Eur J Med Chem (1997) 32, 881–888

Asymmetric synthesis of both enantiomers of 2-(dimethylamino)-1-[3-methoxy-2-(1-methylethoxy)phenyl]ethanol

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(Received 29 January 1997; accepted 24 April 1997)

Summary — Both enantiomers of 2-(dimethylamino)-1-[3-methoxy-2-(1-methylethoxy)phenyl]ethanol were synthetized by a stereoselective route and evaluated in vitro for their uroselectivity in comparison with other α1-adrenoceptor agonists. The most potent enantiomer was structurally characterized by X-ray crystallographic analysis.

α-adrenoceptor agonist / stereochemistry / uroselectivity / urinary incontinence

Introduction

Recently reported as agents for the treatment of urinary incontinence, 2-(dimethylamino)-1-[3-methoxy-2-(1-methylethoxy)phenyl]ethanol, (+/–)-**1** (fig 1), and its enantiomers were described as novel α-adrenoceptor agonists with high selectivity for the urethra [1, 2]. Stress urinary incontinence is particularly common among aged post-menopausal women and pre-menopausal women, especially following pregnancy. It is defined as a small leakage of urine that occurs when an increase of intra-abdominal pressure abnormally overcomes intra-urethral pressure following a mild 'stress' such as laughing, coughing or physical exercices [3]. Pharmacological treatment of this condition has been aiming at directly enhancing insufficient urethral resistance [4, 5]. A few α-adrenoceptor agonists, eg, phenylpropanolamine, ephedrine, midodrine (an orally active glycinamido pro-drug of the α1-adrenoceptor agonist ST1059 [6]), NS-49 [7], have demonstrated clinical effectiveness in the regulation of urethral smooth-muscle tone. However, the use of some of them is limited by cardiovascular side effects [8, 9].

The only literature procedure to gain access to enantiomers of **1** involves low yield crystallization using resolving *O,O'*-di-*p*-toluyl tartaric acid salts [2]. In addition, the absolute configuration at the stereogenic center of enantiomers of **1** has not been reported. In the present paper, we describe an enantioselective route to both optical isomers of **1**, based on Sharpless' asymmetric dihydroxylation (AD) [10], along with their in vitro evaluation for uroselectivity and the elucidation of stereochemisty at the chiral center of the most potent isomer (+)-**1** by X-ray crystallography.

Chemistry

The enantiomers of **1** were prepared according to scheme 1. Etherification with *i*-propyl iodide of *o*-vanillin under phase transfer catalyst conditions, followed by olefination with a Wittig reagent set the stage for Sharpless' asymmetric dihydroxylation [10]. Treatment of a cold solution of styrene **3** with AD-mix-α delivered diol (+)-(*S*)-**4** in excellent yield. The primary alcohol function of diol (+)-(*S*)-**4** was selectively converted to its tosylate (+)-(*S*)-**5**. Displacement of the tosylate by dimethylamine at room temperature in a sealed flask furnished the desired (+)-(*S*)-**1**, in satisfactory yield and with an excellent enantiomeric excess.

The same pathway using AD-mix-β delivered the optical antipode (–)-(*R*)-**1** in a similar fashion. The

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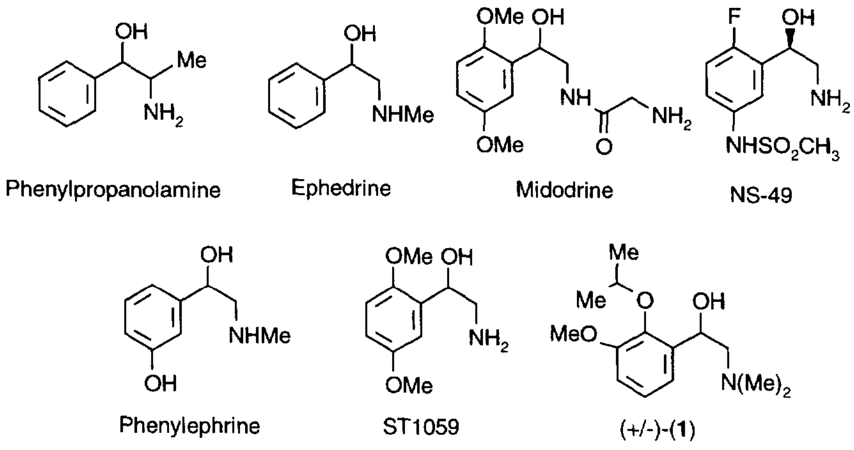
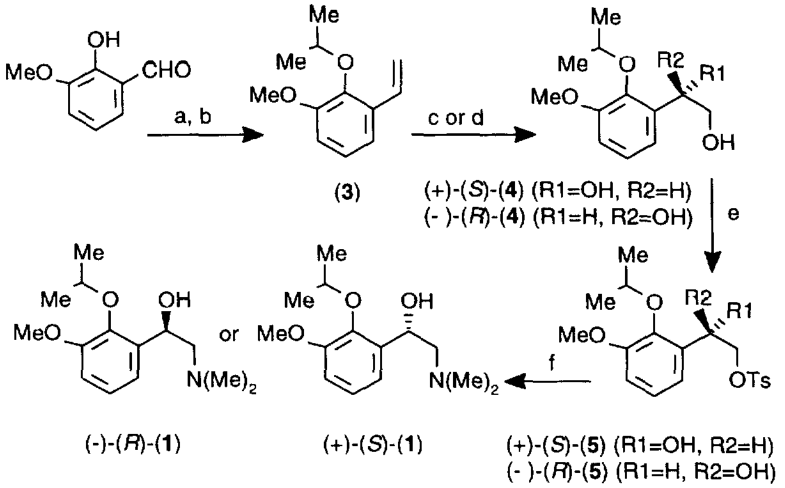


Fig 1. Structure of some α-adrenoceptor agonists.



