

Addition of *tert*-Butyldimethyl- or *tert*-Butyldiphenylsilyl Cyanide to Hindered Ketones

Mirosław Golinski, Carolyn P. Brock, and David S. Watt*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

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The addition of trimethylsilyl cyanide (TMSCN), *tert*-butyldimethylsilyl cyanide (TBDMSCN) or *tert*-butyldiphenylsilyl cyanide (TBDPSCN) to sterically hindered ketones proceeded in good yield under catalysis by Lewis acids (ZnI_2 , CH_2Cl_2 , 25 °C) or bases (KCN, 18-crown-6, CH_2Cl_2 , 25 °C). For example, the ZnI_2 -catalyzed addition of TBDMSCN to 2,2-dimethylcyclohexanone (**3e**), 2,2,6-trimethylcyclohexanone (**3f**), and 2,2,6,6-tetramethylcyclohexanone (**3g**) provided the protected cyanohydrins **4e**, **4f**, and **4g** in 94, 83, and 92% yield, respectively. The C-1 ketone of C-6 dithioketal-protected Wieland–Miescher ketone ((4'aS)-4',4'a,7',8'-tetrahydro-4a'-methylspiro[1,3-dithiolane-2,2'(3'H)-naphthalen]-5'(6'H)-one (+)-(8)) provided (4'aS,5'S)-4',4'a,5',6',7',8'-hexahydro-5'-[(dimethyl(1,1-dimethylethyl)silyl)oxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3'H)-naphthalene]-5'-carbonitrile (+)-(10b) in 94% yield. An X-ray crystallographic study established that the C-5 center in (+)-**10b** has the correct absolute stereochemistry needed for a projected synthesis of the C-1 center in the A ring of taxol using (+)-**10b** as a starting material.

In connection with a synthesis in which the Wieland–Miescher ketone¹ **1** would serve as a enantiospecific precursor to the A ring of the taxanes,² a method for the conversion of the C-1 ketone in **1** to a protected α -hydroxy aldehyde **2** was required (Figure 1). Among the possible solutions³ to this problem, the conversion of the hindered C-1 ketone in **1** to a silyl-protected cyanohydrin⁴⁻⁸ was an attractive option, but the scope of this addition process for sterically hindered ketones was uncertain.

Although the Lewis-acid-catalyzed or cyanide-catalyzed addition of trimethylsilyl cyanide (TMSCN)^{4,5} to aldehydes, ketones, and 1,3-diketones is well documented, the addition of bulky trialkylsilyl cyanides such as triethylsilyl cyanide (TESCN),^{4d,i} triisopropylsilyl cyanide (TISCN),^{4d} or *tert*-butyldimethylsilyl cyanide (TBDMSCN)^{4g,h,6-8} is largely restricted to aldehydes and sterically unencumbered ketones. For example, 4 equiv of TBDMSCN and 0.4 equiv of dicyclohexyl-18-crown-6 and potassium cyanide at 110 °C for 10 days were required to convert 3-propionyl-4-[(tetrahydropyranloxy)methyl]furan to a TBDMS-protected cyanohydrin⁶ in 85% yield. The addition of TISCN to diacetyl required 18 h of heating at 210 °C to produce the bis(TIS)-protected cyanohydrin^{4d}

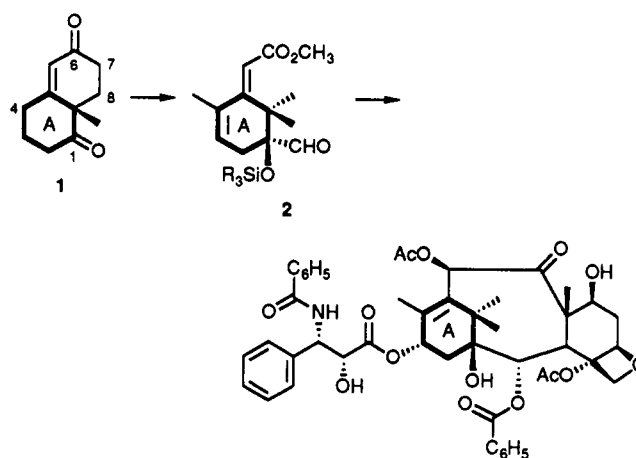


Figure 1.

in only 53% yield. The addition of *tert*-butyldiphenylsilyl cyanide (TBDPSCN), a new reagent that was prepared according to the method of Bither^{9a} and Becu,^{9b} to carbonyl compounds has not been investigated previously. The projected need for a protected cyanohydrin of the Wieland–Miescher ketone **1** capable of surviving various conditions during a multistep synthesis led to an investigation of the addition of TBDMSCN and TBDPSCN to various ketones under Lewis acid or base catalysis.

As shown in Table I, the conditions required for the addition of TBDMSCN or TBDPSCN to hindered and unhindered ketones were not as severe as anticipated from literature precedent using TBDMSCN⁶ or TISCN.^{4d} The addition of TBDMSCN or TBDPSCN to ketones **3** proceeded at 25 °C in the presence of catalytic amounts of zinc iodide or potassium cyanide/18-crown-6 to afford the TBDMS-protected or the TBDPS-protected cyanohydrins **4** and **5**, respectively, in good yield. The base-catalyzed conditions generally failed for the more hindered ketones and in cases where these conditions were successful, required longer reaction times and an excess of

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
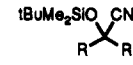
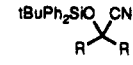

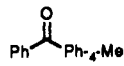
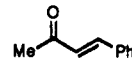






