# Agents for the Treatment of Overactive Detrusor. III. Synthesis and Structure–Activity Relationships of *N*-(4-Amino-2-butynyl)acetamide Derivatives

Kazuhiko TAKE,* Kazuo OKUMURA, Kazunori TSUBAKI, Takao TERAI, and Youichi SHIOKAWA

*New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 1–6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532, Japan.*
*Received September 26, 1991*

**A series of *N*-(4-amino-2-butynyl)acetamides were synthesized and examined for their inhibitory activity on detrusor contraction and mydriatic activity as an index of anticholinergic side effect. Among those compounds synthesized, (+)-2-cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide hydrochloride ((+)-13b·HCl), 2-cyclohexyl-2-hydroxy-*N*-(4-methylamino-2-butynyl)-2-phenylacetamide hydrochloride (13c·HCl), *N*-(4-dimethylamino-2-butynyl)-2,2-diphenyl-2-hydroxyacetamide hydrochloride (14a·HCl), and 2,2-diphenyl-*N*-(4-ethylamino-2-butynyl)-2-hydroxyacetamide hydrochloride (14b·HCl) showed equipotent inhibitory activity on detrusor contraction to oxybutynin (1) and less mydriatic activity. Further evaluation of these compounds as an agent for the treatment of overactive detrusor has been examined.**

**Keywords** acetamide; inhibitory activity; detrusor contraction; mydriasis; oxybutynin; overactive detrusor; anticholinergic

Overactive detrusor is a disease of which the characteristic syndrome is frequent urination. Oxybutynin (**1**), an agent used in treatment of the syndrome, possesses anticholinergic, local anesthetic, and spasmolytic activities which together inhibit detrusor contraction.[1] Clinically, **1** has two defects, one is frequent occurrence of side effects such as mydriasis and a dryness of the mouth, and the other is short duration of action.[2] The former is considered to be caused by its non-selective anticholinergic action, and the latter to be a result of the easy hydrolysis of the ester bond of oxybutynin by liver esterase.[3] Thus, we hoped to create a new drug without these drawbacks by modifying oxybutynin.

In order to reduce side effects we first considered decreasing the anticholinergic action. Second, in order to lengthen the duration of action we considered replacing the ester group with another functional group (amide, ether, or amine) which is not cleaved by esterase (Fig. 1). Modification of the ester function may change the anticholinergic activity of the compound.

Herein, we report the synthesis and structure–activity relationships of oxybutynin related compounds.

**Chemistry** Chart 1 shows the synthetic route to ether (**3**) and amino derivatives (**4**).

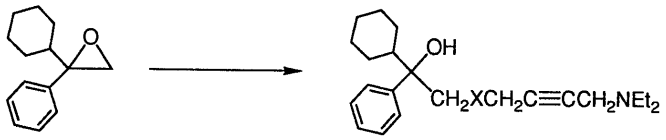
Ring opening of the epoxide (**2**) by alkoxide and amine afforded the compounds **3** and **4**, respectively.

Chart 2 shows the synthetic route to the 2-hydroxyacetamide derivatives (**13**—**16**).

Condensation of chloroacetyl chlorides (**5**—**7**) and diaminobutyne (**9**) and then acid hydrolysis of the obtained benzyl chlorides (**10**—**12**) afforded *N*-(4-amino-2-butynyl)-acetamides (**13**—**15**) (route A). Amidation of acid (**8**) with thionyl chloride and diamine (**9**) afforded compound **16**. Acylation of 4-amino-2-butynol[4a] (**17**) with chloroacetyl chlorides (**5**, **6**) and then acid hydrolysis of the obtained benzyl chlorides (**18**, **19**) afforded *N*-(4-hydroxy-2-butynyl)-acetamides (**20**, **21**). Chlorination of the acetamides (**20**, **21**) with the Vilsmeier reagent afforded *N*-(4-chloro-2-butynyl)-acetamides (**22**, **23**). Amination of the acetamides (**22**, **23**) afforded the *N*-(4-amino-2-butynyl)acetamides (**13**, **14**) (route B). Hydroxymethylation[5] of the *N*-(propargyl)acetamide (**25**) is a better route to compound **21** since 4-chloro-2-butynol,[4b] a precursor of the compound **17**, is very irritative.

The Mannich reaction of compound **25** is another synthetic route to *N*-(4-amino-2-butynyl)acetamide (**14**) (route C). De-4-methoxybenzylation of compound **26** using 1-chloroethyl chloroformate[6] afforded *N*-(4-monoalkylamino-2-butynyl)acetamide (**14**, $R^1=H$, $R^2=Et$) in good yield.

Chiral acetamides ((+)-**13b**, (−)-**13b**) were synthesized by optical resolution of the racemic mixture or by asymmetric synthesis.

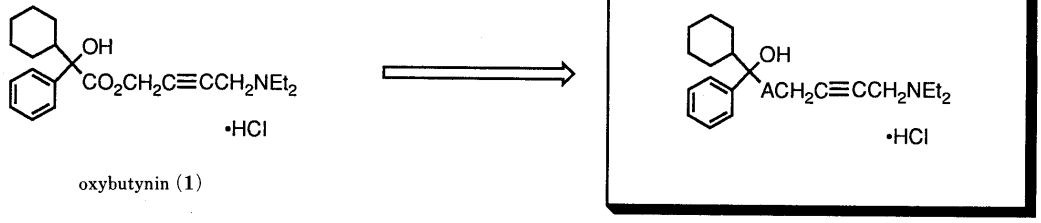



2

3 : X=O

4 : $X=NCH_3$

Chart 1




oxybutynin (1)

