CONVENIENT PREPARATION OF CHIRAL DIPYRROLYLMETHANES CONTAINING A CHIRAL MOIETY

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Dedicated to Professor Štefan Toma on the occasion of his 70th birthday.

A variety of chiral bis-pyrroles have been made readily accessible via acid-catalyzed condensation of chiral ketones with pyrrole. Three representative chiral ketones **2**–**4** taken from the chiral pool were transformed into the corresponding bis-pyrrole derivatives in a straightforward acid-catalyzed condensation. Chiral β-hydroxy ketone derivatives, prepared through proline-catalyzed aldol condensation of acetone and an aldehyde, are readily transformed into the corresponding dipyrrolylmethane by the acid-catalyzed condensation carried out in the same conditions. The crystal structure of the chiral dipyrrolylmethane **2** derived from the (–)-menthone was determined.

Keywords: Dipyrromethanes; Pyrroles; Calixpyrroles; Chiral ketones; Organocatalysis; Proline; Aldol condensation.

The dipyrrolylmethane group is a versatile synthon widely used as a building block for the synthesis of expanded porphyrins[1] and calixpyrroles[2]. The seminal work by Sessler[3] and Gale[4] has marked important milestones in the use of calixpolypyrroles in host–guest chemistry and for molecular recognition of anions. Some dipyrrolylmethanes have found applications as flavors and food additives[5]. These compounds are generally obtained by acid-catalyzed addition of pyrrole or pyrrole derivatives to carbonyl compounds[6]. In coordination chemistry, dipyrrolylmethane has been proven to act as a versatile, dianionic ligand due to the η^1/η^5 bonding ability of the pyrrolide moiety[7]. Used in the chemistry of f-elements, this ligand has promoted unique reactive aggregates[8], capable of forming reactive clusters,

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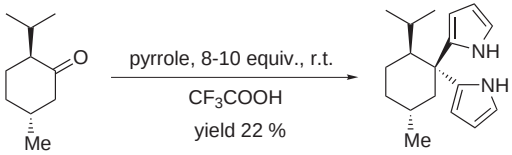
which efficiently stabilize highly reactive low-valent lanthanides, yet boosting the reactivity of the metal centers with respect to metallocene analogues[9]. Macrocyclic dipyrrolylmethane clusters of Sm(II), for example, are able to mediate the four-electron reduction of dinitrogen by the cooperative one-electron oxidation of four Sm(II) centers[10]. Gambarotta has described a few applications of dipyrrolylmethane ligands in the organometallic chemistry of highly reactive metals, such as thorium[11] and thulium[12] in low oxidation states. Love has described interesting complexes with early[13] and late[14] transition metals supported by dipyrrolylmethane ligands. In addition, he has reecently explored the preparation of binuclear macrocyclic clefts derived from dipyrrolylmethane[15] able to activate small molecule like dioxygen[16].

Although planar chiral dipyrrolylmethane ligands $[\eta^5\text{-}(C_4H_3N)(\eta^5\text{-}Cp^*Fe)]_2\text{-}CH_2$ described by Fu[17] have found interesting application in enantioselective catalysis[18], chiral dipyrrolylmethanes as ligands were scarcely considered[19]. Given the versatility of this class of compounds, it is surprising that chiral derivatives, to the best of our knowledge, remain unknown. Conversely, chiral dipyrrolylmethane derivatives may have an interesting potential since could be used in the preparation of chiral metal complexes as well as in the synthesis of chiral calixpyrrole derivatives[20]. As a part of our research program devoted to the study of new chiral calixpyrrole derivatives, we describe herein a simple access to chiral bis-pyrrole building blocks.

RESULTS AND DISCUSSION

As mentioned above, the coordination chemistry of dipyrrolylmethane has been explored with achiral derivatives readily available from aromatic and aliphatic ketones through acid-catalyzed condensation[10–18]. In order to study the synthesis of chiral dipyrrolylmethane derivatives, a suitable, commercially available chiral ketone was chosen. We have performed the reaction with (–)-menthone (**1**) under the reaction conditions employed with various aliphatic and aromatic ketones, without success in the isolation of the chiral dipyrrolylmethane. The condensation of (–)-menthone (**1**) with pyrrole was carefully investigated by varying the acid catalyst (HCl, $MeSO_3H$, TsOH, CF_3COOH, CH_3COOH), the solvents (EtOH, benzene, toluene, $CHCl_3$, AcOEt, CH_2Cl_2), and performing the reactions at various temperatures. We have found that strong acids (HCl, $MeSO_3H$), when used in an amount of 5–10%, can cause the formation of intractable red tars in pure pyrrole, while in other solvents, the formation of polypyrrole oc-

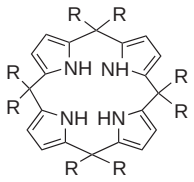
curred. Among the large variety of reaction conditions and solvents tested, we found that the most convenient synthetic route for the preparation of the desired chiral dipyrrolylmethane involves the use of pyrrole as solvent and trifluoroacetic acid as the acid catalyst, and performing the reaction at room temperature (Scheme 1).



