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Functionalized Silica Gel as a Support for Solid-Phase Organic Synthesis

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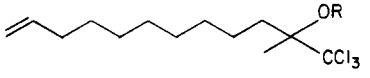
With the aim of extending solid-phase synthetic techniques to the synthesis of other classes of biomolecules such as complex lipids, methodology is described for the attachment of two representative substrates, cholesterol and 1-adamantanamine, to the surface of silica gel by way of chlorocarbonate-derivatized silica gel **10**. The substrates may be liberated under mild conditions from the resulting silica gels **11** (loading, 0.14 mmol/g) and **12** (loading, 0.30 mmol/g), respectively, using Bu_3P–Et_3N–DMF and 3% trifluoroacetic acid in CH_2Cl_2. The synthesis and cleavage of three soluble analogues, carbonates **3** and **14** and carbamate **4**, served as a model for the solid-phase experiments. The immobilization methodology was shown to be applicable to the structurally more complex, orthogonally protected lipid precursor alcohol **18**. Soluble carbonate **19** and silica gel **13** (loading, 0.13 mmol/g) were thus readily prepared from **18**.

The stepwise solid-phase synthesis of oligonucleotides[1,2] and peptides[3-5] is a highly efficient method for the construction of these complex molecules. We became interested in the possibility of extending solid-phase methodology to the synthesis of other classes of biomolecules, for example, certain complex lipids.[6] Herein, we describe methodology for the attachment of synthetic precursors to the surface of silica gel[7] in a manner such that the final (likely multifunctionalized) target molecules may be liberated from the silica gel under mild conditions at the end of the reaction sequence.

Our first objective was alkene alcohol **1**. The carbon chain of this tether molecule serves as a spacer arm that holds the substrate away from the surface of the silica gel.



1, R=H
2, R=COCl
3, R=CO_2-3β-cholesteryl
4, R=CONH-adamantyl

Owing to its similarity to the grouping used so successfully as a protecting group in silica gel supported oligonucleotide synthesis,[2] the trichloromethyl-substituted tertiary alcohol grouping was chosen as the site for synthetic substrate attachment. The initial plan was to hydrosilylate the double bond of **1** for attachment to the silica gel. 11-Dodecen-2-one[8] was prepared from 10-undecenoic acid by reaction with methyllithium[9] and then allowed to react with (trichloromethyl)lithium[10] to give **1**. After numerous unsuccessful attempts to effect catalytic hydrosilylation of the terminal double bond of **1** with triethoxysilane[11] an alternative approach involving oxidation of the double bond to the carboxylic acid was pursued. Lemieux oxidation[12] of **1** with basic $KMnO_4/NaIO_4$ effected oxidation to the carboxylic acid but was accompanied by facile base-catalyzed elimination of the trichloromethyl group to give the corresponding methyl ketone. The desired oxidation to **5** was achieved by using $KMnO_4$ in acetic acid–water.[13]

The first method examined for the attachment of **5** to silica gel involved the synthesis of triethoxysilane amide

(1) Matteucci, M. D.; Caruthers, M. H. *J. Am. Chem. Soc.* **1981**, *103*, 3185.
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(10) Hoeg, D. F.; Lusk, D. I.; Crumbliss, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 4147. Krebs, J.; Weber, A.; Neuenschwander, M. *Chimia* **1981**, *35*, 55. Blumbergs, P.; La Montagne, M. P. *J. Org. Chem.* **1972**, *37*, 1248.
(11) Green, M.; Spencer, J. L.; Stone, F. G. A.; Tsipis, C. A. *J. Chem. Soc., Dalton Trans.* **1977**, 1519. Speier, J. L.; Webster, J. A.; Barnes, G. H. *J. Am. Chem. Soc.* **1957**, *79*, 974. Capka, M.; Hetflejs, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 154. For example, whereas 1-decene underwent hydrosilylation at 65 °C for 4 h with triethoxysilane in the presence of 2×10^{-5} equiv of $H_2PtCl_6 \cdot H_2O$ and a trace of isopropyl alcohol (to simulate the presence of the terminal alcohol group in **3**), alkene **3** did not give the desired hydrosilylated product under these or more vigorous conditions. The reaction also failed when $(Ph_3P)_3RhCl$ was the catalyst (Chalk, A. J. *J. Organomet. Chem.* **1970**, *21*, 207).
(12) See: Pelletier, S. W.; Iyer, K. N.; Chang, C. W. *J. Org. Chem.* **1970**, *35*, 3535.
(13) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749.