Scheme 1. (a) *i*-PrI, $(Bu)_4NBr$, NaOH, H_2O/CH_2Cl_2, 20 °C, 48 h; (b) $CH_3P(Ph)_3Br$, *n*-BuLi, THF; (c) AD-mix-α, *t*-BuOH/H_2O, 0 °C, 3 h; (d) AD-mix-β, *t*-BuOH/H_2O, 0 °C, 3 h, 95%; (e) TsCl, Pyridine, 0 °C, 16 h; (f) $HN(Me)_2$, 20 °C, 72 h.

absolute configuration of intermediates and products is predicted from Sharpless' model for the selectivity of the asymmetric dihydroxylation (AD) reaction [11] and confirmed by X-ray crystallographic analysis of (+)-(*S*)-**1**.

X-ray analysis of (+)-(*S*)-1

Crystallization of the (+)-*O*,*O*'-dibenzoyl-D-tartaric acid salt of (+)-**1** from *N*,*N*-dimethylformamide/water (1:3) allowed the isolation of colorless prismatic needles and led us to ascertain the absolute configuration at the chiral center by X-ray methods. A single crystal (0.12 x 0.15 x 0.06 mm) was used for ambient temperature (295 K) data collection. Structure solution and refinement was performed using the Molen package [12]. The structure was solved in $P2_1$, monoclinic #4 (a = 13.511 (13) Å, b = 7.877 (10) Å, c = 15.783 (17) Å, β = 103.38 (1) °, V = 1641.9 Å^3, Z = 2,

Table I. Positional parameters and their estimated standard deviations.

Atom[a]	*x/a*	*y/b*	*z/c*	*B* (*Å*^{2})
Ow	0.4888(4)	0.372(1)	0.3850(4)	3.6(2)
O7	0.7352(5)	0.280(1)	0.3010(4)	5.6(2)
O12	0.6394(4)	0.240(1)	0.5143(4)	4.2(2)
O17	0.8894(5)	0.497(1)	0.2867(5)	7.4(3)
O26	0.4491(5)	0.123(1)	0.7221(4)	4.3(2)
O27	0.582 (1)	0.2634(9)	0.8092(4)	3.2(2)
O30	0.6563(5)	–0.0443(8)	0.7988(4)	3.8(2)
O31	0.7498(5)	0.0358(9)	0.7068(4)	4.9(2)
O34	0.7132(5)	0.6639(9)	0.7953(4)	4.5(2)
O35	0.5859(5)	0.579(1)	0.6893(4)	4.9(2)
O36	0.7842(4)	0.3572(9)	0.8340(4)	3.4(2)
O38	0.9133(5)	0.438(1)	0.7744(4)	6.7(2)
N14	0.6768(6)	–0.116(1)	0.5243(5)	4.0(2)
C1	0.8048(7)	0.336(2)	0.3770(6)	4.4(3)
C2	0.7898(7)	0.291(1)	0.4571(6)	3.5(3)
C3	0.8545(7)	0.360(2)	0.5297(6)	4.3(3)
C4	0.9310(8)	0.469(2)	0.5251(7)	5.2(3)
C5	0.9435(8)	0.511(2)	0.4447(7)	5.1(3)
C6	0.8829(8)	0.450(2)	0.3692(6)	5.0(3)
C8	0.7802(9)	0.171(2)	0.2432(8)	7.8(4)[b]
C9	0.8060(9)	–0.003(2)	0.281 (1)	7.0[b]
C10	0.6930(9)	0.153(2)	0.164 (1)	7.0[b]
C11	0.7049(7)	0.168(1)	0.4640(6)	3.6(3)
C13	0.7523(7)	0.007(2)	0.5083(6)	4.1(3)
C15	0.6000(9)	–0.162(2)	0.4430(7)	7.2(4)
C16	0.7313(8)	–0.269(2)	0.5652(7)	6.0(3)[b]
C18	0.970 (1)	0.604(2)	0.2787(8)	10.6(5)
C19	0.4398(7)	0.204(1)	0.8666(6)	3.3(3)
C20	0.4877(8)	0.277(2)	0.9441(6)	4.9(3)
C21	0.4395(8)	0.284(2)	1.0133(7)	7.6(4)
C22	0.3430(8)	0.209(2)	1.0018(7)	8.6(4)
C23	0.2937(9)	0.139(2)	0.9232(7)	9.0(5)
C24	0.3459(9)	0.140(2)	0.8560(7)	5.7(3)
C25	0.4873(7)	0.191(1)	0.7879(6)	3.4(3)
C28	0.6399(7)	0.238(1)	0.7445(5)	3.0(2)
C29	0.6867(7)	0.061(1)	0.7494(6)	3.0(3)
C32	0.7156(7)	0.380(1)	0.7536(5)	3.3(3)
C33	0.6653(7)	0.553(1)	0.7426(6)	3.3(3)
C37	0.8824(8)	0.398(1)	0.8378(6)	4.4(3)
C39	0.9449(7)	0.390(2)	0.9276(7)	4.5(3)
C40	0.9043(8)	0.361(2)	0.9966(7)	7.5(4)
C41	0.9701(9)	0.355(2)	1.0792(8)	9.4(5)
C42	1.0683(8)	0.383(2)	1.0926(9)	8.4(4)
C43	1.1085(8)	0.411(2)	1.0233(8)	8.6(4)
C44	1.0470(8)	0.417(2)	0.9406(7)	7.5(4)

