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Directed C-7 Lithiation of 1-(2,2-Diethylbutanoyl)indoles

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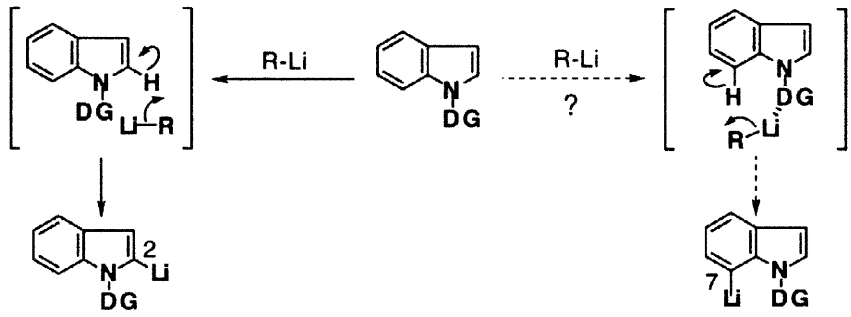
Abstract: Directed lithiation of 1-acylindole derivatives was investigated. It was discovered that a bulky 2,2-diethylbutanoyl (DEB) group could promote unusual C-7 lithiation. Especially in the case of 3-substituted 1-(DEB)indoles, selective C-7 lithiation was achieved in a synthetically useful level. The DEB group was readily removed by H_2O/*tert*-BuOK/THF system after functionalization at C-7. This, therefore, allows easy generation of 3,7-disubstituted indole derivatives which are not readily available by conventional methodologies. © 1999 Elsevier Science Ltd. All rights reserved.

Some biologically significant natural products[1] and synthetic drugs[2] comprise 7-substituted indole nucleus as a key structural unit. For the synthesis of 7-substituted indoles, *de novo* ring construction of the indole nucleus from appropriately substituted benzene precursors has been utilized as a major approach. This includes Leimgruber-Batcho,[3] Sugasawa,[4] Ito-Saegusa,[5] Bartoli[6], and Kondo-Sakamoto[7] procedures. Another ring construction route from pyrrole precursors is also useful, especially for the synthesis of complex natural products such as teleocidins.[8] Compared to these ring annulation methods, 7-selective functionalization of the preexisting indole nucleus is rather limited in spite of its inherent directness. Somei[9] and Iwao[10] utilized 1-protected indolines (2,3-dihydroindoles) as indole equivalents for 7-selective thallation and lithiation, respectively. Rapoport devised general bromine-lithium exchange route to the benzenoid ring-substituted indoles including 7-substituted ones.[11] This approach, however, requires the synthesis of bromoindoles from substituted benzenes. Nucleophilic addition[12] and lithiation[13] routes *via* indole-$Cr(CO)_3$ complexes have also been reported. Since we felt these procedures are lengthy and tedious for the synthesis of rather simple 7-substituted indole derivatives, we decided to explore more straightforward routes.

It is well-known that the lithiation of 1-substituted indoles occurs at 2-position exclusively.[14] Although a number of directing groups (DGs) have been utilized so far, none of them could promote C-7 lithiation. This is apparently due to much higher thermodynamic acidity of C-2 proton compared to C-7. We thought, however, if the coordinating moiety in the directing group were fixed toward H-7, kinetic deprotonation at C-7 could be feasible by complex-induced proximity effect (CIPE)[15] (**Scheme 1**).



DG=Me, CH_2OMe, $CH_2OCH_2SiMe_3$, CH_2NMe_2, SO_2Ph, CO_2Bu-*t*, CO_2Li, CONHBu-*t*, 2-Oxazolinyl, OMe

Scheme 1

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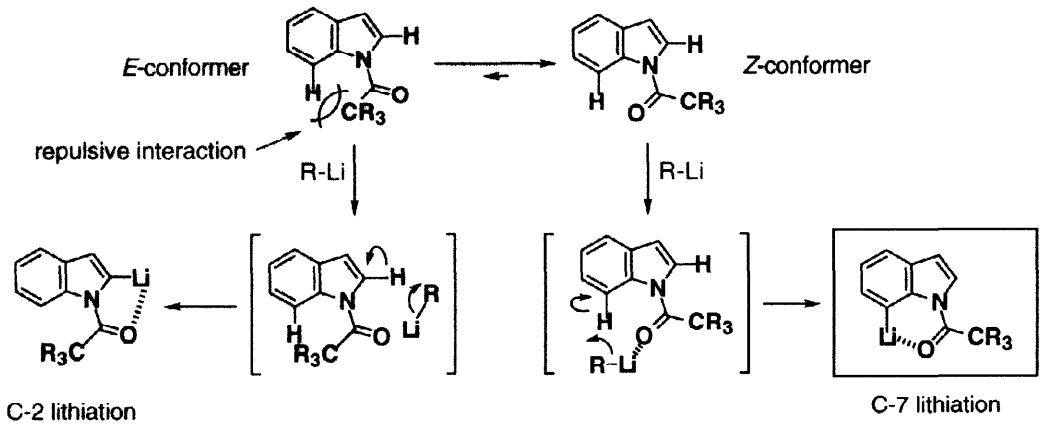
1-Acylindoles are known to exist as equilibrium mixtures of planner *E*- and *Z*-conformers due to restricted rotation around N-C amide bond.[16] In the case of bulky 1-acylindoles, this equilibrium may shift toward the *Z*-conformer because there is repulsive interaction between bulky alkyl substituent and *peri*-hydrogen in the *E*-conformer.[16] Since carbonyl oxygen of the major *Z*-conformer is directed toward benzenoid ring, selective C-7 lithiation may be possible if this orientation could be kept in the transition state of the deprotonation (**Scheme 2**).



Scheme 2

In order to test this idea, 1-pivaloylindole (**1**) and 1-(2,2-diethylbutanoyl)indole (**2**) [hereafter referred to 1-(DEB)indole] were synthesized. The differential NOE measurements of **1** and **2** clearly indicated that both compounds exist in Z-form as we expected. Namely, irradiation of *tert*-butyl protons of **1** resulted in 18.9% enhancement of H-2 absorption and only 1.1% of H-7. Furthermore, irradiation of methylene protons of **2** afforded single very large enhancement of H-2 absorption (30.8%) (**Figure 1**).

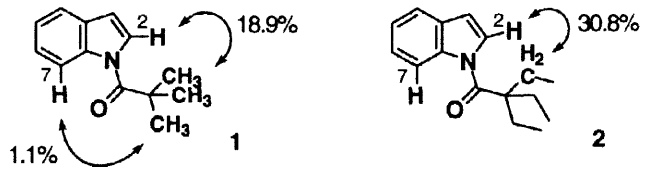
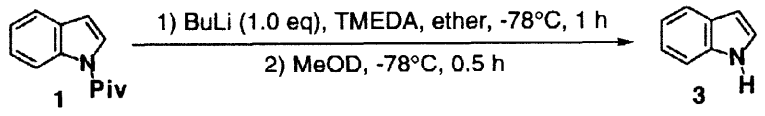


Figure 1

Directed Lithiation of 1-(DEB)indole. Deuteration Experiments

We first examined regioselective lithiation of 1-pivaloylindole (**1**) by treatment with *sec*-BuLi-TMEDA in ether at -78°C for 1h, followed by MeOD quench. After chromatographic purification, we isolated only deprotected indole (**3**), which must be generated by nucleophilic attack of *sec*-BuLi to the pivaloyl carbonyl, and the starting material **1** in 79% and 14% yields, respectively (**Scheme 3**). ^{1}H-NMR analysis of these products indicated no deuterium incorporation at C-7 and C-2 positions. Although we tested a variety of conditions , we isolated **3** as a major product in every case, and could not achieve any ring lithiation.