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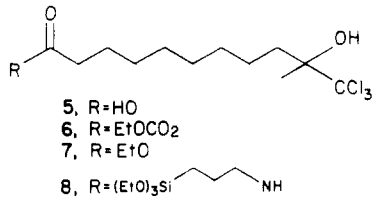
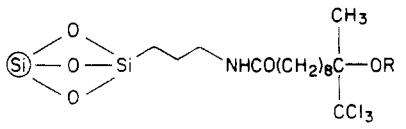
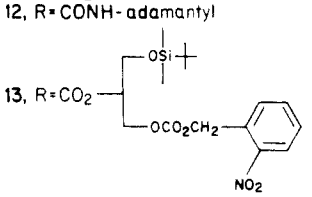


5, R=HO
6, R=EtOCO$_2$
7, R=EtO
8, R=(EtO)$_3$Si–NH

8 followed by coupling to the surface of activated silica gel. The reaction of **5** with ethyl chloroformate and Et_3N[14] at 25 °C led to mixed anhydride **6**, contaminated with ester **7**.[15] Formation of **7** could be avoided by performing the reaction and workup below 0 °C. Crude amide **8** was prepared from **6** by condensation with (3-aminopropyl)-triethoxysilane and then used directly in a coupling reaction[16] with activated[7] silica gel to produce **9** with a loading of 0.14 mmol of the amide alcohol per g of **9**.



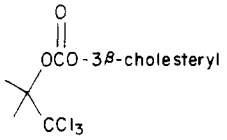
9, R=H
10, R=COCl
11, R=CO$_2$-3β-cholesteryl
12, R=CONH-adamantyl



13, R=CO$_2$

With the aim of increasing the loading in **9**, an alternative method of attachment to silica gel was investigated. After a series of optimization experiments using the corresponding mixed anhydride derived from palmitic acid, (3-aminopropyl)silylated silica gel (loading, 0.67 mmol free NH_2 groups per g)[7] was acylated with freshly prepared **6** to give **9** with a loading of 0.50 mmol per g.[17] Excess **6** was recovered, accompanied by varying amounts of ester **7** (see above).

As a prelude to the envisaged attachment–cleavage chemistry involving silica gel, the respective attachment and release steps were examined in solution first, using alkene alcohol **1** and two respresentative substrates as a model. Treatment of **1** with excess phosgene gave chlorocarbonate **2**, which underwent reaction with cholesterol to give carbonate **3**. Similarly, **2** reacted with adamantanamine to give carbamate **4**. Also prepared for purposes of comparison was the simpler cholesterol carbonate **14**.



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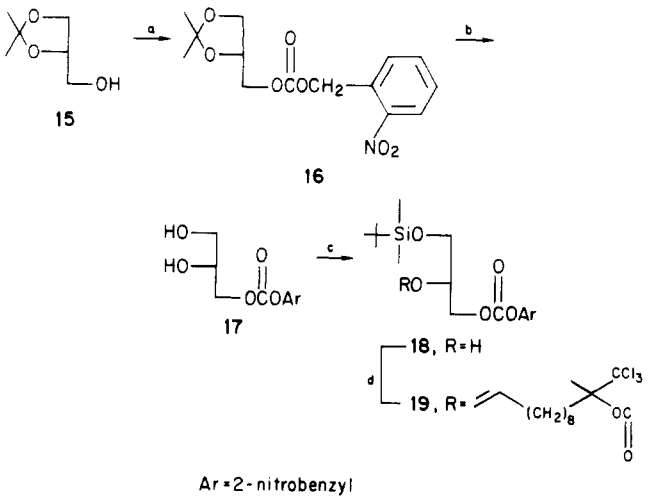
In general, carbonates and carbamates[18] with a β,β,β-trichloroethyl group are cleaved reductively in solution under mild conditions with cobalt(I) phthalocyanine, Zn dust,[19] or by electrolysis.[20] The Bu_3P–Et_3N–DMF

