crystallized from ethanol, had mp 258–259 °C. Anal. ($C_{25}H_{25}NO \cdot HCl \cdot 0.5C_2H_5OH$) C, H, N.

1-Methyl-4-(1,3,3a,12b-tetrahydro-8*H*-dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)piperidine (13). A solution of 4.0 g (0.012 mol) of **6** in 40 mL of EtOH was hydrogenated over 4.0 g of Raney nickel for 6 h at 150 °C and 2000 psi. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give 3.90 g of a viscous oil. This material readily formed a hydrogen oxalate salt (4.0 g) from EtOH. Two recrystallizations of this material from EtOH gave **13**·$C_2H_2O_4$, mp 197–200 °C. Anal. ($C_{23}H_{25}NO \cdot C_2H_2O_4$) C, H, N.

Biological Test Methods. Antiserotonin and antihistamine effects of the test compounds were determined with methods similar to those described by Engelhardt et al.[1] Antiserotonin activity was evaluated in male Sprague–Dawley rats of 160–220-g body weight. The drugs were tested for their effect on edema induced by injection of serotonin in the hind paw. The test drugs, suspended in 1% methylcellulose, were administered subcutaneously (sc) 30 min prior to the injection of serotonin (base), also sc, into the hind paw. Saline, 0.05 mL, was injected sc into the other hind paw which served as the basis for comparison. Thirty minutes after serotonin, the animals were sacrificed and both feet removed and weighed. The results were expressed as the dose necessary to produce 50% inhibition of the weight gain due to serotonin. Each compound was used at three doses with four rats per dose level. Anihistamine activity was evaluated in guinea pigs of the Duncan–Hartley strain of either sex and 200–300-g body weight. The test compounds, suspended in 1% methylcellulose, were administered intraperitoneally (ip). Thirty minutes later the animals were placed in individual chambers and exposed to histamine aerosol spray (0.5% base) for 3 min. The effectiveness of the test compounds was determined as the dose necessary to protect 50% of the animals from death caused by histamine aerosol-induced bronchoconstriction. The test compounds were used at four dose levels with five animals per dose.

Anticholinergic activity was evaluated by the ability of the compound to dilate the pupil of the mouse. Compounds were administered to female Carworth Farms (CF-1) mice at doses of 4, 12, 36, 108, and 324 mg/kg ip, at five mice per dose level. The diameter of the pupil was measured with the aid of an ocular micrometer 55 min after treatment with the test compound using a method previously described.[7] The $ED_{1.5}$ dose range is defined as the dose levels producing dilation of the pupil to 15 μm units in less than (lower limit) and more than (upper limit) 50% of the mice.

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2,3-Disubstituted 1,8-Naphthyridines as Potential Diuretic Agents. 2.[1] 5,7-Dimethyl Derivatives

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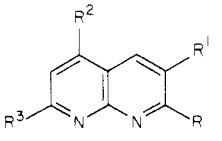
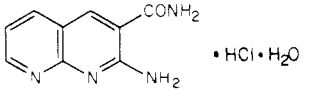
A variety of 2,3-disubstituted 5,7-dimethyl-1,8-naphthyridines was synthesized and tested in saline-loaded rats for their diuretic properties. The 2-amino-3-carbomethoxy and four 2-amino-3-*N*-alkylcarbamoyl compounds exhibited significant activity as measured by volume output; however, they were generally less potent than the corresponding 5,7-unsubstituted naphthyridines previously reported. Further screening without saline-loading indicated that the amides lacked kaliuretic properties; while, interestingly, the ester lacked an effect on either urine volume or sodium excretion.

An earlier paper disclosed that a series of 2,3-disubstituted 1,8-naphthyridines (**1a**) possessed in many cases potent diuretic activity with lack of a kaliuretic effect.[1] This study prompted the investigation of the corresponding 5,7-dimethylnaphthyridines (**1b**). Dimethyl substitution was chosen in view of the enhanced lipophilicity, minimal change in electronic and steric effects, and easier synthetic accessibility in comparison to **1a**. Screening comparison was made to 2-amino-1,8-naphthyridine-3-carboxamide hydrochloride monohydrate (**2**), the most potent member of **1a**, and triamterene (**3**).



