Chemistry of Indolo[1,2-c]quinazoline: An Approach to the Marine Alkaloid Hinckdentine A

Adil D. Billimoria and Michael P. Cava*

The University of Alabama, Department of Chemistry, Box 870336, Tuscaloosa, Alabama 35487

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The basic chemistry of indolo[1,2-c]quinazoline (**2**) has been investigated for the first time. In addition, some attempts to elaborate **2** into the pentacyclic system of the marine alkaloid hinckdentine A (**1A**) are described.

Introduction

Hinckdentine A (**1A**)[1] is an unusual marine alkaloid that has been isolated from the bryozoan *Hincksinoflustra denticulata*, collected off the eastern coast of Tasmania. Hinckdentine A (**1A**) has a unique molecular skeleton consisting of a seven membered lactam ring fused to a tribromoindolo[1,2-c]quinazoline. Certain derivatives of indolo[1,2-c]quinazoline (**2**) are known to have cataleptogenic activity[2,3] making hinckdentine A (**1A**) a potential biologically active molecule. The parent indolo[1,2-c]quinazoline (**2**) was first synthesized in 1956[4] but no chemical transformations of it have been carried out, although a few derivatives have been prepared by independent syntheses.[5–10] We now report a study of the basic chemistry of indolo[1,2-c]quinazoline (**2**) and some attempts to employ it as a synthon for the construction of the pentacyclic skeleton (**1B**) of hinckdentine A.

Results and Discussion

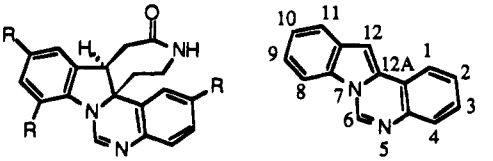
The only study aimed at the synthesis of hinckdentine A which has so far appeared in the literature is by the Joule group.[11] In this approach, attempts to synthesize a model starting compound by a Diels–Alder addition of 2-phenylindole to 2-(benzenesulfonyl)-1,3-butadiene failed.

Our proposed plan for the construction of the seven-membered lactam ring involved the elaboration from position 12 of the tetracycle **2** of a side chain bearing a terminal selenophenyl group. The carbon–selenium bond could then be homolytically cleaved to form a radical which might cyclize, affording the basic skeleton of hinckdentine A (**1B**).

The literature synthesis of **2** involves the intermediacy of 2-(2′-aminophenyl)indole (**5**), which is obtained by the Fischer indole cyclization of the phenylhydrazone of 2′-aminoacetophenone (**3**). Both zinc chloride[4] and polyphosphoric acid (PPA)[5] have been used to effect the cyclization. The PPA method gave, in our hands, a yield of not more than 50%. However, we found that cyclization of the hydrazone using a mixture of methanesulfonic acid and phosphorus pentoxide at 85 °C proceeds in 90% yield. Treatment of the 2-(2′-aminophenyl)indole (**5**) with hot formic acid afforded **2** in 73% yield.

The reduction[12] of **2** was carried out with sodium borohydride in methanol to give 5,6-dihydroindolo[1,2-c]quinazoline (**6**) in 80% yield. The nitrogen of the

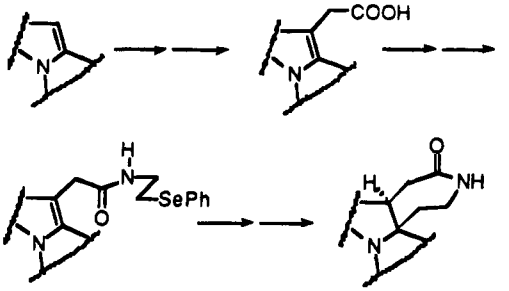
Scheme 1



1A : R = Br **2**

1B : R = H

Scheme 2



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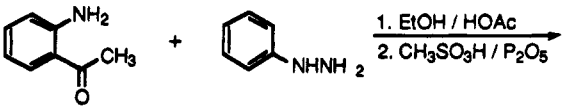
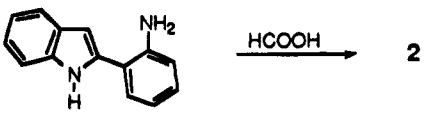


3 **4**



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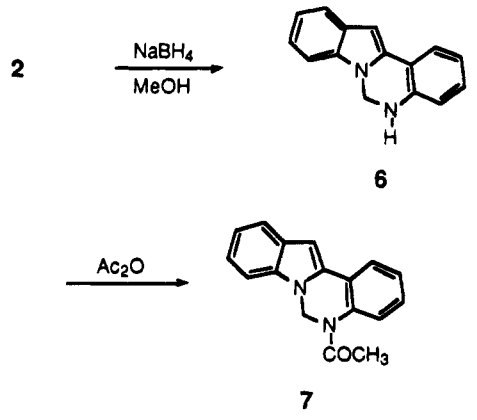
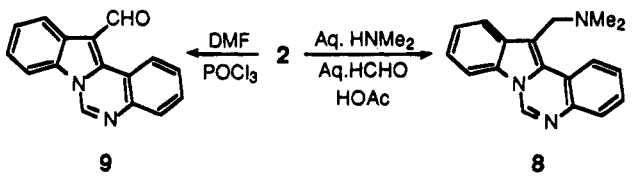
Scheme 4



Scheme 5



dihydropyrimidine ring of **6** was readily acetylated in 91% yield to give 5-acetyl-5,6-dihydroindolo[1,2-*c*]quinazoline (**7**).

The position 12 of indolo[1,2-*c*]quinazoline (**2**) corresponds to position 3 of a simple indole. Mannich reaction[13] of **2** with aqueous dimethylamine and aqueous formaldehyde in acetic acid gave the 12-substituted gramine analog **8** in 82% yield, demonstrating that position 12 is indeed most easily attacked by an electrophile.

Vilsmeier–Haack formylation[14] of **2** with dimethylformamide and phosphorous oxychloride also occurred readily to give the 12-formyl derivative **9** in 87% yield.