Chart I[a]



Ar=2-nitrobenzyl

[a] (a) [(2-nitrobenzyl)oxy]carbonyl chloride, 4-DMAP, CH_2Cl_2; (b) aq H_2SO_4, acetone; (c) *tert*-butyldimethylsilyl chloride, $AgNO_3$, THF; (d) **2**, CH_2Cl_2, pyridine.

cleavage conditions developed by Letsinger et al.[2] for deprotection of nucleoside trichloroethyl phospho triesters supported on silica gel are expected to be compatible with ester groups that may be present elsewhere in a complex lipid molecule. We were therefore interested to learn whether the Letsinger conditions would effect the cleavage of carbonates and carbamate substituted with the β,β,β-trichloroethyl group.

In the event, treatment of cholesterol carbonates **3** and **14** with Bu_3P–Et_3N–DMF led to free cholesterol in high yield. In contrast, carbamate **4** was not cleaved cleanly in solution with this reagent combination (or with the DMF replaced by *N*-methyl-2-pyrrolidinone) under a variety of conditions. However, reductive cleavage by Zn–HOAc gave adamantanamine in 67% yield, while acid hydrolysis using CF_3CO_2H–CH_2Cl_2 gave the amine in high yield isolated as the hydrochloride.

The immobilization of cholesterol and adamantanamine on silica gel and their subsequent release was accomplished as follows. Silica gel **9** was treated with excess phosgene to give **10**. The infrared spectrum (KBr) of **10** exhibited a band at 1790 cm^{-1} characteristic of a chlorocarbonate group as well as bands at 1740–1750 cm^{-1}, likely corresponding to the presence of a dialkyl carbonate group,[21] and 1645 cm^{-1} (amide linkage). A suspension of **10** in ether was treated with cholesterol, giving cholesterol-derivatized silica gel **11**. Loading was estimated to be about 0.14 mmol per g of **11**, based on recovered cholesterol.[22] Cholesterol was released from silica gel **11** in good yield by treatment with Bu_3P–Et_3N–DMF.

A suspension of **10** in CH_2Cl_2 was next treated with adamantanamine to give silica gel **12** containing 0.30 mmol of amine per g of **12**. As expected[2] the cleavage reaction did not take place using Zn–HOAc, likely owing to a lack of reactivity between two heterogeneous phases. Carbamate **12** was cleaved, however, by 3% CF_3CO_2H in CH_2Cl_2, affording adamantanamine in good yield.

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(15) See: Longosz, E. J.; Tarbell, D. S. *J. Org. Chem.* **1961**, *26*, 2161.
(16) Waddell, T. G.; Leyden, D. E.; DeBello, M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5303.
(17) In one series of experiments any unreacted NH_2 groups were "capped off" by reaction with Ac_2O–pyridine (1:9). No significant differences in the subsequent chemistry of capped and uncapped silica gel were observed.
(18) Eckert, H.; Listl, M.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 361.
(19) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555.
(20) Semmelhack, M. F.; Heinsohn, G. E. *J. Am. Chem. Soc.* **1972**, *94*, 5139.
(21) This linkage would be produced if a chlorocarbonate group on one chain were to react with an alcohol group on a nearby chain. The available chlorocarbonate sites are, of course, diminished by this side reaction.
(22) A control experiment in which silica gel **9** was treated under similar conditions with cholesterol showed that the nonspecific binding of cholesterol amounted to no more than 0.04 mmol per g of **9**.

The above immobilization chemistry was also shown to be applicable to the structurally more complex, orthogonally protected lipid precursor alcohol **18** (Chart I). Thus, glycerol acetonide (**15**) was allowed to react with [(2-nitrobenzyl)oxy]carbonyl chloride,[23] giving acetonide **16** containing a photolabile alcohol protecting group. Selective cleavage of the acetonide group gave the crystalline diol **17**, which was selectively silylated at the primary alcohol site[24] to give **18**, containing a photolabile protecting group and one selectively cleavable by fluoride ion. Alcohol **18** reacted smoothly with chlorocarbonate **2** to give **19** and with silica gel **10** to give the silica gel immobilized synthetic substrate **13** (loading, 0.13 mmol/g of **13**).

