Agents for the Treatment of Overactive Detrusor. V.[1a] Synthesis and Inhibitory Activity on Detrusor Contraction of *N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine

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***N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine ((±)-3) was designed to restrict the conformation of terodiline 1 and was synthesized in a 6-step approach starting with diphenylacetaldehyde (10) or in a 4-step approach starting with 2,2-diphenyl-4-pentenoic acid (17). Using di-*p*-toluoyltartaric acid as a resolving agent, the synthetic (±)-3 was resolved into its optically pure forms, (−)- and (+)-3. The (−)-enantiomer (−)-3 · HCl (FK584) showed about ten times more potent inhibitory activity on urinary bladder rhythmic contraction in rats (ED_{30} = 0.18 mg/kg, i.v.) than terodiline (ED_{30} = 1.9 mg/kg, i.v.), while the (+)-enantiomer (+)-3 · HCl showed no inhibitory activity at 1.0 mg/kg i.v.**

Compound (−)-3 · HCl (FK584) has pharmacological properties similar to those of terodiline, as evaluated by *in vitro* assay and is currently in clinical development for the treatment of overactive detrusor.

Key words FK584; 4,4-diphenyl-2-cyclopentenylamine; terodiline; bladder; detrusor; mydriasis

In the previous paper,[1a] we reported that the pyrrolidine derivative **2** showed more potent inhibitory activity on urinary bladder rhythmic contraction than terodiline **1**. Compound **2** was designed to restrict the conformation of terodiline by cyclization at the two methyl groups, as shown in Fig. 1a. Conformational restriction of terodiline has proven to be effective to increase the activity, so our research program has been directed towards the use of conformationally restricted analogs of terodiline constructed by cyclization to other positions, such as the benzylic position and the methyl group (Fig. 1b). Since compound **2** having an isopropylidene group at the 3-position of the pyrrolidine ring showed much more potent activity than the desisopropylidene compound, a double bond was introduced into the new cyclic analog of terodiline, and thus compound **3**, with a double bond in the cyclopentane ring, was designed. The racemate (±)-**3** was synthesized by two different methods and was resolved into (−)- and (+)-**3**. The (−)-enantiomer (−)-**3**·HCl (FK584) showed about ten times more potent inhibitory activity on urinary bladder rhythmic contraction in rats (ED_{30} = 0.18 mg/kg, i.v.) than terodiline (ED_{30} = 1.9 mg/kg, i.v.), while the (+)-enantiomer (+)-**3**·HCl showed no inhibitory activity at 1.0 mg/kg i.v. Compound (−)-**3**·HCl (FK584) has similar pharmacological properties to terodiline as indicated by *in vitro* assay and is currently in clinical development for the treatment of overactive detrusor. Herein, we report the practical synthesis of **3** and its pharmacological properties.

Chemistry

We planned two routes for the synthesis of **3**. One employs 4,4-diphenyl-2-cyclopentenone (**4**) as a key intermediate (Charts 1 and 2, routes A—D) and the other uses 5,5-diphenyl-2-cyclopentenone (**5**) (Charts 3 and 4, route E).

A 6-step synthesis of 4,4-diphenyl-2-cyclopentenone (**4**) has already been reported in the literature (19% yield),[2] but it is not applicable to a practical synthesis because it requires high temperature reaction (250 °C) and oxidation using hazardous chromium trioxide. Consequently, we investigated a safe and short practical synthesis of compound **4** starting with the condensation of diphenyla-