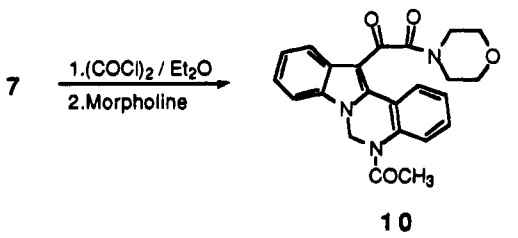
The importance of the Mannich reaction and the Vilsmeier–Haack formylation lies in the fact that they both provide a handle at position 12 of indolo[1,2-*c*]-quinazoline (**2**) for further synthetic elaboration.

Surprisingly, the attempted reaction of **2** with oxalyl chloride, followed by treatment of the product with morpholine, did not give the desired keto amide but instead **2** was recovered. A possible explanation of this result is that oxalyl chloride may rapidly form an acylium salt at N-5 of **2**, deactivating the system to further substitution and leading to the regeneration of **2** on aqueous workup. In accord with this hypothesis, the reaction of **7** with oxalyl chloride followed by the treatment of the product with morpholine did give the desired keto amide **10** in 75% yield.

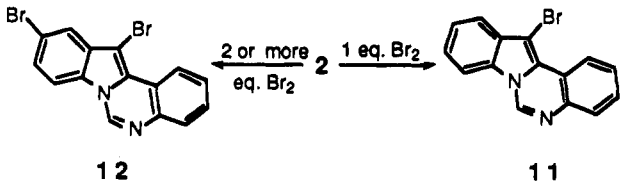
The natural product hinckdentine A (**1A**) contains three bromo substituents. The direct bromination of **2** with 1 equiv of bromine in pyridine at ice-bath conditions gave the 12-bromo compound **11** in 75% yield along with 10% of the 10,12-dibromo compound **12**. Use of 2 equiv of bromine under similar conditions leads to the formation of **12** in 80% yield, as well as a small amount of **11**.

Use of more than 2 equiv of bromine gave only the dibromo product. This result suggests that the three bromines of the natural product **1A** are not introduced

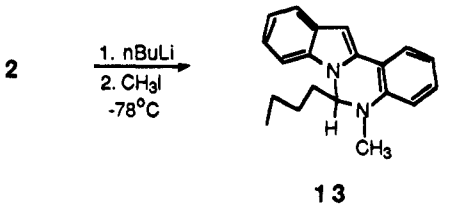
Scheme 6



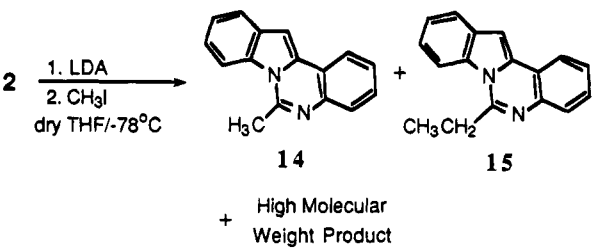
Scheme 7



Scheme 8



Scheme 9



biogenetically from a fully aromatic indolo[1,2-*c*]quinazoline precursor.

6-Methylindolo[1,2-*c*]quinazoline (**14**) was synthesized by reacting 2-(2′-amino)phenyl)indole (**5**) with acetyl chloride.[4] The metalation reaction of **2** with 1 equiv n-butyllithium in anhydrous tetrahydrofuran at −78 °C followed by the addition of methyl iodide did not give either 6-methyl or 12-methyl indolo[1,2-*c*]quinazoline, but rather the 5,6 addition product **13** in 65% yield.

Instead of abstracting the proton from the position 6 of **2**, the butyl anion adds at position 6 across the 5,6 double bond putting a negative charge on the nitrogen at position 5. This negative charge was then quenched on addition of the methyl iodide, giving the addition product **13**.

When 1.25 equiv of the non-nucleophilic base, lithium diisopropylamide (LDA), was used at −78 °C, followed by the addition of methyl iodide, **14** was indeed obtained in about 70% yield. In addition, about 5% of the 6-ethyl derivative **15** was also obtained along with 10% of a high molecular weight product.

The ethyl derivative **15** is formed through the intermediacy of **14**. The excess LDA forms an anion by abstracting a proton from the methyl group at position 6, which is then quenched by the excess methyl iodide.

The unknown product has been tentatively assigned the dimeric structure **16** based on the NMR and mass spectroscopy studies and elemental analysis. We propose

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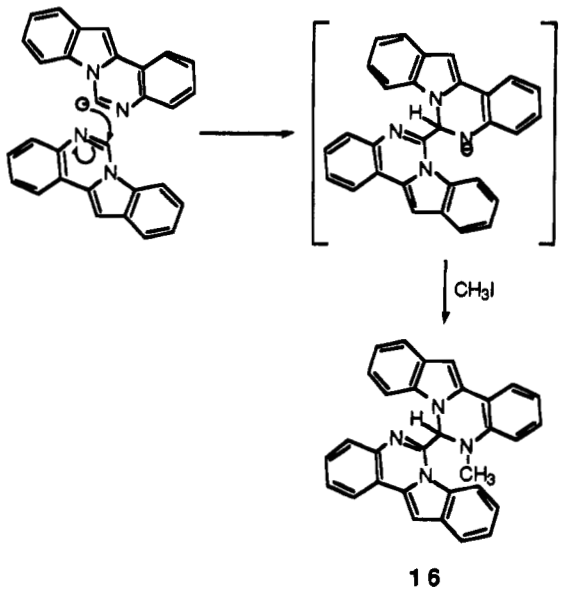
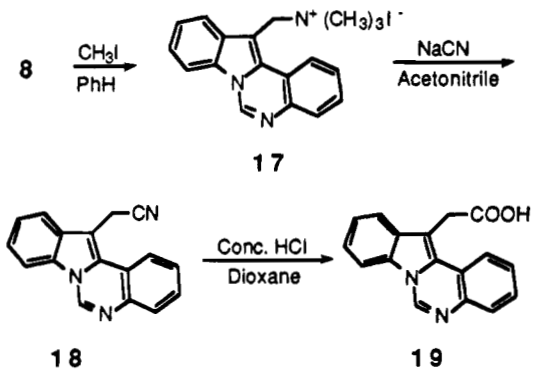
Scheme 10



