Agents for the Treatment of Overactive Detrusor. IV.[1] Synthesis and Structure–Activity Relationships of Cyclic Analogues of Terodiline

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A series of pyrrolidine derivatives were synthesized and examined for inhibitory activity on detrusor contraction *in vivo*. Among those compounds, 5,5-dimethyl-2-(2,2-diphenylethyl)-3-isopropylidenepyrrolidine hydrochloride (41·HCl), 2-(2,2-di(4-fluorophenyl)ethylene)-5,5-dimethyl-3-isopropylidenepyrrolidine hydrochloride (42·HCl), (+)-5,5-dimethyl-2-(*N*,*N*-diphenylaminomethyl)-3-isopropylidenepyrrolidine hydrochloride (+)-(43a·HCl), (−)-5,5-dimethyl-2-(*N*,*N*-diphenylaminomethyl)-3-isopropylidenepyrrolidine hydrochloride (−)-(43a·HCl), and 2-(*N*,*N*-di(4-fluorophenyl)aminomethyl)-5,5-dimethyl-3-isopropylidenepyrrolidine methanesulfonate (43b·MsOH) showed stronger inhibitory activity on detrusor contraction than terodiline.

Keywords detrusor; pyrrolidine; terodiline; oxybutynin

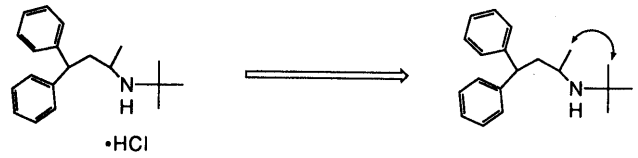
Recently, two new agents (terodiline, oxybutynin) for the overactive detrusor, a disease which shows a high frequency of urination as a characteristic syndrome, have been launched on the market. Terodiline possesses anticholinergic, calcium antagonistic, and local anesthetic activities and exhibits an inhibitory activity on detrusor contraction.[2] Oxybutynin possesses similar activities to those of terodiline with the exception of having spasmolytic activity instead of calcium antagonistic activity.[3] Clinically, terodiline shows milder effectiveness and fewer side effects than oxybutynin. Furthermore, terodiline shows longer lasting activity than oxybutynin.[4] Clinical side effects such as mydriasis and dryness of the mouth may be caused by their anticholinergic activity. The anticholinergic activity of terodiline ($IC_{50} = 9.8 \times 10^{-6}$ g/ml[5]) is much weaker than that of oxybutynin ($IC_{50} = 9.9 \times 10^{-8}$ g/ml[5]). The rate of metabolism of terodiline is slow,[2] while that of oxybutynin is fast.[6] The short duration of action of oxybutynin may be due to its fast metabolism. Therefore, potentiation of the activity of terodiline without increasing its anticholinergic activity will lead to the creation of a new drug with sharp effectiveness, long duration of action and fewer side effects. We planned to increase the activity of terodiline by the following strategy. Since terodiline is an acyclic compound, it can easily take various types of conformations. We considered various spatial placements of the basic nitrogen atom in relation to the two benzene rings since its flexibility possibly dictates its observed multi-pharmacological activities. It is well known that an anticholinergic agent alone cannot completely suppress detrusor contraction (atropine resistance). To overcome this atropine resistance, terodiline especially has calcium antagonistic activity ($IC_{50} = 7.9 \times 10^{-6}$ g/ml[7]) in addition to anticholinergic activity.[2] Fixation of the conformation by cyclization at the appropriate positions of terodiline should lead to an optimization of the balance of its anticholinergic and calcium antagonistic activities. This assumption can be partially supported by the fact that the (−)enantiomer of terodiline is the stronger calcium antagonist,[8] however, with regard to anticholinergic activity, the (+)enantiomer showed stronger activity than the racemate or (−)-enantiomer.[9]

Fixation of the conformation by cyclization between the methyl groups of terodiline as shown in Fig. 1 was carried out. Herein, we report the synthesis and structure–activity relationships of terodiline related compounds.

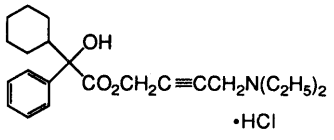
Chemistry Chart 1 shows the synthetic route to morpholino derivative **12**. Bromination of 4,4-diphenyl-2-butanone[10] (**3**) afforded 4:1 mixture of 1-bromo-4,4-diphenyl-2-butanone (**4**) and 3-bromo-4,4-diphenyl-2-butanone (**5**) in an 85% yield. Reduction of the mixture with sodium borohydride ($NaBH_4$), followed by base treatment of the resulting bromohydrine afforded epoxide **7** in a 61% yield. The ring opening of the epoxide **7** with an alkoxide **8** generated from 2-amino-2-methylpropanol and sodium hydride (NaH), followed by protection of the amino group with di-*tert*-butyl dicarbonate, afforded alcohol **10** in a 23% yield. Mesylation of **10** afforded compound **11** in a quantitative yield. Removal of the *tert*-Boc group of **11**, and subsequent heating at 100 °C for 8 h, afforded compound **12** in a quantitative yield.

Condensation of propanoic acid ester **13** with 1,1-dimethylethylenediamine (**14**) at 170 °C for 4 h afforded compound **15** in a 30% yield as shown in Chart 2.

Pyrrolidines **22** and **28** were synthesized *via* γ-nitroketone **19** as a key intermediate as shown in Charts 3 and 4. Acylation of Meldrum's acid[11] with an acid chloride