Numbers in parentheses are the estimated standard deviations for the non-hydrogen atoms. [a]Ow stands for the oxygen atom of water. [b]The C16 atom was refined isotropically, the C9 and C10 atom *B* values were fixed (not refined). Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3) \times [a^2 \times B(1,1) + b^2 \times B(2,2) + c^2 \times B(3,3) + ab(\cos \gamma) \times B(1,2) + ac(\cos \beta) \times B(1,3) + bc(\cos \alpha) \times B(2,3)]$.

d_{calc} = 1.25 g/cm^3). The atomic coordinates are provided in table I. A hemisphere of data ($0 \leq h \leq 16$, $-9 \leq k \leq 9$, $-18 \leq l \leq 18$; $2\theta \leq 50°$) were collected on an Enraf Nonius MACH3 diffractometer (52 kV, 35 mA) using variable speed ω–2θ scans and graphite monochromated molybdenum radiation (λ = 0.71073 Å) yielding 6262 unique reflexions (R_{int} = 0.063 on observed reflexions) which were corrected for Lorentz and polarization factors as well as an isotropic decay. No absorption correction has been made. Full matrix least-squares refinement (for all non-hydrogen atoms except C(8) and C(16), refined isotropically, and C(9) and C(10), B's equiv fixed to 7 Å^2) on F with 1632 observations ($I > 2\sigma(I)$) led to a conventional crystallographic residual of R = 0.0516 and R_w = 0.0586 with GoF = 1.389 for 383 variables. A riding model was used for the treatment of hydrogen atoms (B(H) = 1.3 B_{equ}(C)). A final difference map revealed no significant maxima (< 0.5 e/Å^3). The scattering factor coefficients come from the literature [13]. The molecular structure depicted on the ORTEP diagram (fig 2) revealed that the asymmetric unit of the crystal contains (+)-**1**, (*S*), (*S*)-(+)-*O*,*O*'-dibenzoyl-D-tartaric acid along with water from crystallization. Bond angles and length are within the standard range values.

On the basis of the known absolute configuration of (+)-*O*,*O*'-ddibenzoyl-D-tartaric acid, the stereochemistry at the chiral center of phenylethanolamine (+)-**1**, determined by single crystal X-ray crystallography, unambiguously showed an (*S*)-configuration.

Results and discussion

In vitro uroselectivity of these α1-adtenoceptor agonists was evaluated in a female rabbit model and is reported in table II and figure 3. All compounds showed an appreciable urethral activity, with pEC_{50} values ranging from 0.1 to 1 unit lower than that of phenylephrine. However, in contrast with phenylephrine and ST1059, (+/–)-**1** and its enantiomers only produced a small contraction of the mesenteric artery and were at least 25-fold more potent in the urethra. The (+)-(*S*)-**1** isomer was significantly more potent than its enantiomer.

To rule out the possibility that the unexpected biological behaviour displayed by (+)-(*S*)-**1** comes from an indirect sympathomimetic effect, concentration effect (*E*/[A]) curves in the urethra and in the mesenteric artery were constructed in the presence of both cocaine (3 x 10^{-6} M) and corticosterone (10^{-5} M) as neuronal and extraneuronal uptake blocker [14] respectively and in regular Krebs buffer. No significant difference was observed from this comparative study, performed on tissues obtained from the same rabbits, in either the urethral contractile response (pEC_{50} = 4.80 ± 0.13, E_{max} = 71.9 ± 8.8, n = 5; in the presence of endogenous norepinephrine blockers: pEC_{50} = 4.96 ± 0.11, E_{max} = 67.6 ± 5.4, n = 5) or the vascular response ($pEC_{50} < 3.5$, $E_{max} < 10$, n = 4).

The concentration effect (*E*/[A]) curves to phenylephrine and to ST1059 in urethra were shifted to the right, in a parallel manner, by prazosin (10^{-7} M),