Scheme 11



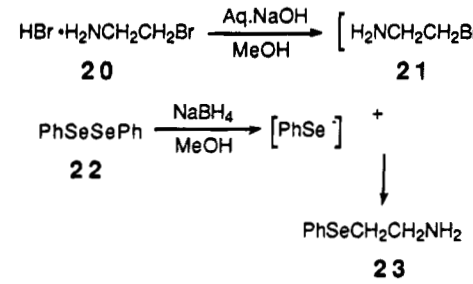
that the anion of **2**, which is formed at position 6, attacks unreacted **2** at position 6, giving an anion at position 5, which is quenched on addition of methyl iodide to give product **16**.

The elemental analysis is consistent with the structure **16**. The high temperature (60 °C) proton NMR resolves the spectrum to some extent as compared to that done at room temperature and the integration matches perfectly for the dimeric ring system with one methyl group. The decoupling, NOE, and COSY experiments were not of much assistance. The methine proton on the carbon atom between the two nitrogen atoms is apparently embedded in the aromatic region and hence cannot be seen. In the mass spectroscopic analysis, the molecular ion peak appears at 450 and the fragmentation pattern is consistent with the proposed formulation.

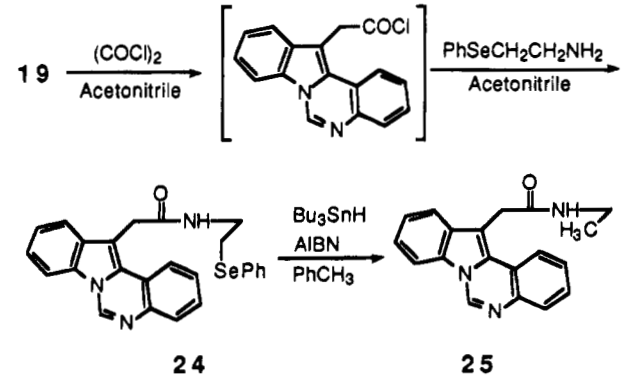
Since our proposed strategy for constructing the seven-member lactam ring of the hinckdentine A (**1A**) involved functionalizing position 12 of **2**, the gramine **8** was quaternized with methyl iodide in benzene to give the methiodide **17** in 97% yield. The trimethylammonium group of **17** was displaced by cyanide ion to give the nitrile **18** in 70% yield. The hydrolysis of **18** to the corresponding acid **19** was carried out with concentrated hydrochloric acid in dioxane in 80% yield.

In order to add an appropriate side chain bearing a terminal phenylseleno group, a new potentially versatile reagent, 2-(phenylseleno)ethylamine (**23**) was synthesized. The amine **21**, liberated by treating the hydrobromide salt of 2-bromoethylamine (**20**) with aqueous sodium hydroxide, was reacted with the phenylseleno anion, formed by the sodium borohydride reduction of diphenyl diselenide (**22**), to give **23** in 82% yield.

Scheme 12



Scheme 13



The treatment of acid **19** with oxalyl chloride gave the corresponding acid chloride which, without isolation, was reacted with **23** to furnish the phenylseleno derivative **24** in 30% yield. The reason for the low yield in this step may be attributed to the basicity of nitrogen N-5 of **19** which competitively forms an acylium salt with oxalyl chloride. This salt precipitates out, preventing further reaction at C-12.

The radical cyclization of **24** using tributyltin hydride was attempted under a variety of conditions, using the radical initiators azobis(isobutyronitrile) (AIBN) and tris-(trimethylsilyl)silane, but these reactions resulted only in the formation of the ethyl derivative **25** in good yield.

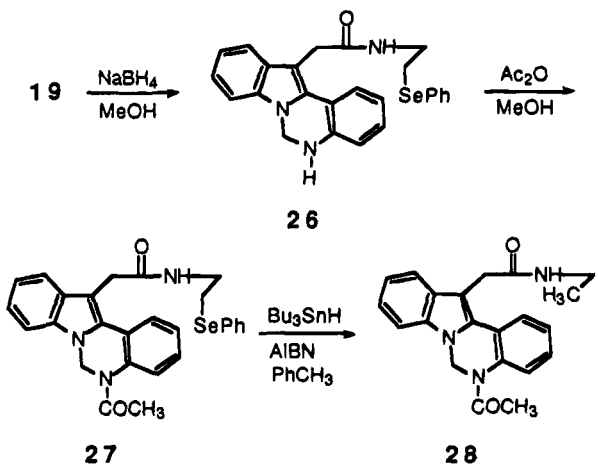
It seemed possible that destroying the aromaticity of the pyrimidine ring by reducing the 5,6 double bond of **24** might facilitate the desired radical cyclization. This was accomplished by treatment of **24** with sodium borohydride, to give the 5,6-dihydro seleno derivative **26**, which was then acetylated to afford **27** in over 70% overall yield.

Unfortunately the radical cyclization of **27** once again failed, and the open chain ethyl derivative **28** was produced in good yield.

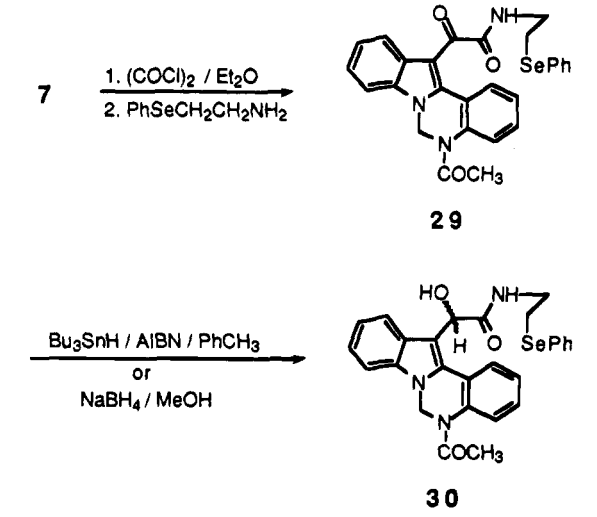
Finally, it seemed possible that a carbonyl functionality in the α position to C-12 of **2** could activate the 12–12A double bond toward a radical addition reaction. To test this possibility, amide **7** was treated with oxalyl chloride in anhydrous diethyl ether to afford the corresponding keto acid chloride, which was reacted with **23** to give the phenylseleno derivative **29** in 75% yield.

