Stereoselective Synthesis of 2-Amino Alcohols by Use of an Isocyanide as an Aminomethylene Equivalent

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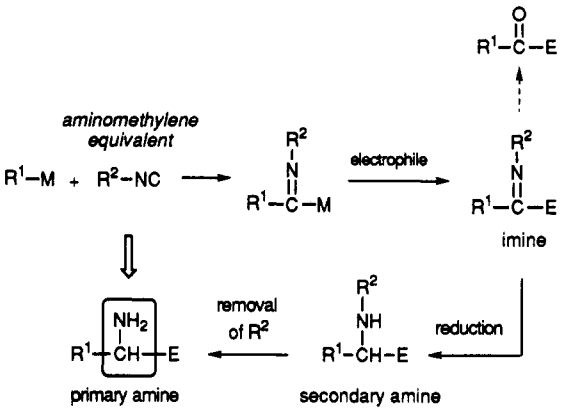
Preparation of an isocyanide having a removable *N*-substituent and its application to the stereoselective synthesis of 2-amino alcohols are described. 4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl isocyanide was prepared from commercially available 3,5-xylenol. The isocyanide underwent a samarium iodide-mediated coupling reaction with organic halides and carbonyl compounds. Reduction of the reaction mixture with $NaBH_4$ selectively afforded *anti* 2-(arylamino) alcohols, which were then deprotected to the corresponding 2-(primary amino) alcohols via desilylation with TBAF followed by oxidation with DDQ. A ceramide was successfully synthesized by use of the present stereoselective synthetic method for 2-amino alcohols, demonstrating a new synthetic utility of the isocyanide as an aminomethylene equivalent.

Carbon monoxide inserts into carbon–metal bonds and can therefore be utilized as a useful carbonyl synthon in a variety of carbonylation reactions.[1] Isocyanides, nitrogen analogs of carbon monoxide in terms of electronic structure, are also known to undergo insertion into carbon–metal bonds. For synthetic purposes, the resulting (α-iminoalkyl)metal compound is reacted with electrophiles to produce imines, which are then converted to the corresponding carbonyl compounds via acid-catalyzed hydrolysis of the imino group.[2] Consequently, the nitrogen atom is lost, the isocyanide being used as a *masked* carbonyl synthon. It would give the isocyanide additional synthetic value, one inaccessible from carbon monoxide, if the imino group of the product could be *unmasked* without the loss of the nitrogen atom. A feasible approach along this line would involve synthetic elaborations of the imine with reduction to a secondary amine and subsequent removal of the *N*-substituent, affording the corresponding primary amine (Scheme I). Although intrinsic, the synthetic utilization of the isocyanide as an aminomethylene equivalent has not yet been well exploited.

Recently, we reported[2f,h] the samarium(II) iodide-mediated[3] three-component coupling of an organic halide, 2,6-xylyl isocyanide, and a carbonyl compound, which gives rise to an α-hydroxy imine. Herein, we report preparation of an isocyanide having a removable *N*-substituent,[4] which is applicable to the stereoselective synthesis of 2-amino alcohols.[5] The synthesis of ceramide (11), of current interest in terms of its biological activities,[6,7] is also described.

Scheme I



Oxidative Removal of a 4-Oxy-2,6-xylyl Substituent of an Amine. The 4-methoxyphenyl group has been used for protection of amide nitrogens in β-lactam synthesis, where it is oxidatively removed.[8] Taking into account that the 2,6-disubstituted phenyl group is suitable for the *N*-substituent of the isocyanide utilized in the samarium-(II) iodide-mediated three-component coupling reaction,[2h] the possibilities of the oxidative cleavage of 4-oxy-2,6-xylidine derivatives **1a–c** were examined (Scheme II). By

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(1) (a) Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W. L.; Archer, C. M. *J. Org. Chem.* **1992**, *57*, 5620. (b) Murai, S.; Ryu, I.; Iriguchi, J.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 2440. (c) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342 and references cited therein.

(2) (a) Niznik, G. E.; Morrison, W. H.; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600. (b) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1981**, *46*, 5405. (c) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1982**, *47*, 52. (d) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1988**, *53*, 4158. (e) Murakami, M.; Ito, H.; Bakar, W. A. W. A.; Baba, A. B.; Ito, Y. *Chem. Lett.* **1989**, 1603. (f) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437. (g) Murakami, M.; Masuda, H.; Kawano, T.; Nakamura, H.; Ito, Y. *J. Org. Chem.* **1991**, *56*, 1. (h) Murakami, M.; Kawano, T.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 1458.

(3) Reviews on synthetic application of organolanthanides: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron*, **1986**, *24*, 6573. (b) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15. (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(4) Although a benzyl group on a nitrogen atom can be easily removed, benzyl isocyanide is not suitable for synthetic manipulations.[2]

(5) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (b) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310. (c) Barrett, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 339. (d) Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271 and references cited therein.

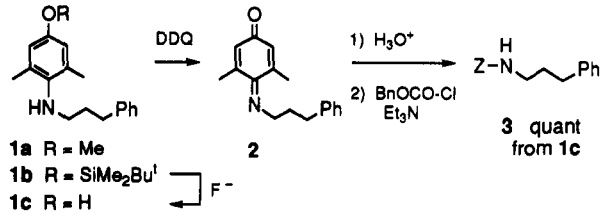
(6) (a) Hakomori, S. *Ann. Rev. Biochem.* **1981**, *50*, 733. (b) Hakomori, S. In *Handbook of Lipid Research: Sphingolipid Biochemistry*; Kanfer, J. N., Hakomori, S., Eds.; Plenum: New York, 1983; Vol. 3, pp 1–150.