In summary, we descibe methodology for the attachment of two representative molecules, cholesterol and adamantanamine, to the surface of silica gel by way of reactive silica gel **10**. The molecules may be liberated from the silica gel under mild conditions. Since the chemical groupings involved in the attachment to the silica gel are expected to be stable toward a variety of synthetic operations, the way is open for chemical modification of the immobilized substrates, e.g., silica gel **13**, before their release.

Experimental Section[25]

1,1,1-Trichloro-2-hydroxy-2-methyl-11-dodecene (1). To a mechanically stirred dry solution of $CHCl_3$ (2.24 mL, 27.8 mmol) in THF (60 mL) at −100 °C was added dropwise butyllithium in hexane (14.5 mL, 1.65 M, 24 mmol). The dark green solution was stirred for 20 min at −100 °C, and then a solution of 11-dodecen-2-one[8] (3.65 g, 20.0 mmol) in THF (60 mL) was added dropwise over 25 min. After 2 h at −95 °C the mixture was warmed to −20 °C, treated with ice (125 mL) and 1 M H_2SO_4 (24 mL), and extracted with ether. The combined extracts were washed with dilute $NaHCO_3$ and brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave 4.99 g of an oily mixture of **1** and starting ketone (2:1 by NMR). Fractional distillation gave recovered ketone [0.92 g, bp 68 °C (0.1 mm)] followed by a fraction (0.657 g, bp 95–104 °C) which was alcohol **1**, contaminated with a small amount of the ketone. The major fraction (2.705 g, 45%, bp 105–108 °C) was pure **1**: NMR δ 1.35 (m, 12), 1.55 (s, 3), 2.0 (m, 4), 2.25 (s, 1, OH), 4.85–5.1 (m, 2), 5.6–6.0 (m, 1); IR (film) 3470, 2940, 2850, 1630 cm^{-1}. Anal. Calcd for $C_{13}H_{23}Cl_3O$: C, 51.76; H, 7.68. Found: C, 52.05; H, 7.78.

11,11,11-Trichloro-10-hydroxy-10-methylundecanoic Acid (5). To a stirred solution of $KMnO_4$ (1.264 g, 8.00 mmol) in water (20 mL) at 0 °C was added dropwise a solution of **1** (0.603 g, 2.00 mmol) in glacial acetic acid (20 mL). After a 2-h stir at 25 °C the mixture was cooled to 0 °C and treated with pentane (40 mL), anhydrous Na_2SO_3 (1.40 g), and 4 N HCl (20 mL). The pentane layer was removed, and the aqueous layer was further extracted with pentane (5 × 40 mL, more 4 N HCl added after the second and fourth extractions). The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of the solvent gave acid **5** (0.594 g, 93%) as a colorless oil suitable for the next reaction. The analytical specimen was obtained by silica gel chromatography ($CHCl_3$ elution): NMR δ 1.2–1.7 (m, 12), 1.57 (s, 3), 1.8–2.0 (m, 2), 2.35 (t, 2); IR 1710 cm^{-1}. Anal. Calcd for $C_{12}H_{21}Cl_3O_3$: C, 45.09; H, 6.62. Found: C, 44.73; H, 6.70.

11,11,11-Trichloro-10-hydroxy-10-methylundecanoic Ethylcarbonic Anhydride (6). To a stirred solution of **5** (1.118 g, 3.50 mmol) in dry ether (30 mL) at 0 °C was added dropwise ethyl chloroformate (0.569 g, 5.25 mmol) followed by a solution of triethylamine (0.389 g, 3.85 mmol) in ether (10 mL). After 3 min the mixture was filtered, and the chilled filtrate was concentrated to dryness below 0 °C. The residue was again dissolved in chilled ether and filtered to remove traces of the amine hydrochloride, yielding mixed anhydride **6** (1.088 g, 80%) as a colorless oil, which was used immediately: NMR δ 1.3–1.8 (m), 1.57 (s, 3), 1.8–2.0 (m, 2), 2.31 (s, 1, OH), 2.47 (t, 2), 4.34 (q, 2); IR 3580, 2940, 2860, 1820, 1760 cm^{-1}.