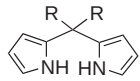
1 **2**

SCHEME 1

As reported by Sessler[3] and Gale[4], the condensation of pyrrole with ketones usually affords calixtetrapyrrole (Fig. 1) as the thermodynamically more stable compounds. In fact, under our optimized reaction conditions the yields of dipyrrolylmethane **2** are generally rather poor, ranging between 20 and 30%. In addition, it is known from literature that dipyrrolylmethanes are often contaminated by the formation of isolable tripyrrolylmethane[6b]. Nonetheless, in the case of the condensation between (–)-menthone and pyrrole both materials are inexpensive and available thus allowing large-scale preparations. The excess of pyrrole can be recovered by low-pressure distillation. The chiral 2,2′-(*p*-menthone-3,3-diyl)dipyrrole (**2**) can be isolated after chromatography and purified further by crystallization in pentane at –15 °C. Suitable crystals for the X ray structure determination were obtained by crystalization with pentane. Figure 2 presents two different views found in the asymmetric unit. Compound **2** crystallizes in the chiral space group $P2_12_12_1$, with two chemically equivalent and crystallographically independent molecules A and B in the asymmetric unit. The



calixtetrapyrrole



dipyrrolylmethane

FIG. 1
Calixtetrapyrrole and dipyrrolylmethane

two independent molecules are conformational isomers arising from different orientations of the isopropyl groups and pyrrole rings. In both conformations A and B molecules are involved in intermolecular N–H···π (pyrrole) hydrogen bonds with the formation of A···B pairs in the solid state.

In order to probe the generality of the reaction conditions we have tested other chiral carbonyl substrates such 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-3-hex-3-ribofuranose (**3**) derived from a carbohydrate and the steroid ketone 5α-cholestan-3-one (**4**), both commercially available (Scheme 2). In both cases we have successfully isolated the desired products **5** and **6** by flash chromatography.

The yields of **6** were particularly promising, giving the established potential of these derivatives for recognition chemistry of anions in membrane layers. Recently, Lee reported the preparation of strapped calixtetrapyrrole starting from the condensation of 4-hydroxy-butan-2-one[19]. The bis-pyrrole congener is an interesting building block for the preparation of functionalized bis- and calix[*n*]polypyrroles. Chiral 3-hydroxy ketones are suitable substrates for obtaining chelating bis-pyrroles in which the hydroxy group can act as either additional coordinating heteroatom or as a reactive function for incorporation of the chiral bis-pyrrole moiety into more complex architectures[20]. A convenient synthesis of chiral 3-hydroxy ketones could be realized taking considerable advantage from organocatalytic methodologies[21]. Syntheses of chiral β-hydroxy ketones were reported by List and Lerner, in their pioneering studies of the aldol condensation promoted by

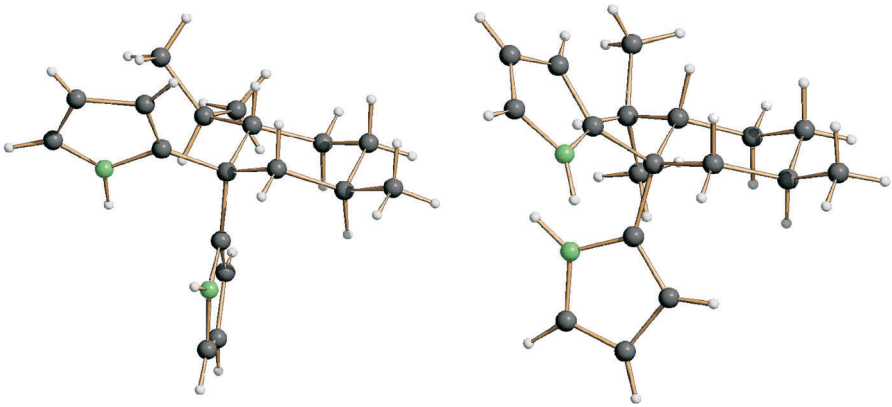
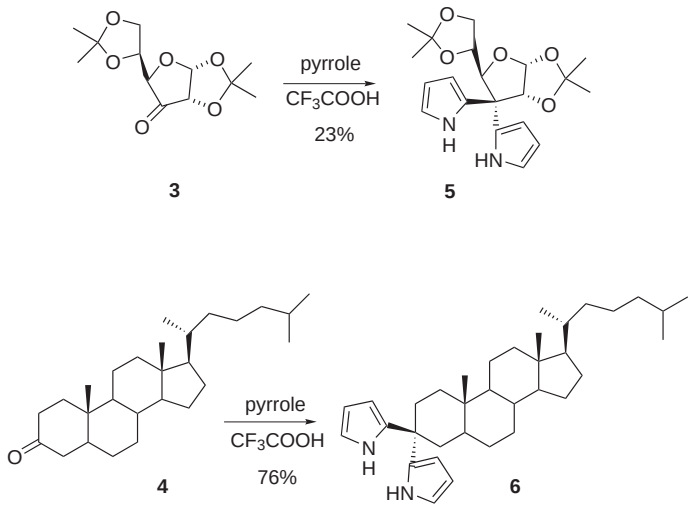