(7) For syntheses of ceramides, see: (a) Koike, K.; Numata, M.; Sugimoto, M.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *158*, 113. (b) Hino, T.; Nakayama, K.; Taniguchi, M.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. I* **1986**, 1687. (c) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368. (d) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154 and references cited therein.

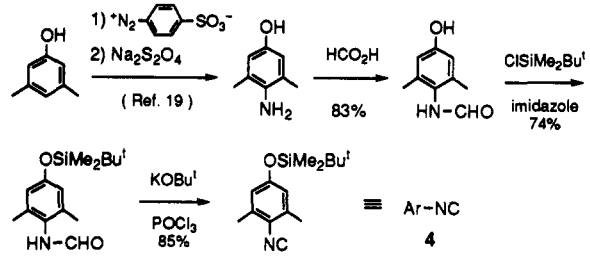
(8) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; p 400. For two-step oxidative removal of a 4-(methoxymethoxy)phenyl group on a β-lactam nitrogen, see: Fukuyama, T.; Frank, R. K.; Jewell, C. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2122.

0022-3263/93/1958-6766$04.00/0

Scheme II



Scheme III



use of ammonium cerium(IV) nitrate (CAN) as an oxidant, **1a** and **1c** were deprotected to afford amine **3** in moderate yields (66% and 56%, respectively),[9] whereas the reaction of **1b** was very slow. When 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as an oxidant, **1a** and **1b** gave a complex mixture.[10] Facile deprotection was achieved with the 4-hydroxyxylidine derivative **1c**; upon treatment with an equimolar amount of DDQ at 0 °C for 15 min, **1c** was converted to quinone monoimine **2** and, after removal of the resulting DDHQ by filtration, acid-catalyzed hydrolysis of the filtrate afforded the deprotected amine quantitatively. Furthermore, the 4-hydroxy derivative **1c** was readily obtained by desilylation of the 4-siloxy derivative **1b** with tetrabutylammonium fluoride (TBAF). These experiments disclosed that the 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl substituent of an amine can be easily removed by desilylation and subsequent oxidation with DDQ.

Synthesis of 2-Amino Alcohols. On the basis of the preliminary studies mentioned above, 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide (**4**) was prepared from commercially available 3,5-xylenol as shown in Scheme III.

Next, the samarium(II) iodide-mediated three-component coupling reaction with isocyanide **4** and subsequent oxidative *N*-dearylation to the corresponding 2-amino alcohol were examined. Following the protocol reported previously,[2h] **4** successfully coupled with an organic halide and a carbonyl compound. The resulting reaction mixture was reduced *in situ* with various hydride reducing agents. Whereas reduction with stereodemanding L-Selectride was sluggish, only poor selectivities were obtained by use of LAH, $NaBH_3CN$, and $NaBH(OAc)_3$. In contrast, $NaBH_4$, one of the simplest of hydride agents, exhibited good selectivity favoring *anti*-**5**. Notably, the stereochemical outcome was influenced by the addition of alcohols to the mixture as a cosolvent and, in particular, 2-propanol improved the selectivity significantly in some cases. The syntheses of a variety of 2-(arylamino) alcohols **5** by use of $NaBH_4$ are summarized in Table I.

Next, the 2-(arylamino) alcohols **5** thus obtained with good stereoselection were deprotected via desilylation with TBAF followed by oxidation with DDQ to afford the corresponding 2-(primary amino) alcohols **6** in high yield (Table I).

For assignment of the stereochemistry, the 2-amino alcohols **5** were converted to the 1,3-oxazolidin-2-ones **7** by treatment with triphosgene. The *cis* relationship of the vicinal 4- and 5-protons of **7** was elucidated on the basis of their ^1H NMR coupling constants (J_{4-5}).[5b,d,11] The major isomer shows a coupling constant of 6.9–7.8 Hz, which suggests a *cis* arrangement, while that of the minor isomer is 5.8–5.9 Hz (Table II). Both 4- and 5-protons of *cis* isomers resonate at lower field than those of *trans* isomers. The stereochemical assignment of **7a** and **7d** was confirmed by NOE experiments.

Synthesis of a Ceramide. Glycosphingolipids are constituents of cell membranes and play biologically important roles,[6] which have stimulated interest in their synthesis.[7] The present stereoselective synthetic method for 2-amino alcohols was next applied to the synthesis of a ceramide, the hydrophobic skeleton of glycosphingolipids. The α-oxy imine, prepared by coupling of benzyl chloromethyl ether, the isocyanide **4**, and 2-hexadecenal, was reduced *in situ* by $NaBH_4$ to give the corresponding *anti*-2-amino alcohol **8** stereoselectively (91:9) (Scheme IV). Then, a palmitoyl group was temporarily introduced onto the allylic hydroxyl group for protection against oxidation in the following step. Desilylation of **9** with TBAF followed by oxidative removal of the aryl group gave a primary amine. Notably, successive treatment of the crude amine with a catalytic amount of 4-(dimethylamino)pyridine promoted migration of the palmitoyl group from the allylic oxygen to the primary amino group, affording the amide **10**. Finally, the benzyl group was removed by Birch reduction to give the (±)-ceramide **11**.[7a] Thus, a convenient and general synthetic route to ceramides was established.