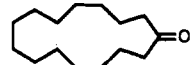
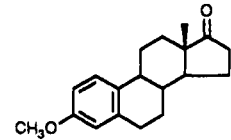
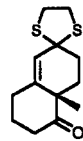
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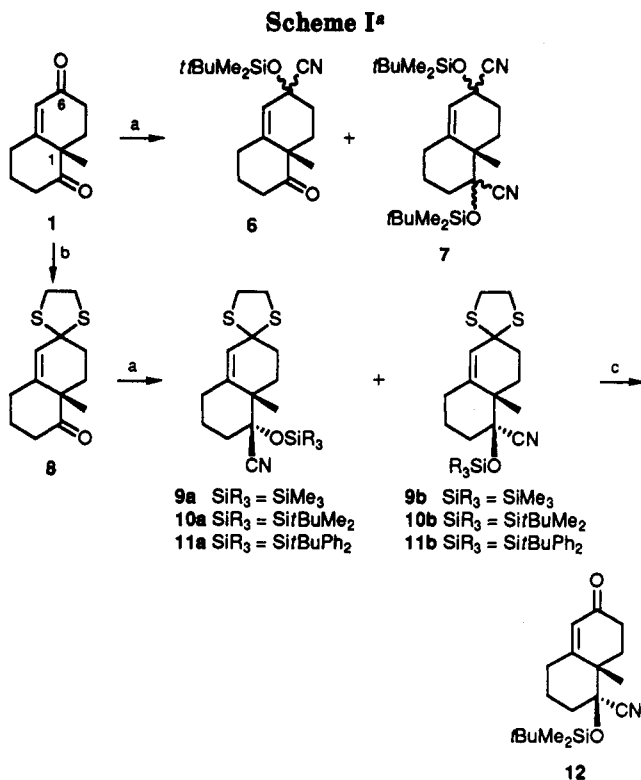
Table I. Addition of TBDMSCN and TBDPSCN to Ketones 3

	 3	 4 % yield (conditions) ^a	 5 % yield (conditions) ^a
a		86 (A, 3 h, 1.2 equiv)	95 (A, 20 h, 1.5 equiv) low yield (B, 10 d, 1.5 equiv)
b		89 (A, 24 h, 2.1 equiv) 87 (B, 5 d, 1.3 equiv)	95 (A, 2 d, 2 equiv)
c		83 (A, 1 h, 1.3 equiv)	81 (A, 3 h, 1.3 equiv)
d			no reaction (A, 14 h, 1.5 equiv) 92 (C, 8 h, 1.5 equiv)
e		94 (A, 2 h, 1.3 equiv)	no reaction (A, 14 h, 1.5 equiv) 92 (C, 8 h, 1.5 equiv)
f		83 (A, 20 h, 1.3 equiv)	no reaction (A, 24 h, 2 equiv)
g		92 (A, 4 d, 1.5 equiv)	85 (C, 6 d, 2 equiv)
h		91 (A, 48 h, 1.8 equiv) low yield (B, 48 h, 1.8 equiv)	57 (A, 4.5 d, 1.5 equiv) no reaction (B, 4 d, 1.5 equiv)
i		85 (A, 2 h, 1.5 equiv)	90 (C, 16 h, 1.5 equiv) no reaction (B, 19 h, 1.5 equiv)
j			97 (, 3 d, 1.5 equiv)
k		95 (A, 2.5 h, 1.3 equiv)	no reaction (B, 1 d, 1.5 equiv) 94 (C, 24 h, 3 equiv)
8		94 (A, 3 h, 1.4 equiv) 85 (B, 2.5 h, 2 equiv) ^b	74 (A, 24 h, 2 equiv)

^a Procedure A: TBDMSCN or TBDPSCN (equivalents shown in table), ZnI₂ (ca. 0.03 equiv), CH₂Cl₂, 25 °C. Procedure B: TBDMSCN or TBDPSCN (equivalents shown in table), KCN (0.1 equiv), 18-crown-6 (0.1 equiv), CH₂Cl₂, 25 °C. Procedure C: TBDMSCN or TBDPSCN (equivalents shown in Table), ZnI₂ (0.23 equiv), CH₂Cl₂, 25 °C. ^b In this experiment, procedure B was modified as follows: KCN (1 equiv) and 18-crown-6 (1 equiv) in CH₃CN.

the reagent and/or catalyst than in the ZnI₂-catalyzed cases. The acid-catalyzed addition of the hindered silylating agent, TBDPSCN, to ketones 3 having two or fewer

α -hydrogens required ca. 0.2 equiv of ZnI₂ (i.e., procedure C, Table I) to achieve efficient conversions to the protected cyanohydrins 5 whereas the less hindered ketones required



^a (a) R_3SiCN , ZnI_2 , CH_2Cl_2 , 25°C (see Table I); (b) $\text{HSCH}_2\text{CH}_2\text{SH}$, $p\text{-TsOH}$, HOAc ; (c) $\text{Tl}(\text{NO}_3)_3$, $\text{THF-H}_2\text{O-MeOH}$.

only ca. 0.03 equiv of ZnI_2 (i.e., procedure A, Table I) for complete conversions. The acid-catalyzed addition of the less hindered TBDMSCN to ketones 3 with zero α -hydrogens, however, provided the protected cyanohydrins 4 in good yield using only ca. 0.03 equivalents of ZnI_2 (i.e., procedure A, Table I).

In the case of the Wieland–Miescher ketone (1), the ZnI_2 -catalyzed addition of TBDMSCN showed, as expected, little regioselectivity and produced a 3:1 mixture of the C-6 monoadduct 6 and the C-1,6 bisadduct 7 as mixtures of diastereomers (Scheme I). To achieve the necessary selectivity for the C-1 ketone, the Wieland–Miescher ketone (1) was converted to the dithioketal 8 according to the procedure of Bosch¹⁰ and treated with TBDMSCN under Lewis acid catalysis to produce a 1:10.1 ratio of diastereomers 10a and 10b ($\text{SiR}_3 = \text{Si}^i(\text{tBu})\text{Me}_2$), respectively. This ratio was the result of a kinetically controlled addition of cyanide to the less hindered α -face of 8 whereas the comparable cyanide-catalyzed addition produced a 1:7.8 ratio of 10a to 10b suggesting partial equilibration. An X-ray crystallographic study (data deposited with the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge, CB2 1EZ, U.K.) confirmed that the major diastereomer 10b possessed the trans arrangement of the angular methyl group and the cyano group, as shown in Figure 2. A comparable ratio (1:10.6 for 9a/9b; 95% yield) was observed for the addition of TMS-CN to 8; however, an unexpectedly small ratio (1:6.8 for 11a/11b; 74% yield) was observed for the addition of TBDPSCN to 8, despite the apparent increase in the steric bulk of TBDPSCN relative to TBDMSCN or TMS-CN. The longer reaction times that were required

