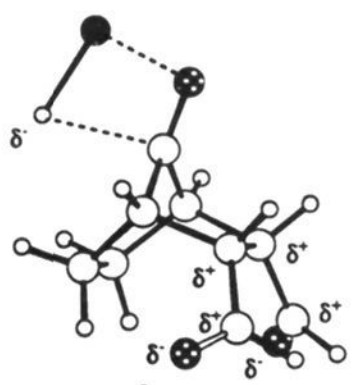
Table I. Calculated Relative Energies (kcal/mol) of Transition Structures for the Reactions of Lithium Hydride with **1a–g** and **2a–c**, Along with Available Experimental Data for $NaBH_4$ Reductions

	$E_{(anti)} - E_{(syn)}$		
compd, R (**1**) or X (**2**)	6-31G*	MP2/6-31G*	experimental[a]
1a, CHO (CC)[b]	3.0	4.0	
CHO (CH)[c]	−0.2	−0.6	
1b, CO_2Me (CC)[b]	2.8		0.9
CO_2Me (CH)[c]	1.0		
1c, CH_2F	0.5	0.7	
1d, CH_2OH	−0.1	−0.1	−0.2[d]
1e, $CH{=}CH_2$	−0.3	−0.4	−0.3
1f, CH_3	−0.5	−0.6	−0.8[e]
1g, SiH_3	−0.8	−0.3	
2a, CH2	−1.8	−3.1	−1.6[h]
2b, O	1.1	0.3	
2c, NH (anti)[f]	0.8	0.2	>2.5[h]
NH (syn)[g]	−2.0	−4.0	

[a] Data for **1** from ref 1, and data for **2** from ref 2. [b] C=O bonds eclipse the ring C_1—C_2 and C_3—C_4 bonds. [c] C=O bonds eclipse C—H bonds. [d] R = CH_2OCH_3. [e] R = CH_2CH_3. [f] NH anti to C_1—C_2. [g] NH syn. [h] MeLi addition; NPh in the experiment (ref 2b) is apparently anti.



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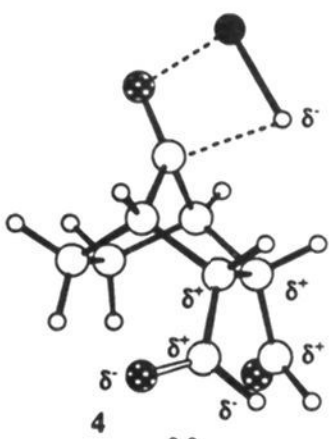
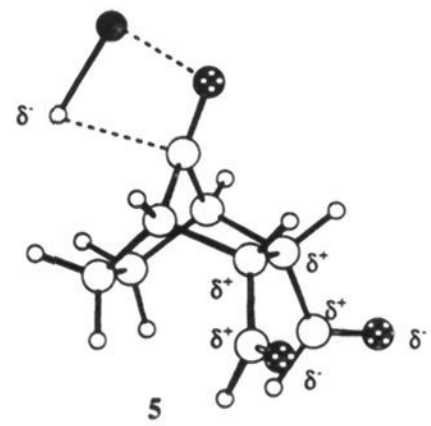


4

TS	4.0	0.0
TS, no LiH	0.0	0.8
TS, no LiH, 0.5 e at H	4.6	0.0



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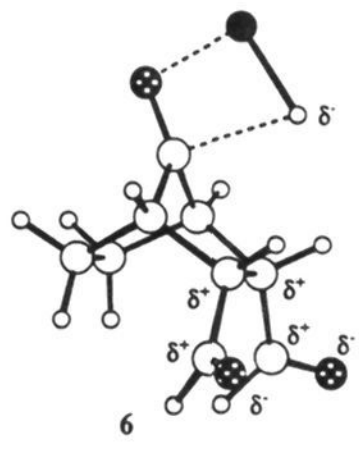