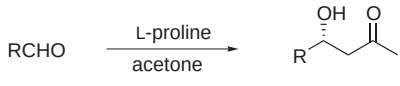
FIG. 2
Different view in the asymmetric unit of the chiral dipyrrolylmethane **2**



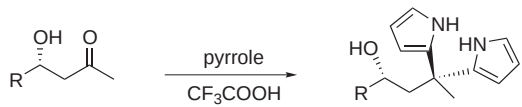
SCHEME 2

proline[22]. Several authors have now considerably expanded these findings[23], enlarging the scope of the reaction by subtle adjustments of the system. Many proline derivatives have been reported as enhancing the enantiomeric excesses of the reaction. In addition, the use of different solvents, such as water[24] or ionic liquids[25], have been tested in organocatalytic reactions. Finally, as the high loading of organocatalytic reaction sometimes hampered their application in industry, the supported proline has the advantage of being recyclable[26]. With the purpose of testing optically active β-hydroxy ketones in our condensation reaction, we have employed the conditions described by List, and performed the reaction with acetone in the presence of proline. The synthesis is inexpensive if acetone is used both as a solvent and a reagent. Also commercially available aldehydes can be used and proline acts as a catalyst. By enhancing the scale, we have prepared the hydroxy ketones illustrated in Scheme 3 in moderate enantiomeric excesses. The optically active ketones were subjected to the CF_3COOH-promoted acid condensation in neat pyrrole, and the compounds **11**–**14** were isolated after chromatographic purification. HPLC analysis performed with compounds **13** and **14** confirmed the retention of enantiomeric excess during the acid-catalyzed condensation. The isolated yields were in the range of those obtained with other chiral ketones. As reported by Lee for his preparation of calixpyrrole, the acid-catalyzed condensation could be performed with unprotected alcohols, also using CF_3COOH and neat pyrrole.

As many other organocatalytic reactions have been introduced in recent years for the synthesis of a plethora of chiral carbonyl derivatives, our condensation reaction could be, in principle, applied to other highly functionalized enantio-enriched carbonyl derivatives[27]. It is worthy to emphasize that the condensation with pyrrole could be performed under very mild conditions, using only catalytic amounts of CF_3COOH. The acid is quenched with an addition of Et_3N or simply evaporated under reduced pressure. The pyrrole used in excess is recovered from the reaction mixture by a simple distillation. No inert conditions and nitrogen atmosphere are required.



	R	%	ee%
7	Ph	46	68
8	4-$O_2NC_6H_4$	48	76
9	cyclohexyl	42	42
10	1-naphthyl	48	70



	R	%
11	Ph	23
12	4-$O_2NC_6H_4$	22
13	cyclohexyl	15
14	1-naphthyl	34

SCHEME 3

We have described a straightforward preparation of chiral bis-pyrrole derivatives, potentially useful building blocks in coordination chemistry, chiral recognition and asymmetric synthesis using an acid-catalyzed condensation performed in neat pyrrole. Different enantiopure ketones from the chiral pool, and enatio-enriched β-hydroxy ketones undergoes the acid-catalyzed condensation, affording the desired products in low to moderate yields. The use of these chiral building blocks in preparation of chiral calixtetrapyrrole will be the focus of further investigations.