Scheme 3

We next examined the selective C-7 lithiation of more bulky 1-(DEB)indole (**2**) to avoid undesirable nucleophilic attack. The results of the lithiation-deuteration experiments were summarized in **Table 1**. When **2** was treated with *sec*-BuLi-TMEDA in ether at -78°C for 1 h followed by MeOD, the deuterated substrate **4** was recovered in good yields (Entries 1-4). ^{1}H-NMR analyses of **4** indicated that the lithiation occurred at both C-7 and C-2 positions. The best result with respect to both total deuterium incorporation and 7-selectivity was achieved by using 1.5 eq of *sec*-BuLi (Entry 3). When larger amount of the base was used, over lithiation occurred to give 2,7-dilithio species[17] (Entry 4). In entries 1-4, indole (**3**) was not isolated but small amount of 7-(DEB)indole (**5**) was formed. This by-product may be generated by intramolecular rearrangement of DEB group in the 7-lithio species. In the absence of TMEDA, the hemiaminal **6**[18] and indole (**3**) were formed as major products (Entry 5). Thus, TMEDA was indispensable for the efficient lithiation of **2**. Although we tested other bases (Entries 6, 7), solvents (Entries 8-10), and additives (Entries 11, 12), we could not establish much better conditions for selective C-7 lithiation. Only in the case where DME was used as a solvent, somewhat improved C-7 selectivity was observed, though the total deuterium incorporation was rather low and considerable amount of indole (**3**) was formed as a by-product (Entry 10).

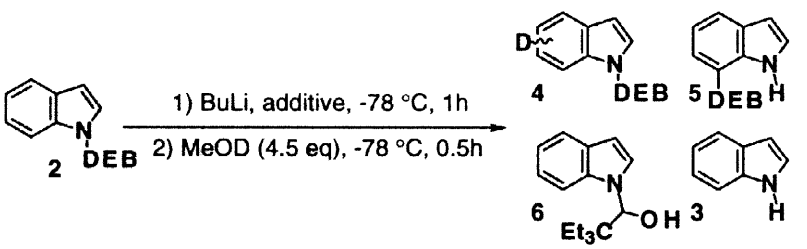


Table 1. Deuteration of 1-(DEB)indole (**2**)

Entry	Solvent	Additive (eq)	BuLi (eq)	**4** (%)[a]	Deuterium Content in **4** (%)[b]				**5** (%)[a]	**6** (%)[a]	**3** (%)[a]
					C-7	C-2	C-3	total			
1	ether	TMEDA (1.5)	*sec* (1.0)	80	26	35	0	61	5	0	0
2	ether	TMEDA (1.9)	*sec* (1.25)	78	41	50	0	91	6	0	0
3	ether	TMEDA (2.3)	*sec* (1.5)	81	52	49	0	101	2	0	0
4	ether	TMEDA (2.6)	*sec* (1.75)	83	59	51	0	110[c]	2	0	0
5	ether	none	*sec* (1.5)	14	12	51	0	63	0	30	47
6	ether	TMEDA (2.3)	*n* (1.5)	52	0	0	0	0	0	0	40
7	ether	TMEDA (2.3)	*tert* (1.5)	88	13	80	0	93	3	4	0
8	THF	TMEDA (2.3)	*sec* (1.5)	73	39	44	15	98	0	0	24
9	THF	none	*sec* (1.5)	56	12	33	30	75	0	3	32
10	DME	TMEDA (2.3)	*sec* (1.5)	73	42	32	1	75	3	0	20
11	ether	sparteine (2.3)	*sec* (1.5)	36	0	95	0	95	0	14	45
12	ether	DABCO (2.3)	*sec* (1.5)	64	0	0	0	0	0	14	19

a) Isolated yield.
b) Deuterium content was estimated by ^{1}H-NMR (200 MHz) analysis.
c) Formation of 2,7-dilithio species was indicated by a methylation experiment; see: ref. 17.

Directed Lithiation of 3-Substituted 1-(DEB)indoles. Synthesis of 3,7-Disubstituted Indole Derivatives

Since the feasibility of selective C-7 lithiation of 1-(DEB)indole derivatives was suggested by the deuteration experiments of **2**, we next examined the lithiation of 3-substituted 1-(DEB)indoles. The substituents lacking the directing ability such as alkyl and trialkylsilyl groups exert steric hindrance against the approach of a lithiating agent to the neighboring protons.[19] Therefore, improvement of C-7 selectivity was expected for the lithiation of 1-(DEB)indoles having such a substituent at 3-position.

The lithiation of 1-(DEB)-3-methylindole (**7**) under the conditions established above [*sec*-BuLi (1.5 eq),

TMEDA (2.3 eq), ether. -78 °C, 1h] followed by MeOD quenching afforded C-7 and C-2 deuterated products in a ratio of 6:1. Since a good regioselectivity was confirmed by this experiment, electrophilic substitution with a range of common electrophiles were carried out. The results were summarized in **Table 2**. In general, 7-substituted products **8** were isolated in good yields. The minor 2-substituted products **9** were readily removed from **8** by column chromatography or simple crystallization. Only when DMF was used as an electrophile, the expected 7-formyl derivative **8c** was isolated in a poor yield due to formation of some by-products derived from a normal addition product (see experimental).

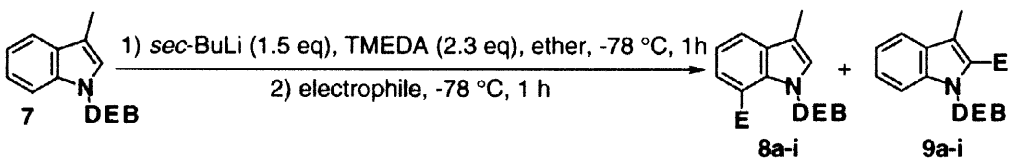
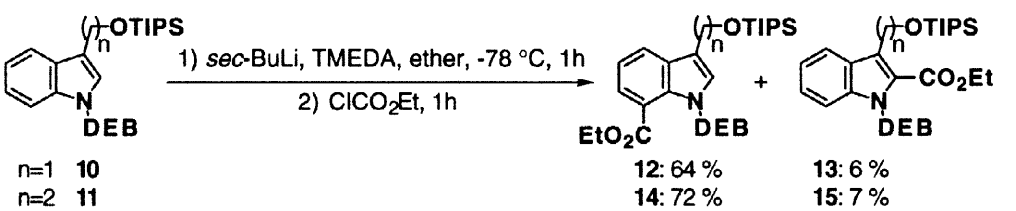


Table 2. Selective C-7 Functionalization of **7**

Entry	Electrophile	E	C-7 Product	Yield[a)]	C-2 Product	Yield[a)]
1	MeOD	D	**8a**	74[b)]	**9a**	12[b)]
2	MeI	Me	**8b**	62	**9b**	8
3	DMF	CHO	**8c**	17	**9c**	0
4	CO_2	CO_2H	**8d**	65	**9d**	0
5	$ClCO_2Et$	CO_2Et	**8e**	77	**9**	6
6	Cl_3CCCl_3	Cl	**8f**	81	**9f**	11
7	BrF_2CCBrF_2	Br	**8g**	67	**9g**	13
8	TMSCl	TMS	**8h**	75	**9h**	7
9	PhSSPh	SPh	**8i**	73	**9i**	9

a) Isolated yield unless otherwise noted.
b) Yield was determined by ^{1}H-NMR (200 MHz) analysis.