terodiline 1



oxybutynin 2

Fig. 1

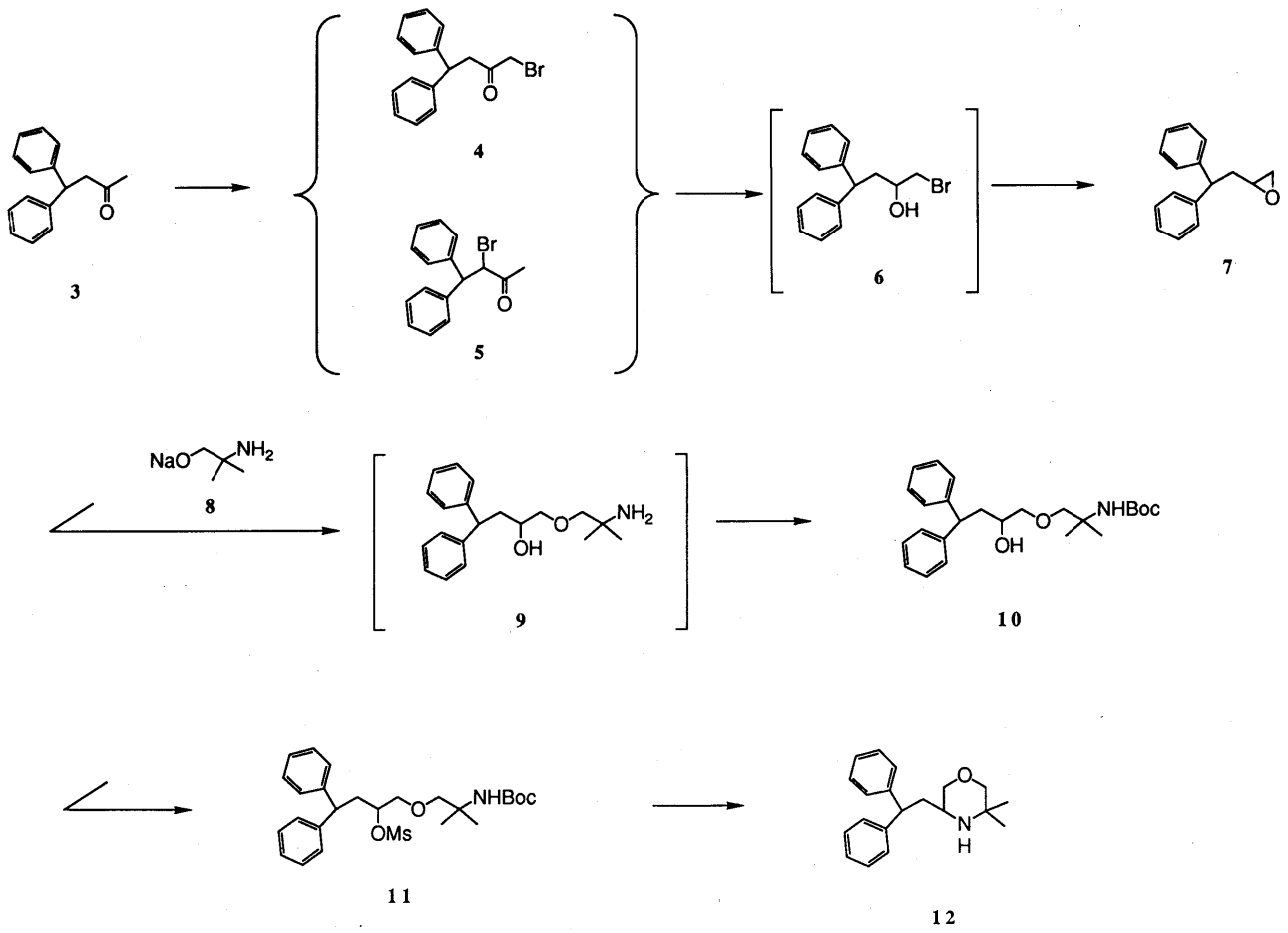


Chart 1

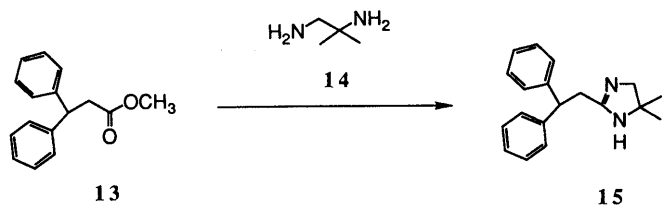


Chart 2

prepared from **16**, followed by decarboxylation of the resulting diester afforded 3-oxopentanoic acid ester **17** in a 72% yield. A Michael addition of 2-nitropropane[12] to compound **18**, which was prepared *in situ* by treating compound **17** with formalin and NaOAc,[13] afforded nitro compound **19** in a 61% yield. Conversion of **19** to pyrrolidine **22** was accomplished as follows. Acid-catalyzed hydrolysis of **19**, followed by decarboxylation, led to γ-nitroketone **20**. Reduction of the nitro group of **20** with Fe/NH_4Cl and subsequent treatment of the resulting pyrroline derivative **21** with lithium aluminum hydride ($LiAlH_4$) afforded pyrrolidine **22**.

Reduction of the nitro group in compound **19** with Fe/NH_4Cl afforded pyrroline **23** having a methoxycarbonyl group at the 3-position in a 91% yield. Conversion of this methoxycarbonyl group to an *exo*-methylene group was accomplished as follows. Reduction of both the imino and the ester groups of **23** with $LiAlH_4$ afforded pyrrolidine **24** in a 79% yield. After protection of the amino group with the *tert*-butoxycarbonyl (*tert*-Boc) group, alcohol **25** was converted to iodo compound **27** *via* methanesulfonate **26**. Treatment of **27** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 60 °C for 6.5 h, followed by removal of *tert*-Boc group, afforded the desired pyrrolidine derivative **29**.

Chart 5 shows the synthetic route to pyrrolidine derivatives (**41**—**45**) with an isopropylidene group at the 3-position. Condensation of nitriles (**30**—**34**) with 2,5-dimethyl-2,5-hexanediol (**35**) was carried out in the presence of conc. sulfuric acid (H_2SO_4) according to the Meyers' procedure[14] to afford pyrrolines (**36**—**40**). It is desirable to use chloroform as a solvent to prevent polymerization. The requisite nitriles (**30**—**34**) were prepared by the following methods as shown in Chart 6: A, dehydration of 3,3-diphenylpropionamide or 3-phenyl-3-(2-pyridyl)propionamide; B, condensation of *N*-phenylbenzylamine and iodoacetonitrile; C, cyanomethylation of *N*,*N*-diphenylamine or substituted *N*,*N*-diphenylamine with formaline and sodium cyanide; D, Horner–Emmons reaction of 4,4′-difluorobenzophenone and diethyl cyanomethylphosphonate. Treatment of 1-pyrrolines (**36**—**40**) with sodium borohydride ($NaBH_4$) afforded pyrrolidines (**41**—**45**), selectively, as reported by Meyers. Reduction of the imino group of **38a** with chiral reducing agent[15] {sodium tris [(*R*)-*N*-benzoprolyoxy]hydroborate}, instead of $NaBH_4$, afforded chiral pyrrolidine (+)-**43a** in 92.9% ee. Purification of the compound (+)-**43a** was accomplished by recrystallization of its 2 : 1 salt of L-tartaric acid ((+)-**43a**·1/2 L-tartaric acid). The antipode (−)-**43a** was prepared in a

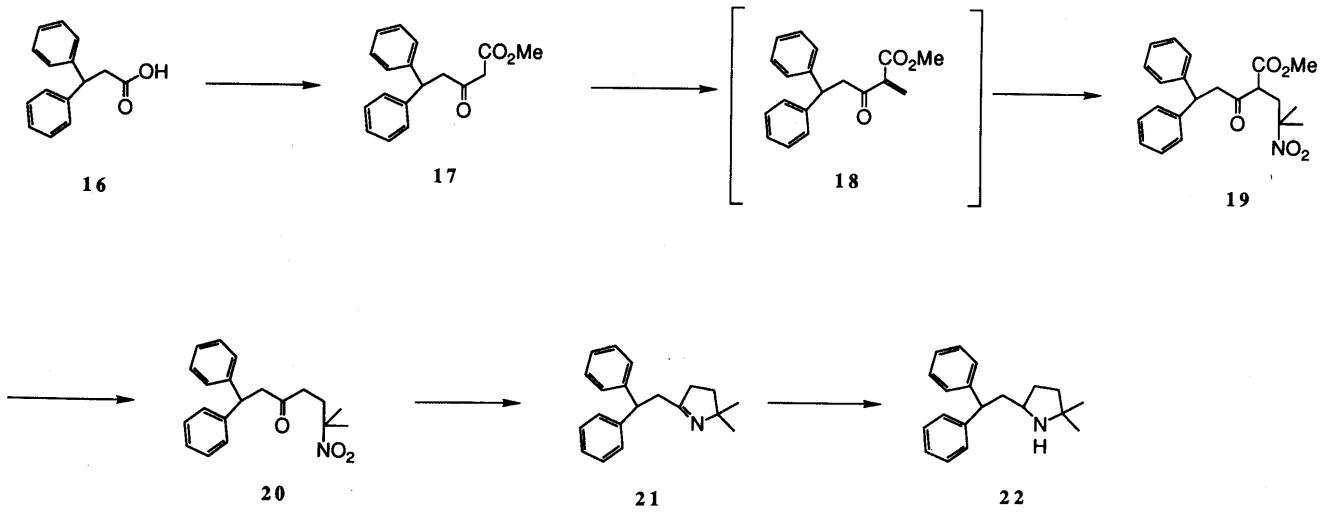
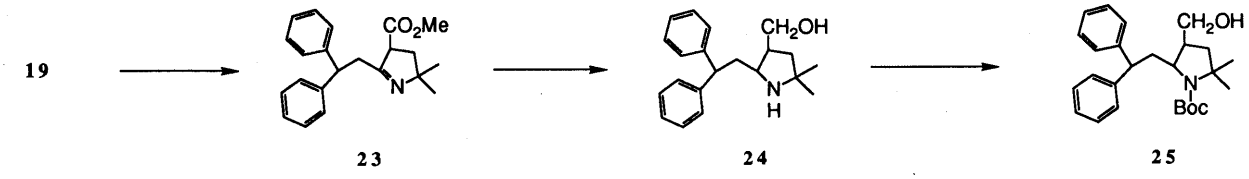
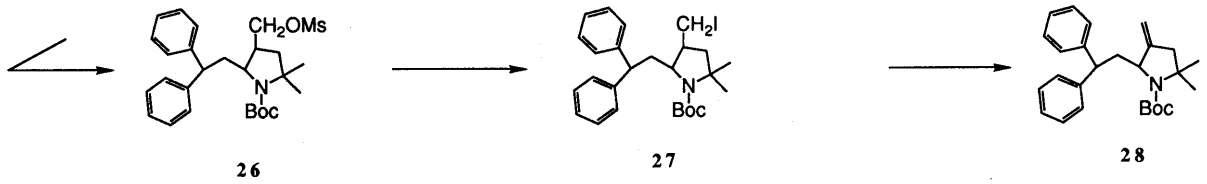