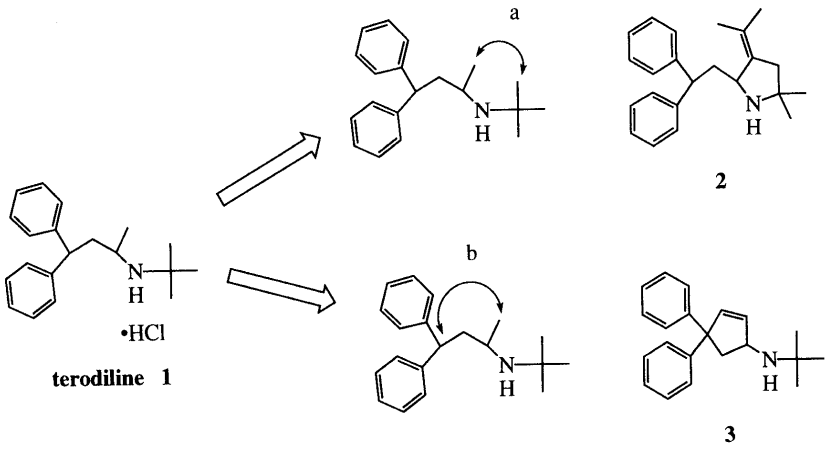


Fig. 1

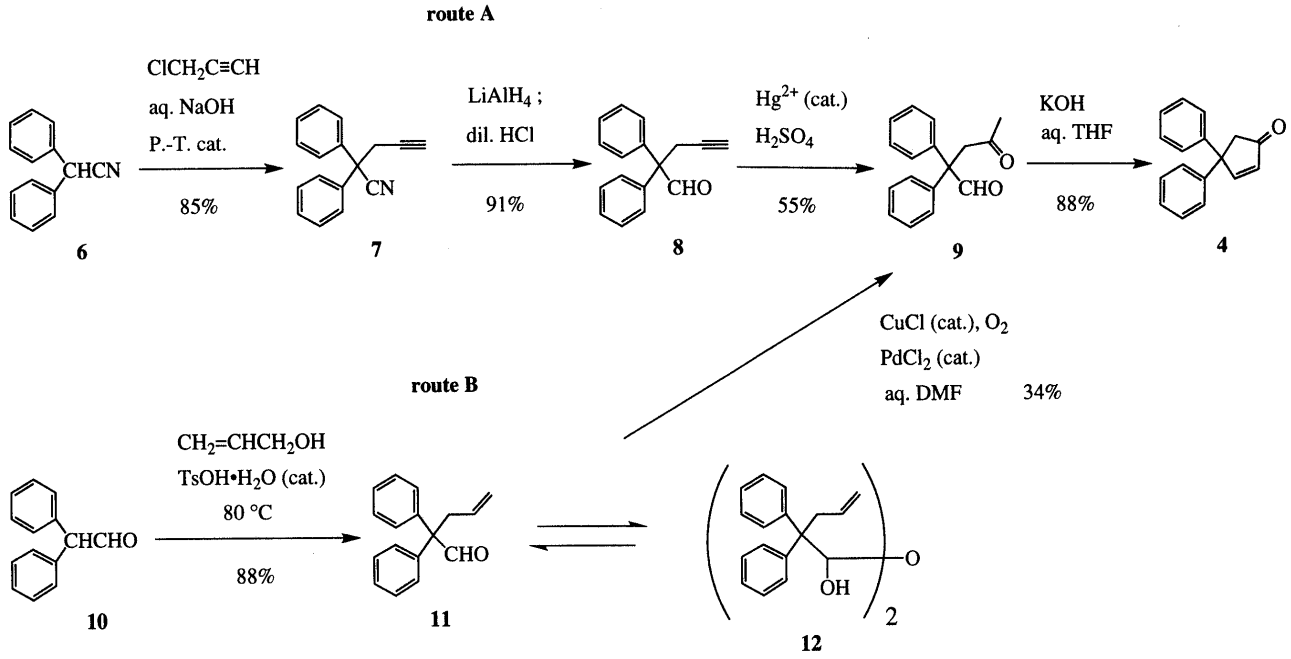


Chart 1

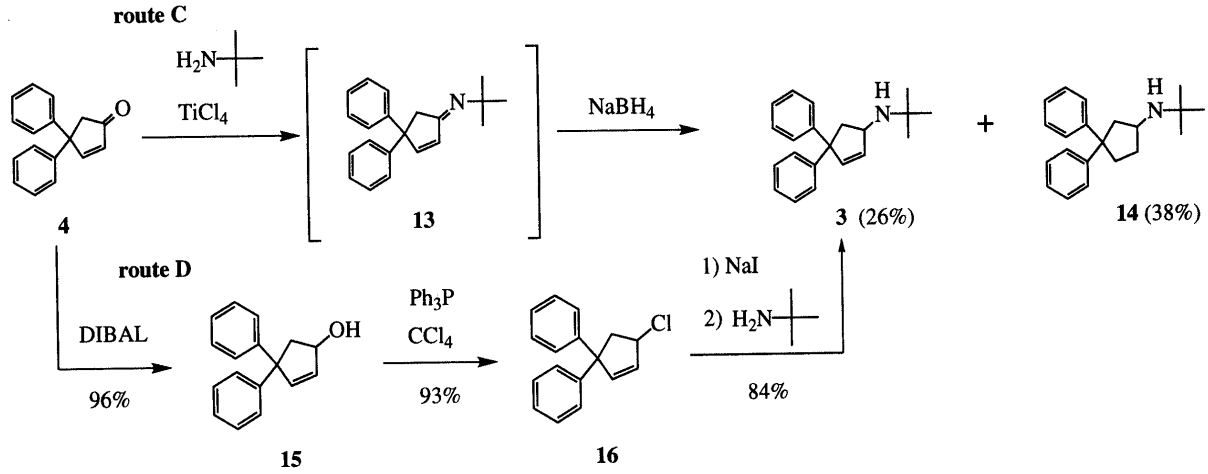


Chart 2

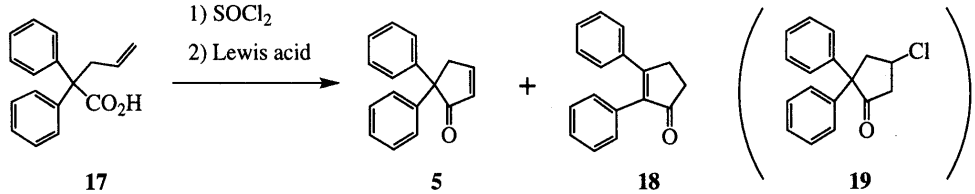


Chart 3

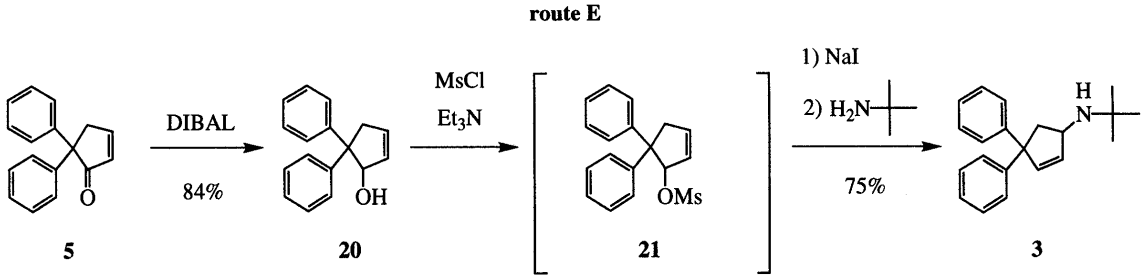
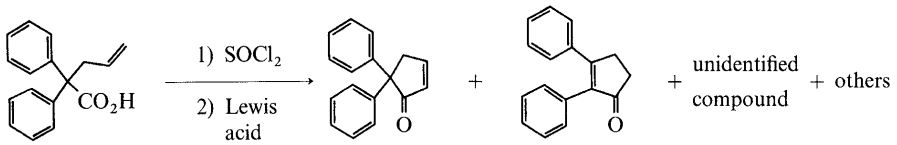


