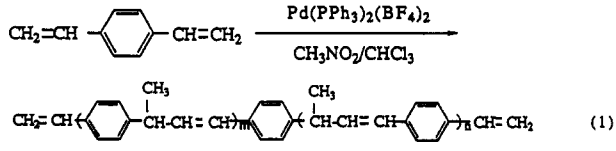
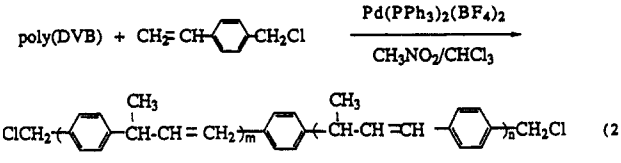
ventional addition polymerization process is not involved; rather, the polymer is formed through a step-growth mechanism involving the terminal vinyl groups. Consistent with this mechanism was the observation of an exponential increase in molecular weight with time (highest observed MW = 6000). For a given reaction time, the molecular weight of the poly(DVB) obtained increased markedly with both increasing temperature and increasing catalyst concentration. Thus, it was possible to control the molecular weight of poly(DVB) by an appropriate choice of reaction conditions. Our procedure for the linear polymerization of DVB appears to be superior to that described earlier in that the use of lower temperatures (<70 °C) and higher monomer concentrations (>0.1 M) does not result in side reactions.




(1)

Lastly, as shown in eq 2, it was possible to synthesize a telechelic ($\alpha,\omega$-difunctional) polymer from preformed poly(DVB) using the Pd(II) catalyst **2**. Indeed, a "one-pot" synthesis of the telechelic polymer was carried out by first adding DVB to the catalyst solution, waiting for poly(DVB) to form, and then adding *p*-(chloromethyl)styrene. The telechelic polymer opens up the possibility of forming block copolymers incorporating highly unsaturated poly(DVB) blocks.




(2)

**Acknowledgment.** Support of this research by the U.S. Department of Energy, Office of Basic Energy Sciences (DE-FG02-84ER13295), is gratefully acknowledged. We also thank Johnson Matthey, Inc., for a generous loan of palladium metal.

**Supplementary Material Available:** The synthesis and characterization of the palladium complexes **2-4** (2 pages). Ordering information is given on any current masthead page.

## Total Synthesis of the Anthelmintic Agent Hikizimycin

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*Received September 18, 1990*

Hikizimycin was isolated from the fermentation broth of *Streptomyces A-5*[1] and was determined to be identical with anthelmycin, which was isolated from *Streptomyces longissimus*.[2] Biochemical studies of hikizimycin revealed significant anthelmintic activity against a variety of common parasites.[3] Degradation studies[4] identified the presence of a cytosine base, a 3-amino-3-deoxyglucose sugar (kanosamine), and a 4-aminoundecose sugar (hikosamine). Eventually, the structure of hikizimycin was proposed as shown in Figure 1.[5] Herein, we report the first total

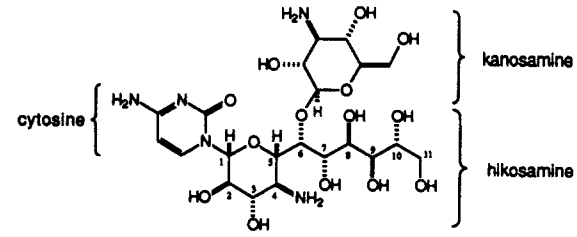
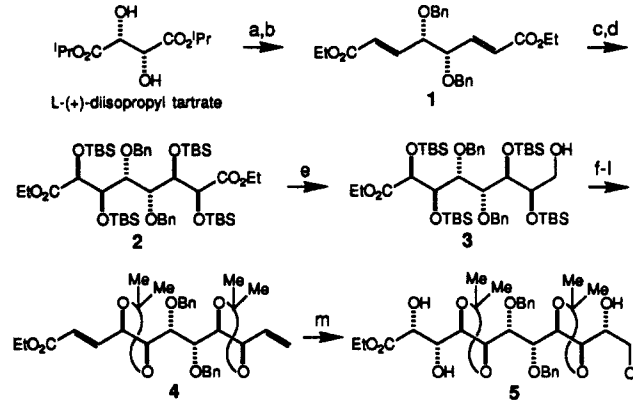