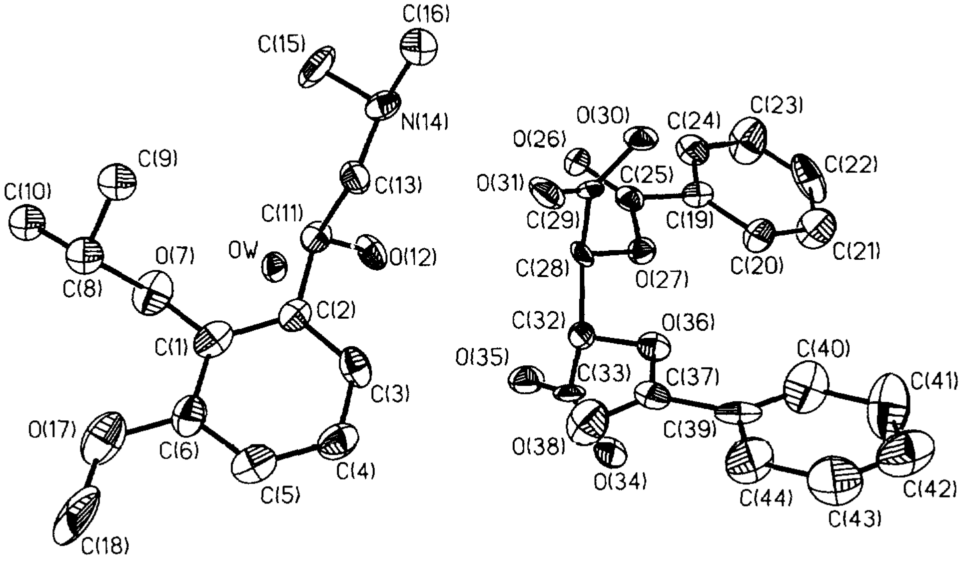


Fig 2. Crystal structure of (+)-(*S*)-**1** as drawn with 30% probability vibrational ellipsoids.

Table II. In vitro efficacy of α1-adrenoceptor agonists in rabbit isolated urethra and mesenteric artery.

Compound	*Urethra*		*Mesenteric Artery*		*Uro selectivity*
	pEC_{50}	E_{max}	pEC_{50}	E_{max}	
Phenylephrine	5.31 ± 0.03	100	5.24 ± 0.10	100	1.2
ST1059	5.20 ± 0.09	84.0 ± 2.1	5.20 ± 0.07	92.8 ± 4.7	1.0
(+/–)-**1**	4.85 ± 0.04	79.6 ± 11.2	< 3.5	< 10	> 25
(+)-(*S*)-**1**	5.07 ± 0.15	97.7 ± 0.4	< 3.5	< 10	> 25
(–)-(*R*)-**1**	4.34 ± 0.10	40.7 ± 9.6	< 3.5	< 10	> 25

suggesting a competitive inhibition with respectively a pK_B value of 7.82 ± 0.03 ($n = 4$) and 8.15 ± 0.15 ($n = 6$). Under the same conditions, the urethral contractile resonse to (+)-(*S*)-**1** showed a non-competitive inhibition with a pD'_2 value of 7.01 ± 0.10 ($n = 3$), suggesting that this urethral contractile response is principally mediated by α1-adrenoceptors.

The stereochemistry of the most potent enantiomer, (+)-**1**, was confirmed to have the (*S*)-configuration by single crystal X-ray crystallography of its (+)-*O,O'*-dibenzoyl-D-tartaric acid salt. This result is very atypical for an α-adrenoceptor agonist because it differs from what the Easson–Stedman hypothesis [15, 16] would have predicted. Nonetheless, the urethral contractile response to (*S*)-(+)-**1** is effectively antagonized by prazosin albeit in a non-competitive manner. Those results may suggest that different α1-adrenoceptor subtypes are implicated in urethral and vascular contractions, with **1** being able to discriminate between those subtypes.

In summary, an enantioselective route to both isomers of 2-(dimethylamino)-1-[3-methoxy-2-(1-methylethoxy)phenyl]ethanol has been developed. The in vitro pharmacological profile of these phenylethanolamines differs from other α1-adrenoceptor agonists, suggesting that it is possible to discriminate between rabbit vascular and urethral α1-adrenoceptors.

Experimental protocols

Chemistry

Reagent-grade chemicals were used without purification. Melting points (mp) were determined on a Buchi SMP-20 capillary melting point apparatus and are uncorrected. Optical rotation was obtained using a Perkin Elmer model 341 polarimeter and concentrations are expressed in grams/100 mL. Infrared (IR) spectra were recorded on a Nicolet FT Impact 400 spectrometer and are reported in cm^{-1}. Proton magnetic resonance spectra (^1H-NMR) were recorded at 200 MHz (Bruker AC 200 and Bruker DPX 200 FT NMR spectrometers). The chemical shifts are reported in parts per million (ppm) and given in δ units relatively to TMS as an internal standard. The splittings were designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; sp, septet. Mass spectrometry analyses (EI at 70 eV) were performed on a VG mass spectrometer type EBE Autospec-Micromass. Elemental analyses were performed on an Exeter Analytical CE-440 analyser. Massic water percentages were determined by the Karl–Fisher method on an Aquaprocessor-Tacussel instrument. Enantiomeric excesses (ee) were determined by chiral high-performance liquid chromatography (HPLC) using a Merck semi-preparative HPLC system with the following conditions: Column: Daicel chiralpak AD, eluent: 99.7:0.2:0.1 hexane–isopropanol–diethylamine at 1 mL/min, detection UV at 274 nM. Retention times (t_R) are reported in minutes. TLC was performed on precoated silica-gel F254 plates (Merck). Silica-gel 60 (Merck; 70–230 mesh) was used for column chromatography.