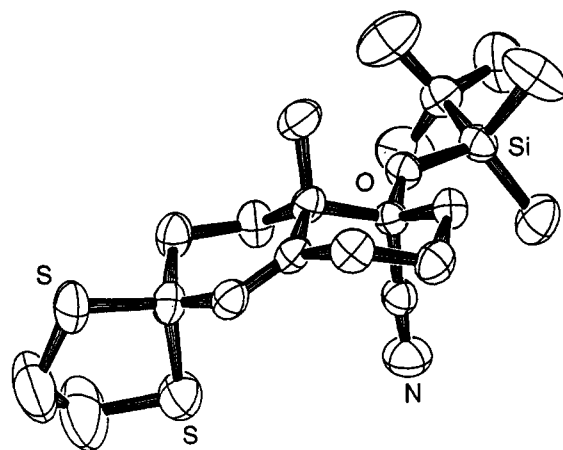


Figure 2. Perspective drawing of the molecule in the crystal structure of (4'aS,5'S)-4',4'a,5',6',7',8'-hexahydro-5'-[(dimethyl(1,1-dimethylethyl)silyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3'H)-naphthalene]-5'-carbonitrile (+)-(10b). The shapes of the ellipsoids correspond to 50% probability contours of atomic displacement. The hydrogen atoms have been omitted for the sake of clarity.

in the case of TBDPSCN may have led to some equilibration and hence to the somewhat lower ratio of 11b to 11a. The 1:10.1 ratio obtained for the addition of TBDMSCN to 8 also compared favorably to the kinetic 1:9 ratio of $\text{CN}_{\text{equatorial}}/\text{CN}_{\text{axial}}$ diastereomers observed in the TMS-CN addition to 4-*tert*-butylcyclohexanone^{4e} and contrasted with the 1:3.5 equilibrium ratio observed in the presence of KCN and 18-crown-6.^{4e} The thallium nitrate-catalyzed deprotection of the thioketal 10b gave the enone 12 in good yield.

Experimental Section

General Procedure for the Addition of R_3SiCN to Ketones 3. Procedure A: To a solution of 1 mmol (1 equiv) of a ketone 3 and 1.2–2 mmol (1.2–2 equiv) of TMS-CN, TBDMSCN, or TBDPSCN in 0.5–2 mL of anhydrous CH_2Cl_2 under N_2 were added ca. 0.03 mmol (0.03 equiv) of anhydrous ZnI_2 . The mixture was stirred at 25°C for the time indicated in Table I. The protected cyanohydrins 4 and 5 were purified by combination of recrystallization and chromatography on silica gel. **Procedure B:** To a solution of 1 mmol (1 equiv) of a ketone 3 and 1.2–2.1 mmol (1.2–2.1 equiv) of TBDMSCN or TBDPSCN in 0.5–2 mL of anhydrous CH_2Cl_2 under N_2 were added 0.1 mmol (0.1 equiv) of KCN and 0.1 mmol (0.1 equiv) of 18-crown-6. In some cases, it was necessary to add additional solvent during a reaction to solubilize a precipitated product. **Procedure C:** The same procedure as A was repeated using 0.23 equiv of anhydrous ZnI_2 .

(1,1-Dimethylethyl)diphenylsilyl Cyanide (TBDPSCN). The exchange method⁹ that employed KF^{aq} and that which was used for the preparation of TBDMSCN was repeated using 7.1 g (71.5 mmol, 1.2 equiv) TMS-CN and 16.4 g (59.6 mmol, 1 equiv) of TBDPSCl to afford 14 g (88%) of TBDPSCN; bp $134\text{--}136^\circ\text{C}$ (1.3 mm); IR (CHCl_3) 2967, 2940, 2868, 2195 (CN), 1464, 1427, 1112, 1105, 818, 696, 628, 612 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.18 (s, 9, $\text{C}(\text{CH}_3)_3$), 7.35–7.57 (m, 6, ArH), 7.70–7.85 (m, 4, ArH). A small singlet at δ 1.34 suggested the presence of a small amount of the isocyanide, $\text{tBuPh}_2\text{SiN}=\text{C}$, as an impurity. Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NSi}$: C, 76.93; H, 7.22. Found: C, 77.04; H, 7.25.

2-[[Dimethyl(1,1-dimethylethyl)silyloxy]-2-phenylpropionitrile (4a): IR (CHCl_3) 2964, 2940, 2864, 1460, 1444, 1260, 1120, 997, 833, 695 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 0.05 (s, 3, CH_3), 0.23 (s, 3, CH_3), 0.94 (s, 9, $\text{C}(\text{CH}_3)_3$), 1.86 (s, 3, CH_3), 7.30–7.50 (m, 3, ArH), 7.50–7.64 (m, 2, ArH). Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{NSi}$: C, 68.91; H, 8.85. Found: C, 69.17; H, 8.89.

2-[[Dimethyl(1,1-dimethylethyl)silyloxy]-2-(4-methylphenyl)-2-phenylacetone nitrile (4b): IR (CHCl_3) 2962, 2938, 2863, 1445, 1257, 1097, 1072, 862, 840, 694 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ

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0.01 (s, 3, CH₃), 0.03 (s, 3, CH₃), 0.98 (s, 9, C(CH₃)₃), 2.35 (s, 3, CH₃), 7.12–7.23 (m, 2, ArH), 7.29–7.46 (m, 5, ArH), 7.46–7.57 (m, 2, ArH). Anal. Calcd for C₂₁H₂₇NOSi: C, 74.73; H, 8.06. Found: C, 74.80; H, 8.11.

