# First Synthesis of 1-Phenyl-3-pyrrol-1-ylindan-2-carboxylic Acid, a New Scaffold of Potential Non-peptide Endothelin Receptor Antagonists

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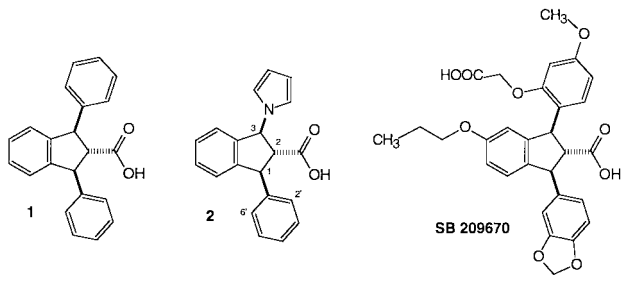
**Abstract:** The first synthesis of *trans*,*trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid, a key-intermediate in the access to new potential non-peptide endothelin receptor antagonists, is reported.

**Key words:** 1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid, non-peptide antagonist, endothelin receptor

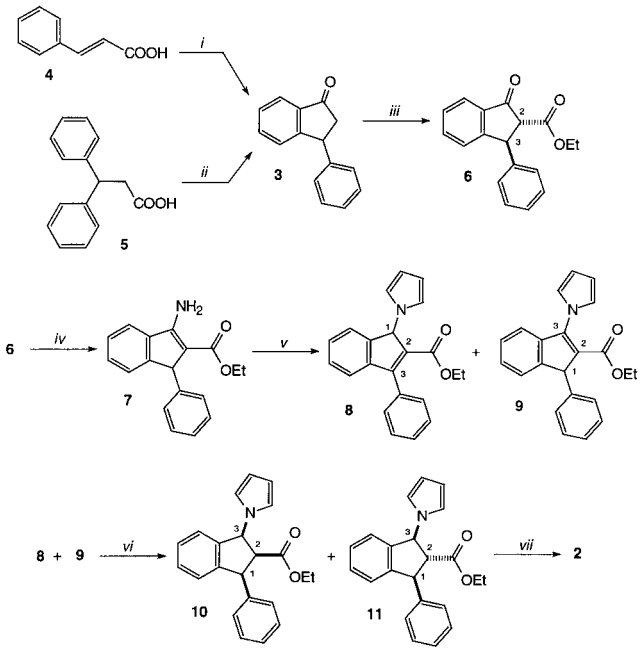
The endothelins (ETs), discovered in 1988, are a family of three isopeptides (ET-1, ET-2 and ET-3) encoded in the human genome. The potent smooth muscle vasoconstrictor activity exerted by endothelins, through selective binding of the ETa/ETb receptors, is suggestive of an important role in cardiovascular and pulmonary diseases.[1] Thus, an intense effort has been exerted by many research groups to prepare antagonists of the two fully characterized endothelin receptors.[2] Recently, the 1,3-diarylindan-2-carboxylic acid **(1)** motif has been described as a useful scaffold to build new potent and selective non-peptide endothelin receptor antagonists such as 3-[2-carboxymethoxy)-4-methoxyphenyl]-1-[3,4-(methylenedioxy)phenyl]-5-(prop-1-yloxy)indan-2-carboxylic acid (**SB 209670**).[3]

In this paper, we reported an efficient synthesis of *trans*,*trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid **(2)**, a scaffold for potential bioisosteres of **1** by replacement of the phenyl by a pyrrole nucleus (Scheme 1).