1a, $R^2 = R^3 = H$
b, $R^2 = R^3 = CH_3$



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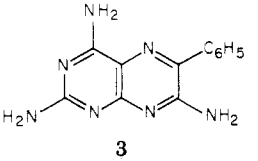
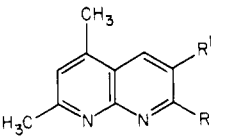


3

Chemistry. The general synthetic schemes developed for 2,3-disubstituted 1,8-naphthyridines were suitable for their 5,7-dimethyl analogues reported in Table I.[1] The Friedländer condensation of 2-amino-4,6-dimethylnicotinaldehyde (**4**) with various methylene compounds afforded compounds **5**–**22** as outlined in Scheme I. The condensation was accomplished with piperidine or, in the case of less activated methylene, with sodium hydroxide as catalyst. Experimental variation in the previously described[2] preparation of the starting material (**4**) from *N*-(2-amino-4,6-dimethylnicotinoyl)-*N'*-*p*-tolylsulfonyl-

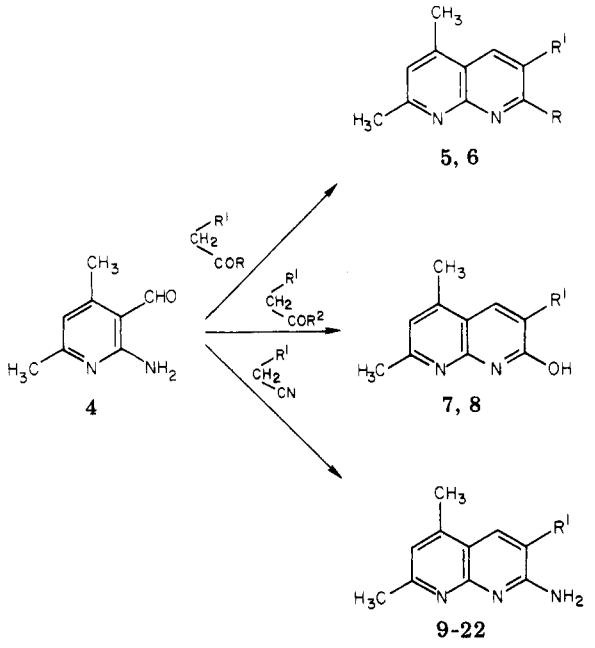
Table I. Chemical Properties of 2,3-Disubstituted 5,7-Dimethyl-1,8-naphthyridines