(3E)-2-[[Dimethyl(1,1-dimethylethyl)silyloxy]-4-phenyl-3-butenitrile (4c): IR (CHCl₃) 2960, 2930, 2857, 1256, 1187, 1129, 1107, 998, 967, 838, 823, 687 cm⁻¹; ¹H NMR (CDCl₃) δ 0.19 (s, 3, CH₃), 0.25 (s, 3, CH₃), 0.92 (s, 9, C(CH₃)₃), 1.74 (s, 3, CH₃), 6.11 (d, *J* = 16 Hz, 1, vinylic H), 6.90 (d, *J* = 16 Hz, 1, vinylic H), 7.28–7.50 (m, 5, ArH). Anal. Calcd for C₁₇H₂₅NOSi: C, 71.03; H, 8.77. Found: C, 71.11; H, 8.72.

1-[[Dimethyl(1,1-dimethylethyl)silyloxy]-2,2-dimethylcyclohexanecarbonitrile (4e): IR (CHCl₃) 2968, 2938, 2867, 1465, 1388, 1363, 1260, 1125, 1058, 885, 860, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.20 (s, 3, SiCH₃), 0.26 (s, 3, SiCH₃), 0.91 (s, 9, C(CH₃)₃), 0.99 (s, 3, CH₃), 1.13 (s, 3, CH₃), 1.32–2.02 (m, 8, (CH₂)₄). Anal. Calcd for C₁₅H₂₉NOSi: C, 67.35; H, 10.93. Found: C, 67.14; H, 10.89.

cis- and trans-1-[[Dimethyl(1,1-dimethylethyl)silyloxy]-2,2,6-trimethylcyclohexanecarbonitrile (4f): 3:1 ratio of cis and trans diastereomers; IR (CHCl₃) 2967, 2940, 2863, 1460, 1387, 1258, 1161, 1138, 1117, 1108, 1080, 1068, 1055, 860, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.26 (s, Si(CH₃)₂ of both isomers), 0.91 (s, C(CH₃)₃ of minor isomer), 0.94 (s, C(CH₃)₃ of major isomer), 0.99 (s, CH₃ of minor isomer), 1.048 (d, *J* = 6.7 Hz, CH₃ of major isomer), 1.054 (s, CH₃ of major isomer), 1.12 (s, CH₃ of minor isomer), 1.13 (s, CH₃ of major isomer). Anal. Calcd for C₁₆H₃₁NOSi: C, 68.27; H, 11.10. Found: C, 68.31; H, 11.09.

1-[[Dimethyl(1,1-dimethylethyl)silyloxy]-2,2,6,6-tetramethylcyclohexanecarbonitrile (4g): IR (CHCl₃) 2967, 2937, 2860, 1412, 1385, 1367, 1258, 1110, 1092, 1029, 1014, 880, 868, 855, 840, 618 cm⁻¹; ¹H NMR (CDCl₃) δ 0.28 (s, 6, Si(CH₃)₂), 0.95 (s, 9, C(CH₃)₃), 1.06 (s, 6, two CH₃), 1.18 (s, 6, two CH₃), 1.45–1.54 (m, 6, CH₂CH₂CH₂). Anal. Calcd for C₁₇H₃₃NOSi: C, 69.09; H, 11.25. Found: C, 69.04; H, 11.25.

2-[[Dimethyl(1,1-dimethylethyl)silyloxy]-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carbonitrile (4h): 3:5 ratio of diastereomers; IR (CHCl₃) 2964, 2938, 2908, 2889, 2864, 1412, 1390, 1259, 1125, 1103, 1089, 921, 840, 832, 670 cm⁻¹; ¹H NMR (CDCl₃) δ 0.22 (s, SiCH₃ of major isomer), 0.23 (s, SiCH₃ of minor isomer), 0.25 (s, SiCH₃ of minor isomer), 0.27 (s, SiCH₃ of major isomer), 0.89 (s, CH₃ of major isomer), 0.90 (s, C(CH₃)₃ of major isomer), 0.91 (s, C(CH₃)₃ of minor isomer), 0.97 (s, CH₃ of major isomer), 1.02 (s, CH₃ of major isomer), 2.00–2.35 (m), 2.52–2.66 (m, minor isomer). Anal. Calcd for C₁₇H₃₁NOSi: C, 69.56; H, 10.65. Found: C, 69.56; H, 10.71.

1-[[Dimethyl(1,1-dimethylethyl)silyloxy]cyclooctanecarbonitrile (4i): IR (CHCl₃) 2967, 2944, 2867, 1469, 1443, 1260, 1141, 1100, 1041, 1008, 938, 840, 670 cm⁻¹; ¹H NMR (CDCl₃) δ 0.22 (s, 6, Si(CH₃)₂), 0.89 (s, 9, C(CH₃)₃), 1.40–1.83 (m, 10, (CH₂)₆), 1.92–2.09 (m, 4, two CH₂). Anal. Calcd for C₁₆H₂₉NOSi: C, 67.35; H, 10.93. Found: C, 67.18; H, 10.98.

(17S)-17-[[Dimethyl(1,1-dimethylethyl)silyloxy]estrone-17-carbonitrile 3-Methyl Ether (4k): mp 148–148.5 °C (from hexane); IR (CHCl₃) 2960, 2940, 2864, 1608, 1497, 1453, 1256, 1233, 1154, 1125, 1100, 1037, 885, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.21 (s, 3, SiCH₃), 0.26 (s, 3, SiCH₃), 0.86 (s, 3, CH₃), 0.91 (s, 9, C(CH₃)₃), 1.30–2.03 (m, 10), 2.17–2.53 (m, 3), 2.78–2.92 (m, 2), 3.78 (s, 3, CH₃O), 6.63 (d, *J* = 2.6 Hz, 1, ArH), 6.72 (dd, *J* = 8.6 and 2.6 Hz, 1, ArH), 7.21 (d, *J* = 8.6 Hz, 1, ArH). Anal. Calcd for C₂₆H₃₉NO₂Si: C, 73.36; H, 9.23. Found: C, 73.21; H, 9.20.

