was then added. The brownish solution was stirred 4 h at -78 °C. The reaction was quenched with 10 mL of a saturated KH_2PO_4 solution and brought to ambient temperature. The aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2, and the organic layer was 3 dried with $MgSO_4$. Removal of the solvent yielded a brown residue with higher than theoretical yields.

The residue from the BBr_3 reaction was dissolved in 1 mL of Ac_2O and 0.1 mL of pyridine/mmol of quinone and stirred overnight at ambient temperature. The excess reagents were removed under reduced pressure, and the residue was passed through a short Florisil column using 3:1 hexane/EtOAc as solvent. The solvent was removed to afford a yellow residue for purification.

BBr_3 Reaction with 1. From 0.31 g (1.3 mmol) of **1** and 1.5 mL (1.5 mmol) of BBr_3 was isolated 0.41 g of a red solid: IR 3400, 3070, 2995, 2950, 1740, 1710, 1670, 1610, 1520, 1450, 1370 cm^{-1}; NMR δ 1.85 (m, 4), 2.35, 2.47 (each m, 7.4), 3.7 (s, 6), 3.8 (s, 3), 3.88 (s, 3), 4.92 (s, 1), 5.5 (br s, 2), 5.85 (s, 1), 6.42 (s, 1), 6.6 (s, 1). Acetylation with 10 mL of acetic anhydride and 4 mL of pyridine, followed by filtration through Florisil, yielded 0.41 g of a yellow oil.

This mixture resisted purification. Several fractions were obtained by HPLC, the purist of which accounted for 30% of the crude mixture and possessed two components by GC: (SE-30 t_i 130 °C for 2 min, 40 °C/min, t_f 280 °C) rt 6.2 (73%), 7 min (27%); IR 2950, 1760, 1730, 1610, 1510, 1440, 1360, 1200, 1160, 1000, 910 cm^{-1}; NMR δ 1.8 (m, 2.5 H), 2.25 (s), 2.27 (s, 3.8 H), 2.3 (s, 3.8 H), 2.4 (m, 2.5 H), 2.5-2.8 (m, 2.5 H), 3.65 (s, 1 H), 3.75 (s, 3.8 H), 3.82 (s, 3 H), 5.9 (s, 0.5 H), 6.67 (s, 1 H), 6.9 (s, 1 H); mass spectrum (GC SE-30) rt 6.2 min, m/z 324 (M^+), 282 ($M^+ - C_2H_2O$), 240 ($M^+ - 2\ C_2H_2O$), 208, 180, 153 (100); mass spectrum (GE SE-30) rt 7 min, m/z 404, 402 (M^+), 362, 360 ($M^+ - C_2H_2O$), 320, 318 ($M^+ - 2\ C_2H_2O$), (320, 94% of 318), 288, 286 ($M^+ - 2\ C_2H_2O + CH_2OH$), 233, 231, 207 (100), 153. The compound with GC retention time of 6.2 min has been assigned to structure **2**. Many of the other HPLC fractions included bromine adducts as determined by GCMS.