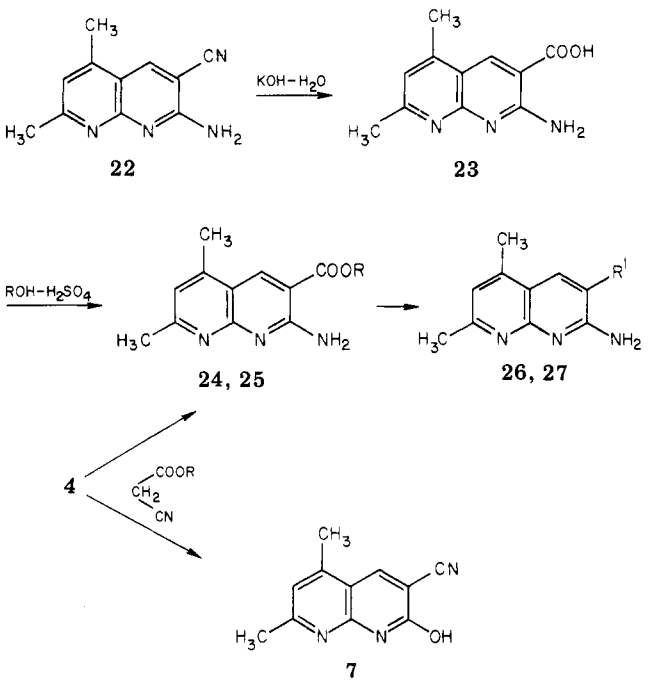
No.	R	R'	Formula	Method[a]	Recrystn solvent	Mp, °C	Yield, %[b]	Analyses
5	C_6H_5	CN	$C_{17}H_{13}N_3$	A (2)	EtOAc	170-172	90	C, H, N
6	CH_3	CH_3	$C_{12}H_{14}N_2$	B-1 (48)	C_6H_{12}	144-146	90	C, H, N
7[c]	OH	CN	$C_{11}H_9N_3O$	A (1), F (48)	Et cellosolve	302-305 dec[c]	88, 22	c
8	OH	$CONH_2$	$C_{11}H_{11}N_3O_2$	A (24)	MeOH	325-330 dec	17	C, H, N
9[d]	NH_2	$CONH_2$	$C_{11}H_{12}N_4O \cdot H_2O$	A (1)	EtOH	283-285 dec[d]	67	C, H, N
9a	$NH_2 \cdot HCl$	$CONH_2$	$C_{11}H_{12}N_4O \cdot HCl$		MeOH	290-292	85	C, H, N, Cl
10	NH_2	$CONHCH_3$	$C_{12}H_{14}N_4O$	A (2)	EtOH	262-264	88	C, H, N
11	NH_2	$CONHC_2H_5$	$C_{13}H_{16}N_4O$	A (24)	Abs EtOH	221-222	84	C, H, N
12	NH_2	CONH-*n*-C_3H_7	$C_{14}H_{18}N_4O$	A (24)	MeOH	210-212	76	C, H, N
13	NH_2	CONH-*n*-C_4H_9	$C_{15}H_{20}N_4O$	A (24)	C_6H_6	205-207	60	C, H, N
14	NH_2	CONH-*n*-C_5H_{11}	$C_{16}H_{22}N_4O$	A (24)	EtOAc	176-177	64	C, H, N
15	NH_2	CONH-*n*-C_6H_{13}	$C_{17}H_{24}N_4O$	A (24)	EtOAc	174-175	55	C, H, N
16	NH_2	$CON(CH_3)_2$	$C_{13}H_{16}N_4O$	B (3)	EtOH	308-310 dec	82	C, H, N
17	NH_2	C_6H_5	$C_{16}H_{15}N_3$	B (2)	EtOAc	214-215	71	C, H, N
18	NH_2	2-Thienyl	$C_{14}H_{13}N_3S$	B (3)	Et cellosolve	217-220	77	C, H, N, S
19	NH_2	*p*-C_6H_4-NO_2	$C_{16}H_{14}N_4O_2$	A (6)	*n*-BuOH	292-294	79	C, H, N
20	NH_2	3-Pyridyl	$C_{15}H_{14}N_4$	A (24)	C_6H_6	237-238	39	C, H, N
21	NH_2	$SO_2C_6H_5$	$C_{16}H_{15}N_3O_2S$	B (24)	MeOH	271-273 dec	98	C, H, N, S
22	NH_2	CN	$C_{11}H_{10}N_4$	A (2)	Et cellosolve	294-295 dec	94	C, H, N
23	NH_2	COOH	$C_{11}H_{11}N_3O_2 \cdot H_2O$	C (24)	MeOH	258-260 dec	92	C, H, N
24	NH_2	$COOCH_3$	$C_{12}H_{13}N_3O_2$	D (3), F (48)	MeOH	230-232 dec	82, 82	C, H, N
25	NH_2	$COOC_2H_5$	$C_{13}H_{15}N_3O_2$	D (3), F (48)	C_6H_6	268-270 dec	75, 77	C, H, N
26	NH_2	$CONHNH_2$	$C_{11}H_{13}N_5O$	E (0.5)	MeOH	255-257 dec	88	C, H, N
27	NH_2	$CONHC(=NH)NH_2$	$C_{12}H_{14}N_6O$	E (1)	H_2O	298-300 dec	48	C, H, N

[a] Under method the capital letters refer to the general procedures given in the Experimental Section and the values in parentheses are reflux times (hour) for the corresponding reaction. [b] Yields are for crude product and were not generally optimized, except for method F where the conditions were optimized, and quoted values are for NMR analysis of the crude mixtures. [c] Previously reported, see ref 2; mp 299-300 °C dec. [d] Previously reported, see ref 2; mp 262 °C dec; analysis not quoted.

Scheme I



Scheme II



hydrazine improved the yield considerably.

Subsequent routine reaction of **22** led to **23–27** (Scheme II). The discovery of the activity of **24** prompted the search for an alternate method to the multistep route to the 2-amino-3-carboxylates (**24** and **25**) outlined in Scheme II. The Friedländer synthesis was consequently reinvestigated. Methyl or ethyl cyanoacetates on reaction with **4** may give **7** and/or **24**, **25**. Previous workers in attempting to synthesize **25** isolated **7** and only traces of the desired product using piperidine as catalyst.[2] Consequently, numerous catalysts ranging in pH from strongly acidic through neutral, to strongly basic were investigated and the reactions monitored by NMR, the 4-H proton having differing chemical shifts. Utilizing zinc chloride as catalyst optimum yields of the desired products, **24** and **25**, were obtained.

