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# A Versatile Synthesis of Unsymmetrical 3,3′-Bioxindoles: Stereoselective Mukaiyama Aldol Reactions of 2-Siloxyindoles with Isatins

J. Michael Ellis, Larry E. Overman,* Huw R. Tanner, and Jocelyn Wang

*Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025*

*leoverma@uci.edu*

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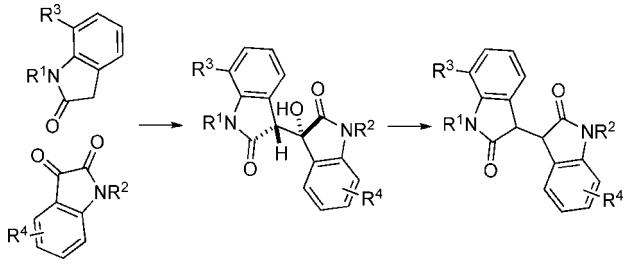

A new synthesis of 3,3′-bioxindoles is reported that is well suited for the preparation of unsymmetrical structures. In the key step, 3-hydroxy-3,3′-bioxindoles are constructed by Mukaiyama aldol reaction of 2-siloxyindoles with isatins. These tertiary carbinols are formed in high diastereoselectivities, with substitution at various positions of the isatin and the 2-siloxyindole being tolerated.

3,3′-Bioxindoles (**1**) are precursors to a variety of complex nitrogen heterocycles (Figure 1). In the alkaloid field, they have been used to synthesize a number of cyclotryptamine alkaloids,[1,2] exemplified by (+)-chimonanthine (**2**),[3] *meso*-calycanthine (**3**),[4] and (−)-idiospermuline (**4**).[5] 3,3′-Bioxindoles have also been employed to access heterocycles containing other polycyclic motifs, such as hexahydrodiazachrysene **5**.[6] In our laboratories, the reaction of dienolates of 3,3′-bioxindoles (**1**) with enantiomerically pure tartrate-derived dielectrophiles has been employed for the enantioselective construction of contiguous quaternary carbon stereocenters.[7,8]

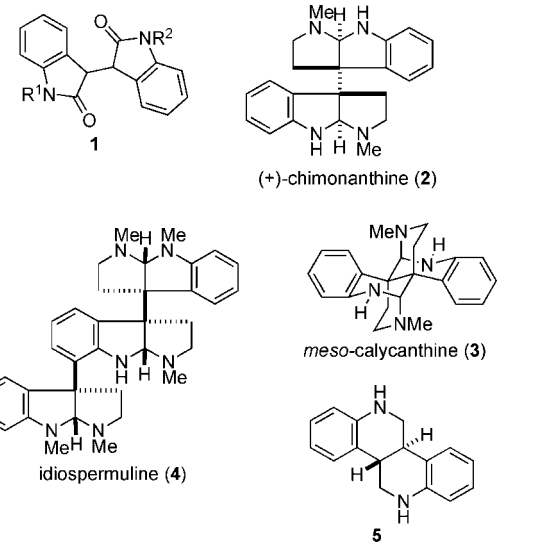


**FIGURE 1.** 3,3′-Bioxindole and representative heterocycles prepared from these intermediates.

3,3′-Bioxindoles (**1**) are commonly prepared by acid-promoted condensation of an isatin and an oxindole to generate an isoindigo, **8**, followed by saturation of the double bond (Scheme 1).[5−9] In ongoing studies, we required access to a series of unsymmetrical 3,3′-bioxindoles (**1**) having variation in both the nitrogen-protecting group and the substituents on the two aromatic rings.[10] As some of the substituents are acid-sensitive, the classical sequence illustrated in Scheme 1 was not viable. We report herein that the Mukaiyama aldol reaction[11] between 2-siloxyindoles[12] and isatins provides access to a variety of 3-hydroxy-3,3′-bioxindoles,[13] intermediates that are readily converted to 3,3′-bioxindoles. We also disclose that the aldol addition occurs with high stereoselectivity to preferentially generate the *syn* aldol stereoisomer.