Interpretation of Stereochemical Outcome. The α-hydroxy imine **12** crystallized in orthorhombic form from hexane. An X-ray diffraction study[12] revealed a conformation involving intramolecular hydrogen bonding[13] (Figure 1). The 2,6-xylyl group is oriented away from the hydroxyl group and is almost perpendicular to the imino plane. As mentioned in the previous report,[2h] the ^{13}C NMR

(9) The produced (3-phenylpropyl)amine was isolated as benzyl carbamate **3**.

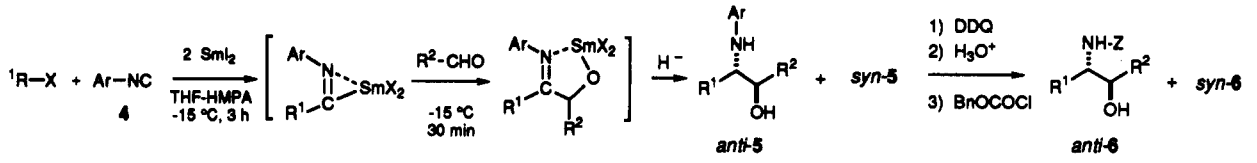
(10) The reaction of **1a** or **1b** with DDQ was much slower than that of **1c** and prolonged stirring led to the formation of a complex mixture involving 3-phenylpropanal, which presumably resulted from competitive dehydrogenative oxidation of the alkyl–nitrogen bond. In contrast, the reaction of **1c** with DDQ proceeded very rapidly and selectively at the aromatic site to give the quinone monoimine derivative **2**.

(11) (a) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308. (b) Rich, D. H.; Sun, E. T. O. *J. Med. Chem.* **1980**, *23*, 27. (c) Raddatz, P.; Jonczyk, A.; Minck, K.-O.; Rippmann, F.; Schittenhelm, C.; Schmitges, C. J. *J. Med. Chem.* **1992**, *35*, 3525.

(12) Crystal data: $C_{17}H_{25}NO$, M = 259.4, orthorhombic, space group *Pbca*, a = 14.182 (3), b = 16.776 (3), and c = 13.264 (3) Å, U = 3156 (1) Å^3, Z = 8, D_c = 1.09 g/cm^3, Cu K_α radiation (λ = 1.54178 Å), μ = 4.45 cm^{-1}. Intensity data were measured on a Mac Science MXC3 diffractometer using the ω–2θ scan technique; 2636 unique reflections within $3 \le 2\theta \le 130°$ were collected. The structure was solved by a direct method and refined anisotropically by the full-matrix least-squares to R = 0.066, R_w = 0.058, and S = 1.43 for 2332 reflections. All hydrogen atoms were located on a difference electron density map. The thermal parameter of each hydrogen atom was assumed to be isotropic and equal to that of the bonded atom. The authors have deposited atomic coordinates for structure **12** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(13) The OH group lies in the imino plane formed by N2, C16, and C17, making a planer 5-membered arrangement. The hydrogen bond N2···H1 is oriented considerably inside of the direction of conventionally viewed nitrogen sp^2 lone pairs (∠C17–N2–H1 = 86.8(8)°) and the O1–H1···N2 geometry is nonlinear (127(2)°), both presumably due to the constraints imposed by the 5-membered arrangement.

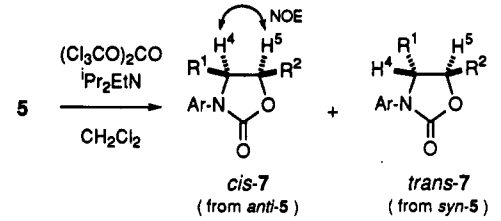
Table I. Stereoselective Syntheses of 2-Amino Alcohols from Organic Halides, 4, and Aldehydes



run	R^1–X	R^2CHO	H⁻	5, yield[a] (%)	*anti*:*syn*	6, yield[b] (%)
1		Et–CHO	$NaBH_4$	**5a**, 99	86:14	
2			$NaBH_4$/EtOH	86	90:10	
3			$NaBH_4$/^{i}PrOH	93	94:6	**6a**, 99
4			$NaBH_4$/^{t}BuOH	88	91:9	
5	Et–Br		$NaBH_4$	**5b**, 86	87:13	
6			$NaBH_4$/^{i}PrOH	83	95:5	**6b**, 89
7	^{i}Pr–I	Et–CHO	$NaBH_4$	**5c**, 99	98:2	**6c**, 90
8			$NaBH_4$/^{i}PrOH	98	98:2	
9	Et–Br	^{i}Pr–CHO	$NaBH_4$	**5d**, 91	97:3	**6d**, 99
10			$NaBH_4$/^{i}PrOH	99	94:6	
11			$NaBH_4$	**5e**, 97		**6e**, 89

[a] Isolated yields based on aldehydes. [b] Isolated yields based on **5**.

