Synthesis of New Macrocyclic Ligands Containing Benzopyran System

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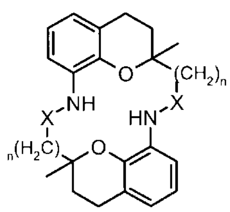
Since Pedersen reported the synthesis and cation-complexing properties of crown ethers,[1] there has been a growing interest in macrocyclic compounds as complexing agents for neutral organic substrates, inorganic and organic cations. Macrocyclic ligands have attracted considerable attention from a wide range of fields of organic, biological, and medicinal chemistry. Applications of macrocyclic ligands, including azacrown ethers,[2] lariat crown ethers,[3] and chiral macrocyclic ligands,[4] have been focused in areas such as host-guest complexation chemistry,[5] chiral recognition,[6] and chiral catalysis.

Benzopyran ring system is one of the most important privileged structures which has valuable and diverse biological properties.[7] Synthetic benzopyran derivatives exemplify the pharmacological importance of this heterocyclic structure such as a potassium channel opener.[8] In connection with research program for the development of cardiovascular drugs based on benzopyran ring system,[9] we tried to synthesize new macrocyclic ligands *via* dimerization of benzopyran derivative containing amine and carboxylic acid groups.

Our first designed target compounds are chiral or non-chiral macrocyclic azacrown ether type compounds as depicted in Figure 1. Interesting structural features are cyclic dimer of benzopyran derivative containing two amide moieties (**1**, **3**) or amine moieties (**2**, **4**). The cavity size and the shape of molecule can be varied by changing the length of alkyl chains. Moreover, the compounds can be further transformed to bicyclic cryptands or lariat crown ethers having side chains anchored at two nitrogen atoms. In this paper we would like to report the synthetic studies on chiral and non-chiral 14-membered macrocyclic ligands, **1** and **2**. We believe that these macrocyclic ligands may serve as a good candidate for metal complexation and chiral catalysis.

The synthetic pathway for the preparation of the key benzopyran derivatives **14**, **16** is described in Scheme 1. Nitration of 2'-hydroxyacetophenone with nitric acid in sulfuric acid gave an 1 : 1 ratio of inseparable mixture of *o*- and *p*-nitro compounds **6**. Without separation, the pyrrolidine-catalyzed Kabbe condensation[10] of nitro compound mixture with pyruvic aldehyde dimethylacetal provided the cyclized 4-chromanone compound mixture which were easily separated by recrystallization. Sodium borohydride reduction of compound **7** in methanol at 0 °C produced alcohol compound **8**. The benzopyran compound **9** was obtained by the conversion of alcohol compound **8** to mesylated derivative using methanesulfonyl chloride and Hünig base in CH_2Cl_2 followed by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene. Hydrolysis of acetal group of compound **9** with trifluoroacetic acid afforded aldehyde compound **10**. The carboxylic acid compound **12** was obtained from aldehyde **10** by oxidation to corresponding methyl ester **11** using iodine with potassium hydroxide in methanol[11] followed by hydrolysis with LiOH. To elongate the carbon chain by one carbon, Arndt-Eistert synthesis was performed.[12] After conversion of acid compound **12** to acid chloride with oxalyl chloride, treatment of acid chloride with diazomethane gave diazo ketone, which was converted to methyl ester **13** on treatment with silver benzoate and triethylamine in methanol. Reduction of the nitro group and double bond of compound **13** by catalytic hydrogenation provided corresponding amine compound **14**. The other coupling part, carboxylic acid **16**, was obtained from compound **14** by protection with carbobenzyloxy group[13] followed by hydrolysis of ester.

