of Neurological Disorders and Stroke (W.D.B.) and no. DA04988 from the National Institute on Drug Abuse (W.D.B.). We wish to express our sincere appreciation to Noel Whittaker and Wesley White for performing mass and ^{1}H NMR spectral analyses of all compounds and intermediates synthesized in this study.

Registry No. (–)-1, 67198-19-0; (+)-4, 135211-15-3; (–)-4, 135093-19-5; (+)-4·HBr, 135093-12-8; (–)-4·HBr, 134970-03-9; (+)-5, 135211-17-5; (–)-5, 135211-16-4; (+)-5·HBr, 135093-13-9; (–)-5·HBr, 135093-14-0; (±)-6, 134970-10-8; (±)-6·HBr, 134970-09-5; (±)-6 benzamide, 128387-88-2; (±)-7, 133488-96-7; 8·HCl, 135093-09-3; (±)-9, 69420-67-3; 10, 118207-34-4; (–)-11, 135093-10-6; (+)-11, 135093-11-7; (–)-11 fumarate, 135211-10-8; (+)-11 fumarate, 135211-11-9; (–)-12, 135093-15-1; (+)-12, 135093-16-2; (–)-12·HI, 134970-06-2; (+)-12·HI, 135211-13-1; (–)-13, 134970-04-0; (+)-13, 135093-17-3; (–)-13 fumarate, 134970-05-1; (+)-13 fumarate, 135211-12-0; (–)-14, 134970-07-3; (+)-14, 135093-18-4; (–)-14 fumarate, 134970-08-4; (+)-14 fumarate, 135211-14-2; cyclohexene oxide, 286-20-4.

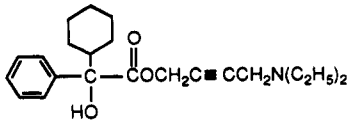
Analogues of Oxybutynin. Synthesis and Antimuscarinic and Bladder Activity of Some Substituted 7-Amino-1-hydroxy-5-heptyn-2-ones and Related Compounds

J. Paul Carter,† Lalita Noronha-Blob,‡ Vicki H. Audia,† Andrea C. Dupont,† Daniel W. McPherson,† Kenneth J. Natalie, Jr.,† W. Janusz Rzeszotarski,† Ciro J. Spagnuolo,† Philip P. Waid,† and Carl Kaiser*,†

Nova Pharmaceutical Corporation, 6200 Freeport Centre, Baltimore, Maryland 21224-6522. *Received February 25, 1991*

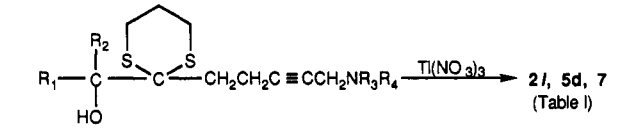
Oxybutynin chloride [4-(diethylamino)-2-butynyl α-cyclohexyl-α-hydroxybenzeneacetate hydrochloride, Ditropan] is widely used for the relief of symptoms in neurogenic bladder. This is a result of its combined anticholinergic, antispasmodic, and local anesthetic activities. In a study directed toward development of agents possessing the beneficial properties of oxybutynin, but having a longer duration of action, a series of metabolically more stable keto analogues of the parent ester, i.e. substituted 7-amino-1-hydroxy-5-heptyn-2-ones along with some analogues and derivatives, was prepared and evaluated for in vitro and in vivo antimuscarinic action in guinea pig preparations. Several members of the series were potent antimuscarinics having a longer duration of activity than that of oxybutynin in a guinea pig cystometrogram model. On the basis of its in vitro and in vivo antimuscarinic activity, coupled with a 5-fold greater duration of action than that of oxybutynin, 1-cyclobutyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one (**14b**) was selected for clinical evaluation.

Oxybutynin (1)[1,2] is extensively utilized for relief of urinary urgency, frequency, and urge incontinence in patients with uninhibited and reflex neurogenic bladder.[3-5] The effectiveness of this agent is attributed to a combination of M_3[6-8] selective muscarinic receptor subtype antagonism and antispasmodic,[9,10] local anesthetic, and calcium channel blocking actions.[11,12] The duration of action of 1 in man is about 6 h. In rats, it reaches a peak blood level about 2 h after dosing and a minimally detectable amount is present for 72 h.[4] The recommended clinical dosing regimen is 5 mg two to four times a day.[13] As this product is generally administered chronically, synthesis and identification of a similar substance having an increased duration of action was initiated. An understanding of the metabolism of oxybutynin is important for the design of such compounds. Unfortunately, the metabolic fate of 1 in humans has not been described; however, studies in rats indicate comparatively rapid metabolism that involves ester hydrolysis, N-deethylation, 4-hydroxylation of the cyclohexane ring, and conjugation.[14] Although a different metabolic route is followed in rat microsomes, where N-deethylation and *N*-oxide formation predominate,[15a] and in rabbits, where the hydrolysis product is not the major metabolite,[4] structural modification of 1 to give hydrolysis-resistant analogues was undertaken.



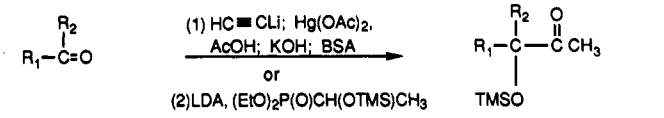
1

Scheme I. Method A

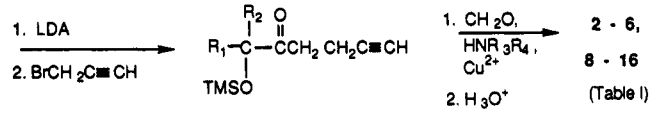


23

Scheme II. Method B



24



25

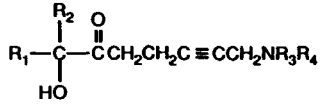
A series of substituted 7-amino-1-hydroxy-5-heptyn-2-ones (**2–16**, Table I), as well as some analogues and de-

† Division of Medicinal Chemistry.
‡ Division of Pharmacology.

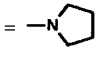
(1) Majewski, R. F.; Campbell, K. N.; Dykstra, S.; Covington, R.; Simms, J. C. Anticholinergic Agents. Esters of 4-Dialkyl (or 4-Polymethylene-)amino-2-butynols. *J. Med Chem.* **1965**, *8*, 719–720.
(2) Campbell, K. N.; Majewski, R. F. Substituted Aminobutynyl Acetates. U.S. Patent 3,176,019, 1965.
(3) Moisey, C. V.; Stephenson, T. P.; Brendler, C. B. The Urodynamic and Subjective Results of Treatment of Detrusor Instability with Oxybutynin Chloride. *Br. J. Urol.* **1980**, *52*, 472–475.

0022-2623/91/1834-3065$02.50/0

Table I. Physical and Pharmacological Data for Substituted 7-Amino-1-hydroxy-5-heptyn-2-ones (2–16)