Chart 4

cetonitrile (**6**) and propargyl chloride. The obtained compound **7** was successively treated with lithium aluminum hydride ($LiAlH_4$) and dilute hydrochloric acid (HCl) to afford aldehyde **8** in 91% yield. Hydrolysis of the acetylene group in the usual manner led to compound **9** in 55% yield and intramolecular aldol condensation of **9** afforded the requisite cyclopentenone **4** in 88% yield. The new 4-step route A gave a moderate total yield (Chart 1, 37%). However, since a by-product in the propargylation step showed potent irritating effect, we pursued an alternative route B to **4**. Refluxing a solution of diphenylacetaldehyde (**10**) and 1 eq of allyl alcohol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the rearranged product **11** in 88% yield.[3] Compound **11** was purified by distillation under reduced pressure as a 2:1 mixture of monomer **11** and dimer **12**. The ratio was determined by proton nuclear magnetic resonance (^{1}H-NMR) measurements; the chemical shifts of the aldehyde proton in **11** and the proton at the carbon atom bearing the hydroxyl group in **12** were δ 9.82 and δ 6.51, respectively. Wacker oxidation[4] of the double bond in the mixture of **11** and **12** afforded **9** (34% yield). Intramolecular aldol condensation of **9** as mentioned above afforded the cyclopentenone **4** in 88% yield. This 3-step route B afforded **4** in a moderate total yield (Chart 1, 26%). Initial attempts at the synthesis of **3** involved a condensation of **4** and *tert*-butylamine using titanium tetrachloride, followed by *in situ* treatment with sodium borohydride ($NaBH_4$) to afford the desired compound **3** in only 26% yield (Chart 2, route C); the major product was the saturated cyclopentylamine **14** (38% yield). The low selectivity in the reduction of compound **13** (**14**:**3**=1.5:1) led us to pursue an alternative method (Chart 2, route D), *i.e.*, reaction of *tert*-butyl amine and 4,4-diphenyl-2-cyclopentenylchloride (**16**), which was obtained in two steps by the regioselective reduction of cyclopentenone **4** using diisobutyl aluminum hydride (DIBAL) (96%) and conversion of the resulting cyclopentenol **15** to **16** with triphenylphosphine and carbon tetrachloride (93%). Activation of the cyclopentenyl chloride **16** with sodium iodide, followed by treatment with *tert*-butylamine afforded the desired compound **3** in 84% yield. This 6-step synthesis of **3** from commercially available **10** was achieved in 20% total yield (Charts 1 and 2, routes B, D).

Since the starting material **10** was expensive, another synthetic route to **3** using 5,5-diphenyl-2-cyclopentenone (**5**) as a key intermediate was investigated (Charts 3 and 4, route E). The synthesis of **5** by cyclization of 2,2-diphenyl-4-pentenoic acid (**17**) has been reported in the literature,[5] but the yield of Friedel–Crafts type cyclization using tin(IV) chloride ($SnCl_4$) as a Lewis acid was low. Examination of this cyclization revealed that one of the major by-products was a rearranged compound **18**[6] and this reaction proceeds *via* the β-chloroketone **19**[7] (Chart 3). The effect of Lewis acid and reaction temperature was examined using gas chromatographic (GC) analysis and the results are shown in Table 1. Using bidentate $SnCl_4$, the reaction occurred at $-10\,^\circ$C and the GC yields of **5** and **18** were 48.4% and 8.1%, respectively (entry 1). The isolated yield of **5** was 37% and a large quantity of a by-product, considered to be a polymeric compound, was also obtained. Ferric chloride and zinc bromide caused a small increase in the formation of compound **18'** which was not identified. In the case of monodentate aluminum chloride at $-15\,^\circ$C, polymer formation was suppressed, but the rearranged compound **18** was formed in 24.5% yield (entry 2). Reducing the Lewis acidity (ethyl aluminum dichloride, entry 3) led to an increased yield of the desired product **5** and a smaller quantity of the by-product **18**. Lowering the temperature enhanced this tendency, and the isolated yield of **5** was 62.5% (entry 4). In the case of diethyl aluminum chloride, no cyclization occurred, probably due to the low Lewis acidity. Titanium tetrachloride and trichlorotitanium methoxide afforded good results but the formation of the rearranged compound **18** was greater than in the case of $EtAlCl_2$. The yield of cyclization was increased, so conversion of the cyclopentenone **5** to **3** was investigated starting with selective reduction of **5** with DIBAL (84% yield). Applying Luche's method ($NaBH_4$, $CeCl_3$) to the reduction[8] gave poor selectivity in this case (2,2-diphenylcyclopentanol:**20**=1:7). Activation of **20** with methanesulfonyl chloride and triethylamine, followed by *in situ* treatment with sodium

Table 1. Effect of Lewis Acids and Temperature on the Cyclization of Compound **17**



17 **5** **18** **18'**

Entry	Lewis acid[a]	Temp. (°C)	GC yield[b] (%)		Isolated yield of **5** (%)
			5	**18**	
1	$SnCl_4$	−10	48.4	8.1	37.0
2	$AlCl_3$	−15	60.9	24.5	35.5
3	$EtAlCl_2$	−15	62.0	18.2	42.0
4	$EtAlCl_2$	−60	73.4	15.1	62.5

a) No reaction occurred at 0 °C using the following Lewis acids: CuCl, $CuCl_2$, $MgCl_2$, $BF_3 \cdot OEt_2$, $FeCl_2$, $TiCl_3$, and Et_2AlCl. *b*) Gas chromatographic (GC) spectra were recorded on a Shimadzu GC-2D gas chromatograph and GC analysis was performed under the following conditions: column, SE-30, 2.4 × 2000 mm; column temperature, 220 °C; initial temperature, 250 °C; detector temperature, 250 °C; flow rate, 40 ml/min; t_R of **5**, 3.8 min; t_R of **18**, 5.3 min; t_R of **18'**, 4.8 min.

iodide and *tert*-butylamine afforded **3** in 75% yield (Chart 4, route E). This reaction may proceed *via* a cationic species as an intermediate, with attack of *tert*-butylamine occurring from the least hindered position, since the optically active cyclopentenol **20** ($[\alpha]_D^{21}$ +100.8° (c=1.19, MeOH))[9] afforded racemic **3**, and no regioisomer (*N*-*tert*-butyl-5,5-diphenyl-2-cyclopentenylamine) was detected in the crude product by ^{1}H-NMR measurement. Compound **17** was prepared from commercially available diphenylacetic acid in two steps (91% yield), as described by Arnold and Searles,[10] and thus a new 6-step practical synthetic route to **3** was established in 36% total yield (Charts 3 and 4, route E).