Table II. Diuretic and Saluretic Effects in Compounds Active in Rat Saline-Loaded Screen

Compd	Saline-loaded rat screen[a] Increase from control (% of load excreted) 2 mg/kg	15 mg/kg	Activity as compared to triamterene 2 mg/kg	15 mg/kg	Determination on the 6-h cumulative excretion in nonloaded rats (15 mg/kg)[b] Av mequiv, excreted drug/control Na^+	K^+	Av urine vol, mL, drug/control	Na^+/K^+, drug/control
11		47.7		0.83	0.495/0.262	0.301/0.297	3.7/2.2	1.64/0.88
12		53.7		0.93	0.410/0.262	0.250/0.297	3.9/2.2	1.64/0.88
13	43.2	152.7	1.25	2.64	0.427/0.262	0.250/0.297	4.1/2.2	1.71/0.88
14		23.4		0.40	0.390/0.262	0.263/0.297	2.9/2.2	1.48/0.88
24		47.3		0.82	0.221/0.262	0.210/0.297	1.6/2.2	1.05/0.88
Triamterene	34.5	57.8	1.00	1.00	0.804/0.228	0.136/0.136	4.9/1.7	5.84/1.68
2	62.9	67.5	3.00	1.41	0.765/0.182	0.161/0.140	5.3/2.4	4.75/1.30

[a] 50 control groups excreted an average of 72.3% of the volume of the saline load in 6 h with a standard deviation of 10.9%; a blank indicates an insignificant response of less than 21.8% above control. The data for **2** are from ref 1. [b] Means of eight rats, data obtained for **13** at 2 mg/kg were Na^+ 0.471/0.262; K^+ 0.217/0.297; vol 3.7/2.2; Na^+/K^+ 2.17/0.88.

Diuretic Screening and Structure–Activity Relationships. All the 23 compounds reported in Table I were evaluated in saline-loaded rats for their diuretic activity as measured by volume output using a previously described modification[3] of the classical method of Lipschitz.[4] Initial screening was at 15 mg/kg ip and active compounds were also tested at 2 mg/kg; these data are recorded in Table II.

Only five compounds were active in this series (**1b**) as opposed to ten in the previously reported series (**1a**). Although fewer compounds are reported here, the advantage of lead compounds must be considered; only two of the ten analogues of the **1a** series were active (**12** and **13**). Apart from the 2-amino-3-carbomethoxy compound **24**, the remainder were *N*-alkylcarboxamides **11–14**. The latter compounds, part of the homologous series **9–15**, proved to be a rare illustration of SAR normally found in structurally nonspecific drugs. Activity increased regularly, reaching a maximum with the *N*-butyl (**13**) and being absent in the *N*-hexyl (**15**). Compound **13** was the only compound active at 2 mg/kg, appearing to be as potent as triamterene but less than **2**.

Only the five active compounds were further tested for volume output, natriuresis, and kaliuresis in nonloaded rats at 2 and 15 mg/kg, using the previously published methodology.[1] These data are also recorded in Table II. Only **13** was active at the low dose level, there being little difference in the data for the two dose levels for that compound. The carboxamides **11–14** were diuretic and natriuretic but appeared less active in this screen than either triamterene or **2**. More encouraging for these compounds was their lack of kaliuretic effect. The data for **24**, which was reproducible, were interesting in that sodium and urine output values were less than control.

In summary, the introduction of lipophilic electropositive substituents in the 5 and 7 positions of the 1,8-naphthyridine ring gave a series of compounds which were generally less potent in their effect on urine volume or sodium excretion than their unsubstituted parent analogues. This confirms the high order of structural specificity of 1,8-naphthyridine diuretics for drug–receptor interaction.

Experimental Section

Synthesis. Melting points were determined with a Gallenkamp block and are uncorrected. Where analyses (Dr. Strauss, Oxford, England, or Mr. R. James, College of Pharmacy, University of Saskatchewan) are reported by symbols of the elements, analytical results were within 0.4% of the calculated value. Infrared spectra were routinely obtained with a Beckman AccuLab 4 spectrometer. For selected compounds NMR spectra were recorded with DSS as internal standard on a Varian T-60 spectrometer and mass spectral data were obtained on an AEI MS-12 mass spectrometer. All spectral data obtained were considered consistent with the assigned structures.