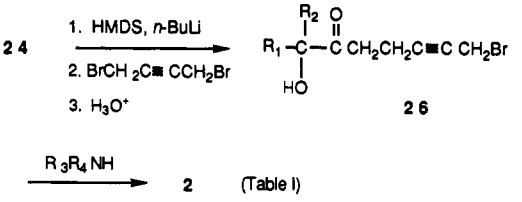
2 - 16

compd[a]	R_1	R_2	R_3	R_4	method[b]	mp, °C	formula[c]	isolated bladder detrusor[d] antimuscarinic K_b, nM ± SEM	in vivo cystometrogram[d] potency (iv) ID_{50}, mg/kg ± SEM	in vivo cystometrogram[d] duration, at ID_{80}, min ± SEM
2a	Ph	*c*-C_6H_{11}	H	H	C	52–55	$C_{19}H_{25}NO_2$[e]	2100 ± 1300		
2b	Ph	*c*-C_6H_{11}	H	CH_3	B	*f*	$C_{20}H_{27}NO_2$	71.2 ± 79	0.48 ± 0.11	48 ± 10
2c	Ph	*c*-C_6H_{11}	H	C_2H_5	C	80–81	$C_{21}H_{29}NO_2$[e]	232 ± 97	0.98 ± 0.29	85 ± 7
2d	Ph	*c*-C_6H_{11}	H	*i*-C_3H_7	C	*f*	$C_{22}H_{31}NO_2$	292 ± 119	2.1 ± 0.2	35 ± 3
2e	Ph	*c*-C_6H_{11}	H	*t*-C_4H_9	C	*f*	$C_{23}H_{33}NO_2$	4300 ± 2900	8.9 ± 4.9	
2f	Ph	*c*-C_6H_{11}	H	CH_2Ph	B	*f*	$C_{27}H_{33}NO_2$	4200 ± 2600		
2g	Ph	*c*-C_6H_{11}	CH_3	CH_3	B	98–100	$C_{21}H_{29}NO_2 \cdot 0.5C_4H_4O_4$[e,g]	38.7 ± 15.3	0.48 ± 0.11	126 ± 10
(*R*)-**2g**	Ph	*c*-C_6H_{11}	CH_3	CH_3	*h*	108–110	$C_{21}H_{29}NO_2 \cdot 0.5C_4H_4O_4$[e,g]	17.0 ± 6.4	0.19 ± 0.06	257 ± 38
(*S*)-**2g**	Ph	*c*-C_6H_{11}	CH_3	CH_3	*h*	100–102	$C_{21}H_{29}NO_2 \cdot 0.5C_4H_4O_4$[g]	209 ± 34	3.6 ± 0.9	88 ± 4
2h	Ph	*c*-C_6H_{11}	CH_3	C_2H_5	C	*f*	$C_{22}H_{31}NO_2$	37.0 ± 9.6	0.45 ± 0.05	39 ± 4
2i	Ph	*c*-C_6H_{11}	CH_3	*i*-C_3H_7	C	*f*	$C_{23}H_{33}NO_2$	267 ± 93	4.2 ± 1.0	41 ± 7
2j	Ph	*c*-C_6H_{11}	CH_3	$Ph(CH_2)_2$	B	*f*	$C_{28}H_{35}NO_2$	551 ± 138	>10.0	
2k	Ph	*c*-C_6H_{11}	CH_3	$(CH_2)_2OH$	B	*f*	$C_{22}H_{31}NO_3$	257 ± 23		
2l	Ph	*c*-C_6H_{11}	C_2H_5	C_2H_5	A	140–143	$C_{25}H_{35}NO_4 \cdot C_2H_4O_4$[i]	175 ± 70	2.8 ± 0.5	30 ± 2
2m	Ph	*c*-C_6H_{11}	C_2H_5	*i*-C_3H_7	C	*f*	$C_{24}H_{35}NO_2$	217 ± 40	3.3 ± 0.7	23 ± 7
2n	Ph	*c*-C_6H_{11}	NR_3R_4 = 		B	*f*	$C_{23}H_{31}NO_2$	202 ± 70	>10.0	44 ± 4
2o	Ph	*c*-C_6H_{11}	*i*-C_3H_7	*i*-C_3H_7	C	*f*	$C_{25}H_{37}NO_2$	260 ± 64	5.3 ± 1.3	32 ± 3
2p	Ph	*c*-C_6H_{11}	*n*-C_3H_7	*n*-C_4H_9	B	*f*	$C_{25}H_{37}NO_2$	142 ± 59	2.6 ± 0.4	74 ± 21
2q	Ph	*c*-C_6H_{11}	*n*-C_4H_9	*n*-C_4H_9	B	*f*	$C_{27}H_{41}NO_2$	>5000		
3a	Ph	*c*-C_5H_9	CH_3	CH_3	B	90–91	$C_{20}H_{27}NO_2 \cdot 0.5C_4H_4O_4$[g]	2.0 ± 0.2	0.33 ± 0.06	98 ± 3
3b	Ph	*c*-C_5H_9	C_2H_5	C_2H_5	B	123–125	$C_{22}H_{31}NO_2 \cdot 0.5C_4H_4O_4$[g]	21.0[j]	3.1 ± 0.4	
4a	Ph	*c*-C_3H_5	H	C_2H_5	B	*f*	$C_{18}H_{23}NO_2$	224 ± 49	1.1 ± 0.2	103 ± 17
4b	Ph	*c*-C_3H_5	CH_3	CH_3	B	*f*	$C_{18}H_{23}NO_2$	35.0 ± 7.4	0.48 ± 0.10	89 ± 6
4c	Ph	*c*-C_3H_5	CH_3	C_2H_5	B	*f*	$C_{19}H_{25}NO_2$	241 ± 114	1.3 ± 0.4	127 ± 34
4d	Ph	*c*-C_3H_5	C_2H_5	C_2H_5	B	*f*	$C_{20}H_{27}NO_2$	58.0 ± 6.2	0.98 ± 0.47	80 ± 4
5a	Ph	Ph	H	C_2H_5	B	83–84	$C_{21}H_{23}NO_2$	200 ± 87	1.5 ± 0.4	54 ± 2
5b	Ph	Ph	CH_3	CH_3	B	102–103	$C_{21}H_{23}NO_2$	70.1 ± 24	0.59 ± 0.26	45 ± 3
5c	Ph	Ph	CH_3	C_2H_5	B	85–86	$C_{22}H_{25}NO_2$	75.4 ± 9.3	0.90 ± 0.13	69 ± 11
5d	Ph	Ph	C_2H_5	C_2H_5	A	70–72	$C_{23}H_{27}NO_2$	70.7 ± 27		
6	Ph	1-adamantyl	CH_3	CH_3	B	*f*	$C_{25}H_{33}NO_2$	>5000		
7	Ph	CH_3	C_2H_5	C_2H_5	A	118–122	$C_{18}H_{25}NO_4 \cdot C_2H_2O_4$[i]	5200 ± 700		
8	Ph	1-bicyclo[2.2.2]oct-2-yl	CH_3	CH_3	B	*f*	$C_{23}H_{31}NO_2$	115 ± 17	4.4 ± 1.3	
9a	Ph	2-norbornyl	CH_3	CH_3	B	*f*	$C_{22}H_{29}NO_2$	90.0 ± 17	0.90 ± 0.20	242 ± 37
9b	Ph	2-norbornyl	H	C_2H_5	B	*f*	$C_{22}H_{29}NO_2$	65.0 ± 13	1.1 ± 0.17	165 ± 38
10	Ph	3-cyclohexenyl	CH_3	CH_3	B	*f*	$C_{21}H_{27}NO_2$	37.1 ± 2.9	2.0 ± 0.87	

11	Ph	*i*-C_4H_9	CH_3	CH_3	B	*f*	$C_{19}H_{27}NO_2$	30.5 ± 15	4.1 ± 0.5	
12	Ph	1-CH_3-*c*-C_3H_4	CH_3	CH_3	B	90–92	$C_{19}H_{25}NO_2$	24.0 ± 8.0	0.28 ± 0.09	291 ± 68
13	Ph	*i*-C_3H_7	CH_3	CH_3	B	*f*	$C_{18}H_{23}NO_2$	18.3 ± 5.0	0.48 ± 0.05	80 ± 5
14a	Ph	*c*-C_4H_7	H	C_2H_5	B	*f*	$C_{19}H_{23}NO_2$	224 ± 49	1.1 ± 0.19	103 ± 17
14b	Ph	*c*-C_4H_7	CH_3	CH_3	B	86–88	$C_{19}H_{25}NO_2 \cdot 0.5C_4H_4O_4$[c,e,j]	4.9 ± 0.80	0.12 ± 0.01	116 ± 18[k]
(+)-**14b**	Ph	*c*-C_4H_7	CH_3	CH_3	*h*	120–121	$C_{19}H_{25}NO_2 \cdot HCl$[l]	6.2 ± 0.20[m]	0.06 ± 0.01	88 ± 11[k]
(−)-**14b**	Ph	*c*-C_4H_7	CH_3	CH_3	*h*	120–121	$C_{19}H_{25}NO_2 \cdot HCl$[l]	149 ± 19[m]	2.5 ± 0.6	40 ± 4[k]
14c	Ph	*c*-C_4H_7	CH_3	C_2H_5	B	*f*	$C_{20}H_{27}NO_2$	7.5 ± 2.0	0.86 ± 0.18	168 ± 24
15a	4-FPh	*c*-C_6H_{11}	CH_3	CH_3	B	*f*	$C_{21}H_{28}NO_2$	67.7 ± 6.2	0.90 ± 0.20	104 ± 12
15b	4-FPh	*c*-C_6H_{11}	H	C_2H_5	B	*f*	$C_{21}H_{28}NO_2$	504 ± 336	1.8 ± 0.80	116 ± 2
16		*c*-C_6H_{11}	CH_3	CH_3	B	*f*	$C_{21}H_{35}NO_2$	169 ± 80	15.3 ± 1.3	
oxybutynin chloride								41.6 ± 10.1	0.14 ± 0.03	48 ± 5

[a] All isomeric compounds are mixtures, unless indicated otherwise. [b] See Experimental Section for description of the general method. [c] All compounds were analyzed for C, H, and N; values were within 0.4% of those calculated. [d] See the Experimental Section for description of the testing protocol. [e] Hydrate. [f] Obtained as an oil which failed to crystallize. [g] Hemifumarate. [h] See the Experimental Section for method of preparation. [i] Hydrogen oxalate. [j] Hydrochloride, mp 130–131 °C. [k] These data were determined at the ID_{50} dose. The duration of **14b** at ID_{50} was 228 ± 55 min. [l] Hydrochloride. [m] This value was determined using guinea pig ileal strip as described previously.[23]

Scheme III. Method C



rivatives (**17–22**, Table II) having an altered bridge between the benzylic carbon and amine terminus, was prepared as hydrolysis-resistant congeners of **1**. These compounds were examined as muscarinic receptor antagonists at M_3 (or $M_{2\beta}$) sites[15b] in a guinea pig bladder muscle strip preparation. An in vivo guinea pig cystometrogram model that mimics the natural filling of the bladder was used to measure urodynamic parameters associated with neurogenic bladder and duration of action of the compounds. The results of this study, which led to the identification of 1-cyclobutyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one (**14b**) as a clinical candidate for treatment of bladder dysfunction, are described in this article.

Chemistry

The most extensively investigated group of analogues

(4) A compendium Ditropan oxybutynin chloride 5 mg tablets. A New Urinary Tract Antispasmodic, Department of Research and Development, Marion Laboratories, Inc., September 1975, Kansas City, MO 64137.

(5) Thompson, I. M.; Lauvetz, R. Oxybutynin in Bladder Spasm, Neurogenic Bladder, and Enuresis. *Urology* **1976**, *8*, 452–454.

(6) Noronha-Blob, L.; Kachur, J. F. Enantiomers of oxybutynin: In vitro pharmacological characterization at M_1, M_2 and M_3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydrasis and salivary secertion in ginuea pigs. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 562–567.

(7) Levin, R. M.; Wein, A. J. Direct measurement of the anticholinergic activity of a series of pharmacological compounds on the canine and rabbit urinary bladder. *J. Urology* **1982**, *128*, 396–398.

(8) Nilvebrant, L.; Sparf, B. Dicyclomine, benzhexol and oxybutynine distinguish between subclasses of muscarinic binding sites. *Eur. J. Pharmacol.* **1986**, *123*, 133–143.

(9) Fredericks, C. M.; Green, R. L.; Anderson, G. F. Comparative in vitro effects of imipramine, oxybutynin, and flavoxate on rabbit detrussor. *Urology* **1978**, *12*, 487–491.

(10) Anderson, G. F.; Fredericks, C. M. Characterization of the oxybutynin antagonism of drug-induced spasms in detrusor. *Pharmacology* **1977**, *15*, 31.

(11) Tonini, M.; Rizzi, C. A.; Perucca, E.; DePonti, F.; D'Angelo, A.; Del Vecchio, A.; Crema, A. Depressant action of oxybutynin on contractility of intestinal and urniary tract smooth muscle. *J. Pharm. Pharmacol.* **1987**, *39*, 103–107.

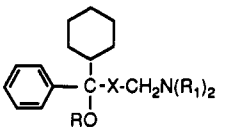
(12) Lish, P. M.; Labudde, J. A.; Peters, E. L.; Robbins, S. I. Oxybutynin—a musculotropic antispasmodic drug with moderate anticholinergic action. *Arch. Int. Pharmacodyn.* **1965**, *156*, 467–488.

(13) *Physicians Desk Reference*, 44th ed.; Barnhart, E., Ed.; Medical Economics: Oradell, NJ, 1990; 1262–1263.

(14) Akimoto, Y.; Kobayashi, H.; Shinozaki, Y. Studies on the Metabolic Fate of Oxybutynin Hydrochloride 4. Metabolism in Rats. *Iyakuhin Kenkyu* **1986**, *17*, 1070; *Chem. Abstr.* **1987**, *106*, 95489*k*.

(15) (a) Lindeke, B.; Hallstroem, G.; Johansson, C.; Ericsson, O.; Olsson, L. I.; Stroenberg, S. Metabolism of oxybutynin: establishment of desethyloxybutynin and oxybutynin *N*-oxide formation in rat liver preparations using deuterium substitution and gas chromatographic mass spectrometric analysis. *Biomed. Mass Spectrom.* **1981**, *8*, 506–513. (b) Peterson, J. S.; Noronha-Blob, L. Effects of selective cholinergic antagonists and α,β-methylene ATP on guinea-pig urinary bladder contractions *in vivo* following pelvic nerve stimulation. *J. Auton. Pharmacol.* **1989**, *9*, 303–311.