Chart 3





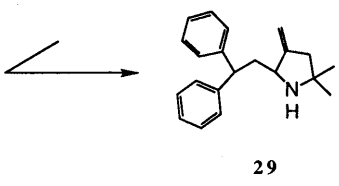


Chart 4

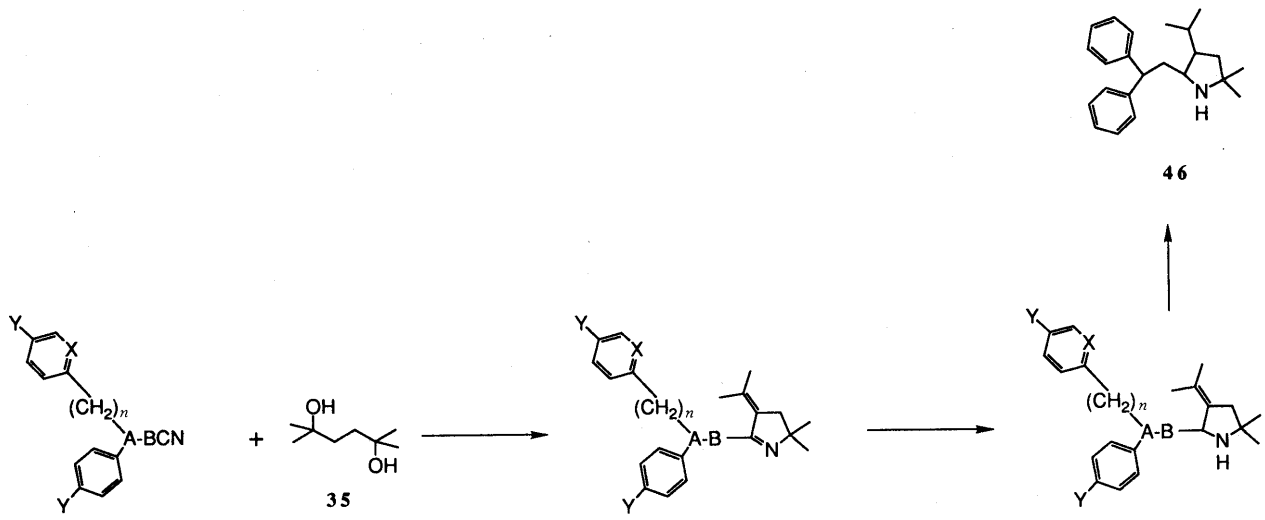
similar manner to the (+)-isomer using sodium tris [(*S*)-*N*-benzoprolyoxy]hydroborate as a reducing agent and D-tartaric acid as a resolving agent. Catalytic hydrogenation of the isopropylidene group of **41** afforded isopropyl derivative **46**.

Structure–Activity Relationships and Discussion The inhibitory activity of cyclic analogues of terodiline on urinary bladder rhythmic contractions in rat cystometry was evaluated. The test procedure was described in the preceding paper.[16] Tables I, II, and III show the results.

Morpholine-(**12**) and imidazoline-(**15**) derivatives showed a remarkable decrease of the activity. However, the simple pyrrolidine derivative **22** was found to retain activity.

Compounds **29** and **41** were synthesized to restrict spatial positions of the diphenylethyl side chain at the 2-position within a definite area by introducing methylene and isopropylidene substituents into the 3-position of the pyrrolidine ring. Methylene compound **29** reduced the activity, but isopropylidene compound **41** exhibited stronger activity than terodiline. On the other hand, conversion of isopropylidene compound **41** into isopropyl compound **46** remarkably decreased the activity.

These results may suggest that the bulky isopropylidene group located on the pyrrolidine ring interacts the two



30: X=CH, Y=H, n=0, A=CH, B=CH_2

31: X=CH, Y=F, n=0, A-B : C=CH

32a: X=CH, Y=H, n=0, A=N, B=CH_2

32b: X=CH, Y=F, n=0, A=N, B=CH_2

32c: X=CH, Y=MeO, n=0, A=N, B=CH_2

33: X=N, Y=H, n=0, A=CH, B=CH_2

34: X=CH, Y=H, n=1, A=N, B=CH_2

36: X=CH, Y=H, n=0, A=CH, B=CH_2

37: X=CH, Y=F, n=0, A-B : C=CH

38a: X=CH, Y=H, n=0, A=N, B=CH_2

38b: X=CH, Y=F, n=0, A=N, B=CH_2

38c: X=CH, Y=MeO, n=0, A=N, B=CH_2

39: X=N, Y=H, n=0, A=CH, B=CH_2

40: X=CH, Y=H, n=1, A=N, B=CH_2

41: X=CH, Y=H, n=0, A=CH, B=CH_2

42: X=CH, Y=F, n=0, A-B : C=CH

43a: X=CH, Y=H, n=0, A=N, B=CH_2

43b: X=CH, Y=F, n=0, A=N, B=CH_2

43c: X=CH, Y=MeO, n=0, A=N, B=CH_2

44: X=N, Y=H, n=0, A=CH, B=CH_2

45: X=CH, Y=H, n=1, A=N, B=CH_2

Chart 5

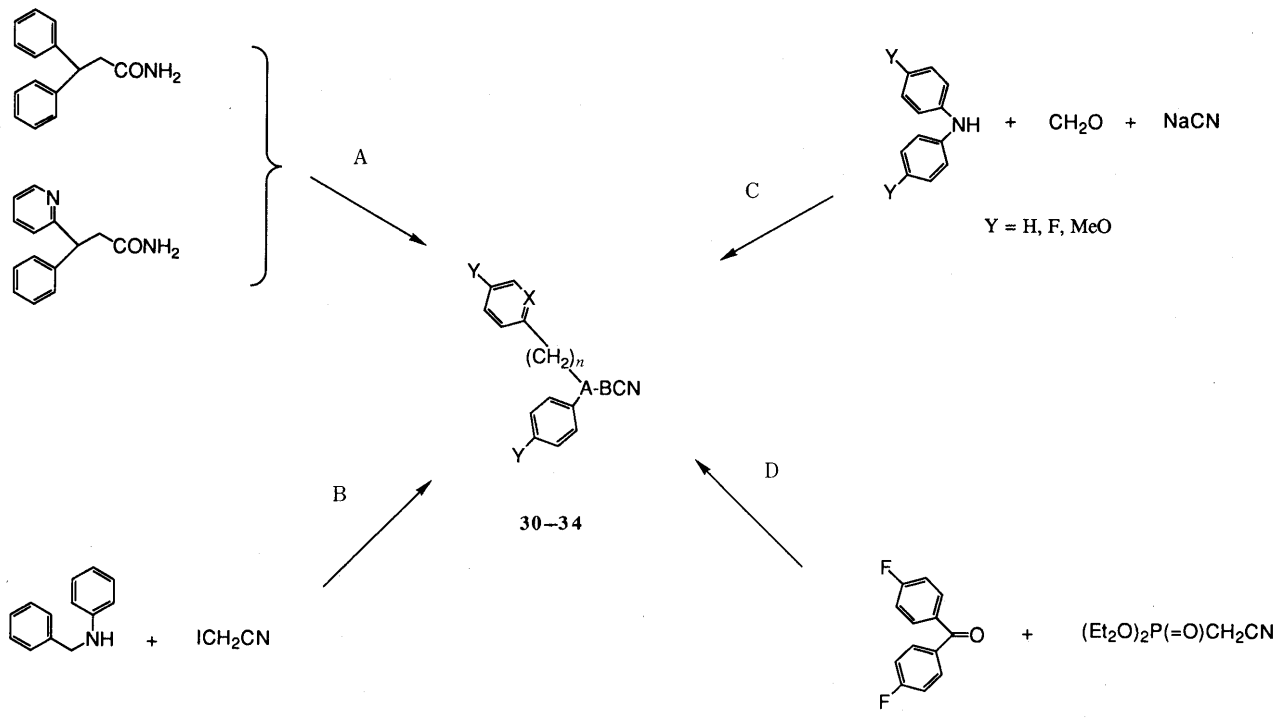


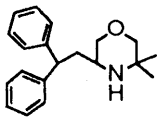
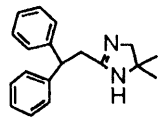
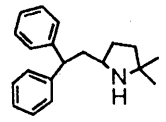
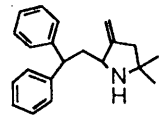
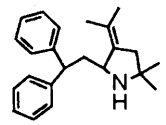
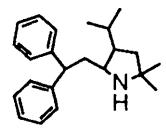
Chart 6

aromatic rings and determines the beneficial conformation to the activity.

Introduction of a double bond in the substituent at the 2-position (**42**) increased the activity. Shortening the length between the two aromatic rings and the isopropylidene group might increase their interaction and increase the activity.

Compound **41** had stronger activity in intravenous (i.v.)

Table I. Effect of Pyrrolidine Derivatives and Related Compounds on the Urinary Bladder Rhythmic Contractions in Rat Cystometry

Compd.	Structure	Salt	Inhibitory activity of bladder contraction: Dose (mg/kg) i.v.	% inhibition	Duration of action (min)
1	Terodiline		1	18.5	10
			3.2	35.0	15
12		MsOH	1	2.2	—
15		HCl	1	3.3	—
22		MsOH	1	22.0	2
29		MsOH	1	3.5	—
41		HCl	1	66.7	10
46		AcOH	1	10.5	—

The test compounds were administered as the salt indicated.

administration than terodiline, but it had less activity in intraduodenal (i.d.) administration (100 mg/kg, 31.7%) than terodiline (10 mg/kg, 38.2%). The lesser activity of **41** in i.d. administration was considered to be due to its poor i.d. absorption due to its high lipophilicity. To increase absorption, introduction of a hydrophilic nitrogen atom into compound **41** was attempted. Introduction of a nitrogen atom into the benzylic position (**43a**) retained the activity. On the other hand, introduction of a nitrogen atom into the benzene ring (**44a**, **44b**) or replacement of the benzene ring of **43a** with the benzyl group (**45**) decreased the activity. In the case of **43a**, the weak basicity of the amine in the substituent at the 2-position of the pyrrolidine ring is considered to make properties of the compound resemble those of the carbon analog (**41**) and to maintain the activity. It is of interest that each enantiomer of **43a** showed equipotent activity. Furthermore, the compound (−)-**43a** exhibited equipotent activity in i.d. administration (10 mg/kg, 37.7%) to terodiline as shown in Table III. The absorption of (−)-**43a** may be better than that of **41** by having a hydrophilic nitrogen atom at the benzylic position as we expected. As for the substituent at the 4-position of the benzene ring, fluorine atom (**43b**) maintained the activity. Further pharmacological evaluation of compounds **42**, (+)-**43a**, (−)-**43a**, **43b** is now in progress.