***N*-[3-(Triethoxysilyl)propyl]-11,11,11-trichloro-10-hydroxy-10-methylundecanamide (8).** To a stirred solution of **6** (138 mg, 0.350 mmol) in $CHCl_3$ at 0 °C was added (3-aminopropyl)triethoxysilane (94 mg, 0.42 mmol), and the mixture was stirred for 3 h and then filtered. The filtrate was concentrated to dryness, giving crude **8** (195 mg, theoretical yield, 185 mg) as a pale yellow oil, which was used in the next experiment: NMR δ 0.62 (m, 2), 1.2–2.1 (m, 16), 1.23 (t, 9), 2.14 (m, 2), 3.24 (m, 2), 3.82 (q, 6), 5.78 (br s, 1); IR ($CHCl_3$) 3580, 3450, 2970, 2925, 1660 cm^{-1}.

(Aminopropyl)silylated Silica Gel. Silica gel (Baker, 60–200 mesh) was activated by heating at 100 °C (0.05 mm) for 4 h. To the activated silica gel (4.815 g) was added 30 mL of a 10% (v/v) solution of (3-aminopropyl)triethoxysilane in dry benzene, and the suspension was refluxed for 3 h. The silica gel was continuously extracted with hot benzene in a Soxhlet apparatus for 2 h and then dried [100 °C (0.05 mm)], giving 5.290 g (loading based on weight increase, 0.67 mmol per g of gel) of the derivatized silica gel. The loading varied somewhat among runs.[7]

Silica Gel 9. A. From 8. To activated silica gel (0.504 g, see above) was added a solution of **8** (107 mg, 0.205 mmol) in 4.0 mL of dry toluene. The mixture was gently stirred for 1.5 h at 25 °C and then filtered. The silica gel was washed with dry toluene and dried (25 °C, 3 h, 0.05 mm) to give **9** (0.536 g). The loading was 0.14 mmol per g of **9**, calculated on the basis of the weight increase. The combined filtrate and washes were evaporated to give 69 mg of unreacted **8**. Based on recovered **8**, the loading was 0.14 mmol per g of **9**.

B. From 6 and (Aminopropyl)silylated Silica Gel. To a stirred solution of mixed anhydride **6** (298 mg, 0.76 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added (3-aminopropyl)silylated silica gel (564 mg, 0.38 mmol of amino groups). After a 8.5-h stir at 0 °C the silica gel was filtered and then washed with 60 mL of CH_2Cl_2 followed by 60 mL of ether. The silica gel was dried at 25 °C and 0.025 mm for 3 h, giving 664 mg of **9**: IR (KBr) 2940, 2860, 1645 cm^{-1}. The combined filtrates were evaporated below 0 °C, giving recovered **6** (152 mg). The loading of **9** on the basis of weight increase of the silica gel corresponded to 0.50 mmol of per g of **9**. Based on recovered **6**, the loading was 0.56 mmol per g of **9**.

[(1,1,1-Trichloro-2-methyl-11-dodecen-2-yl)oxy]carbonyl Chloride (2). To a solution of alcohol **1** (272 mg, 0.900 mmol, dried by azeotropic removal of CS_2) in 6 mL of CH_2Cl_2 at −20 °C was added a solution of phosgene in toluene (1.78 mL, 2.25 mmol) followed by a solution of dry pyridine (107 mg, 1.35 mmol) in 0.5 mL of CH_2Cl_2. After 27 h at 25 °C more phosgene (0.75 mmol), in toluene, and pyridine (0.45 mmol) were added, and the mixture was stirred for another 15 h. At 0 °C the mixture was diluted with ether and water was added followed by CH_2Cl_2 and 10 mL of 2 N H_2SO_4. The organic phase was washed with water and then dried ($MgSO_4$). Removal of the solvent gave an orange oil, which was chromatographed over silica gel. Elution with hexane–benzene gave pure **2** (278 mg, 85%) as a colorless oil: NMR δ 1.34 (m), 2.00 (s, 3), 4.8–5.1 (m, 2), 5.6–6.1 (m, 1); IR ($CHCl_3$) 1780 cm^{-1}.