Interestingly, when **29** was subjected to the radical cyclization conditions, it gave the alcohol **30** in 81% yield. No cyclized product or open chain ethyl compound was obtained. The same alcohol **30** could be prepared by the sodium borohydride reduction of the **29.**

Scheme 14



Scheme 15



A possible explanation of this result is that the ketonic carbonyl group is reduced rapidly, giving an *O*-tributylstannyl derivative of alcohol **30**. The bulky tin substituent may sterically prevent further radical attack at the selenium atom even when a large excess of tributyltin hydride is used.

Experimental Section

Melting points were determined on a MEL-TEMP II Laboratory Devices apparatus and are not corrected. NMR and mass spectral data were obtained using Bruker AM 360 and VG Auto Spec spectrometers, respectively. Elemental analyses were performed by the Atlanta Microlab Inc., Atlanta, GA. All chromatography was carried out using silica columns.

2-(2′-Aminophenyl)indole (5). Methanesulfonic acid (100.0 mL) was heated to 80 °C and phosphorus pentoxide (13.5 g) was added to it with stirring until it dissolved completely. The phenylhydrazone of **3**[4] (10.0 g, 44.4 mmol) was slowly added maintaining the temperature between 80 and 100 °C. The solution was then further heated at 80 °C for 30 min. The reaction mixture was then cooled to room temperature and poured over crushed ice containing sodium hydroxide (65.0 g). The solid precipitate was filtered, washed with water, and dried to afford the crude product which was crystallized from ethanol (8.2 g; 90%): mp 146 °C (lit.[4] 148–150 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.10 (bs, 2H), 6.73 (s, 1H), 6.85 (m, 2H), 7.20 (m, 3H), 7.41 (m, 2H), 7.65 (d, 1H, J = 1.67 Hz), 8.50 (bs, 1H); *m/z* (relative intensities) 208 (M^+, 100.0), 206 (23.5), 180 (21.3).

Indolo[1,2-*c*]quinazoline (2). 2-(2′-Aminophenyl)indole (**5**) (1.0 g, 4.8 mmol) was added to formic acid (88%, 7.5 mL) and the solution was heated at 90 °C for 1.0 h. The reaction mixture was then cooled to room temperature and poured over crushed ice. The solid precipitate was filtered, washed with water, and dried to afford crude **2** which was crystallized from ethanol (0.78 g, 73%): mp 201 °C (lit.[4] 200–201 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.06 (s, 1H), 7.47 (m, 4H), 7.80 (t, 2H, J = 7.15 Hz), 7.75 (d, 1H, J = 9.00 Hz), 8.05 (d, 1H, J = 8.80 Hz), 9.01 (s, 1H); *m/z* (relative intensities) 218 (M^+ 100.0), 190 (25.0), 164 (9.7), 109 (17.3).

5,6-Dihydroindolo[1,2-*c*]quinazoline (6). To a solution of indolo[1,2-*c*]quinazoline (**2**) (1.0 g, 4.59 mmol) in methanol (50.0 mL) was added sodium borohydride (0.5 g, 13.2 mmol), and the reaction mixture was refluxed for 5.0 h under nitrogen atmosphere. It was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was extracted into methylene chloride (25.0 mL) and the organic extract was washed with water (3 × 20.0 mL) and dried over sodium sulfate. The solvent was then removed under reduced pressure and the residue was chromatographed with hexanes/methylene chloride 1:1 as eluent to give **6** (0.82 g, 80%): mp 246.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.28 (bs, 1H), 5.34 (s, 2H), 6.77 (d, 1H, J = 7.99 Hz), 6.80 (s, 1H), 6.92 (t, 1H, J = 7.51 Hz), 7.12 (m, 4H), 7.62 (d, 1H, J = 7.65 Hz), 7.67 (d, 1H, J = 8.20 Hz); *m/z* (relative intensity) 220 (M^+, 77.1), 219 (100.0), 218 (61.4), 190 (20.3). Anal. Calcd for $C_{15}H_{12}N_2$ C: 81.81; H, 5.46; N, 12.73. Found: C, 81.78; H, 5.48; N, 12.67.

5-Acetyl-5,6-dihydroindolo[1,2-*c*]quinazoline (7). To a solution of **6** (0.8 g; 3.64 mmol) in pyridine (15.0 mL), was added acetic anhydride (2.5 mL) and the reaction mixture was refluxed for 5.0 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was extracted into methylene chloride (25.0 mL). The organic extract was washed with water (3 × 20.0 mL) and was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was then chromatographed with hexanes/methylene chloride 1:1 as eluent to give **7** (0.87 g, 91%); mp 136.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.21 (bs, 3H), 5.87 (bs, 2H), 6.86 (s, 1H), 7.12 (t, 1H, J = 7.43 Hz), 7.23 (t, 1H, J = 6.0 Hz), 7.30 (m, 3H), 7.43 (d, 1H, J = 8.1 Hz), 7.62 (d, 1H, J = 7.8 Hz), 7.77 (m, 1H); *m/z* (relative intensity) 262 (61.5), 219 (100.0), 190 (21.3), 165 (24.2). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.64. Found: C, 77.75; H, 5.39; N, 10.72.