2-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-2-phenylpropionitrile (5a): mp 91–91.5 °C; IR (CHCl₃) 3078, 2968, 2938, 2865, 1425, 1152, 1112, 995, 820, 697, 612 cm⁻¹; ¹H NMR (CDCl₃) δ 1.10 (s, 9, C(CH₃)₃), 1.75 (s, 3, CH₃), 7.28–7.78 (m, 15, ArH). Anal. Calcd for C₂₅H₂₇NOSi: C, 77.88; H, 7.06. Found: C, 77.72; H, 7.08.

2-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-2-(4-methylphenyl)-2-phenylacetone (5b): mp 115–116.5 °C; IR (CHCl₃) 3077, 2967, 2937, 2864, 1423, 1113, 1103, 1093, 1073, 849, 818, 695, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.11 (s, 9, C(CH₃)₃), 2.30 (s, 3, CH₃), 6.97–7.07 (m, 2, ArH), 7.18–7.32 (m, 9, ArH), 7.32–7.45 (m, 4, ArH), 7.45–7.62 (m, 4, ArH). Anal. Calcd for C₃₁H₃₁NOSi: C, 80.65; H, 6.77. Found: C, 80.45; H, 6.82.

(3E)-2-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-4-phenyl-3-butenitrile (5c): IR (CHCl₃) 3018, 2968, 2939, 2865, 1424,

1190, 1130, 1112, 1102, 996, 969, 840, 700, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.08 (s, 9, C(CH₃)₃), 1.72 (s, 3, CH₃), 5.96 (d, *J* = 15.9 Hz, 1, vinylic H), 6.58 (d, *J* = 15.9 Hz, 1, vinylic H), 7.05–7.20 (m, 2, ArH), 7.21–7.52 (m, 9, ArH), 7.66–7.80 (m, 4, ArH). Anal. Calcd for C₂₇H₂₉NOSi: C, 78.79; H, 7.10. Found: C, 78.84; H, 7.06.

cis- and trans-1-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-2-methylcyclohexanecarbonitrile (5d): 2.6:1 ratio of cis to trans diastereomers; IR (CHCl₃) 2970, 2948, 2865, 1460, 1425, 1132, 1115, 1106, 1059, 960, 820, 700, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (s, C(CH₃)₃ of major isomer), 1.12 (s, C(CH₃)₃ of minor isomer), 1.27 (d, *J* = 6.6 Hz, CH₃ of major isomer), 7.30–7.52 (m, 6, ArH), 7.70–7.84 (m, 4, ArH). Anal. Calcd for C₂₄H₃₁NOSi: C, 76.34; H, 8.28. Found: C, 76.32; H, 8.36.

1-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-2,2-dimethylcyclohexanecarbonitrile (5e): IR (CHCl₃) 2967, 2940, 2866, 1468, 1112, 1055, 978, 843, 820, 700, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.11 (s, 9, C(CH₃)₃), 1.16 (s, 3, CH₃), 1.27 (s, 3, CH₃), 1.27–1.59 (m, 8, (CH₂)₄), 7.32–7.52 (m, 6, ArH), 7.68–7.84 (m, 4, ArH). Anal. Calcd for C₂₅H₃₃NOSi: C, 76.67; H, 8.49. Found: C, 76.66; H, 8.51.

1-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-2,2,6,6-tetramethylcyclohexanecarbonitrile (5g): mp 106–107.5 °C; IR (CHCl₃) 2940, 1458, 1424, 1390, 1198, 1110, 1103, 1013, 858, 818, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04 (s, 6, two CH₃), 1.13 (s, 9, C(CH₃)₃), 1.15 (s, 6, two CH₃), 1.33–1.59 (m, 6, CH₂CH₂CH₂), 7.33–7.52 (m, 6, ArH), 7.79–7.89 (m, 4, ArH). Anal. Calcd for C₂₇H₃₇NOSi: C, 77.27; H, 8.89. Found: C, 77.28; H, 8.91.

2-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carbonitrile (5h): 5:8 ratio of diastereomers; IR (CHCl₃) 2967, 2938, 2893, 2863, 1587, 1467, 1450, 1423, 1389, 1308, 1112, 1102, 1085, 1004, 996, 932, 868, 821, 697, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (s, CH₃ of minor isomers), 0.91 (s, CH₃ of major isomers), 0.98 (s, CH₃ of major isomers), 1.08 (s, C(CH₃)₃ of minor isomer), 1.11 (s, CH₃ of minor isomer), 1.12 (s, C(CH₃)₃ of major isomer), 1.16 (s, CH₃ of major isomer), 1.18 (s, CH₃ of minor isomer), 2.00–2.15 (m), 2.27–2.44 (m), 7.30–7.52 (m, 6, ArH), 7.63–7.87 (m, 4, ArH). Anal. Calcd for C₂₇H₃₅NOSi: C, 77.64; H, 8.45. Found: C, 77.60; H, 8.49.

1-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]cyclooctanecarbonitrile (5i): IR (CHCl₃) 2966, 2934, 2862, 1469, 1423, 1139, 1106, 1103, 1093, 1084, 820, 700, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.07 (s, 9, C(CH₃)₃), 1.33–1.84 (m, 10), 1.84–2.12 (m, 4), 7.33–7.52 (m, 6, ArH), 7.68–7.80 (m, 4, ArH). Anal. Calcd for C₂₆H₃₃NOSi: C, 76.67; H, 8.49. Found: C, 76.97; H, 8.69.

1-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]cyclopentadecanecarbonitrile (5j): IR (CHCl₃) 2936, 2863, 1459, 1424, 1110, 820, 700, 610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.07 (s, 9, C(CH₃)₃), 1.14–1.46 (m, 24, (CH₂)₁₂), 1.58–1.85 (m, 4, two CH₂), 7.33–7.53 (m, 6, ArH), 7.65–7.80 (m, 4, ArH). Anal. Calcd for C₃₂H₄₇NOSi: C, 78.47; H, 9.67. Found: C, 78.56; H, 9.70.