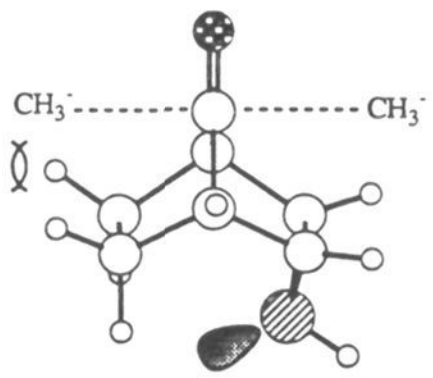
6

TS	5.6	6.0
TS, no LiH	2.4	2.6
TS, no LiH, 0.5 e⁻ at H	3.9	4.4

Figure 1. Transition structures of lithium hydride addition to 2,3-diformyl-7-norbornanone. Relative energies (kcal/mol, MP2/6-31G*) of the transition structures (TS), TS without LiH (TS, no LiH), and TS without LiH but with 0.5 unit of negative charge placed at the hydride position.

at C_2 and C_3 (**1a–c**, **2b**, and **2c**), and syn addition is favorable. On the other hand, electron-donating substituents (**1f**,**1g**,**2a**) induce negative charges at C_2 and C_3, and anti addition becomes favorable. Hydroxymethyl (**1d**) and vinyl (**1e**) substituents are weakly electron-withdrawing, and the anti preference for them is caused by electrostatic repulsions in the syn transition structure between the hydride and the electronegative OH or vinyl group, similar to that in structure **6**.

The low calculated stereoselectivity of **2c** deserves special comment. The structure with the NH anti to the norbornyl ring (see **7**) is about 1 kcal/mol more stable than the syn structure, for steric reasons. Syn addition of LiH is calculated to be favorable, but the magnitude of the calculated stereoselectivity is much smaller than that observed for the MeLi addition.[2b] Anti addition by MeLi is significantly destabilized by steric interactions between the methyl group and C_4-H and C_5-H, as shown in **7**. This steric effect will also operate in **2a** and **2b**.[2]



7

In summary, we have shown that electrostatic effects of remote substituents can have a significant influence on the stereoselectivities of nucleophilic additions, while hyperconjugative effects have little influence. The combination of torsional[7,10,11] and electrostatic effects[6,7] rationalizes the large body of observed stereoselectivities.

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Carbon-Linked Galactosphingolipid Analogs Bind Specifically to HIV-1 gp120

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The principal mode of infection by the human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) involves the interaction of the HIV envelope protein gp120 with CD4, a molecule on host lymphoid cells.[1] The susceptibility of many CD4-negative cell lines to HIV infection, however, strongly suggests the presence of an alternative entry pathway.[2] Recently, Harouse et al. have

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(1) (a) Dalgleish, A. G.; Beverly, P. C. L.; Clapham, P. R.; Crawford, D. H.; Greaves, M. F.; Weiss, R. A. *Nature* **1984**, *312*, 763. (b) Klatzmann, D.; Champagne, E.; Chamaret, S.; Gruest, J.; Guetard, D.; Hercend, T.; Gluckman, J.-C.; Montagnier, L. *Nature* **1984**, *312*, 767. (c) Maddon, P. J.; Dalgleish, A. G.; McDougal, J. S.; Clapham, P. R.; Weiss, R. A.; Axel, R. *Cell* **1986**, *47*, 333. (d) McDougal, J. S.; Nicholson, J. K. A.; Cross, G. D.; Cort, S. P.; Kennedy, M. S.; Mawle, A. C. *J. Immunol.* **1986**, *137*, 2937. (e) Lifson, J. D.; Reyes, G. R.; McGrath, M. S.; Stein, B. S.; Engleman, E. G. *Science* **1986**, *232*, 1123. (f) Sattentau, Q. J.; Dalgleish, A. G.; Weiss, R. A.; Beverly, P. C. L. *Science* **1986**, *234*, 1120. (g) Jameson, B. A.; Rao, P. E.; Kong, L. I.; Hahn, B. H.; Shaw, G. M.; Hood, L. E.; Kent, S. B. H. *Science* **1988**, *240*, 1335. (h) Collman, R.; Godfrey, B.; Cutilli, J.; Rhodes, A.; Hassan, N. F.; Sweet, R.; Douglas, S. D.; Friedman, H.; Nathanson, N.; Gonzalez-Scarano, F. *J. Virol.* **1990**, *64*, 4468.