Table II. Physical and Pharmacological Data for Analogues and Derivatives of 1-Cyclohexyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one (17–22)



17 - 22

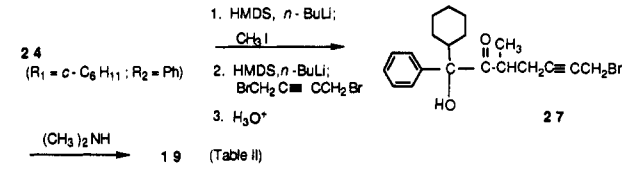
compd[a,b]	R	X	R_1	mp, °C	formula[c]	isolated bladder detrusor[d] antimuscarinic K_b, nM ± SEM	in vivo cystometrogram[d] potency (iv) ID_{50}, mg/kg ± SEM	in vivo cystometrogram[d] duration, at ID_{80}, min ± SEM
17[e]	TMS	$-COCH_2CH_2C{\equiv}C-$	CH_3	*f*	$C_{24}H_{37}NO_2Si$	>5000		
18	H	$-CO(CH_2)_4-$	CH_3	*f*	$C_{21}H_{33}NO_2$	43.0 ± 0.43	1.27 ± 0.43	294 ± 43
19	H	$-COCH(CH_3)CH_2C{\equiv}C-$	CH_3	85–86	$C_{22}H_{31}NO_2$	163 ± 19	2.10 ± 0.20	39 ± 7
20	H	$-CH(CH_2OH)C{\equiv}C-$	CH_3	112–113	$C_{20}H_{29}NO_2$	99.7 ± 32	7.38 ± 1.77	
21	H	$-CH(OH)CH_2CH_2C{\equiv}C-$	C_2H_5	104–105	$C_{23}H_{35}NO_2$[g]	1600 ± 560	6.30 ± 1.00	123 ± 9
22	H	$-COCH_2CH_2$-4-C_6H_4-	CH_3	*f*	$C_{25}H_{33}NO_2$	1900 ± 500		
oxybutynin chloride						41.6 ± 0.10	0.14 ± 0.03	48 ± 5

[a] All compounds are isomeric mixtures. [b] See the Experimental Section for description of the method of synthesis. [c] All compounds were analyzed for C, H, N; values were within 0.4% of those calculated unless otherwise indicated. [d] See the Experimental Section for description of testing protocol. [e] See the Experimental Section, general method B for method of preparation. [f] Obtained as an oil, bp <135 °C (0.1 Torr), which failed to crystallize. [g] Anal. ($C_{23}H_{35}NO_2$) H; C: calcd, 76.09; found, 75.61; N: calcd, 4.23; found, 3.73.

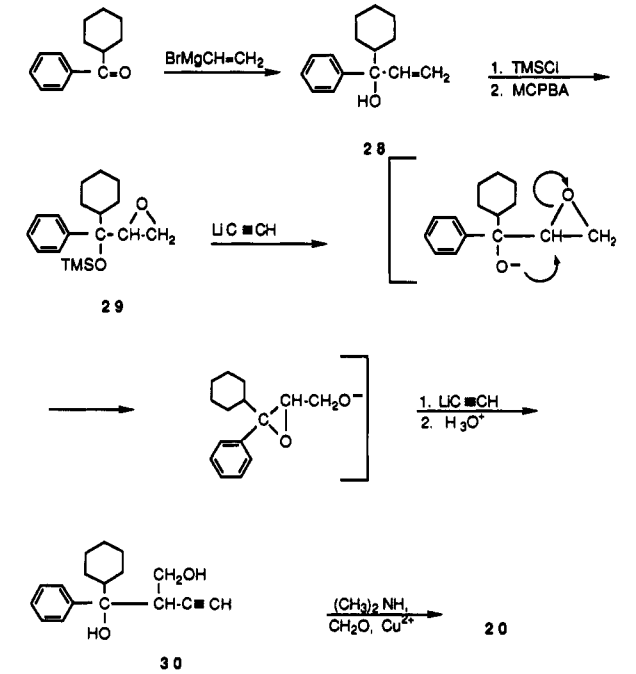
had the general structures **2–16** (Table I), i.e. ketonic relatives of the parent ester **1**. Three principal routes were utilized to prepare these compounds. In one route (method A), as outlined in Scheme I, 2,2-disubstituted 1,3-dithianes **23**[16] were treated with thallium nitrate[17] in methanol to afford substituted 7-amino-1-hydroxy-5-heptyn-2-ones **21**, **5d**, and **7** (Table I).

A second, more preferred, route for the synthesis of compounds **2–16** (Table I) is illustrated in Scheme II (method B). Accordingly, lithium acetylide was added to the appropriate ketone to give a disubstituted propargyl alcohol which was hydrolyzed in the presence of mercuric acetate. Trimethylsilyl protection of the alcohol afforded ketone **24**, which was more conveniently obtained in a single step process[18,19] in which the LDA-generated anion of 1-(diethylphosphinyl)-1-(trimethylsiloxy)ethane[20] was added to the appropriate ketone. Addition of propargyl bromide to **24** produced acetylenes **25**, which were aminomethylated via Mannich reaction[21,22] to give, following

Scheme IV



Scheme V



hydrolytic removal of the trimethylsilyl group, the substituted 7-amino-1-hydroxy-5-heptyn-2-ones **2–6** and **8–16** (Table I). The intermediate trimethylsiloxy derivative **17** (Table II) was isolated prior to removal of the protecting group. For synthesis of the *R* and *S* enantiomers of **2g** and the (+)- and (−)-isomers of **14b**, the appropriately substituted mandelic acid isomers were treated with methyllithium to give the corresponding antipodal hydroxy-

(16) Adams, T. C.; Dupont, A. C.; Carter, J. P.; Kachur, J. F.; Guzewska, M. E.; Rzeszotarski, W. J.; Farmer, S. G.; Noronha-Blob, L.; Kaiser, C. Aminoalkynyldithianes. A New Class of Calcium Channel Blockers. *J. Med. Chem.* **1991**, *34*, 1585–1593.
(17) Fujita, E.; Naogao, Y.; Kaneko, K. Dethioacetylization with Thallium(III) Nitrate. *Chem. Pharm. Bull. Jpn.* **1976**, *24*, 1115–1118.
(18) Koenigkramer, R. E.; Zimmer, H. α-Heterosubstituted Phosphonate Carbanions. 11. Benzoins via an Acyl Anion Equivalent. Novel One-Pot Preparation of Benzo[*b*]furans via Benzoins Using Hydriodic Acid. *J. Org. Chem.* **1980**, *45*, 3994.
(19) Koenigkramer, R. E.; Zimmer, H. α-Heterosubstituted Phosphonate Carbanions IX: Diethyl 1-Phenyl-1-Trimethylsiloxymethane Phosphonate as an Acyl Anion Equivalent; A Novel Method for the Preparation of α-Hydroxyketones. *Tetrahedron Lett.* **1980**, *21*, 1017–1020.
(20) Birum, G. H.; Richardson, G. A. Silicon–phosphorus compounds. U.S. Patent 3,113,139, 1963; *Chem. Abstr.* **1964**, *61*, 5551*d*.
(21) For a review, see: Blicke, F. F. The Mannich Reaction. *Org. React.* **1942**, *10*, 303–341.
(22) Matsumoto, K. Synthesis under High Pressure: Mannich Reaction of Ketones and Esters with Dichloromethane and Secondary Amines. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 922.

propanones, which were silylated to afford the isomeric **24** (R_1 = Ph, R_2 = c-C_6H_{11}) and **24** (R_1 = Ph, R_2 = c-C_4H_7). These optically active methyl ketones were converted to *R* and *S*-**2g** and (+)- and (−)-**14b** as indicated in Scheme II.

A third method (method C) employed for the synthesis of compounds of general structure **2**, especially those in which the amino substituents R_3 and R_4 are varied, is outlined in Scheme III. In this sequence, trimethylsiloxy ketone **24** was alkylated with 1,4-dibromo-2-butyne and hydrolyzed to afford a 1,1-disubstituted 7-bromo-1-hydroxy-5-heptyn-2-one (**26**), which was aminated with an appropriate amine or amine precursor (**2a** was derived via a phthalimide intermediate) to give substituted 7-amino-1-cyclohexyl-1-hydroxy-1-phenyl-5-heptyn-2-ones **2** indicated in Table I. A similar sequence utilizing α,α-dibromo-*p*-xylene in place of the dibromobutyne resulted in 1,4-phenylene analogue **22** (Table II) of **2g**.

For synthesis of the branched-chain bridged analogue **19** (Table II) a route similar to that shown in Scheme III was employed. Thus, as outlined in Scheme IV, **24** (R_1 = c-C_6H_{11}; R_2 = Ph) was sequentially alkylated with methyl iodide and 1,4-dibromo-2-butyne to give **27**, which was employed for alkylation of dimethylamine to afford **19**.

Branched-chain 1,3-diol **20** was obtained via the sequence illustrated in Scheme V. Thus, addition of vinylmagnesium bromide to cyclohexyl phenyl ketone afforded **28**, which was converted to the TMS ether. MCPBA oxidation of the latter gave epoxide **29**, which upon treatment with lithium acetylide apparently underwent ether cleavage and rearrangement as indicated via the postulated intermediates shown in brackets to produce acetylene derivative **30**. Mannich condensation of **30** with formaldehyde and dimethylamine resulted in **20** (Table II).

Platinum-catalyzed hydrogenation of **2g** afforded the acetylene bridge reduced derivative **18** (Table II). A 1,2-diol, **21** (Table II), was obtained by lithium aluminum hydride reduction of **2l**.

Results and Discussion

The antimuscarinic effects of analogues **2–22** (Tables I and II) were determined by comparing their ability to inhibit carbachol-induced guinea pig detrusor muscle contractions. Potencies are expressed as affinity constants (K_b), defined as the molar concentration of test compound that produced a 2-fold rightward shift of the control carbachol concentration–response curve.[23]

Among a series of 1-cyclohexyl-substituted 5-heptyn-2-ones (**2a–q**), the primary amine 7-amino-1-cyclohexyl-1-hydroxy-1-phenyl-5-heptyn-2-one (**2a**) lacked significant activity in the bladder preparation; however, several secondary (**2b–d**) and tertiary amines (**2g–i,k–p**) were effective as muscarinic receptor antagonists. Amine substituents as large or larger than butyl, as in **2e**, **2f**, **2j**, and **2q**, markedly decreased potency. Greatest potency was observed with the *N,N*-dimethyl (**2g**) and *N*-ethyl, *N*-methyl (**2h**) tertiary amines. These compounds were about 4.5 times more potent than the *N,N*-diethyl homologue **2l**. Likewise, in the related cyclopentyl **3** and cyclopropyl **4** series the dimethylated derivatives **3a** and **4b** were more effective antimuscarinics than their diethyl counterparts **3b** and **4d** whereas in the phenyl series **5** the *N,N*-dimethyl (**5b**), *N*-ethyl, *N*-methyl (**5c**), and *N,N*-diethyl (**5d**) amines were approximately equipotent. For this reason the influence of substitution of position 1 on antimuscarinic potency was examined primarily in a series of 7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-ones. A variety of 1-substituted dimethylamines (**2–16**) was examined. Potency increased in the following order: 1-adamantyl (**6**) < methyl (*N,N*-diethyl) (**7**) < 1-bicyclo-[2.2.2]oct-2-yl (**8**) < 2-norbornyl (**9a**) < phenyl (**5b**) < cyclohexenyl (**10**) < cyclohexyl (**2g**) < cyclopropyl (**4b**) < isobutyl (**11**) < 1-methylcyclopropyl (**12**) < isopropyl (**13**) < cyclobutyl (**14b**) < cyclopentyl (**3a**).