2-(4,5-Dibromopentyl)-5-methoxy-2,5-cyclohexadiene-1,4-dione (4) and 2-(4,5-Dibromopentyl)-5-methoxy-1,4-benzenediol Diacetate (5). From the reaction of 0.059 g (0.029 mmol) of quinone **3** and BBr_3 followed by acetylation was obtained 0.12 g (92%) of **4** and **5**. These compounds were in a 1:1 ratio and separated by HPLC. From 0.025 g was isolated 0.011 g of quinone **4**: IR 3030, 2915, 2860, 1760, 1720, 1670, 1650, 1605, 1440, 1370, 1220, 1200, 1170, 990, 895, 855 cm^{-1}; NMR δ 1.7 (m, 1 H, coupled to δ 2.5), 1.83 (m, 2 H, coupled to δ 4.18, 2.5, 2.22), 2.22 (m, 1 H), 2.5 (m, 2 H), 3.62 [dd, 1 H, coupled to δ 3.85 (d), 4.18], 3.83 (s, 3 H), 3.85 [dd, 1 H, coupled to δ 3.62 (d) and 4.18], 4.18 [m, 1 H, coupled to δ 1.85, 3.62 (d), 3.85 (d)], 5.9 (s, 1 H), 6.55 (s, 1 H); HRMS for $C_{12}H_{16}O_3Br_2$ ($M^+ + 2$) obsd m/z 369.9433, 367.9400, 365.9311, calcd 369.94258, 367.94458, 365.94658; LRMS m/z 370 ($M^+ + 2$), 368, 366, 287, 285, 277, 260, 248, 153 (100). Benzenediacetate **5** was isolated as an oil (0.010 g): IR 2930, 2860, 1760, 1630, 1510, 1445, 1370, 1200, 1100, 1015, 925 cm^{-1}; NMR δ 1.65 (m, 1 H), 1.79 (m, 2 H, coupled to δ 2.47, 4.15), 2.15 (m, 1 H, coupled to δ 1.79, 1.65), 2.3 (s, 3 H), 2.34 (s, 3 H), 2.47 (m, 2 H, coupled to δ 1.79, 1.65), 3.6 [dd, 1 H, J = 10 Hz, coupled to δ 3.8 (d), 4.15], 3.79 (s, 3 H), 3.81 [dd, 1 H, J = 4.5 and 10 Hz, coupled t δ 3.6 (d), 4.15 (br t)] 4.15 [m, 1 H, coupled to δ 3.6 (d), 3.8 (d), 2.15, 1.79], 6.67 (s, 1 H), 6.92 (s, 1 H); HRMS for $C_{16}H_{20}O_5Br_2$, obsd m/z 452.11587, 412.16771, 410.1185, 408.12539 ($M^+ - C_2H_2O$), 370.40789, 368.38688 (100), 366.43804, calcd 452.1546, 412.1166 ($M^+ - C_2H_2O$), 410.1186, 412.1166.

Methyl 8,9-Diacetoxy-2-(bromomethyl)-3,4,5,6-tetrahydro-2*H*-1-benzoxocin-4-carboxylate (7a) and Methyl 2-(2-Propenyl)-4-(2,5-diacetoxy-4-methoxyphenyl)butanoate (8). From the reaction of 0.25 g (0.9 mmol) of quinone **6** followed by column chromatography on 10 g of silica gel using 8:2 hexane/EtOAc was isolated 0.12 g (41% yield) of **7a**: IR 3010, 2940, 2865, 1760, 1630, 1510, 1450, 1360, 1200, 1160, 1100, 1020, 930, 910 cm^{-1}; NMR δ 1.72 (m, 2 H), 2.02 (m, 1 H), 2.28 (s, 3 H), 2.32 (s, 3 H), 2.58 (m, 4 H), 3.5 (dd, 2 H, J = 6, 6 Hz), 3.75 (s, 3 H), 4.52 (m, 1 H), 6.62 (s, 1 H), 6.87 (s, 1 H); ^{13}C NMR δ 177.2 (s), 169.2 (s), 168.6 (s), 149.8 (s), 146.6 (s), 137.1 (s), 124.2 (s), 123.4 (d), 107.1 (d), 75.6 (d), 55.9 (q), 39.4 (d), 2 × 33.3 (t), 30.2 (t), 26.5 (t), 20.7 (q), 20.4 (q); MS, m/z 388 ($M^+ - 42$), 346 (94% of 344), 344 ($M^+ - 2\ CH_2CO$), 293, 248, 195, 166, 153 (100); HMRS for $C_{16}H_{19}O_6Br$, obsd m/z 388.2203, 386.2313, calcd 388.2283, 386.2303. Continued elution yielded 0.11 g (36%) of an oil containing 90% **8**: GC (SE-30, t_i 130 °C for 2 min, 40 °C/min, t_f 280 °C) rt 6.2, 6.7 min (1:9 ratio); IR 2950, 2820, 1765, 1730, 1510, 1370, 1200, 1160, 910 cm^{-1}; ^1H NMR δ 1.8 (m), 2.28 (s), 2.35 (s), 2.45 (m), 2.7 (m), 3.65 (s), 3.7 (s), 3.78 (s), 4.9-5.15 (m), 5.7 (m), 6.65 (s), and 6.9 ppm (s); MS (70 eV, GC SE-30; rt 6.7 min) m/z 364, 322, ($M^+ - C_2H_2O$), 280 ($M^+ - 2\ C_2H_2O$), 248 ($M^+ - 2\ C_2H_2O$ & $HOCH_3$), 153 (100).