Optical resolution of the racemate **3** using chiral acids such as di-*p*-toluoyltartaric acid, 10-camphorsulfonic acid, tartaric acid, dibenzoyltartaric acid, and lactic acid was attempted, and the 2:1 salt of the amine and di-*p*-toluoyltartaric acid gave a good result. From a solution of one molar racemate and 1/6 molar di-*p*-toluoyl-L-tartaric acid, the 2:1 salt of (+)-**3** and the acid crystallized first (77% ee). Then 1/4 molar di-*p*-toluoyl-L-tartaric acid was added to the (−)-**3**-rich mother liquor and the resulting precipitates (2:1 salt of (−)-**3** and acid) were collected by filtration. Recrystallization of the 2:1 salt of (−)-**3** and di-*p*-toluoyl-L-tartaric acid twice from a mixture of methanol and water afforded (−)-**3** (99.8% ee). The salt of (+)-**3** and di-*p*-toluoyl-L-tartaric acid was converted to the 2:1 salt of (+)-**3** and di-*p*-toluoyl-D-tartaric acid and two recrystallizations of the salt afforded (+)-**3** (99.8% ee).

Table 2. Effect of (±)-, (−)-, (+)-**3**·HCl, and Terodiline on Urinary Bladder Rhythmic Contraction in Rats

Compd.	Inhibitory activity on bladder contraction			
	Dose (mg/kg) i.v.	% inhibition	Duration of action (min)	ED_{30} (mg/kg)
(±)-**3**·HCl	1	40	20	0.44
(−)-**3**·HCl	1	55	>30	0.18
(+)-**3**·HCl	1	8	—	—
Terodiline	1	18.5	10	1.9

i.v. = intravenous.

Pharmacological Results

The inhibitory activity on rat urinary bladder rhythmic contraction of synthetic (±)-**3**·HCl, as well as (−)- and (+)-**3**·HCl, was examined (Tables 2 and 3) in comparison with that of terodiline. The (−)-enantiomer (−)-**3**·HCl showed about ten times more potent inhibitory activity (ED_{30}=0.18 mg/kg, i.v.) than terodiline (ED_{30}=1.9 mg/kg, i.v.), while the (+)-enantiomer, (+)-**3**·HCl, showed no inhibitory activity at 1.0 mg/kg i.v. The ED_{30} values of (−)-**3**·HCl and terodiline in *per os* (*p.o.*) administration were 5.5 mg/kg and 32 mg/kg, respectively with a similar duration of action. The *p.o.*/i.v. ED_{30} ratios of 30.6 for (−)-**3**·HCl and 16.8 for terodiline indicate similar levels of oral availability for the two compounds. Compound (−)-**3**·HCl demonstrated moderate *in vitro* activity, at potency levels similar to those of terodiline, against KCl, $BaCl_2$, and ATP tested as shown in Table 4. The pharmacological profile of (−)-**3**·HCl basically resembles that of terodiline, with the exception of about forty and twenty times more potent activity against electrical field stimulation and carbacol, respectively. It is concluded that (−)-**3**·HCl has potent spasmolytic and antimuscarinic activity and thus should be efficacious for the treatment of overactive detrusor, since the contraction induced by electrical field stimulation is considered to reflect atropine resistance.[11] Mydriatic activity was evaluated as an index of a side effect based on antimuscarinic activity, as shown in Table 3. The minimum effective dose (MED) levels of (−)-**3**·HCl and terodiline

Table 3. Effect of (−)-**3**·HCl and Terodiline on Urinary Bladder Rhythmic Contraction and Mydriasis in Rats

Compound	Inhibitory activity on bladder contraction				Mydriatic activity MED (mg/kg) *p.o.*	Selectivity (MED/ED_{30})
	Dose (mg/kg) *p.o.*	% inhibition	Duration of action (min)	ED_{30} (mg/kg)		
(−)-**3**·HCl	1	—	—			
	3.2	19	30	5.5	32	5.8
	10	42	60			
Terodiline	3.2	9	—			
	10	16	30	32	100	3.1
	32	29	60			

p.o. = *per os*. MED = minimum effective dose.

Table 4. Effects of (−)-**3**·HCl and Terodiline on Detrusor Contraction *in Vitro* Induced by Electrical Field Stimulation, KCl, Carbacol, $BaCl_2$, and ATP in Guinea-Pigs

Compound	IC_{50} (g/ml)				
	Electrical field stimulation	KCl	Carbacol	$BaCl_2$	ATP
(−)-**3**·HCl	3.4×10^{-7}	1.8×10^{-5}	4.6×10^{-7}	3.8×10^{-5}	3.5×10^{-5}
Terodiline	1.4×10^{-5}	7.9×10^{-6}	9.8×10^{-6}	4.3×10^{-5}	8.8×10^{-5}

were 32 mg/kg *p.o.* and 100 mg/kg *p.o.*, respectively. Since terodiline 25 mg twice daily is effective and well tolerated in patients[12] and the safety margin (MED/ED_{30}) of (−)-**3**·HCl is larger than that of terodiline, (−)-**3**·HCl is expected to be effective and safe, and is currently in clinical development under the designation FK584.