**Figure 1.** Hikizimycin (anthelmycin).

**Scheme I**[a]




[a] (a) NaH, BnBr (2.1 equiv), $NBu_4NI$, THF (53% product; 12% monobenzyl ether); (b) $(EtO)_2POCHLiCO_2Et$ (2.6 equiv), $CH_2Cl_2$, DIBAL-H (2.6 equiv) (53%); (c) $OsO_4$ (0.05 equiv), NMO (3 equiv), acetone-$H_2O$ (8:1) (71%); (d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$ (100%); (e) DIBAL-H (2.3 equiv), $CH_2Cl_2$, -78 °C (82%); (f) oxalyl chloride, DMSO, $Et_3N$ (97%); (g) $Cp_2TiCH_2ClAlMe_2$, tol-THF-Py, -78 to -15 °C (82%); (h) DIBAL-H, $CH_2Cl_2$ (95%); (i) oxalyl chloride, DMSO, $Et_3N$ (98%); (j) $(EtO)_2POCHLiCO_2Et$ (97%); (k) $nBu_4NF$, THF, 0 °C (86%); (l) acetone, $H_2SO_4$ (89%); (m) $OsO_4$ (0.05 equiv), NMO (3 equiv), acetone-$H_2O$ (10:1) (88% yield; 75% of mixture is desired diastereomer).

synthesis of hikizimycin, the most structurally complex member of the long-chain carbohydrate class of natural products.[6]

The undecose fragment of hikizimycin[7] was prepared by a chain extension/osmylation strategy,[8] conducted efficiently by a two-directional chain synthesis.[9] L-(+)-Diisopropyl tartrate furnished the C6 and C7 stereocenters, which served as handles for introducing the remaining stereocenters (Scheme I). Bisbenzylation followed by a one-pot reduction/homologation procedure[10] furnished the $\alpha,\beta$-unsaturated ester **1**. This was oxidized with catalytic osmium tetraoxide and excess *N*-methylmorpholine *N*-oxide (NMO)[11] to yield the tetraol as a pure crystalline solid (mp 113-115 °C).[12] The tetraol was protected as its tetrakis(*tert*-butyldimethylsilyl ether) **2**.[13]

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(12) The diastereofacial selectivity at each olefin was determined to be 12.9:1 based on HPLC ratios of the tetraacetates obtained from acetylation following osmylation of HPLC-purified **1**.
(13) The stereochemistry was confirmed by correlation with D-*threo*-L-*galacto*-octitol octaacetate. Reduction followed by deprotection and peracetylation afforded material possessing comparable melting point and optical rotation.

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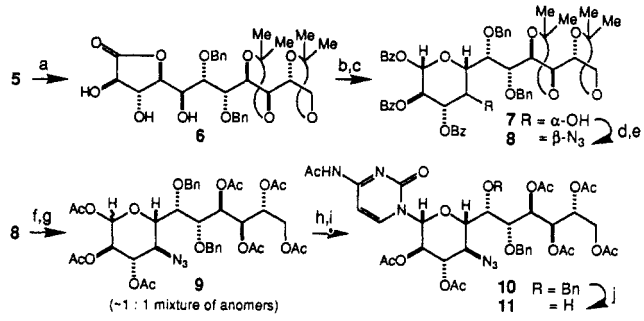
**Scheme II**[a]