Our initial studies focused on the union of *N*-(2-(trimethylsilyl)ethoxy)methyl (SEM)-protected oxindole **9** and 4-vinylisatin **10** (Scheme 2). Addition of the lithium enolate of oxindole **9** to isatin **10** generated aldol adduct **11a** and its epimer (3:1

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(11) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

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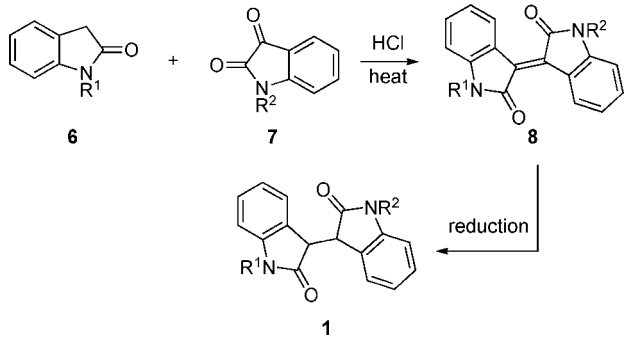
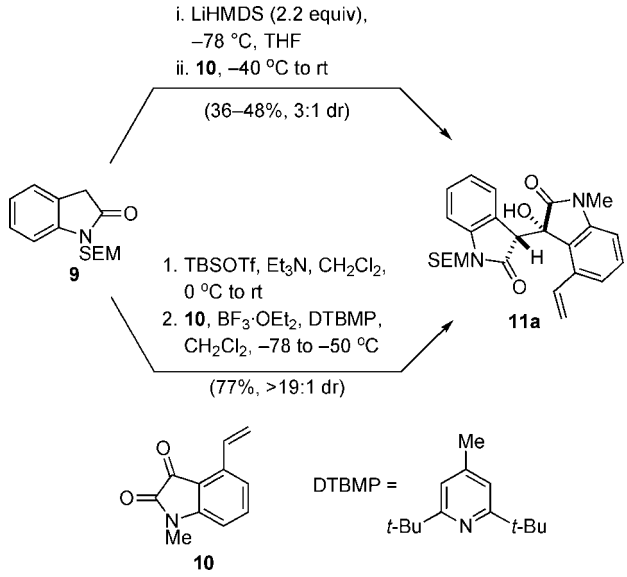
**SCHEME 1. Typical Synthesis of 3,3′-Bioxindoles**




**SCHEME 2. Aldol Reaction of 2-Siloxyoxindoles with Isatins**

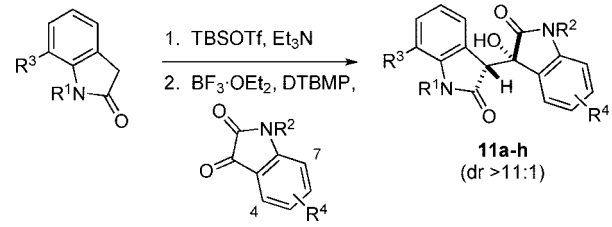



dr, *syn*:*anti*);[14] however, the yield was low. In contrast, Mukaiyama aldol reaction of the 2-siloxyindole derivative of **9** with 2 equiv of isatin **10** in the presence of excess $BF_3 \cdot OEt_2$ (8 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 7 equiv) beginning at −78 °C, then warming to −50 °C, yielded aldol adduct **11a** in 78% yield and high diastereoselectivity (>19:1 *syn*:*anti*). Further investigation revealed that the optimal conditions for this transformation involved the use of 1.0 equiv of the isatin, 2.0 equiv of $BF_3 \cdot OEt_2$, and 2.5 equiv of DTBMP at −78 to −50 °C, conditions that provided adduct **11a** in 77% yield.