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 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-90H or Bruker AC-200P NMR spectrometers with tetramethylsilane as an internal standard. Mass (MS) spectra were recorded on a JEOL JMS D-300 MS spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400CHN elemental analyzer. Yields are not optimized.

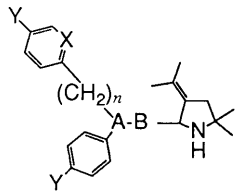
4,4-Diphenyl-1,2-epoxybutane (7) To a solution of 4,4-diphenyl-2-butanone (**3**)[10] (17.13 g) in MeOH (30 ml), HCl in MeOH (6.2 M, 10 ml) and a solution of bromine (4.2 ml) in MeOH (10 ml) were added at room temperature. The solution was poured into ice water and extracted with diisopropyl ether. The extract was washed successively with water, sat. $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with toluene as an eluent to afford an 8 : 2 mixture of 1-bromo-4,4-diphenyl-2-butanone (**4**) and 3-bromo-4,4-diphenyl-2-butanone (**5**) (19.77 g, 85%). **4**; NMR ($CDCl_3$, 90 MHz): 3.35 (2H, d, J=8 Hz), 3.66 (2H, s), 4.55 (1H, t, J=8 Hz), 7.03—7.50 (10H, m). **5**; NMR ($CDCl_3$, 90 MHz): 2.16 (3H, s), 4.50 (1H, d, J=11 Hz), 5.00 (1H, d, J=11 Hz), 7.03—7.50 (10H, m). To a solution of the compound obtained above (1.67 g) in MeOH (5 ml), $NaBH_4$ (0.06 g) was added. After stirring for 30 min, dil. HCl was added to the solution. Diisopropyl ether and brine were added to the solution and the organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in MeOH (2 ml) and sodium methoxide (28% in MeOH, 1.1 ml) was added to the solution. After stirring for 15 min, brine and EtOAc were added to the solution. 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 benzene as an eluent to afford **7** (0.75 g, 61%) as an oil. IR (neat) cm^{-1}: 1600, 1495, 1450. NMR ($CDCl_3$, 90 MHz): 2.16—2.46 (3H, m), 2.56—2.96 (2H, m), 4.16 (1H, t, J=8 Hz), 7.06—7.40 (10H, m). MS *m/z*: 224 (M^+), 206, 193, 167.

***tert*-Butyl *N*-[2-(2-Hydroxy-4,4-diphenylbutyloxy)-1,1-dimethylethyl]-carbamate (10)** To a solution of 2-amino-2-methyl-1-propanol (6.08 g) in *N*,*N*-dimethylformamide (DMF) (3 ml), NaH (60% dispersion in oil, 0.90 g) was added and the mixture was stirred for 15 min. To the mixture, **7** (3.30 g) was added and stirred for 2 d. The mixture was poured into cold water and extracted with diisopropyl ether. The extract was washed with water and then treated with dil. H_2SO_4. The aqueous layer was separated, made alkaline with NaOH solution, and extracted with diisopropyl ether. The extract was evaporated *in vacuo* to afford an oil (2.32 g). The obtained oil was dissolved in CH_2Cl_2 (6 ml) and di-*tert*-butyl dicarbonate (1.77 g) was added thereto. After stirring for 1 d, water and EtOAc were added to the solution. The organic layer was separated, washed with NaOH solution, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and EtOAc (9 : 1) as an eluent to afford **10** (1.40 g, 23%) as an oil. IR (neat) cm^{-1}: 3420, 1720, 1600, 1500. NMR ($CDCl_3$, 90 MHz): 1.25 (6H, s), 1.40 (9H, s), 2.12 (2H, dd, J=8, 6 Hz), 2.25 (1H, d, J=3 Hz), 3.16—3.83 (3H, m), 3.33 (2H, s), 4.23 (1H, t, J=8 Hz), 4.56 (1H, br s), 7.25 (10H, s).

***tert*-Butyl *N*-[1,1-Dimethyl-2-(2-methylsulfonyl-4,4-diphenylbutyloxy)-ethyl]carbamate (11)** To a solution of **10** (0.70 g) in pyridine (6 ml), methanesulfonyl chloride (0.22 g) was added. After stirring for 3 d, dil. HCl and EtOAc were added to the solution. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford **11** (0.84 g, 100%) as an oil. IR (neat) cm^{-1}: 3400, 1720, 1600, 1500, 1175. NMR ($CDCl_3$, 90 MHz): 1.26 (6H, s), 1.39 (9H, s), 2.46 (2H, t, J=7 Hz), 2.91 (3H, s), 3.37 (2H, s), 3.44—3.76 (2H, m), 4.14 (1H, t, J=7 Hz), 4.43—4.80 (2H, m), 7.20 (10H, s).

3-(2,2-Diphenylethyl)-5,5-dimethylmorpholine Methanesulfonate (12·MsOH) To a solution of **11** (0.84 g) in CH_2Cl_2 (20 ml), trifluroacetic acid (1 ml) was added. After stirring for 1 d, the solution was evaporated *in vacuo* and the residue was dissolved in EtOAc. The solution was washed with NaOH solution and then brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in DMF and heated at 100 °C for 8 h. After cooling, the solution was poured into dil. NaOH solution and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column

TABLE II. Effect of Pyrrolidine Derivatives on the Urinary Bladder Rythmic Contractions in Rat Cystometry



Compd.	X	Y	n	A	B	Salt	Inhibitory activity of bladder contraction		
							Dose (mg/kg) i.v.	% inhibition	Duration of action (min)
1				Terodiline			1	18.5	10
							3.2	35.0	15
42	CH	F	0	C=CH		HCl	1	100	10
43a	CH	H	0	N	CH_2	MsOH	1	35.5	2
(−)-**43a**	CH	H	0	N	CH_2	HCl	1	37.0	2
							3.2	73.0	10
(+)-**43a**	CH	H	0	N	CH_2	HCl	1	37.0	2
							3.2	80.0	10
43b	CH	F	0	N	CH_2	MsOH	1	27.2	10
							3.2	73.4	>30
43c	CH	MeO	0	N	CH_2	MsOH	1	16.7	—
44a[a]	N	H	0	CH	CH_2	2HCl	1	4.9	—
44b[b]	N	H	0	CH	CH_2	2HCl	1	−4.0	—
45	CH	H	1	N	CH_2	MsOH	1	10.7	—

The test compounds were administered as the salt indicated. *a*) Diastereomer mixture A, higher *Rf* value. *b*) Diastereomer mixture B, lower *Rf* value.

TABLE III. Effect of (−)-**43a**, (+)-**43a** on the Urinary Bladder Rhythmic Contractions in Rat Cystometry in Intraduodenal Administration

Compd.	Dose (mg/kg) i.d.	% inhibition
Terodiline	10	38.2
	32	46.8
(−)-**43a**	10	37.7
	32	80.2
(+)-**43a**	10	12.0
	32	91.0

chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (9 : 1) as an eluent to afford **12** (0.50 g, 100%) as an oil. IR (neat) cm^{-1}: 3090, 3060, 3030, 1600, 1495. NMR ($CDCl_3$, 90 MHz): 0.94 (3H, s), 1.04 (3H, s), 1.84—2.07 (2H, m), 2.74—3.94 (5H, m), 4.04 (1H, t, J=8 Hz), 7.23 (10H, s). MS *m/z*: 295 (M^+), 280, 250, 167. To a solution of **12** (0.72 g) in MeOH, methanesulfonic acid (225 mg) was added and the solution was evaporated *in vacuo*. The residue was dissolved in hot EtOAc and the solution was allowed to stand at room temperature. The resulting precipitates were collected by filtration and dried to afford **12**·MsOH (0.61 g, 64%), mp 190—192 °C. *Anal.* Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.58; H, 7.80; N, 3.56. IR (Nujol) cm^{-1}: 2510, 1610, 1220, 1160, 1040. NMR ($CDCl_3$, 90 MHz): 1.11 (3H, s), 1.30 (3H, s), 2.03—2.88 (2H, m), 2.76 (3H, s), 2.98—3.88 (5H, m), 4.08 (1H, t, J=8 Hz), 7.04—7.40 (10H, m), 8.30—9.20 (2H, br m).