The lithiations of other 3-substituted 1-(DEB)indoles **10** and **11** also went smoothly under the similar conditions to give 3,7-disubstituted compounds **12** and **14**, respectively, after quenching with ethyl chloroformate. The C-7 *vs.* C-2 selectivities were essentially same as in the case of the lithiation of 3-methyl compound **7** (**Scheme 4**).



Scheme 4

Deprotection of DEB group

In order to establish the practical utility of this C-7 functionalization reaction of the indole ring, deprotection of DEB group was next investigated. Preliminarily we tested four different conditions by using **2** as a model substrate (**Table 3**). When **2** was allowed to react with K_2CO_3 in MeOH or with NaOEt in EtOH, it took for 1 day to complete the reaction at room temperature (Entries 1, 2). By using 2M aqueous NaOH in EtOH, longer reaction time was required (Entry 3). On the other hand, the deprotection using H_2O/*tert*-BuOK[20] in THF was found to be very efficient. The reaction was completed within 5 min at room temperature (Entry 4). This procedure was successfully applied for deprotection of DEB group from more hindered 7-substituted compounds **8g** and **8i**, although it took somewhat longer reaction time (Entries 5, 6).

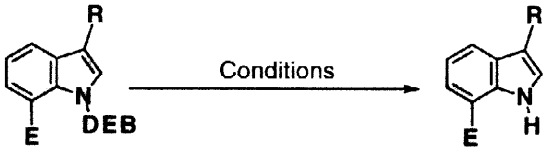


Table 3. Deprotection of DEB Group

Entry	Conditions	R	E	Time	Product	Yield (%)
1	K_2CO_3, MeOH	H	H	1 day	**3**	97
2	NaOEt, EtOH	H	H	1 day	**3**	87
3	NaOHaq, EtOH	H	H	1.7 day	**3**	90
4	*tert*-BuOK, H_2O, THF	H	H	5 min	**3**	84
5	*tert*-BuOK, H_2O, THF	Me	SPh	30 min	**16**	96
6	*tert*-BuOK, H_2O, THF	Me	Br	2 h	**17**	85

In conclusion, we discovered the first example of the directed C-7 lithiation of indole ring which was promoted solely by a directing group (DEB) on indole nitrogen. Good C-7 selectivity was achieved when 3-substituted 1-(DEB)indoles were employed as the substrates. Since DEB group was readily removed by H_2O/*tert*-BuOK in THF, this method allows easy generation of a variety of 3,7-disubstituted indole derivatives which are not readily available by using conventional protocols.

Experimental

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin Elmer System 2000 instrument. ^{1}H-NMR spectra were recorded at 200 MHz on a Varian Gemini-200 instrument, at 300 MHz on a Varian Gemini-300 instrument. The differential NOE measurements were carried out on a JEOL JMS GX-400 instrument. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). High resolution mass spectra were recorded on a JEOL JMS-DX303 instrument. Elemental analyses were performed at the microanalytical laboratory in Nagasaki University. Column chromatography was conducted on Silica Gel 60, 70-230 mesh ASTM (E.Merck), unless otherwise mentioned. Flash chromatography was conducted on Silica Gel 60, 230-400 mesh ASTM (E.Merck). Solvents were dried (Na-benzophenone ketyl for ether and THF, CaH_2 for DME) and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen or argon if necessary. *sec*-BuLi was purchased from Kanto Chemical Co., Inc. *n*- and *tert*-BuLi were purchased from Aldrich Chemical Co., Inc. All butyllithiums were used after titration with 2,5-dimethoxybenzyl alcohol. 1-Pivaloylindole (**1**) was synthesized according to the literature procedure.[21]

1-(2,2-Diethylbutanoyl)indole (2). Indole (1.07 g, 9.14 mmol) was added portionwise to a suspension of NaH (60% dispersion in mineral oil, 549 mg, ca. 13.7 mmol, prewashed with pentane) in THF (18 mL) at 0 °C. After stirring at the same temperature for 1 h, 2,2-diethylbutanoyl chloride[22] (1.49g, 9.14 mmol) was added dropwise at 0 °C and the whole mixture was gradually warmed to room temperature. After being stirred for 1 h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude **2** was purified by Kügelrohr distillation (180 °C/ 2 mmHg) after column chromatography (SiO_2, hexane-ethyl acetate= 30:1), to give pure **2** (2.17 g, 98%) as colorless oil: IR (neat) 3182, 3051, 2970, 2880, 1694, 1584, 1538, 1471, 1448, 1382, 1344, 1306, 1284, 1223, 1208, 1184, 1174, 1153, 1102, 1076, 1020, 935, 880, 823, 768, 750, 713 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.51 (dd, *J*= 0.8 and 8.2 Hz, 1H), 7.78 (d, *J*= 3.8 Hz, 1H), 7.56 (dd, *J*= 0.8 and 7.1 Hz, 1H), 7.34 (dt, *J*= 1.4 and 7.1 Hz, 1H), 7.26 (dt, *J*= 1.1 and 7.4 Hz, 1H), 6.61 (dd, *J*= 0.6 and 3.8 Hz, 1H), 1.90 (q, *J*= 7.4 Hz, 6H), 0.84 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76%. Found: C, 79.27; H, 8.83; N, 5.74%.

1-(2,2-Diethylbutanoyl)-3-methylindole (7). This compound was prepared from 3-methylindole (skatole) as described above in 96% yield: Bp 160-170 °C/ 0.9 mmHg (Kügelrohr); IR (neat) 3049, 2969, 2942, 2880, 1690, 1608, 1471, 1449, 1386, 1347, 1311, 1212, 1172, 1157, 1121, 1061, 1038, 1022, 922, 825, 770, 748 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.50 (d, *J*= 7.7 Hz, 1H), 7.53 (br s, 1H), 7.49 (dd, *J*= 1.4 and 7.6 Hz, 1H), 7.37-7.26 (m, 2H), 2.30 (d, *J*= 1.1 Hz, 3H), 1.89 (q, *J*= 7.4 Hz, 6H), 0.83 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44%. Found: C, 79.72; H, 9.19; N, 5.38%.