***O*-[((1,1,1-Trichloro-2-methyl-11-dodecen-2-yl)oxy)carbonyl]cholesterol (3) and *O*-[((1,1,1-Trichloro-2-methylprop-2-yl)oxy)carbonyl]cholesterol (14).** To a chilled stirred solution of cholesterol (65 mg, 0.17 mmol) and pyridine (44 mg, 0.55 mmol) in dry ether (2.5 mL) was added dropwise a solution of **2** (76 mg, 0.21 mmol) in 0.5 mL of ether. The suspension was stirred for 7.5 h at 25 °C, and then ether was added. The mixture was washed with 2 N HCl and water and then dried (Na_2SO_4). Removal of the solvent and silica gel chromatography of the residue gave **3** (98 mg, 82%) as a pure solid. The analytical specimen was obtained as colorless needles by crystallization from acetone: mp 119–120 °C. Anal. Calcd for $C_{41}H_{67}Cl_3O_3$: C, 68.94; H, 9.45. Found: C, 69.04; H, 9.51. Similarly prepared was **14** as colorless needles (EtOAc) in 87% yield: mp 207–208 °C; IR 1745 cm^{-1}. Anal. Calcd for $C_{32}H_{51}Cl_3O_3$: C, 65.13; H, 8.71. Found: C, 65.02; H, 8.68.

***N*-[((1,1,1-Trichloro-2-methyl-11-dodecen-2-yl)oxy)carbonyl]adamantanamine (4).** To a stirred solution of **2** (160

(23) Amit, B.; Zehavi, U.; Patchornik, A. *J. Org. Chem.* **1974**, *39*, 192.
(24) Ogilvie, K. K.; Hakimelahi, G. H. *Carbohydr. Res.* **1983**, *115*, 234.
(25) Footnote 20 of Keana et al. (Keana, J. F. W.; Seyedrezai, S. E.; Gaughan, G. *J. Org. Chem.* **1983**, *48*, 2644) applies here.

mg, 0.44 mmol) in 8 mL of CH_2Cl_2 was added fresly sublimed 1-adamantanamine (133 mg, 0.88 mmol). After 24 h, the suspension was diluted with CH_2Cl_2, then washed with 2 N HCl and water, and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue gave **4** (203 mg, 97%) as a colorless oil. Anal. Calcd for $C_{24}H_{38}Cl_3NO_2$: C, 60.19; H, 8.00; N, 2.92. Found: C, 60.39; H, 8.15; N, 2.69.

Cleavage of Carbonates 3 and 14. A stirred solution of carbonate **3** (24 mg, 0.034 mmol), Bu_3P (0.2 mL), and Et_3N (0.1 mL) in dry DMF (0.4 mL) was heated at 80 °C for 2 h, then cooled, and diluted with either (15 mL). This was washed with 2 N HCl and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed over silca gel, giving 11.0 mg (85%) of cholesterol, mp 147.5 °C, after recrystallization from MeOH. A 21.0-mg sample of **14** was cleaved similarly, giving 12.1 mg (88%) of cholesterol.

Cleavage of Carbamate 4. A solution of 16.6 mg of **4** in 1 mL of 3% (v/v) trifluoroacetic acid in dry CH_2Cl_2 was stirred for 87 h at 25 °C and then concentrated to dryness. Crystallization from MeOH–ether gave 9.7 mg of crystals, which were dissolved in EtOH–HCl and evaporated to give the crude amine hydrochloride. Silica gel chromatography gave 1-adamantanamine hydrochloride (6.1 mg, 94%) as white needles (identified by IR and NMR spectral comparisons with authentic material). Alcohol **1** (10.3 mg, 98%) was recovered by chromatography of the combined mother liquors.

Silica Gel 10. To a slurry of silica gel **9** (0.651 g, 0.325 mmol of alcohol groups) in 2 mL of dry CH_2Cl_2 at −20 °C was added a solution of phosgene in toluene (5.14 mL, 6.50 mmol) followed in 5 min by a solution of pyridine (0.308 g, 3.90 mmol) in 1 mL of CH_2Cl_2. A white precipitate formed, and the mixture was warmed to 25 °C and stirred gently for 46 h. The treated silica gel was collected by filtration, rapidly washed with dry CH_2Cl_2 and ether, and then dried for 10 min at 25 °C (0.05 mm) to give 0.692 g of **10**, which was used immediately: IR (KBr) 2940, 2860, 1790, 1740, 1645 cm^{-1}.