2-(2,2-Diphenylethyl)-5,5-dimethylimidazoline Hydrochloride (15·HCl) A mixture of **13** (3.05 g) and 1,1-dimethylethylenediamine (**14**) (1.34 g) was heated at 170 °C for 4 h. After cooling, the mixture was purified by column chromatography on silica gel with a mixture of EtOH and $CHCl_3$ (saturated with ammonia) (1 : 20) as an eluent. The purified **15** was dissolved in diisopropyl ether. To the solution was added 3 N HCl in MeOH (4 ml) and evaporated *in vacuo* to afford **15**·HCl (1.21 g, 30%) as a powder, mp 171—173 °C (recrystallized from isopropyl alcohol). *Anal.* Calcd for $C_{19}H_{22}N_2$·HCl: C, 72.48; H, 7.36; N, 8.90. Found: C, 72.19; H, 7.55; N, 8.83. IR (Nujol) cm^{-1}: 3230, 3060, 2700, 1605, 1500. NMR ($CDCl_3$, 200 MHz): 1.10 (6H, s), 3.25 (2H, s), 3.43 (2H, d, J=8.8 Hz), 5.12 (1H, t, J=8.8 Hz), 7.06—7.50 (10H, m), 10.58 (1H, s), 10.95 (1H, s).

Methyl 3-Oxo-5,5-diphenylpentanoate (17) To a suspension of **16** (50.70 g) in CH_2Cl_2 (100 ml), $SOCl_2$ (27.99 g) and 5 drops of DMF were added and the mixture was stirred for 4 h. The above solution was added dropwise to a solution of Meldrum's acid (32.29 g) in pyridine (70.90 g) and CH_2Cl_2 (100 ml) at 4—13 °C and the whole was stirred at room temperature overnight. To the mixture, ice (150 g) and CH_2Cl_2 (200 ml) were added and the mixture was acidified with conc. HCl (60 ml). The organic layer was separated, washed successively with aq. $NaHCO_3$, water, and brine, dried over Na_2SO_4, and evaporated *in vacuo*. To the residue, MeOH (350 ml) was added and refluxed for 4.5 h. After cooling, the mixture was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel with a mixture of *n*-hexane and EtOAc (8 : 1) as an eluent to afford **17** (53.80 g) as an oil. This oil was crystallized from petroleum ether (45.24 g, 72%), mp 55—56.5 °C. *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.45; H, 6.65. IR (Nujol) cm^{-1}: 1740, 1710, 1600, 1490. NMR ($CDCl_3$, 90 MHz): 3.30 (2H, d, J=7 Hz), 3.63 (3H, s), 4.56 (1H, t, J=7 Hz), 7.20 (10H, s).

Methyl 2-(2-Methyl-2-nitropropyl)-3-oxo-5,5-diphenylpentanoate (19) To a solution of NaOAc (7.02 g) in 37% formaline (6.78 g), a solution of **17** (20.00 g) in MeOH (90 ml) was added dropwise at 25—30 °C. After stirring for 1 h, water (210 ml) and EtOAc (300 ml) were added to the mixture. The organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to afford **18** (20.83 g). This compound was used to the next reaction without purification. To a solution of 2-nitropropane (6.31 g) in DMF (70 ml), NaOMe (28% in MeOH, 13.66 g) was added at 4—8 °C and the whole was stirred for 30 min. To the mixture, a solution of **18** (20.83 g) in DMF (100 ml) was added dropwise at 4—10 °C and the whole was stirred at room temperature overnight. The mixture was poured into ice water and extracted with a mixture of diisopropyl ether and EtOAc. 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 (7 : 1) as an eluent to afford **19** (16.53 g, 61%) as an oil. IR (neat) cm^{-1}: 1740, 1715, 1535. NMR ($CDCl_3$, 90 MHz): 1.35 (3H, s), 1.46 (3H, s), 2.36 (2H, d, J=6 Hz), 3.33 (2H, dd, J=2, 8 Hz), 3.46 (1H, t, J=6 Hz), 3.60 (3H, s), 4.60 (1H, t, J=8 Hz), 7.00—7.20 (10H, m). MS *m/z*: 384 (M^++1), 337, 335.

6-Methyl-6-nitro-1,1-diphenylheptan-3-one (20) To a solution of **19** (8.00 g) in 2-methoxyethanol (107 ml), water (18 ml) and conc. H_2SO_4 (4.1 ml) were added and stirred for 24 h at 100 °C. After cooling, the mixture was treated with water and extracted with diisopropyl ether. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was triturated with petroleum ether to afford **20** (4.85 g, 71%), mp 89—91 °C (recrystallized from diisopropyl ether). *Anal.* Calcd for

$C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.48; H, 7.18; N, 4.24. IR (Nujol) cm^{-1}: 1700, 1600, 1525, 1490. NMR ($CDCl_3$, 90 MHz): 1.43 (6H, s), 1.86—2.40 (4H, m), 3.33 (2H, d, $J=8$ Hz), 4.51 (1H, d, $J=8$ Hz), 7.00—7.30 (10H, m).

2-(2,2-Diphenylethyl)-5,5-dimethyl-1-pyrroline (21) To a suspension of iron powder (4.06 g) and NH_4Cl (1.29 g) in EtOH (80 ml) and water (24 ml), **20** (3.93 g) was added at 74—78 °C and the whole was stirred for 4 h at 80 °C. The insoluble material was filtered off and the filtrate was evaporated *in vacuo*. To the residue, sat. $NaHCO_3$ (20 ml) was added and extracted with EtOAc (80 ml). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford **21** (3.06 g, 91%), mp 137—140 °C (recrystallized from diisopropyl ether). *Anal.* Calcd for $C_{20}H_{23}N$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.58; H, 7.84; N, 4.76. IR (Nujol) cm^{-1}: 1595, 1490, 1250, 1215. NMR ($CDCl_3$, 90 MHz): 1.26 (6H, s), 1.65—1.86 (2H, m), 2.10—2.35 (2H, m), 3.20 (2H, d, $J=8$ Hz), 4.50 (1H, t, $J=8$ Hz), 7.13—7.35 (10H, m).

2-(2,2-Diphenylethyl)-5,5-dimethylpyrrolidine Methanesulfonate (22·MsOH) To a suspension of $LiAlH_4$ (0.38 g) in tetrahydrofuran (THF) (28 ml), **21** (1.40 g) was added at 22—28 °C and stirred for 30 min. Excess $LiAlH_4$ was destroyed with 2 N HCl (5 ml) and the solution was made alkaline with 2 N NaOH (7 ml). The insoluble material was filtered off and the organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford **22** (1.06 g, 75%), mp 114.5—116 °C (recrystallized from diisopropyl ether). *Anal.* Calcd for $C_{20}H_{25}N \cdot H_2O$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.84; H, 8.94; N, 4.77. IR (Nujol) cm^{-1}: 3260, 1600, 1500. NMR ($CDCl_3$, 90 MHz): 0.96 (3H, s), 1.20 (3H, s), 1.30—1.90 (4H, m), 1.90—2.30 (1H, m), 2.53—3.25 (2H, m), 3.96 (1H, dd, $J=10$, 7 Hz), 4.23 (1H, br s), 7.05—7.30 (10H, m). To a solution of **22** (0.30 g) in MeOH, a solution of methanesulfonic acid (103 mg) in MeOH was added. The solution was evaporated *in vacuo* to afford **22**·MsOH (0.40 g, 99%), mp 169 °C (dec.) (recrystallized from ethyl acetate). *Anal.* Calcd for $C_{21}H_{29}NSO_3 \cdot H_2O$: C, 64.09; H, 7.94; N, 3.56. Found: C, 64.36; H, 7.80; N, 3.57. IR ($CHCl_3$) cm^{-1}: 3000—2150,1600, 1495, 1450. NMR ($CDCl_3$, 90 MHz): 1.16 (3H, s), 1.60 (3H, s), 1.65—2.40 (4H, m), 2.53—3.50 (3H, m), 3.96 (1H, dd, $J=10$, 7 Hz), 7.00—7.35 (10H, m), 12.20 (1H, s), 12.26 (1H, s).

Methyl 2-(2,2-Diphenylethyl)-5,5-dimethyl-1-pyrroline-3-carboxylate (23) To a suspension of iron powder (6.55 g) and NH_4Cl (0.62 g) in EtOH (80 ml) and water (45 ml), **19** (7.50 g) was added at 75—80 °C and stirred for 4 h at 80 °C. The insoluble material was filtered off and the filtrate was evaporated *in vacuo*. To the residue, sat. $NaHCO_3$ was added and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was triturated with petroleum ether to afford **23** (5.99 g, 91%) as a powder, mp 96—97.5 °C (recrystallized from a mixture of *n*-hexane and EtOAc). IR (Nujol) cm^{-1}: 1730, 1590, 1495. NMR ($CDCl_3$, 90 MHz): 1.10 (3H, s), 1.42 (3H, s), 1.92 (1H, dd, $J=15$, 9 Hz), 2.15 (1H, dd, $J=15$, 6 Hz), 2.82 (1H, dd, $J=15$, 9 Hz), 3.13 (1H, dd, $J=9$, 6 Hz), 3.68 (1H, dd, $J=15$, 9 Hz), 3.73 (3H, s), 4.56 (1H, t, $J=9$ Hz), 7.00—7.35 (10H, m).