Fig. 1

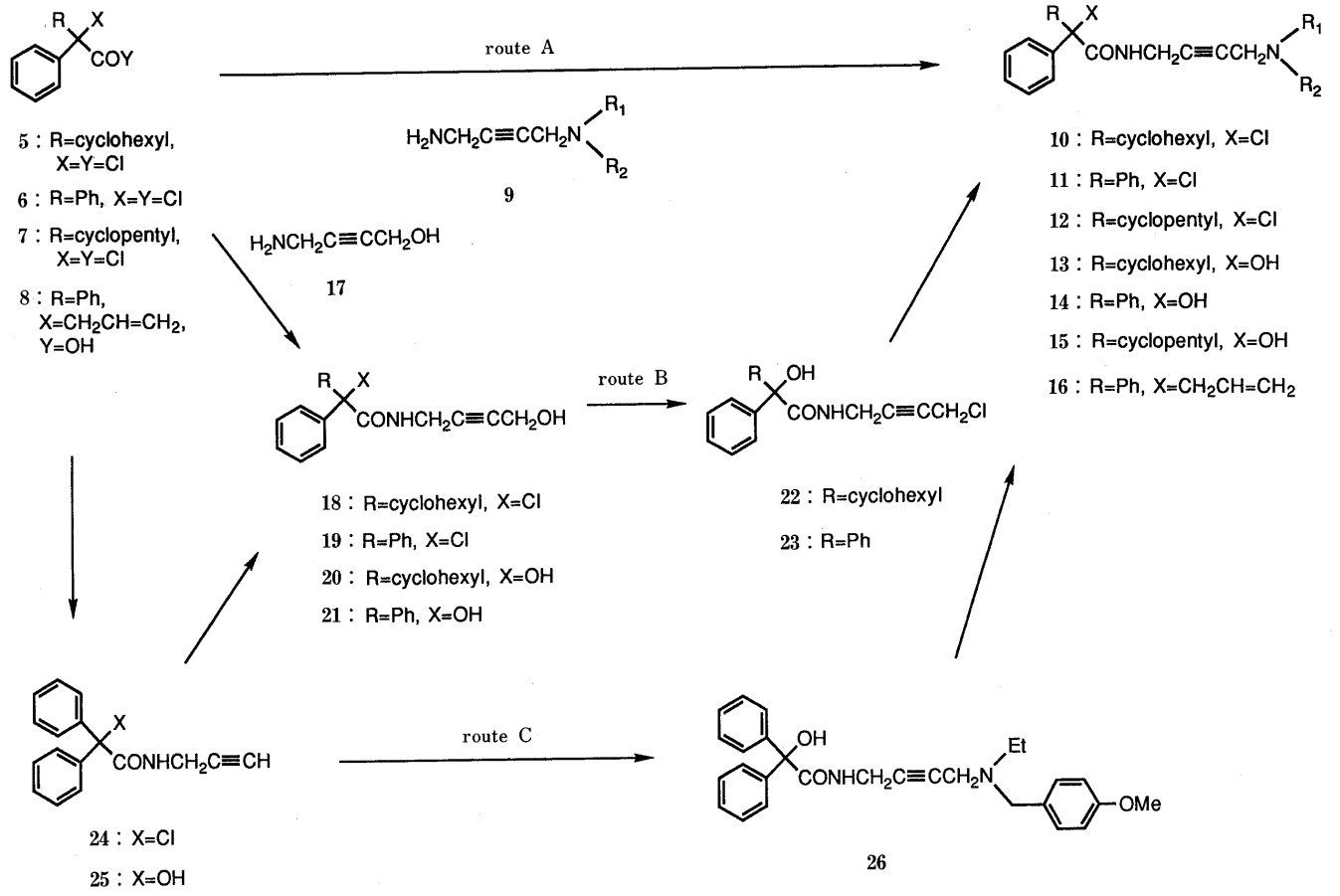



Chart 2

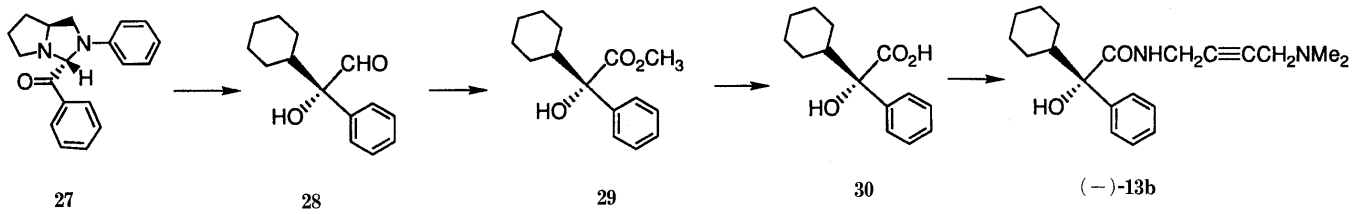



Chart 3

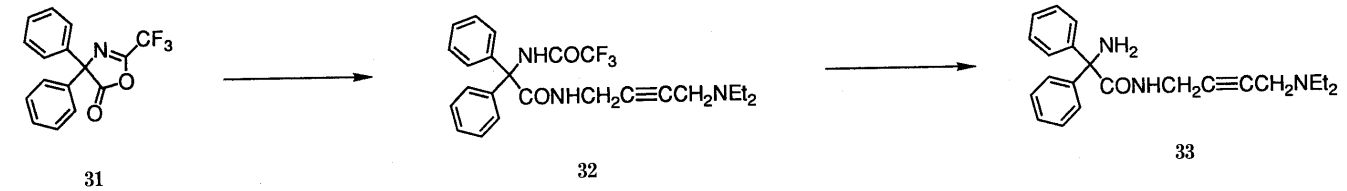


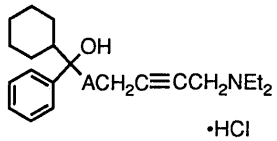

Chart 4

Optically active carboxylic acid ((*S*)-(+)-(**30**)) was obtained by optical resolution of its racemic carboxylic acid (±)-(**30**) using quinine as a resolving agent[7a-e] or by asymmetric synthesis starting from alkylation of aminal (**27**) as shown in Chart 3 in accordance with the literature.[7f]

Applying Mukaiyama's methodology,[8] chiral acetaldehyde ((*S*)-(+)-(**28**)) was obtained by alkylation of the animal (**27**) which was prepared from phenylglyoxal and (*S*)-2-(anilinomethyl)pyrrolidine and then acid hydrolysis. Oxidation of the acetaldehyde ((*S*)-(+)-(**28**)) using $I_2$/KOH–MeOH[9] afforded methyl acetate ((*S*)-(+)-(**29**)) and then hydrolysis of the ester afforded chiral acetic acid ((*S*)-(+)-(**30**)). Direct conversion of the acetaldehyde ((*S*)-(+)-(**28**)) to acetic acid ((*S*)-(+)-(**30**)) using $NaOCl_2$/2-methyl-2-butene[10] also afforded ((*S*)-(+)-(**30**)). Amidation of the optically active carboxylic acid ((*S*)-(+)-(**30**)) with carbonyldiimidazole and diamine (**9**) afforded optically active acetamide ((−)-(**13b**)).

For the optical resolution of racemate ((±)-(**13b**)), the use of 2 : 1 ratio salt prepared from (±)-(**13b**) and D-tartaric acid was better than that of 1 : 1 ratio. Before recrystallization, crude ((+)-(**13b**)·1/2 D-tartaric acid) was converted

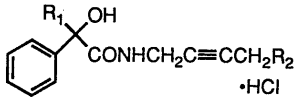
TABLE I. Effect of Compounds with Ether, Amino, and Amido Groups Instead of the Ester Function of Oxybutynin on Urinary Bladder Rhythmic Contractions[a] and Mydriasis[b] in Rats

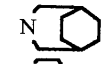
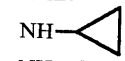



| Compound No. | A | Inhibitory activity of bladder contraction | | | Mydriatic activity | Selectivity |
|---|---|---|---|---|---|---|
| | | % inhibition at 1 mg/kg i.v. | Duration of action (min) | $ED_{30}$ (mg/kg) | MED[c] (mg/kg) | $MED/ED_{30}$ |
| **1**[d] | $CO_2$ | 61.5 | >30 | 0.21 | 0.1 | 0.48 |
| **3**[d] | $CH_2O$ | 14.7 | — | | NT | |
| **4**[d] | $CH_2NMe \cdot HCl$ | 7.4 | — | | NT | |
| **13a**[d] | CONH | 58.5 | >30 | 0.28 | 1.0 | 3.6 |

The test compounds were administered as hydrochloride. *a*) The inhibitory activity of bladder contraction was examined as described in the preceding paper.[15] *b*) The mydriatic activity was examined by the method of Parry and Heathcote.[16] *c*) MED=minimum effective dose. *d*) Racemate. NT=not tested.

TABLE II. Effect of Acetamide Derivatives on Urinary Bladder Rhythmic Contractions[a] and Mydriasis[b] in Rats




| Compound No. | $R_1$ | $R_2$ | Inhibitory activity of bladder contraction | | | Mydriatic activity | Selectivity |
|---|---|---|---|---|---|---|---|
| | | | % inhibition at 1 mg/kg i.v. | Duration of action (min) | $ED_{30}$ (mg/kg) | MED[c] (mg/kg) | $MED/ED_{30}$ |
| **13b**[d] |  | $NMe_2$ | 58.7 | >30 | 0.1 | 1.0 | 10 |
| (+)-**13b** |  | $NMe_2$ | 47.0 | >30 | 0.07 | 0.32 | 4.6 |
| (−)-**13b** |  | $NMe_2$ | 5.1 | — | | NT | |
| **13c**[d] |  | NHMe | 51.2 | >30 | 0.54 | 3.2 | 5.9 |
| **13d**[d] |  |  | −7.4 | — | | NT | |
| **13e**[d] |  |  | 5.7 | — | | NT | |
| **13f**[d] |  |  | 10.4 | — | | NT | |
| **13g**[d] |  |  | 9.6 | — | | NT | |
| **13h**[d] |  |  | 2.0 | — | | NT | |
| **13i**[d] |  | $NHCH_2CO_2Et$ | 1.1 | — | | NT | |
| **14a** | Ph | $NMe_2$ | 57.8 | >30 | 0.068 | 1.0 | 14.7 |
| **14b** | Ph | NHEt | 48.5 | >30 | 0.48 | 3.2 | 6.7 |
| **14c** | Ph |  | 47.3 | 5 | | NT | |
| **14d** | Ph | NH-*n*-Pr | 57.3 | 5 | | NT | |
| **15**[d] |  | $NMe_2$ | 63.8 | >30 | 0.056 | 0.1 | 1.8 |

The test compounds were administered as hydrochloride except compound **14d**. Compound **14d** was administered as a free form. *a*) The inhibitory activity of bladder contraction was examined as described in the preceding paper.[15] *b*) The mydriatic activity was examined by the method of Parry and Heathcote.[16] *c*) MED=minimum effective dose. *d*) Racemate. *e*) 2HCl salt. NT=not tested.

into its hydrochloride to remove more easily crystallized hydrochloride of racemate ((±)-(**13b**)·HCl), and then (+)-(**13b**)·HCl was again converted into the tartarate. Recrystallization of the (+)-(**13b**)·1/2 D-tartaric acid afforded optically pure (+)-(**13b**). The antipode, (−)-(**13b**), was obtained by an analogous method using L-tartaric acid.

Chart 4 shows the synthetic route to the 2,2-diphenylacetamides (**32**, **33**).

Amination of compound **31**[11] afforded 2-trifluoroacetylaminoacetamide (**32**). Acid hydrolysis of the compound **32** afforded 2-aminoacetamide (**33**).

**Structure–Activity Relationships and Discussion** Table I

shows the pharmacological activities of compounds when the ester group of oxybutynin is replaced by other functional groups.

The modification revealed that the ether (**3**) or the amine (**4**) decreased the inhibitory activity on detrusor contraction, but the amide (**13a**) retained the activity. Furthermore, the compound **13a** had weaker mydriatic activity than oxybutynin (**1**). These results were considered to be due to a decrease in the proportion of anticholinergic activity to inhibitory activity on detrusor contraction rather than to an increase in the selectivity of muscarinic acetylcholine receptors for the following reasons: 1) Generally, the muscarinic acetylcholine receptors in the pupil and the detrusor are classified as the same $M_3$ type.[12] 2) In a study of benactydine, a typical anticholinergic agent, the anticholinergic activity was decreased by replacing the ester group with the amido group.[13] Since the compound **13a** had less activity in i.d. administration (10 mg/kg, 12.6%) than oxybutynin (10 mg/kg, 47%), compound **13a** was investigated further.

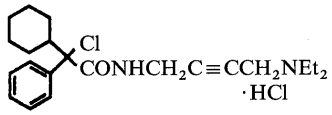
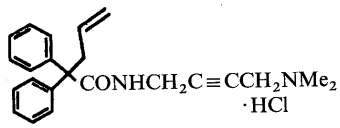
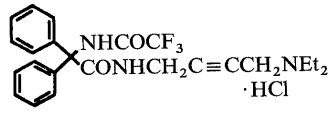
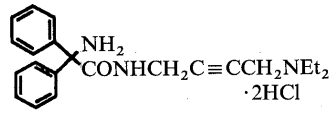
Table II shows the pharmacological results of compounds **13b—i**, **14a—d**, and **15**.