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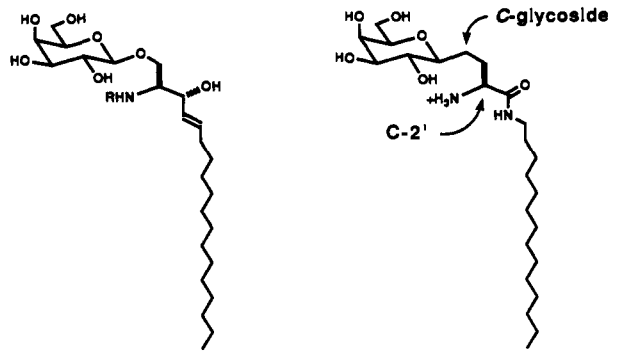
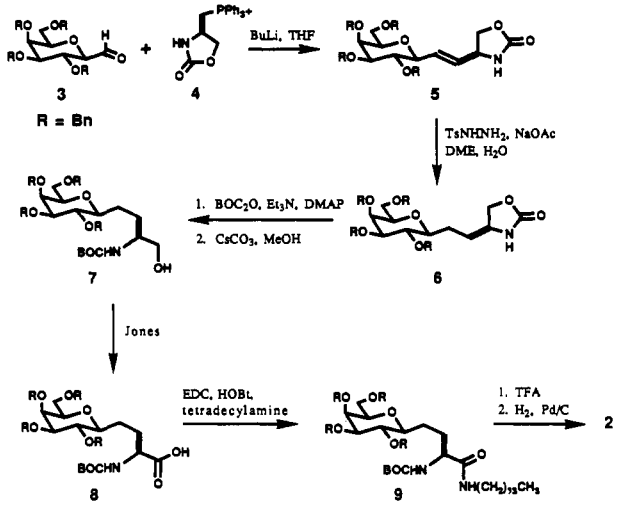


1 (GalCer): R = *hydroxystearoyl* 2

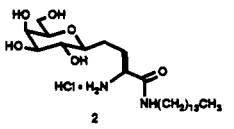
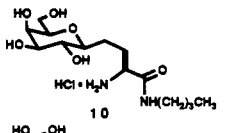
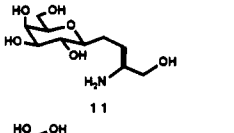
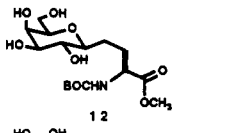
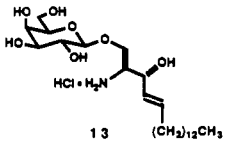
Figure 1.

Scheme I



shown that antibodies specific for the sphingolipid galactosyl ceramide (GalCer, **1**, Figure 1) inhibit HIV-1 infection of two CD4-negative neural cell lines.[3] Further evidence for the involvement of glycolipids in HIV infection comes from Bhat and co-workers, who have found that galactosphingolipids bind to purified recombinant gp120.[4] More recently, GalCer has been implicated in HIV-1 infection of colorectal-derived cells, which may serve as portals for HIV entry from the mucosal surface epithelium into the bloodstream.[5] *In this communication, we report the synthesis of water-soluble, carbon-linked galactosphingolipid analogs that bind specifically to recombinant gp120 and block the interaction of gp120 with GalCer.* This discovery suggests that synthetic ligands that are stable in vivo can serve as soluble inhibitors of viral uptake and infection in CD4-negative cells.[6]

Table I[a]

Entry	Compound	% Inhibition at 1 mg/mL
1		86 (IC_{50} = 120 μM)
2		34
3		0
4		0
5		96 (IC_{50} = 160 μM)

[a] See the supplementary material for details of the competition binding assay and control experiments.