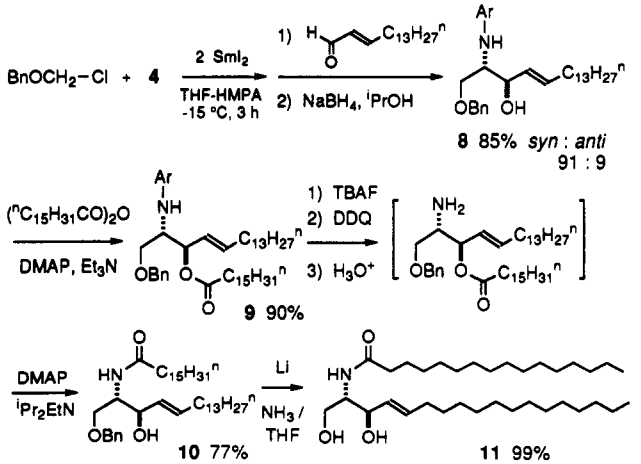
Table II. ^{1}H NMR Data of 7 in $CDCl_3$



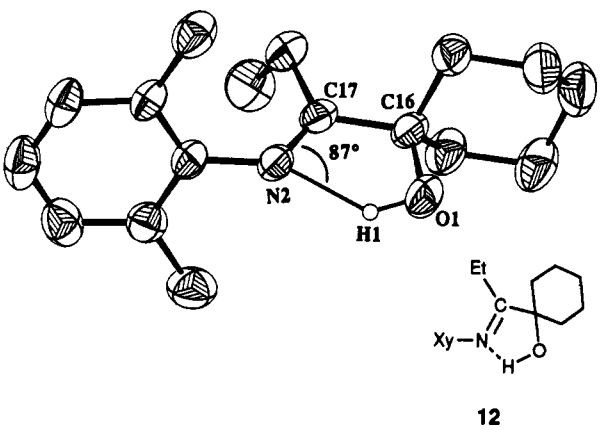
	cis isomer (major)			*trans* isomer (minor)		
7	H^4 (δ)	H^5 (δ)	J_{4-5} (Hz)	H^4 (δ)	H^5 (δ)	J_{4-5} (Hz)
7a	4.12	4.56	7.4	3.66	4.25	5.8
7b	4.05	4.64	7.8	3.53	4.26	5.9
7c	3.91	4.48	6.9		*a*	
7d	3.89	4.37	7.3	3.65	4.04	5.8

[a] Not specified.

Scheme IV



spectra of α-hydroxy imines show only one set of signals for the carbons in the 2,6-xylyl group; with α-hydroxy imines derived from symmetrical ketones, five signals are observed for the eight carbons in the 2,6-xylyl group due to experiencing magnetic equivalence. On the other hand, α-hydroxy imines which are derived from aldehydes and consequently have an asymmetric center in the molecule exhibit magnetic nonequivalence of the eight carbons in the 2,6-xylyl group. This magnetic behavior is consistent with the presence of intramolecular hydrogen bonding in solution as well as in the crystalline state.



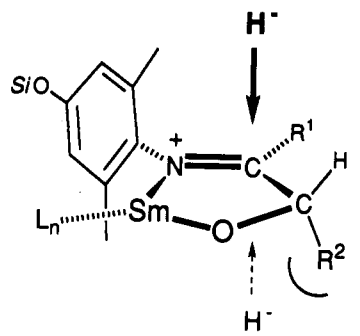
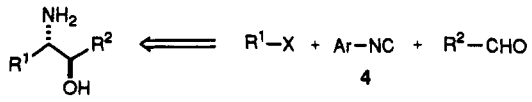


Figure 1. Top: single-crystal structure of α-hydroxy imine **12** (35% probability ellipsoids). Selected bond lengths (Å): O1-H1, 0.97(3); N2-H1, 1.83(3); N2-C17, 1.276(2). Bottom: proposed course of hydride attack.

Considering the Lewis acidity of samarium(III), one might expect that the intermediary samarium(III) alkoxide takes an analogous conformation involving 5-membered chelation instead of the hydrogen bonding.[14] On the basis of this conformation, the stereoselection observed in the

(14) Isolation of a single crystal of the intermediary samarium(III) alkoxide has been unsuccessful so far.

Scheme V



hydride reduction is reasonably attributed to the attack of hydride from the less-hindered side of the 5-membered ring.

Lanthanide(III) ions, being frequently used as shift reagents, are well known to bind to alcohols.[15] In addition, lanthanide ions catalyze the reaction of $NaBH_4$ with alcohols to give sodium alkoxyborohydrides,[16] which are more reactive than $NaBH_4$.[17] Although the precise species involved in the present reduction is unclear, alcohol complexation with samarium(III) ion and/or formation of sodium alkoxyborohydrides are probably responsible for the effect of the alcohol cosolvents on the stereoselectivity.

Conclusions

The present stereoselective synthesis of 2-amino alcohols from alkyl halides, the isocyanide 4, and aldehydes demonstrates an *intrinsic* synthetic utility of the isocyanide as an aminomethylene equivalent (Scheme V). In addition, two step removal of the 4-siloxyaryl group of an amine will provide new procedures of reductive and alkylative amination of carbonyl compounds, which are now under investigation in our laboratory.

Experimental Section

General. Column chromatography was performed with silica gel (Wakogel C-200). Preparative TLC was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d*. Where appropriate, NMR data only for the major stereoisomer are described. Na_2SO_4 was used to dry organic layers after extraction. All reactions were performed under a dry nitrogen atmosphere.

Unless otherwise noted, materials were obtained from commercial sources and purified appropriately. THF was distilled from sodium diphenyl ketyl, DMF, CH_2Cl_2, and HMPA from CaH_2, and toluene from $LiAlH_4$. 2-Hexadecenal was prepared by the literature procedure.[18]

4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl Isocyanide (4). A mixture of 4-amino-3,5-xylenol (5.7 g, 41.5 mmol), prepared from 3,5-xylenol by the literature procedure,[19] and formic acid (11 mL) in toluene (80 mL) was heated at reflux for 3 h in a Dean–Stark apparatus. On cooling, white solids precipitated. After filteration, the solids were washed with water and toluene, and dried to give crude 4-formamido-3,5-xylenol (5.7 g, 83%).