2-Amino-4,6-dimethylnicotinaldehyde (4). A suspension of 40 g (0.120 mol) of *N*-(2-amino-4,6-dimethylnicotinoyl)-*N'*-*p*-tolylsulfonylhydrazine[2] in 240 mL of ethylene glycol was stirred at 170 °C for 15 min to ensure complete dissolution. The solution was treated with 40 g (0.476 mol) of $NaHCO_3$ and after 1 min the mixture was rapidly cooled by pouring into 500 mL of an ice–water mixture and subsequently extracted several times with Et_2O. The combined extracts were dried (Na_2SO_4) and the Et_2O was removed. The residue on Soxhlet extraction for 18 h with petroleum ether (bp 40–60 °C), gave 17.97 g (71%, lit.[2] 25%) of aldehyde, mp 155–158 °C (lit.[2] 161–162 °C), which was sufficiently pure for subsequent reactions. Overall yield of **4** from ethyl cyanoacetate was 34%.

2,3-Disubstituted 5,7-Dimethyl-1,8-naphthyridines (5–27, Table I). Method A. 2-Amino-5,7-dimethyl-*N*-butyl-1,8-naphthyridine-3-carboxamide (13). Using the previously reported general procedure,[1] a mixture of 0.450 g (3.0 mmol) of **4**, 0.841 g (6.0 mmol) of *N*-butylcyanoacetamide, and 0.075 mL (0.76 mmol) of piperidine in 5.0 mL of absolute EtOH was heated under reflux for 24 h. Cooling and filtration yielded a yellow solid which recrystallized as yellow plates.

Method B. 2-Amino-5,7-dimethyl-3-phenyl-1,8-naphthyridine (17). Using the previously reported general procedure,[1] a mixture of 0.450 g (3.0 mmol) of **4**, 0.703 g (6.0 mmol) of benzyl cyanide, and 0.4 mL (1.0 mmol) of 10% aqueous NaOH in 5.0 mL of absolute EtOH was heated under reflux for 2 h. Cooling and filtration yielded a cream solid which recrystallized as cream needles.

Method B-1. 2,3,5,7-Tetramethyl-1,8-naphthyridine (6). A mixture of 0.450 g (3.0 mmol) of **4** and 0.4 mL (1.0 mmol) of 10% aqueous NaOH in 5.0 mL of ethyl methyl ketone was heated under reflux for 48 h. The excess solvent was removed; the residue was poured into 100 mL of H_2O and extracted several times with Et_2O. The combined extracts were dried (Na_2SO_4); the Et_2O was removed and triturated with petroleum ether (bp 40–60 °C) to yield a cream solid which recrystallized as cream plates.

Method C. 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylic Acid Monohydrate (23). A mixture of 3.887 g (19.6 mmol) of **22**, 5.882 g (0.105 mmol) of KOH, 20 mL of H_2O, and 30 mL of EtOH was heated under reflux for 24 h. The ethanol was evaporated, 30 mL of H_2O added, and the solution acidified with acetic acid to precipitate the acid. Filtering and washing with H_2O yielded a yellow solid which recrystallized as yellow plates.

Method D. Methyl 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (24). A mixture of 50.0 mL of MeOH and 5.0 mL of H_2SO_4 was added dropwise to 2.052 g (8.72 mmol) of **23** in 16.0 mL of H_2SO_4. The resulting mixture was heated under reflux for 3 h with the addition every 0.5 h of 10 mL of MeOH and 2.5 mL of H_2SO_4. The excess solvent was removed; the residue was poured over ice, basified using Na_2CO_3, and extracted several times with $CHCl_3$. The combined extracts were dried (Na_2SO_4) and the $CHCl_3$ was removed to yield the ester which recrystallized

as yellow needles: NMR (CF_3COOH) δ 2.97 (s, 6, CH_3), 4.17 (s, 3, CH_3), 7.68 (s, 1, C_6-H), 9.39 (s, 1, C_4-H).

Method E. 2-Amino-*N*-amidino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (27). To a stirred solution of 0.20 g (8.70 mg-atom) of Na metal in 10 mL of anhydrous MeOH was added 0.80 g (8.37 mmol) of guanidine hydrochloride. After 5 min 0.465 g (2.01 mmol) of **24** was added. The mixture was refluxed for 1 h and the solvent removed. The cream solid was treated with H_2O and filtered to yield the crude product which recrystallized as cream flakes.