Antimuscarinic enantioselectivity was established for **2g** in the guinea pig bladder muscle preparation and for **14b** in a similar test utilizing guinea pig ileal longitudinal muscle.[23] Consistent with the enantioselectivity demonstrated by the isomers of oxybutynin (**1**),[6,23] in both the cyclohexyl (**2g**) and cyclobutyl (**14b**) analogues, the *R* or (+)-enantiomers were about twice as potent as the racemate whereas the *S* or (−)-isomers were significantly less potent.

p-Fluoro substitution of the 1-phenyl ring of **2g**, i.e. to afford 1-cyclohexyl-7-(dimethylamino)-1-hydroxy-1-(4-fluorophenyl)-5-heptyn-2-one (**15a**), resulted in decreased antimuscarinic activity. An even greater decrease followed replacement of the 1-phenyl substituent of **2g** with a cyclohexyl group, i.e. to give **16**. The importance of the 1-hydroxyl function, presumably for muscarinic receptor interaction, was suggested by the failure of the trimethylsilyl derivative **17** to demonstrate notable activity. Several congeners of **2g** having a modified bridge between the benzylic carbon and amine terminus were also studied. The derivative **18** in which the acetylene bridge was reduced was almost as potent as **2g**. The methylated derivative **19** and a rearrangement product **20** had decreased, yet significant, antimuscarinic activity. Reduction of the carbonyl, i.e. to produce diol **21**, as well as replacement of the acetylene linkage with a 1,4-phenylene bridge, i.e. **22**, markedly decreased potency.

As indicated in Tables I and II, selected members from the present series of oxybutynin analogues were examined for potency and duration of action in an in vivo guinea pig cystometrogram (CMG) model in which functional detrusor muscle contraction strength was measured in terms of intravesical bladder pressure (P_{ves}).[24] ID_{50} values are defined as the calculated dose of compound inhibiting peak P_{ves} by 50%. Duration of action (half-life, $t_{1/2}$) in the CMG model was determined from the slope of recovery of the depressed P_{ves} response followed over time until P_{ves} returned to its initial level. For comparison, compounds were given intravenously at a single (ID_{80}) equieffective dose.

The rank order of potency of the compounds as inhibitors of in vivo bladder contractility roughly correlated with their rank order of antimuscarinic potency in isolated bladder muscle preparations. These results are similar to findings with many other muscarinic receptor antagonists where their anticholinergic activity has been shown to play a role in the suppression of bladder hyperactivity.[26] Ox-

(23) Kachur, J. F.; Peterson, J. S.; Carter, J. P.; Rzeszotarski, W. J.; Hanson, R. C.; Noronha-Blob, L. R and S Enantiomers of Oxybutynin: Pharmacological Effects in Guinea Pig Bladder and Intestine. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 867–872.

(24) Peterson, J. S.; Hanson, R. C.; Noronha-Blob, L. In Vivo Cystometrogram Studies in Urethane-Anesthesized and Conscious Guinea Pigs. *J. Pharmacol. Methods* **1989**, *21*, 231–241.

(25) Barlow, R. B.; Franks, F. M.; Pearson, J. D. M. Studies on the Stereospecificity of Closely Related Compounds Which Block Postganglionic Acetylcholine Receptors in the Guinea-Pig Ileum. *J. Med. Chem.* **1973**, *16*, 439–446.

(26) Noronha-Blob, L.; Lowe, V. C.; Peterson, J. S.; Hanson, R. C. The Anticholinergic Activity of Agents Indicated for Urinary Incontinence is an Important Property for Effective Control of Bladder Dysfunction. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 586–593.

ybutynin (1) and (dimethylamino)-1-cyclobutyl analogue **14b** were the most potent compounds tested; (+)-**14b** was about twice as potent as racemic **14b**. Duration of action in the CMG model varied from 35 to 294 min. This appears to be influenced by the 1-substituent, amine substitution, and the nature of the bridge between the benzylic carbon and the amino group. No clearly defined relationship between structure and duration of action was established, although it is noteworthy that the acetylene-reduced analogue **18** was equally long acting as the substituted 5-heptyn-2-ones **2** having the greatest duration of action.

On the basis of a composite profile of antimuscarinic potency in vitro and in vivo, coupled with a 5-fold greater duration than that of oxybutynin in the CMG model and an almost 3-fold greater $t_{1/2}$ (174 vs 65 min) when 10 mg/kg of both compounds were given orally to unanesthetized guinea pigs, **14b** was selected for clinical evaluation in the treatment of urinary incontinence.

Experimental Section

Melting points were determined with a Bristoline hot-stage microscope or a Thomas-Hoover Unimelt melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman FT 1300 spectrophotometer. ^{1}H NMR spectra were obtained on either a Varian EM 360A, an IBM NR80, or a General Electric QE300 spectrometer with Me_4Si as an internal standard. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLC was done on precoated plates (silica gel, 60F-254) with fluorescent indicator. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA; they are indicated by symbols of the elements and were within 0.4% of calculated values.

Chemistry. General Methods. Method A. 1-Cyclohexyl-7-(diethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one Hydrogen Oxalate (21). To a solution of 3.0 g (6.73 mmol) of 2-[5-(diethylamino)-3-pentynyl]-2-(**α-cyclohexyl-α-phenyl-α-hydroxymethyl**)-1,3-**dithiane** (**23**, R_1 = c-C_6H_{11}; R_2 = Ph; R_3 = R_4 = C_2H_5)[16] in a solution of 120 mL of methanol and 30 mL of THF was added 3.13 g (6.9 mmol) of thallium trinitrate trihydrate[17] in 15 mL of methanol. After being stirred for 5 min at ambient temperature, the reaction mixture was concentrated and the residue was dissolved in chloroform. The resulting solution was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on C-18 silica gel. Elution with 98:2 acetonitrile/methanol gave 0.34 g (14.2%) of a colorless liquid: bp > 135 °C (0.15 Torr); NMR ($CDCl_3$) δ 1.0 – 2.0 (m, 17 H), 2.3–2.9 (m, 9 H), 3.4 (m, 2 H), 7.2–7.76 (m, 5 H); IR (neat) 1710 cm^{-1}. A solution of 0.3 g (0.8 mmol) of the product in methanol was treated with 0.1 g (1.1 mmol) of oxalic acid and ether was added to give the hydrogen oxalate **21** (Table I).

Method B. 3-Cyclohexyl-3-hydroxy-3-phenylpropyne. To a stirred solution of 47.8 g (0.52 mol) of lithium acetylide in 70 mL of THF at 0 °C was added a solution of 97.9 g (0.52 mol) of cyclohexyl phenyl ketone in 100 mL of THF over a period of 15 min. After the solution was warmed to ambient temperature, it was stirred for 16 h. The mixture was then cooled to 0 °C and 50 mL of 5 N hydrochloric acid was added. After being diluted with 200 mL of water, the mixture was extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated. Distillation of the residual liquid gave 60.3 g (82.9%) of a pale yellow liquid: bp 111–114 °C (0.8 Torr); NMR ($CDCl_3$) δ 7.7–7.2 (m, 5 H), 0.9–2.1 (m, 11 H), 2.3 (s, 1 H), 2.6 (s, 1 H), 7.2–7.7 (m, 5 H); IR (neat) 3433, 3304, 2111, 1448, 1016 cm^{-1}.

1-Cyclohexyl-1-hydroxy-1-phenylpropan-2-one. To a solution of 21.57 g (0.10 mol) of 3-cyclohexyl-3-hydroxy-3-phenylpropyne in 100 mL of glacial acetic acid was added 35.20 g (0.11 mol) of mercuric acetate with stirring. After 72 h, 8.3 g (0.11 mol) of thioacetamide was added and the mixture was stirred for 3 h. The mixture was diluted with 300 mL of ether and washed with water and saturated sodium bicarbonate solution, dried over sodium sulfate (Na_2SO_4), and concentrated to afford 18.36 g (67%) of a white crystalline solid (from petroleum ether, mp 81–83 °C): ^{1}H NMR ($CDCl_3$) δ 0.8–1.9 (m, 11 H, C_6H_{11}), 1.9 (s, 3 H, CH_3), 2.2 (s, 3 H, CH_3), 7.2–7.5 (m, 5 H, C_6H_5).

To a solution of 16.42 g (0.06 mol) of 1-acetoxy-1-cyclohexyl-1-phenylpropan-2-one in 55 mL of 90% aqueous methanol was added 3.2 g of potassium hydroxide. The mixture was refluxed for 15 min, cooled, and diluted with 90 mL of a saturated sodium chloride solution. The mixture was extracted with ether, dried (Na_2SO_4), and concentrated to a crude oil. Distillation afforded 10.51 g (75.4%) of a clear oil: bp 125–128 °C (0.1 Torr); NMR ($CDCl_3$) δ 0.9–2.5 (m, 11 H, C_6H_{11}), 2.1 (s, 3 H, CH_3), 4.5 (s, 1 H, OH), 7.2–7.6 (m, 5 H, C_6H_5); IR (neat) 3456, 3057, 1705, 1448, 1358, 1209, 1124 cm^{-1}.

1-Cyclohexyl-1-phenyl-1-(trimethylsiloxy)propan-2-one (24). To a solution of 15.44 g (66.5 mmol) of 1-cyclohexyl-1-hydroxy-1-phenylpropan-2-one in 35 mL of DMF was added 16.2 g (79.7 mmol) of bis(trimethylsilyl)acetamide. The mixture was heated to 130 °C for 12 h, cooled, diluted with water, and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to an oil. Distillation of the crude oil gave 19.86 g (98.1%) of a yellow oil, **24**: bp 100 °C (1.0 Torr); NMR ($CDCl_3$) δ 0.2 (s, 9 H, CH_3), 0.9–2.4 (m, 11 H, C_6H_{11}), 2.1 (s, 3 H, CH_3), 7.2–7.6 (m, 5 H, C_6H_5).