1-(2,2-Diethylbutanoyl)-3-triisopropylsilyloxymethylindole (10). This compound was prepared in three steps from indole-3-carboxaldehyde. NaH (60% in mineral oil, 400 mg, ca. 10 mmol) was added portionwise to a solution of indole-3-carboxaldehyde (1.45 g, 10.0 mmol) in THF (30 mL) at -20 °C. The mixture was gradually warmed to room temperature. After being stirred for 1 h, the mixture was added dropwise to a solution of 2,2-diethylbutanoyl chloride (1.63 g, 10.0 mmol) in THF (60 mL) at -20 °C over 40 min and the whole was stirred for additional 2 h. The mixture was quenched with water and extracted with ethyl acetate. The extract was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified successively by silica gel (hexane-ethyl acetate= 5:1) and aluminium oxide column chromatography (hexane-ethyl acetate= 10:1) to give 1-(2,2-diethylbutanoyl)indole-3-carboxaldehyde (1.33 g, 49%) as a white solid: Mp 68.0-68.5 °C; IR (KBr) 3164, 2970, 2943, 2879, 2817, 1713, 1676, 1605, 1551, 1481, 1469, 1450, 1397, 1381, 1345, 1305, 1290, 1245, 1198, 1168, 1154, 1125, 1059, 1039, 1021, 933, 819, 784, 759, 716 cm^{-1}; ^{1}H-NMR (300 MHz) δ 10.15 (s, 1H), 8.43-8.39 (m, 1H), 8.36 (s, 1H), 8.31-8.27 (m, 1H), 7.47-7.37 (m, 2H), 1.94 (q, *J*= 7.5 Hz, 6H), 0.87 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16%. Found: C, 74.91; H, 7.76; N, 5.07%.

$NaBH_4$ (404 mg, 10.7 mmol) was added portionwise to a solution of 1-(2,2-diethylbutanoyl)indole-3-carboxaldehyde (1.45 g, 5.34 mmol) in MeOH (20 mL) and THF (20 mL) at 0 °C. The mixture was stirred for 1 h and quenched with water (20 mL). The whole was extracted with ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane-ethyl acetate= 3:1) to give 1-(2,2-diethylbutanoyl)indole-3-methanol (1.40 g, 96%) as colorless oil: IR (neat) 3429, 3052, 2971, 2880, 1698, 1607, 1571, 1449, 1383, 1349, 1313, 1208, 1170, 1156, 1123, 1060, 1038, 1019, 922, 825, 798, 750 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.50 (d, *J*= 8.2 Hz, 1H), 7.76 (s, 1H), 7.63 (dd, *J*= 1.2 and 7.1 Hz, 1H), 7.36 (dt, *J*= 1.4 and 7.7 Hz, 1H), 7.29 (dt, *J*= 1.2 and 7.4 Hz, 1H), 4.88 (s, 2H), 1.89 (q, *J*= 7.5 Hz, 6H), 0.83 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{17}H_{23}NO_2$ (M^+): 273.1729. Found 273.1719.

Triisopropylsilyl chloride (1.15 mL, 5.38 mmol) was added to a solution of 1-(2,2-diethylbutanoyl)indole-3-methanol (1.40 g, 5.13 mmol) and imidazole (733 mg, 10.8 mmol) in *N,N*-dimethylformamide (5.0 mL) at 0 °C. The mixture was stirred for 3 h at the same temperature and then water (30 mL) and ethyl acetate (50 mL) were added to this mixture. Two phases were separated and the organic layer was washed successively with water (twice) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by Kügelrohr distillation (240 °C/ 2 mmHg) to give **10** (1.66 g, 75%) as colorless oil: IR (neat) 3051, 2965, 2943, 2866, 1695, 1608, 1464, 1449, 1381, 1351, 1309, 1207, 1169, 1156, 1126, 1102, 1068, 1045, 883, 823, 774, 749, 684 cm^{-1}; ^{1}H-NMR: δ 8.51 (d, *J*= 8.2 Hz, 1H), 7.77 (br s, 1H), 7.50 (br d, *J*= 7.7 Hz, 1H), 7.34 (dt, *J*= 1.1 and 7.1 Hz, 1H), 7.26 (dt, *J*= 1.1 and 7.5 Hz, 1H), 5.01 (d, *J*= 1.4 Hz, 2H), 1.89 (q, *J*= 7.4 Hz, 6H), 1.27-1.07 (m, 21H), 0.83 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd. for $C_{26}H_{43}NO_2Si$: C, 72.67; H, 10.09; N, 3.26%. Found: C, 72.26; H, 9.98; N, 3.29%.

1-(2,2-Diethylbutanoyl)-3-(2-triisopropylsilyloxyethyl)indole (11). This compound was prepared in two steps from 2-(3-indole)ethanol. Triisopropylsilyl chloride (1.12 mL, 5.25 mmol) was added to a solution of 2-(3-indole)ethanol (806 mg, 5.00 mmol) and imidazole (715 mg, 10.5 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature. The mixture was stirred overnight and then water (30 mL) and ethyl acetate

(50 mL) were added to this mixture. Two phases were separated and the organic layer was washed successively with water (three times) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane-ethyl acetate= 5:1) to give 3-(2-triisopropylsilyloxyethyl)indole (1.57 g, 99%) as colorless oil: IR (neat) 3420, 2943, 2892, 2866, 1620, 1457, 1421, 1383, 1351, 1338, 1249, 1226, 1100, 1069, 1012, 996, 919, 883, 826, 740, 682 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.93 (br s, 1H), 7.61 (d, *J*= 7.0 Hz, 1H), 7.34 (dt, *J*= 1.2 and 8.0 Hz, 1H), 7.18 (ddd, *J*= 1.2, 7.0 and 8.1 Hz, 1H), 7.11 (ddd, *J*= 1.2, 7.0 and 7.8 Hz, 1H), 7.04 (d, *J*= 2.3 Hz, 1H), 3.95 (t, *J*= 7.5 Hz, 2H), 3.03 (dt, *J*= 0.8 and 7.5 Hz, 2H), 1.17-1.04 (m, 21H). *Anal.* Calcd for $C_{19}H_{31}NOSi$: C, 71.87; H, 9.84; N, 4.41%. Found: C, 71.65; H, 9.75; N, 4.46%.

A solution of 3-(2-triisopropylsilyloxyethyl)indole (1.55 g, 4.87 mmol) in THF (5 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 292 mg, ca. 7.3 mmol, prewashed with pentane) in THF (5 mL) at 0 °C. After stirring at the same temperature for 1 h, 2,2-diethylbutanoyl chloride (872 mg, 5.36 mmol) was added dropwise at 0 °C and stirred for additional 1h at the same temperature. The mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate and the extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude **13** was purified by Kügelrohr distillation (240 °C/ 0.6 mmHg) after column chromatography (SiO_2, hexane-ethyl acetate= 30:1), to give pure **11** (1.88 g, 87%) as colorless oil: IR (neat) 3051, 2964, 2943, 2866, 1692, 1606, 1449, 1383, 1355, 1307, 1219, 1171, 1154, 1121, 1103, 1066, 1014, 920, 883, 825, 749, 682 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.51 (br d, *J*= 7.4 Hz, 1H), 7.69 (br s, 1H), 7.51 (dd, *J*= 1.4 and 7.1 Hz, 1H), 7.33 (dt, *J*= 1.4 and 7.1 Hz, 1H), 7.26 (dt, *J*= 1.4 and 7.4 Hz, 1H), 4.01 (t, *J*= 6.3 Hz, 2H), 2.95 (dt, *J*= 0.5 and 6.3 Hz, 2H), 1.89 (q, *J*= 7.4 Hz, 6H), 1.17-0.99 (m, 21H), 0.83 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd. for $C_{27}H_{45}NO_2Si$: C, 73.08; H, 10.22; N, 3.16%. Found: C, 73.16; H, 10.35; N, 3.17%.