*(+/–)-2-(Dimethylamino)-1-[3-methoxy-2-(1-methylethoxy)-phenyl]ethanol hydrochloride (+/–)-**1***

(+/–)-**1** was prepared, as the free base, following the literature procedure [2] and converted by treatment with an ethereal solution of anhydrous hydrochloric acid to its hydrochloride salt, white solid, mp = 87 °C. ^1H-NMR (DMSO–d_6) δ 10.02 (bs, 1H), 7.11 (m, 2H), 7.03 (m, 1H), 5.32 (t, $J = 6$ Hz, 1H), 4.73 (bs, 1H), 4.60 (sp, $J = 8$ Hz, 1H), 3.82 (s, 3H), 3.10 (m, 2H), 2.87 (m, 6H), 1.33 (d, $J = 8$ Hz, 3H), 1.20 (d, $J = 8$ Hz, 3H). IR (KBr) 3442, 3300, 3059, 2978, 1588, 1484, 1266, 1114, 1065, 937, 778, 756. Anal calc for $C_{14}H_{24}ClNO_3{\cdot}6.0H_2O$: C, 54.54; H, 8.52; N, 4.54. Found C, 54.67; H, 8.58; N, 4.49.

*3-Methoxy-2-(1-methylethoxy)benzaldehyde **2***

A solution of *o*-vanillin (51 g, 335 mmol), tetrabutylammonium bromide (100 g, 310 mmol), *iso*-propyl iodide (80 mL, 802 mmol) and sodium hydroxide (14 g, 350 mmol) in a mixture of dichloromethane (1000 mL) and water (500 mL)

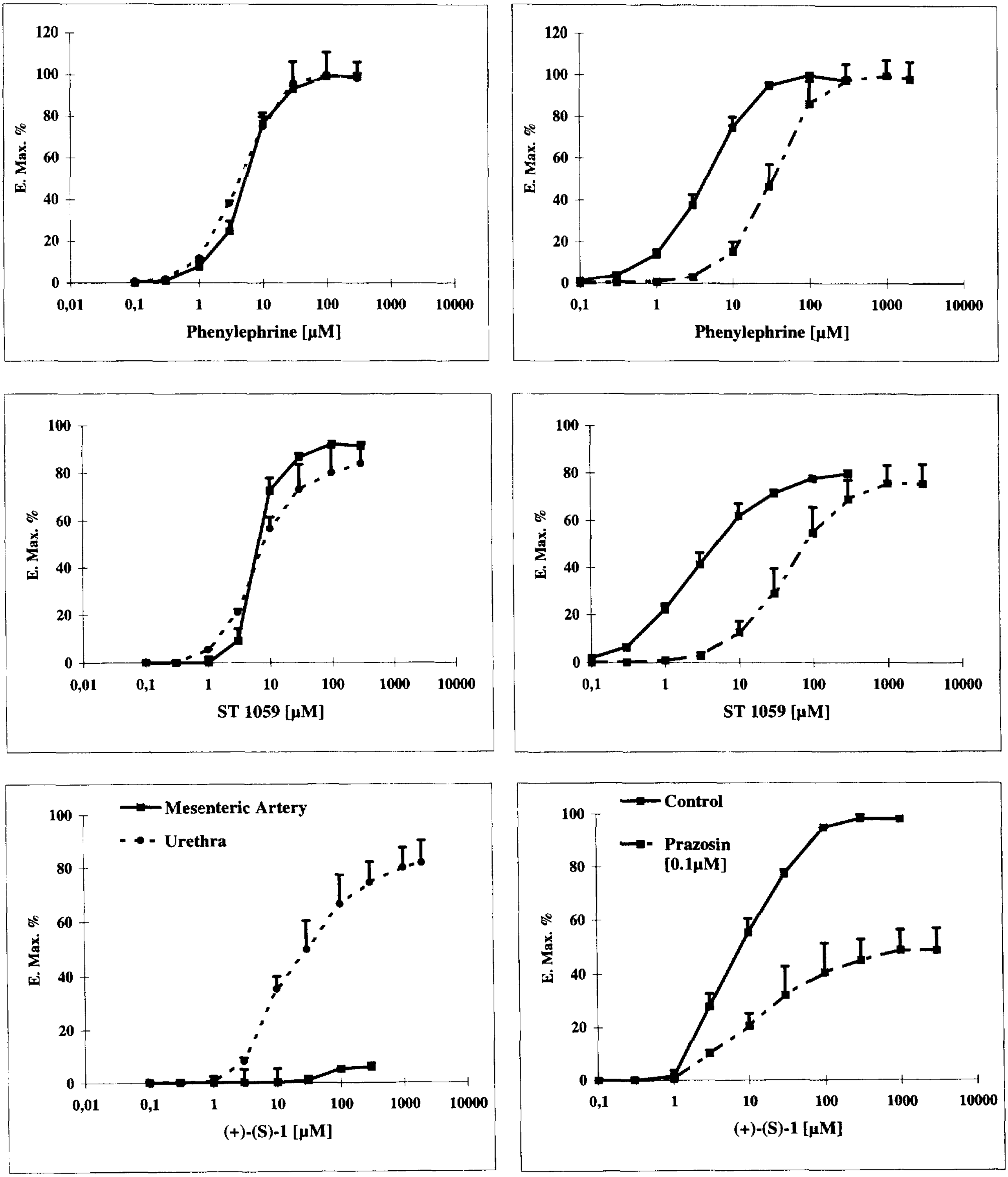


Fig 3. Contractile responses to α1-adrenoceptor agonists in rabbit urethra and mesenteric artery and prazosin inhibition of contractile responses to α1-adrenoceptor agonists in rabbit urethra.

was stirred at room temperature for 36 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica-gel chromatography, using a mixture of ethyl acetate in petroleum ether (5:95) as eluent, to give **2** (55.24 g, 85%) as an orange oil. ^{1}H-NMR ($CDCl_3$) δ 10.43 (s, 1H), 7.40 (m, 1H), 7.12 (m, 2H), 4.63 (sp, *J* = 8 Hz, 1H), 3.87 (s, 3H), 1.32 (d, *J* = 8 Hz, 6H). IR (neat) 3096, 2974, 2944, 2842, 1575, 1475, 1460, 1264, 1070, 936, 779, 742.