EXPERIMENTAL

^{1}H NMR spectra were measured on Varian 220 and 300 MHz spectrometers. Chemical shifts are reported in ppm (δ-scale) from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shifts, multiplicity, coupling constants (*J*) in Hz. ^{13}C NMR spectra were recorded on a Varian 50 MHz and Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm (δ-scale) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was made with 240–400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett–Packard HP 6890 gas chromatograph, with a flame ionization detector and split-mode capillary injection system, using a crosslinked 5% PH ME Siloxane (30 m) column. Analytical high performance liquid chromatography (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm), using a Daicel Chiralcel™ OD column (0.46 × 25 cm) (Daicel Inc.) and a Daicel Chiralcel™ AD column (0.46 × 25 cm) (Daicel Inc.). HPLC grade isopropyl alcohol and hexane were used as the eluting solvents. IR spectra (wavenumbers in cm^{-1}) were measured on a FT-IR Nicolet 380 spectrometer. All the reactions were carried out under nitrogen atmosphere in flame-dried glassware, using standard inert techniques to introduce reagents and solvents. All ketones were used as received. All the aldehydes were distilled under reduced pressure prior to their use. CF_3COOH and pyrrole were used as received. Anhydrous CH_2Cl_2, diethyl ether, toluene and THF were purchased from Fluka (SureSeal bottle).

2,2′-(*p*-Menthone-3,3-diyl)dipyrrole (**2**)

CF_3COOH (0.6 ml) was added to a solution of (–)-menthone (3.5 g) in pyrrole (6.5 ml) and the reaction mixture was stirred at room temperature for 72 h. The reaction was quenched by the addition of Et_3N (0.5 ml) and the excess pyrrole evaporated under reduced pressure. The crude residue was carefully purified by flash chromatography (cyclohexane–Et_2O 9:1–8:2) and the resulting yellow oil was dissolved in a minimum amount of pentane. The solution was kept at –15 °C for 5 days affording white crystals of **2**. Yield 23%; m.p. 90 °C; $[\alpha]_D$ –9.5 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 7.83 bs, 1 H (NH); 7.78 bs, 1 H (NH); 6.66–6.62 m, 2 H (pyrrole); 6.31–6.29 m, 1 H (pyrrole); 6.18–6.13 m, 2 H (pyrrole); 6.03–6.00 m, 1 H (pyrrole); 2.22–1.90 m, 1 H; 2.10 sept, 1 H, *J* = 6.6 (MeCHMe); 1.92 m, 1 H; 1.90–1.80 m, 2 H; 1.60–1.30 m, 3 H; 1.00–0.90 m, 1 H; 0.88 d, 6 H, *J* = 6.6 (CH_3); 0.26 d, 3 H, *J* = 6.6 (CH_3). ^{13}C NMR (50 MHz, $CDCl_3$,): 139.8, 133.4, 116.1, 115.9, 108.3 (2 C); 103.6 (2 C); 51.2, 49.9, 45.5, 35.4, 29.6, 27.9, 24.2, 23.0, 22.8, 17.5. For $C_{18}H_{26}N_2$ (270.4) calculated: 79.95% C, 9.69% H, 10.36% N; found: 79.89% C, 9.60% H, 10.44% N.

Compound **5**

A mixture of pyrrole (0.432 ml, 6.2 mmol) and ketone 3 (0.4 g, 1.56 mmol) was treated with CF_3COOH (0.11 ml), which was added dropwise into the reaction vessel. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched by the addition of Et_3N (0.1 ml) and the excess pyrrole evaporated under reduced pressure. The residue was carefully purified by flash chromatography (diethyl ether) to give a yellow solid. Yield 0.135 g (23%); m.p. 130 °C; $[\alpha]_D$ +101 (*c* 0.54, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 9.40 bs, 1 H (NH); 8.40 bs, 1 H (NH); 6.77–6.67 m, 2 H (pyrrole); 6.25–6.17 m, 2 H (pyrrole);

6.07–6.05 m, 1 H (pyrrole); 6.00 d, 1 H, *J* = 3.2 (pyrrole); 4.89 d, 1 H, *J* = 3.4 (CHO); 4.58 d, 1 H, *J* = 8 (CHO); 3.85–3.61 m, 4 H; 1.35 s, 6 H (Me); 1.54 s, 6 H (Me). ^{13}C NMR (50 MHz, $CDCl_3$): 129.1, 127.9, 117.4, 117.2, 112.3, 108.4, 108.3, 108.2, 107.0, 104.3 (2 C); 87.2, 81.8, 70.6, 64.5, 54.7, 26.9, 26.8, 26.3 (2 C). IR (Nujol): 2921, 2843, 1459, 1371, 1090. For $C_{20}H_{26}N_2O_5$ (374.4) calculated: 64.15% C, 7.00% H, 7.48% N; found: 64.10% C, 6.93% H, 7.39% N.