Directed Lithiation of 2. Deuteration Experiment. A solution of **2** (96.6 mg, 0.397 mmol) and an appropriate additive in ether (5.0 mL) was cooled to -78 °C. Fresh *sec*-BuLi[23] (640 μL, 0.928 M in hexane-cyclohexane) was added dropwise to the solution over 5 min at the same temperature. After being stirred for 1 h, MeOD (72.6 μL, 1.79 mmol) was added to the mixture and stirred for additional 30 min. To this mixture was added saturated aqueous NH_4Cl at -78 °C and whole was warmed to room temperature. The mixture was extracted with ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash chromatography (SiO_2, hexane-ethyl acetate = 50:1 to 10:1) to give corresponding products. The deuterium content in **4** was determined by integration of the signals H-7 and H-2 protons of the ^{1}H-NMR spectra (200 MHz). The signals at δ 8.51 and δ 7.78 were assigned to be H-7 and H-2 protons, respectively. Spectroscopic data of by-products **5** and **6** were as follows.

7-(2,2-Diethylbutanoyl)indole (5): IR (neat) 2971, 2881, 1653, 1592, 1467, 1396, 1347, 1291, 1263, 1235, 1208, 1167, 1085, 844, 819, 791, 739, 709 cm^{-1}; ^{1}H-NMR (300 MHz) δ 10.62 (s, 1H), 7.72 (d, *J*= 4.0 Hz, 1H), 7.19 (t, *J*= 7.7 Hz, 1H), 7.01 (dd, *J*= 1.1 and 7.7 Hz, 1H), 6.90 (dd, *J*= 1.1 and 7.7 Hz, 1H), 6.62 (d, *J*= 4.0 Hz, 1H), 1.91 (q, *J*= 7.5 Hz, 6H), 0.87 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{16}H_{21}NO$ (M^+): 243.1623. Found 243.1667.

1-(2,2-Diethyl-1-hydroxybutyl)indole (6): IR (neat) 3525, 2968, 2941, 2882, 1610, 1514, 1458, 1382, 1296, 1214, 1199, 1155, 1126, 1096, 1059, 1017, 908, 884, 819, 766, 739 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.60 (d, *J*= 7.9 Hz, 1H), 7.39 (d, *J*= 3.3 Hz, 1H), 7.38 (d, *J*= 8.0 Hz, 1H), 7.18 (ddd, *J*= 1.3, 7.0 and 8.3 Hz, 1H), 7.09 (dt, *J*= 1.0 and 7.8 Hz, 1H), 6.55 (d, *J*= 3.3 Hz, 1H), 5.83 (s, 1H), 2.35 (br s, 1H), 1.48 (dq, *J*= 2.4 and 7.5 Hz, 6H), 0.84 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{16}H_{23}NO$ (M^+): 245.1780. Found 245.1793.

Directed Lithiation of 7 and Subsequent Reaction with Electrophiles. General Procedure. To a solution of **7** (102 mg, 0.397 mmol) in ether (5 mL) was added TMEDA (135 μL, 0.893 mmol) and cooled to -78 °C. Fresh *sec*-BuLi (650 μL, 0.953 M in hexane-cyclohexane, 0.596 mmol) was added dropwise to the

solution over 5 min at the same temperature. After stirring at the same temperature for 1 h, an appropriate electrophile was added and the mixture was stirred for additional 1 h. The whole was gradually warmed to room temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether, and the extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash chromatography (SiO_2, hexane-ethyl acetate = 50:1) to give **8** and **9**. The results of the reactions with each electrophile were as follows.

Reaction with Iodomethane. Iodomethane (111 μL, 1.78 mmol) was added as a neat liquid to give **8b** (67 mg, 62%) as colorless oil and **9b** (9 mg, 8%) as colorless oil.

1-(2,2-Diethylbutanoyl)-3,7-dimethylindole (8b): IR (neat) 2970, 2941, 2881, 1699, 1608, 1456, 1405, 1384, 1347, 1305, 1234, 1205, 1171, 1158, 1115, 1075, 1036, 1010, 941, 899, 822, 785, 764, 743, 723 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.35 (d, *J*= 6.9 Hz, 1H), 7.34 (s, 1H), 7.20 (t, *J*= 7.5 Hz, 1H), 7.12 (d, *J*= 7.2 Hz, 1H), 2.36 (s, 3H), 2.28 (d, *J*= 1.2 Hz, 3H), 1.90 (q, *J*= 7.5 Hz, 6H), 0.89 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{18}H_{25}NO$ (M^+): 271.1936. Found 271.1925.

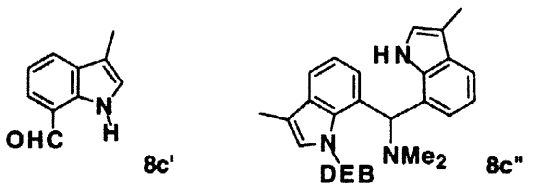
1-(2,2-Diethylbutanoyl)-2,3-dimethylindole (9b): IR (neat) 2971, 2941, 2882, 1698, 1457, 1387, 1345, 1289, 1202, 1127, 1093, 1055, 1022, 839, 739, 667 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.46-7.35 (m, 2H), 7.17-7.11 (m, 2H), 2.33 (s, 3H), 2.20 (s, 3H), 1.84 (q, *J*= 7.5 Hz, 6H), 0.86 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{18}H_{25}NO$ (M^+): 271.1936. Found 271.1946.

Reaction with *N,N*-Dimethylformamide. This reaction was carried out according to the general procedure except for quenching and purification procedures. After addition of *N,N*-dimethylformamide (131 μL, 1.79 mmol), the reaction mixture was stirred for 1 h at -78 °C and then quenched with saturated aqueous NH_4Cl at the same temperature. The mixture was warmed to room temperature and extracted with ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash chromatography (SiO_2, hexane-ethyl acetate = 50:1 to 10:1) to give **8c** (19 mg, 17%) as colorless oil, **8c'** (9 mg, 14%) as a white solid, and **8c''** (20 mg, 23%) as a white solid. The products derived from the C-2 lithio species could not be isolated.

1-(2,2-Diethylbutanoyl)-3-methylindole-7-carboxaldehyde (8c): IR (neat) 3157, 2970, 2880, 1697, 1595, 1575, 1459, 1419, 1396, 1345, 1304, 1252, 1231, 1203, 1173, 1158, 1111, 1005, 970, 947, 902, 821, 797, 757, 724 cm^{-1}; ^{1}H-NMR (300 MHz) δ 10.26 (s, 1H), 7.72 (d, *J*= 7.7 Hz, 1H), 7.69 (d, *J*= 7.7 Hz, 1H), 7.54 (s, 1H), 7.39 (t, *J*= 7.7 Hz, 1H), 2.32 (s, 3H), 1.93 (q, *J*= 7.5 Hz, 6H), 0.88 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{18}H_{23}NO_2$ (M^+): 285.1729. Found 285.1708.