3-Methoxy-2-(1-methylethoxy)styrene 3

To a solution of methyltriphenylphosphonium bromide (37.50 g, 100 mmol) in anhydrous THF (100 mL) was added dropwise, at room temperature, a solution of *n*-butyllithium (62.5 mL, 1.6 M) in hexane. The mixture was stirred for 0.5 h and **2** (19.40 g, 100 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 h and water (5 mL) was added. The precipitate was filtered off and washed with ether. The filtrate was dried over $MgSO_4$ and evaporated. The residue was purified by silica-gel chromatography, using a mixture of ethyl acetate in petroleum ether (2:98) as eluent, to give **3** (11.75 g, 61%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 7.14 (m, 2H), 7.02 (d of d, *J* = 12 Hz, *J'* = 8 Hz, 1H), 6.85 (d, *J* = 5 Hz, 1H), 5.73 (d, *J* = 12 Hz, 6H), 5.28 (d, *J* = 8 Hz, 1H), 4.46 (sp, *J* = 8 Hz, 1H), 3.87 (s, 3H), 1.30 (d, *J* = 8 Hz, 6H). IR (neat) 3080, 2974, 2944, 2842, 1574, 1475, 1460, 1264, 1070, 778.

(+)-2-Hydroxy-1-(S)-[3-methoxy-2-(1-methylethoxy)phenyl]-ethanol (+)-(S)-4

To an ice-cold suspension of AD-mix-α (65.80 g) in *tert*-butanol (200 mL) and water (200 mL) was added **3** (9.03 g, 47 mmol). The mixture was stirred for 3 h at 3 °C and sodium sulfite (40 g, 317 mmol) was added. The cooling bath was removed, the suspension was stirred at room temperature for an additional 1 h and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, concentrated and the residue was purified by silica-gel chromatography, using a mixture of ethyl acetate in petroleum ether (4:6) as eluent, to give (+)-(*S*)-**4** (10.1 g, 95%) as a white solid, mp 57 °C. $[\alpha]^{20}_{D}$ = + 9.5° (*c* = 1.190, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.04 (m, 2H), 6.88 (m, 1H), 5.18 (m, 1H), 4.68 (sp, *J* = 8 Hz, 1H), 3.86 (s, 3H), 3.83 (m, 2H), 3.69 (m, 2H), 2.82 (d, *J* = 3 Hz, 1H), 2.12 (t, *J* = 3.6 Hz, 1H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (KBr) 3315, 2972, 2935, 2842, 1591, 1478, 1261, 1032, 760.

The same reaction performed using AD-mix-β gave (–)-(*R*)-**4** (95%), mp 60 °C. $[\alpha]^{20}_{D}$ = –9.2° (*c* = 1.004, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.03 (m, 2H), 6.86 (m, 1H), 5.15 (m, 1H), 4.68 (sp, *J* = 8 Hz, 1H), 3.86 (s, 3H), 3.83 (m, 2H), 3.69 (m, 2H), 2.76 (d, *J* = 3 Hz, 1H), 2.08 (t, *J* = 3.6 Hz, 1H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (KBr) 3319, 2971, 2934, 2834, 1590, 1479, 1261, 1032, 759.

(+)-2-(4-Methylbenzenesulfonate)-1-(S)-[3-methoxy-2-(1-methylethoxy)phenyl]ethanol (+)-(S)-5

To an ice-cold solution of (+)-(*S*)-**4** (10.63 g, 47 mmol) in pyridine (150 mL) was added tosyl chloride (8.07 g, 42.3 mmol) and dimethylaminopyridine (DMAP, 0.05 g). The reaction mixture was stirred for 16 h at room temperature, concentrated and purified by silica-gel chromatography, using a mixture of ethyl acetate in petroleum ether (1:3) as eluent, to give (+)-(*S*)-**5** (10.96 g, 68%) as a colorless oil. $[\alpha]^{20}_{D}$ = +34.6° (*c* = 1.019, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.80 (d, *J* = 6 Hz, 2H), 7.35 (d, *J* = 6 Hz, 2H), 7.03 (m, 2H), 6.88 (m, 1H), 5.31 (m, 1H), 4.65 (sp, *J* = 8 Hz, 1H), 4.28 (d of d, *J* = 6 Hz, *J'* = 3 Hz, 1H), 3.99 (d of d, *J* = 6 Hz, *J'* = 6 Hz, 2H), 3.81 (s, 3H), 2.68 (d, *J* = 3 Hz, 1H), 2.45 (s, 3H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (neat) 3549, 2973, 2935, 2838, 1595, 1455, 1176, 787. MS *m/z*: 380 (M+).

The same reaction performed on (–)-(*R*)-**4** gave (–)-(*R*)-**5** (56%). $[\alpha]^{20}_{D}$ = –34.2° (*c* = 1.004, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.80 (d, *J* = 6 Hz, 2H), 7.35 (d, *J* = 6 Hz, 2H), 7.03 (m, 2H), 6.88 (m, 1H), 5.31 (m, 1H), 4.65 (sp, *J* = 8 Hz, 1H), 4.28 (d of d, *J* = 6 Hz, *J'* = 3 Hz, 1H), 3.99 (d of d, *J* = 6 Hz, *J* = 6 Hz, 2H), 3.81 (s, 3H), 2.68 (d, *J* = 3 Hz, 1H), 2.45 (s, 3H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (neat) 3545, 2974, 2842, 1600, 1477, 1177, 785.