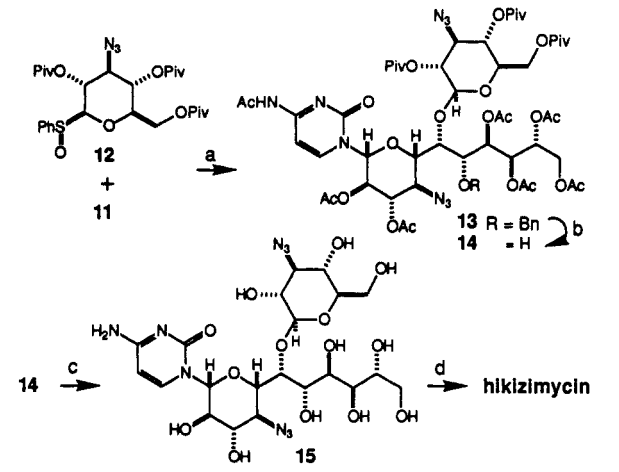
[a](a) TFA–MeOH (1:3), reflux 2.5 days; TFA–THF (1:100) reflux 10 h; $H_2SO_4$–acetone (65%); (b) DIBAL-H (5 equiv), $CH_2Cl_2$; (c) BzCl (5 equiv) (34%, two steps); (d) $Tf_2O$ (2 equiv), Py (3 equiv), $CH_2Cl_2$, 1 h, room temperature; (e) $nBu_4NN_3$ (3 equiv), PhH, 15 min, room temperature (81%, two steps); (f) Amberlyst-15, MeOH, reflux, 9 h; (g) NaOMe, MeOH, 3 h; $Ac_2O$, Py, DMAP, 12 h (83%, overall); (h) bis-TMS-cytosine (3 equiv), TMSOTf (3.3 equiv), $PhNO_2$, 3.5 h, 127 °C (76%); (i) $Ac_2O$, Py, DMAP (96%); (j) DDQ (5 equiv), $CH_2Cl_2$–$H_2O$ (10:1) (74%).

Terminus differentiation of the $C_2$-symmetric chain was achieved at this stage by a monofunctionalization of the two homotopic ester groups of **2**. The alcohol **3** was prepared efficiently by reduction with DIBAL-H added slowly at −78 °C. The undecose chain was constructed sequentially in two directions. Swern oxidation[14] of **3** followed by Tebbe olefination[15] established the terminal vinyl group, and the $\alpha,\beta$-unsaturated ester moiety was introduced by a reduction, oxidation, and Horner–Emmons olefination sequence. Desilylation and ketalization furnished **4**. Catalytic osmylation of **4** in the presence of a chiral amine catalyst, dihydroquinine *p*-chlorobenzoate,[16] afforded the tetraol **5** with good diastereoselectivity. In 11 steps, all performed on a multigram scale, the undecose chain was constructed with the necessary oxidation level and stereochemistry at each carbon.

The diastereomerically pure lactone **6** was prepared from **5** by deketalization and lactonization followed by selective ketalization (Scheme II). Reduction of **6** with DIBAL-H and selective benzoylation[17] of the crude lactol afforded the pure alcohol **7** after purification by preparative HPLC. With the C4 hydroxyl group differentiated, a nitrogen substituent was introduced by formation of the triflate and displacement with tetrabutylammonium azide[18] to afford the azide **8**.[19]

The cytosyl group was introduced by the silyl Hilbert–Johnson reaction,[20] which has been studied extensively by Vorbrüggen.[21] Initial failures led to model studies, which identified several crucial elements necessary for success with this reaction. Acetyl protecting groups instead of benzoyl groups about the pyranose ring resulted in increased yields. Thus, the derivative **9** was prepared as a mixture of anomers by deketalization and debenzoylation followed by peracetylation. Reaction in nitrobenzene was significantly faster than in acetonitrile, a solvent typically used with TMSOTf-catalyzed reactions.[22] Treatment of **9** with bis(trimethylsilyl)cytosine and TMSOTf in nitrobenzene (127 °C) yielded the nucleoside in 76% yield. Acetylation then furnished **10**. The site-selective unmasking of the C6 hydroxyl group was achieved by oxidative debenzylation with DDQ, which is commonly used to remove *p*-methoxybenzyl ethers.[23] Treatment of **10** with excess DDQ in dichloromethane–water selectively afforded the alcohol **11** with high selectivity. The slower rate of oxidative debenzylation at C7 may reflect in part the decreased electron density at this site relative to C6.