Methyl 8,9-Diacetoxy-2-(1-bromoethyl)-3,4,5,6-tetrahydro-2*H*-1-benzoxocin-4-carboxylate (7b). From reaction of 0.47 g (1.91 mmol) of **9** was obtained 0.35 g of crude product. From 0.05 g was isolated 0.03 g of **10** (40%) by HPLC: IR 3000, 2940, 2860, 1765, 1610, 1505, 1445, 1370, 1200, 1010, 920 cm^{-1}; NMR δ 1.70 (m, 2 H), 1.76 (d, 3 H, J = 7 Hz), 2.10 (m, 1 H), 2.3 (s, 3 H), 2.34 (s, 3 H), 2.60 [m, 4 H, coupled to δ 4.28, 2.28 (d), 1.70], 3.79 (s, 3 H), 4.07 [m, 1 H, J = 7 Hz coupled to δ 4.28, 1.76 (s)], 4.28 [m, 1 H, coupled to δ 4.07 (q) 2.60, 1.70], 6.68 (s, 1 H), 6.91 (s, 1 H); HRMS for $C_{17}H_{21}O_6Br$ obsd m/z 402.0479, 400.0509 ($M^+ - C_2H_2O$), calcd 402.05013, 400.05213; MS, m/z 444, 442, 402 ($M^+ - C_2H_2O$), 400 (equal intensity to 402), 360 ($M^+ - 2\ C_2H_2O$), 358 (equal intensity to 360), 335 ($M^+ - C_2H_4Br$), 279, 195, 177, 166, 153 (100), 125, 110.

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Registry No. **1**, 105563-73-3; **2**, 105563-74-4; **3**, 105597-48-6; **4**, 105563-75-5; **5**, 105563-76-6; **6**, 105563-77-7; **7a**, 105563-78-8; **7b**, 105563-79-9; **8**, 105563-80-2; **9**, 105563-81-3; BBr_3, 10294-33-4.

Supplementary Material Available: Spectral data for **1**, **3**, **6**, and **9** as well as all synthetic precursors (4 pages). Ordering information is given on any current masthead page.

Preparation of Hindered Lithium Amide Bases and Rates of Their Reaction with Ether Solvents

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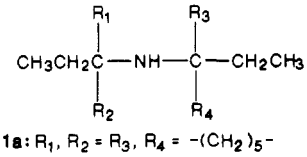
We previously described[2] methods for the preparation of a series of highly branched secondary amines (**1a-f**).



1a: R_1, $R_2 = R_3$, $R_4 = -(CH_2)_5-$
b: $R_1 = R_2 = R_3 = R_4 = CH_3$
c: $R_1 = R_2 = R_3 = CH_3$, $R_4 = CH_2CH_3$
d: $R_1 = R_3 = CH_3$, $R_2 = R_4 = CH_2CH_3$
e: $R_1 = CH_3$, $R_2 = R_3 = R_4 = CH_2CH_3$
f: $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$

We report here our observations on the preparation and ether stability of the lithium amide bases derived from this series and from other commercially available, secondary amines.