Method F. Ethyl 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (25). A mixture of 0.900 g (6.0 mmol) of **4**, 1.358 g (12.0 mmol) of ethyl cyanoacetate, 0.20 g (1.5 mmol) of zinc chloride, and 10 mL of C_6H_6 was heated under reflux for 48 h with separation of water. The benzene suspension was washed with water, dried, and evaporated to yield 1.46 g (99%) of crude product, mp 235–238 °C, which on NMR analysis indicated 22% of **7** and 77% of **25**. Fractional crystallization from C_7H_8 afforded 0.195 g (16%) of **7** [NMR (CF_3COOH) δ 2.97 (s, 6, CH_3), 7.63 (s, 1, C_6-H), 9.00 (s, 1, C_4-H)] and 0.995 g (68%) of **25** [NMR (CF_3COOH) δ 1.52 (t, 3, $-CH_2CH_3$), 2.97 (s, 6, CH_3), 4.65 (q, 2, $-CH_2-$), 7.72 (s, 1, C_6-H), 9.40 (s, 1, C_4-H)].

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Cardenolide Analogues. 2. 22-Methylenecard-14-enolides[1,2]

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22-Methylene-3β-hydroxy-5β,20(*S*)-card-14-enolide (**11**) and 22-methylene-3β-hydroxy-5β,20(*R*)-card-14-enolide (**12**) were synthesized from digitoxin (**1**). Attempts to prepare the 14β-hydroxy-22-methylene analogues were unsuccessful. The 20(*R*) isomer (**12**) was found in Na^+,K^+-ATPase inhibition studies to be twice as active as 14-dehydrodigitoxigenin (**17**). The 20(*S*) isomer (**11**) was significantly less active than **17**. The hydrolysis of steroid 3β-*tert*-butyldimethylsilyl ethers was also found to be much more difficult than with nonsteroids.

Cardenolides such as digitoxin (**1**) are very important in treating congestive heart failure.[3] The activity of analogues **2**[1], **3**[4], and **4**[4], the more reversibly acting AY-22 241 [3β-D-glucopyranosyl-14β,24-dihydroxy-21,23-bisnor-5β-chol-20(22)-ene-20-carboxylic acid lactone (**5**)],[5-7] and current models of digitalis bonding[4,8] suggested to us the following features at C_{17} for new analogues in structure–activity studies: (1) increased reactivity or polarizability or (2) geometrically altered unsaturation. The 22-methylene analogues **6**, **11**, and **12** have these features. α-Methylene butyrolactones are quite reactive.[8,9] 14-Dehydrocardenolides retain significant albeit decreased Na^+,K^+-ATPase inhibiting activity.[10] Our efforts to synthesize **6** are continuing.

Chemistry. Digitoxin (**1**) was hydrolyzed to digitoxigenin **7**[11], hydrogenated to **8**[11], and converted to the *tert*-butyldimethylsilyl (*t*-$BuMe_2Si$) ether[12,13] **9**. Although the 22-methylene group could be added to **9** using the method used for the preparation of **11** and **12**, the *t*-$BuMe_2Si$ group could not be removed without the loss of the 14β-OH. Other protecting groups investigated either had the same disadvantages as the *t*-$BuMe_2Si$ or could not withstand the conditions used for the introduction of the 22-methylene group. Attempts to introduce the 22-methylene group in **8** were unsuccessful. Dehydration of **9** with thionyl chloride gave exclusively **13**. The enolate of **13** was treated with anhydrous CO_2[14] to give **14**, and reaction with aqueous formaldehyde and diethylamine[15] gave 20(*R*,*S*)-22-methylene lactone **15**.

Table I

	Yield of expected alcohol	
	With $(n\text{-Bu})_4\text{NF}$[b] in THF, 25 °C	With HOAc in H_2O-THF, 100 °C
15	<5%, 96 h[a]	65%, 13 h
16 (mp 186–187 °C)	<5%, 96 h[a]	78%, 9 h
Cholesterol 3β-*t*-$BuMe_2Si$ (mp 151–152 °C)	82%, 7 h	85%, 7 h

[a] The starting material decomposed when the reaction was heated at 100 °C. [b] Synthesis of $(n\text{-Bu})_4\text{NF}$ followed the method of Fowler et al.,[16] as modified by Corey.[12]

The acid-catalyzed hydrolysis of **15** to a mixture of **11** and **12** was unexpectedly slow (Table I). Tetra-*n*-butylammonium fluoride did not hydrolyze **15**, probably due

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