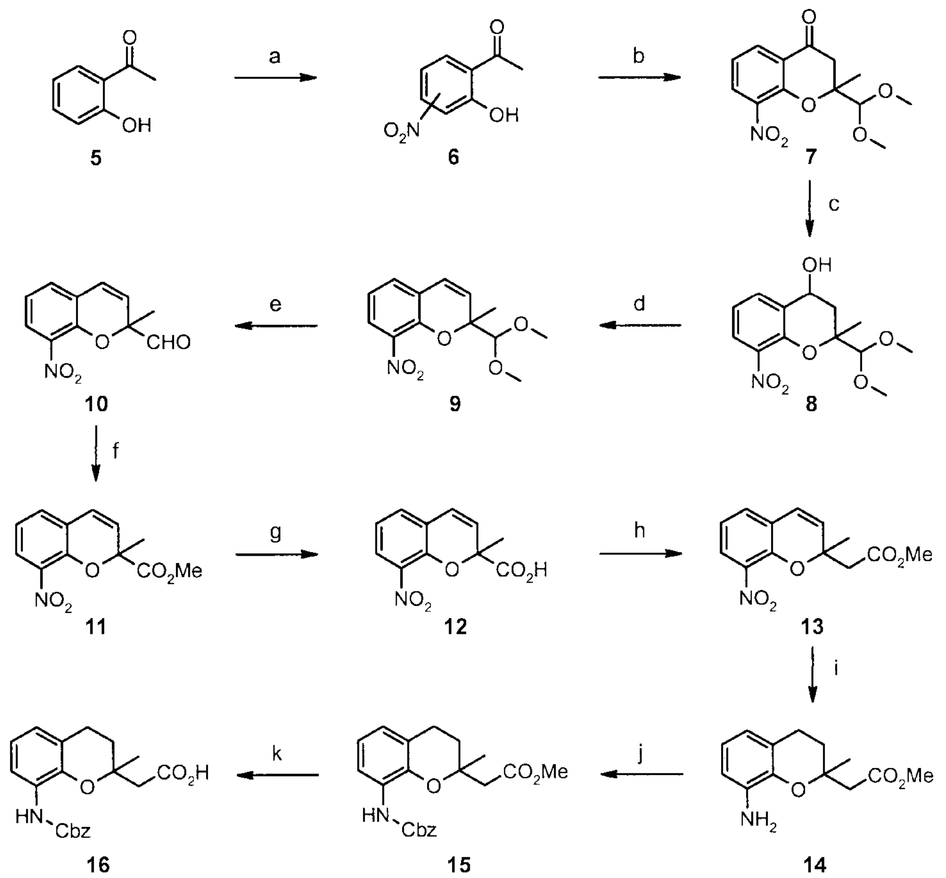


1 : n = 1, X = CO
2 : n = 1, X = CH_2
3 : n = 2, X = CO
4 : n = 2, X = CH_2

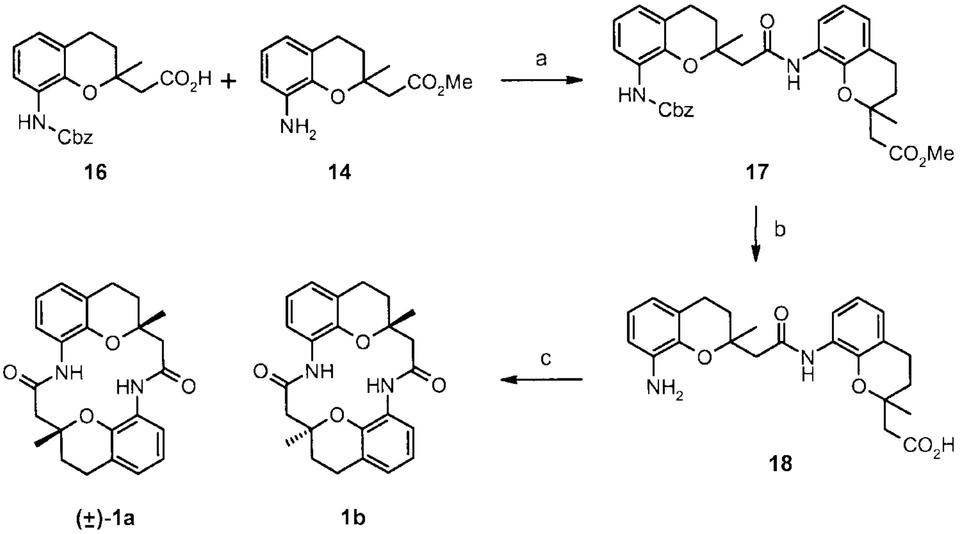
Figure 1

For the synthesis of macrocyclic ligands from benzopyran derivatives **14** and **16** containing carboxylic acid and amine functional groups respectively, amide formation was initially performed using DCC-HOBT in DMF to afford amide **17** as shown in Scheme 2. Deprotection of Cbz group in compound **17** by hydrogenolysis followed by hydrolysis of ester afforded amino acid compound **18**. Intramolecular cyclization reaction of compound **18** was carried out using DCC-HOBT condition initially. However, the cyclized product could not be isolated as a pure form due to contamination of dicyclohexylurea. The problem was easily resolved by using a water soluble coupling reagent, 3-ethyl-1-(3-dimethylaminopropyl)carbodidiimide hydrochloride (EDCI).[14] Although EDCI method gave the products in fairly good yield (70%), better yield (76%) was obtained by using Mukaiyama's reagent (PyS-SPy, PPh_3).[15] It is noteworthy that the above intramolecular cyclization methods do not require high dilution conditions.