**Scheme III**[a]



[a](a) $Tf_2O$, tol–$CH_2Cl_2$, 2,6-$tBu_2$-4-MePy (38%, 41% SM); (b) DDQ. $CH_2Cl_2$, 43 h, 58 °C (52%, 17% SM); (c) $nBu_4NOH$, MeOH, reflux, 2 h; (d) $H_2$ (1 atm), Lindlar cat., $H_2O$, 30 min (quant, two steps).

Glycosidation was achieved by applying the sulfoxide activation method of Kahne.[24] Addition of $Tf_2O$ to the sulfoxide **12**[25] followed by the alcohol **11** yielded the glycoside **13** (Scheme III). Conversion of **13** to hikizimycin required debenzylation of the C7 hydroxyl group, deacylation of the undecose and hexose sugar moieties as well as the cytosine residue, and reduction of the two azido groups. Debenzylation under various reducing conditions was unsuccessful because of the sensitivity of the cytosyl group. The oxidative debenzylation with DDQ was again studied. The slow reaction led to decomposition of **13** resulting from acidic products formed from hydrolysis of DDQ. It was subsequently found that debenzylation did not require the presence of added water;[26] thus, treatment of **13** with excess DDQ in dry dichloromethane at 58 °C for 2 days resulted in clean debenzylation to afford the desired alcohol **14**. Complete deacylation with refluxing methanolic tetrabutylammonium hydroxide[27] readily afforded the polyol **15**, and hydrogenation with Lindlar catalyst[28] reduced the azido groups to yield hikizimycin in quantitative yield. The synthetic substance was identical with natural hikizimycin in all respects.

The studies reported herein serve as another illustration of the potential of the two-directional chain synthesis strategy and confirm the proposed structure of the highly unusual anthelmintic agent hikizimycin.

**Acknowledgment**. We thank the NIGMS (GM-38627) and Pfizer for their support of this research and Dr. R. Nagarajan

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(Lilly Research Laboratories) for a gift of natural hikizimycin.

**Supplementary Material Available:** IR, $^1H$ and $^{13}C$ NMR, and mass spectral and analytical data for **1-6, 8, 9, 11, 12, 14**, and hikizimycin and $^1H$ NMR spectra of natural and synthetic hikizimycin (8 pages). Ordering information is given on any current masthead page.

## Strong Binding of Ditopic Substrates by a Doubly Linked Occlusive $C_1$ "Clamshell" as Distinguished from an Aversive $C_2$ "Loveseat" Cyclodextrin

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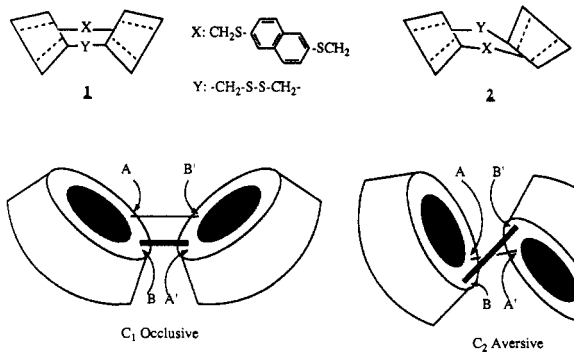
*Received August 28, 1990*

We[1] and others[2,3] have described various dimers of β-cyclodextrin linked at the C-6 carbon. With some of them, and appropriate rigid ditopic substrates, we saw[1] binding constants in water up to $7 \times 10^8$ $M^{-1}$, into the region of many antigen-antibody binding constants. One would expect even stronger binding with dimers having better defined optimal geometry. We have now prepared two cyclodextrin dimers doubly linked at adjacent sugar residues, converting the previous flexible linkage into a hinge. As hoped, the isomer **1** with occlusive geometry can close on a ditopic




**1** **2**

substrate like a clamshell, leading to very strong binding. The isomer **2** with aversive geometry aims the two cyclodextrin rings away from each other and shows no cooperative binding of ditopic substrates.