2-(2,2-Diphenylethyl)-5,5-dimethylpyrrolidine-3-methanol (24) To a suspension of $LiAlH_4$ (1.36 g) in THF (45 ml), **23** (1.50 g) was added at 23—28 °C. After stirring for 4.5 h, excess $LiAlH_4$ was destroyed with 2 N HCl and the solution was made alkaline with 2 N NaOH. The insoluble material was filtered off and the organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford **24** (1.09 g, 79%), mp 133.5—136.5 °C (recrystallized from a mixture of *n*-hexane and EtOAc). IR (Nujol) cm^{-1}: 3300, 1600, 1490, 1050. NMR ($CDCl_3$, 90 MHz): 1.02 (3H, s), 1.20 (3H, s), 1.20—2.00 (2H, m), 2.20—3.00 (4H, m), 3.00 (1H, br s), 3.20—3.70 (2H, m), 3.96—4.40 (2H, m), 7.00—7.35 (10H, m).

***N-tert*-Butoxycarbonyl-2-(2,2-diphenylethyl)-5,5-dimethylpyrrolidine-3-methanol (25)** To a suspension of **24** (0.97 g) and Et_3N (0.38 g) in aqueous acetone (4 ml of water and 10 ml of acetone), di-*tert*-butyl dicarbonate (0.82 g) was added and the mixture was stirred at room temperature overnight. Water (25 ml) was added to the mixture and the whole was stirred for 1 h. The resulting precipitates were collected by filtration and dried to afford **25** (1.21 g, 95%), mp 151—152 °C (dec.). *Anal.* Calcd for $C_{26}H_{35}NO_3 \cdot 0.75H_2O$: C, 73.81; H, 8.70; N, 3.31. Found: C, 73.48; H, 8.61; N, 3.29. IR (Nujol) cm^{-1}: 3400, 1745, 1595, 1490. NMR ($CDCl_3$, 90 MHz): 1.03 (3H, s), 1.22 (3H, s), 1.46 (9H, s), 1.40—1.65 (1H, m), 1.70—2.46 (4H, m), 2.85—3.13 (1H, m), 3.30—3.60 (2H, m), 4.23 (1H, t, $J=8$ Hz), 7.00—7.33 (10H, m).

***N-tert*-Butoxycarboxyl-2-(2,2-diphenylethyl)-5,5-dimethyl-3-methylsulfonyloxymethylpyrrolidine (26)** To a solution of **25** (0.89 g) and Et_3N (0.26 g) in THF (8 ml), a solution of methanesulfonyl chloride (0.25 g) in THF (2 ml) was added dropwise at 3—9 °C. After stirring for 3 h, brine was added to the mixture. The organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (40 : 1) as an eluent to afford **26** (1.06 g, 100%) as an oil. IR (neat) cm^{-1}: 1760, 1600, 1490. NMR ($CDCl_3$, 90 MHz): 1.06 (3H, s), 1.23 (3H, s), 1.46 (9H, s), 1.50—1.63 (1H, m), 1.75—2.46 (4H, m), 2.80 (3H, s), 2.86—3.20 (1H, m), 4.00 (2H, d, $J=5$ Hz), 4.20 (1H, t, $J=8$ Hz), 7.00—7.35 (10H, m). MS *m/z*: 487 (M^+), 411, 387, 372.

***N-tert*-Butoxycarbonyl-2-(2,2-diphenylethyl)-3-iodomethyl-5,5-dimethylpyrrolidine (27)** A mixture of **26** (0.78 g) and NaI (0.31 g) in hexamethylphosphoramide (HMPA) (0.8 ml) and benzene (8 ml) was stirred at 70 °C for 4 h. After cooling, brine (40 ml) and diisopropyl ether were added to the mixture. The organic layer was separated, washed with $Na_2S_2O_3$ solution and then 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 and EtOAc (25 : 1) as an eluent to afford **27** (0.76 g, 92%) as an oil. IR (neat) cm^{-1}: 1760, 1600, 1490. NMR ($CDCl_3$, 90 MHz): 1.08 (3H, s), 1.22 (3H, s), 1.46 (9H, s), 1.46—1.63 (1H, m), 1.75—2.40 (4H, m), 2.70—3.25 (3H, m), 4.26 (1H, t, $J=8$ Hz), 7.00—7.30 (10H, m). MS *m/z*: 463 ($M^+ - tert$-Bu), 435, 420, 308, 254, 238.

***N-tert*-Butoxycarbonyl-2-(2,2-diphenylethyl)-5,5-dimethyl-3-methylenepyrrolidine (28)** A solution of **27** (0.66 g) and DBU (0.21 g) in dimethylsulfoxide (DMSO) (0.8 ml) and benzene (8 ml) was stirred at 60 °C for 6.5 h. After cooling, benzene was removed by evaporation and EtOAc and brine were added thereto. The organic layer was separated, 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 (20 : 1) as an eluent to afford **28** (0.44 g, 88%) as an oil. IR (neat) cm^{-1}: 1765, 1600, 1495. NMR ($CDCl_3$, 90 MHz): 1.02 (3H, s), 1.23 (3H, s), 1.51 (9H, s), 2.20—2.55 (4H, m), 3.40—3.80 (1H, m), 4.26 (1H, t, $J=8$ Hz), 4.73—4.93 (2H, m), 7.00—7.33 (10H, m). MS *m/z*: 390 ($M^+ - 1$), 341, 323, 307, 289, 274.

2-(2,2-Diphenylethyl)-5,5-dimethyl-3-methylenepyrrolidine Methanesulfonate (29·MsOH) To a solution of **28** (0.38 g) in CH_2Cl_2 (8 ml), trifluoroacetic acid (0.37 ml) was added at 0 °C. After stirring for 1 h, the solvent was removed by evaporation. The residue was made alkaline with NaOH solution and extracted with EtOAc. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chrommatography on silica gel with a mixture of *n*-hexane and EtOAc as an eluent to afford **29** (0.31 g) as an oil. This product was triturated with petroleum ether to afford a powder (0.21 g, 75%), mp 96—98 °C. IR (Nujol) cm^{-1}: 3280, 1600, 1495. NMR ($CDCl_3$, 90 MHz): 0.95 (3H, s), 1.15 (3H, s), 2.13—2.36 (2H, m), 2.46 (2H, dd, $J=6$, 8 Hz), 3.00—3.35 (1H, m), 3.35—3.60 (1H, m), 4.30 (1H, t, $J=8$ Hz), 4.70—4.95 (2H, m), 7.00—7.35 (10H, m). To a solution of **29** (184 mg) in MeOH, a solution of methanesulfonic acid (61 mg) in MeOH was added and then evaporated *in vacuo* to afford **29**·MsOH (245 mg, 100%) as an viscous oil. IR ($CHCl_3$) cm^{-1}: 3500—2200, 1600, 1490, 1035. NMR ($CDCl_3$, 90 MHz): 1.22 (3H, s), 1.55 (3H, s), 2.20—2.90 (4H, m), 2.76 (3H, s), 3.73—4.00 (1H, m), 4.45 (1H, dd, $J=6$, 11 Hz), 4.96—5.20 (2H, m), 7.00—7.36 (10H, m). MS *m/z*: 290 ($M^+ - 1$), 167, 126.

3-Phenyl-3-(2-pyridyl)propionitrile (33) (Method A) A mixture of 3-phenyl-3-(2-pyridyl)propionic acid[17] (3.03 g) and urea (0.62 g) was stirred at 150 °C for 1 h. After cooling, the mixture was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (20 : 1) as an eluent to afford 3-phenyl-3-(2-pyridyl)propionamide (2.30 g) as a powder, mp 149—151 °C (recrystallized from EtOAc). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 73.90; H, 6.29; N, 12.27. IR (Nujol) cm^{-1}: 3340, 3150, 1670, 1635. NMR ($CDCl_3$, 200 MHz): 2.83 (1H, dd, $J=5.8$, 14.4 Hz), 3.41 (1H, dd, $J=9.2$, 14.4 Hz), 4.65 (1H, dd, $J=5.8$, 9.2 Hz), 5.40 (1H, br s), 5.86 (1H, br s), 7.05—7.70 (8H, m), 8.50—8.66 (1H, m). A solution of 3-phenyl-3-(2-pyridyl)propionamide (2.30 g), methanesulfonyl chloride (2.30 g), and Et_3N (2.00 g) in CH_2Cl_2 (5 ml) was stirred at room temperature for 2 d. To the solution, $CHCl_3$ and NaOH solution were added. The organic layer was separated and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and EtOAc (9 : 1) as an eluent to afford **33** (1.55 g, 73%) as an oil. IR (neat) cm^{-1}: 2240, 1580, 1560. NMR ($CDCl_3$, 90 MHz): 3.03 (1H, dd, $J=8$, 18 Hz), 3.40 (1H, dd, $J=8$, 18 Hz), 4.37 (1H, q, $J=8$ Hz), 7.00—7.66 (8H, m), 8.56 (1H, d, $J=5$ Hz). MS *m/z*: 208 (M^+), 180, 167, 131. Compound **30**[18] was prepared in a similar manner.