3-Methylindole-7-carboxaldehyde (8c'): Mp 79.0-81.0 °C; IR (KBr) 3384, 2933, 2861, 1661, 1608, 1586, 1553, 1455, 1407, 1383, 1351, 1216, 1181, 1132, 1062, 997, 833, 808, 790, 748, 713, 691 cm^{-1}; ^{1}H-NMR (300 MHz) δ 10.11 (s, 1H), 9.84 (br s, 1H), 7.88 (d, *J*= 7.6 Hz, 1H), 7.64 (d, *J*= 7.6 Hz, 1H), 7.25 (t, *J*= 7.6 Hz, 1H), 7.10 (s, 1H), 2.37 (s, 3H). HREIMS m/z. Calcd. for $C_{10}H_9NO$ (M^+): 159.0684. Found 159.0690.

***N,N*-Dimethyl[1-(2,2-diethylbutanoyl)-3-methyl-7-indolyl](3-methyl-7-indolyl)methylamine (8c''):** Mp 153.5-154.0 °C; IR (KBr) 3386, 2971, 2949, 2880, 2862, 2822, 2776, 1688, 1612, 1457, 1435, 1413, 1385, 1346, 1336, 1290, 1223, 1200, 1186, 1154, 1109, 1061, 1038, 1001, 936, 862, 820, 808, 798, 757, 747 cm^{-1}; ^{1}H-NMR (300 MHz) δ 10.07 (br s, 1H), 7.47-7.39 (m, 4H), 7.32 (dd, *J*= 1.2 and 7.6 Hz, 1H), 7.13 (t, *J*= 7.7 Hz, 1H), 7.05 (t, *J*= 7.6 Hz, 1H), 6.95 (s, 1H), 5.43 (s, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.19 (s, 6H), 2.12-1.87 (m, 6H), 0.97 (t, *J*= 7.5 Hz, 9H). HREIMS m/z. Calcd. for $C_{29}H_{37}N_3O$ (M^+): 443.2937. Found 443.2947.



8c' 8c"

Reaction with CO_2. This reaction was carried out according to the general procedure except for quenching and purification procedures. After addition of excess amount of dry ice as an electrophile, the reaction mixture was stirred for 1 h at -78 °C and then warmed to room temperature. The mixture was quenched with 2M aqueous HCl and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was collected by filtration and washed with a small amount of ether, and dried *in vacuo* to give **8d** (77 mg, 65%) as a white powder. The product derived from the C-2 lithio species could not be isolated.

1-(2,2-Diethylbutanoyl)-3-methylindole-7-carboxylic Acid (8d): Mp 211.0-213.0 °C (hexane-ether); IR (KBr): 2965, 2879, 1698, 1608, 1595, 1583, 1466, 1454, 1421, 1382, 1347, 1311, 1255, 1202, 1165, 1150, 1101, 1067, 1044, 1016, 941, 926, 896, 822, 811, 766, 748, 731 cm^{-1}. ^{1}H-NMR (300 MHz) δ7.71 (d, *J*= 7.5 Hz, 1H), 7.66 (dd, *J*= 1.2 and 8.0 Hz, 1H), 7.53 (s, 1H), 7.34 (t, *J*= 7.5 Hz, 1H), 2.32 (s, 3H), 1.90 (q, *J*= 7.5 Hz, 6H), 0.86 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65%. Found: C, 71.48; H, 7.62; N, 4.53%.

Reaction with Ethyl Chloroformate. The scale of this reaction was doubled in comparison with that of the general procedure. Ethyl chloroformate (125 μL, 1.31 mmol) was added as a neat liquid to give **8e** (193 mg, 77%) as a white solid, and **9e** (16 mg, 6%) as colorless oil.

Ethyl 1-(2,2-Diethylbutanoyl)-3-methylindole-7-carboxylate (8e): Mp 119.5-120.0 °C; IR (KBr) 3157, 2965, 2879, 1724, 1699, 1610, 1579, 1467, 1412, 1372, 1346, 1313, 1282, 1208, 1184, 1169, 1135, 1098, 1064, 1039, 1019, 946, 928, 864, 824, 764, 746 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.60 (d, *J*= 7.6 Hz, 1H), 7.54 (d, *J*= 7.6 Hz, 1H), 7.53 (s, 1H), 7.29 (t, *J*= 7.6 Hz, 1H), 4.39 (q, *J*= 7.2 Hz, 2H), 2.30 (s, 3H), 1.90 (q, *J*= 7.5 Hz, 6H), 1.38 (t, *J*= 7.2 Hz, 3H), 0.87 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd. for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25%. Found: C, 72.87; H, 8.25; N, 4.24%.

Ethyl 1-(2,2-Diethylbutanoyl)-3-methylindole-2-carboxylate (9e): IR (neat) 2976, 2941, 2884, 1713, 1548, 1447, 1413, 1384, 1324, 1297, 1248, 1219, 1135, 1051, 1035, 838, 743 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.63 (d, *J*= 8.0 Hz, 1H), 7.40 (t, *J*= 8.4 Hz, 1H), 7.33 (d, *J*= 8.4 Hz, 1H), 7.19 (t, *J*= 7.4 Hz, 1H), 4.39 (q, *J*= 7.1 Hz, 2H), 2.56 (s, 3H), 1.68 (q, *J*= 7.4 Hz, 6H), 1.40 (t, *J*= 7.1 Hz, 3H), 0.79 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{20}H_{27}NO_3$ (M^+): 329.1991. Found 329.2009.

Reaction with Hexachloroethane. A solution of hexachloroethane (155 mg, 0.655 mmol) in ether (1 mL) was added to give **8f** (94 mg, 81%) as colorless oil and **9f** (13 mg, 11%) as colorless oil.

7-Chloro-1-(2,2-diethylbutanoyl)-3-methylindole (8f): IR (neat) 3060, 2969, 2941, 2881, 1714, 1606, 1464, 1415, 1385, 1346, 1307, 1251, 1206, 1196, 1163, 1150, 1085, 1070, 1039, 930, 861, 829, 821, 786, 762, 735, 721 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.42 (d, *J*= 7.7 Hz, 1H), 7.33 (s, 1H), 7.32 (d, *J*= 7.7 Hz, 1H), 7.19 (t, *J*= 7.7 Hz, 1H), 2.28 (s, 3H), 1.90 (q, *J*= 7.4 Hz, 6H), 0.91 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd. for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80%. Found: C, 69.96; H, 7.61; N, 4.78%.

2-Chloro-1-(2,2-diethylbutanoyl)-3-methylindole (9f): IR (neat) 3052, 2974, 2943, 2882, 1732, 1713, 1447, 1385, 1345, 1275, 1221, 1197, 1159, 1125, 1052, 1033, 924, 834, 741 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.47-7.43 (m, 1H), 7.38-7.33 (m, 1H), 7.25-7.14 (m, 2H), 2.26 (s, 3H), 1.85 (q, *J*= 7.4 Hz, 6H), 0.86 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{17}H_{22}ClNO$ (M^+): 291.1390. Found 291.1393.