Variation of the amino group revealed that alkyl substituents on the amino moiety (**13b, c**) maintained the activity but cyclic amines (**13d—h**) abolished the activity. Replacement of the cyclohexyl group with a benzene ring (**14a—d**) or a cyclopentane ring (**15**) retained the activity.

Conversion of the hydroxyl group to another (**10a**, **16**, **32**, **33**) revealed that a neutral hydrophilic substituent (hydroxyl group) is necessary for the activity (Table III).

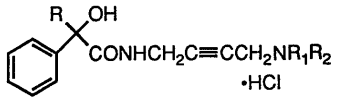
Since the compounds with dimethylamino, diethylamino, ethylamino, and methylamino groups showed strong

TABLE III. Effect of Acetamide Derivatives with Chloro, Trifluoroacetamido, Amino, and Allyl Groups at the 2-Position on Urinary Bladder Rhythmic Contractions[a] and Mydriasis[b] in Rats

| Compound No. | Structure | Inhibitory activity of bladder contraction | | | Mydriatic activity | Selectivity |
|---|---|---|---|---|---|---|
| | | % inhibition at 1 mg/kg i.v. | Duration of action (min) | $ED_{30}$ (mg/kg) | MED[c] (mg/kg) | $MED/ED_{30}$ |
| **10a**[d] |  | 18.2 | — | | NT | |
| **16** |  | 20.3 | — | | NT | |
| **32** |  | 8.6 | — | | NT | |
| **33** |  | 0 | — | | NT | |

The test compounds were administered as hydrochloride. *a*) The inhibitory activity of bladder contraction was examined as described in the preceding paper.[15] *b*) The mydriatic activity was examined by the method of Parry and Heathcote.[16] *c*) MED = minimum effective dose. *d*) Racemate. NT = not tested.

TABLE IV. Effects of Acetamide Derivatives on Detrusor Contraction *in Vitro* Induced by Electrical Field Stimulation, KCl, Carbacol, $BaCl_2$ and ATP



| Compound No. | R | $R_1$ | $R_2$ | $IC_{50}$ (g/ml) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Electrical field stimulation | KCl | Carbacol | $BaCl_2$ | ATP |
| **1**[a] | | Oxybutynin | | $2.1 \times 10^{-5}$ | $2.2 \times 10^{-5}$ | $9.9 \times 10^{-8}$ | $2.3 \times 10^{-5}$ | $1.6 \times 10^{-5}$ |
| **13b**[a] |  | Me | Me | $2.7 \times 10^{-5}$ | 44.6%[b] | $4.4 \times 10^{-7}$ | | |
| (+)-**13b** |  | Me | Me | $1.3 \times 10^{-5}$ | $6.5 \times 10^{-5}$ | $2.0 \times 10^{-7}$ | $1.9 \times 10^{-5}$ | $4.0 \times 10^{-5}$ |
| **13c**[a] |  | Me | H | $8.4 \times 10^{-6}$ | 7.8%[b] | $6.6 \times 10^{-6}$ | | |
| **14a** | Ph | Me | Me | $8.4 \times 10^{-5}$ | 9.1%[b] | $6.1 \times 10^{-7}$ | 11.4%[b] | 4.5%[b] |
| **14b** | Ph | Et | H | $1.1 \times 10^{-5}$ | 10%[b] | $5.8 \times 10^{-6}$ | 27%[b] | 14.5%[b] |

The test was carried out as described earlier.[15] *a*) Racemate. *b*) % inhibition at $10^{-4}$ g/ml. ATP, adenosine 5′-triphosphate.

activity, mydriatic activity of those compounds was then examined as a parameter of anticholinergic side effects. Good separation was observed in four compounds **13b**, **13c**, **14a**, and **14b**. For compound **13b**, enantiomers ((+)-**13b**, (−)-**13b**) were prepared, and testing revealed that (+)-enantiomer ((+)-**13b**) was active.

Table IV shows the results of the *in vitro* assays.

The *in vitro* study showed that the mode of action between 2-cyclohexyl-2-phenylacetamide and 2,2-diphenylacetamide derivatives was different, and that their anticholinergic activity was less than that of oxybutynin. While the compound (+)-**13b** like oxybutynin suppressed detrusor contraction induced by all agonists, the compounds **14a, b** suppressed only that contraction induced by electrical field stimulation and carbachol. Since atropine, a typical anticholinergic agent, cannot suppress the detrusor contraction induced by electrical field stimulation (no effect at $1 \times 10^{-5}$ g/ml), the 2,2-diphenylacetamide derivatives (**14a, b**) may have a certain activity concerned with atropine resistance because they suppressed detrusor contraction induced by electrical field stimulation in addition to anticholinergic activity. It is interesting that a clear difference in mode of action exists between the 2,2-diphenylacetamide and the 2-cyclohexyl-2-phenylacetamide derivatives. Further evaluation of these compounds 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 a Bruker AC-200P NMR spectrometer with tetramethylsilane as an internal standard ($\delta$ value, ppm). Mass (MS) spectra were recorded on JEOL JMS D-300 MS spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400CHN elemental analyzer. Yields are not optimized.

**1-Cyclohexyl-1-phenyl-1,2-epoxyethane (2)** To a solution of cyclohexylphenylketone (7.00 g) and trimethylsulfonium iodide (7.97 g) in dimethyl sulfoxide (DMSO) (35 ml) was added NaH (60% dispersion in oil, 1.95 g) at room temperature and stirring followed for 2 d. The solution was poured into ice water (175 ml) 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) as an eluent to afford **2** (7.47 g, 99%) as an oil. IR (neat) cm$^{-1}$: 2930, 2855, 1450. NMR ($CDCl_3$, 90 MHz): 0.73—1.86 (11H, m), 2.63 (1H, d, $J$=5 Hz), 2.96 (1H, d, $J$=5 Hz), 7.23 (5H, s).

**1-Cyclohexyl-2-(4-diethylamino-2-butynyloxy)-1-phenylethanol Hydrochloride (3·HCl)** To a solution of 4-diethylamino-2-butyn-1-ol (3.49 g) in *N,N*-dimethylformamide (DMF) (16 ml) was added NaH (60% dispersion in oil, 1.09 g). After stirring for 20 min, a solution of **2** (1.00 g) in DMF (5 ml) was added and the mixture was stirred at 70°C for 3 h. After cooling, the mixture was poured into ice water (50 ml) 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 $CHCl_3$ and MeOH (20 : 1) as an eluent to afford **3** (1.55 g, 91%). To a $CHCl_3$ solution of **3** (0.52 g) was added 6 N methanolic HCl (0.4 ml) and the solution was evaporated *in vacuo*. The residue was triturated with ether to afford **3**·HCl (0.48 g, 83%), mp 104—105 °C (recrystallized from EtOAc). *Anal.* Calcd for $C_{22}H_{33}NO_2$·HCl: C, 69.54; H, 9.02; N, 3.69. Found: C, 69.63; H, 8.54; N, 3.61. IR (Nujol) cm$^{-1}$: 3310, 3270, 2410. NMR ($CDCl_3$, 90 MHz): 0.70—1.90 (11H, m), 1.45 (6H, t, $J$=8 Hz), 2.25 (2H, s), 2.85—3.40 (4H, m), 3.76 (1H, d, $J$=9 Hz), 3.90 (1H, d, $J$=9 Hz), 3.85—3.96 (2H, m), 4.05—4.20 (2H, m), 7.10—7.40 (5H, m).

**1-Cyclohexyl-2-[*N*-(4-diethylamino-2-butynyl)-*N*-methyl]amino-1-phenylethanol Dihydrochloride (4·2HCl)** A mixture of **2** (0.70 g) and *N,N*-diethyl-*N'*-methyl-2-butyne-1,4-diamine (0.80 g) in EtOH (5 ml) was refluxed for 34 h. After cooling, the solution was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (30 : 1) as an eluent to afford **4** (1.00 g, 81%). To a $CHCl_3$ solution of **4** (0.83 g) was added 6 N methanolic HCl (1.0 ml) and the solution was evaporated *in vacuo*. The residue was triturated with ether to afford **4**·2HCl (0.81 g, 81%), mp 173 °C (dec.). *Anal.* Calcd for $C_{23}H_{36}N_2O$·2HCl·1/4$H_2O$: C, 63.66; H, 8.94; N, 6.46. Found: C, 63.61; H, 8.97; N, 6.42. IR (Nujol) cm$^{-1}$: 3225, 3125, 2600. NMR (DMSO-$d_6$, 90 MHz): 0.40—2.00 (11H, m), 1.33 (6H, t, $J$=7 Hz), 2.23—2.60 (3H, m), 2.86 (1H, br s), 2.90—4.33 (10H, m), 5.83 (1H, br s), 7.05—7.60 (5H, m), 9.56 (1H, br s).