The scope of this aldol reaction is illustrated by the examples summarized in Table 1. Crude 2-siloxyindoles were employed, which were isolated by adding a small volume of methanol to the silylation reaction mixture, removing volatiles under reduced pressure, extracting the resultant oil with pentane, and concentration. *N*-Methyl, *N*-benzyl, and *N*-SEM substituents were tolerated on both the oxindole and the isatin. Substitution at each position on the aromatic ring of the isatin had no adverse effect on the aldol reaction (entries 1 and 5−8). Substitution at the 7-position of the oxindole was also viable (entries 2, 3, and 8). Additionally, the Mukaiyama aldol reaction was effective for a substrate containing a pyridine appended to the isatin (entry 7), although the yield in this case was slightly lower. In all reactions, diastereoselectivity was high (>11:1).[15] The reactions

(14) Relative configuration is assigned in analogy to **11c** (vide infra).

**TABLE 1. Mukaiyama Aldol Reactions of 2-Siloxyindoles and Isatins**[a]




| entry | $R^1$ | $R^3$ | $R^2$ | $R^4$ | **11** | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | SEM | H | Me | 4-vinyl | **11a** | 77 |
| 2 | Me | MeO | SEM | H | **11b** | 87 |
| 3 | Me | MeO | Bn | H | **11c** | 80 |
| 4 | SEM | H | Bn | H | **11d** | 76 |
| 5 | Bn | H | SEM | 7-F | **11e** | 83 |
| 6 | SEM | H | Bn | 6-phenyl | **11f** | 84 |
| 7 | SEM | H | Bn | 5-(3-pyridyl) | **11g** | 60 |
| 8 | Me | MeO | Me | 4-vinyl | **11h** | 52[c] |

[a] Conditions: oxindole (1.0 equiv), isatin (1.0 equiv), $BF_3 \cdot Et_2O$ (2.0 equiv), DTBMP (2.5 equiv), −78 to −50 °C. [b] Yield over two steps of the aldol adduct after purification by silica gel flash column chromatography. [c] The starting oxindole (15−20%) was recovered.

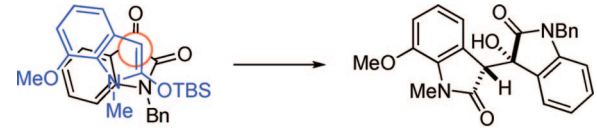



**FIGURE 2.** Pretransition state model rationalizing *syn* selectivity.

summarized in Table 1 were carried out at various scales (0.50 to 40 mmol), with the best result being observed in the largest scale reaction (entry 2). Although only oxindoles having substituents at C7 of the aromatic ring were included in this study, we anticipate that oxindoles having substituents at C4−C6 will also successfully undergo Mukaiyama aldol condensation with isatins.

The *syn* relative configuration of aldol adduct **11c** was established by single-crystal X-ray analysis.[16] The pretransition state arrangement **12** of the 2-siloxyindole and the isatin, depicted in Figure 2, would be consistent with the observed *syn* stereoselection. This orientation places the bulky silyl group away from the aromatic ring of the isatin and also allows for some degree of $\pi$-overlap of the two aromatic moieties.[17,18]

The conversion of the aldol adducts to the corresponding 3,3′-bioxindole was best accomplished by reaction with $SOCl_2$ and diisopropylethylamine[19] to give the corresponding isoindigo, which without purification was reduced with zinc and acetic acid.[20−22] Representative examples are shown in Table 2.

In conclusion, Mukaiyama aldol reactions of 2-siloxyindoles with isatins take place in good yield and with high stereoselectivity to give *syn* diastereomers of 3-hydroxy-3,3′-bioxindoles.

(15) $^1$H NMR analysis of the crude reaction product prior to purification typically showed the presence of only one stereoisomer.

(16) The relative configurations of other aldol adducts were assigned in analogy to **11c**.

(17) Open transition states with the enoxysilane and carbonyl $\pi$-bonds antiperiplanar are typically proposed for Mukaiyama aldol reactions. See: Marhwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120.