Experimental

All melting points were determined in open glass capillaries on a Thomas–Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker AC-200P NMR spectrometer with tetramethylsilane as an internal standard (δ value, ppm). Mass spectra (MS) were recorded on a JEOL JMS D-300 mass spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400CHN Elemental Analyzer.

(Route A) 2,2-Diphenyl-4-pentynonitrile (7) A mixture of **6** (180.99 g, 940 mmol), propargyl chloride (70 ml, 970 mmol) and tetrabutylammonium hydrogen sulfate (0.51 g, 1.5 mmol) in 50% NaOH solution (90 ml) was stirred at room temperature for 6 h. The mixture was poured into water and extracted with diethyl ether. The extract was washed with dilute HCl and brine and evaporated *in vacuo*. The residue was distilled under reduced pressure to afford **7** (184.72 g, 85%) as an oil, bp 138—142 °C/0.3 mmHg. IR (neat) cm^{-1}: 3290, 3060, 2240, 1600. NMR ($CDCl_3$) δ: 2.13 (1H, t, J=2.6 Hz), 3.25 (2H, d, J=2.6 Hz), 7.22—7.53 (10H, m). MS *m/z*: 205 ($M^+ - CN$).

2,2-Diphenyl-4-pentyn-1-al (8) A mixture of **7** (14.31 g, 62 mmol) and $LiAlH_4$ (1.77 g, 47 mmol) in tetrahydrofuran (THF) (50 ml) was stirred at 40 °C to 45 °C for 2 h. After cooling, the reaction mixture was poured into cold water. The mixture was acidified with HCl and extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane–benzene (1:1) to afford **8** (13.18 g, 91%) as an oil. IR (neat) cm^{-1}: 3280, 3050, 1715, 1595. NMR ($CDCl_3$) δ: 1.92 (1H, t, J=2.7 Hz), 3.15 (2H, d, J=2.7 Hz), 7.16—7.54 (10H, m), 9.85 (1H, s). MS *m/z*: 234 (M^+), 205 ($M^+ - CHO$).

2,2-Diphenyl-4-ketopentan-1-al (9) A solution of **8** (83.00 g, 354 mmol) in acetic acid (83 ml) was added dropwise to a solution of $Hg(OAc)_2$ (3.12 g, 10 mmol) and H_2SO_4 (18.28 g) in a mixture of AcOH (300 ml) and water (75 ml) over a period of 2 h at room temperature and the whole was stirred for 1 h. The mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated $NaHCO_3$ solution and brine, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane–EtOAc (5:1) to afford **9** (48.90 g, 55%) as an oil. IR (neat) cm^{-1}: 3060, 1720, 1600. NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.59 (2H, s), 7.14—7.45 (10H, m), 10.02 (1H, s).

4,4-Diphenyl-2-cyclopenten-1-one (4) A 10% KOH solution (15 ml) was added to a solution of **9** (48.90 g, 194 mmol) in a mixture of THF (55 ml) and MeOH (30 ml) at room temperature. The solution was stirred for 2 h and evaporated *in vacuo*. The residue was partitioned between brine and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane–EtOAc (5:1) to afford **4** (39.76 g, 88%) as an oil. IR (neat) cm^{-1}: 3080, 1700, 1665, 1580. NMR ($CDCl_3$) δ: 3.12 (2H, s), 6.25 (1H, d, J=5.6 Hz), 7.06—7.49 (10H, m), 7.99 (1H, d, J=5.6 Hz). The physical data were identical with those reported by Zimmerman and Little.[2]

(Route B) 2,2-Diphenyl-4-penten-1-al (11) A mixture of 2,2-diphenylacetaldehyde (**10**) (10.00 g, 51 mmol), allyl alcohol (3.64 ml, 54 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 g, 0.3 mmol) in benzene (10 ml) was refluxed for 20 h with continuous removal of water (8.5 ml) in a Dean–Stark apparatus. After cooling, the solution was evaporated *in vacuo* and the residue was distilled under reduced pressure to afford **11** (10.60 g, 88%), bp 123—126 °C/0.15 mmHg. IR (neat) cm^{-1}: 1720. NMR ($CDCl_3$) δ: 3.09 (2H, ddd, J=7.0, 1.2, 1.2 Hz), 4.88—5.06 (2H, m), 5.48—5.72 (1H, m), 7.12—7.48 (10H, m), 9.82 (1H, s). MS *m/z*: 236 (M^+), 207. This compound **11** was obtained as a mixture with dimeric compound **12** as shown by NMR measurement (**11**:**12**=2:1). **12**; NMR ($CDCl_3$) δ: 4.42 (4H, ddd, J=5.4, 1.5, 1.5 Hz), 5.18—5.44 (4H, m), 5.85—6.09 (2H, m), 6.51 (2H, s), 7.12—7.48 (20H, m).

2,2-Diphenyl-4-ketopentan-1-al (9) A suspension of CuCl (1.27 g, 12.8 mmol) and $PdCl_2$ (0.46 g, 2.6 mmol) in DMF (12.7 ml) and water (1.5 ml) was bubbled with oxygen at room temperature for 2 h and then **11** (3.00 g, 12.7 mmol) was added. The mixture was bubbled with oxygen at room temperature for 4.5 h, adjusted to pH 2 with 10% HCl and extracted with diisopropyl ether. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane and EtOAc (50:1) to afford **9** (1.09 g, 34%) as an oil. The physical data were identical with those of **9** obtained by route A.