To a mixture of 4-formamido-3,5-xylenol (5.7 g, 34.5 mmol) and *tert*-butylchlorodimethylsilane (7.8 g, 52 mmol) in DMF (40 mL) was added Et_3N (10.5 g, 104 mmol). The mixture was stirred at rt for 20 h, diluted with water, and extracted with ether. Filtration of the organic layer through a short column of silica gel followed by recrystallization from ether–hexane gave *N*-formyl-4-(*tert*-butyldimethylsiloxy)-2,6-xylidine (7.1 g, 74%).

A solution of trichloromethyl chloroformate (1.6 mL, 13.3 mmol) in CH_2Cl_2 (10 mL) was added to *N*-formyl-4-(*tert*-butyldimethylsiloxy)-2,6-xylidine (2.58 g, 9.23 mmol) in CH_2Cl_2 (8 mL) and Et_3N (9 mL) at −78 °C over 1 h.[20] The mixture was stirred at −78 °C for an additional 1 h, allowed to warm to rt, diluted with aqueous NH_3, stirred for 2 h, extracted with ether, and washed with saturated aqueous NaCl. The title compound was obtained by vacuum distillation (2.08 g, 86%): bp 107 °C (0.35 mmHg); ^1H NMR δ 0.20 (s, 6 H), 0.97 (s, 9 H), 2.36 (s, 6 H), 6.55 (s, 2 H); ^{13}C NMR δ −4.4, 18.2, 19.0, 25.6, 119.1, 120.3 (t, J_{C-N} = 12.5 Hz), 136.4, 155.5, 166.3. Anal. Calcd for $C_{15}H_{23}NOSi$: C, 68.91; H, 8.87; N, 5.36. Found: C, 68.67; H, 8.97; N, 5.20.

4-[[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino]-6-phenyl-3-hexanol (5a). A mixture of samarium powder (180 mg, 1.2 mmol) and 1,2-diiodoethane (282 mg, 1.0 mmol) in THF (12 mL) was stirred at rt for 2 h. HMPA (0.6 mL, 3.4 mmol)[21] was added and, after the reaction mixture was cooled to −15 °C, 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide (4, 105 mg, 0.40 mmol) and (2-bromoethyl)benzene (93 mg, 0.50 mmol) were successively added. The reaction mixture was stirred for 2 h and propionaldehyde (18 mg, 0.31 mmol) was added. Stirring was continued for an additional 30 min and then 2-propanol (1 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added. The mixture was stirred for 16 h at −15 °C, diluted with water (3 drops) and hexane (30 mL), and filtered through a short column of Florisil. The filtrate was subjected to preparative TLC (ether:hexane = 1:3) to afford the title compound **5a** as an oil (123 mg, 93%): ^1H NMR δ 0.18 (s, 6 H), 0.93 (t, J = 7.5 Hz, 3 H), 0.98 (s, 9 H), 1.35–1.55 (m, 2 H), 1.65–1.95 (m, 2 H), 2.22 (s, 6 H), 2.45–2.70 (m, 1 H), 2.75–2.95 (m, 1 H), 3.16 (ddd, J = 2.9, 4.9, 7.8 Hz, 1 H), 3.44–3.60 (m, 1 H), 6.50 (s, 2 H), 7.06–7.32 (m, 5 H); ^{13}C NMR δ −4.4, 10.7, 18.1, 19.2, 25.7, 26.1, 32.2, 32.9, 59.5, 74.0, 120.3, 125.7, 128.3, 130.4, 138.1, 142.1, 149.8. Anal. Calcd for $C_{26}H_{41}NO_2Si$: C, 73.02; H, 9.66; N, 3.27. Found: C, 72.76; H, 9.86; N, 3.21.

4-[[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino]-1-phenyl-3-hexanol (5b). By a procedure similar to that for **5a**, the title compound was obtained from bromoethane, 4, and 3-phenylpropanal (83%): ^1H NMR δ 0.19 (s, 6 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.99 (s, 9 H), 1.38–1.56 (m, 2 H), 1.65–1.80 (m, 2 H), 2.24 (s, 6 H), 2.40–3.00 (m, 4 H), 3.08 (dt, J = 3.4, 6.8 Hz, 1 H), 3.60–3.72 (m, 1 H), 6.50 (s, 2 H), 7.15–7.35 (m, 5 H); ^{13}C NMR δ −4.4, 11.1, 18.1, 19.2, 23.7, 25.7, 32.7, 34.3, 62.6, 71.3, 120.2, 125.9, 128.4, 130.8, 137.9, 142.0, 150.0. Anal. Calcd for $C_{26}H_{41}NO_2Si$: C, 73.02; H, 9.66; N, 3.27. Found: C, 72.76; H, 9.38; N, 3.24.

4-[[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino]-5-methyl-3-hexanol (5c). By a procedure similar to that for **5a**, the title compound was obtained from 2-iodopropane, 4, and propionaldehyde (98%): ^1H NMR δ 0.16 (s, 6 H), 0.92–1.03 (m, 18 H), 1.26–1.64 (m, 2 H), 1.85–2.10 (m, 2 H), 2.25 (s, 6 H), 2.87–3.18 (br, 1 H), 3.14 (t, J = 5.0 Hz, 1 H), 3.41–3.61 (m, 1 H), 6.47 (s, 2 H); ^{13}C NMR δ −4.5, 10.7, 18.1, 19.0, 19.4, 21.2, 25.7, 26.1, 30.1, 64.1, 74.4, 120.5, 128.7, 139.1, 149.1. Anal. Calcd for $C_{21}H_{39}NO_2Si$: C, 68.99; H, 10.75; N, 3.83. Found: C, 68.72; H, 10.54; N, 3.89.