(17S)-17-[[Dimethyl(1,1-dimethylethyl)diphenylsilyloxy]estrone-17-carbonitrile 3-Methyl Ether (5k): an amorphous solid (MeOH) that softens at ca. 80 °C, becomes transparent at mainly 83–86 °C (still keeping its shape), and finally melts at 90–93 °C; IR (CHCl₃) 2938, 1596, 1423, 1150, 1113, 1102, 1035, 820, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (s, 3, CH₃), 1.10 (s, 9, C(CH₃)₃), 1.17–2.08 (m, 11), 2.15–2.52 (m, 2), 2.74–2.89 (m, 2), 3.77 (s, 3, CH₃O), 6.62 (d, *J* = 2.8 Hz, 1, ArH), 6.72 (dd, *J* = 8.5 and 2.8 Hz, 1, ArH), 7.21 (d, *J* = 8.5 Hz, 1, ArH), 7.33–7.53 (m, 6, ArH), 7.66–7.82 (m, 4, ArH); ¹³C NMR (CDCl₃) δ 12.9 (CH₃), 19.2, 22.9, 26.1, 26.8 (C(CH₃)₃), 29.4, 33.3, 37.6, 39.0, 43.1, 48.0, 48.9, 55.0, 82.3 (C-17), 111.6, 113.9, 121.5 (CN), 126.4, 127.6, 127.8, 130.2, 130.3, 132.2, 132.8, 133.5, 136.5, 136.6, 137.9, 157.7 (C-3). Anal. Calcd for C₃₆H₄₃NO₂Si: C, 78.64; H, 7.88. Found: C, 78.55; H, 7.94.

Wieland–Miescher Ketone (±)-(1) and TBDMSCN: (2†)-2,3,4,4a,7,8-Hexahydro-2-[[dimethyl(1,1-dimethylethyl)silyloxy]-4a-methyl-5(6E)-oxonaphthalene-2-carbonitrile (6) and (1†,6†)-1,2,3,4,6,7,8,8a-Octahydro-1,6-bis[[dimethyl(1,1-dimethylethyl)silyloxy]-8a-methylnaphthalene-1,6-dicarbonitrile (7). The general procedure described above was repeated using 178 mg (1.0 mmol) of (±)-1 and 190 mg (1.35 mmol, 1.35 equiv) of TBDMSCN that was added in portions over a 5-h period to afford, after stirring for 24 h and chromatography on silica gel using EtOAc–hexane (gradient: 1:20; 1:8;

1:5), 198 mg (62%) of (\pm)-6 as the major product (1:3 ratio of diastereomers; stereochemistry not investigated) and 92 mg (20%) of (\pm)-7 (1:8 ratio of diastereomers; stereochemistry not investigated). The spectral data for (\pm)-6: IR (CHCl₃) 2962, 2938, 2864, 1708 (C=O), 1460, 1258, 1143, 1100, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.14 (s, 3, SiCH₃ of minor isomer), 0.23 (s, 3, SiCH₃ of minor isomer), 0.23 (s, 3, SiCH₃ of major isomer), 0.86 (s, 9, SiC(CH₃)₃ of minor isomer), 0.90 (s, 9, SiC(CH₃)₃ of major isomer), 1.327 (s, 3, C-4a CH₃ of minor isomer), 1.334 (s, 3, C-4a CH₃ of major isomer), 1.45–2.80 (m), 5.49–5.57 (m, 1, vinylic H of major isomer), 5.58–5.64 (m, 1, vinylic H of minor isomer). Anal. Calcd for C₁₈H₂₆NOS₂Si: C, 67.66; H, 9.15. Found: C, 67.69; H, 9.22.

The physical and spectral data for (\pm)-7: mp 123–130 °C; IR (CHCl₃) 2962, 2938, 2864, 1462, 1258, 1127, 1000, 871, 842 cm⁻¹; ¹H NMR (CDCl₃) δ 0.21, 0.23, 0.24, 0.29 (four s, 12, SiCH₃ of major isomer), 0.27, 0.28 (two s, 6, SiCH₃ of minor isomer), 0.89 (s, 9, SiC(CH₃)₃ of major isomer), 0.91 (s, 9, SiC(CH₃)₃ of minor isomer), 1.16 (s, 3, C-4a CH₃), 1.63–2.52 (m), 5.53–5.63 (m, 1, vinylic H of major isomer), 5.64–5.68 (m, 1, vinylic H of minor isomer). Anal. Calcd for C₂₅H₄₄N₂O₂Si₂: C, 65.16; H, 9.62. Found: C, 65.25; H, 9.62.

(4*a*RS)-4',4'a,7',8'-Tetrahydro-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalen]-5'(6*H*)-one (8). The procedure of Bosch^{10a,b} was repeated using 1.78 g (10 mmol) of (\pm)-1 and 1.04 g (11 mmol) of 1,2-ethanedithiol for 15 min to afford 2.49 g (98%) of a crude product (\pm)-8 that was contaminated with only traces of the bis(dithioketal).^{10c} Reaction times longer than 15 min (e.g., the literature recommended 5 h) gave more of the bis(dithioketal) impurity. The product was purified by a combination of recrystallization using 1:5 EtOAc-hexane and chromatography on silica gel using hexane-EtOAc (gradient 8:1, 5:1, 3:1) to give 1.92 g (90%) of (\pm)-8 having spectral data consistent with literature values.^{10c}

(4*a*S)-4',4'a,7',8'-Tetrahydro-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalen]-5'(6*H*)-one (8). The procedure was repeated using 26 g (146 mmol) of (+)-1 and 15.1 g (160 mmol) of 1,2-ethanedithiol for only 15 min to afford (+)-8 having the 4*a*S configuration. An analytical sample was prepared by recrystallization from hexane-EtOAc: mp 146.5–147.5 °C, [α]_D = +113.0° (CHCl₃, *c* = 1.00).