**2-Chloro-2-cyclohexyl-*N*-(4-diethylamino-2-butynyl)-2-phenylacetamide Hydrochloride (10a·HCl) (Route A)** A solution of *N,N*-diethyl-2-butyne-1,4-diamine (0.14 g) in benzene (2.5 ml) was added dropwise to a solution of **5** (0.27 g) in benzene (2.5 ml) below 25 °C. After stirring at room temperature for 19.5 h, the resulting precipitates were collected by filtration and recrystallized from a mixture of acetone and ether to afford **10a**·HCl (0.19 g, 46%), mp 148—152 °C (dec.). *Anal.* Calcd for $C_{22}H_{31}ClN_2O$·HCl·1/4$H_2O$: C, 63.53; H, 7.88; N, 6.74. Found: C, 63.67; H, 7.80; N, 6.83. IR (Nujol) cm$^{-1}$: 3280, 2470, 2420, 1665. NMR ($CDCl_3$, 90 MHz): 0.95—1.90 (16H, m), 2.50—3.25 (5H, m), 3.70—3.90 (2H, m), 3.90—4.10 (2H, m), 7.00—7.75 (6H, m), 12.65 (1H, br s).

**2-Cyclohexyl-*N*-(4-diethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide Hydrochloride (13a·HCl)** A solution of **10a**·HCl (0.10 g) in water (1 ml) was refluxed for 20 min. After cooling, the solution was made alkaline (pH 10) with sat. $NaHCO_3$ 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 $CHCl_3$ and MeOH (10 : 1) as an eluent to afford **13a**. To a $CHCl_3$ solution of **13a** was added 4.1 N methanolic HCl (0.2 ml), and the solution was evaporated *in vacuo* to afford **13a**·HCl (0.09 g, 96%) as a viscous residue. IR ($CHCl_3$) cm$^{-1}$: 3420, 2450, 1670. NMR ($CDCl_3$, 90 MHz): 0.80—1.95 (16H, m), 2.30—3.25 (7H, m), 3.65—3.86 (2H, m), 3.86—4.10 (2H, m),7.16—7.73 (5H, m), 9.40 (1H, br s). MS (*m/z*): 356 (M)$^+$.

Compounds **13b**, **14a**, **15**, and **16** were prepared in a similar manner. Phosphorous pentachloride was used to activate the acetic acid **7**, and thionyl chloride and *N, N'*-carbonyldiimidazole were used to activate acetic acids **8** and **30**, respectively. Compounds **13b** and **14a** were also prepared *via* route B as shown in Chart 2. Activation of acetic acid **30** with *N,N'*-carbonyldiimidazole was also used in the synthesis of optically active acetamide (−)-**13b** as mentioned later.

**2-Chloro-2-cyclohexyl-*N*-(4-hydroxy-2-butynyl)-2-phenylacetamide (18) (Route B)** A solution of **5** (9.00 g) in $CH_2Cl_2$ (50 ml) was added dropwise to a solution of **17**[4] (5.38 g) and $Et_3N$ (30.8 ml) in $CH_2Cl_2$ (120 ml) at 0 °C. The mixture was stirred at the same temperature for 10 min and then at room temperature for an additional 3.5 h. The mixture was acidified with 1 N HCl and the organic layer was separated, washed with sat. $NaHCO_3$ solution and then water, 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 (6 : 1) as an eluent to afford **18** (7.32 g, 69%) as a powder, mp 97—98 °C. IR (Nujol) cm$^{-1}$: 3400, 3250, 1650. NMR ($CDCl_3$, 90 MHz): 1.00—1.90 (11H, m), 2.50—2.90 (1H, m), 3.93—4.13 (2H, m), 4.14—4.30 (2H, m), 6.83—7.16 (1H, m), 7.16—7.43 (3H, m), 7.53—7.73 (2H, m).

**2-Cyclohexyl-2-hydroxy-*N*-(4-hydroxy-2-butynyl)-2-phenylacetamide (20)** To a solution of **18** (7.88 g) in 1,4-dioxane (180 ml) was added 1 N HCl (85 ml) and the mixture was heated at 90 °C for 45 min. After cooling, the solution was poured into ice water and extracted with EtOAc. The extract was washed successively with sat. $NaHCO_3$ solution, water, and 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 EtOAc (5 : 1) as an eluent to afford **20** (6.56 g, 88%) as a powder, mp 121—122 °C. *Anal.* Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.74; H, 7.97; N, 4.64. IR (Nujol) cm$^{-1}$: 3400, 1660. NMR ($CDCl_3$, 90 MHz): 0.67—1.97 (10H, m), 2.00—2.23 (1H, m), 2.23—2.63 (1H, m), 2.83 (1H, s), 3.90—4.07 (2H, m), 4.07—4.30 (2H, m), 6.93 (1H, t, $J$=6 Hz), 7.20—7.50 (3H, m), 7.50—7.73 (2H, m).

***N*-(4-Chloro-2-butynyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide (22)** Thionyl chloride (4.8 ml) was added dropwise to a mixture of **20** (6.56 g) and DMF (5 drops) in $CHCl_3$ (145 ml) at 0 °C, and the mixture was refluxed for 1 h. After cooling, the mixture was washed successively with water, 1 N NaOH, and 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 (5 : 1) as an eluent to afford **22** (6.70 g, 96%) as a white powder, mp 65—71 °C. *Anal.* Calcd for $C_{18}H_{22}ClNO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.21; H, 6.93; N,

4.41. IR (Nujol) $cm^{-1}$: 3400, 1660. NMR ($CDCl_3$, 90 MHz): 0.67—2.17 (10H, m), 2.17—2.60 (1H, m), 2.60 (1H, s), 3.87—4.00 (2H, m), 4.00—4.13 (2H, m), 6.67—7.00 (1H, m), 7.10—7.50 (3H, m), 7.50—7.63 (2H, m).

**2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide Hydrochloride (13b·HCl)** A mixture of **22** (0.50 g), NaI (0.10 g), and 50% aq. $Me_2NH$ (1.5 ml) in 1,4-dioxane (5 ml) was stirred at room temperature overnight. The mixture was evaporated *in vacuo* and to the residue were added sat. $NaHCO_3$ 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 $CHCl_3$ and MeOH (20 : 1) as an eluent to afford **13b** (0.49 g, 95%) as an oil. IR ($CHCl_3$) $cm^{-1}$: 3400, 1650. NMR ($CDCl_3$, 90 MHz): 0.75—1.96 (11H, m), 2.09—2.49 (1H, m), 2.23 (6H, s), 3.13—3.25 (2H, m), 3.92—4.13 (2H, m), 6.64—6.98 (1H, m), 7.23—7.44 (3H, m), 7.50—7.69 (2H, m). MS (*m/z*): 329 ($M^+$), 328, 189.

To a solution of **13b** (0.48 g) in MeOH (5 ml) was added 6.4 N methanolic HCl (1.5 ml) and the solution was evaporated *in vacuo*. The residue was triturated with a mixture of isopropyl alcohol (IPA) and EtOAc to afford **13b**·HCl (0.30 g, 56%) as a powder, mp 204—205 °C (recrystallized from a mixture of IPA and petroleum ether). *Anal.* Calcd for $C_{20}H_{28}N_2O_2 \cdot HCl \cdot 1/2H_2O$: C, 64.24; H, 8.09; N, 7.49. Found: C, 64.12; H, 7.74; N, 7.41. IR (Nujol) $cm^{-1}$: 3420, 3300, 2400, 1640. NMR (DMSO-$d_6$, 90 MHz): 0.86—1.86 (10H, m), 2.06—2.40 (1H, m), 2.60 (6H, s), 3.73—4.00 (4H, m), 5.51 (1H, s), 7.12—7.40 (3H, m), 7.43—7.64 (2H, m), 8.26 (1H, t, $J$=5 Hz), 10.77—11.27 (1H, br m).

**2,2-Diphenyl-2-hydroxy-*N*-(4-hydroxy-2-butynyl)acetamide (21)** To a mixture of **17** (4.33 g) and $Et_3N$ (15 ml) in $CHCl_3$ (50 ml) was added **6** (9.12 g). After stirring at room temperature for 2 h, the mixture was washed with 1 N HCl and then water and evaporated *in vacuo*. To the residue were added 1 N HCl (25 ml) and 1,4-dioxane (50 ml) and the mixture was refluxed for 24 h. After cooling, the mixture was evaporated *in vacuo*. To the residue were added water and $CHCl_3$. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CH_2Cl_2$ and EtOAc (1 : 0 to 0 : 1) as an eluent to afford **21** (4.12 g, 41%) as a powder, mp 141—143 °C. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.21; H, 5.88; N, 4.66. IR (Nujol) $cm^{-1}$: 3350, 3200, 1650. NMR (DMSO-$d_6$, 200 MHz): 3.95 (2H, dt, $J$=5.8, 1.8 Hz), 4.04 (2H, dt, $J$=5.9, 1.8 Hz), 5.14 (1H, t, $J$=5.9 Hz), 6.76 (1H, s), 7.26—7.40 (10H, m), 8.44 (1H, t, $J$=5.8 Hz).

***N*-(4-Chloro-2-butynyl)-2,2-diphenyl-2-hydroxyacetamide (23)** To a solution of **21** (3.32 g) in a mixture of DMF (6 drops) and $CHCl_3$ (20 ml) was added thionyl chloride (0.81 ml) and the solution was stirred at 40 °C for 1 h. After cooling, the solution was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and EtOAc (5 : 1) as an eluent to afford **23** (4.12 g, 75%) as an oil. IR (neat) $cm^{-1}$: 3380, 1650. NMR ($CDCl_3$, 90 MHz): 3.67 (1H, s), 4.04—4.34 (4H, m), 6.65—6.98 (1H, br m), 7.40 (10H, s). MS (*m/z*): 313 ($M^+$), 296, 183.