(Route C) *N*-*tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (3) A solution of titanium tetrachloride (0.50 g, 1.3 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of **4** (0.40 g, 1.7 mmol) and *tert*-butylamine (0.75 g, 10.2 mmol) in CH_2Cl_2 (9 ml) at −70 °C to −60 °C. The mixture was stirred for 2 h, then sodium borohydride (0.35 g, 9.3 mmol) and MeOH (6 ml) were added successively at 0 °C. Stirring was continued for 0.5 h, then the resulting precipitates were filtered off using a Celite pad and the filtrate was evaporated *in vacuo*. The residue was taken up in 1 N NaOH solution and EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$–MeOH (1:0 to 20:1) to afford **3** (0.13 g, 26%) and **14** (0.19 g, 38%) as oils. *N*-*tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (**3**): IR (neat) cm^{-1}: 1600, 1490, 1475, 1445, 1390, 1380. NMR ($CDCl_3$) δ: 0.80—1.40 (1H, br m), 1.12 (9H, s), 2.04 (1H, dd, J=7.6, 13.0 Hz), 3.09 (1H, dd, J=6.8, 13.0 Hz), 3.94—4.10 (1H, m), 5.85 (1H, dd, J=1.7, 5.6 Hz), 6.21 (1H, dd, J=2.0, 5.6 Hz), 7.09—7.38 (10H, m). MS *m/z*: 291 (M^+), 276. *N*-*tert*-Butyl-3,3-diphenylcyclopentylamine (**14**): IR (neat) cm^{-1}: 3350. NMR ($CDCl_3$) δ: 1.03 (9H, s), 1.49—1.72 (1H, m), 1.93—2.63 (5H, m), 2.74—2.89 (1H, m), 3.14—3.37 (1H, m), 7.02—7.14 (10H, m). MS *m/z*: 294 ($M^+ + 1$), 278.

***N*-*tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine Hydrochloride (3·HCl)** A 4 N solution of HCl in EtOAc (0.23 ml) was added to a solution of **3** (0.24 g, 0.8 mmol) in isopropyl alcohol (0.5 ml) and EtOAc (2.4 ml) and the whole was stirred at 0 °C for 0.5 h. The resulting precipitates were collected by filtration and dried to afford **3**·HCl (0.23 g, 87%), mp 260—263 °C (dec.). *Anal.* Calcd for $C_{21}H_{25}N \cdot HCl \cdot 1/2H_2O$: C, 74.87; H, 8.08; N, 4.16. Found: C, 75.25; H, 8.08; N, 4.03. IR (Nujol) cm^{-1}: 2730, 2690, 2530, 2490, 2430. NMR (DMSO-d_6) δ: 1.37 (9H, s), 2.51 (1H, dd, J=13.3, 8.1 Hz), 3.34 (1H, dd, J=13.3, 7.2 Hz), 4.44 (1H, br m), 6.16 (1H, d, J=5.6 Hz), 6.72 (1H, d, J=5.6 Hz), 7.10—7.38 (10H, m), 8.89 (1H, br s), 9.52 (1H, br s).

(Route D) 4,4-Diphenyl-2-cyclopenten-1-ol (15) A 1 M solution of diisobutylaluminum hydride in *n*-hexane (2.0 ml, 2.0 mmol) was added to a solution of **4** (0.30 g, 1.3 mmol) in toluene (3 ml) at −5 °C to 4 °C. The mixture was stirred for 20 min, then EtOAc (3 ml) and 10% HCl (2 ml) were added successively, and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with CH_2Cl_2 to afford **15** (0.29 g, 96%) as an oil. IR (neat) cm^{-1}: 3375. NMR ($CDCl_3$) δ: 1.56 (1H, br s), 2.41 (1H, dd, J=4.7, 13.9 Hz), 3.00 (1H, dd, J=6.9, 13.9 Hz), 4.95—5.10 (1H, m), 5.98 (1H, dd, J=2.0, 5.6 Hz), 6.39 (1H, dd, J=1.1, 5.6 Hz), 7.10—7.42 (10H, m). MS *m/z*: 236 (M^+), 218.

4,4-Diphenyl-2-cyclopentenyl Chloride (16) A mixture of **15** (0.30 g, 1.3 mmol) and triphenylphosphine (0.43 g, 1.7 mmol) in carbon tetrachloride (3 ml) was refluxed for 8 h and then cooled. *n*-Hexane (5 ml) was added to it and the mixture was stirred for 10 min at room temperature. The insoluble material was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and silica gel (1 g) was added to the solution. The mixture was stirred for 10 min, then the silica gel was removed by filtration and the filtrate was evaporated *in vacuo* to afford **16** (0.30 g, 93%) as an oil. IR (neat) cm^{-1}: 1595, 1490, 1445. NMR ($CDCl_3$) δ: 2.87 (1H, dd, J=4.7, 14.6 Hz), 3.22 (1H, dd, J=7.3, 14.6 Hz), 5.05—5.20 (1H, m), 5.98 (1H, dd, J=2.1, 5.5 Hz), 6.39 (1H, dd, J=1.2, 5.5 Hz), 7.10—7.40 (10H, m). MS *m/z*: 254 (M^+), 219 ($M^+ - Cl$).

***N*-*tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (3)** A mixture of **16** (0.26 g, 1.0 mmol) and sodium iodide (0.15 g, 1.0 mmol) in acetone (5 ml) was refluxed for 90 min. The insoluble material was removed by filtration, then *tert*-butylamine (1.5 ml, 14.3 mmol) and acetone (5 ml) were added to the filtrate. The solution was refluxed for 2 h and cooled. The solution was evaporated *in vacuo*, and water and EtOAc were added to

the residue. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$–MeOH (20 : 1) to afford **3** (0.25 g, 84%) as an oil. The physical data were identical with those of **3** obtained by route C.

(Route E) 5,5-Diphenyl-2-cyclopenten-1-ol (20) A 1.5 M solution of diisobutylaluminum hydride in toluene (0.9 ml, 1.4 mmol) was added dropwise to a solution of **5** (0.30 g, 1.3 mmol) in toluene (1.5 ml) at −78 °C to −60 °C. The mixture was stirred for 1 h, then saturated NH_4Cl (1 ml) and 10% HCl (2 ml) were added successively. The whole was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with CH_2Cl_2 to afford **20** (0.25 g, 84%) as an oil. IR (neat) cm^{-1}: 3550, 3420. NMR ($CDCl_3$) δ: 1.28 (1H, br s), 2.82—3.00 (1H, m), 3.40—3.55 (1H, m), 5.45 (1H, s), 5.88—5.98 (1H, m), 6.08—6.20 (1H, m), 7.10—7.40 (10H, m). MS *m/z*: 296 (M^+).