(4*a*RS,5'*SR*)-4',4'a,5',6',7',8'-Hexahydro-5'-[(trimethylsilyloxy)-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (9a). The general procedure described above (procedure A) was repeated using 509 mg (2 mmol) of (\pm)-8, 300 mg (3 mmol, 1.5 equiv) of TMSCN, and 3.2 mg (0.01 mmol, 0.005 equiv) of ZnI₂ to afford, after recrystallization and chromatography on silica gel using EtOAc-hexane (gradient 1:40, 1:30), 55 mg (8%) of a minor diastereomer (\pm)-9a and 617 mg (87%) of a major diastereomer (\pm)-9b. The minor isomer (\pm)-9a had the following physical and spectral data: mp 104.5–105.5 °C (from hexane and a trace of Et₂O); IR (CHCl₃) 2963, 1436, 1253, 1116, 1106, 1035, 1021, 1011, 893, 848 cm⁻¹; ¹H NMR (CDCl₃) δ 0.28 (s, 9, Si(CH₃)₃), 1.27 (d, *J* = 0.74 Hz, 3, CH₃), 1.50–1.82 (m, 3), 1.87–2.52 (m, 7), 3.13–3.45 (m, 4, SCH₂CH₂S), 5.69 (t, *J* = 1.4 Hz, 1, vinylic H). Anal. Calcd for C₁₇H₂₇NOS₂Si: C, 57.74; H, 7.70. Found: C, 57.63; H, 7.77.

(4*a*RS,5'*RS*)-4',4'a,5',6',7',8'-Hexahydro-5'-[(trimethylsilyloxy)-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (9b). The major isomer (\pm)-9b had the following physical and spectral data: mp 146–147 °C (from hexane-EtOAc); IR (CHCl₃) 2952, 1435, 1253, 1145, 1122, 1080, 1069, 1028, 895, 873, 848 cm⁻¹; ¹H NMR (CDCl₃) δ 0.24 (s, 9, Si(CH₃)₃), 1.09 (s, 3, CH₃), 1.63–2.35 (m, 10), 3.15–3.48 (m, 4, SCH₂CH₂S), 5.77 (t, *J* = 1.3 Hz, 1, vinylic H). Anal. Calcd for C₁₇H₂₇NOS₂Si: C, 57.74; H, 7.70. Found: C, 57.81; H, 7.73.

(4*a*RS,5'*SR*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[dimethyl(1,1-dimethylethyl)silyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (10a). The minor isomer (\pm)-10a had the following physical and spectral data: mp 89–92.5 °C; IR (CHCl₃) 2962, 2938, 2863, 1461, 1436, 1258, 1100, 1032, 1019, 1008, 888, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.25 (s, 3, CH₃), 0.31 (s, 3, CH₃), 0.95 (s, 9, C(CH₃)₃), 1.30 (s, 3, CH₃), 1.63–2.49 (m, 10), 3.13–3.47 (m, 4, SCH₂CH₂S), 5.63–5.67 (m, 1, vinylic H). Anal. Calcd for C₂₀H₃₃NOS₂Si: C, 60.71; H, 8.41. Found: C, 60.63; H, 8.42.

(4*a*RS,5'*RS*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[dimethyl(1,1-dimethylethyl)silyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (10b). The general procedure described above (procedure A) was repeated using 637 mg (2.5 mmol) of (\pm)-8, 495 mg (3.5 mmol, 1.4 equiv) of TBDMSCN, and 8 mg (0.025 mmol, 0.01 equiv) of ZnI₂ to afford, after recrystallization and chromatography on silica gel using 1:20 EtOAc-hexane, 84 mg (9%) of a minor diastereomer (\pm)-10a and 848 mg (86%) of a major diastereomer (\pm)-10b. The major isomer (\pm)-10b had the following physical and spectral data: mp 149–150 °C (from hexane with a trace of CHCl₃); IR (CHCl₃) 2960, 2930, 1460, 1433, 1252, 1120, 864, 838 cm⁻¹; ¹H NMR (CDCl₃) δ 0.20 (s, 3, CH₃), 0.28 (s, 3, CH₃), 0.90 (s, 9, C(CH₃)₃), 1.12 (s, 3, CH₃), 1.63–2.37 (m, 10), 3.15–3.48 (m, 4, SCH₂CH₂S), 5.74–5.80 (m, 1, vinylic H); ¹³C NMR (CDCl₃) δ -4.5 (SiCH₃), -3.5 (SiCH₃), 17.4, 17.8(C(CH₃)₃), 22.2, 25.2 (C(CH₃)₃), 29.4, 33.3, 34.2, 37.3, 39.5, 39.9, 43.4 (C-4'a), 64.4 (C-2), 79.5 (C-5'), 120.7 (CN), 130.0 (C-1'), 138.8 (C-8'a). Anal. Calcd for C₂₀H₃₃NOS₂Si: C, 60.71; H, 8.41. Found: C, 60.55; H, 8.36.

(4*a*S,5'*R*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[dimethyl(1,1-dimethylethyl)silyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (10a). The minor isomer 10a had the following physical and spectral data: mp 98.5–100 °C (from hexane); [α]_D = too little material to determine. Anal. Calcd for C₂₀H₃₃NOS₂Si: C, 60.71; H, 8.41. Found: C, 60.81; H, 8.46.

(4*a*S,5'*S*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[dimethyl(1,1-dimethylethyl)silyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (10b). The major isomer (+)-10b had the following physical and spectral data: mp 187–187.6 °C (from Et₂O); [α]_D = +64.5° (CHCl₃, *c* = 1.00). Crystals of (+)-10b (C₂₀H₃₃NOS₂Si) were grown from (C₂H₅)₂O; *a* = 6.861 (1) Å, *b* = 17.416 (2) Å, *c* = 19.006 (2) Å, *V* = 2271.1 (5) Å³, space group P2₁2₁2₁ (no. 19), *Z* = 4, *D*_{calcd} = 1.157 g cm⁻³ at 296 K. A total of 5193 independent reflections (a quadrant of data having $\theta \leq 27.5^\circ$) were measured on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo K α radiation; the 3543 reflections having *I* > 3 σ (*I*) were included in the refinement. The structure was solved using the program packages MULTAN and DIRDIF and was refined anisotropically (282 variables) to *R* = 0.040.¹¹ Anal. Calcd for C₂₀H₃₃NOS₂Si: C, 60.71; H, 8.41. Found: C, 60.69; H, 8.41.