Results and Discussion

Preparation of Lithium Amides. The commonly used metal amides, lithium diisopropylamide (LDA) and

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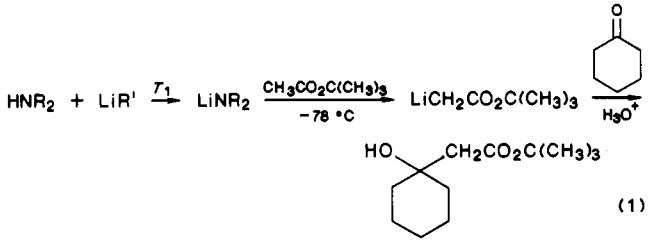
Table I. Reaction of Amines with Organolithium Reagents[a]

HNR_2	LiR′ (solvent)	reactn time,[b] h	$LiNR_2$,[c] %
none	CH_3Li (ether)		0
	n-C_4H_9 (hexane)		0
$HN[CH(CH_3)_2]_2$	n-C_4H_9 (hexane)	0.1	98
1a	CH_3Li (ether)	12	36
		24	32
	n-C_4H_9Li (hexane)	12	10
		24	15
		5 (reflux)	60
		12 (reflux)	55
	sec-C_4H_9Li (cyclohexane)	12	10
1b	CH_3Li (ether)	12	8
	n-C_4H_9Li (hexane)	12	10
	C_6H_5Li (cyclohexane–ether)	12	9
1f	CH_3Li (ether)	12	0
	n-C_4H_9Li (hexane)	12	0
	n-C_4H_9Li (hexane)	12 (reflux)	0
	sec-C_4H_9Li (cyclohexane)	12	0

[a] Reactions are 1 M in HNR_2 and LiR′ in the indicated solvent at 25 °C. [b] T_2 in eq 1. [c] Yield of $LiNR_2$ is based on yield of β-hydroxy ester formed by the sequence of eq 1.

2,2,6,6-tetramethylpiperidine (LTMP),[3] are prepared by reaction of the appropriate secondary amine with organolithium reagents, usually for periods of 15 min or less at 25 °C. Our initial results, obtained by manometric measurement of n-butane, indicated that amines **1a–f** react with n-butyllithium exceedingly slowly, if at all. A more general method for detecting lithium amide formation was devised, based on quantitative GLC analysis for β-hydroxy ester **2** formed by the reaction sequence of eq 1.[4] Results



(1)

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obtained for the reactions of amines **1a**, **1b**, and **1f** with a variety of organolithium reagents, as well as the results of suitable control experiments for the method, are shown in Table I. The less hindered amines (**1a**, **1b**) react only sluggishly with organolithium reagents in hydrocarbon or ether solution and give low (<60%) conversions to the amide. The most hindered amine (**1f**) of the series is totally inert to organolithium reagents under these conditions. This last result appears to be unprecedented for compounds possessing an N–H bond.

The chelating agent, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), is often used to accelerate metalation reactions of organolithium reagents.[5] Addition of 1 equiv of TMEDA to a hexane solution (previously saturated with n-butane) of amine **1b** and n-butyllithium resulted in a rapid (<1 min) and quantitative evolution of n-butane. Quenching with *tert*-butyl acetate and cyclohexanone according to the sequence of eq 1 produced a 97% yield of β-hydroxy ester **2**. By a similar technique, successful metalation of all the amines in the series (**1a–f**) was achieved (Table II). With 1 equiv of TMEDA, the most hindered amine, **1f**, is quantitatively converted to the lithium amide in less than 24 h. With 0.5 equiv of TMEDA, this time is increased to 48 h. The less hindered amines (**1a**, **1b**) are metalated rapidly with as little as 0.1 equiv of TMEDA.

Table II. Reaction of Amines with n-Butyllithium in the Presence of TMEDA[a]

NHR_2	TMEDA/ NMR_2	T_{50}[b]	T_{90}[c]
$HN[CH(CH_3)_2]_2$	0 or 1.0	<1 min	<1 min
2,2,6,6-tetramethylpiperidine	0 or 1.0	<1 min	<1 min
1a	0.1	1.5 h	4 h
	1.0	<1 min	<1 min
1b	0.5 or 1.0	<1 min	<1 min
1c	0.5 or 1.0	<1 min	<1 min
1d	0.5	10 min	35 min
	1.0	1.5 min	4 min
1e	0.5	65 min	4 h
	1.0	10 min	25 min
1f	0.5	7 h	40 h
	1.0	3 h	20 h

[a] Reactions are 1 M in HNR_2 and n-BuLi in hexane previously saturated with n-butane at 25 °C. [b] Time for evolution of 50% of theoretical volume of n-butane. [c] Time for evolution of 90% of theoretical volume of n-butane.