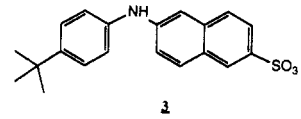
Reaction of β-cyclodextrin 6A,6B diiodide[4] with naphthalene-2,6-dithiol afforded a mixture of iodocyclodextrin dimers linked A-A′, A-B′, and B-B′. This mixture was directly converted to the bisthioacetate esters by displacement with potassium thioacetate, which were then hydrolyzed to the dithiol and air oxidized to the disulfide. The major dimeric product from this, isolated by repeated chromatography, was the aversive isomer **2**, whose $C_2$ symmetry was revealed in its H NMR spectrum, with three 2-proton naphthalene signals.[5] It had the expected FAB-MS peak at M + 1 = 2455. Strikingly, one of the two possible $C_2$ isomers predominated, to which we tentatively assign the structure **2**, with the naphthalene ring linking B and B′ positions. The 6A and 6B positions are diastereomeric, and molecular models suggest that C-6A could be strongly shielded by the iodine on C-6B. Only weak signals were seen from the other $C_2$ isomer, to which we assign the A-naphthalene-A′ structure.

**Table I.** Binding Constants in $H_2O$ at 25 °C

| host | substrate | $K_f$, $M^{-1}$ |
|---|---|---|
| **1** (occlusive) | BNS **3** | $4 \times 10^6$ |
| **1** (occlusive) | **4** | $(4.0 \pm 0.2) \times 10^8$ |
| **1** (occlusive) | **5** | $(1.0 \pm 0.1) \times 10^{10}$ |
| **2** (aversive) | BNS **3** | $2 \times 10^5$ |
| **2** (aversive) | di-*p*-*tert*-butylphenyl phosphate | $1 \times 10^5$ |
| **2** (aversive) | 4,4′-di-*tert*-butylphenyl benzoate | $<5 \times 10^4$ |
| β-cyclodextrin-6,6′-disulfide | BNS **3** | $5 \times 10^6$ [1] |

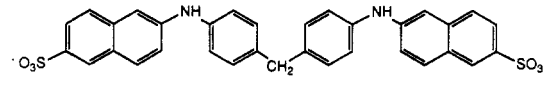
Because one of the two positions in the diiodide is more reactive than the other, the A-naphthalene-B′-linked dimer **1** was formed in lower yield than was **2**, but it could be isolated by selective precipitation and chromatography. It showed six 1-proton signals for the naphthalene hydrogens in the H NMR[6] and also had the expected FAB-MS peak at M + 1 = 2455. The structure assignments to **1** and **2** were confirmed by their binding properties.

The aversive dimer **2** cannot bind a simple ditopic substrate using both its cavities simultaneously. The binding constant of the fluorescent ditopic substrate BNS **3** (Table I) is only slightly



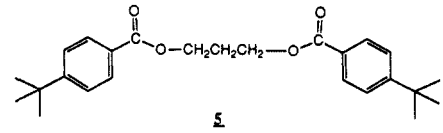

**3**

higher than that for β-cyclodextrin itself, presumably because of some extra hydrophobic interaction with the naphthalene linker. However, **1** binds BNS more strongly, even though BNS is a little short to occupy both cavities of **1** well. Ditopic substrates with appropriate length bind very strongly, and fluorescence competition techniques were needed to determine the binding constant. The fluorescent dimer **4** was prepared by Bucherer reaction[1,7] of




**4**

bis-*p*-anilinomethane with 2-aminonaphthalene-6-sulfonic acid. Substrate **4** is fluorescent when bound to **1**, but the fluorescence is quenched in free $H_2O$ solution. The binding constant of **4** to **1** was determined by dilution; the value, $4 \times 10^8$ $M^{-1}$, is listed in Table I. Then an excess of **4** was allowed to compete for **1** with the long flexible substrate **5**, and from this competition the binding




**5**

constant of **5** to **1** was determined. The value of $1 \times 10^{10}$ $M^{-1}$ puts it in the range of very strong antigen-antibody complexes.

The particular linkages selected in **1** hold the two cyclodextrin rings at an angle, so **1** should more readily bind bent substrates than linear ones. Indeed, we find that the rigid nonlinear substrate **6** has a $K_f$ with **1** even higher than that of **5**, while binding of the linear analogue **7** is considerably weaker. Thus, **1** is a good candidate to use some of its very large binding energy for rate

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