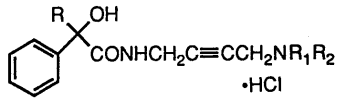
***N*-(4-Dimethylamino-2-butynyl)-2,2-diphenyl-2-hydroxyacetamide (14a)** A mixture of **23** (0.70 g), NaI (0.10 g) and 50% aq. $Me_2NH$ (2.2 ml) in 1,4-dioxane (7 ml) was stirred at room temperature overnight. The mixture was evaporated *in vacuo* and to the residue were added sat. $NaHCO_3$ solution and EtOAc. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (20 : 1) as an eluent to afford **14a** (0.35 g, 49%) as a powder, mp 103—104 °C (recrystallized from EtOAc). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.16; H, 6.83; N, 8.63. IR (Nujol) $cm^{-1}$: 3290, 1660. NMR ($CDCl_3$, 200 MHz): 2.17 (6H, s), 3.14 (2H, t, $J$=2.0 Hz), 4.11 (2H, dt, $J$=2.0, 5.4 Hz), 4.55 (1H, br s), 6.84 (1H, t, $J$=5.4 Hz), 7.26—7.52 (10H, m).

***N*-(4-Dimethylamino-2-butynyl)-2,2-diphenyl-2-hydroxyacetamide Hydrochloride (14a·HCl)** To a solution of **14a** (0.35 g) in MeOH (5 ml) was added 6.4 N methanolic HCl (3 ml) and the solution was evaporated *in vacuo*. The residue was triturated with a mixture of IPA and EtOAc to afford **14a**·HCl (0.21 g, 54%) as a powder, mp 164—165 °C (recrystallized from EtOH). *Anal.* Calcd for $C_{20}H_{22}N_2O_2 \cdot HCl$: C, 66.94; H, 6.46; N, 7.81. Found: C, 66.86; H, 6.42; N, 7.82. IR (Nujol) $cm^{-1}$: 3300, 2700, 1650. NMR (DMSO-$d_6$, 90 MHz): 2.65 (6H, s), 3.90—4.13 (4H, m), 6.59—6.94 (1H, m), 7.19—7.50 (10H, m), 8.53—8.76 (1H, br m), 11.06 (1H, br s).

Compounds **13c—i**, **14b—d** in Table II were prepared in a similar manner. Table V shows their physical data.

**2,2-Diphenyl-2-hydroxy-*N*-propargylacetamide (25)** To a solution of **6** (321.21 g) in $CHCl_3$ (321 ml) was added a mixture of propargylamine (64.11 g) and $Et_3N$ (125.14 g) in $CHCl_3$ (125 ml) below 25 °C. After stirring at room temperature for 30 min, the reaction mixture was washed with water and evaporated *in vacuo*. The residue was dissolved in 1,4-dioxane (320 ml). To the solution was added 0.3 N HCl (320 ml) and the mixture was refluxed for 1 h. After cooling, the solution was evaporated *in vacuo* and to the residue were added $CHCl_3$ and water. The organic layer was separated, washed with 3% NaOH and then brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. The residue was triturated with diisopropyl ether to afford **25** (252.05 g, 82%) as a powder, mp 105—106 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.05; H, 5.78; N, 5.28. IR (Nujol) $cm^{-1}$: 3400, 3280, 2110, 1660. NMR ($CDCl_3$, 200 MHz): 2.24 (1H, t, $J$=2.6 Hz), 3.72 (1H, s), 4.05 (2H, dd, $J$=5.4, 2.6 Hz), 6.78

TABLE V. Physical Properties of Acetamide Derivatives as Hydrochlorides




| Compound No. | mp (°C) | Recryst. solv.[a] | Route | Yield[b] (%) | Formula | Analysis (%) Calcd C | Calcd H | Calcd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **13a**[c] | Oil[e] | | A | 44 | | | | | | | |
| **13b**[c] | 204—205 | IPA–P.E | A, B | 83, 54 | $C_{20}H_{28}N_2O_2 \cdot HCl \cdot 1/2H_2O$ | 64.24 | 8.09 | 7.49 | 64.12 | 7.74 | 7.41 |
| **13c**[c] | 185—186 | IPA–EtOAc | B | 61 | $C_{19}H_{26}N_2O_2 \cdot HCl \cdot 1/4H_2O$ | 64.21 | 7.80 | 7.88 | 64.45 | 7.76 | 7.75 |
| **13d**[c] | 143—146 | IPA–EtOAc | B | 48 | $C_{23}H_{33}N_3O_2 \cdot 2HCl \cdot 3/2H_2O$ | 57.14 | 7.92 | 8.69 | 56.92 | 8.16 | 8.60 |
| **13e**[c] | 120—122 | IPA–EtOAc | B | 80 | $C_{22}H_{30}N_2O_3 \cdot HCl \cdot H_2O$ | 62.18 | 7.83 | 6.59 | 61.92 | 7.90 | 6.55 |
| **13f**[c] | 170—172 | EtOAc[h] | B | 71 | $C_{26}H_{36}N_2O_2 \cdot HCl \cdot 1/2H_2O$ | 68.78 | 8.44 | 6.17 | 68.77 | 8.70 | 6.16 |
| **13g**[c] | Oil[f] | | B | 76 | | | | | | | |
| **13h**[c] | Oil[g] | | B | 65 | | | | | | | |
| **13i**[c] | 121—124 | IPA–EtOAc | B | 20 | $C_{22}H_{30}N_2O_4 \cdot HCl \cdot H_2O$ | 59.92 | 7.54 | 6.35 | 60.28 | 7.51 | 6.42 |
| **14a** | 164—165 | EtOH | A, B | 84, 26 | $C_{20}H_{22}N_2O_2 \cdot HCl$ | 66.94 | 6.46 | 7.81 | 66.86 | 6.42 | 7.82 |
| **14b** | 187—188 | EtOAc–MeOH | B, C | 57, 89 | $C_{20}H_{22}N_2O_2 \cdot HCl$ | 66.94 | 6.46 | 7.81 | 66.67 | 6.42 | 7.77 |
| **14c** | 135—136 | IPA–IPE | B | 25 | $C_{21}H_{22}N_2O_2 \cdot HCl$ | 68.01 | 6.25 | 7.55 | 67.53 | 6.32 | 7.29 |
| **14d**[d] | 135—136 | EtOAc–IPE | B | 55 | $C_{21}H_{24}N_2O_2 \cdot 1/4H_2O$ | 73.98 | 7.24 | 8.22 | 74.04 | 7.24 | 8.05 |
| **15**[c] | 154—155 | IPA–EtOAc | A | 16 | $C_{19}H_{26}N_2O_2 \cdot HCl$ | 65.04 | 7.76 | 7.98 | 64.64 | 7.81 | 8.13 |
| **16** | 199—201 | EtOH | A | 48 | $C_{23}H_{26}N_2O \cdot HCl$ | 72.14 | 7.11 | 7.32 | 71.90 | 7.19 | 7.40 |

*a*) IPA, isopropyl alcohol; P.E, petroleum ether; IPE, diisopropyl ether. *b*) For route A, the yields from **5**—**8** to **13**—**16** of their hydrochlorides are shown. For route B, the yields from **22**, **23** to **13**, **14** of their hydrochlorides are shown. For route C, the yield from compound **26** to **14b** of the free form is shown. *c*) Racemate. *d*) Physical properties of this compound are shown as the free base. *e*) MS (*m/z*): 356 ($M^+$). *f*) MS (*m/z*): 384 ($M^+$), 189. *g*) MS (*m/z*): 398 ($M^+$), 367, 189. *h*) Crystallizing solvent.

(1H, m), 7.22—7.51 (10H, m).

**2,2-Diphenyl-2-hydroxy-*N*-(4-hydroxy-2-butynyl)acetamide (21)** A mixture of **25** (165.20 g), CuCl (2.50 g), and $K_2CO_3$ (1.73 g) in DMSO (330 ml) was stirred at 75 °C for 45 min under a nitrogen atmosphere. To the mixture was added paraformaldehyde (25.30 g) and the mixture was stirred at 85 °C for 5 h. After cooling, the mixture was poured into a mixture of 5% HCl and 10% aq. NaCl (1 : 5) and extracted with EtOAc. The extract was washed successively with brine, 5% $Na_2S_2O_3$ solution, and brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. The residue was triturated with a mixture of diisopropyl ether and $CHCl_3$ to afford **21** (119.70 g, 65%) as a powder, mp 141—143 °C. The physical data of this compound were identical with those of the compound obtained by using compound **19**.

**2,2-Diphenyl-*N*-[4-(*N'*-ethyl-*N'*-4-methoxybenzyl)amino-2-butynyl]-2-hydroxyacetamide (26) (Route C)** A mixture of **25** (3.00 g), *N*-ethyl-4-methoxybenzylamine (2.06 g), CuCl (0.02 g) and paraformaldehyde (0.41 g) in 1,4-dioxane (15 ml) was refluxed for 30 min and cooled. The mixture was extracted with EtOAc. The extract was washed with water 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 $CHCl_3$ and MeOH (50 : 1) as an eluent to afford **26** (4.80 g, 96%) as an oil. IR (neat) $cm^{-1}$: 3410, 1670. NMR ($CDCl_3$, 200 MHz): 1.08 (3H, t, $J$=7.2 Hz), 2.52 (2H, q, $J$=7.2 Hz), 3.27 (2H, t, $J$=1.9 Hz), 3.50 (2H, s), 3.79 (3H, s), 4.13 (2H, dt, $J$=5.4, 1.9 Hz), 6.66 (1H, br t, $J$=5.4 Hz), 6.84 (2H, d, $J$=8.6 Hz), 7.22 (2H, d, $J$=8.6 Hz), 7.27—7.55 (10H, m). MS (*m/z*): 443 ($M^+$+1), 442 ($M^+$), 441 ($M^+$−1).