4-[[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino]-2-methyl-3-hexanol (5d). By a procedure similar to that for **5a** except for the absence of 2-propanol, the title compound was obtained from bromoethane, 4, and 2-methylpropanal (91%): ^1H NMR δ 0.17 (s, 6 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.98 (s, 9 H), 1.08 (d, J = 7.3 Hz, 3 H), 1.39–1.75 (m, 3 H), 2.25 (s, 6 H), 3.06–3.21 (m, 2 H), 6.49 (s, 2 H); ^{13}C NMR δ −4.5, 11.6, 18.1, 19.1, 19.6, 22.2, 25.7, 31.1, 59.5, 76.3, 120.2, 130.2, 138.6, 149.5. Anal. Calcd for $C_{21}H_{39}NO_2Si$: C, 68.99; H, 10.75; N, 3.83. Found: C, 68.94; H, 10.76; N, 3.72.

1-[1-[[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino]-3-phenylpropyl]cyclohexanol (5e). By a procedure similar to that for **5a** except for the absence of 2-propanol, the title compound was obtained from (2-bromoethyl)benzene, 4, and cyclohexanone (97%): ^1H NMR δ 0.22 (s, 6 H), 1.02 (s, 9 H), 1.40–2.15 (m, 12 H), 2.15–2.38 (m, 1 H), 2.26 (s, 6 H), 2.44–2.61 (m, 1 H), 3.07 (dd, J = 2.6, 8.1 Hz, 1 H), 3.20–3.60 (br, 1 H), 6.55 (s, 2 H), 6.85–6.93 (m, 2 H), 7.10–7.25 (m, 3 H); ^{13}C NMR δ −4.4, 18.2, 19.5, 21.5, 22.1, 25.7, 26.1, 32.0, 33.9, 34.9, 35.4, 63.6, 72.9, 120.6, 125.7, 128.18, 128.22, 129.3, 138.9, 141.8, 149.7. Anal. Calcd for $C_{29}H_{45}NO_2Si$: C, 74.46; H, 9.70; N, 2.99. Found: C, 74.39; H, 9.71; N, 2.90.

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4-[(Benzyloxycarbonyl)amino]-6-phenyl-3-hexanol (6a). To **5a** (62 mg, 0.145 mmol) in THF (0.5 mL) was added TBAF (1 M in THF, 0.2 mmol). The reaction mixture was stirred for 1 h at rt and then filtered through a short column of silica gel. After evaporation of volatiles, the residue was dissolved in CH_2Cl_2 (1 mL), to which DDQ (33 mg, 0.145 mmol) was added at 0 °C. The mixture was stirred for 30 min, filtered through Celite, evaporated, dissolved in MeOH (1 mL) and aqueous HCl (0.1 M, 0.5 mL), and stirred at rt for 10 h. Saturated aqueous Na_2CO_3 (0.5 mL) and benzyl chloroformate (120 mg, 0.70 mmol) were added to the mixture at 0 °C. The mixture was allowed to warm up to rt over 10 h. Extraction with ether followed by column chromatography (ether:hexane = 1:1) gave **6a** (47 mg, 99%): ^1H NMR δ 0.94 (t, J = 7.3 Hz, 3 H), 1.35–1.52 (m, 2 H), 1.65–1.95 (m, 2 H), 2.08 (br d, J = 4.9 Hz, 1 H), 2.50–2.85 (m, 2 H), 3.45–3.80 (m, 2 H), 4.95–5.05 (m, 1 H), 5.12 (s, 2 H), 7.05–7.45 (m, 10 H); ^{13}C NMR δ 10.3, 26.2, 30.8, 32.5, 55.1, 66.9, 76.0, 125.9, 128.1, 128.2, 128.3, 128.4, 128.5, 136.4, 141.6, 156.7. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.38; H, 7.88; N, 4.13.

The syntheses of **6b–e** were carried out according to the above procedure.

4-[(Benzyloxycarbonyl)amino]-1-phenyl-3-hexanol (6b): ^1H NMR δ 0.94 (t, J = 7.3 Hz, 3 H), 1.25–1.80 (m, 4 H), 2.36 (br d, J = 5.2 Hz, 1 H), 2.65 (dt, J = 13.8, 8.2 Hz, 1 H), 2.89 (dt, J = 13.8, 6.9 Hz, 1 H), 3.47–3.79 (m, 2 H), 4.70–4.93 (m, 1 H), 5.11 (s, 2 H), 7.14–7.40 (m, 10 H); ^{13}C NMR δ -4.4, 11.1, 18.1, 19.2, 23.7, 25.7, 32.7, 34.3, 62.6, 71.3, 120.2, 125.9, 128.4, 130.8, 137.9, 142.0, 150.0. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.12; H, 7.66; N, 4.25.

4-[(Benzyloxycarbonyl)amino]-5-methyl-3-hexanol (6c): ^1H NMR δ 0.89–1.04 (m, 9 H), 1.25–1.65 (m, 3 H), 1.85–2.03 (m, 1 H), 3.45–3.65 (m, 2 H), 4.60–4.75 (br, 1 H), 5.11 (s, 2 H), 7.30–7.40 (m, 5 H); ^{13}C NMR δ 10.3, 17.7, 20.3, 25.7, 28.3, 60.5, 67.0, 74.2, 128.1, 128.2, 128.5, 136.4, 157.2. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.75; H, 8.51; N, 5.27.