Gramine 8. A solution of dimethylamine (40%, 0.64 mL) and formaldehyde (37%, 0.4 mL) in acetic acid (20.0 mL) was stirred for 10 min at room temperature. Indolo[1,2-*c*]quinazoline (**2**) (2.0 g, 9.2 mmol) was added and the solution was stirred for 3.0 h at room temperature. The reaction mixture was then poured over crushed ice and then basified with aqueous sodium hydroxide (20% solution). The solid that precipitated out was filtered, washed with water, and dried to give crude **8** which was crystallized from ethanol (2.1 g, 82%): mp 125 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.42 (s, 6H), 3.94 (s, 2H), 7.50 (m, 4H), 7.85 (m, 4H), 8.45 (s, 1H), 9.00 (s, 1H); *m/z* (relative intensities) 275 (M^+, 5.7), 231 (100.0), 218 (4.4). Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.42; H, 6.20; N, 15.60.

12-Formylindolo[1,2-*c*]quinazoline (9). Phosphorous oxychloride (0.78 g, 5.08 mmol) was slowly added to *N,N*-dimethylformamide (30.0 mL) at 0 °C and the solution was stirred for 15 min. Indolo[1,2-*c*]quinazoline (**2**) (1.0 g; 4.59 mmol) was added and the mixture was stirred for a further 15 min and then warmed to 60 °C for a further 30 min. It was then cooled to room temperature and poured over crushed ice. The precipitate was filtered, washed with water (3 × 20.0 mL) and boiled with aqueous sodium hydroxide (5%, 20.0 mL). The solid was then filtered, washed with water till free of alkali, and dried. The crude material was crystallized from methanol to give the aldehyde **9** (0.98 g, 87%): mp 233.7 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.69 (t, 1H, J = 7.63 Hz), 7.89 (t, 1H, J = 7.49 Hz), 7.98 (d, 2H, J = 8.15 Hz), 8.53 (d, 1H, J = 7.87 Hz), 9.05 (d, 1H, J = 7.82 Hz), 9.18 (s, 1H), 10.91 (s, 1H); HRMS calcd for $C_{16}H_{10}N_2O$ 246.079313,

found 246.078811. Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.05; H, 4.07; N, 11.38. Found: C, 77.91; H, 4.10; N, 11.34.

Morpholine Derivative (10). To a chilled solution of **7** (1.0 g, 3.82 mmol) in anhydrous diethyl ether (100.0 mL) (nitrogen atmosphere) was added oxalyl chloride (0.5 g, 3.93 mmol). The mixture was stirred for 1.0 h at 0 °C, after which it was warmed to room temperature and further stirred for 2.0 h. The yellow precipitate of the acid chloride was filtered and washed with diethyl ether (3 × 15 mL). The resultant solid was suspended in anhydrous diethyl ether (50.0 mL). Morpholine (0.62 g, 7.13 mmol) was added and the mixture was stirred overnight at 25 °C. The solid obtained was filtered, washed with diethyl ether (3 × 15 mL), and dried. Crystallization of the crude product from methanol afforded **10** (0.86 g, 75%): mp 246.3 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.43 (t, 2H, J = 4.57 Hz), 3.60 (t, 2H, J = 4.75 Hz), 3.83 (s, 4H), 5.91 (bs, 2H), 7.34 (m, 3H), 7.56 (m, 3H), 7.81 (d, 1H, J = 8.00 Hz), 8.77 (d, 1H, J = 8.04); *m/z* (relative intensity) 403 (M^+, 1.0), 359 (79.5), 316 (38.2), 289 (58.4), 245 (62.6), 218 (100.0), 190 (41.8). Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.49; H, 5.21; N, 10.42. Found: C, 68.23; H, 5.24; N, 10.52.

12-Bromoindolo[1,2-c]quinazoline (11). To a chilled solution of **2** (0.5 g, 2.29 mmol) in pyridine (25.0 mL), was added bromine (0.37 g, 2.31mmol) slowly. The reaction mixture was stirred for 15 min at 0 °C and then poured into ice–water (100.0 mL). The precipitate was filtered, washed with water (3 × 25 mL), and dried. The crude product was chromatographed using methylene chloride as an eluent to give **11** (0.51 g, 75%): mp 204.7 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (m, 4H), 7.79 (t, 2H, J = 9.15 Hz), 7.89 (d, 1H, J = 7.99 Hz), 8.92 (s, 1H), 8.98 (d, 1H, J = 7.27 Hz); HRMS calcd for $C_{15}H_9BrN_2$ 295.994909, found 295.994950.

10,12-Dibromoindolo[1,2-c]quinazoline (12). To a chilled solution of **2** (0.5 g, 2.29 mmol) in pyridine (25.0 mL), was added bromine (0.73 g, 4.56 mmol) slowly. The reaction mixture was stirred at 0 °C for 30 min after which it was warmed to room temperature, stirred for a further 1.0 h, and then was poured into ice–water (100.0 mL). The precipitate was filtered, washed with water (3 × 25.0 mL), and dried. The crude material was chromatographed using methylene chloride as an eluent to give **12** (0.69 g, 80%): mp 283.5 °C; *m/z* (relative intensity %): 376 (M^+ 100.0), 297 (29.4), 216 (35.8), 163 (29.0); Anal. Calcd for $C_{15}H_8Br_2N_2$: C, 47.87; H, 2.13; N, 7.45. Found: C, 47.95; H, 2.17; N, 7.40.

Compound 13. To a solution of **2** (1.00 g; 4.59 mmol) in anhydrous tetrahydrofuran (50.0 mL) maintained at −78 °C under a nitrogen atmosphere was added n-butyllithium (2.3 mL of 2.0 M in hexanes, 4.59 mmol) and stirring was continued for 15 min. Methyl iodide (0.66 g, 4.59 mmol) was added and the reaction was warmed to room temperature and stirred for 1.5 h. The solvent was removed under reduced pressure and the residue was extracted into methylene chloride (25.0 mL). The organic extract was washed with water (3 × 25.0 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed using hexanes/methylene chloride 9:1 as eluent to give **13** as an oil (0.80 g, 65%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.68 (t, 3H, J = 6.98 Hz), 1.10 (m, 4H), 1.75 (m, 2H), 2.95 (s, 3H), 5.50 (dd, 1H, J = 5.30, 1.38 Hz), 6.68 (d, 1H, J = 8.07 Hz), 6.71 (s, 1H), 6.85 (t, 1H, J = 7.49 Hz), 7.15 (m, 3H), 7.22 (d, 1H, J = 7.97 Hz), 7.65 (m, 2H); HRMS calcd for $C_{20}H_{22}N_2$ 290.178229, found 290.180954.