**2,2-Diphenyl-*N*-(4-ethylamino-2-butynyl)-2-hydroxyacetamide (14b)** A mixture of **26** (5.61 g) and 1-chloroethyl chloroformate (1.6 ml) in 1,2-dichloroethane (56 ml) was refluxed for 1 h. After cooling, the mixture was evaporated *in vacuo* and MeOH (40 ml) was added to the residue. The solution was refluxed for 20 min and cooled. The solvent was evaporated *in vacuo* and the pH of the residue was adjusted to 1 with dil. HCl. The acidic solution was washed with diisopropyl ether, 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 triturated with diisopropyl ether to afford **14b** (3.62 g, 89%) as a powder, mp 131—134 °C (recrystallized from IPA). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.21; H, 7.05; N, 8.56. IR (Nujol) $cm^{-1}$: 3375, 3275, 1665. NMR ($CDCl_3$, 200 MHz): 1.08 (3H, t, $J$=7.1 Hz), 2.65 (2H, q, $J$=7.1 Hz), 3.36 (2H, t, $J$=2.0 Hz), 4.10 (2H, dt, $J$=2.0, 5.3 Hz), 6.73 (1H, br t, $J$=5.3 Hz), 7.23—7.60 (10H, m).

**(−)-[2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide]·L-Tartaric Acid [(−)-13b·L-Tartaric Acid]** A mixture of (*S*)-(+)-**30**[14] [1.13 g, 4.8 mmol, $[\alpha]_D$ +19.3° ($c$=5.0, EtOH)] and *N,N'*-carbonyldiimidazole (0.77 g, 4.8 mmol) in $CHCl_3$ (5 ml) was stirred at room temperature for 2 h. To the solution was added *N,N*-dimethyl-2-butyne-1,4-diamine (0.54 g, 4.8 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was poured into water and extracted with EtOAc. The extract was washed with water and re-extracted with 1 N HCl. The acidic solution was made alkaline with aq. NaOH 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 (9 : 1) as an eluent to afford (−)-**13b** [0.60 g, 38%, $[\alpha]_D$ −4.6° ($c$=5.43, MeOH)]. To a solution of the obtained (−)-**13b** (0.26 g, 0.8 mmol) in EtOH was added a solution of L-tartaric acid (0.12 g, 0.8 mmol) in EtOH and the solution was allowed to stand at room temperature overnight. The resulting precipitates were collected by filtration to afford (−)-**13b**·L-tartaric acid (0.26 g, 68%). The enantiomeric excess of this compound was determined to be 91% by high performance liquid chromatography (HPLC) analysis of the corresponding free amine (column, Sumipax OA-2000 (Sumitomo) 4.6 × 250 mm; eluent, 20 : 2 : 1 *n*-hexane–$CH_2Cl_2$–EtOH mixture; flow rate, 1.0 ml/min; $t_R$ of (−)-**13b**, 22.9 min; $t_R$ of (+)-**13b**, 21.9 min). This compound was used as seeds for optical resolution of the racemate (±)-**13b** to obtain (+)-**13b**·1/2 D-tartaric acid.

**Optical Resolution of Racemates (±)-13b; (+)-[2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide]·1/2 D-Tartaric Acid [(+)-13b·1/2 D-Tartaric Acid]** A small amount of (−)-**13b**·L-tartaric acid obtained in the above manner was added to a hot solution of (±)-**13b** (1.96 g, 6.0 mmol) and L-tartaric acid (0.90 g, 6.0 mmol) in a mixture of EtOH (5 ml) and MeOH (1 ml). After standing at room temperature for 2 h, the resulting precipitates were collected by filtration and dried to afford an equimolar salt of the (−)-isomer (1.58 g, 3.3 mmol). The mother liquor was evaporated *in vacuo*, and the residue was made alkaline with aq. NaOH and extract with EtOAc. The extract was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to afford (+)-**13b** [0.91 g, 2.8 mmol, $[\alpha]_D$ +4.24° ($c$=7.8, EtOH)]. To a solution of (+)-**13b** (0.73 g, 2.2 mmol) in EtOH was added a solution of D-tartaric acid (0.14 g, 0.9 mmol) in MeOH and the solution was allowed to stand at room temperature overnight. The resulting precipitates were collected by filtration to afford (+)-**13b**·1/2 D-tartaric acid (0.44 g, wet). This compound was used as seeds for optical resolution of the racemate (±)-**13b**.

**(−)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide·Hydrochloride [(−)-13b·HCl]** (+)-**13b**·1/2 D-Tartaric acid (7.12 g, 17.6 mmol) obtained in the above manner was added to a hot solution of (±)-**13b** (71.27 g, 217.0 mmol) and D-tartaric acid (16.03 g, 106.8 mmol) in a mixture of EtOH (350 ml) and MeOH (50 ml). After standing at room temperature for 6 h, the resulting precipitates were collected by filtration, washed with EtOH (50 ml), and dried to afford (+)-**13b**·1/2 D-tartaric acid (39.07 g, 96.8 mmol). The filtrate was evaporated *in vacuo* and the residue was made alkaline with 10% NaOH and extracted with EtOAc. The extract was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. The residue was dissolved in EtOH (35 ml) and 20% ethanolic HCl (35 ml) was added to the solution. The solution was then treated with a mixture of EtOAc (210 ml) and diisopropyl ether (70 ml) and the resulting precipitates of (±)-**13b**·HCl (42.00 g, 115.0 mmol) were removed by filtration. The filtrate was evaporated *in vacuo* and the residue was dissolved in EtOAc (50 ml). The solution was stirred at room temperature for 4 h. The resulting precipitates were collected by filtration and dried to afford crude (−)-**13b**·HCl (11.24 g, 30.8 mmol).

**(+)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide Hydrochloride [(+)-13b·HCl]** The previously obtained (+)-**13b**·1/2 D-tartaric acid (31.17 g, 77.2 mmol) was partitioned between aq. NaOH and EtOAc. The organic layer was separated, washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. The residue was similarly treated with EtOH (15 ml), 20% ethanolic HCl (15 ml), EtOAc (75 ml) and diisopropyl ether (25 ml). After removing (±)-**13b**·HCl (17.96 g, 49.2 mmol), the filtrate was evaporated *in vacuo* and the residue was crystallized from EtOAc (50 ml) to afford crude (+)-**13b**·HCl (10.05 g, 36%).

**(+)-[2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide]·1/2 D-Tartaric Acid [(+)-13b·1/2 D-Tartaric Acid]** Crude (+)-**13b**·HCl (5.74 g, 15.7 mmol) was partitioned between EtOAc and NaOH solution. The organic layer was separated, washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. The residue and D-tartaric acid (1.08 g, 7.2 mmol) in EtOH (100 ml) was refluxed until a clear solution was obtained. After standing at room temperature overnight, the resulting precipitates were collected by filtration, washed with EtOH (10 ml), and recrystallized from EtOH twice to afford (+)-**13b**·1/2 D-tartaric acid (4.21 g, 66%), mp 188—188.5 °C. $[\alpha]_D^{23}$ −4.10° ($c$=1.75, MeOH). *Anal.* Calcd for $C_{22}H_{31}N_2O_5$: C, 65.49; H, 7.74; N, 6.94. Found: C, 65.34; H, 7.78; N, 6.92. IR (Nujol) $cm^{-1}$: 3460, 3360, 2725, 2660, 1660. NMR (DMSO-$d_6$, 200 MHz): 0.89—1.42 (6H, m), 1.42—1.81 (4H, m), 2.18 (6H, s), 2.21—2.39 (1H, m), 3.26 (2H, s), 3.70—4.00 (2H, m), 4.21 (1H, s), 5.31—5.80 (1H, br s), 7.16—7.40 (3H, m), 7.53—7.63 (2H, m), 8.16 (1H, t, $J$=5.8 Hz). The enantiomeric excess of this compound was determined to be >96% by HPLC analysis of the corresponding free amine.

**(−)-[2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide]·1/2 L-Tartaric Acid [(−)-13b·1/2 L-Tartaric acid]** (−)-**13b**·1/2 L-Tartaric acid was obtained in a similar manner to that of 1/2 D-tartaric acid salt of (+)-isomer, mp 188—188.5 °C. $[\alpha]_D^{22}$ +3.69° ($c$=1.67, MeOH). *Anal.* Calcd for $C_{22}H_{31}N_2O_5$: C, 65.49; H, 7.74; N, 6.94. Found: C, 65.33; H, 7.84; N, 6.76. IR (Nujol) $cm^{-1}$: 3460, 3360, 2725, 1660. NMR (DMSO-$d_6$, 200 MHz): 0.87—1.42 (6H, m), 1.46—1.77 (4H, m), 2.15 (6H, s), 2.17—2.34 (1H, m), 3.22 (2H, s), 3.67—3.95 (2H, m), 4.18 (1H, s), 5.20—5.69 (1H, br s), 7.13—7.36 (3H, m), 7.49—7.63 (2H, m), 8.12 (1H, t, $J$=5.8 Hz). The enantiomeric excess of this compound was determined to be >96% by HPLC analysis of the corresponding free amine.