The benzopyran moiety has one chiral center at C2 position. Therefore, the intramolecular cyclization reaction produced two diastereoisomers in 1 : 1 ratio which were



Scheme 1. *Reagents and conditions*: (a) HNO_3, H_2SO_4, -20 °C, 2 hr, 95%; (b) pyruvic aldehyde dimethylacetal, cat. pyrrolidine, toluene, reflux, 3 hr, 33% after separation; (c) $NaBH_4$, MeOH, 0 °C, 2 hr, 98%; (d) i) CH_3SO_2Cl, (i-Pr)$_2$NEt, CH_2Cl_2, rt, 15 hr, ii) DBU, toluene, reflux, 15 hr, 91%; (e) TFA-CH_2Cl_2 (1 : 1), rt, 8 hr; (f) I_2, KOH, MeOH, rt, 15 hr, two steps 60%; (g) 1 N LiOH, THF-H_2O, rt, 98%; (h) i) oxalyl chloride, cat. DMF, CH_2Cl_2, 2 hr, ii) CH_2N_2, Et_2O, 0 °C, 10 min, two steps 93%, iii) $PhCO_2Ag$, triethylamine, MeOH, 50 °C, 20 min, 76%; (i) H_2, cat. Pd/C, MeOH, 15 hr, 84%; (j) benzyl 2-pyridyl carbonate, DMF, 80 °C, 15 hr, 82%; (k) 1 N LiOH, THF-H_2O, 1 hr, 85%.



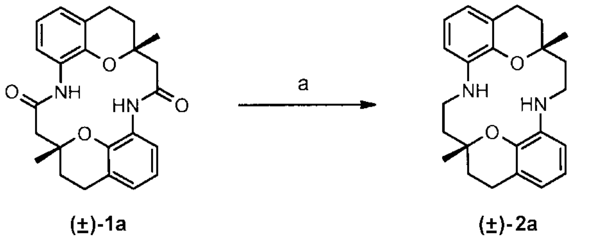
Scheme 2. *Reagents and conditions*: (a) DCC, HOBT, DMF, rt, 15 hr, 90%; (b) i) H_2, cat. Pd/C, MeOH, rt, 15 hr, 96%, ii) 1 N LiOH, THF-H_2O, rt, 1 hr, 85%; (c) PyS-SPy, Ph_3P, CH_3CN, reflux, 15 hr, 76% (1 : 1).

separable by chromatography. As shown in Scheme 2, one isolated product is an enantiomeric mixture (±)-**1a**, and the other is a *meso* compound **1b**. The above two isomers were subjected to the stereochemical structure determination, but it was difficult to determine the stereochemistry by spectroscopic means.

In an attempt to synthesize optically pure macrocyclization product, there was a need to resolve the compound **14**. After conversion of racemic amine compound **14** to amide with (R)-(α)-methoxyphenylacetic acid using DCC-HOBT coupling method, the diastereomeric mixture was separable by silica gel colum chromatography to give optically pure isomers **19** and **20**, respectively. Hydrolysis of amide **20** with 6 N HCl afforded enantiomerically pure amine compound **(-)-14**: $[\alpha]_D$ −44.8 (c 1, MeOH). Using same procedure as described in Scheme 2, the compound **(-)-14** was converted to the dimeric amide compound **(-)-18**, which was cyclized with Mukaiyama's reagent to afford enantiomerically pure macrocyclic ligand **(-)-1a**; $[\alpha]_D$ −94.4 (c 0.25, MeOH).

For the preparation of amine analogs, we tried to reduce the amide group of **(±)-1a** to amine with lithium aluminum hydride without success. However, treatment of amides compound **(±)-1a** with excess of borane[16] in THF at room temperature smoothly produced corresponding azacrown ether compounds **(±)-2a** as white solids in fairly good yields.

In summary, we designed and synthesized new chiral and non-chiral macrocyclic ligands containing benzopyran ring system. It may serve as a good candidate in future studies for metal complexation and chiral catalysis.