(4*a*RS,5'*SR*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[1,1-dimethylethyl)diphenylsilyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (11a). The minor isomer (\pm)-11a had the following physical and spectral data: mp 176–178 °C; IR (CHCl₃) 2965, 2935, 2863, 1465, 1425, 1112, 1103, 1008, 886, 840, 820, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.14 (s, 9, C(CH₃)₃), 1.26 (s, 3, CH₃), 1.35–2.45 (m, 9), 2.74–2.94 (m, 1), 3.15–3.48 (m, 4, SCH₂CH₂S), 5.71–5.75 (m, 1, vinylic H), 7.30–7.54 (m, 6, ArH), 7.68–7.90 (m, 4, ArH). Anal. Calcd for C₃₀H₃₇NOS₂Si: C, 69.32; H, 7.17. Found: C, 69.08; H, 7.08.

(4*a*RS,5'*RS*)-4',4'a,5',6',7',8'-Hexahydro-5'-[[1,1-dimethylethyl)diphenylsilyloxy]-4a'-methylspiro[1,3-dithiolane-2,2'(3*H*)-naphthalene]-5'-carbonitrile (11b). The general procedure described above (procedure A) was repeated using 254 mg (1 mmol) of (\pm)-8, 531 mg (2 mmol, 2 equiv) of TBDPSCN, and 16 mg (0.05 mmol, 0.05 equiv) of ZnI₂ to afford, after chromatography twice on silica gel using 1:1 benzene-hexane followed by 1:20 EtOAc-hexane, 49 mg (9%) of a minor diastereomer (\pm)-11a and 334 mg (64%) of a major diastereomer (\pm)-11b. The major isomer (\pm)-11b had the following physical and spectral data: mp 153–155 °C (hexane); IR (CHCl₃) 2950, 2863, 1463, 1424, 1113, 1068, 1029, 818, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.10 (s, 9, C(CH₃)₃), 1.26 (s, 3, CH₃), 1.35–2.60 (m, 10), 3.15–3.48 (m, 4, SCH₂CH₂S), 5.71–5.75 (m, 1, vinylic H), 7.33–7.54 (m, 6, ArH), 7.67–7.88 (m, 4, ArH). Anal. Calcd for C₃₀H₃₇NOS₂Si: C, 69.32; H, 7.17. Found: C, 69.14; H, 7.19.

(1*RS*,8*aRS*)-1,2,3,4,8,8a-Hexahydro-1-[[dimethyl(1,1-dimethylethyl)silyloxy]-8a-methyl-6(7*H*)-oxonaphthalene-1-carbonitrile (12). To a solution of 1.42 g (3.58 mmol) of (\pm)-10b in 140 mL of 1:1 THF-methanol was added 40 mL of water followed by a solution of 3.83 g (8.61 mmol, 2.4 equiv) of thallium-

(11) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* 1983, 16, 146.

(III) nitrate trihydrate¹² in 25 mL of methanol. The mixture was stirred at 25 °C for 7 min and was poured into cold water. The product was extracted with Et₂O, and the combined Et₂O solutions were dried over anhydrous MgSO₄. The product was chromatographed on a silica gel column with CHCl₃ and secondly on silica gel with hexane-EtOAc (gradient 8:1, 5:1, 3:1) to afford 1.07 g (93%) of (±)-12: mp 102–104 °C (from hexane); IR (CHCl₃) 2962, 2938, 2863, 1665 (C=O), 1462, 1332, 1258, 1138, 1126, 865, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.24 (s, 3, SiCH₃), 0.29 (s, 3, SiCH₃), 0.92 (s, 9, C(CH₃)₃), 1.29 (s, 3, CH₃), 1.74–2.23 (m, 5), 2.23–2.62 (m, 5), 5.89–5.93 (m, 1, vinylic H). Anal. Calcd for C₁₈H₂₉NO₂Si: 67.66; H, 9.15. Found: C, 67.70; H, 9.19.

(1*S*,8*aS*)-1,2,3,4,8,8*a*-Hexahydro-1-[[dimethyl(1,1-dimethylethyl)silyloxy]-8*a*-methyl-6(7*H*)-oxonaphthalene-1-carbonitrile (12). To a stirred solution of 45.2 g (114 mmol, 1 equiv) of (+)-10*b* in a mixture of 342 mL of methanol, 342 mL of CHCl₃, and 228 mL of THF at 15 °C was added 114 mL of water followed by a solution of 117 g (262 mmol, 2.3 equiv) of thallium(III) nitrate trihydrate¹² in 300 mL of methanol. The mixture was stirred for 20 min and filtered. The filter cake was washed with CHCl₃. The filtrate was poured into 1.5 L of cold water and extracted with three 400-mL portions of CHCl₃. The combined

extracts were dried over anhydrous MgSO₄ and concentrated. The residue was chromatographed on a silica gel column using CHCl₃, and the residue was recrystallized from hexane to afford 19.5 g (54%) of 12: mp 84.5–85.5 °C, [α]_D = +52.7° (CHCl₃, c 1.00); ¹³C NMR (CDCl₃) δ -4.6 (SiCH₃), -3.5 (SiCH₃), 16.3 (CH₃), 17.8 (C(CH₃)₃), 21.2, 25.1 (C(CH₃)₃), 30.1, 31.3, 33.5, 33.7, 44.9 (C-8*a*), 78.9 (C-1), 120.2 (CN), 127.5 (C-5), 163.2 (C-4*a*), 198.1 (CO). The IR (CHCl₃) and ¹H NMR (CDCl₃) data were identical to data collected with racemic material. The mother liquors and impure fractions from the first chromatography were combined and chromatographed on silica gel using hexane-EtOAc (gradient 8:1, 6:1, 5:1, 4:1) to afford an additional 10.3 g (28%, total yield 82%) of 12: mp 80.0–84.5 °C, [α]_D = +52.2°. An analytical sample was prepared by recrystallization from hexane, mp 84.5–86 °C, [α]_D = +53.7°. Anal. Calcd for C₁₈H₂₉NO₂Si: C, 67.66; H, 9.15. Found: C, 67.60; H, 9.20.

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