4-[(Benzyloxycarbonyl)amino]-2-methyl-3-hexanol (6d): ^1H NMR δ 0.85–1.04 (m, 9 H), 1.25–1.50 (m, 1 H), 1.52–1.90 (m, 3 H), 3.29 (dd, J = 3.3, 8.0 Hz, 1 H), 3.61–3.77 (m, 1 H), 4.95–5.10 (br, 1 H), 5.11 (s, 2 H), 7.30–7.40 (m, 5 H); ^{13}C NMR δ 10.6, 18.9, 19.0, 21.0, 30.8, 54.6, 66.6, 79.8, 128.0, 128.1, 128.5, 136.6, 156.4. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.67; H, 8.72; N, 5.23.

1-[1-[(Benzyloxycarbonyl)amino]-3-phenylpropyl]cyclohexanol (6e): ^1H NMR δ 1.1–1.8 (m, 12 H), 1.88–2.10 (m, 1 H), 2.53–2.85 (m, 2 H), 3.63 (dt, J = 2.6, 10.6 Hz, 1 H), 4.90–5.25 (m, 1 H), 7.10–7.45 (m, 10 H); ^{13}C NMR δ 21.7, 21.8, 25.5, 31.0, 32.7, 34.5, 34.8, 58.2, 66.8, 73.5, 125.8, 127.99, 128.05, 128.3, 128.5, 136.6, 142.0, 157.0. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.09; H, 7.89; N, 3.85.

***Preparation of* 1,3-Oxazolidin-2-ones 7.** To a mixture of 2-(arylamino) alcohol **5** (0.5 mmol) and *i*-Pr_2EtN (0.2 mL) in CH_2Cl_2 (0.5 mL) at 0 °C was added triphosgene (0.3 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at rt overnight. After the addition of aqueous NH_4OH (30%, 0.5 mL), the mixture was extracted with ether, dried, and subjected to column chromatography to give **7** (80–90%). **7a**: ^1H NMR δ 0.20 (s, 6 H), 0.98 (s, 9 H), 1.14 (t, J = 7.3 Hz, 3 H), 1.60–2.00 (m, 4 H), 2.07 (s, 3 H), 2.24 (s, 3 H), 2.41 (t, J = 8.1 Hz, 2 H), 4.12 (q, J = 7.4 Hz, 1 H), 4.56 (ddd, J = 7.4, 4.6, 3.3 Hz, 1 H), 6.54–6.60 (m, 2 H), 6.90–6.97 (m, 2 H), 7.16–7.30 (m, 3 H). **7b**: ^1H NMR δ 0.19 (s, 6 H), 0.73 (t, J = 7.4 Hz, 3 H), 0.97 (s, 9 H), 1.20–1.70 (m, 2 H), 1.80–2.20 (m, 2 H), 2.17 (s, 3 H), 2.21 (s, 3 H), 2.70–3.15 (m, 2 H), 4.05 (ddd, J = 9.2, 7.8, 5.0 Hz, 1 H), 4.64 (ddd, J = 11.2, 7.8, 2.3 Hz, 1 H), 6.50–6.59 (m, 2 H), 7.15–7.40 (m, 5 H). **7c**: ^1H NMR δ 0.18 (s, 6 H), 0.54 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.97 (s, 9 H), 1.15 (t, J = 7.2 Hz, 3 H), 1.70–2.00 (m, 3 H), 2.18 (s, 3 H), 2.26 (s, 3 H), 3.91 (dd, J = 9.1, 6.9 Hz, 1 H), 4.48 (ddd, J = 10.1, 6.9, 3.3 Hz, 1 H), 6.50–6.59 (m, 2 H). **7d**: ^1H NMR δ 0.18 (s, 6 H), 0.75 (t, J = 7.4 Hz, 3 H), 0.96 (s, 9 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.51–1.95 (m, 2 H), 2.00–2.18 (m, 1 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 3.89 (q, J = 7.3 Hz, 1 H), 4.37 (q, J = 7.3 Hz, 1 H), 6.50–6.57 (m, 2 H).

(*E*)-1-(Benzyloxy)-2-[[4-(*tert*-butyldimethylsiloxy)-2,6-xylyl]amino]octadec-4-en-3-ol (8). By a procedure similar to that for **5a**, the title compound was obtained from benzyl chloromethyl ether, **4**, and 2-hexadecenal (85%): ^1H NMR δ 0.19 (s, 6 H), 0.90 (t, J = 6.8 Hz, 3 H), 0.99 (s, 9 H), 1.20–1.44 (br, 22 H), 2.03 (q, J = 6.6 Hz, 2 H), 2.24 (s, 6 H), 3.13 (q, J = 3.4 Hz, 1 H), 3.22 (d, J = 9.1 Hz, 1 H), 3.50 (dd, J = 3.4, 9.3 Hz, 1 H), 3.71 (dd, J = 2.9, 9.3 Hz, 1 H), 4.23–4.35 (m, 1 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 5.50 (dd, J = 5.4, 15.4 Hz, 1 H), 5.65–5.85 (m, 1 H), 6.50 (s, 2 H), 7.25–7.42 (m, 5 H); ^{13}C NMR δ -4.4, 14.1, 18.1, 18.8, 22.7, 25.7, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 60.0, 70.4, 73.8, 73.9, 120.0, 127.7, 127.9, 128.4, 130.2, 131.1, 132.1, 137.5, 137.7, 150.1. Anal. Calcd for $C_{39}H_{65}NO_3Si$: C, 75.06; H, 10.50; N, 2.24. Found: C, 74.92; H, 10.30; N, 2.35.