6-Methylindolo[1,2-c]quinazoline (14), 6-Ethylindolo-[1,2-c]quinazoline (15), and Dimer 16. Anhydrous tetrahydrofuran (10.0 mL) was cooled to −78 °C and n-butyllithium (0.68 mL of 2.14 M, 1.44 mmol) was added under a nitrogen atmosphere, followed by the addition of diisopropylamine (0.15 g, 1.44 mmol). The reaction mixture was stirred for 30 min to generate lithium diisopropylamide in situ. Indolo[1,2-c]-quinazoline (**2**) (0.25 g, 1.15 mmol), dissolved in anhydrous tetrahydrofuran (10.0 mL), was added, and the stirring was continued at −78 °C for 30 min. Methyl iodide (0.16 g, 1.15 mmol) was added and the solution was then warmed to room temperature and stirred for further 1.0 h. The solvent was removed under reduced pressure and the residue was extracted into methylene chloride (15.0 mL). The organic extract was washed with water (3 × 10.0 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed using neat methylene chloride as an eluent to give **14** (0.19 g, 70%), **15** (0.013 g, 5%), and **16** (0.03 g, 10%).

Compound 14: mp 110.5 °C (lit.[4] 112–114 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.02 (s, 3H), 7.05 (s, 1H), 7.44 (t, 1H, J = 7.67 Hz), 7.54 (q, 2H, J = 7.20 Hz), 7.67 (t, 1H, J = 7.41 Hz), 7.88 (t, 2H, J = 7.69 Hz), 7.98 (dd, 2H, J = 2.92, 4.88 Hz); *m/z* (relative intensity) 232 (M^+, 100.0), 218 (12.9), 204 (12.1), 190 (22.8). Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.76; H, 5.17; N, 12.07. Found: C, 82.61; H, 5.15; N, 12.09.

Compound 15: mp 96.7 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.55 (t, 3H, J = 7.25 Hz), 3.39 (q, 2H, J = 6.73 Hz), 7.15 (s, 1H), 7.35 (m, 3H), 7.45 (t, 1H, J = 10.26 Hz), 7.68 (d, 1H, J = 12.6 Hz), 7.78 (d, 1H, J = 12.1 Hz), 7.98 (m, 2H); *m/z* (relative intensity) 246 (M^+, 35.0), 245 (100.0), 231 (13.4), 218 (33.4), 190 (30.8); HRMS calcd for $C_{17}H_{14}N_2$: 246.009762, found 246.011365.

Compound 16: mp 225.2 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.87 (d, 1H, J = 7.92 Hz), 7.40 (bm,14H), 7.91 (d, 2H, J = 8.39 Hz), 8.01 (bs, 1H), 8.45 (bs, 1H); *m/z* (relative intensity) 450 (M^+, 0.5), 434 (1.0), 233 (29.0), 218 (100.0), 190 (24.2). Anal. Calcd for $C_{31}H_{22}N_4$: C, 82.67; H, 4.88; N, 12.45. Found: C, 82.55; H, 4.99; N, 12.31.

Nitrile 18. To a solution of gramine **8** (5.0 g; 18.18 mmol) in benzene (25.0 mL), methyl iodide (2.8 g; 19.7 mmol) was added. After stirring for 12.0 h at room temperature, the precipitate was filtered, washed with benzene, and dried to give **17** (7.3 g; 97%): mp dec > 210 °C. To a suspension of **17** (5.0 g; 12.0 mmol) in aqueous acetonitrile (200.0 mL, 25% v/v water) was added sodium cyanide (0.73 g; 14.9 mmol), and the mixture was refluxed for 5.0 h. On cooling to room temperature, white flaky crystals of **18** separated out. The crystalline product was filtered, washed with acetonitrile, and dried (2.15 g, 70%): mp 226 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.25 (s, 2H), 7.60 (m, 5H), 7.90 (m, 3H), 9.00 (s, 1H); *m/z* (relative intensities) 257 (M^+, 100.0), 231 (38.9), 217 (3.4). Anal. Calcd for $C_{17}H_{11}N_3$: C, 79.35; H, 4.31; N, 16.33. Found: C, 79.18; H, 4.37; N, 16.27.

Acid 19. To a solution of **18** (1.0 g; 3.89 mmol) in dioxane (30.0 mL) was added concentrated hydrochloric acid (50.0 mL), and the reaction mixture was refluxed for 96 h. The reaction mixture was cooled to room temperature when the acid precipitated out as the hydrochloride salt. The hydrochloride salt was filtered and washed thoroughly with water (250 mL). The crude product was dried and crystallized from methanol to afford the free acid **19** (0.8 g, 80%): mp 247 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.71 (s, 2H), 7.12 (d, 1H, J = 7.93 Hz), 7.20 (t, 1H, J = 7.53 Hz), 7.35 (m, 2H), 7.43 (t, 1H, J = 9.85 Hz), 7.62 (d, 1H, J = 8.99 Hz), 7.69 (d, 2H, J = 7.84 Hz), 7.78 (s, 1H), 8.30 (s, 1H); *m/z* (relative intensity) 276 (M^+, 60.7), 258 (24.4), 231 (100.0), 217 (56.9). Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.91; H, 4.35; N, 10.15. Found: C, 74.20; H, 4.80; N, 10.55.