We have designed a series of water-soluble, carbon-linked galactosphingolipid derivatives, represented by compound **2** (Figure 1), that bind specifically to HIV-1 gp120. These molecules contain the essential β-linked galactose functionality of GalCer,[4] with a *C*-glycosyl linkage rather than an *O*-glycosyl linkage, and modifications to the sphingosine side chain. Substitution of the *C*-glycoside confers resistance to both chemical and enzymatic deglycosylation, an important property for in vivo applications.[7] The tetradecylamide linkage of compound **2** substitutes for the allylic alcohol and hydrocarbon tail of sphingosine. This linkage can also be readily substituted with alkylamines to afford a variety of amides with different hydrocarbon tail lengths. Finally, compound **2** lacks a fatty acid group on the C-2′ amine to enhance water solubility.

Compound **2** was synthesized as outlined in Scheme I. Briefly, condensation of *C*-glycosyl aldehyde **3**[8] with Wittig reagent **4**[9] afforded the desired oxazolidinone **5**, which was elaborated into the *C*-glycosyl amino acid **8** using a procedure that we have recently described.[10] Compound **8** can then be transformed into a variety of amide derivatives using standard methods.

Direct binding of recombinant gp120 (rgp120)[11] to compound **2** was examined in an ELISA-type assay using peroxidase-con-

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jugated rgp120 and was found to be comparable to rgp120–GalCer binding (see supplementary material). To demonstrate that the observed interaction is specific, compound **2** and a series of related derivatives (**10–12**, Table I) were tested for their inhibitory activity against rgp120–GalCer binding using a high-performance thin-layer chromatography (HPTLC) competition binding assay.[3,4] Rgp120 was preincubated with increasing concentrations of each of the compounds shown in Table I, and the solutions were then incubated with GalCer immobilized on HPTLC plates. Inhibition of rgp120–GalCer binding by compounds **2** and **10–13** was quantified by measuring a decrease in the level of bound rgp120. Table I shows the degree of inhibition by 1 mg/mL solutions of the test compounds, as well as concentrations required for 50% inhibition (IC_{50}) for compounds that block rgp120–GalCer binding at micromolar concentrations.

Compound **2** (entry 1) has the highest affinity for rgp120 (IC_{50} = 120 μM) and competes slightly better than the soluble O-linked glycolipid psychosine hydrochloride (**13**, IC_{50} = 160 μM, entry 5).[12] Both psychosine and compound **2** exhibit almost complete inhibition of rgp120–GalCer binding (85–100%) at a concentration of 1 mg/mL. A dramatic reduction in inhibitory activity is seen when the length of the hydrocarbon tail is decreased. Compound **10** (entry 2), which contains a C_4 tail, inhibits rgp120–GalCer binding by only 34% at a concentration of 3 mM (1 mg/mL), whereas compounds **11** and **12** (entries 3 and 4) show no inhibitory activity at all, even at concentrations above 3 mM.

The GalCer binding site on gp120 tolerates substitution of a *C*-glycoside for the *O*-glycoside as well as substitution of an alkyl amide for the allylic alcohol and hydrocarbon tail of sphingosine. The slightly increased inhibitory activity of compound **2** relative to psychosine (**13**) may arise from the hydrophobicity (poor solvation) of the *C*-glycosyl linkage relative to the *O*-glycosyl linkage.[13] Interestingly, the fatty acid group can be removed altogether from the C-2′ position of GalCer (affording psychosine) without a significant loss in gp120 binding activity, despite an obvious reduction in the hydrophobicity of the molecule.[4] Compound **2** also lacks the C-2′ fatty acid and still binds to gp120. Shortening the hydrocarbon tail of compound **2** results in a drastic reduction in inhibitory activity (compare entries 1 and 2), and conversion of the butyl amide to the alcohol (entry 3) or methyl ester (entry 4) completely eliminates binding activity. The rigid amide linkage of compounds **2** and **10** (entries 1 and 2) is positioned similarly to the allylic alcohol of sphingosine and may be a key structural element for gp120 recognition.