[1-(Diethoxyphosphinyl)ethoxy]trimethylsilane. To a stirred solution of 31.7 mL (0.25 mol) of chlorotrimethylsilane and 42.9 mL (0.25 mol) of triethyl phosphite was added 17.0 mL (0.30 mol) of acetaldehyde. The mixture was maintained at 35–45 °C during the addition. After addition was completed, the mixture was heated to 90 °C for 1 h. The product was distilled to give 52 g (90%) of a colorless oil, bp 85 °C (0.2 Torr).

1-Cyclohexyl-1-phenyl-1-(trimethylsiloxy)propan-2-one (24). To a stirred solution of 35 mL (0.25 mol) of diisopropylamine in 800 mL of dry THF at −78 °C was added 100 mL (0.25 mol) of *n*-butyllithium (2.5 M in hexane). The mixture was stirred at −78 °C for 1 h then 52 g (0.225 mol) of [1-(diethoxyphosphinyl)ethoxy]trimethylsilane was added dropwise. After the mixture was stirred for 1.5 h at −78 °C, 42.5 g (0.225 mol) of cyclohexylphenyl ketone was added. The mixture was stirred at −78 °C for 0.5 h, warmed to ambient temperature over 0.5 h, and poured into water. The mixture was extracted with ether and then washed with cold dilute hydrochloric acid and saturated aqueous sodium chloride, dried over $NaSO_4$, and concentrated. The residue was purified by chromatography with 98:2 hexane/ethyl acetate eluant to afford 51 g (75%) of **24** as a colorless oil. Spectral data corresponded to that of material obtained by the alternative lithium acetylide method.

1-Cyclohexyl-1-phenyl-1-(trimethylsiloxy)-5-hexyn-2-one (25). To a solution of 90.9 mL (0.65 mol) of diisopropylamine in 1.6 L of THF at −78 °C was added 280 mL of *n*-butyllithium (2.5 M in hexane). The mixture was warmed to −5 °C over 0.5 h and 192 g (10.6 mol) of 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)propan-2-one (**24**) in 100 mL of THF was added. After 1 h, this mixture was cannulated into a solution of 200 mL (1.8 mol) of 80% propargyl bromide in toluene and 800 mL of THF at −78 °C. The mixture was allowed to warm to room temperature over 1 h, poured into cold dilute hydrochloric acid, and extracted twice with ether. The combined organic layers were dried ($MgSO_4$) and concentrated to give 216 g of a light brown oil, **25**, which was used immediately without further purification.

1-Cyclohexyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one (2g). A solution of 20 g (0.67 mol) of paraformaldehyde, 75 g (0.67 mol) of 40% dimethylamine in water, and 200 mg of copper acetate in 50 mL of dioxane was heated to 60 °C for 1 h. To this mixture was added a solution of 216 g (0.63 mol) of the 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)-5-hexyn-2-one (**25**) in 150 mL of dioxane. The mixture was heated at 90 °C for 3 h, cooled to room temperature, and diluted with 200 mL of cold aqueous 10% KOH. The slurry was filtered through Celite and the pad was washed with ether. The filtrate was extracted with cold dilute hydrochloric acid and the organic layer discarded. The aqueous layer was neutralized with sodium bicarbonate and extracted with ether. The ether extract was dried ($MgSO_4$), concentrated, and purified by chromatography (Florisil, 30% ethyl acetate/hexane to 10% methanol/methylene chloride) to give 170 g (82%) of a light brown oil. Spectral data corresponded to that of material obtained by method A.

Method C. 7-Bromo-1-cyclohexyl-1-hydroxy-1-phenyl-5-heptyn-2-one (26). To a solution of 11.6 g (71.6 mmol) of

1,1,1,3,3,3-hexamethyldisilazane in 75 mL of THF at −10 °C was added 19.8 g (71.3 mmol) of *n*-butyllithium (2.2 M in hexane). The solution was stirred for 30 min and a solution of 21.99 g (72.2 mol) of 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)propan-2-one (**24**) in THF (75 mL) was added over a period of 15 min. After 1 h, 59.9 g (0.3 mmol) of 1,4-dibromo-2-butyne was added. After an additional hour, the reaction was quenched by the addition of a solution of glacial acetic acid (7 mL) in ether (20 mL). The mixture was partitioned between ether and water. The organic layer was dried ($MgSO_4$), concentrated, and dissolved in 150 mL of methanol and 0.2 mL of concentrated hydrochloric acid. This solution was stirred at 40 °C for 30 min, cooled to room temperature, and diluted with water to the point of turbidity. The mixture was partitioned between ether and water, and the organic layer separated, dried ($MgSO_4$), and evaporated to afford a yellowish brown oil. Chromatography on silica [hexane/ethyl acetate (98:2)] afforded 16.1 g (59.5%) of an orange oil: NMR ($CDCl_3$) δ 1.1–1.9 (m, 11 H, C_6H_{11}), 2.3–2.5 (m, 2 H, CH_2), 2.6–2.8 (m, 2 H, CH_2), 3.8 (t, 2 H, CH_2), 7.2–7.6 (m, 5 H, C_6H_5); IR (neat) 3461, 2234, 1705, 609 cm^{-1}; TLC (silica, petroleum ether/ethyl acetate (95:5)) R_f = 0.53.

1-Cyclohexyl-7-(diethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one (21). To a solution of 7.51 g (17.2 mmol) of 1-cyclohexyl-7-bromo-1-hydroxy-1-phenyl-5-heptyn-2-one (**26**) in 75 mL of ether was added 70.7 g (0.1 mol) of diethylamine. After 3 h, the mixture was filtered, washed twice with water, separated, dried ($MgSO_4$), and concentrated to afford a yellowish orange oil (7.11 g, 100%): NMR ($CDCl_3$) δ 1.0 (t, 6 H, CH_3), 1.0–1.9 (m, 11 H, C_6H_{11}), 2.2–2.5 (m, 2 H, CH_2), 2.3 (q, 4 H, CH_2) 2.6–2.8 (m, 2 H, CH_2), 3.3 (t, 2 H, CH_2), 4.4 (s, 1 H, OH), 7.2–7.6 (m, 5 H, C_6H_5); IR (neat) 3456, 1707 cm^{-1}. Hemifumarate: mp 140–142 °C (from 2-butanone); NMR ($CDCl_3$) δ 1.1 (t, J = 7.2, 6 H, CH_3), 1.0–1.9 (m, 11 H, C_6H_{11}), 2.3–2.5 (m, 2 H, CH_2), 2.8 (q, J = 7.3, 4 H, CH_2), 2.7–2.9 (m, 2 H, CH_2), 3.6 (s, J = 1.8, 2 H, CH_2), 6.8 (s, 1 H, CH), 7.2–7.8 (m, 5 H, C_6H_5); IR (KBr) 2234, 1710 cm^{-1}. Anal. ($C_{25}H_{35}NO_4$) C, H, N.

1-Cyclohexyl-7-(dimethylamino)-1-phenyl-1-(trimethylsiloxy)-5-heptyn-2-one (17). To a stirred solution of 140 mL (0.65 mol) of 1,1,1,3,3,3-hexamethyldisilizane in 1.6 L of THF at −78 °C was added 280 mL of a solution of *n*-butyllithium (2.5 M in hexane). The mixture was warmed to −5 °C over 0.5 h, then 192 g (0.63 mol) of siloxy ketone **24** was added as a solution in 100 mL of THF, and the mixture was stirred at −5 °C for 1 h. The mixture was added via cannula to a solution of 200 mL (1.8 mol) of 80% propargyl bromide/toluene in 800 mL of THF at −78 °C. The mixture was warmed slowly to ambient temperature over 1 h, poured into cold dilute aqueous hydrochloric acid, and extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to afford 216 g of a light brown oil that was used immediately in the next reaction step (87% by GC analysis).

A solution of 20 g (0.67 mol) of paraformaldehyde, 75 g (0.67 mol) of 40% dimethylamine in water, and 200 mg of copper acetate in 50 mL of dioxane was heated at 60 °C for 1 h, and then 216 g (0.63 mol) of the 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)-5-hexyn-2-one in 150 mL of dioxane was added. The mixture was heated to 90 °C for 3 h, then cooled, diluted with 200 mL of cold 10% aqueous KOH solution, and filtered through a Celite pad with ether washes. The ether filtrates were extracted with cold aqueous dilute hydrochloric acid. The acid extracts were neutralized with $NaHCO_3$ and extracted with ether. The ether extracts were dried (Na_2SO_4), filtered, and concentrated to afford a brown oil. Chromatography (Florisil, 7:3 hexane/ethyl acetate, then 9:1 dichloromethane/methanol) gave 170 g (82%) of a light brown oil: NMR ($CDCl_3$) δ 0.2 (s, 9 H), 1.10–1.90 (m, 10 H), 2.20 (s, 6 H), 2.30–2.50 (m, 3 H), 2.70 (t, 2 H), 3.10 (t, 2 H), 7.20–7.50 (m, 5 H); IR (neat) 2945, 2850, 1715, 1250 cm^{-1}. Anal. ($C_{24}H_{37}SiNO_2$) C, H, N.

1-Cyclohexyl-7-(dimethylamino)-1-hydroxy-1-phenylheptan-2-one (18). To 100 mL of ethyl acetate in a Parr hydrogenation bottle were added 1.0 g (3 mmol) of 1-cyclohexyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one and 20 mg of 5% palladium on carbon. The mixture was hydrogenated under 30 psi of hydrogen for 2 h. Excess hydrogen was removed under a stream of argon, and the mixture filtered through a pad of Celite. The pad was washed with ethyl acetate, and the filtrates were combined and concentrated to give 0.94 g (94%) of 1-cyclohexyl-7-(dimethylamino)-1-hydroxy-1-phenylheptan-2-one as a viscous brown oil: NMR ($CDCl_3$) δ 2.4 (m, 2 H), 1.1–1.8 (m, 17 H), 2.1 (s, 6 H), 2.2 (m, 2 H), 2.4 (m, 2 H), 7.2–7.5 (m, 5 H); IR (neat) 3448, 2936, 2859, 1705, 1445 cm^{-1}. Anal. ($C_{21}H_{33}NO_2$) C, H, N.