2-(Phenylseleno)ethylamine (23). To the chilled solution of 2-bromoethylamine hydrobromide (**20**) (3.0 g, 14.6 mmol) in methanol (50.0 mL) was slowly added aqueous sodium hydroxide solution (40% w/v, 8.0 mL), and the reaction mixture was stirred for 30 min to liberate the amine **21**. To a chilled solution of diphenyl diselenide (**22**) (3.0 g, 9.6 mmol) in methanol (100.0 mL) (nitrogen atmosphere) was added an aqueous solution of sodium borohydride (2.0 g, 52.6 mmol in 5.0 mL water) slowly to produce sodium phenylselenolate. After stirring for 15 min, the solution of amine **21** was added slowly and the reaction mixture was stirred overnight at room temperature (nitrogen atmosphere). The solvent was removed under reduced pressure and the residue was extracted into methylene chloride (25.0 mL). The organic extract was washed with water (3 × 25.0 mL) and the solvent was again removed. The residue was extracted with dilute hydrochloric acid (2% v/v, 2 × 20.0 mL) and the aqueous acidic extract was washed with hexanes (3 × 15 mL) and basified with aqueous sodium hydroxide solution (20% w/v). The liberated amine **23** was extracted into methylene chloride (2 × 15.0 mL). The organic extract was washed with water (3 × 25.0 mL) and dried over

anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford **23** as a yellow liquid (2.95 g, 82%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.92 (m, 2H), 3.01 (m, 2H), 7.23 (t, 3H, J = 4.01 Hz), 7.40 (dd, 2H, J = 2.68, 4.16 Hz); HRMS calcd for $C_8H_{11}NSe$ 201.005670, found 201.005134.

Selenium Compound 24. To a solution of **19** (0.5 g, 1.6 mmol) in dry acetonitrile (25.0 mL) and *N,N*-dimethylformamide (0.1 mL) (nitrogen atmosphere) was added oxalyl chloride (0.5 g, 4.0 mmol) slowly, and the reaction mixture was stirred at room temperature for 5.0 h. The solvent and unreacted oxalyl chloride were removed by distillation under reduced pressure to give the acid chloride (0.51 g, 96%). The crude acid chloride was suspended in acetonitrile (15.0 mL) and pyridine (15.0 mL), and **23** (0.38 g, 1.9 mmol) was added. The reaction mixture was stirred (nitrogen atmosphere) for a period of 3.0 h at room temperature, the solvent was removed and the residue was extracted into methylene chloride (25.0 mL). The organic extract was washed with water (3 × 15 mL) and dried over anhydrous sodium sulfate. The removal of solvent under reduced pressure afforded crude **24** which was purified by crystallization from methanol (0.25 g, 30%): mp 194 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.80 (t, 3H, J = 6.84 Hz), 3.35 (q, 2H, J = 6.46 Hz), 4.19 (s, 2H), 6.15 (bt, 1H), 7.14 (m, 5H), 7.52 (m, 4H), 7.78 (t, 2H, J = 7.61 Hz), 7.96 (d, 1H, J = 7.78 Hz), 8.07 (d, 1H, J = 9.31 Hz), 8.98 (s, 1H); *m/z* (relative intensity) 459 (M^+, 22.8), 301 (77.7), 257 (42.5), 231 (100.0), 218 (48.7). Anal. Calcd for $C_{25}H_{21}N_3OSe$: C, 65.50; H, 4.59; N, 9.17. Found: C, 65.25; H, 4.64; N, 9.15.

Ethyl Derivative 25. To a solution of **24** (0.04 g, 0.09 mmol) in toluene (10.0 mL), was added AIBN (0.03 g) (nitrogen atmosphere). Tributyltin hydride (0.03 g, 0.1 mmol) was introduced and the reaction mixture was refluxed for 4.0 h. The solvent was then removed and the residue was chromatographed using benzene/ethyl acetate 1:1 as eluent to give **25** (0.02 g, 75%): mp 273.7 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.14 Hz), 3.19 (p, 2H, J = 6.37 Hz), 4.20 (s, 2H), 5.72 (bt, 1H), 7.50 (m, 4H), 7.78 (m, 2H), 7.98 (dd, 1H, J = 1.47, 5.77 Hz), 8.08 (dd, 1H, J = 1.97, 5.48 Hz), 9.00 (s, 1H); *m/z* (relative intensity) 303 (M^+, 56.5), 256 (11.8), 231 (100.0), 218 (22.5). Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.25; H, 5.61; N, 13.81. Found: C, 75.02; H, 5.63; N, 13.93.

Reduced Selenium Compound 26. To a solution of **24** (0.5 g; 1.0 mmol) in methanol (50.0 mL) was added sodium borohydride (0.5 g; 13.2 mmol), and the reaction mixture was refluxed for 10.0 h. The solvent was removed under reduced pressure and the residue was decomposed with water after which it was extracted into methylene chloride (10.0 mL). The organic extract was washed with dilute hydrochloric acid (2%, 3 × 10.0 mL) and water (3 × 15.0 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed using benzene/ethyl acetate 9:1 as eluent to give **26** (0.4 g, 80%): mp 139.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.80 (t, 2H, J = 6.86 Hz), 3.35 (q, 2H, J = 6.57 Hz), 3.99 (s, 2H), 5.37 (s, 2H), 6.25 (bt, 1H), 6.85 (d, 1H, J = 7.92 Hz), 6.98 (t, 1H, J = 7.48 Hz), 7.18 (m, 5H), 7.27 (m, 3H), 7.56 (d, 1H, J = 7.88 Hz), 7.62 (d, 1H, J = 7.92 Hz); *m/z* (relative intensity) 461 (M^+, 3.0), 301 (10.2), 231 (100.0), 203 (7.2). Anal. Calcd for $C_{25}H_{23}N_3OSe$: C, 65.22; H, 5.00; N, 9.13. Found: C, 65.09; H, 5.08; N, 9.19.