Compound **6**

A mixture of pyrrole (0.430 ml, 6.2 mmol) and ketone 4 (0.3 g, 0.78 mmol) was treated with CF_3COOH (0.045 ml, 0.58 mmol), which was introduced dropwise into the reaction vessel. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched by the addition of Et_3N (0.1 ml) and the excess pyrrole evaporated under reduced pressure. The residue was carefully purified by chromatography (cyclohexane–Et_2O 7:3) to give a yellow solid. Yield 0.33 g (78%); m.p. 150 °C; $[\alpha]_D$ +35.3 (*c* 0.92, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 7.85 bs, 1 H (NH); 7.60 bs, 1 H (NH); 6.71–6.69 m, 1 H (pyrrole); 6.52–6.50 m, 1 H (pyrrole); 6.22–6.19 m, 2 H (pyrrole); 6.11–6.08 m, 1 H (pyrrole); 6.02–6.00 m, 1 H (pyrrole); 2.20–1.00 m, 34 H; 0.90–0.85 m, 12 H. ^{13}C NMR (50 MHz, $CDCl_3$,): 141.1, 135.0, 117.1, 116.1, 107.8, 106.4, 101.6 (2 C); 56.4, 56.2, 53.9, 42.5, 42.0, 39.9, 39.5, 36.1, 36.0, 35.9, 35.8, 35.4, 35.3, 32.9, 31.7, 28.6, 28.2, 27.9, 24.1, 23.8, 22.8, 22.5, 20.8, 18.6, 12.1, 12.0. IR (neat): 2929, 2843, 1460, 1382. For $C_{35}H_{54}N_2$ (502.8) calculated: 83.60% C, 10.82% H, 5.57% N; found: 83.52% C, 10.79% H, 5.52% N.

Preparation of Hydroxy Ketones **7**, **8**, **9** and **10**

Compounds **7**–**10** were obtained following the general procedure described by List and Barbas[22].

(4R)-4-Hydroxy-4-phenylbutan-2-one **7**. Yield 46%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.20–7.10 m, 5 H (Ph); 4.95 m, 1 H (PhC**H**OH); 3.78 bs, 1 H (OH); 2.65 m, 2 H (C**H**$_2$CHOH); 2.00 s, 3 H (CH_3). HPLC (Daicel OJ, hexane–*i*-PrOH 95:5, flow rate 1 ml/min) t_R(major) 35.76 min, t_R(minor) 38.50 min; ee 58%.

(4R)-4-Hydroxy-(4-nitrophenyl)butan-2-one **8**. Yield 48%. ^{1}H NMR (200 MHz, $CDCl_3$): 8.20 d, 2 H, *J* = 7.0 (Ar); 7.52 d, 2 H, *J* = 7 (Ar); 5.25 m, 1 H (ArC**H**OH); 3.56 d, 1 H, *J* = 3.2 (OH); 2.83 m, 2 H (C**H**$_2$CHOH); 2.21 s, 3 H (CH_3). HPLC (Daicel AD hexanes–*i*-PrOH 97:3, flow rate 1 ml/min) t_R(major) 18.76 min, t_R(minor) 22.56 min; ee 74%.

(4*R*)-4-Cyclohexyl-4-hydroxybutan-2-one **9**

Cyclohexanecarbaldehyde (0.36 ml, 3 mmol) was added to a suspension of L-proline (0.1 g, 0.9 mmol) in acetone (2 ml). The reaction mixture was stirred at room temperature for 48 h and then quenched with a saturated solution of NH_4Cl. The mixture was diluted with diethyl ether (10 ml) and the organic phase was separated. The aqueous phase was extracted with diethyl ether. The combined organic phases were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (cyclohexane–Et_2O 1:1). Yield 0.19 g (42%). ^{1}H NMR (200 MHz, $CDCl_3$): 3.80 m 1 H (CHC**H**OH); 2.89 bs, 1 H (OH); 2.55 m, 2 H (C**H**$_2$CHOH); 2.18 s, 3 H (CH_3); 1.77–1.62 m, 5 H; 1.25–0.97 m, 6 H. HPLC (Daicel AD, hexane–*i*-PrOH 97:3), flow rate 1 ml/min, t_R(major) 12.94 min, t_R(minor) 15.30 min; ee 74%.