7-Bromo-1-cyclohexyl-1-hydroxy-3-methyl-1-phenyl-5-heptyn-2-one (27). To a solution of 4.4 mL (20.9 mmol) of 1,1,1,3,3,3-hexamethyldisilizane in 50 mL of THF at −10 °C was added 9.5 mL (23.5 mmol) of *n*-butyllithium (2.5 M in hexane). After 45 min, a solution of 5.20 g (17.1 mmol) of 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)propan-2-one in 50 mL of THF was added over 1 h. After an additional hour, 4.5 mL (72.3 mmol) of iodomethane was added and the mixture stirred at 25 °C overnight. The mixture was partitioned between water and ether and the organic layer was washed twice with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica and eluted with a gradient of hexane to ethyl acetate/hexane (2:98) to give 5.26 (94%) of a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.2 (s, 9 H, CH_3), 0.9 (t, 3 H, CH_3), 1.7–2.0 (m, 11 H, C_6H_{11}), 2.5 (q, 2 H, CH_2), 7.2–7.5 (m, 5 H, C_6H_5). This material was treated as in the preparation of **26** to give **27** as a pale yellow liquid: NMR ($CDCl_3$) 0.6 (d, 3 H, CH_3), 1.1–1.9 (m, 11 H, C_6H_{11}), 2.3 (d, 2 H, CH_2), 2.5 (m, 1 H, CH), 3.8 (s, 2 H, CH_2), 4.1 (s, 1 H, OH), 7.2–7.6 (m, 5 H, C_6H_5); TLC (silica, petroleum ether/ethyl acetate (95:5)) R_f = 0.61, 0.65.

1-Cyclohexyl-7-(dimethylamino)-1-hydroxy-3-methyl-1-phenyl-5-heptyn-2-one (19). Excess dimethylamine was bubbled into a solution of 1.94 g (5.1 mmol) of 7-bromo-1-cyclohexyl-1-hydroxy-3-methyl-1-phenyl-5-heptyn-2-one in 50 mL of ether and reaction progress was monitored by GC. After 1 h the mixture was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to an oil. Chromatography on Merck silica gel (240–400 mesh) with 95:5:0.2 petroleum ether/ethyl acetate/triethylamine afforded a solid (0.61 g, 35%, mp 85 °C) upon crystallization from petroleum ether/ethyl acetate (95:5): NMR ($CDCl_3$) δ 0.6 (d, 3 H, CH_3), 1.0–1.9 (m, 10 H, CH_2), 2.2 (s, 6 H, CH_3), 2.3 (m, 2 H, CH_2), 2.5 (m, 1 H, CH), 3.1 (s, 2 H, CH_2), 4.1 (s, 1 H, CH), 7.2–7.6 (m, 5 H, C_6H_5); IR (KBr) 3392, 1707 cm^{-1}. Anal. ($C_{22}H_{31}NO_2$) C, H, N.

1-Cyclohexyl-1-hydroxy-1-phenyl-2-propene (28). To a mixture of 40 mL (40.0 mmol) of vinylmagnesium bromide (1.0 M in THF) in 50 mL of THF was added a solution of 7.59 g (40.3 mmol) of cyclohexyl phenyl ketone in 50 mL of THF. After 2 h, the mixture was poured into ice-cold 6 M hydrochloric acid and extracted with ether. The organic layer was dried (Na_2SO_4), concentrated, and Kugelrohr distilled (100–110 °C) to give 8.15 g (94%) of **28** as a pale yellow oil: NMR ($CDCl_3$) δ 1.0–1.9 (m, 11 H, C_6H_{11}) 5.2 (d, 1 H, CH_2), 5.3 (d, 1 H, CH_2) 6.3 (d, 1 H, CH), 7.2–7.5 (m, 5 H, C_6H_5); IR (neat) 3482, 3057, 1679, 1448 cm^{-1}.

1-Cyclohexyl-1-hydroxy-1-phenyl-1-(trimethylsiloxy)-2,3-oxirane (29). To a solution of 23.19 g (0.11 mol) of 1-cyclohexyl-1-hydroxy-1-phenyl-2-propene in 100 mL of DMSO was added 15.06 g (0.22 mol) of imidazole and 16.3 mL (13.95 mol) of chlorotrimethylsilane. The mixture was heated at 70 °C overnight, allowed to cool, and partitioned between water and ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified by Kugelrohr distillation (105 °C) to afford 31.34 g (99%) of a colorless liquid.

A solution of 20.75 g (76.1 mmol) of 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)-2-propene in 90 mL of THF was added to a mixture of 20.16 g (120 mmol) of *m*-chloroperoxybenzoic acid in 100 mL of THF at −15 °C. The cooling bath was removed and the mixture stirred for 1 h. The mixture was concentrated and the residue triturated with hexane. The hexane extract was concentrated and the residue chromatographed on silica (hexane to 90:10 hexane/ethyl acetate) to give 9.85 g (42%) of **29** as a heavy oil, which was used for reaction without additional purification: NMR ($CDCl_3$) δ 0.9–1.4 (m, 10 H), 1.6–2.0 (m, 10 H), 2.7 (d, 2 H, CH_2), 3.55 (m, 1 H, CH), 7.2–7.6 (m, 5 H, C_6H_5); IR (neat) 1447, 1249, 1113, 874, 838 cm^{-1}.

1-Cyclohexyl-5-(dimethylamino)-1-hydroxy-2-(hydroxymethyl)-1-phenyl-4-pentyne (20). A solution of 2.5 g (8.3 mmol) of paraformaldehyde, 0.90 g (8 mmol) of a 40% solution of dimethylamine in water, and 5 mg of copper(II) acetate was heated to 60 °C for 1 h. To this mixture was added a solution of 1.79

g (6.9 mmol) of crude alcohol **30** in 20 mL of dioxane and the reaction heated to 70 °C overnight. The solution was allowed to cool to 25 °C and filtered through a Celite pad, and the pad was washed with ether. The filtrate was washed with brine and dried ($NaSO_4$), and the solvent removed to give a brown oil. Repeated chromatography on silica gave 0.59 (28%) of a pale yellow solid: mp 112–113 °C; NMR ($CDCl_3$) δ 1.0–2.1 (m, 11 H, C_6H_{11}), 2.3 (3, 6 H, CH_3), 3.2 (s, 2 H, CH_2), 3.3 (m, 2 H, CH_2), 3.7 (m, 1 H, CH), 4.1 (bs, 1 H), 7.3–7.6 (m, 5 H); IR (KBr) 3410, 1448 cm^{-1}. Anal. ($C_{20}H_{30}NO_2$) C, H, N.

1-Cyclohexyl-1-hydroxy-1-phenyl-2-(hydroxymethyl)-3-propyne (30). To a solution of 7.01 g (76.1 mmol) of lithium acetylide ethylenediamine complex in 75 mL of DMSO was added dropwise a solution of 7.29 g (23.9 mmol) of epoxide **29** in 45 mL of DMSO. After 46 h, 25 mL of a saturated solution of NH_4Cl was added to the mixture. This mixture was extracted with ether, washed with an aqueous solution of NH_4Cl, dried ($MgSO_4$), and concentrated. Repeated chromatography with hexane/ethyl acetate (95:5) and then chloroform/methanol (98:2) afforded 5.40 g (85%) of an orange oil: NMR ($CDCl_3$) δ 2.2 (d, 2 H, CH_2), 2.6 (t, 1 H, CH) 3.3 (s, 1 H, OH), 3.4–3.6 (m, 12 H, C_6H_{11}), 7.2–7.5 (m, 5 H, C_6H_5); IR (neat) 3410, 1448, 1041, 687 cm^{-1}.

1-Cyclohexyl-7-(diethylamino)-1,2-dihydroxy-1-phenyl-5-heptyne (21). To a solution of 1.18 g (3.3 mmol) of 1-cyclohexyl-7-(diethylamino)-1-phenyl-5-heptyn-2-one in 75 mL of tetrahydrofuran (THF) was added 10.0 mL (10.0 mmol) of a 1.0 M solution of lithium aluminum hydride in THF. The mixture was heated at 100 °C for 2.5 h, cooled, carefully diluted with 20 mL of a 0.5% sodium hydroxide, and extracted with ethyl acetate. The ethyl acetate layers were washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated to afford a pale orange oil. Crystallization from hexane provided a white solid: 0.60 g, 52%; mp 104 °C; NMR δ 0.5–0.9 (m, 11 H), 1.1 (t, 6 H), 1.6 (m, 1 H), 1.9 (m, 2 H), 2.4 (m, 2 H), 2.5 (q, 4 H), 3.4 (t, 2 H), 4.37 (s, 1 H), 4.41 (s, 1 H), 7.2–7.6 (m, 5 H); IR (KBr) 3512, 1443 cm^{-1}. Anal. ($C_{23}H_{35}NO_2$) C, H, N.

1-Cyclohexyl-4-[4-[(dimethylamino)methyl]phenyl]-1-hydroxy-1-phenyl-2-butanone (22). To a solution of 3.1 mL (14.7 mmol) of 1,1,1,3,3,3-hexamethyldisilizane in 50 mL of THF was added 6.0 mL (15.0 mmol) of *n*-butyllithium (2.5 M in hexane) at −10 °C. After the mixture was stirred for 45 min, 4.06 g (13.3 mmol) of 1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)-2-propanone (**24**) in 50 mL of THF was added over 0.5 h. After 1 h a solution of 14.6 g (55.3 mmol) of α,α-dibromo-*p*-xylene in 25 mL of THF was added at −10 °C, and the mixture was stirred at −10 °C overnight. The mixture was warmed to 25 °C, diluted with 25 mL of water and extracted with chloroform and ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a crude yellow solid. The yellow solid was washed with ether, filtered, and set aside. The ether filtrate was concentrated to a pale yellow residue that was used in the next step without further purification.

To a solution of the residue in 100 mL of methanol was added 0.2 mL of concentrated hydrochloric acid, and the mixture was heated to 40 °C for 2 h. After being cooled, the mixture was diluted with water and extracted with ether. The ether layers were washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated to give a yellow residue. The residue was rinsed with hexane; the solids were filtered, and set aside. The filtrate was concentrated to a residue which upon chromatography (230–400 Merck silica gel) with a gradient of hexane to 70:30 hexane/ethyl acetate gave a pale yellow oil, 1.63 g of which was taken immediately to the next step.

To a solution of 1.63 g (3.90 mmol) of the 4-[4-(bromomethyl)phenyl]-1-cyclohexyl-1-hydroxy-1-phenyl-2-butanone in 50 mL of ether was added gaseous dimethylamine over 1 h. The solution was sealed in a pressure tube and stirred overnight. A white precipitate was filtered, and the filtrate was washed with water and saturated sodium chloride solution and dried ($MgSO_4$). Filtration and removal of solvent afforded an oil. Chromatography (230–400 Merck silica gel) with 97:1:2 to 70:28:2 hexane/ethyl acetate/triethylamine gave 1.24 g (32%) of an oil: NMR ($CDCl_3$) δ 1.0–1.9 (m, 10 H), 2.2 (s, 6 H), 2.4 (m, 1 H), 2.6 (m, 1 H), 2.8 (m, 3 H), 3.35 (s, 2 H), 4.5 (s, 1 H), 6.95 (d, 2 H), 7.15 (d, 2 H), 7.2–7.6 (m, 5 H); IR (neat) 3453, 3057, 1705 cm^{-1}. Anal. ($C_{25}H_{33}NO_2$) C, H, N.