5-Acetyl Selenium Compound 27. To a solution of **26** (0.2 g; 0.44 mmol) in pyridine (5.0 mL), was added acetic anhydride (2.0 mL), and the mixture was heated at 80 °C for 30 min. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was extracted into methylene chloride and the organic extract was washed with water (3 × 10.0 mL) and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure and the residue was chromatographed using benzene/ethyl acetate 9:1 as eluent to give **27** (0.2 g, 90%): mp 145.2 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.20 (bs, 3H), 2.85 (t, 2H, J = 6.83 Hz), 3.40 (q, 2H, J = 6.60 Hz), 4.00 (s, 2H), 5.90 (bs, 2H), 6.25 (bt, 1H), 7.15 (m, 5H), 7.55 (m, 8H); *m/z* (relative intensities) 503 (14.9), 395 (7.52), 345 (47.2), 302 (29.2), 275 (91.4), 231 (100.0), 219 (39.8), 204 (20.2), 158 (19.3). Anal. Calcd for $C_{27}H_{25}N_3O_2Se$: C, 64.54; H, 4.97; N, 8.37. Found: C, 64.27; H, 4.99; N, 8.33.

Ethyl Derivative 28. To a solution of **27** (0.1 g, 0.2 mmol) in toluene (25.0 mL) were added AIBN (0.1 g) and tributyltin hydride (0.08 mL), and the mixture was refluxed under nitrogen for 1.0 h. The solvent was removed under reduced pressure after cooling the reaction mixture to room temperature and the residue was chromatographed using benzene/ethyl acetate 9:1 as eluent to give **28** (0.06 g, 79%): mp 229 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.16 Hz), 2.23 (s, 3H), 3.25 (p, 2H, J = 6.86 Hz), 3.99 (s, 2H), 5.79 (bt, 1H), 5.93 (bs, 2H), 7.21 (t, 1H, J = 8.01 Hz), 7.34 (t, 1H, J = 7.87, 8.15 Hz), 7.41 (m, 3H), 7.51 (d, 1H, J = 7.96 Hz), 7.60 (d, 1H, J = 7.95 Hz), 7.77 (m, 1H); *m/z* (relative intensity) 347 (M^+, 18.2), 275 (72.0), 233 (71.3), 208 (100.0), 180 (36.2). Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.62; H, 6.06; N, 12.10. Found: C, 72.62; H, 6.05; N, 12.16.

Compound 29. To a solution of **7** (1.0 g; 4.55 mmol) in anhydrous diethyl ether (100.0 mL) cooled to 0 °C was added oxalyl chloride (0.73 g, 5.7 mmol), and the mixture was stirred under nitrogen atmosphere for 1.0 h. It was then warmed to room temperature and stirred for another 1 h. The product precipitated out of the reaction mixture and was filtered. The residue was washed with diethyl ether (3 × 25.0 mL) and dried to give the acid chloride. The acid chloride was suspended in anhydrous diethyl ether (30.0 mL), 2-(selenophenyl)ethylamine (0.72 g, 3.58 mmol) was added, and the mixture was stirred at room temperature for 12.0 h (nitrogen atmosphere). The product precipitated out of the reaction mixture and was filtered, washed with diethyl ether (3 × 25.0 mL), and dried. The crystallization of the crude material from methanol afforded **29** (1.48 g, 75%): mp 152.3 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.09 (t, 2H, J = 6.69 Hz), 3.60 (q, 2H, J = 6.65 Hz), 5.80 (bs, 2H), 7.39 (m, 6H), 7.41 (d, 2H, J = 8.02 Hz), 7.49 (d, 1H, 8.08 Hz), 7.55 (m, 2H), 7.70 (d, 1H, J = 7.82 Hz), 7.99 (d, 1H, J = 7.91 Hz); *m/z* (relative intensity) 517 (M^+, 1.0), 359 (11.3), 289 (100.0), 245 (55.1), 219 (66.2). Anal. Calcd for $C_{27}H_{23}N_3O_3Se$: C, 62.67; H, 4.45; N, 8.12. Found: C, 62.83; H, 4.47; N, 8.06.

Alcohol 30. Method 1. To a solution of **29** (0.05 g, 0.1 mmol) in methanol (3.0 mL) was added sodium borohydride (0.05 g, 1.32 mmol), and the mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The solid which precipitated was filtered, washed with water, and dried to give **30** (0.05 g, 100%): mp 188.4 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.95 (m, 2H), 3.55 (m, 2H), 3.65 (s, 1H), 5.68 (s, 1H), 5.87 (bd, 2H), 6.65 (bt, 1H), 7.14 (t, 1H, J = 7.53 Hz), 7.19 (m, 3H), 7.31 (m, 1H), 7.50 (m, 6H), 7.67 (d, 1H, J = 8.02 Hz), 8.15 (d, 1H, J = 9.22 Hz); ^{13}C NMR ($CDCl_3$) δ 22.12 (s), 26.96 (d), 39.51 (d), 51.74 (d), 66.93 (t), 108.71 (q), 109.39 (t), 119.92 (t), 120.91 (t), 123.40 (t), 123.97 (t), 125.01 (t), 126.15 (q), 127.37 (t), 127.48 (q), 128.45 (t), 128.61 (q), 129.22 (t), 131.36 (q), 133.03 (t), 134.67 (q), 136.06 (q), 169.51 (CO), 172.53 (CO); *m/z* (relative intensity) 520 (M^+, 1.0), 503 (7.4), 359 (11.7), 345 (37.4), 301 (24.6), 276 (53.7), 231 (52.5), 219 (100.0), 190 (25.1). Anal. Calcd for $C_{27}H_{25}N_3O_3Se$: C, 62.42; H, 4.81; N, 8.08. Found: C, 62.59; H, 4.89; N, 8.12.

Method 2. To a solution of **29** (0.5 g, 0.96 mmol) in toluene (25.0 mL) were added AIBN (0.25 g) and tributyltin hydride (0.2 mL), and the reaction mixture was refluxed for 4.0 h (nitrogen atmosphere). The solvent was then removed under reduced pressure and the residue was subjected to chromatography using methanol/methylene chloride 1:100 as eluent to obtain **30** (0.41 g, 81%): mp 188.2 °C which is identical with the sample prepared via method 1.

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