(4R)-4-Hydroxy-4-(1-naphthyl)butan-2-one **10**. Yield 48%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.82 m, 4 H (Ar); 7.45 m, 3 H (Ar); 5.34 m, 1 H (CHC**H**OH); 3.44 bs, 1 H (OH); 2.95 m, 2 H (C**H**$_2$CHOH); 2.21 s, 3 H (CH_3). HPLC (Daicel AD, hexanes–*i*-PrOH 92.5:7.5), flow rate 1 ml/min, t_R(major) 18.64 min, t_R(minor) 22.85 min; ee 73%.

Synthesis of Compounds **11**–**14**. General Procedure

CF_3COOH (0.2 mmol) was added at room temperature to a mixture of hydroxy ketone (2 mmol) in pyrrole (14 mmol). The temperature of the reaction mixture increased immediately and pyrrole started refluxing in the flask. The mixture was stirred for additional 24 h and then quenched with 1 M NaOH (10 ml). After extraction with CH_2Cl_2, the solvent was evaporated under reduced pressure and the excess of pyrrole removed by distillation at low pressure. The residue was purified by flash chromatography (cyclohexane–Et_2O) giving the desired dipyrrolylmethane derivatives.

Compound **11**. Yield 23%; $[\alpha]_D$ +8.8 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 10.29 bs, 1 H (NH); 10.4 bs 1 H (NH); 7.30–7.20 m, 5 H (Ph); 6.72–6.54 m, 2 H (pyrrole); 6.22–6.18 m, 4 H (pyrrole); 4.80–4.78 m, 1 H (CHC**H**OH); 2.48 dd, 1 H, *J* = 14.8, 9.6 (C**H**$_2$CHOH); 2.26 dd, 1 H, *J* = 14.8, 2.6 (C**H**$_2$CHOH); 2.08 bs, 1 H (OH); 1.78 s, 3 H (CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 145.1, 137.5, 136.9, 128.3, 127.2, 125.5, 117.3, 117.1, 107.9, 107.8, 100.7 (2 C); 71.6, 50.8, 38.7, 28.1. IR (Nujol): 2924, 2851, 1550, 1470, 1379. For $C_{18}H_{20}N_2O$ (280.4) calculated: 77.11% C, 7.19% H, 9.99% N; found: 77.15% C, 7.65% H, 9.91% N.

Compound **12**. Yield 22%; $[\alpha]_D$ +6.8 (*c* 0.74, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 10.29 bs, 1 H (NH); 10.4 bs, 1 H (NH); 8.17 d, 2 H, *J* = 8.8 (Ar); 7.42 d, 2 H, *J* = 8.8 (Ar); 6.72–6.68 m, 2 H (pyrrole); 6.22–6.14 m, 4 H (pyrrole); 4.93–4.87 m, 1 H (CHC**H**OH); 2.46 dd, 1 H, *J* = 14.8, 9.2 (C**H**$_2$CHOH); 2.27 dd, 1 H, *J* = 14.6, 2.2 (C**H**$_2$CHOH); 2.10 bs, 1 H (OH); 1.77 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 147.1, 140.0, 132.4, 133.3, 128.5, 123.7, 117.4, 117.2, 108.1, 107.8, 104.4, 103.1, 68.5, 51.2, 30.3, 27.4. IR (neat): 2918, 2845, 1464, 1372. For $C_{18}H_{19}N_3O_3$ (325.4) calculated: 66.45% C, 5.89% H, 12.91% N; found: 66.48% C, 5.86% H, 12.84% N.

Compound **13**. Yield 15%; $[\alpha]_D$ –6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 8.22 bs, 2 H (NH); 6.68–6.63 m, 2 H (pyrrole); 6.16–6.11 m, 4 H (pyrrole); 3.60–3.51 m, 1 H (CHC**H**OH); 2.20–2.00 m, 3 H (C**H**$_2$CHOH, OH); 1.80–1.60 m, 5 H; 1.67 s, 3 H (CH_3); 1.40–1.00 m, 6 H. ^{13}C NMR (75 MHz, $CDCl_3$): 136.8, 136.3, 117.4, 117.1, 108 (2 C); 104.8, 104.2, 67.6, 45.5, 44.6, 42.9, 38.3, 28.9, 28.3, 27.6, 26.8, 26.5. HPLC (Daicel AD, hexanes–*i*-PrOH 99.05:05 to 90:10 in 20 min), flow rate 0.7 ml/min, t_R(major) 16.25 min, t_R(minor) 20.29 min; ee 74%. IR (neat): 3388, 3098, 2932, 2839, 1560, 1454, 1255, 1089, 1029. For $C_{18}H_{26}N_2O$ (286.4) calculated: 75.48% C, 9.15% H, 9.78% N; found: 75.51% C, 9.10% H, 9.72% N.