**(+)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide [(+)-13b]** (+)-**13b**·1/2 D-Tartaric acid (1.34 g, 3.3 mmol) was partitioned between 10% NaOH and EtOAc. The organic layer was separated, washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to afford (+)-**13b** (1.09 g, 100%), mp 120.5—121 °C. $[\alpha]_D^{22}$ +5.12° ($c$=5.28, EtOH). *Anal.* Calcd for $C_{22}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.05; H, 8.66; N, 8.25. IR (Nujol) $cm^{-1}$: 3400, 3320, 1660. NMR ($CDCl_3$, 200 MHz): 0.73—1.50 (6H, m), 1.59—1.89 (4H, m), 2.23 (6H, s), 2.44 (1H, t, $J$=11.7 Hz), 2.86 (1H, s), 3.19 (2H, t, $J$=1.9 Hz), 3.92 (1H, dd, $J$=17.4, 5.1 Hz), 4.08 (1H, dd, $J$=17.4, 5.1 Hz), 6.87 (1H, t, $J$=5.1 Hz), 7.20—7.41 (3H, m), 7.56—7.65 (2H, m). The enantiomeric excess of this compound was determined to be >96% by HPLC analysis of the corresponding free amine.

**(−)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide [(−)-13b]** (−)-**13b** was obtained in a similar manner to that of (+)-isomer, mp 121—122.5 °C. $[\alpha]_D^{22}$ −4.85° (*c*=5.11, EtOH). *Anal.* Calcd for $C_{22}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.76; H, 8.58; N, 8.43. IR (Nujol) $cm^{-1}$: 3400, 3320, 1660. NMR ($CDCl_3$, 200 MHz): 0.74—1.52 (6H, m), 1.58—1.93 (4H, m), 2.23 (6H, s), 2.43 (1H, t, *J*=11.8 Hz), 2.94 (1H, s), 3.18 (2H, t, *J*=1.9 Hz), 3.92 (1H, dd, *J*=17.4, 5.1 Hz), 4.08 (1H, dd, *J*=17.4, 5.1 Hz), 6.88 (1H, t, *J*=5.1 Hz), 7.21—7.41 (3H, m), 7.56—7.67 (2H, m). The enantiomeric excess of this compound was determined to be >96% by HPLC analysis of the corresponding free amine.

**(+)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide Hydrochloride [(+)-13b·HCl]** To a solution of (+)-**13b** (1.01 g, 3.1 mmol) in EtOH (15 ml) was added 20% ethanolic HCl (1 ml) and the solution was evaporated *in vacuo*. The residue was dissolved in EtOAc and the solution was stirred at room temperature overnight. The resulting precipitates were collected by filtration, washed with EtOAc, and dried to afford (+)-**13b**·HCl (0.99 g, 87%), mp 170.5—171 °C. $[\alpha]_D^{23}$ +3.92° (*c*=3.67, MeOH). *Anal.* Calcd for $C_{20}H_{28}N_2O_2$·HCl: C, 65.83; H, 8.01; N, 7.68. Found: C, 65.19; H, 7.76; N, 7.66. IR (Nujol) $cm^{-1}$: 3330, 2560, 2400, 1660, 1650. NMR (DMSO-$d_6$, 200 MHz): 0.88—1.83 (10H, m), 2.15—2.39 (1H, m), 2.63 (6H, s), 3.88 (2H, d, *J*=5.6 Hz), 3.96 (2H, s), 5.60 (1H, s), 7.13—7.38 (3H, m), 7.52—7.65 (2H, m), 8.35 (1H, t, *J*=5.6 Hz), 11.18 (1H, s). The enantiomeric excess of this compound was determined to be >98% by HPLC analysis of the corresponding free amine.

**(−)-2-Cyclohexyl-*N*-(4-dimethylamino-2-butynyl)-2-hydroxy-2-phenylacetamide Hydrochloride [(−)-13b·HCl]** (−)-**13b**·HCl was obtained in a similar manner to that of (+)-isomer, mp 171.5—173 °C. $[\alpha]_D^{23}$ −3.93° (*c*=3.83, MeOH). *Anal.* Calcd for $C_{20}H_{28}N_2O_2$·HCl: C, 65.83; H, 8.01; N, 7.68. Found: C, 65.73; H, 8.05; N, 7.98. IR (Nujol) $cm^{-1}$: 3340, 2380, 1660, 1650. NMR (DMSO-$d_6$, 200 MHz): 0.88—1.79 (10H, m), 2.16—2.40 (1H, m), 2.63 (6H, s), 3.88 (2H, d, *J*=5.6 Hz), 3.96 (2H, s), 5.59 (1H, s), 7.15—7.38 (3H, m), 7.50—7.64 (2H, m), 8.35 (1H, t, *J*=5.6 Hz), 11.06 (1H, s). The enantiomeric excess of this compound was determined to be >99% by HPLC analysis of the corresponding free amine.

**(*S*)-(+)-2-Cyclohexyl-2-hydroxy-2-phenylacetaldehyde [(*S*)-(+)-(28)]** To a solution of **27**[8] (1.93 g) in tetrahydrofuran (THF) (20 ml) was added cyclohexyl magnesium bromide (1.85 g) in ether (30 ml) at −70 °C. After stirring for 1 h, sat. $NH_4Cl$ solution was added to the reaction mixture. The organic layer was separated and washed with 1 N NaOH solution. The ethereal layer was treated with 1 N HCl at 0 °C for 12 h, then was separated and washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to afford (*S*)-(+)-**28** (1.41 g, 98%), mp 96.5—97 °C (recrystallized from petroleum ether). $[\alpha]_D^{26.8}$ +214.5° (*c*=1.91, $CCl_4$). Lit.[7e]: mp 95 °C, $[\alpha]_D$ +230° (*c*=1.9, $CCl_4$); lit.[7f]: mp 93—95 °C, $[\alpha]_D^{25}$ +78° (*c*=1, EtOH), $[\alpha]_D^{24}$ +225° (*c*=1.9, $CCl_4$). *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.67; H, 8.20. IR (Nujol) $cm^{-1}$: 3490, 1710. NMR ($CDCl_3$, 90 MHz): 0.96—2.40 (11H, m), 3.66 (1H, s), 7.20—7.63 (5H, m), 9.63 (1H, s).

**Methyl (*S*)-(+)-2-Cyclohexyl-2-hydroxy-2-phenylacetate [(*S*)-(+)-(29)]** To a solution of (*S*)-(+)-**28** (0.30 g) and $I_2$ (0.56 g) in MeOH (3 ml) was added dropwise 4% methanolic KOH solution (17 ml) at 40 °C and the mixture was stirred for 20 min. After cooling, the solution was poured into ice water (50 ml) and saturated with sodium chloride. The solution was extracted with diisopropyl ether and 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 *n*-hexane and EtOAc (25:1) as an eluent to afford (*S*)-(+)-**29** (0.32 g, 94%) as an oil. $[\alpha]_D^{22}$ +3.8° (*c*=2.267, MeOH). Lit.[7e]: mp 54 °C, $[\alpha]_D$ +30° (*c*=2, $CHCl_3$), $[\alpha]_D$ +6.0° (*c*=2, MeOH); lit.[7f]: mp 49—52 °C, $[\alpha]_D^{25}$ +5.7° (*c*=1, EtOH), $[\alpha]_D^{24}$ +33.5° (*c*=2, $CHCl_3$). IR (neat) $cm^{-1}$: 3510, 1720. NMR ($CDCl_3$, 90 MHz): 0.92—1.90 (10H, m), 1.96—2.36 (1H, m), 3.60 (1H, s), 3.73 (3H, s), 7.13—7.40 (3H, m), 7.43—7.66 (2H, m). MS (*m/z*): 248 ($M^+$), 190.

**(*S*)-(+)-2-Cyclohexyl-2-hydroxy-2-phenylacetic Acid [(*S*)-(+)-(30)]** To a solution of (*S*)-(+)-**29** (0.20 g) in MeOH (6 ml) was added a solution of KOH (0.17 g) in water (1.7 ml). The mixture was stirred at 45 °C for 6 h. After cooling, the mixture was evaporated *in vacuo* and water (15 ml) was added thereto. The aqueous solution was washed with diisopropyl ether and was acidified with 1 N HCl (3 ml). The acidic solution was extracted with EtOAc and the extract was washed with brine, dried over $Na_2SO_4$, and treated with activated carbon (0.02 g). The solution was evaporated *in vacuo* to afford (*S*)-(+)-**30** (0.17 g, 90%), mp 140.5—142.5 °C. $[\alpha]_D^{20}$ +25.5° (*c*=2.267, EtOH). Lit.[7a]: mp 137—139 °C, $[\alpha]_D^{20}$ +23.4°; lit.[7b]: mp 139—142 °C, $[\alpha]_D$ +24.6° (*c*=5.0, EtOH); lit.[7c]: mp 140.6—141.1 °C, $[\alpha]_D^{25}$ +24.8° (*c*=4.5, EtOH); lit.[7d]: mp 142—143 °C, $[\alpha]_D$ +25.2±1° (*c*=4.48, EtOH); lit.[7e]: mp 140 °C, $[\alpha]_D$ +22.6° (*c*=1.4, EtOH); lit.[7f]: mp 133—136 °C, $[\alpha]_D^{24}$ +25.2° (*c*=1.4, EtOH). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.97; H, 7.77. IR (Nujol) $cm^{-1}$: 3430, 1725. NMR ($CDCl_3$, 90 MHz): 0.90—2.45 (11H, m), 7.15—7.40 (3H, m), 7.45—7.70 (2H, m).