Table III. Lithium Amide Stability in Ether Solutions at 24 °C

$LiNR_2$	time, h	recovd $LiNR_2$,[a] %	$LiNR_2$	time, h	recovd $LiNR_2$,[a] %
LDA	12	98 (95)	Li-**1d**	6	25
LTMP	6	60 (50)		12	12 (96)
	12	50 (40, 35[b])	Li-**1e**	6	50
Li-**1b**	6	20 (65)		12	25 (98)
	12	10 (50)	Li-**1f**	6	60
Li-**1c**	6	15 (95)		12	50 (98)
	12	5 (90)			

[a] Determined by yield of β-hydroxy ester produced in the sequence of eq 1. Solvent is THF; results in parentheses are for diethyl ether solvent. [b] No TMEDA present.

Reactions of Lithium Amides with Ether Solvents. Ether solvents are commonly used for reactions of LDA and LTMP. It is recognized that ether solutions of these amides are not stable indefinitely at room temperature,[6] presumably due to abstraction of ether α-hydrogens as reported for organolithium reagents,[7] but apparently no studies of the rate of decomposition have been reported. Clearly, knowledge of this rate would be desirable for synthetic applications of LDA and LTMP and of the hindered lithium amides described here. Since the ether decomposition products are unlikely to cause enolate formation with *tert*-butyl acetate, the sequence of eq 1 provides a simple method for obtaining this rate.

A series of lithium amides was prepared from n-butyllithium and TMEDA in hexane. The solvent was removed under vacuum, and the amide–TMEDA complex was dissolved in either THF or diethyl ether. After an appropriate interval of time, the entire solution was subjected to the sequence of eq 1, with the results shown in Table III.

Although LDA is reasonably stable in both solvents, LTMP has a half-life of only 12 h in THF and only 4 h

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in diethyl ether. Surprisingly, TMEDA has little effect on the stability of LTMP. The stability of the remaining amides bears little relationship to their bulk. The most hindered amide in the series, Li-**1f**, is about as stable as LDA in diethyl ether solution.

Conclusions

The synthesis of a series of exceptionally hindered lithium amides has been accomplished. Studies on synthesis applications with these amides as proton-selective bases will be reported shortly.

Experimental Section

Methyllithium (1.4 M in ether), *n*-butyllithium (1.6 M in hexane), *sec*-butyllithium (1.3 M in cyclohexane), and phenyllithium (2 M in cyclohexane–ether) were obtained from Aldrich Chemical Co. and used directly after verification of concentration by titration with *sec*-butyl alcohol.[8] Diethyl ether and THF were distilled from $LiAlH_4$ and stored under argon. Diisopropylamine, tetramethylpiperidine, and TMEDA were distilled from CaH_2 and stored over molecular sieves under argon. Amines **1a-f** were prepared as previously described.[2] Cyclohexanone and *tert*-butyl acetate were purchased from Aldrich and used directly. GLC analyses were obtained with Varian 90-P chromatographs equipped with 6 ft × $^1/_4$ in. columns packed with 5% OV-101 on AW-DMCS-treated Chromasorb W.

Preparation of Hexane Solutions of Lithium Amides. The following procedure is representative of the techniques used to obtain the results of Table II and of Table I (for which case no TMEDA is added). A 10-mL round-bottomed flask equipped with a septum side arm and magnetic stirring bar was fitted with all-glass connections to a 100-mL mercury manometer. The system was flushed with *n*-butane, and the flask was charged with *n*-butyllithium (3 mmol, 1.84 mL) solution and sufficient hexane to make a 1 M. The reaction flask was thermostated at 24.0 (±0.2) °C, and the *n*-butane pressure was allowed to stabilize. This generally required about 1 h. TMEDA (3 mmol) was injected and the *n*-butane pressure again allowed to stabilize (20 min). The secondary amine (3 mmol) was then injected, and the extent of reaction was followed by monitoring butane volume.

