diester groups have been synthesized.[6–8] However, relatively little has been done with respect to the synthesis of chiral macrocyclic diamide–diester ligands. In this report, the synthesis of a series of new chiral macrocyclic lactam–lactones and their antibacterial and antifungal activities are described.



R = Et (*R*), iso-Pr (*S*), Ph (*R*) or Benzyl (*S*).

Scheme 1.

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As shown in Scheme 1, 2,6-isophthalic acid or 2,6-pyridine dicarboxylic acid (**1**) undergo reaction with $SOCl_2$ to form the corresponding dicarbonyl dichlorides (**2**). Condensation of **2** with the C-substituted chiral aminoethanols, yields compounds **3**.[9] In the subsequent steps, 2,6-isophthalic dicarbonyl dichloride, 2,6-pyridine dicarbonyl dichloride or 2,5-thiophene dicarbonyl dichloride undergo reaction with **3** to form the macrolides **4**.[10] All of the macrocycles synthesized and some of their properties are listed in Table 1.[11]

In the cyclization procedure, the inorganic base K_2CO_3 showed no catalytic activity. By adding Et_3N or pyridine, the reaction can be improved, but with a relatively low product yield. An alternate catalyst system was sought to promote cyclization. It was found that in the presence of pyridine and *N*,*N*′-dimethyl-4-amino pyridine (DMAP) a high cyclization yield was achieved. In the synthesis of macrocycle 1, the influence of the catalyst used on the reaction yield is significant and the results are listed in Table 2. The yield of 65% was the highest reached in this type of cyclization. Employing this new dual catalyst system not only increased the yield of the product, but also improved the reaction rate by a factor of three.

One of the aims of the investigation was to determine the biological properties of these new chiral macrocycles. As shown in Table 1, the macrocycles synthesized possess heterocyclic subunits including pyridine and/or thiophene. This allowed us to determine the influence of the incorporated heterocyclic groups on biological

Table 1. Compounds synthesized and their physical properties

Entry	Ar (X)	R	Ar (Y)	Yield (%)	mp (°C)	$[\alpha]_D^{25}$
4a	Ph	Et	Ph	65	272–274	−105.8
4b	Ph	Et	Py	28	239–241	+260.2
4c	Ph	Et	Thio	36	233–235	−61.6
4d	Ph	*iso*-Pr	Ph	50	>300	−272.0
4e	Ph	*iso*-Pr	Py	22	148–151	−312.4
4f	Ph	*iso*-Pr	Thio	37	>280	−85.9
4g	Ph	Ph	Ph	30	245–247	+161.5
4h	Ph	Ph	Py	26	142–144	+340.9
4i	Ph	Ph	Thio	29	195–197	+255.8
4j	Ph	Benzyl	Ph	67	>280	−205.1
4k	Py	Et	Ph	47	219–221	+354.6
4l	Py	Et	Py	42	244–246	+260.2
4m	Py	Et	Thio	62	215–217	−96.3
4n	Py	*iso*-Pr	Ph	41	258–260	−278.6
4o	Py	*iso*-Pr	Py	44	263–265	−342.7
4p	Py	*iso*-Pr	Thio	20	175–178	−82.9
4q	Py	Benzyl	Ph	50	239–243	−125.8
4r	Py	Benzyl	Py	28	272–275	−188.8
4s	Py	Benzyl	Thio	22	220–222	−94.5

Table 2. Influence of the catalyst on the product yield for macrolide **4a**

Catalyst	K_2CO_3	Et_3N	Pyridine	DMAP	Et_3N + DMAP	Pyridine + DMAP
Yield%	2	10	25	28	58	65

Table 3. Antibacterial and antifungal activity of the synthesized macrolides (the concentration used in the experiment, $C_{macrolide} = 0.2$ mg/L)

Compound	Bacterials[a]				Fungals[a]			
	E. coli	*B. subtilis*	*M. tetragenus*	*S. aureus*	*S. schenckii*	*M. gypseum*	*A. niger*	*C. globosum*
4a	+	+	+	+	+++	+++	++	++
4e	++	−	++	++	+++	++	+++	+++
4j	+	−	−	+	+++	++	++	++
4k	+	+	+	+	+++	++	++	+++
4m	++	+	++	++	+++	+++	+++	+++
4n	++	+	++	++	+++	+	+++	+++
4o	++	++	++	++	+++	+	+++	+++

+++, Bacteria or fungus are totally to be inhibited. ++, Almost to be inhibited. +, Only partially to be inhibited. –, The growth of the bacteria and fungus was not different from control.