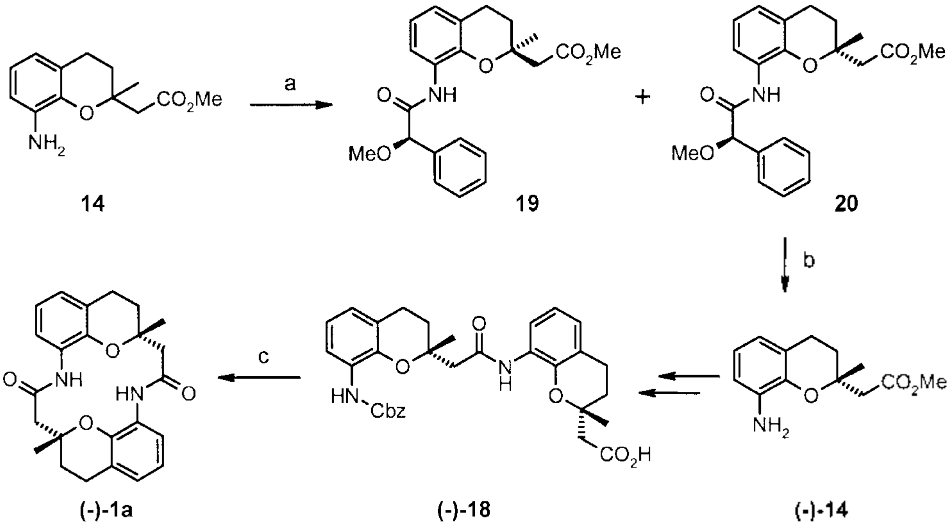
Scheme 4. *Reagents and conditions*: (a) BH_3, THF, rt, 40 min, 88%.

Experimental Section

All chemicals used were purchased from commerical sources and were used as received unless otherwise stated. IR spectra were recorded on a Mattson Genesis II FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 or a Varian Gemini 200 spectrometer. ^{13}C NMR were obtained on a Bruker AMX-500 spectrometer. Mass spectra were recorded on a micromass AutoSpec instrument.

{8-[2-(8-Benzyloxycarbonylamino-2-methylchroman-2-yl)acetylamino]-2-methylchroman-2-yl}acetic acid methyl ester (17). To a stirred solution of compound **14** (500 mg, 2.1 mmol) and compound **16** (824 mg, 2.3 mmol) in DMF (8 mL) were added 1-hydroxybenzotriazole hydrate (332 mg, 2.5 mmol) and 1,3-dicyclohexylcarbodiimide (500 mg, 2.1 mmol). The mixture was stirred at r.t. for 15 hr. Water (50 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue on solica gel (hexane/EtOAc, 2 : 1) afforded 1.10 g (90%) of **17**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H), 1.53 (s, 3H), 1.84-2.15 (m, 4H), 2.47 (s, 1H), 2.54 (s, 1H), 2.69-2.72 (m, 4H), 2.84 (m, 2H), 3.61 (s, 3H), 5.11 (d, J = 5.50 Hz, 1H), 6.78-6.91 (m, 4H), 7.34 (s, 6H), 7.99 (d, J = 7.33 Hz, 1H), 8.09 (s, 1H), 8.17 (d, J = 7.53 Hz, 1H). IR (NaCl) 744, 971, 1102, 1189, 1253, 1443, 1531, 1592, 1682, 1752, 2892, 2964, 3070, 3275, 3502 cm^{-1}. HRMS (EI): Calcd for $C_{33}H_{36}N_2O_7$, 572.2522; Found, 572.2523.

{8-[2-(8-Amino-2-methylchroman-2-yl)acetylamino]-2-methylchroman-2-yl}acetic acid (18). A solution of **17** (820 mg, 1.4 mmol) in methanol (10 mL) was hydrogenated for 15 hr at atmospheric pressure using 10% palladium on carbon catalyst (80 mg). The catalyst was filtered off, and the filtrate was concentrated. The crude product was chromatographed on silica gel (hexane/EtOAc, 2 : 1) to give amine compound (550 mg, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (d, 3H), 1.48 (s, 3H), 1.86-2.16 (m, 4H), 2.52 (s, 1H), 2.62 (s, 1H), 2.68-2.83 (m, 6H), 3.48 (b, 2H), 3.65 (d, J = 4.76 Hz, 3H), 6.52 (dd, J = 7.73 Hz, 2H), 6.69 (dd, J = 7.73



Scheme 3. *Reagents and conditions*: (a) (R)-(α)-methoxyphenylacetic acid, DCC, HOBT, DMF, rt, 15 hr, 96% (1 : 1), separation by chromatography, (b) 6 N HCl, MeOH, reflux, 15 hr; (c) PyS-SPy, Ph_3P, CH_3CN, reflux, 15 hr, 65%.