(18) The yield of the aldol reaction was somewhat lower when the 7-position of the oxindole and the 4-position of the isatin were both substituted (entry 8). The 7-position of the oxindole and 4-position of the isatin would be in close proximity in pretransition state ensemble **12**.

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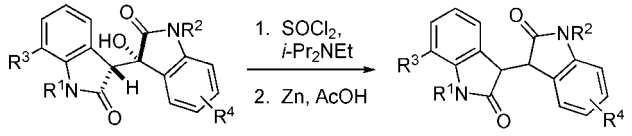
**TABLE 2. 3,3′-Bioxindole Formation from 3-Hydroxy-3,3′-Bioxindoles**[a]




11 13

| entry | 11 | $R^1$ | $R^3$ | $R^2$ | $R^4$ | 13 | yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **11b** | Me | MeO | SEM | H | **13a** | 87[c] |
| 2 | **11c** | Me | MeO | Bn | H | **13b** | 89 |
| 3 | **11d** | SEM | H | Bn | H | **13c** | 85 |
| 4 | **11e** | Bn | H | SEM | 7-F | **13d** | 79 |
| 5 | **11f** | SEM | H | Bn | 6-Ph | **13e** | 90 |

[a] Conditions: step 1: **11** (1.0 equiv), $SOCl_2$ (1.2 equiv), *i*-$Pr_2NEt$ (3.0 equiv), 0 °C to rt; step 2: Zn (30 equiv), AcOH (18 equiv), 0 °C to rt. [b] Yield over two steps after purification of **13** by silica gel flash column chromatography. [c] Reduction performed with a modified procedure: Zn (6.0 equiv), AcOH (5.6 equiv), 0 °C to rt.

These aldol products can be reduced in good yield to give the corresponding 3,3′-bioxindoles. By use of this method, a variety of substituents, including those that are acid-sensitive, can be introduced at various positions of the 3,3′-bioxindole product.

## Experimental Section

**Representative Procedure for Generating 2-Siloxyindole Intermediates and Their Mukaiyama Aldol Reaction with Isatins. Preparation of 3-Hydroxy-7′-methoxy-*N*′-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)-3,3′-biindoline-2,2′-dione (11b).** To a stirring solution of 7-methoxy-*N*-methyloxindole (**S5**) (6.60 g, 37.3 mmol, 1.0 equiv), triethylamine (15.6 mL, 112 mmol, 3.0 equiv), and dichloromethane (700 mL) at 0 °C was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (12.8 mL, 55.9 mmol, 1.5 equiv). The resultant solution was maintained at 0 °C for 25 min and then allowed to warm to rt. Methanol (1.5 mL, 37 mmol, 1.0 equiv) was added, and the solution was concentrated under reduced pressure (~30 mmHg). The resulting biphasic mixture was extracted with pentane (3 × 120 mL), and the combined organic extracts were concentrated under reduced pressure to provide the corresponding 2-siloxyindole as a pale red/pink solid, which was used in the subsequent reaction without further purification.