**Scheme 1**

The synthesis of carboxylic acid **2** was achieved according to the following sequence. The previously reported 3-phenylindan-1-one **(3)** was prepared either by condensation between benzene and cinnamic acid **(4)** in the presence of aluminium chloride[4] or by cyclization of commercial 3,3-diphenylpropionic acid **(5)** using polyphosphoric acid (PPA).[5] Compound **3** was then reacted with ethyl carbonate giving ethyl 1-oxo-3-phenylindane-2-carboxylate **(6)**.[6] The *trans* structure of **6** was caracterized by $^1$H NMR and coupling constants of 4.90 Hz were measured for the H-2 and H-3 protons. The new enaminoester **7** was prepared in 94% yield starting from **6** by using large excess of ammonium acetate in refluxing ethanol. The reaction of **7** according to the Clauson-Kaas reaction with 2,5-dimethoxytetrahydrofuran (2,5-diMeOTHF) in refluxing 1,4-dioxane with 4-chloropyridine hydrochloride as catalyst yielded a mixture of the isomers **8** and **9**, presumably due to a thermal [1,3] sigmatropic rearrangement.[7] Compounds **8** and **9** have been separated by chromatography on silica gel and the position of the indene double bond was determined by $^1$H NMR on the basis of previous results of the indene series.[8] In fact, compound **8** showed one singlet for H-1 at 5.97 ppm, whereas proton H-1 for derivative **9** was present at 4.94 ppm. Hydrogenation of the indenes **8** and **9** at room temperature using $NaBH_4$-$NiCl_2$, $6H_2O$[9] provided ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylate as a mixture of the all-*cis* **10** and all-*trans* **11** epimers. A sample of the two diastereomers **10** and **11** was readily separated by chromatography and their relative stereochemistry was confirmed from NOE spectra. Irradiation of H-2 in **10** led to an NOE with both H-1 and H-3, while similar irradiation of H-2 in C-2-*epi* **11** failed to show an NOE with either H-1 or H-3. These observations support the all-*cis* arrangement of H-1, -2 and -3 in **10** and are in accordance with a *trans* stereochemical relationship between H-2 and H-1 and H-3 in C-2-*epi* **11**. The crude mixture of **10** and **11**, when subjected to treatment with aqueous base, underwent epimerization at C-2 and saponification to afford the *trans*-*trans* 1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid **2** (Scheme 2). Assignment of the relative configuration of **2** was also made on the basis of NOE experiments. Specifically, irradiation of H-2 in **2** led to an NOE with H-2' and H-6' of the 1-phenyl group and H-α of the pyrrole. These observations were consistent with a *trans* stereochemical relationship between H-2 and the hydrogens 1 and 3 in **2** (Scheme 1).



**Scheme 2** Reagents: *i*, $AlCl_3$, $C_6H_6$, 38%; *ii*, PPA, 30%; *iii*, $(C_2H_5O)_2CO$, Na, 82%; *iv*, $CH_3COONH_4$, $C_2H_5OH$, 94%; *v*, 2,5-di-MeOTHF, $C_5H_4ClN.HCl$, 1,4-dioxane, 88% (**8**/**9** : 1/1); *vi*, $NiCl_2.6H_2O$, $NaBH_4$, $CH_3OH$, 86% (**10**/**11** : 1/3); *vii*, a: NaOH, $C_2H_5OH$, $H_2O$; b: HCl, $H_2O$, 79% from **10** and **11**.

In conclusion, we have developed the first synthesis of the *trans*,*trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid **(2)**,[10] an original framework for the preparation of new non-peptide endothelin receptor antagonists.

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## References and Notes

(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411-415.

(2) Aria, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. *Nature* **1990**, *348*, 730-732; Sakurai, T.; Yanagisawa, M.; Takuwa, Y.; Miyazaki, H.; Kimura, S.; Goto, K.; Masaki, T. *Nature* **1990**, *348*, 732-735.

(3) Elliott, J.D.; Amparo Lago, M.; Cousins, R.D.; Gao, A.; Leber, J.D.; Erhard, K.F.; Nambi, P.; Elshourbagy, N.A.; Kumar, C.; Lee, J.A.; Bean, J.W.; DeBrosse, C.W.; Eggleston, D.S.; Brooks, D.P.; Feuerstein, G.; Ruffolo, R.R.; Weinstock, J.; Gleason, J.G.; Peishoff, C.E.; Ohlstein, E.H. *J. Med. Chem.* **1994**, *37*, 1553-1557; Clark, W.M.; Tickner-Eldridge, A.M.; Huang, G.K.; Pridgen, L.N.; Olsen, M.A.; Mills, R.J.; Lantos, I.; Baine, N.H. *J. Am. Chem. Soc.* **1998**, *120*, 4550-4551; Xiang, J.-N.; Nambi, P.; Ohlstein, E.H.; Elliott, J.D. *Bioorg. Med. Chem.* **1998**, *6*, 695-700.