Comound **14**. Yield 34%; $[\alpha]_D$ + 7.4 (*c* 0.74, acetone). ^{1}H NMR (200 MHz, $CDCl_3$): 10.2 bs, 2 H (NH); 7.80–7.40 m, 7 H (Ar); 6.73–6.60 m, 2 H (pyrrole); 6.20–6.15 m, 4 H (pyrrole); 4.94–4.85 m, 2 H (CHC**H**OH, OH); 2.56 dd, 1 H, *J* = 14.6, 9.2 (C**H**$_2$CHOH); 2.40 dd, 1 H, *J* = 14.6, 2.5 (C**H**$_2$CHOH); 1.78 s, 3 H (CH_3). ^{13}C NMR (50 MHz, DMSO): 145.7, 139.8, 138.1, 133.3, 132.5, 128.0, 127.8, 126.2, 125.7, 125.1, 123.9, 117.1, 116.9, 106.8, 106.7, 104.9, 103.9, 70.8, 50.9, 31.1, 26.5. HPLC (Daicel AD, hexanes–*i*-PrOH 99.5:0.5 to 90:10 in 20 min), flow rate 0.7 ml/min, t_R(major) 30.82 min, t_R(minor) 40.39 min; ee 73%. IR (Nujol): 2931, 2847, 1461, 1371, 1095. For $C_{22}H_{22}N_2O$ (330.4): 79.97% C, 6.71% H, 8.48% N; found: 80.00% C, 6.68% H, 8.44% N.

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REFERENCES AND NOTES

1. a) Jasat A., Dolphin D.: *Chem. Rev.* **1997**, *97*, 2267; b) Lee C.-H., Lisdey J. S.: *Tetrahedron* **1994**, *50*, 11427; c) Burrel A. K., Officer D. L., Plieger P. G., Reid D. C.-W.: *Chem. Rev.* **2001**, *101*, 2751.
2. Baeyer A.: *Ber Dtsch. Chem. Ges.* **1886**, *19*, 2184.
3. a) Gale P. A., Sessler J. L., Král V., Lynch V.: *J. Am. Chem. Soc.* **1996**, *118*, 5140; b) Gale P. A., Sessler J. L., Král V.: *Chem. Commun.* **1998**, 1; c) Allen W. E., Gale P. A., Brown C. T., Lynch V. M., Sessler J. M.: *J. Am. Chem. Soc.* **1996**, *118*, 12471; d) Miyaji H., Sato W., Sessler J. L.: *Angew. Chem., Int. Ed.* **2000**, *39*, 1777; e) Anzenbacher P., Jr., Jursíková K. K., Sessler J. L.: *J. Am. Chem. Soc.* **2000**, *122*, 9350; f) Sessler J., Gross D. E., Cho W.-S., Lynch V. M., Schmidtchen F. P., Bates G. W., Light M. E., Gale P. A.: *J. Am. Chem. Soc.* **2006**, *128*, 9350.
4. a) Gale P. A.: *Coord. Chem. Rev.* **2000**, *199*, 181; b) Gale P. A.: *Coord. Chem. Rev.* **2001**, *213*, 79; c) Beer P. D., Gale P. A.: *Angew. Chem., Int. Ed.* **2001**, *40*, 486.
5. a) Stoll M., Winter M., Gautschi F., Flamment L., Willhalm B.: *Helv. Chim. Acta* **1967**, *50*, 628; b) Frattini C., Bicchi C., Barettini C., Nano G. M.: *J. Agric. Food Chem.* **1977**, *25*, 1238; c) Shimoda M., Shibamoto T.: *J. Agric. Food Chem.* **1990**, *38*, 802.
6. a) Sobral A. J. F. N., Rebanda N. G. C. L., da Silva M., Lampreia S. H., Ramos Silva M., Matos Beja A., Paixão J. A., Rocha Gonsalves A. M. dA.: *Tetrahedron Lett.* **2003**, *44*, 3971. For the condensation of pyrrole to aldehydes, see: b) Biaggi C., Benaglia M., Raimondi L., Cozzi F.: *Tetrahedron* **2006**, *62*, 12375; and references therein. For a recent synthesis of dipyrrolylmethane in water, see: c) Král V., Vašek P., Dolenský B.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 1126.
7. a) Floriani C.: *Chem. Commun.* **1996**, 1257; b) Dubé T., Gambarotta S., Yap G. P. A.: *Angew. Chem., Int. Ed.* **1999**, *38*, 432.
8. a) Ganesan M., Bérubé C. D., Gambarotta S., Yap G. P. A.: *Organometallics* **2002**, *21*, 1707; b) Dubé T., Freckmann D., Conoci S., Gambarotta S., Yap G. P. A.: *Organometallics* **2000**, *19*, 209; c) Dubé T., Gambarotta S., Yap G. P. A.: *Organometallics* **2000**, *19*, 817.
9. Ganesan M., Gambarotta S., Yap G. P. A.: *Angew. Chem., Int. Ed.* **2001**, *40*, 766.
10. Dubé T., Conoci S., Gambarotta S., Yap G. P. A., Vasapollo G.: *Angew. Chem., Int. Ed.* **1999**, *38*, 3657.
11. Arunachalampillai A., Gambarotta S., Korobkov I.: *Can. J. Chem.* **2005**, *86*, 832.
12. Korobkov I., Aharonian G., Gambarotta S., Yap G. P. A.: *Organometallics* **2002**, *21*, 4899.
13. Novak A., Blake A. J., Wilson C., Love J. B.: *Chem. Commun.* **2002**, 2796.
14. Reid S. D., Blake A. J., Köckenberger W., Wilson C., Love J. B.: *Dalton Trans.* **2003**, 4387.
15. Givaja G., Volpe M., Leeland J. W., Edwards M. A., Young T. K., Darby S. B., Reid S. D., Blake A. J., Wilson C., Wolowska J., McInnes E. J. L., Schröder M., Love J. B.: *Chem. Eur. J.* **2007**, *13*, 3707.
16. Gonzalo G., Manuel V., Edwards M. A., Blake A. J., Wilson C., Schröder M., Love J. B.: *Angew. Chem., Int. Ed.* **2007**, *46*, 584.
17. Fu G. C.: *Acc. Chem. Res.* **2006**, *39*, 853.