Reaction of Lithium Amides with Ether Solvents. A hexane solution of the appropriate lithium amide was prepared as described above. The hexane was removed by vacuum distillation and the residual oil of lithium amide–TMEDA complex was dissolved in 3.0 mL of diethyl ether or THF. The solution was thermostated at 24.0 (±0.2 °C and, after an appropriate interval of time, was cooled with a dry ice–acetone bath and analyzed for residual lithium amide as described below.

Analysis for Lithium Amides. A diethyl ether or THF solution of lithium amide (3 M), prepared as described above, was thermostated at −78 °C. *tert*-Butyl acetate (3 mmol, 0.39 mL) was injected dropwise (5 min), and the solution was allowed to stir an additional 15 min to complete the formation of the ester enolate. Cyclohexanone (3 mmol, 0.32 mL) was then injected. After an additional 15 min, aqueous HCl (1 mL of 3 M) was added and the solution was then allowed to reach room temperature. One gram of anhydrous Na_2SO_4 was added to the flask together with *n*-pentadecane (3 mmol, 0.84 mL). A sample aliquot was analyzed for ethyl 2-hydroxycyclohexanecarboxylate (**2**), with *n*-pentadecane as internal GLC standard.

Registry No. **1a**, 74986-50-8; **1a**·Li, 105597-47-5; **1b**, 2978-47-4; **1b**·Li, 104653-84-1; **1c**, 74986-60-0; **1c**·Li, 105563-70-0; **1d**, 74986-61-1; **1d**·Li, 105563-71-1; **1e**, 74986-62-2; **1e**·Li, 105563-72-2; **1f**, 74986-49-5; **1f**·Li, 104653-85-2; $HN[CH(CH_3)_2]_2$, 108-18-9; *n*-C_4H_9Li, 109-72-8; CH_3Li, 917-54-4; *sec*-C_4H_9Li, 598-30-1; C_6H_5Li, 591-51-5; THF, 109-99-9; $LiN(Pr\text{-}i)_2$, 4111-54-0; LTMP, 38227-87-1; 2,2,6,6-tetramethylpiperidine, 768-66-1; tetramethylethylenediamine, 110-18-9; diethyl ether, 60-29-7.

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Pseudodistomins A and B, Novel Antineoplastic Piperidine Alkaloids with Calmodulin Antagonistic Activity from the Okinawan Tunicate *Pseudodistoma kanoko*

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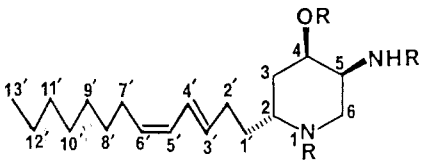
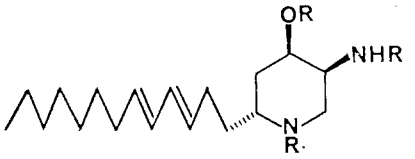
The role of the Ca^{2+}–calmodulin system in the control of cellular proliferation and tumor formation has been of great interest. Recently, W-7, a well-known calmodulin antagonist has been found to inhibit proliferation of Chinese hamster cells[2] and formation of mouse skin tumors.[3] In our continuing studies on bioactive substances from tunicates,[4] pseudodistomins A (**1**) and B (**2**), potent



1 R=H, **3** R=Ac



2 R=H, **4** R=Ac

antineoplastic piperidine alkaloids with calmodulin antagonistic activity, have been isolated from the Okinawan tunicate *Pseudodistoma kanoko*.[5] In this paper, we describe the isolation and structure of **1** and **2**. This is the first isolation of piperidine alkaloids[6] from marine sources.

The orange-colored compound tunicate (400 g, wet weight) was collected at Ie Island, Okinawa, by SCUBA (−5 to −10 m), and kept frozen until needed. The methanol–toluene (3:1) extract of *P. kanoko* was partitioned between toluene and water. The chloroform extract of the aqueous layer, which showed potent cytotoxicity against L1210 murine leukemia cells, was subjected to flash column chromatography on silica gel ($CHCl_3$/*n*-BuOH/

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