Hz, 1H), 6.77-6.88 (m, 2H), 8.10-8.15 (m, 2H). IR (NaCl) 731, 935, 1091, 1206, 1348, 1439, 1479, 1531, 1614, 1680, 1735, 2289, 2397, 2851, 2933, 2977, 3363, 3470 cm^{-1}. HRMS (EI): Calcd for $C_{25}H_{30}N_2O_5$, 438.2155; Found, 438.2148.

To a solution of amine compound (550 mg, 1.3 mmol) obtained above in THF-water (20 mL, 1 : 1), was added 1 N LiOH (2.6 mL, 2 eq). After stirring for 1 hr at r.t., the reaction mixture was neutralized with 1 N HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc, 1 : 2) to afford 511 mg (96%) of **18**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 4.88 Hz, 3H), 1.53 (s, 3H), 1.85-2.28 (m, 6H), 2.60-2.98 (m, 6H), 4.75 (b, 2H), 6.66-6.86 (m, 5H), 7.92-8.02 (m, 1H), 8.20 (s, 1H). IR (KBr) 730, 773, 932, 1090, 1208, 1348, 1442, 1478, 1535, 1614, 1678, 1721, 1810, 1905, 2551, 2931, 3043, 3365 cm^{-1}. HRMS (EI): Calcd for $C_{24}H_{28}N_2O_5$, 424.1998; Found, 424.1998.

Compound (±)-1a and 1b. A solution of compound **18** (511 mg, 1.2 mmol) in acetonitrile (3 mL) was added to a solution of 2,2'-dipyridyl disulfide (660 mg, 3.0 mmol) and triphenylphosphine (787 mg, 3.0 mmol) in acetonitrile (7 mL). The reaction mixture was heated at reflux for 14 hr cooled, and diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, dired, and concentrated. The residue was purified by silica gel chromatography (Hexane/EtOAc, 5 : 1) to give 186 mg (38%) of **(±)-1a** and 186 mg (38%) of **1b**. **(±)-1a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 6H), 1.88-2.00 (m, 4H), 2.74-2.98 (m, 8H), 6.81-6.93 (m, 4H), 8.25 (d, J = 9.73 Hz, 2H), 8.32 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.65, 21.72, 31.52, 51.31, 76.63, 18.19, 120.30, 120.41, 124.36, 126.89, 141.22, 167.40. IR (NaCl) 730, 773, 932, 1090, 1208, 1348, 1442, 1478, 1545, 1657, 1737, 2924, 3334 cm^{-1}. HRMS (EI): Calcd for $C_{24}H_{26}N_2O_4$, 406.1893; Found, 406.1885. **1b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 6H), 1.90-1.99 (m, 1H), 2.42 (s, 1H), 2.49 (s, 1H), 2.81-2.88 (m, 4H), 2.95 (s, 1H), 3.00 (s, 1H), 6.82-6.96 (m, 4H), 8.22 (s, 2H), 8.37 (d, J = 7.73 Hz, 2H). HRMS (EI): Calcd for $C_{24}H_{26}N_2O_4$, 406.1893; Found, 406.1880.

Compound (±)-2a. To a solution of compound **(±)-1a** (186 mg, 0.46 mmol) in tetrahydrofuran (6 mL) was added dropwise excess of borane (1.0 M solution in THF, 6 mL, 6.0 mmol). After stirring at r.t. for 40 min, the reaction mxiture was quenced by 1 N HCl (12 mL) with cooling, then heated to gentle reflux for 10 min. After dilution with water (60 mL) and addition of 1 N NaOH (12 mL), the mixture was extracted with ethyl acetate (100 mL), washed with water, and dried ($MgSO_4$). Concentration in vacuo gave the crude product, which was purified by flash column chromatography (Hexane/EtOAc, 6 : 1) to afford 153 mg (88%) of **(±)-2a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (s, 6H), 1.67-1.78 (m, 2H), 1.87-2.02 (m, 4H), 2.22-2.37 (m, 2H), 2.63-3.00 (m, 4H), 3.35-3.39 (m, 4H), 5.21 (b, 2H), 6.42 (d, J = 7.73 Hz, 4H), 6.78 (dd, J = 7.73 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.46, 21.8, 32.90, 39.63, 39.82, 77.59, 106.57, 116.74, 119.16, 120.11, 137.97, 140.22. IR (NaCl) 726, 762, 860, 928, 956, 1123, 1182, 1206, 1394, 1439, 1511, 1588, 1608, 2844, 2920, 3445 cm^{-1}. HRMS (EI): Calcd for $C_{24}H_{30}N_2O_2$, 378.2307; Found, 378.2300.

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