***N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (3)** Methanesulfonyl chloride (0.12 ml, 1.5 mmol) and triethylamine (0.21 ml, 1.5 mmol) were added to a solution of **20** (0.30 g, 1.3 mmol) in acetone (3 ml) below 5 °C. The mixture was stirred for 15 min, then NaI (0.23 g, 1.5 mmol) and *tert*-butylamine (2.70 ml, 26.8 mmol) were added at 0 °C. Stirring was continued at room temperature overnight, then the mixture was poured into ice water (9 ml) and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$–MeOH (20 : 1) to afford **3** (0.28 g, 75%) as an oil. The physical data were identical with those of **3** obtained by route C.

(−)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (−)-Di-*p*-toluoyl-L-tartrate (2 : 1) A solution of (−)-di-*p*-toluoyl-L-tartaric acid (37.96 g, 98 mmol) in a mixture of acetone–water (95 : 5, 171 ml) was added to a solution of N-*tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (171.83 g, 589 mmol) in a mixture of acetone–water (95 : 5, 344 ml) and the whole was left standing at room temperature overnight. The resulting precipitates [(+)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (−)-di-*p*-toluoyl-L-tartrate (2 : 1), 125.80 g, 130 mmol, wet] were collected by filtration. The filtrate was evaporated *in vacuo*. The residue was dissolved in a solution of (−)-di-*p*-toluoyl-L-tartaric acid (56.93 g, 147 mmol) in a mixture of acetone–water (95 : 5, 687 ml) and the solution was left standing at room temperature for 3 h. The resulting precipitates [(−)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (−)-di-*p*-toluoyl-L-tartrate (2 : 1), 177.58 g, 183 mmol, wet] were collected by filtration. (−)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (−)-di-*p*-toluoyl-L-tartrate (2 : 1) (177.58 g) was recrystallized twice from a mixture of methanol–water (4 : 1, 700 ml, 1600 ml) to afford the pure salt (57.78 g), mp 184—185 °C (dec.). $[\alpha]_D^{27.6}$ −182.6° (c = 0.60, MeOH). *Anal.* Calcd for $C_{62}H_{68}N_2O_8 \cdot H_2O$: C, 75.43; H, 7.14; N, 2.83. Found: C, 75.41; H, 7.03; N, 2.69. IR (Nujol) cm^{-1}: 1715, 1630, 1580, 1260, 1175, 1100, 1030, 1020. NMR (DMSO-d_6) δ: 1.18 (18H, s), 2.24 (2H, dd, J = 13.2 Hz, 8.2 Hz), 2.35 (6H, s), 3.20 (2H, dd, J = 13.2, 6.9 Hz), 2.50—4.20 (4H, br s), 4.20 (2H, br t, J = 7.2 Hz), 5.58 (2H, s), 5.94 (2H, dd, J = 5.7, 1.5 Hz), 6.42 (2H, dd, J = 5.7, 2.0 Hz), 7.10—7.38 (24H, m), 7.83 (4H, d, J = 8.1 Hz).

(+)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (+)-Di-*p*-toluoyl-D-tartrate (2 : 1) (+)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (−)-di-*p*-toluoyl-L-tartrate (2 : 1) (156.30 g, 161 mmol) obtained in the above manner was partitioned between 10% NaOH solution and diethyl ether. The organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford (+)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (90.10 g, 309 mmol). The amine was dissolved in a solution of (+)-di-*p*-toluoyl-D-tartaric acid (38.70 g, 100 mmol) in a mixture of MeOH and water (10 : 1, 165 ml) and the whole was left standing at room temperature to afford (+)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (+)-di-*p*-toluoyl-D-tartrate (2 : 1) (86.16 g, 89 mmol). This salt was recrystallized from a mixture of methanol–water (4 : 1, 1460 ml) to afford the pure salt (52.55 g), mp 182—184 °C (dec.). $[\alpha]_D^{28.4}$ +188.2° (c = 0.54, MeOH). *Anal.* Calcd for $C_{62}H_{68}N_2O_8 \cdot H_2O$: C, 75.43; H, 7.14; N, 2.83. Found : C, 75.27; H, 7.01; N, 2.64. IR (Nujol) cm^{-1}: 1710, 1630, 1580, 1260, 1175, 1100, 1030, 1020. NMR (DMSO-d_6) δ: 1.18 (18H, s), 2.24 (2H, dd, J = 13.2, 8.2 Hz), 2.35 (6H, s), 3.20 (2H, dd, J = 13.2, 6.9 Hz), 2.50—4.20 (4H, br s), 4.20 (2H, br t, J = 7.2 Hz), 5.58 (2H, s), 5.94 (2H, dd, J = 5.7, 1.5 Hz), 6.42 (2H, dd, J = 5.7, 2.0 Hz), 7.10—7.38 (24H, m), 7.83 (4H, d, J = 8.1 Hz).