**(*S*)-(+)-2-Cyclohexyl-2-hydroxy-2-phenylacetic Acid [(*S*)-(+)-(30)]** To a solution of (*S*)-(+)-**28** [0.30 g, $[\alpha]_D^{26.8}$ +214.5° (*c*=1.91, $CCl_4$)] and 2-methyl-2-butene (1.5 ml) in *tert*-butanol (3 ml) was added a solution of sodium chlorite (0.18 g, 85%) in $NaH_2PO_4$ buffer (pH 3.5) (1.4 ml) and the mixture was stirred at room temperature for 3 h. To the solution was added brine and the mixture was extracted with diisopropyl ether. The organic layer was made alkaline with 1 N NaOH solution (2 ml). The aqueous layer was separated, washed with diisopropyl ether, and the solution was acidified with 1 N HCl (2.5 ml). The acidic solution was extracted with diisopropyl ether and the extract was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to afford (*S*)-(+)-**30** (0.31 g, 97%), mp 136—141.5 °C. $[\alpha]_D^{24.8}$ +23.7° (*c*=2.285, EtOH).

***N*-(4-Diethylamino-2-butynyl)-2,2-diphenyl-2-trifluoroacetylaminoacetamide Hydrochloride (32·HCl)** To a solution of **31**[11] (0.75 g) in acetonitrile (2.5 ml) was added *N*,*N*-diethyl-2-butyne-1,4-diamine (0.45 g) and the mixture was stirred at room temperature for 1 h. The mixture was evaporated *in vacuo* and 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 **32** (0.69 g, 63%) as an oil. IR (neat) $cm^{-1}$: 3330, 1735, 1680. NMR ($CDCl_3$, 90 MHz): 1.03 (6H, t, *J*=8 Hz), 2.45 (4H, q, *J*=8 Hz), 3.33 (2H, t, *J*=2 Hz), 3.95—4.10 (2H, m), 5.60 (1H, br s), 7.23—7.46 (10H, m), 8.63 (1H, br s). To a solution of **32** (0.47 g) in $CHCl_3$ (3 ml) was added methanolic HCl (0.15 g/ml, 0.5 ml) and the solution was evaporated *in vacuo* to afford **32**·HCl (0.51 g, 100%) as a viscous residue. IR ($CHCl_3$) $cm^{-1}$: 3420, 3340, 2600—2000, 1730, 1680. NMR ($CDCl_3$, 90 MHz): 1.38 (6H, t, *J*=8 Hz), 2.70—3.23 (4H, m), 3.70—3.86 (2H, m), 3.96—4.16 (2H, m), 6.20 (1H, br s), 7.33 (10H, s), 8.43 (1H, br s). MS (*m/z*): 445 ($M^+$), 430.

**2-Amino-*N*-(4-diethylamino-2-butynyl)-2,2-diphenylacetamide Dihydrochloride (33·2HCl)** To a solution of **32** (0.11 g) in acetone (2 ml) was added 6 N HCl (1 ml) and the mixture was refluxed for 24 h. After cooling, the mixture was evaporated *in vacuo* and the residue was made alkaline with aq. NaOH. The alkaline solution was extracted with EtOAc and 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 (20:1) as an eluent to afford **33** (0.05 g, 58%) as an oil. IR (neat) $cm^{-1}$: 3430, 3390, 1670. NMR ($CDCl_3$, 90 MHz): 1.03 (6H, t, *J*=8 Hz), 2.26 (2H, s), 2.50 (4H, q, *J*=8 Hz), 3.35 (2H, t, *J*=2 Hz), 4.02 (2H, dt, *J*=5, 2 Hz), 7.10—7.46 (11H, m). To a solution of **33** (0.60 g) in $CHCl_3$ (5 ml) was added methanolic HCl (0.15 g/ml, 1 ml) and the solution was evaporated *in vacuo* to afford **33**·2HCl (0.67 g, 92%) as a viscous residue. IR (KBr) $cm^{-1}$: 3600—2200, 1680, 1670. NMR (DMSO-$d_6$, 90 MHz): 1.26 (6H, t, *J*=7 Hz), 2.90—3.40 (4H, m), 3.90—4.20 (4H, m), 7.20—7.60 (10H, m), 8.40 (1H, br s), 9.43 (3H, br s). MS (*m/z*): 350 ($M^+$), 334.

**Acknowledgement** We wish to thank the staff of the Division of Analytical Research laboratories for elemental analyses and spectral measurements.

**References and Notes**

1) *a*) G. F. Anderson and C. M. Fredericks, *Pharmacology* (Basal), **15**, 31 (1977); *b*) P. M. Lish, J. A. LaBudde, E. L. Peters, and S. I. Robbins, *Arch. Int. Pharmacodyn.*, **156**, 467 (1965); *c*) M. Tonini, C. A. Rizzi, E. Perucca, F. DePonti, L. D'Angelo, A. DelVecchio, and A. Crema, *J. Pharm. Pharmacol.*, **39**, 103 (1987).
2) *a*) H. Kinoshita, H. Miyakita, Y. Katsuoka, K. Matsusita, K. Okada, and N. Kawamura, *Nishinihon Hinyokika*, **48**, 2035 (1986); *b*) H. Yokozeki, K. Akiyama, M. Yano, T. Inai, H. Takigawa, S. Kagawa, and K. Kurokawa, *ibid.*, **48**, 2041 (1986); *c*) The clinical dosage of oxybutynin is 6—9 mg, 3 times a day.
3) Y. Shinozaki, R. Monden, A. Manaka, H. Hisa, S. Naito, T. Igarashi, H. Sakai, Y. Iwata, T. Kasama, Y. Akimoto, and G. Urakubo, *Yakubutsu Dotai*, **1**, 341 (1986).
4) *a*) E. C. Juenge and P. Spangler, *J. Org. Chem.*, **29**, 226 (1964); *b*) W. J. Bailey and E. Fujiwara, *J. Am. Chem. Soc.*, **77**, 165 (1955).
5) S. I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, **1947**, 1586.

6) J. H. Cooley and E. J. Evain, *Synthesis*, **1989**, 1.
7) *a*) S. G. Kuznetsov and Z. I. Bobysheva, *Zh. Obshch. Khim.*, **32**. 3779 (1962); *b*) W.-S. Chen, G. H. Cocolas, C. J. Cavallito, and K. J. Chai, *J. Med. Chem.*, **20**, 1617 (1977); *c*) E. R. Atkinson, D. D. McRitchie, and L. F. Shoer, *ibid.*, **20**, 1612 (1977); *d*) C. H. Boehringer Sohn, British Patent 708370 (1954) [*Chem. Abstr.*, **49**, 11031 (1955)]; *e*) T. D. Inch, R. V. Ley, and P. Rich, *J. Chem. Soc.* (*C*), **1968**, 1693; *f*) A. Tambute and A. Collet, *Bull. Chem. Soc. Fr.*, **1—2** Part 2, 77 (1984).
8) *a*) T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Lett.*, **1978**, 1253; *b*) *Idem*, *ibid.*, **1979**, 705.
9) J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.*, **106**, 2943 (1984).
10) *a*) M. Isobe, Y. Ichikawa, and T. Goto, *Tetrahedron Lett.*, **27**, 963 (1986); *b*) G. A. Kraus and M. J. Taschnen, *J. Org. Chem.*, **45**, 1175 (1980); *c*) G. A. Kraus and B. Roth, *ibid.*, **45**, 4825 (1980); *d*) B. S. Bal, W. E. Childers, Jr., and H. W. Pinnick, *Tetrahedron*, **37**, 2091 (1981); *e*) B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, **27**, 888 (1973).
11) M. R. Johnson and L. R. Sousa, *Synthesis*, **1978** 318.
12) *a*) C. A. P. F. Su, P. Transwell, G. Nehmiz, and G. Heinzel, *Trends Pharmacol. Sci.*, **10** (Suppl. Subtypes Muscarinic Recept. IV), 98 (1989); *b*) H. Ladinsky, E. Giraldo, E. Monferini, G. B. Schiavi, M. A. Vigano, L. DeConti, R. Micheletti, and R. Hammer, *ibid.*, **9** (Suppl. Subtypes Muscarinic Recept. III), 44 (1988); *c*) L. Noronha-Blob and J. F. Kachur, *J. Pharmacol. Exp. Ther.*, **256**, 562 (1991).
13) H. A. Smith, C. A. Buehler, T. A. Magee, K. V. Nayak, and D. M. Glenn, *J. Org. Chem.*, **24**, 1301 (1959).
14) This compound was obtained by optical resolution of the racemic compound using quinine as a resolving agent.
15) K. Take, K. Okumura, K. Takimoto, M. Kato, and Y. Shiokawa, *Chem. Pharm. Bull.*, **39**, 2915 (1991).
16) M. Parry and B. V. Heathcote, *Life Sci.*, **31**, 1465 (1982).