18. Maier T. C., Fu G. C.: *J. Am. Chem. Soc.* **2006**, *128*, 4594; and references therein.
19. a) Yoon D.-W., Hwang H., Lee C.-H.: *Angew. Chem., Int. Ed.* **2002**, *41*, 1757. Chiral atropisomeric racemic calixtetrapyrroles were prepared, see: b) Anzenbacher P., Jr., Jursíková K., Lynch V. L., Gale P. A., Sessler J. L.: *J. Am. Chem. Soc.* **1999**, *121*, 11020; c) Bonomo L., Solari E., Toraman G., Scopelliti R., Latronico M., Floriani C.: *Chem. Commun.* **1999**, 2413.
20. A Binol-strapped calixtetrapyrrole as a receptor for enantioselective recognition was recently described by Lee, see: Miyaji H., Hong S.-J., Jeong S.-D., Yoon D.-W., Na H.-K., Hong J., Ham S., Sessler J. L., Lee C.-H.: *Angew. Chem., Int. Ed.* **2007**, *46*, 2508.
21. List B.: *Chem. Commun.* **2006**, 819.
22. a) List B., Lerner R. A., Barbas C. F.: *J. Am. Chem. Soc.* **2000**, *122*, 2395. For an improved method, see: b) Tang Z., Jiang F., Yu L.-T., Cui X., Gong L.-Z., Mi A.-Q., Jiang Y.-Z., Wu Y.-D.: *J. Am. Chem. Soc.* **2003**, *125*, 5262.
23. Berkessel A., Groger H.: *Asymmetric Organic Catalysis*. Wiley-VCH, Weinheim 2005.
24. Mase N., Nakai Y., Ohara N., Yoda H., Takabe K., Tanaka F., Barbas III C. F.: *J. Am. Chem. Soc.* **2006**, *128*, 734.
25. a) Mečiarová M., Toma Š.: *Chem. Eur. J.* **2007**, *13*, 1268; b) Mečiarová M., Toma Š., Kotrusz P.: *Org. Biomol. Chem.* **2006**, *4*, 1420; c) Kotrusz P., Alemayehu S., Toma Š., Schmalz H.-G., Adler A.: *Eur. J. Org. Chem.* **2005**, 4904; d) Kotrusz P., Toma Š., Schmalz H.-G., Adler A.: *Eur. J. Org. Chem.* **2004**, 1577; e) Kotrusz P., Kmentová I., Gotov B., Toma Š., Solčániová E.: *Chem. Commun.* **2002**, 2510.
26. Benaglia M.: *New J. Chem.* **2006**, *30*, 1525.
27. a) Paras N. A., MacMillan D. W. C.: *J. Am. Chem. Soc.* **2001**, *123*, 4370; b) Marigo M., Jørgensen K. A.: *Chem. Commun.* **2006**, 2001.