(+)-2-(Dimethylamino)-1-(S)-[3-methoxy-2-(1-methylethoxy)-phenyl]ethanol hydrochloride (+)-(S)-1

A solution of (+)-(*S*)-**5** (10.96 g, 28.81 mmol) in dimethylamine (50 mL) was introduced in a stainless steel reactor, sealed and stirred at room temperature for 72 h. The excess dimethylamine was evaporated and the residue purified by silica-gel chromatography, using a mixture of methanol in dichloromethane (5:95) as eluent, to give, as the free base, (+)-(*S*)-**1** (4.58 g, 63%) as a wax $[\alpha]^{20}_{D}$ = +51.1° (*c* = 0.996; ethanol) ([2]: $[\alpha]^{20}_{D}$ = +52° (*c* = 1.000, ethanol)). Ee > 99.5% with t_R = 29.58. ^{1}H-NMR ($CDCl_3$) δ 7.17 (d of d, *J* = 6 Hz, *J'* = 2 Hz, 1H), 7.08 (d of d, *J* = 6 Hz, *J'* = 6 Hz, 1H), 6.82 (d of d, *J* = 6 Hz, *J'* = 2 Hz, 1H), 5.15 (m, 1H), 4.63 (sp, *J* = 8 Hz, 1H), 3.85 (s, 3H), 2.50 (m, 2H), 2.36 (s, 6H), 1.63 (bs, 1H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (neat) 3438, 2974, 2940, 2825, 2783, 1592, 1476, 1260, 945, 779, 751.

(+)-(*S*)-**1** was converted by treatment with an ethereal solution of anhydrous hydrochloric acid to its hydrochloride salt, white solid, mp 87 °C. $[\alpha]^{20}_{D}$ = +19.0° (*c* = 0.607, water). ^{1}H-NMR (D_2O) δ 7.22 (m, 1H), 7.10 (m, 2H), 5.46 (m, 1H), 4.61 (sp, *J* = 8 Hz, 1H), 3.88 (s, 3H), 3.30 (m, 2H), 3.02 (s, 3H), 2.98 (s, 3H), 1.63 (bs, 1H), 1.37 (d, *J* = 8 Hz, 3H), 1.23 (d, *J* = 8 Hz, 3H) IR (KBr) 3272, 2972, 2679, 1586, 1478, 1213, 1060, 780, 754. Anal calc for $C_{14}H_{24}ClNO_3\cdot 9.0H_2O$: C, 52.80; H, 8.60; N, 4.40. Found C, 52.71; H, 8.52; N, 4.43.

(–)-2-(Dimethylamino)-1-(R)-[3-methoxy-2-(1-methylethoxy)-phenyl]ethanol hydrochloride (–)-(R)-1

The same reaction performed on (–)-(*R*)-**5** gave, as the free base, (–)-(*R*)-**1** (85%). $[\alpha]^{20}_{D}$ = –44.8° (*c* = 0.989, ethanol). Ee > 99.5% with t_R = 31.36. ^{1}H-NMR ($CDCl_3$) δ 7.17 (d of d, *J* = 6 Hz, *J'* = 2 Hz, 1H), 7.08 (d of d, *J* = 6 Hz, *J'* = 6 Hz, 1H), 6.82 (d of d, *J* = 6 Hz, *J'* = 2 Hz, 1H), 5.15 (m, 1H), 4.63 (sp, *J* = 8 Hz, 1H), 3.85 (s, 3H), 2.50 (m, 2H), 2.36 (s, 6H), 1.63 (bs, 1H), 1.36 (d, *J* = 8 Hz, 3H), 1.25 (d, *J* = 8 Hz, 3H). IR (neat) 3438, 2973, 2940, 2825, 2783, 1591, 1477, 1261, 945, 779, 751.

(–)-(*R*)-**1** was converted by treatment with an ethereal solution of anhydrous hydrochloric acid to its hydrochloride salt, white solid, mp 87 °C, $[\alpha]^{20}_{D}$ = +19.1° (*c* = 0.971, water). ^{1}H-NMR (D_2O) δ 7.22 (m, 1H), 7.10 (m, 2H), 5.46 (m, 1H), 4.61 (sp, *J* = 8 Hz, 1H), 3.88 (s, 3H), 3.30 (m, 2H), 3.02 (s, 3H), 2.98 (s, 3H), 1.63 (bs, 1H), 1.37 (d, *J* = 8 Hz, 3H), 1.23 (d, *J* = 8 Hz, 3H). IR (KBr) 3438, 2974, 2940, 2825, 2783, 1591, 1477, 1461, 1261, 1060, 953, 779, 751. Anal calc for $C_{14}H_{24}ClNO_3\cdot 10.7H_2O$: C, 51.82; H, 8.65; N, 4.32. Found C, 51.70; H, 8.70; N, 4.25.