In summary, we have designed water-soluble, C-linked galactosphingolipid analogs that block the interaction of recombinant HIV-1 gp120 with GalCer. Given the growing body of evidence suggesting a role for the gp120–GalCer interaction in viral entry, these compounds represent potential inhibitors of the first step in the infection process. Furthermore, determination of the structural elements required for gp120 recognition allows modification of these compounds for receptor-mediated immunochemistry.[14,15] We are currently investigating these possibilities.

Acknowledgment. Recombinant gp120 and anti-gp120 antibodies were gifts from Dr. Raymond Sweet at SmithKline Beecham (King of Prussia, PA). M.D.B. thanks the American Cancer Society, Proctor & Gamble, and Eli Lilly for Junior Investigator Awards. C.R.B. thanks the ACS Division of Medicinal Chemistry for a graduate fellowship and AT&T Bell Laboratories for a GRPW grant. This research was supported by National Institutes of Health Awards R29 GM43037-02, NS-27405, and NS-31067.

(12) The competition between glycolipids in solution and glycolipids on HPTLC plates for rgp120 binding is not necessarily an equilibrium process under these conditions. Therefore, these values do not represent true solution binding affinities and cannot be considered K_i values. However, the concentrations required to inhibit rgp120 binding to immobilized GalCer provide a qualitative measurement of the relative binding affinities for rgp120.

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Supplementary Material Available: Experimental details and spectral and analytical data for compounds **2** and **5–12** and all synthetic intermediates and experimental details and results for ELISA and HPTLC binding assays (14 pages). Ordering information is given on any current masthead page.

Topological Rearrangement within a Single Crystal from a Honeycomb $[Cd(CN)_2]_n$ 3D Net to a Diamond Net

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A veritable cornucopia of interesting structural chemistry is provided by cadmium cyanide and its derivatives. The parent itself consists of two completely independent but interpenetrating diamond-related frameworks,[1] while certain derivatives, as Iwamoto has shown, possess single, non-interpenetrating diamond structures[2] and others show a variety of 2D and 3D structures.[3] We report here a remarkable single crystal to single crystal transformation in which an infinite 3D $[Cd(CN)_2]_n$ net undergoes extensive topological change.

When recrystallized from aqueous *tert*-butyl alcohol, cadmium cyanide yields $Cd(CN)_2 \cdot {}^2/_3 H_2O \cdot t$-BuOH with the infinite 3D honeycomb-like $[Cd(CN)_2]_n$ framework shown in Figure 1.[3a] These crystals are stable in contact with 50% aqueous *tert*-butyl alcohol or, while free of liquid, in an atmosphere saturated with the vapors of water and *tert*-butyl alcohol, but they degenerate on exposure to air as a result of solvent loss, rapidly becoming white, opaque conglomerates of microparticles which retain the outward "shape" of the original crystal. When an X-ray oscillation photograph of a conglomerate was taken, a powder diffraction pattern was obtained, the indexing of which indicated that the conglomerate consisted of microcrystals of $Cd(CN)_2$. Crystals which had degenerated in this way could not be "revived" by addition of solvent. When crystals of the butanol solvate are exposed to chloroform vapor, a "solvate exchange" process occurs (verified by IR spectroscopy); $CHCl_3$ is incorporated and butanol and water are lost (complete substitution within a day at room temperature). This is achieved reproducibly by placing crystals of $Cd(CN)_2 \cdot {}^2/_3 H_2O \cdot t$-BuOH together with a little mother liquor on a porous tile inside a sealable chamber containing an atmosphere saturated with chloroform vapor above a reservoir of liquid chloroform, such that no liquid chloroform comes into contact with the tile or the crystals. The crystals retain their transparency and well-defined external form throughout the solvent exchange process. The daughter crystals are stable in the chloroform vapor-saturated atmosphere or in contact with liquid chloroform but degenerate on exposure to the atmosphere in just the same way as the parent crystals, giving conglomerates of $Cd(CN)_2$

† University of Melbourne.
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