A solution of the crude 2-siloxyindole, *N*-((2-(trimethylsilyl)-ethoxy)methyl)isatin (10.4 g, 37.6 mmol, 1.01 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (19.1 g, 93.2 mmol, 2.5 equiv), and dichloromethane (630 mL) was cooled to −78 °C, and boron trifluoride diethyl ether complex (9.20 mL, 74.6 mmol, 2.0 equiv) was added dropwise. After 2 h at −78 °C, the solution was allowed to warm to −50 °C, where it was maintained overnight. This solution was then poured into water (250 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 250 mL). The combined organic extracts were washed with brine (40 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure to provide a brown oil. Purification of this oil by silica gel flash column chromatography (dry loaded on Celite, gradient: 1:6 EtOAc/hexanes to 1:3 EtOAc/hexanes) provided alcohol **11b** (14.8 g, 87%) as a pale brown solid: mp 129−132 °C; $R_f$ 0.54 (1:4 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 7.4 Hz, 1H), 7.42 (ddd, $J$ = 8.8, 8.0, 7.7 Hz, 1H), 7.24 (t, $J$ = 7.6 Hz, 1H), 7.02 (d, $J$ = 7.7 Hz, 1H), 6.76 (d, $J$ = 8.3 Hz, 1H), 6.67 (dd, $J$ = 8.3, 7.7 Hz, 1H), 6.45 (br s, 1H), 5.60 (d, $J$ = 7.6 Hz, 1H), 4.90 (d, $J$ = 11.4 Hz, 1H), 4.82 (d, $J$ = 11.4 Hz, 1H), 3.91(s, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 3.10 (ddd, $J$ = 10.4, 9.9, 6.4 Hz, 1H), 3.02 (ddd, $J$ = 10.4, 9.9, 6.1 Hz, 1H), 0.80−0.66 (m, 2H), −0.07 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 176.0 (C), 175.5 (C), 145.5 (C), 143.0 (C), 132.8 (C), 130.8 (CH), 127.5 (C), 124.5 (CH), 124.1 (C), 123.9 (CH), 123.1 (CH), 116.6 (CH), 112.8 (CH), 110.2 (CH), 77.4 (C), 69.2 ($CH_2$), 65.6 ($CH_2$), 55.8 ($CH_3$), 49.3 (CH), 29.8 ($CH_3$), 17.5 ($CH_2$), −1.3 ($CH_3$); IR (film) 3365, 2952, 1733, 1713, 1615 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{24}H_{30}N_2NaO_5Si$ 477.1822, found 477.1823.

**Representative Procedure for Converting Aldol Adducts to 3,3′-Bioxindoles. Preparation of 7′-Methoxy-*N*′-methyl-*N*-(2-(trimethylsilyl)ethoxymethyl)-3,3′-dihydroisoindigo (13a).** To a solution of tertiary alcohol **11b** (14.8 g, 32.5 mmol, 1.0 equiv) and dichloromethane (275 mL) at 0 °C were added over 5 min diisopropylethylamine (17.0 mL, 97.5 mmol, 3.0 equiv) and then freshly distilled thionyl chloride (2.85 mL, 39.0 mmol, 1.2 equiv). The resulting solution was maintained for 25 min at 0 °C, before being allowed to warm to rt, where it was maintained for 45 min. The reaction mixture was then poured into a saturated aqueous solution of sodium hydrogencarbonate (150 mL). The aqueous layer was separated and extracted with dichloromethane (4 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure to yield a brown oil that was used without further purification in the subsequent reaction.

In a separate experiment, purification of this product by silica gel flash column chromatography (1:9 EtOAc/hexanes) gave the corresponding isoindigo **S20** as a dark burgundy solid: mp 84−85 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.17 (d, $J$ = 8.0 Hz, 1H), 8.73 (m, 1H), 7.36 (td, $J$ = 7.7, 0.9 Hz, 1H), 7.09 (d, $J$ = 7.5 Hz, 1H), 7.01 (d, $J$ = 7.8 Hz, 1H), 6.96 (m, 2H), 5.24 (s, 2H), 3.87 (s, 3H), 3.62 (t, $J$ = 8.2 Hz, 2H), 3.57 (s, 3H), 0.94 (t, $J$ = 8.2 Hz, 2H), −0.02 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.2, 168.0, 144.8, 143.8, 134.8, 134.3, 133.7, 133.3, 132.6, 129.6, 122.9, 122.7, 122.3, 121.6, 116.8, 109.1, 69.5, 66.2, 56.3, 29.7, 17.9, −1.4; IR (film) 2954, 1698, 1609 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_4Si$ 437.1897, found 437.1912.