***N*-Benzyl-*N*-phenylaminoacetonitrile[19] (34)** (Method B) A solution of iodoacetonitrile (19.20 g) and *N*-phenylbenzylamine (21.04 g) in acetone (3 ml) was heated at 100 °C for 5 h. After cooling, diisopropyl ether and

TABLE IV. Physical Properties of Nitrile Derivatives

Compd.	mp (°C) (Recryst. solvent)	Method	Yield (%)	IR (cm^{-1})	NMR ($CDCl_3$, δ)
30[18]	84—86[a] (EtOH–pet. ether)	A	75	(Nujol) 2250, 1600, 1500	3.03 (2H, d, J=8 Hz), 4.40 (1H, t, J=8 Hz), 7.10—7.56 (10H, m)
31	78—79[b] (IPE)	D	85	(Nujol) 2200, 1595, 1495	5.63 (1H, s), 6.90—7.60 (8H, m)
32a[21]	Oil[c]	C	45	(neat) 2230, 1590, 1480	4.33 (2H, s), 6.80—7.40 (10H, m)
32b	Oil[d]	C	69	(neat) 2240, 1600, 1500	4.40 (2H, s), 6.80—7.30 (8H, m)
32c	63[e] (IPA)	C	86	(Nujol) 1500, 1280, 1240, 1035, 820	3.70 (6H, s), 4.30 (2H, s), 6.66—7.00 (8H, m)
33	Oil[f]	A	73	(neat) 2240, 1580, 1560	3.03 (1H, dd, J=8, 18 Hz), 3.40 (1H, dd, J=8, 18 Hz), 4.37 (1H, q, J=8 Hz), 7.00—7.66 (8H, m), 8.56 (1H, d, J=5 Hz)
34[19]	Oil[g]	B	33	(neat) 2250, 1600, 1500	4.03 (2H, s), 4.47 (2H, s), 6.76—7.43 (10H, m)

a) *Anal.* Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.86; H, 6.31; N, 6.75. *b*) *Anal.* Calcd for $C_{15}H_9F_2N$: C, 74.68; H, 3.76; N, 5.81. Found: C, 74.87; H, 3.65; N, 5.84. *c*) bp 125—140 °C (1 mmHg), MS *m/z*: 208 (M^+), 180, 168, 167, 77. *d*) 116—121 °C (0.09 mmHg), MS *m/z*: 244 (M^+), 204, 184, 157, 122, 95. *e*) *Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.37; H, 5.95; N, 10.36. *f*) MS *m/z*: 208 (M^+), 180, 167, 131. *g*) MS *m/z*: 222 (M^+), 180, 105, 91, 77. Pet. ether, petroleum ether; IPE, diisopropyl ether; IPA, isopropyl alcohol.

TABLE V. Physical Properties of 1-Pyrroline Derivatives

Compd.	mp (°C) (Recryst. solvent)	Yield (%)	IR (cm^{-1})	NMR ($CDCl_3$, δ)
36	Oil[a]	49	(neat) 1650, 1590	0.96 (6H, s), 1.76 (3H, s), 2.00 (3H, s), 2.20 (2H, s), 3.30 (2H, d, J=8 Hz), 4.46 (1H, t, J=8 Hz), 7.00—7.40 (10H, m)
37	117—119[b] (IPE)	18	(Nujol) 3430, 1660, 1600, 1565, 1500	1.05 (6H, s), 1.73 (3H, s), 1.98 (3H, br s), 2.30 (2H, br s), 6.60 (1H, s), 6.73—7.40 (8H, m)
39	Oil[c]	52	(neat) 3370, 1650, 1590, 1495, 1435	0.92 (3H, s), 1.00 (3H, s), 1.74 (3H, s), 2.02 (3H, s), 3.22 (1H, dd, J=14, 7 Hz), 3.61 (1H, dd, J=14, 8 Hz), 4.69 (1H, dd, J=7, 8 Hz), 6.90—7.66 (7H, m), 8.40—8.60 (1H, m)

Since pyrrolines **38a**, **38b**, **38c**, **40** were unstable, they were used to the next reaction without purification. *a*) MS *m/z*: 317 (M^+), 302, 240, 226, 167. *b*) *Anal.* Calcd for $C_{23}H_{23}F_2N$: C, 78.61; H, 6.60; N, 3.99. Found: C, 78.53; H, 6.46; N, 3.89. *c*) MS *m/z*: 318 (M^+), 303, 275, 240, 227. IPE, diisopropyl ether.

NaOH solution were added to the solution. The organic layer was separated and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with toluene as an eluent to afford **34** (8.42 g, 33%) as an oil. IR (neat) cm^{-1}: 2250, 1600, 1500. NMR ($CDCl_3$, 90 MHz): 4.03 (2H, s), 4.47 (2H, s), 6.76—7.43 (10H, m). MS *m/z*: 222 (M^+), 180, 105, 91, 77.

***N,N*-Bis(4-fluorophenyl)aminoacetonitrile (32b)** (Method C) To a solution of *N,N*-di-4-fluorophenylamine[20] (18.85 g) in acetic acid (40 ml), formaline (37% solution, 7.0 ml) and NaCN (4.67 g) were added at 5—7 °C and the whole was stirred at 45 °C for 2 h. After cooling, the solution was made alkaline with NaOH solution and extracted with diisopropyl ether. The extract was washed with NaOH solution and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by distillation under reduced pressure to afford **32b** (15.47 g, 69%), bp 116—121 °C (0.09 mmHg). IR (neat) cm^{-1}: 2240, 1600, 1500. NMR ($CDCl_3$, 90 MHz): 4.40 (2H, s), 6.80—7.30 (8H, m). MS *m/z*: 244 (M^+), 204, 184, 157, 122, 95. Compounds **32a**[21] and **32c** were prepared in a similar manner.

3,3-Bis(4-fluorophenyl)-2-propenonitrile (31) (Method D) To a suspension of NaH (60% dispersion in oil, 2.61 g) in THF (80 ml), a solution of diethyl cyanomethylphosphonate (10.50 g) in THF (70 ml) was added with ice bath cooling. After stirring for 2 h, a solution of 4,4'-difluorobenzophenone (8.62 g) in THF (50 ml) was added to the mixture. After stirring for 5 d, the solution was poured into ice water (100 ml) and NaCl was added to the mixture. The organic layer was separated and the aqueous layer was extracted with diisopropyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was triturated with a mixture of petroleum ether and diisopropyl ether to afford **31** (8.09 g, 85%), mp 78—79 °C (recrystallized from diisopropyl ether). *Anal.* Calcd for $C_{15}H_9F_2N$: C, 74.68; H, 3.76; N, 5.81. Found: C, 74.87; H, 3.65; N, 5.84. IR (Nujol) cm^{-1}: 2200, 1595, 1495. NMR ($CDCl_3$, 90 MHz): 5.63 (1H, s), 6.90—7.60 (8H, m).

2-(2,2-Diphenylethyl)-3-isopropylidene-5,5-dimethyl-1-pyrroline (36) A solution of **30** (3.57 g) and **35** (2.52 g) in $CHCl_3$ (45 ml) was added dropwise to conc. H_2SO_4 (15 ml) with ice bath cooling. After stirring for 2.5 h, the mixture was poured into ice water (150 ml) and made alkaline with NaOH solution. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was 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 $CHCl_3$ and MeOH (50 : 1) as an eluent to afford **36** (2.65 g, 49%) as an oil. IR (neat) cm^{-1}: 1650, 1590, 1495. NMR ($CDCl_3$, 90 MHz): 0.96 (6H, s), 1.76 (3H, s), 2.00 (3H, s), 2.20 (2H, s), 3.30 (2H, d, J=8 Hz), 4.46 (1H, d, J=8 Hz), 7.00—7.40 (10H, m). MS *m/z*: 317 (M^+), 302, 167.

Other pyrrolines (**37**—**40**) in Table V were prepared in a similar manner using nitriles (**31**—**34**) in Table IV.