(*R*)-1-Cyclohexyl-1-hydroxy-1-phenyl-2-propanone. To a mixture of 315 mL of 1.4 M methyllithium (0.44 mol) in ether and 750 mL of THF at 25 °C was added a solution of 26 g (0.11 mol) of (*R*)-cyclohexylmandelic acid, prepared by the method of Barlow et al.,[25] in THF. Following the addition, the mixture was stirred at 25 °C for 3.5 h and then brought to reflux for 3 h. The mixture was cooled and then added dropwise to a mixture of 300 mL of glacial acetic acid and 700 mL of water. This mixture was extracted with ether, the organic layer was separated, washed with water and saturated aqueous sodium bicarbonate, and dried, and the solvent was removed. The mixture was distilled to give 20 g of a clear liquid: bp 120 °C (0.1 Torr); NMR ($CDCl_3$) δ 1.0–1.9 (m, 10 H), 2.0 (s, 3 H), 2.4 (t, 1 H), 4.5 (s, 1 H), 7.5 (m, 5 H).

(*R*)-1-Cyclohexyl-1-phenyl-1-(trimethylsiloxy)-2-propanone. To a solution of 12 mL (95 mmol) of trimethylsilyl chloride and 11.6 g (172 mmol) of imidazole in 100 mL of DMF was added 20 g (86 mmol) of (*R*)-1-cyclohexyl-1-hydroxy-1-phenyl-2-propanone. This mixture was heated to 85 °C overnight. The next day, the mixture was cooled and poured onto a mixture of 100 mL of petroleum ether and 100 mL of ether. This was extracted with water. The organic layer was separated and dried, and the solvent removed. The residue was chromatographed on silica gel with hexane as the eluent to give 18.0 g of clear oil: NMR ($CDCl_3$) δ 0.2 (s, 9 H, CH_3), 0.9–2.4 (m, 11 H, C_6H_{11}), 2.1 (s, 3 H, CH_3), 7.2–7.6 (m, 5 H, C_6H_5); IR 2950, 1730 cm^{-1}.

(*R*)-1-Cyclohexyl-1-hydroxy-1-phenyl-7-(dimethylamino)-5-heptyn-2-one Hemifumarate Hemihydrate [(*R*)-2g]. To a solution of 6.6 mL (0.031 mol) of 1,1,1,3,3,3-hexamethyldisilizane in 350 mL of THF at 0 °C was added 14.3 mL (0.031 mol) of a 2.2 M solution of *n*-butyllithium in hexane. The mixture was stirred for 30 min, and then a solution of 8 g (0.026 mol) of (*R*)-1-cyclohexyl-1-phenyl-1-(trimethylsiloxy)-2-propanone in 50 mL of THF was added dropwise. The reaction mixture was stirred for 45 min and then it was added dropwise to a solution of 11 mL (0.1 mol) of propargyl bromide in 350 mL of THF at −78 °C. Following the addition, the cooling bath was removed and the mixture allowed to warm to room temperature over a 3-h period. It was then partitioned between ether and water. The organic layer was washed three times with water and once with brine, dried, and concentrated. The residue was carried to the next step without additional purification.

To a solution of 8 g of 40% aqueous dimethylamine in 30 mL of dioxane was added 1 g of paraformaldehyde. This mixture was heated at 60 °C for 30 min, and then the crude reaction mixture from the preceding reaction was added as a solution in 100 mL of dioxane. This was heated at 90 °C for 1 h and then allowed to cool. The mixture was partitioned between ether and saturated aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel and eluted with a gradient from hexane to triethylamine/ethyl acetate/hexane (3:20:77) to give 6.0 g of a heavy oil, homogeneous by GLPC.

This compound was dissolved in 250 mL of THF and cooled to 0 °C. To this solution was added 7.8 g (25 mmol) of tetrabutylammonium fluoride. The mixture was stirred for 1 h and then partitioned between ether and saturated sodium bicarbonate. The organic layer was separated, washed three times with water, once with brine, and dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel and eluted with a gradient from 1% methanol in methylene chloride to 10% methanol in methylene chloride to give 3.1 g of a heavy oil that was homogeneous by GLPC. This oil was dissolved in ether and to the solution was added 0.58 g of fumaric acid in 6 mL of methanol. The mixture was stirred for 10 min and the solvent was removed under reduced pressure. The residue was suspended in 250 mL of ether and cooled to 0 °C. The solid was isolated by filtration and dried under high vacuum: mp 108–110 °C; NMR ($CDCl_3$) δ 1.2 (m, 7 H), 1.5 (m, 1 H), 1.8 (m, 3 H), 2.4 (m, 3 H), 2.5 (m, 2 H), 2.8 (m, 2 H), 3.4 (s, 2 H), 6.8 (s, 1 H), 7.5 (m, 5 H); IR 3400, 2980, 1710 cm^{-1}; TLC (silica gel, triethylamine/ethyl acetate/hexane (3:20:77) R_f = 0.24; $[\alpha]^{20}_D$ +27.19° (*c* 1.0, MeOH) (ee was not determined). Anal. ($C_{21}H_{29}NO_2 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

(*S*)-1-Cyclohexyl-1-hydroxy-1-phenyl-7-(dimethylamino)-5-heptyn-2-one Hemifumarate [(*S*)-2g] was prepared

from (S)-cyclohexylmandelic acid[25] in the same fashion described for the R isomer, $[\alpha]^{20}_D$ -28.4° (c 1.0, MeOH) (ee was not determined. Anal. ($C_{21}H_{29}NO_2 \cdot 0.5C_4H_4O_4$) C, H, N.

(-)-1-Cyclobutyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one [(-)-14b]. A solution of 1.3 kg (6.31 mol) of cyclobutylmandelic acid[27] and 2385 g (6.31 mol) of quinine trihydrate in 8 L of anhydrous ethanol was briefly brought to reflux and allowed to cool overnight. The resulting solid was filtered, washed with a small portion of fresh solvent, and recrystallized from a minimum amount of ethanol six times. At that point a constant rotation of the acid, $[\alpha]^{20}_D$ -11.56° (c 6.15, MeOH), was obtained. The filtrates were collected, and the material was recycled as outlined below to obtain the (+) enantiomer. The salt was suspended in 2 N hydrochloric acid and the mixture extracted twice with methylene chloride. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed to give 128.2 g (0.62 mol) of a greenish white semisolid. This material was suspended in 1 L of anhydrous THF and 1.6 L of a 1.5 M solution (2.4 mol) of methyllithium in ether was added dropwise. The mixture was stirred overnight at 25 °C, brought to reflux for 2 h, and then cooled. This mixture was added under argon via a cannula to a solution of 500 mL of glacial acetic acid in 1.5 L of water. The mixture was extracted twice with ether. The organic layers were combined, washed with brine, and dried ($MgSO_4$), and the solvent was removed. The residue was distilled (Kugelrohr, bath temperature 110 °C) to give the isomer of 1-cyclobutyl-1-hydroxy-1-phenyl-2-propanone (78.2 g, 0.35 mol).

To a solution of 59.4 g (0.45 mol) of chlorotrimethylsilane and 52 g (0.76 mol) of imidazole in 1 L of anhydrous DMF was added 78 g (0.35 mol) of the substituted 2-propanone. The mixture was stirred overnight at room temperature, poured onto a mixture of 1.2 L of hexane and 600 mL of ether, and washed three times with water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give 106.5 g (0.38 mol) of the isomer of 1-cyclobutyl-1-phenyl-1-(trimethylsiloxy)-2-propanone as a light yellow oil.

To a solution of 53.2 mL (0.38 mol) of diisopropylamine in 800 mL of anhydrous THF at 0 °C was added 172 mL of a 2.2 M solution of n-butyllithium in hexane. This mixture was stirred for 30 min at 0 °C and cooled to -78 °C, and a solution of 106.5 g (0.38 mol) of (-)-1-cyclobutyl-1-phenyl-1-(trimethylsiloxy)-2-propanone in 100 mL of anhydrous THF was added. The mixture was allowed to warm to -10 °C, and then it was stirred for 45 min. The cooled mixture was added via a cannula to a solution of 125 mL (1.12 mol) of propargyl bromide in 400 mL of THF at -78 °C and then it was stirred for 30 min. The mixture was stirred at -10 °C for an additional h and then it was partitioned between ether and water. The organic layer was washed twice with water and once with brine and dried ($MgSO_4$), and the solvent was removed to give a brown oil. This oil was added to a solution of 11.7 g (0.38 mol) of paraformaldehyde, 42.7 g (0.38 mol) of a 40% aqueous dimethylamine, and 0.2 g copper(II) acetate in 500 mL of dioxane, heated to 80 °C for 2 h, and allowed to cool. The solvent was removed under reduced pressure and the residue partitioned between ether and 2 N hydrochloric acid. The aqueous layer was separated, extracted twice more with ether, and then carefully made basic (pH > 8) by addition of solid potassium carbonate. This mixture was extracted twice with methylene chloride, the organic layers were combined and dried over $MgSO_4$, and the solvent was removed to give a brown oil, which was chromatographed on silica (methylene chloride to 3% methanol in methylene chloride) to give 42.4 g of a brown oil: $[\alpha]^{20}_D$ -37.8° (c 1.07, EtOH) (ee was not determined); NMR ($CDCl_3$) 2.8-1.8 (m, 16 H), 3.1 (s, 2 H), 3.4 (m, 1 H), 4.8 (m, 1 H), 7.4 (m, 5 H); IR (neat) 3300, 2950, 1720 cm^{-1}. Anal. ($C_{19}H_{25}NO_2$) C, H, N. A hydrochloride had mp 120-121 °C (from EtOH/ether). Anal. ($C_{19}H_{25}NO_2 \cdot HCl$) C, H, N.

(+)-1-Cyclobutyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one [(+)-14b]. The ethanolic filtrates from the resolution of (-)-cyclobutylmandelic acid from the previous recrystallizations were combined and concentrated under reduced pressure. The residue was partitioned between methylene chloride and 1 N hydrochloric acid. The aqueous layer was separated and extracted three times with methylene chloride. The organic layers were combined, washed with 1 N hydrochloric acid, and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 1.14 kg (5.5 mol) of cyclobutylmandelic acid.