The unpurified isoindigo intermediate was dissolved in THF (315 mL) and cooled to 0 °C. To this solution were added zinc dust (12.8 g, 195 mmol, 6.0 equiv) and glacial acetic acid (3.2 mL, 180 mmol, 5.6 equiv). The resulting suspension was vigorously stirred at 0 °C for 1.5 h, and then allowed to warm to rt over 45 min. The reaction mixture was then filtered through a pad of Celite eluting with EtOAc (250 mL). The organic solution was washed with saturated aqueous sodium hydrogencarbonate (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a black foamy oil. This residue was further purified by silica gel flash column chromatography (dry loaded on Celite, gradient: 1:4 EtOAc/hexanes to 1:1 EtOAc/hexanes) to afford bioxindole **13a** as a 1.6:1 mixture of epimers (12.4 g, 87%) as an orange foam: $R_f$ 0.20 (1:1 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28 (t, $J$ = 7.8 Hz, 0.6H), 7.12 (t, $J$ = 7.7 Hz, 0.4H), 7.06−7.02 (m, 0.6H), 6.99 (t, $J$ = 7.3 Hz, 0.6H), 6.93−6.80 (m, 3.0H), 6.74−6.65 (m, 0.8H), 6.55 (d, $J$ = 7.2 Hz, 0.3H), 6.33 (m, 0.5H), 5.22 (d, $J$ = 10.8 Hz, 0.4H), 5.18 (d, $J$ = 10.9 Hz, 0.4H), 5.04 (s, 1.2H), 4.34 (d, $J$ = 3.5 Hz, 0.3H), 4.25 (m, 0.8H), 4.12 (d, $J$ = 3.3 Hz, 0.6H), 3.87−3.81 (m, 1.9H), 3.80−3.74 (m, 1.1H), 3.59−3.52 (m, 1.1H), 3.47 (s, 0.5H), 3.55−3.44 (m, 2.7H), 0.97 (m, 0.8H), 0.84 (t, $J$ = 7.8 Hz, 1.3H), 0.10 (s, 3.2H), −0.05 (s, 5.8H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 176.4 (C), 175.9 (C), 175.0 (C), 174.8 (C), 145.2 (C), 145.1 (C), 143.4 (C), 142.7 (C), 132.9 (C), 131.9 (C), 128.7 (CH), 128.3 (CH), 127.1 (C), 126.3 (C), 125.5 (C), 124.4 (C), 123.4 (CH), 123.3 (CH), 122.9 (CH), 122.82 (CH), 122.78 (CH), 122.75 (CH), 116.1 (CH), 115.9 (CH), 112.6 (CH), 112.3 (CH), 109.8 (CH), 109.4 (CH), 69.8 ($CH_2$), 69.3 ($CH_2$), 66.6 ($CH_2$), 65.8 ($CH_2$), 55.74 ($CH_3$), 55.71

(20) Additional methods have been demonstrated for the conversion of 3-hydroxy-3,3′-bioxindoles to 3,3′-bioxindoles. These include acid-mediated dehydration of the tertiary alcohol to afford an isoindigo that is subsequently reduced by catalytic hydrogenation,[6−9] and direct reduction with trimethylsilyl iodide[21] or HI.[22]

(21) (a) Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 3817–3818. (b) For an example of the reduction of a 3-hydroxy-3,3′-bioxindole, see: Peterson, E. A. Ph.D. Dissertation, University of California, Irvine, 2005.

(22) Metwally, S. A. M.; Younes, M. I.; Abbas, H. H. *Acta Chim. Hung.* **1989**, *126*, 591–597.

($CH_3$), 46.5 (CH), 46.2 (CH), 46.0 (CH), 29.6 ($CH_3$), 29.5 ($CH_3$), 17.9 ($CH_2$), 17.6 ($CH_2$), −1.4 ($CH_3$), −1.5 ($CH_3$); IR (film) 2950, 1716, 1612 $cm^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_4Si$ 439.2053, found 439.2048.

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**Supporting Information Available:** Experimental procedures and copies of $^1H$ and $^{13}C$ NMR spectra of all new compounds; CIF file for compound **11c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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