Reaction with 1,2-Dibromo-1,1,2,2-tetrafluoroethane. The scale of this reaction was doubled in comparison with that of the general procedure. 1,2-Dibromo-1,1,2,2-tetrafluoroethane (157 μL, 1.31 mmol) was added as a neat liquid to give **8g** (178 mg, 67%) as colorless oil and **9g** (34 mg, 13%) as colorless oil.

7-Bromo-1-(2,2-diethylbutanoyl)-3-methylindole (8g): IR (neat) 3057, 2970, 2942, 2881, 1713, 1605, 1552, 1471, 1410, 1385, 1347, 1305, 1250, 1162, 1150, 1066, 1038, 929, 840, 819, 785, 762, 736, 720 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.53 (dd, *J*= 0.8 and 7.7 Hz, 1H), 7.46 (dd, *J*= 0.8 and 7.7 Hz, 1H), 7.35 (d, *J*= 1.0 Hz, 1H), 7.12 (t, *J*= 7.7 Hz, 1H), 2.28 (d, *J*= 1.0 Hz, 3H), 1.91 (q, *J*= 7.4 Hz, 6H), 0.92 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{17}H_{22}BrNO$ (M^+): 335.0885. Found 335.0891.

2-Bromo-1-(2,2-diethylbutanoyl)-3-methylindole (9g): IR (neat) 3051, 2974, 2941, 2882, 1728, 1712, 1446, 1385, 1340, 1272, 1211, 1158, 1123, 1049, 1028, 932, 837, 740 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.50-7.45 (m, 1H), 7.33 (dd, *J*= 1.6 and 6.9 Hz, 1H), 7.23-7.12 (m, 2H), 2.27 (s, 3H), 1.85 (q, *J*= 7.4 Hz, 6H), 0.88 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{17}H_{22}BrNO$ (M^+): 335.0885. Found 335.0890.

Reaction with Chlorotrimethylsilane. Chlorotrimethylsilane (83 μL, 0.655 mmol) was added as a neat liquid to give **8h** (99 mg, 75%) as a white solid and **9h** (9 mg, 7%) as a white solid.

1-(2,2-Diethylbutanoyl)-3-methyl-7-trimethylsilylindole (8h): Mp 74.0-74.5 °C; IR (KBr) 3160, 3060, 2971, 1912, 1854, 1797, 1688, 1618, 1555, 1473, 1389, 1348, 1326, 1303, 1242, 1220, 1166, 1130, 1088, 1040, 1013, 931, 870, 839, 813, 762, 747, 695, 666, 640, 617 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.67 (dd, *J*= 1.1 and 7.1 Hz, 1H), 7.54 (d, *J*= 0.8 Hz, 1H), 7.49 (dd, *J*= 1.1 and 7.4 Hz, 1H), 7.27 (t, *J*= 7.4 Hz, 1H), 2.27 (d, *J*= 0.8 Hz, 3H), 1.90 (q, *J*= 7.4 Hz, 6H), 0.84 (t, *J*= 7.4 Hz, 9H), 0.35 (s, 9H). *Anal.* Calcd. for $C_{20}H_{31}NOSi$: C, 72.89; H, 9.48; N, 4.25%. Found: C, 72.68; H, 9.44; N, 4.27%.

1-(2,2-Diethylbutanoyl)-3-methyl-2-trimethylsilylindole (9h): IR (KBr) 2971, 1672, 1583, 1529, 1448, 1377, 1348, 1296, 1274, 1245, 1201, 1152, 1107, 1035, 951, 841, 797, 759, 741, 680, 637, 624 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.75 (d, *J*= 8.0 Hz, 1H), 7.52 (d, *J*= 7.1 Hz, 1H), 7.29-7.16 (m, 2H), 2.38 (s, 3H), 2.02 (q, *J*= 7.4 Hz, 6H), 0.83 (t, *J*= 7.4 Hz, 9H), 0.36 (s, 9H). HREIMS m/z. Calcd. for $C_{20}H_{31}NOSi$ (M^+): 329.2175. Found 329.2186.

Reaction with Diphenyldisulfide. The scale of this reaction was doubled in comparison with that of the general procedure. A solution of diphenyldisulfide (286 mg, 1.31 mmol) in ether (2 mL) was added to give **8i** (212 mg, 73%) as colorless crystals and **9i** (26 mg, 9%) as colorless oil.

1-(2,2-diethylbutanoyl)-3-methyl-7-(phenylthio)indole (8i): Mp 143.5-144.0 °C (hexane-CH_2Cl_2); IR (KBr) 3143, 3053, 2962, 2876, 1687, 1604, 1554, 1460, 1440, 1406, 1384, 1347, 1311, 1251, 1215, 1198, 1170, 1155, 1084, 1071, 1024, 932, 920, 853, 821, 785, 765, 752, 741, 722, 694 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.41-7.24 (m, 7H), 7.11 (t, *J*= 7.7 Hz, 1H), 7.00 (dd, *J*= 1.1 and 7.7 Hz, 1H), 2.30 (d, *J*= 1.4 Hz, 3H), 1.94 (q, *J*= 7.4 Hz, 6H), 0.93 (t, *J*= 7.4 Hz, 9H). *Anal.* Calcd. for $C_{23}H_{27}NOS$: C, 75.57; H, 7.45; N, 3.83%. Found: C, 75.58; H, 7.41; N, 3.98%.

1-(2,2-diethylbutanoyl)-3-methyl-2-(phenylthio)indole (9i): IR (neat) 3059, 2974, 2940, 2881, 1726, 1706, 1582, 1479, 1442, 1383, 1351, 1275, 1200, 1160, 1126, 1080, 1053, 1026, 933, 834, 738, 689 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.57 (d, *J*= 7.9 Hz, 1H), 7.40 (d, *J*= 8.2 Hz, 1H), 7.33-7.00 (m, 5H), 6.91 (d, *J*= 7.4 Hz, 2H), 2.35 (s, 3H), 1.83 (q, *J*= 7.5 Hz, 6H), 0.79 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd. for $C_{23}H_{27}NOS$: C, 75.57; H, 7.45; N, 3.83%. Found: C, 75.90; H, 7.78; N, 3.61%.

Directed Lithiation of 10 Followed by a Reaction with Ethyl Chloroformate. This reaction was carried out in a similar manner as described for the lithiation of **7**. Compound **10** (171 mg, 0.397 mmol) and ethyl chloroformate (63 μL, 0.655 mmol) was used to give **12** (128 mg, 64%) as a white solid and **13** (11 mg, 6%) as colorless oil.

Ethyl 1-(2,2-diethylbutanoyl)-3-triisopropylsilyloxymethylindole-7-carboxylate (12): Mp 83.0-83.5 °C; IR (KBr) 2943, 2866, 1716, 1703, 1608, 1582, 1471, 1415, 1383, 1366, 1344, 1307, 1277, 1254, 1200,

1159, 1137, 1103, 1059, 946, 881, 837, 824, 792, 746, 683, 660 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.74 (s, 1H), 7.62 (dd, *J*= 1.2 and 7.5 Hz, 1H), 7.54 (dd, *J*= 1.2 and 7.5 Hz, 1H), 7.28 (t, *J*= 7.5 Hz, 1H), 4.99 (d, *J*= 1.2 Hz, 2H), 4.39 (q, *J*= 7.1 Hz, 2H), 1.90 (q, *J*= 7.5 Hz, 6H), 1.38 (t, *J*= 7.1 Hz, 3H), 1.31-1.06 (m, 21H), 0.87 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd. for $C_{29}H_{47}NO_4Si$: C, 69.42; H, 9.44; N, 2.79%. Found: C, 69.39; H, 9.40; N, 2.73%.