To a solution of 682 g (3.73 mL) of (1R,2S)-(-)-ephedrine in 1.5 L of ethanol was added 769 g (3.73 mol) of the recovered cyclobutylmandelic acid. The mixture was heated briefly to reflux and allowed to cool overnight. The mixture was diluted with 4 L of ether and stirred briefly. The resulting solid was collected and suspended in 4 L of ethanol and the mixture was refluxed briefly and allowed to cool overnight. The resulting solid was collected and recrystallized six times from aqueous ethanol, until no further change in rotation of the acid was noted, to give 40.7 g of a solid, $[\alpha]^{20}_D$ +11.7° (c 3.1, EtOH).

This (+)-cyclobutylmandelic acid (40.7 g, 0.19 mol) was converted into (+)-1-cyclobutyl-7-(dimethylamino)-1-hydroxy-1-phenyl-5-heptyn-2-one by the method outlined above, to give 6.8 g (0.022 mol) of a heavy brown oil: $[\alpha]^{20}_D$ +37.3° (c 1.125, EtOH) (ee was not determined); NMR ($CDCl_3$) δ 2.8-1.8 (m, 16 H), 3.1 (s, 2 H), 3.4 (m, 1 H), 4.8 (m, 1 H), 7.4 (m, 5 H); IR (neat) 3300, 2950, 1720 cm^{-1}. A hydrochloride had mp 120-121 °C (from EtOH/ether). Anal. ($C_{19}H_{25}NO_2 \cdot HCl$) C, H, N.

Pharmacology. Isolated Bladder Strips. Strips of bladder detrusor muscle (2 cm long × 2 mm thick) were cut longitudinally and suspended under a resting tension of 0.5 g at 35 °C in oxygenated (95% O_2-5% CO_2) Krebs solution (composition in mM: 133 NaCl, 4.7 KCl, 1.3 NaH_2PO_4, 16.3 $NaHCO_3$, 0.6 $MgSO_4 \cdot 7H_2O$, 2.5 $CaCl_2 \cdot 2H_2O$, 7.7 dextrose). Isometric contractions were recorded by means of an electromechanical displacement transducer and a potentiometric recorder. The strips were allowed to equilibrate for 36 min with three buffer changes at 12-min intervals.

Antimuscarinic studies were conducted by constructing concentration-response curves to carbachol in the absence and presence of several concentrations of antagonist. Carbachol doses were added cumulatively after each contraction elicited by the preceding drug concentration had reached a steady value. A control concentration curve was first constructed, the tissue was washed several times, and then additional curves were constructed in the presence of increasing concentrations of test antagonists. Responses were expressed as a percentage relative to the maximum contraction elicited by carbachol in absence of antagonist. Antimuscarinic potencies are expressed as K_b values calculated from the following equation:

$$K_b = \frac{[\text{antagonist}]}{DR - 1}$$

where DR is the dose ratio calculated as the EC_{50} for carbachol in the presence of the antagonist divided by the EC_{50} for the control.

Cystometrogram. A guinea pig model was developed for the slow-filling cystometrogram (CMG) that mimics the natural filling of the bladder.[24] The CMG is widely used in humans and animals to measure urodynamic parameters associated with bladder dysfunction.[28]

Briefly, female Hartley guinea pigs (400-600 g) were anesthetized with a 15% (w/v) urethane solution (1.5 g/kg body weight ip) and their bladders catheterized via the urethra with PE-150 tubing. The urethral opening was tightly sutured to prevent leakage during the filling phase of the procedure. The tubing was connected to a pressure transducer (Gould Electronics, Cleveland, OH), a syringe pump for bladder filling, and an exit port to empty the bladder between trials.

The bladder was infused with saline at a constant rate (0.41 mL/min). Filling continued until a coordinated sustained contraction occurred. The bladder was then emptied and a fixed 5-min rest begun. Pressure measurements made in kilopascals

(27) Blumbergs, P.; LaMontagne, M. P.; Stevens, J. I. The Preparation and Oxidation of α-Hydroxybenzaldehydes. *J. Org. Chem.* **1972**, *37*, 1248-1251.

(28) Maggi, C. A.; Santicioli, P.; Meli, A. The nonstop transvesical cystometrogram in urethane-anesthetized rats: A simple procedure for quantitative studies on the various phases of urinary bladder voiding cycle. *J. Pharmacol. Methods* **1986**, *15*, 157-167.

included the peak intravesical bladder pressure (P_{ves}) defined as the difference between the maximum pressure and the threshold pressure. Threshold pressure is defined as the intravesical pressure just before the elicited contraction. Each animal served as its own control. Drug potencies were assessed by iv (femoral) infusions of increasing drug doses given during the rest phase of a series of CMGs. The resultant reduction in peak contraction was expressed relative to control peak P_{ves} values obtained in absence of drug. ID_{50} and ID_{80} values were defined as the contraction of drug that inhibited peak P_{ves} by 50% and 80%, respectively, and were calculated by using probit analysis.

Acknowledgment. We acknowledge Greg A. Erickson, Valerie C. Lowe, and Jan S. Peterson for valuable technical assistance. We are grateful to Carol L. Friend for the preparation of the manuscript.

3-Methyl-2*H*-1-benzopyran Potassium Channel Activators

Rolf Gericke,* Jürgen Harting, Inge Lues, and Christine Schittenhelm

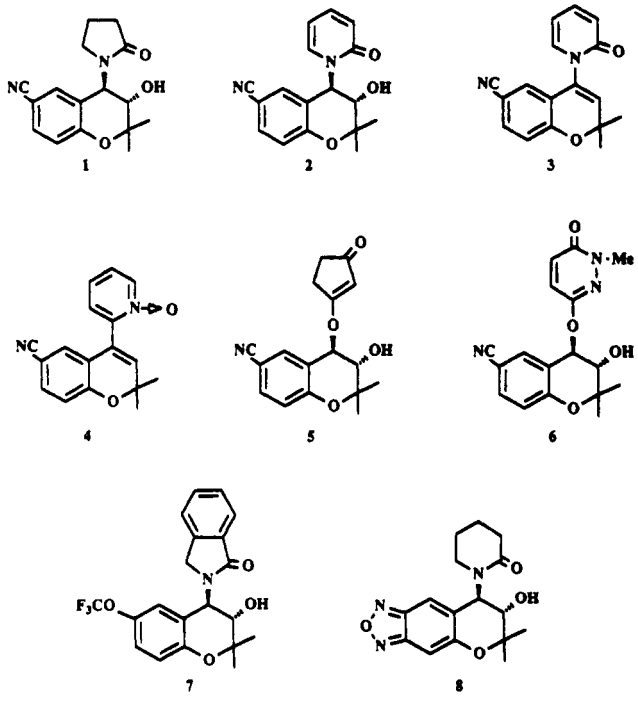
Preclinical Pharmaceutical Research, E. Merck, Postfach 4119, 6100 Darmstadt, Germany. *Received February 5, 1991*

By aldol condensation of 4-chromanones with paraformaldehyde, 3-alkylenechromanones **10** were obtained which gave 3-alkylchromenes following reduction and dehydration. Subsequent 3-chloroperbenzoic acid oxidation produced the versatile epoxide intermediates **15**, from which 3,4-epoxy-3,4-dihydro-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (**15a**) was resolved into its enantiomers by entrainment. In addition to the methyl group, the benzyl, alkyloxymethyl, and 2-nitroethyl residues could be introduced in the 3-position. Treatment of **15a** with 2-pyridone simultaneously gave N- and O-substituted products **19a** and **20**. **19a** easily gave 4-(1,2-dihydro-2-oxo-1-pyridyl)chromene **21** by treatment with base. The corresponding pyrrolidinone compounds **26** and **27** were obtained by a slightly modified procedure. Reaction with 2,4-dihydroxypyridine or 3,6-pyridazinediol resulted in the exclusive formation of 4-(heterocyclyloxy)chromanols (**31** and **32**). Treatment of **15a** with 3-amino-6-pyridazinol gave 4-(3-amino-1,6-dihydro-6-oxo-1-pyridazinyl)chromanol derivative **34** lacking an NH bridge. This could be established after methylation of the ring-nitrogen atom (→**35**). Trans-configurated 3-methyl-4-pyridone compound **36** was obtained by addition of methyllithium to chromene **3**. Hyperpolarizing and antispasmodic or relaxing effects of the compounds were determined in organ bath studies using pig coronary arteries precontracted with acetylcholine or rabbit main pulmonary arteries precontracted with noradrenaline. In the 3-methyl series the classical pyridone and pyrrolidinone structures (**9**, **21**, **26**, **27**) were only weakly active or inactive, but the corresponding 4-(heterocyclyloxy) and 4-(heterocyclylamino) derivatives (**31**, **32**, **35**) were even more potent than the demethyl analogues. In conformation/activity investigations it was found that the activity of the 4-substituted benzopyran derivatives seems to be dependent on the relative orientation of their ring systems.

K^+ channels play an important and complex role in the basic electrical and mechanical functions of a wide variety of tissues, including smooth muscle, cardiac muscle, and glands. Recent publications[1,2] have indicated that various compounds which increase the open probability of specific potassium channels are relaxants of a number of smooth muscle types. The first therapeutic drug shown to possess this mechanism of action was the coronary vasodilator nicorandil. Other substances that open adenosine triphosphate sensitive potassium channels are the vasodilators pinacidil, minoxidil sulfate, diazoxide, and RP 52 891. None of these substances is structurally related to any of the others.

In addition, the 2*H*-1-benzopyrans should be considered. Although up to now no product based on this structural class has been brought to the market, it is already clear that these are of immense importance within the potassium channel activators. A number of compounds are currently being developed by several pharmaceutical companies, and clinical trials are being carried out in different therapeutic areas. Development has proceeded furthest with cromakalim and its enantiomer lemakalim (**1**; Chart I). Structure/activity investigations[3,4] have shown that the

Chart I. The Chroman-Type Potassium Channel Openers



structure of **1** can be varied in many ways. The substitution of the 4-(2-oxo-1-pyrrolidinyl) group with other heterocyclic groups was successful. Substitution with an α-pyridone, for example, led to EMD 56 431 (**2**).[5] In the

(1) Robertson, D. W.; Steinberg, M. I. Potassium Channel Modulators: Scientific Applications and Therapeutic Promise. *J. Med. Chem.* **1990**, *33*, 1529-1541.
(2) Steinberg, M. I.; Robertson, D. W. The body's potassium channels. *CHEMTECH* **1990**, 432-438.
(3) Edwards, G.; Weston, A. H. Structure-activity relationships of K^+ channel openers. *Trends Pharmacol. Sci.* **1990**, *11*, 417-422.
(4) Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C.; Howlett, D. R.; Smith, D. M.; Stemp, G. Synthesis and Antihypertensive Activity of 4-(Substituted-carbonylamino)-2*H*-1-benzopyrans. *J. Med. Chem.* **1990**, *33*, 2667-2672.
(5) Bergmann, R.; Gericke, R. Synthesis and Antihypertensive Activity of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans and Related Compounds, New Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 492-504.

0022-2623/91/1834-3074$02.50/0