(−)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine Hydrochloride ((−)-3 · HCl, FK584) A mixture of (−)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (−)-di-*p*-toluoyl-L-tartrate (2 : 1) (57.31 g, 59 mmol) and 5% NaOH solution (250 ml) was stirred for 0.5 h and extracted with diethyl ether (100 ml × 2). The extract was washed with 5% NaOH solution (50 ml) and brine (50 ml), dried over Na_2SO_4, and evaporated *in vacuo* to afford (−)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine (34.54 g, 100%). A solution of the amine (8.82 g, 30.3 mmol) in a mixture of diethyl ether (50 ml) and water (15 ml) was treated with concentrated HCl (5 ml) at 0 °C and the whole was stirred for 0.5 h. The resulting precipitates were collected by filtration and dried to afford (−)-**3** · HCl (9.70 g, 98%), mp 259—261 °C (dec.). $[\alpha]_D^{26}$ −189.4° (c = 1.07, MeOH). *Anal.* Calcd for $C_{21}H_{25}N \cdot HCl$: C, 76.92; H, 7.99; N, 4.27. Found: C, 76.80; H, 7.90; N, 4.29. IR (Nujol) cm^{-1}: 2730, 2700, 2640, 2620, 2480, 2440. NMR (DMSO-d_6) δ: 1.38 (9H, s), 2.46—2.65 (1H, m), 3.25—3.43 (1H, m), 4.34—4.54 (1H, m), 6.19 (1H, dd, J = 1.4, 5.6 Hz), 6.72 (1H, dd, J = 1.9, 5.6 Hz), 7.15—7.43 (10H, m), 8.83—9.08 (1H, m), 9.50—9.76 (1H, m). The enantiomeric excess of this compound was determined to be >99.8% by HPLC analysis of the corresponding amine (column, Sumipax OA-4400 (Sumitomo) 4.6 × 250 mm; eluent, 10 : 3 : 3 *n*-hexane–CH_2Cl_2–EtOH mixture; flow rate, 0.8 ml/min; t_R of (−)-**3**, 6.6 min; t_R of (+)-**3**, 8.6 min).

(+)-*N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine Hydrochloride ((+)-3 · HCl) This compound was prepared in a similar manner to that used for the (−)-isomer. mp 259—260 °C (dec.). *Anal.* Calcd for $C_{21}H_{25}N \cdot HCl$: C, 76.92; H, 7.99; N, 4.27. Found: C, 77.13; H, 8.11; N, 4.36. $[\alpha]_D^{23}$ +189.2° (c = 0.60, MeOH). IR (Nujol) cm^{-1}: 2750, 2700, 2650, 2630, 2500, 2450. NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.34—2.57 (1H, m), 3.28—3.46 (1H, m), 4.44—4.61 (1H, m), 6.03 (1H, br d, J = 5.6 Hz), 6.76 (1H, br d, J = 5.6 Hz), 7.15—7.43 (10H, m), 8.50—8.68 (1H, m), 8.90—9.15 (1H, m). The enantiomeric excess of this compound was determined to be >99.8% by HPLC analysis of the corresponding amine.

Biological Tests Inhibitory Activity against Urinary Bladder Rhythmic Contraction in Rats: Sprague Dawley rats, weighing 220—320 g, were anesthetized with a subcutaneous dose of 1.0 g/kg of urethane and fixed in a supine position. The lower abdomen was opened along the midline to expose fully the urinary bladder. A rubber balloon was inserted into the bladder through a small incision in the wall around the apex, and was connected with a pressure transducer *via* a polyethylene tube. The bladder was carefully packed with a cotton-wool pad soaked in warm saline and kept warm. The balloon was filled with approximately 1 ml of water, and then pressurized. Rhythmic contractions of the urinary bladder became constant at a threshold intravesical pressure of between 5 and 15 mmHg, and reached a maximum contraction at 50 to 70 mmHg with an amplitude of contraction of 40 to 60 mmHg. After this control period, the drugs were administered intravenously or orally, and the inhibitory effects were estimated in terms of the reduction in amplitude of the bladder contractions.

Inhibitory Activities against Detrusor Contractions *in vitro* Induced by Electrical Field Stimulation, KCl, Carbacol, $BaCl_2$, and ATP: Guinea-pigs weighing 320—650 g were killed by exsanguination. The lower abdomen was opened and longitudinally oriented strips of the urinary bladder, 15—20 mm long and 5 mm wide, were excised. The strips were suspended in tissue baths containing 25 ml of Krebs solution. Throughout the experiment, the bathing solution was maintained at 37 °C and continuously aerated with a 95% oxygen and 5% carbon dioxide gas mixture. Bladder strip contractions were recorded isometrically with an electromechanical displacement transducer and a polygraph. All muscle strips were stretched initially under a tension of 1 g and acclimated to the bath milieu for at least 30 min before any drug additions. In all cases, 15 min intervals were allowed between drug additions. Individual strips were exposed only to electrical stimulation or a single agonist and a drug.

To stimulate the bladder strips electrically, two platinum electrodes were placed parallel to each other and 15 mm apart on both sides of the tissue preparation. The intensity of square wave stimuli was adjusted to obtain submaximal contractions at a constant frequency of 10 Hz and a duration of 1 ms. Usually the electrical intensity was around 10 V, and stimulation was applied to the detrusor strips for 5 s every 5 min. Fixed doses of KCl (30 mmol), carbacol (10 μmol), $BaCl_2$ (2 mmol), and ATP (100 μmol) were used as agonists. The effects of agents upon the action of the electrical stimuli or the agonists were examined by adding various concentrations of the drugs to the bath 10 min prior to the administration of electrical stimuli or the agonists.

Mydriatic activity in rats was examined by the methods of Parry and

Heathcote.[13]

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7) mp 105—108 °C (recrystallized from diisopropyl ether). *Anal.* Calcd for $C_{17}H_{15}ClO$: C, 75.41; H, 5.58. Found: C, 75.31; H, 5.50. IR (Nujol) cm^{-1}: 1745. NMR ($CDCl_3$) δ: 2.71 (1H, dd, J=9.2, 19.2 Hz), 2.85 (1H, dd, J=10.7, 13.3 Hz), 3.11 (1H, ddd, J=2.4, 7.9, 19.2 Hz), 3.44 (1H, ddd, J=2.4, 5.9, 13.3 Hz), 4.25—4.50 (1H, m), 7.05—7.45 (10H, m). MS m/z: 269 ($M^+ - 2$).
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