Silica Gel 11. To a gently stirred solution of cholesterol (0.257 g, 0.665 mmol) and pyridine (0.154 g, 1.95 mmol) in 12 mL of dry ether at 0 °C was added **10** (0.680 g, ≈0.33 mmol of chlorocarbonate groups). After a 24-h stir at 25 °C the silica gel was collected by filtration, rinsed with ether, CH_2Cl_2, and EtOAc, and dried (25 °C, 3 h, 0.025 mm), giving 0.689 g of **11**: IR (KBr) 2940, 2860, 1745, 1645 cm^{-1}. The combined filtrate and ether rinse gave 219 mg of recovered cholesterol. No cholesterol was found in the subsequent washes. The loading of cholesterol on **11** was 0.14 mmol per g, based on recovered cholesterol.

Release of Cholesterol from 11. A gently stirred suspension of **11** (0.683 g, estimated to contain 37.2 mg of cholesterol), Bu_3P (0.8 mL), and Et_3N (0.4 mL) in 1.6 mL of dry DMF was heated for 5 h at 80 °C and then cooled. The mixture was filtered, and the residue was rinsed with 50 mL of ether. The combined filtrate and rinse was washed with 2 N HCl (removes Et_3N) and water and then dried ($MgSO_4$). Evaporation of the solvent followed by chromatography of the residue over silica gel gave 26.6 mg (72%) of cholesterol, mp 147–148 °C.

Silica Gel 12. Freshly prepared silica gel **9** (1.29 g, 0.623 mmol of alcohol groups) was treated as above with phosgene in toluene to give 1.375 g of **10**. A 1.369-g sample was suspended in 12 mL of dry CH_2Cl_2 and treated with 1-adamantanamine (0.188 g, 1.25 mmol). The slurry was stirred for 27 h at 25 °C and then filtered. The residue was washed with 50 mL each of 10% and 20% MeOH in $CHCl_3$ and then dried [25 °C (0.025 mm), 3 h] to give 1.386 g of **12**. The combined filtrates were evaporated and the residue was treated with ethanolic HCl to give 1-adamantanamine hydrochloride (0.155 g). This indicated a loading of 0.30 mmol of adamantanamine per g of **12**.

Release of Adamantanamine from 12. A suspension of **12** (140 mg, 0.042 mmol) in 2 mL of 3% (v/v) trifluoroacetic acid in dry CH_2Cl_2 was gently stirred for 69 h at 25 °C and then filtered. The residue was rinsed with 60 mL of MeOH–$CHCl_3$ (1:9). The combined filtrate and rinse was evaporated, and the residue was treated with ethanolic HCl and evaporated. The 14-mg residue was chromatographed over silica gel. Elution with MeOH–$CHCl_3$ (1:9) gave 1-adamantanamine hydrochloride (6.5 mg, 83%).

1-*O*-[((2-Nitrobenzyl)oxy)carbonyl]-2,3-*O*-isopropylideneglycerol (16). To a stirred solution of glycerol acetonide (1.616 g, 12.23 mmol) and 4-(dimethylamino)pyridine (2.988 g, 24.46 mmol) in 16 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of [(2-nitrobenzyl)oxy]carbonyl chloride[23] (2.900 g, 13.45 mmol) in 16 mL of CH_2Cl_2. After a 2-h stirr 50 mL of CH_2Cl_2 was added, and the solution was washed with water and brine and dried ($MgSO_4$). Concentration gave a residue, which was chromatographed over silica gel. Elution with benzene–CH_2Cl_2 gave **16** (3.552 g, 93%) as a pale yellow oil: NMR δ 1.38 (s, 3), 1.45 (s, 3) 3.7–4.5 (m, 5) 5.61 (s, 2), 7.4–7.8 (m, 3), 8.14 (d, 1).