(*E*)-1-(Benzyloxy)-2-[[4-(*tert*-butyldimethylsiloxy)-2,6-xylyl]amino]-3-(palmitoyloxy)octadec-4-ene (9). To a mixture of **8** (72 mg, 0.12 mmol), Et_3N (0.5 mL, 3.6 mmol), and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added palmitic anhydride (200 mg, 0.4 mmol). The reaction mixture was stirred at rt overnight and then subjected to column chromatography (ethe :hexane = 1:10) to give **9** (89 mg, 90%): ^1H NMR δ 0.16 (s, 6 H), 0.89 (t, J = 6.8 Hz, 6 H), 0.97 (s, 9 H), 1.26 (br s, 46 H), 1.45–1.65 (m, 2 H), 2.02 (q, J = 6.2 Hz, 2 H), 2.19 (s, 6 H), 2.10–2.25 (m, 2 H), 3.10–3.20 (br, 1 H), 3.25–3.50 (m, 3 H), 4.41 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 5.44–5.62 (m, 2 H), 5.77 (dt, J = 14.6, 6.2 Hz, 1 H), 6.47 (s, 2 H), 7.25–7.40 (m, 5 H); ^{13}C NMR δ -4.4, 14.1, 18.1, 18.8, 22.7, 24.9, 25.7, 28.9, 29.17, 29.22, 29.3, 29.5, 29.7, 31.9, 32.4, 34.5, 59.2, 68.8, 73.2, 74.4, 120.1, 125.1, 127.5, 127.6, 128.3, 130.6, 135.6, 137.8, 138.1, 149.9, 172.6. Anal. Calcd for $C_{55}H_{95}NO_4Si$: C, 76.60; H, 11.10; N, 1.62. Found: C, 76.85; H, 11.29; N, 1.53.

(*E*)-1-(Benzyloxy)-2-palmitamidooctadec-4-en-3-ol (10). To **9** (43 mg, 0.05 mmol) in THF (0.5 mL) was added TBAF (1 M in THF, 0.08 mmol). The reaction mixture was stirred for 30 min at rt and then filtered through a short column of silica gel. After evaporation of volatiles, the residue was dissolved in CH_2Cl_2 (0.5 mL), to which at 0 °C was added DDQ (12 mg, 0.05 mmol). The mixture was stirred for 30 min, filtered through Celite, evaporated, dissolved in MeOH (1 mL) and aqueous HCl (0.1 M, 0.2 mL), and stirred at rt for 6 h. Saturated aqueous Na_2CO_3 (0.5 mL) was added and the mixture was extracted with AcOEt, dried, and evaporated. To the residue were added CH_2Cl_2 (0.5 mL), Et_3N (0.5 mL, 3.6 mmol), and 4-(dimethylamino)-pyridine (5 mg, 0.04 mmol). The mixture was stirred at reflux for 2 days, evaporated, and subjected to column chromatography ($CHCl_3$) to afford **10** (20 mg, 77%): ^1H NMR δ 0.88 (t, J = 6.2 Hz, 6 H), 1.25 (br s, 46 H), 1.50–1.70 (m, 2 H), 2.01 (q, J = 6.3 Hz, 2 H), 2.19 (t, J = 7.3 Hz, 2 H), 3.32 (d, J = 8.4 Hz, 1 H), 3.61 (dd, J = 9.6, 2.9 Hz, 1 H), 3.80 (dd, J = 9.6, 3.1 Hz, 1 H), 3.98–4.24 (m, 2 H), 4.44 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 12.0 Hz, 1 H), 5.44 (dd, J = 15.7, 5.9 Hz, 1 H), 5.73 (dt, J = 15.7, 6.3 Hz, 1 H), 6.16 (d, J = 7.8 Hz, 1 H), 7.25–7.40 (m, 5 H); ^{13}C NMR δ 14.1, 22.7, 25.8, 29.19, 29.25, 29.30, 29.4, 29.5, 29.67, 29.72, 31.9, 32.3, 36.9, 52.7, 70.0, 73.7, 74.3, 127.9, 128.1, 128.6, 129.1, 133.4, 137.3, 173.3. Anal. Calcd for $C_{41}H_{73}NO_3$: C, 78.41; H, 11.72; N, 2.23. Found: C, 78.12; H, 11.71; N, 2.22.

(*E*)-2-Palmitamidooctadec-4-ene-1,3-diol (11). To lithium (4.5 mg, 0.65 mmol) in liquid NH_3 at -78 °C was added **10** (12 mg, 19 μmol) in THF (0.5 mL). After the reaction mixture was stirred at -78 °C for 2 h and at -40 °C for 4 h, NH_4Cl and MeOH were added. The mixture was allowed to warm up to rt, filtered, evaporated, and subjected to column chromatography (MeOH: $CHCl_3$ = 1:10) to afford **11** (10 mg, 99%), the ^{13}C NMR spectrum of which was identical to that of a natural sample: ^{13}C NMR δ 14.1, 22.7, 25.7, 29.1, 29.2, 29.3, 29.5, 29.7, 31.9, 32.3, 36.8, 54.4, 62.5, 74.7, 128.8, 134.3, 173.9.

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