(4) Liebermann, C.; Hartmann, A. *Ber.* **1892**, *25*, 2124-2131; Pfeiffer, P.; de Waal, H.L. *Ann. Chem.* **1935**, *520*, 185-200; Koelsch, C.F.; Hochmann, H.; Le Claire, C.D. *J. Am. Chem. Soc.* **1943**, *65*, 59-60.

(5) Levshina, K.V.; Kolodkina, I.I. *J. Gen. Chem. USSR (Engl. Transl.)* **1964**, *34*, 3455-3457; Vebrel, J.; Carrié, R. *Bull. Soc. Chim. Fr.* **1982**, *3-4*, 116-124; Bogeso, K.P. *J. Med. Chem.* **1983**, *26*, 935-947.

(6) Baker, W.; McOmie, J.F.W.; Parfitt, S.D.; Watkins, D.A.M. *J. Chem. Soc.*, **1957**, 4026-4037.

(7) Hoeger, C.A.; Johnston, A.D.; Okamura, W.H. *J. Am. Chem. Soc.* **1987**, *109*, 4690-4698; Auvray, P.; Moslemi, S.; Sourdaine, P.; Galopin, S.; Séralini, G.-E.; Enguehard, C.; Dallemagne, P.; Bureau, R.; Sonnet, P.; Rault, S. *Eur. J. Med. Chem.* **1998**, *33*, 451-462.

(8) Komendantov, M.I.; Bekmukhametov, R.R.; Domnin, I.N. *J. Org. Chem. USSR (Engl. Transl.)* **1978**, *14*, 701-704; Pridgen, L.N.; Huang, G.K. *Tetrahedron Lett.* **1998**, *39*, 8421-8424.

(9) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1984**, *32*, 2421-2425; Ganem, B.; Osby, J.O. *Chem. Rev.* **1986**, *86*, 763-780.

(10) Procedure for preparation of carboxylic acid **2**: to a solution of ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylates **(10)** and **(11)** (10.6 g, 32 mmol) in EtOH (110 mL) were added 85 mL of aq NaOH (2 M) and the reaction mixture was refluxed for 4 h. The solvent was evaporated *in vacuo* and the residue was dissolved in water (100 mL). The aqueous layer was washed with diethyl ether (80 mL). Acidification with 3 N HCl solution gave a precipitate which was extracted twice with diethyl ether (2 x 80 mL). The organic layers were collected, dried over $MgSO_4$, filtered over active carbon and evaporated to dryness under reduced pressure. The solid residue was recrystallized from diethyl ether/petroleum ether (2/1-v/v) to give **2** as white crystals (79%): mp 66°C. IR (KBr): ν = 3250-2500 (OH), 1715 (CO). $^1$H NMR (400 MHz, $CDCl_3$): δ = 10.41 (brs, 1H, OH), 7.28 (m, 2H, ArH), 7.19 (m, 5H, ArH), 7.03 (m, 1H, H-5), 6.86 (m, 1H, H-6), 6.71 (dd, 2H, *J* = 2.10 and 2.10 Hz, H-α), 6.14 (dd, 2H, *J* = 2.10 and 2.10 Hz, H-β), 5.87 (d, 1H, *J* = 8.50 Hz, H-3), 4.52 (d, 1H, *J* = 9.30 Hz, H-1), 3.39 (dd, 1H, *J* = 9.30 and 8.50 Hz, H-2). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.7 (CO), 143.5 (C-1'), 141.8 (C-7a), 140.1 (C-3a), 129.1 (C-3' and C-5'), 128.8 (C-4), 128.4 (C-2' and C-6'), 128.0 (C-7), 127.4 (C-6), 125.1 (C-4'), 124.4 (C-5), 119.8 (C-a), 108.9 (C-b), 65.7 (C-3), 63.2 (C-2), 52.6 (C-1). MS (EI): m/z = 304 ($M^{+\cdot}$+1, 28), 303 ($M^{+\cdot}$, 100), 251 (20), 162 (33), 115 (24). Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.20; H, 5.55; N, 4.86.

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