(+)-2-(Dimethylamino)-1-(S)-[3-methoxy-2-(1-methylethoxy)-phenyl]ethanol (+)-O,O'-dibenzoyl-D-tartarate

A solution of (+)-*O,O'*-dibenzoyl-D-tartaric acid (14.51 g, 40.5 mmol) in ethyl acetate (15 mL) was added to a solution of (+)-(*S*)-**1** (10.22 g, 40.5 mmol) in ethyl acetate (35 mL). A white solid (16 g) crystallized after 48 h at room temperature, was recrystallized twice from a mixture of DMF in water (1:3), dried under vacuum to afford (+)-*O*,*O*'-dibenzoyl-D-tartaric acid salt of (+)-(*S*)-**1** (5.8 g, 22%) as colorless prismatic needles from which a suitable single crystal was selected for X-ray analysis. mp 123 °C. $[\alpha]_D^{20} = +63.2°$ (c = 1.005, CH_3OH). ^{1}H-NMR (DMSO–d_6) δ 7.88 (d, J = 9 Hz, 4H), 7.62 (m, 2H), 7.48 (m, 4H), 7.05 (m, 3H), 5.65 (s, 3H), 5.22 (m, 1H), 4.65 (sp, J = 7 Hz, 1H), 3.78 (s, 3H), 3.35 (bs), 2.85 (m, 2H), 2.70 (s, 6H), 1.30 (d, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 3H). IR (KBr) 3466, 2974, 2857, 2366,1738, 1699, 1646, 1468, 1262, 1123, 728. Anal calc for $C_{32}H_{36}NO_{11}{\cdot}3.08H_2O$: C, 61.00; H, 6.10; N, 2.22. Found C, 60.83; H, 6.15; N, 2.19.

(+/–)-2-Amino-1-(2,5-dimethoxyphenyl)ethanol hydrochloride ST1059

To a solution of 2,5-dimethoxybenzaldehyde (10 g, 60 mmol) in trimethylsilyl cyanide (9.6 mL, 72 mmol) was added a catalytic amount of zinc iodide (0.08 g). An exothermic reaction took place immediately and the mixture was stirred for 1 h at room temperature. To a suspension of lithium aluminum hydride (2.50 g, 66 mmol) in anhydrous THF (150 mL) was carefully added dropwise the previously prepared trimethylsilyl cyanohydride and the resulting mixture was heated at reflux for 2 h. To the cooled mixture was carefully added, dropwise and successively, water (8 mL) and a 15% solution of sodium hydroxide (5 mL). A white precipitate appeared and was filtered off. The filtrate was dried over $MgSO_4$ and concentrated. To a solution of the residue in methanol (20 mL) was added an ethereal solution of anhydrous chlorohydric acid. The resulting chlorohydrate was concentrated under vacuum and recrystallized twice from a mixture of ethanol and ether to afford ST1059 (9.30 g, 66%), mp 159–160 °C. ^{1}H-NMR (DMSO–d_6) δ 8.22 (bs, 3H), 7.08 (d, J = 2.5 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 6.82 (d of d, J = 9 Hz, J' = 2.5 Hz, 1H), 5.95 (bs, 1H), 5.08 (d of d, J = 10 Hz, J' = 3.5 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 2.99 (d of d, J = 12 Hz, J' = 2.5 Hz, 1H), 2.71 (d of d, J = 12 Hz, J' = 9 Hz, 1H). IR (KBr) 3408, 2956, 2725, 2632, 2539, 2446, 2057, 1971, 1611, 1505, 1223, 1178, 1043, 804. Anal calc for $C_{10}H_{16}ClNO_3$: C, 51.40; H, 6.90; N, 5.99. Found C, 51.22; H, 6.66; N, 6.03.

Pharmacological methods

Phenylephrine hydrochloride was purchased from Sigma®. All compounds (ST1059, (+/–)-**1**, (+)-(*S*)-**1** and (–)-(*R*)-**1**) were tested as their hydrochloride salts. Female New-Zealand rabbits (~ 18 weeks) weighing 3–4 kg were killed by cervical dislocation and bled. Ring segments of urethra and endothelium denuded mesenteric artery were mounted under a resting tension of 1 g in an organ bath (containing Krebs buffer, 37 °C, gassed with 95% O_2/5% CO_2) for isometric tension measurements. In each tissue, a single concentration effect (*E*/[A]) curve to phenylephrine was obtained by cumulative dosing. Following a 60 min washout period, a second (*E*/[A]) curve was obtained to one of the α1-adrenoceptor agonists reported in table II. For the studies in the presence of prazosin (10^{-7} M), the second (*E*/[A]) curve was realized after a 30 min incubation period. For each (*E*/[A]) curve, the maximum concentration (E_{max}, expressed as % of the maximum concentration to phenylephrine) and midpoint location (pEC_{50}) were determined. The individual estimates of E_{max} and pEC_{50} were then used to calculate the mean + s.e. mean values (n = 2–8). The antilog of the difference between the pEC_{50} estimates in urethra and mesenteric artery was taken as a measurement of uroselectivity. From the pEC_{50} values obtained in the absence and presence of prazosin, pK_B values and a pD'_2 value were estimated following the literature equations [17, 18].

Acknowledgments

We would like to thank Miss Marie-Blanche Harnois and Miss Séverine Boulenger for their assistance in preparing the compounds. We also thank Miss Geneviève Comte and Mrs Chantal Duquenne for the biological data and Mrs Granier-Loyaux for chiral HPLC work.

Supplementary information

A list of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited at the Cambridge Crystallographic Data Center.

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