[a] Culture temperature 25–37°C and times 1–6 days.

Table 4. MIC values of antifungal activity (mg/L)

Compound	*S. schenckii*	*M. gypseum*	*A. niger*	*C. globosum*
4e	0.20	0.25	0.20	0.13
4j	0.10	0.25	0.22	0.22
4k	0.10	0.25	0.22	0.20
4m	0.18	0.20	0.20	0.20

activity. The results of the tests are summarized in Table 3. The minimum inhibitory concentration (MIC) for the active compounds are listed in Table 4.

It is to be noted that the compounds synthesized are not active as antibacterial agents. However, a significant antifungal effect is demonstrated in some cases. It can be seen that, of the 19 macrocycles tested, seven possess antifungal activity. Macrocyclic compounds **4e**, **4j**, **4k** and **4m** show the best activity. Correlating the structure of the macrocycles to their antifungal activity revealed that the most active compound contains one pyridine and a thiophene moiety in the macrocycle. The best compound, **4m**, completely inhibited the growth of *Sporothrix schenckii*, *Microsporum gypseum*, *Aspergillus niger* as well as *Chaetonmium globosum*. The enhanced antifungal activity of this compound was attributed to the simultaneous presence of N and S heterocyclic subunits in the chiral macrolide.

Acknowledgements

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9. The following procedure was used for the synthesis of diol **3**: 0.01 mol of solid **2** was added to 15 ml CH_2Cl_2. After the solution was cooled, it was added dropwise to 60ml of CH_2Cl_2 solution containing 0.024 mmol chiral (*R* or *S*) 2-aminoethanol derivatives and 30 ml Et_3N over a period of 2 h. The mixture was allowed to react at 0°C for 4 h and at 25°C for an additional 4 h. The solid product that separated was washed with 20 ml H_2O, and a mixture of acetone and petroleum ether (7:3) 20 ml. By re-crystallization from methanol, diol **3** was obtained as white crystals. (yield $\sim$80%).
10. The following procedure was used for the synthesis of the macrolide **4**: A dry flask was charged with 1.2 mmol of compound **3** and 40 ml MeCN. On heating the system to 50°C and stirring magnetically, 2 ml Et_3N and 20 mg of DMAP was added. To the above system, 0.5 g compound **2** in 20 ml MeCN was added dropwise over a period of 1 h. The reaction solution was stirred for another 10 h. White solid, $Et_3N{\cdot}HCl$ formed, and was separated. The remaining solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel.
11. Compound **4m**: IR_{ν}, 3332, 3279, 3084, 2968, 2932, 2877, 1727, 1656, 1531, 1450, 1367, 1346, 1305, 1124, 1203, 1144, 1101, 1028, 997, 962, 842, 744, 664 cm^{-1}. ^1H NMR, δ_H: 0.97–1.03 (6H, t, $J=7.0$ Hz, CH_3), 1.71–1.93 (4H, m, CH_2), 4.12–4.17 (2H, m, CH), 4.35–4.38 (2H, dd, $J=4.0$, 10.5 Hz, CH_2O), 4.58–4.61 (2H, dd, $J=5.5$, 11.0 Hz, CH_2O), 7.76 (2H, s, thiophene-H), 8.14–8.17 (1H, dd, $J=7.0$, 8.0 Hz, Py-H), 8.25 (2H, d, $J=7.5$ Hz, Py-H), 8.32 (2H, d, $J=8.5$ Hz, CONH); ^{13}C, NMR, δ_C: 11.15, 25.53, 52.60, 66.08, 125.47, 133.25, 139.41, 139.62, 151.43, 160.72, 164.55; MS (FAB): 446 (*M*+1, 100%), 155, 111, 77, 55.