1-*O*-[((2-Nitrobenzyl)oxy)carbonyl]glycerol (17). A mixture of **16** (2.685 g), 60 mL of 1% aqueous sulfuric acid, and 120 mL of acetone was stirred for 31 h at 25 °C and then cooled to 0 °C and neturalized with aqueous $NaHCO_3$. This was extracted with CH_2Cl_2, and the extract was washed with brine, dried, and concentrated, affording 2.24 g of crude **17**. Recrystallization from EtOAc–hexane gave pure **17** (1.867 g, 80%) as colorless crystals: mp 81–81.5 °C; NMR δ 2.70 (br s, 1), 3.16 (br s, 1), 3.60–3.78 (m, 2), 3.86–4.14 (m, 1), 4.27 (d, 2), 5.62 (s, 2), 7.4–7.7 (m, 3), 8.1 (m, 1). Anal. Calcd for $C_{11}H_{13}NO_7$: C, 48.71; H, 4.83; N, 5.16. Found: C, 48.89; H, 4.87; N, 5.18.

1-*O*-[((2-Nitrobenzyl)oxy)carbonyl]-3-*O*-(*tert*-butyldimethylsilyl)glycerol (18). To a stirred solution of **17** (190 mg, 0.700 mmol) in 10 mL of dry THF was added a solution of *tert*-butyldimethylsilyl chloride (158 mg, 1.05 mmol) in 0.4 mL of THF followed by finely divided silver nitrate (167 mg, 0.980 mmol). The white suspension was stirred for 30 h at 25 °C and filtered, and the residue was washed with THF. The combined filtrate and wash was diluted with 20 mL of water and extracted with $CHCl_3$. The usual workup gave a yellow oil (269 mg), which was purified by preparative TLC over silica gel (95:5 $CHCl_3$–MeOH) to give **18** (209 mg, 78%) as a pale yellow oil: NMR δ 0.10 (s, 6), 0.92 (s, 9), 2.50 (br s, 1), 3.64–3.76 (m, 2), 3.80–4.10 (m, 1), 4.26 (d, 2), 5.62 (s, 2), 7.4–7.8 (m, 3), 8.08–8.24 (m, 1). Anal. Calcd for $C_{17}H_{27}NO_7Si$: C, 52.97; H, 7.06; N, 3.63. Found: C, 52.58; H, 7.11; N, 3.53.

1-*O*-[((2-Nitrobenzyl)oxy)carbonyl]-2-*O*-[((1,1,1-trichloro-2-methyl-11-dodecen-2-yl)carbonyl]-3-*O*-(*tert*-butyldimethylsilyl)glycerol (19). To a stirred solution of **18** (71 mg, 0.18 mmol) and 4-(dimethylamino)pyridine (23 mg, 0.18 mmol) in 1.5 mL of dry CH_2Cl_2 at 0 °C was added a solution of **2** (34 mg, 0.090 mmol) in 0.5 mL of CH_2Cl_2. After 3 h ether was added, the mixture was washed with cold 2 N HCl and water, and then the ether phase was dried ($MgSO_4$). Concentration gave 97 mg of oily residue, which was chromatographed over silica gel. Elution with benzene gave **19** (49 mg, 75%) as a colorless oil: NMR δ 0.10 (s, 6), 0.92 (s, 9), 1.20–1.70 (m), 1.94 (s, 3), 1.88–2.40 (m), 3.81 (d, 2), 4.20–4.60 (m, 2), 4.80–5.10 (m, 3), 5.62 (s, 2), 5.60–6.00 (m, 1), 7.40–7.74 (m, 3), 8.14 (d, 1). Anal. Calcd for $C_{31}H_{48}Cl_3NO_9Si$: C, 52.21; H, 6.78; N, 1.96. Found: C, 52.50; H, 6.85; N, 2.23.

Silica Gel 13. To a stirred solution of **18** (0.220 g, 0.571 mmol) in 4 mL of CH_2Cl_2 were added silica gel **10** (0.527 g, ≈0.25 mmol) and 4-(dimethylamino)pyridine (58 mg, 0.514 mmol). The slurry was gently stirred for 8 h at 0 °C and then filtered. The silica gel was washed with 50 mL of CH_2Cl_2 and 50 mL of MeOH–$CHCl_3$ (1:4) and then dried (25 °C, 0.05 mm, 12 h) to give **13** (0.560 g). The above combined filtrate and CH_2Cl_2 was washed with cold 5% HCl and water and then dried ($MgSO_4$). Evaporation gave unreacted **18** (0.192 g). The loading was 0.13 mmol per g of **13**, calculated on the basis of recovered **18**.

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