2-(2,2-Diphenylethyl)-3-isopropylidene-5,5-dimethylpyrrolidine Hydrochloride (41·HCl) To a solution of **36** (0.14 g) in MeOH (3 ml), $NaBH_4$ (17 mg) was added. After stirring for 1.5 h, the solution was evaporated *in vacuo*. To the residue, water was added and 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 a mixture of $CHCl_3$ and MeOH (10 : 1) as an eluent to afford **41** (0.19 g, 92%) as an oil. IR (neat) cm^{-1}: 1600, 1595, 1450. NMR ($CDCl_3$, 90 MHz): 1.00 (3H, s), 1.23 (3H, s), 1.52 (3H, s), 1.60 (3H, s), 1.83—2.65 (4H, m), 3.45—3.85 (1H, m), 4.18 (1H, dd, J=12, 3 Hz), 6.90—7.43 (10H, m). MS *m/z*: 319 (M^+), 304, 167, 138. A mixture of **41** (1.03 g) and 1 N HCl (10 ml) was refluxed until a clear solution was obtained and the solution was allowed to cool. The resulting precipitates were collected by filtration and dried to afford **41**·HCl (0.95 g, 83%), mp 253—256 °C (dec.). *Anal.* Calcd for $C_{23}H_{29}N$·HCl: C, 77.60; H, 8.49; N, 3.94. Found: C, 77.58; H, 8.50; N, 3.84. IR (Nujol) cm^{-1}: 2720, 2700, 2570, 2500, 1585. NMR ($CDCl_3$, 90 MHz): 1.29 (3H, s), 1.40 (3H, s), 1.63 (6H, s), 2.20—2.70 (3H, m), 3.02 (1H, ddd, J=13, 9, 4 Hz), 4.03 (1H, br d, J=9 Hz), 4.42 (1H, dd, J=11, 4 Hz), 7.03—7.56 (10H, m).

Other compounds in Table VI (**42**, **43a**, **43b**, **43c**, **44a**, **44b**, **45**) were prepared in a similar manner.

(+)-2-(*N,N*-Diphenylaminomethyl)-3-isopropylidene-5,5-dimethylpyrrolidine Hydrochloride ((+)-43a·HCl) A solution of **38a** (2.00 g) in $CHCl_3$ was added to a solution of sodium tris [(*R*)-*N*-benzoprolyoxy]hydroborate[15] (8.75 g) in $CHCl_3$ at −20 °C and the solution was stored in a refrigerator overnight. To the solution, 7.5% HCl was added and stirred

TABLE VI. Physical Properties of Pyrrolidine Derivatives

Compd.	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
41	253—256 (dec.)	H_2O	76	$C_{23}H_{29}N \cdot HCl$	77.60	8.49	3.94	77.58	8.50	3.84
42	214—217 (dec.)	IPE	15	$C_{23}H_{25}F_2N \cdot HCl \cdot 0.5H_2O$	69.25	6.82	3.51	69.22	6.72	3.35
43a	159—162	EtOAc	16	$C_{23}H_{32}N_2SO_3 \cdot 0.25H_2O$	65.59	7.79	6.65	65.78	7.84	6.59
(+)-**43a**	238—240 (dec.)	EtOAc	39	$C_{22}H_{28}N_2 \cdot HCl \cdot 0.5H_2O$	72.21	8.26	7.66	72.50	7.93	7.50
(−)-**43a**	238—240 (dec.)	EtOAc	57	$C_{22}H_{28}N_2 \cdot HCl \cdot 0.5H_2O$	72.21	8.26	7.66	72.55	8.40	7.53
43b	182—186	EtOAc	10	$C_{23}H_{30}F_2N_2O_3S$	61.04	6.68	6.19	61.01	6.88	6.15
43c	147—149	EtOAc–IPE	6	$C_{25}H_{36}N_2O_5S$	63.00	7.61	5.88	63.19	7.88	5.82
44a	218—221	EtOAc	7	$C_{22}H_{28}N_2 \cdot 2HCl \cdot 1.5H_2O$	62.85	7.91	6.66	63.21	8.02	7.08
44b	196—199 (dec.)	EtOAc	26	$C_{22}H_{28}N_2 \cdot 2HCl \cdot 2H_2O$	61.53	7.98	6.52	61.86	8.37	6.40
45	125—127	EtOAc–EtOH	15	$C_{23}H_{30}N_2 \cdot 2HCl \cdot H_2O$	64.93	8.05	6.58	65.13	8.17	6.61
46	126—130	IPE	54	$C_{25}H_{35}F_2NO_2$	78.70	9.25	3.67	79.07	9.04	3.59

IPE, diisopropyl ether.

for 20 min. The mixture was made alkaline with NaOH solution and the organic layer was separated, washed with dil. HCl and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was crystallized from EtOAc to afford (+)-**43a**·HCl (1.18 g, 53%). $[\alpha]_D$ +160.4° (c=1.034, $CHCl_3$). The enantiomeric excess of this compound was determined to be 92.9% by high performance liquid chromatography (HPLC) analysis (column, SUMIPAX OA-3000 (Sumitomo) 4.6×250 mm; eluent, 100:2:0.05 *n*-hexane–EtOH–AcOH mixture; flow rate, 1.0 ml/min; t_R of (+)-**43a**, 18.1 min; t_R of (−)-**43a**, 19.9 min).

The above obtained salt [(+)-**43a**·HCl] (1.06 g, 2.97 mmol) was partitioned between EtOAc and NaOH solution. The organic layer was separated and washed with brine. To this solution, a solution of L-tartaric acid (221.8 mg, 1.48 mmol) in EtOH was added and evaporated *in vacuo*. The residue was recrystallized from EtOAc to afford (+)-**43a**·1/2L-tartaric acid (0.91 g, 2.30 mmol). This salt was partitioned between $CHCl_3$ and NaOH solution and the organic layer was separated, washed with dil. HCl, and evaporated *in vacuo*. The residue was recrystallized from EtOAc to afford pure (+)-**43a**·HCl (0.77 g, 2.16 mmol, 73%), mp 238—240 °C (dec.). $[\alpha]_D$ +186.5° (c=0.554, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{28}N_2 \cdot HCl \cdot 0.5H_2O$: C, 72.21; H, 8.26; N, 7.66. Found: C, 72.50; H, 7.93; N, 7.50. IR (Nujol) cm^{-1}: 2850—2200, 1600, 1585, 1490. NMR ($CDCl_3$, 90 MHz): 1.40 (3H, s), 1.60 (3H, s), 1.63 (6H, s), 2.43 (2H, s), 2.70—4.30 (1H, m), 4.50—4.85 (2H, m), 6.83—7.40 (10H, m), 8.40—9.15 (1H, br m), 11.15—12.10 (1H, br m). The enantiomeric excess of this compound was determined to be 98.1% by HPLC analysis.

(−)-2-(*N,N*-Diphenylaminomethyl)-3-isopropylidene-5,5-dimethylpyrrolidine Hydrochloride ((−)-43a·HCl) This compound was prepared in a similar manner to the (+)-isomer using sodium tris[(*S*)-*N*-benzoproloyoxy]hydroborate[15] as a reducing agent and D-tartaric acid as a resolving agent. mp 238—240 °C (dec.). $[\alpha]_D$ −181.5° (c=0.522, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{28}N_2 \cdot HCl \cdot 0.5H_2O$: C, 72.21; H, 8.26; N, 7.66. Found: C, 72.55; H, 8.40; N, 7.53. IR (Nujol) cm^{-1}: 2850—2200, 1600, 1585, 1490. NMR ($CDCl_3$, 90 MHz): 1.40 (3H, s), 1.60 (3H, s), 1.63 (6H, s), 2.42 (2H, s), 2.70—4.30 (1H, m), 4.50—4.85 (2H, m), 6.83—7.40 (10H, m), 8.40—9.05 (1H, br m), 11.15—12.10 (1H, br m). The enantiomeric excess of this compound was determined to be 97.3% by HPLC analysis.

2-(2,2-diphenylethyl)-3-isopropyl-5,5-dimethylpyrrolidine Acetate (46·AcOH) A solution of **41** (1.53 g) in a mixture of EtOH (50 ml) and AcOH (2 ml) was hydrogenated with 10% Pd on carbon (0.35 g) under atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was made alkaline with NaOH solution and 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 a mixture of $CHCl_3$ and MeOH (95:5) as an eluent to afford **46** (0.83 g) as an oil. To a solution of the obtained oil in diisopropyl ether was added AcOH (0.16 g). The resulting precipitates were collected by filtration and dried to afford **46**·AcOH (0.98 g, 54%), mp 126—130 °C. *Anal.* Calcd for $C_{25}H_{35}NO_2$: C, 78.70; H, 9.25; N, 3.67. Found: C, 79.07; H, 9.04; N, 3.59. IR (Nujol) cm^{-1}: 2800—2000, 1630, 1540. NMR (DMSO-d_6, 90 MHz): 0.88 (3H, s), 1.16 (3H, s), 1.50 (6H, d, J=7 Hz), 1.66—2.60 (6H, m), 1.86 (3H, s), 3.23—3.40 (1H, m), 4.10 (1H, dd, J=4, 12 Hz), 6.20 (2H, br s), 7.03—7.40 (10H, m).

References and Notes

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