Ethyl 1-(2,2-diethylbutanoyl)-3-triisopropylsilyloxymethylindole-2-carboxylate (13): IR (neat) 2943, 2867, 1719, 1548, 1461, 1409, 1384, 1330, 1222, 1138, 1128, 1086, 1065, 883, 838, 817, 744, 688, 667 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.04 (d, *J*= 8.0 Hz, 1H), 7.39 (d, *J*= 8.5 Hz, 1H), 7.34 (ddd, *J*= 1.2, 6.7 and 8.5 Hz, 1H), 7.18 (ddd, *J*= 1.2, 6.7 and 8.0 Hz, 1H), 5.32 (s, 2H), 4.38 (q, *J*= 7.1 Hz, 2H), 1.67 (q, *J*= 7.4 Hz, 6H), 1.39 (t, *J*= 7.1 Hz, 3H), 1.26-1.04 (m, 21H), 0.79 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{29}H_{47}NO_4Si$ (M^+): 501.3275. Found 501.3246.

Directed Lithiation of 11 Followed by a Reaction with Ethyl Chloroformate. This reaction was carried out in a similar manner as described for the lithiation of **11** to give **14** (147 mg, 72%) as a white solid and **15** (14 mg, 7%) as colorless oil.

Ethyl 1-(2,2-diethylbutanoyl)-3-(2-triisopropylsilyloxyethyl)indole-7-carboxylate (14): Mp 71.5-72.0 °C; IR (KBr) 2962, 2943, 2865, 1723, 1697, 1583, 1460, 1421, 1389, 1365, 1351, 1299, 1274, 1260, 1198, 1185, 1162, 1143, 1104, 1083, 1054, 1017, 997, 930, 903, 881, 825, 800, 744, 734, 680, 661 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.68 (s, 1H), 7.62 (dd, *J*= 1.2 and 7.5 Hz, 1H), 7.53 (dd, *J*= 1.2 and 7.5 Hz, 1H), 7.28 (t, *J*= 7.5 Hz, 1H), 4.39 (q, *J*= 7.1 Hz, 2H), 3.99 (t, *J*= 6.4 Hz, 2H), 2.94 (t, *J*= 6.4 Hz, 2H), 1.90 (q, *J*= 7.5 Hz, 6H), 1.38 (t, *J*= 7.1 Hz, 3H), 1.14-0.99 (m, 21H), 0.87 (t, *J*= 7.5 Hz, 9H). *Anal.* Calcd. for $C_{30}H_{49}NO_4Si$: C, 69.86; H, 9.58; N, 2.72%. Found: C, 69.86; H, 9.41; N, 2.87%.

Ethyl 1-(2,2-diethylbutanoyl)-3-(2-triisopropylsilyloxyethyl)indole-2-carboxylate (15): IR (neat) 2943, 2867, 1713, 1543, 1460, 1413, 1384, 1329, 1296, 1251, 1219, 1129, 1102, 1069, 1014, 883, 839, 743, 682 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.70 (d, *J*= 8.0 Hz, 1H), 7.39 (d, *J*= 8.5 Hz, 1H), 7.33 (ddd, *J*= 1.2, 6.8 and 8.5 Hz, 1H), 7.18 (ddd, *J*= 1.2, 6.8 and 8.0 Hz, 1H), 4.39 (q, *J*= 7.1 Hz, 2H), 3.93 (t, *J*= 7.2 Hz, 2H), 3.30 (t, *J*= 7.2 Hz, 2H), 1.68 (q, *J*= 7.4 Hz, 6H), 1.39 (t, *J*= 7.1 Hz, 3H), 1.09-0.95 (m, 21H), 0.79 (t, *J*= 7.4 Hz, 9H). HREIMS m/z. Calcd. for $C_{30}H_{49}NO_4Si$ (M^+): 515.3431. Found 515.3432.

Deprotection of DEB group. The following procedures are representative.

3-Methyl-7-(phenylthio)indole (16). To a solution of **8i** (95.3 mg, 0.26 mmol) in THF (5.0 mL) was added *tert*-BuOK (234 mg, 2.1 mmol) and deionized water (9.4 μL, 0.52 mmol) at room temperature. After being stirred for 30 min at the same temperature, the reaction mixture was concentrated and the residue was dissolved in water. The mixture was extracted with ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2, hexane-ethyl acetate = 10:1) to give **16** (58.6 mg, 96%) as a colorless needles: Mp 82.5-83.0 °C (hexane-CH_2Cl_2); IR (KBr): 3385, 1618, 1583, 1478, 1437, 1343, 1322, 1224, 1205, 1077, 1047, 1024, 895, 811, 786, 735, 688, 623 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.12 (br s, 1H), 7.65 (d, *J*= 8.0 Hz, 1H), 7.43 (dd, *J*= 0.8 and 7.1 Hz, 1H), 7.22-7.06 (m, 6H), 6.94 (br d, *J*= 1.1 Hz, 1H), 2.34 (d, *J*= 1.1 Hz, 3H). *Anal.* Calcd. for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85%. Found: C, 75.43; H, 5.59; N, 5.88%.

7-Bromo-3-methylindole (17). This compound was prepared from **8g** in a similar manner as described above except for the reaction time (2 h) (92 mg, 85%): IR (neat) 3428, 3061, 2917, 2888, 2862, 1618, 1568, 1551, 1488, 1435, 1401, 1383, 1343, 1326, 1231, 1200, 1145, 1076, 1047, 878, 826, 801, 775, 734, 571, 544 cm^{-1}; ^{1}H-NMR (300 MHz) δ 8.03 (br s, 1H), 7.51 (d, *J*= 7.5 Hz, 1H), 7.33 (d, *J*= 7.5 Hz, 1H), 6.99 (t, *J*= 7.5 Hz, 2H), 2.31 (d, *J*= 0.8 Hz, 3H). HREIMS m/z. Calcd. for C_9H_8BrN (M^+): 208.9840. Found 208.9852.

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17. Four different indoles were identified by GC-MS analysis of the crude methylation product [MS spectrum was taken at an ionizing voltage of 70 eV on a JEOL JMS-AMII 15. GC analysis: J&W capillary column DB-1 (ID 0.32 mm, length 30 m), 180 °C]. 1-(DEB)indole (**2**): R_t = 6.2 min; m/z 243 (M^+). 1-(DEB)-2-methylindole: R_t = 7.2 min; m/z 257 (M^+). 1-(DEB)-7-methylindole: R_t = 8.5 min; m/z 257 (M^+). 1-(DEB)-2,7-dimethylindole: R_t = 10.1 min; m/z 271 (M^+).
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23. For successful lithiation of 1-(DEB)indoles, use of fresh *sec*-BuLi is essential. If aged *sec*-BuLi was used, considerable amount of 7-(DEB)indoles were formed. We kept a bottle of *sec*-BuLi under Ar atmosphere in a refrigerator to prevent deterioration.