Acknowledgment. This work was supported by grants from the National Institute of General Medical Sciences (GM29332) and Glaxo, Inc.

Supplementary Material Available: Complete tabulated data from the NOE experiments performed on **9** and **29** as well as the COSY spectrum for **9** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Reagents for Bioorganic Synthesis. 5. The Synthesis of Two Potential Cross-Linking Reagents: 2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2-oxoethyl)propenamide] (SBBOP) and 2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2-chloroethyl)propenamide] (SBBCP)

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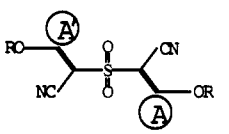
The syntheses of the title bifunctional organic reagents **3** and **4**, containing reactive bis(aldehyde) and bis(alkyl halide) functionalities, respectively, are reported. The reagents have potential applications for biomacromolecular cross-linking, in particular for cross-linking hemoglobin subunits.

One of our research objectives concerns the design and synthesis of novel mono-, bi-, and polyfunctional organic reagents for potential biomedical applications.[1] Our current focus is on bifunctional organic reagents for specifically cross-linking cell-free hemoglobins. The modified hemoglobins have potential use as blood substitutes for emergency transfusions.[2] The need for such an alternative is becoming increasingly pressing in view of scarcity of blood especially when rare types are needed, current limitations on storage of intact blood, the necessity for blood typing/cross-matching before transfusion, and the current public fear, in the wake of the AIDS epidemic, of possible transmission of blood-borne diseases including AIDS and hepatitis.

Cross-linking is anticipated to correct the two major problems associated with cell-free hemoglobin, which otherwise prevents its usage as a viable oxygen carrier: (1) the oxygen affinity of cell-free hemoglobin is too high to enable it to adequately deliver oxygen acquired from lungs to tissues and (2), outside of red blood cells, the tetrameric hemoglobin readily dissociates into α,β-dimers that are quickly eliminated by kidneys, causing hemoglobinuria.[3]

We have recently reported the synthesis, reactions, and applications of a few such bifunctional organic reagents (BORs).[1a-d] These BORs, as exemplified by reagents **1** and **2**, contained either bis(enol–ether)[1a,b,d] or bis(enamine)[1c] functionalities as the sites of cross-linking. Both are highly



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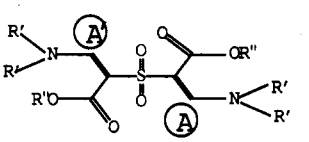


2

electrophilic reagents and operate by initial conjugate addition of amine nucleophiles to their respective cross-linking sites (A,A′), followed by elimination of either alcohol or dialkylamine, producing stable secondary enamines as products. We have also demonstrated[1b,d] the versatility and high reactivity of **1** toward the building blocks of both proteins (amino acids) and nucleic acids (heterocyclic bases). Furthermore, we have shown reagent **1**'s utility in covalently cross-linking deoxy- and oxyhemoglobins.[1a] Likewise, reagent **2** was shown to undergo facile amine exchange reactions with a variety of primary amines.[1c] Nevertheless, the two reagents suffer from a couple of major drawbacks: one, their cross-linking tethers, as revealed by single-crystal X-ray diffraction analyses[4] of **1** (R = Me) and **2** (R′ = R″ = Me), are too short to make effective cross-links between the two diagonally opposed subunits (α_1 to α_2 or β_1 to β_2) of tetrameric hemoglobin, an essential characteristic sought in a cross-linker for

(1) (a) Hosmane, R. S.; Bertha, C. M. *Biochem. Biophys. Res. Commun.* **1990**, *166*, 567. (b) Hosmane, R. S.; Bertha, C. M.; Siriwardane, U.; Hosmane, N. S. *J. Org. Chem.* **1990**, *55*, 5206. (c) Hosmane, R. S.; Bertha, C. M. *Synth. Commun.* **1990**, *20*, 2921. (d) Hosmane, R. S.; Bertha, C. M. *Tetrahedron Lett.* **1988**, *29*, 5847. (e) Hosmane, R. S.; Lim, B. B. *Tetrahedron Lett.* **1985**, *26*, 1915. (f) Lim, B. B.; Hosmane, R. S. *J. Org. Chem.* **1985**, *50*, 5111. (g) Hosmane, R. S. *Tetrahedron Lett.* **1984**, *25*, 363. (h) Hosmane, R. S.; Burnett, F. N.; Albert, M. S. *J. Org. Chem.* **1984**, *49*, 1212. (i) Hosmane, R. S.; Rossman, M. A.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 5497. (j) Hosmane, R. S.; Bakthavachalam, V.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 235. (k) Hosmane, R. S.; Leonard, N. J. *J. Org. Chem.* **1981**, *46*, 1457. (l) Leonard, N. J.; Hosmane, R. S.; Agasimundin, Y. S.; Kostuba, L. J.; Oakes, F. T. *J. Am. Chem. Soc.* **1984**, *106*, 6847. (m) Shahbaz, M.; Urano, S.; LeBreton, P. L.; Rossman, M. A.; Hosmane, R. S.; Leonard, N. J. *J. Am. Chem. Soc.* **1984**, *106*, 2805. (n) Bertha, C. M.; Hosmane, R. S. *Tetrahedron Lett.* **1992**, *33*, 3425.

(2) For leading reviews and monographs on this subject, see: (a) *Advances in Blood Substitutes Research*; Bolin, R. B., Beyer, R. P., Nemo, G. J., Eds.; Alan R. Liss: New York, 1983. (b) Miller, I. F. Synthetic Blood Substitutes: Where Are We and Where Do We Go from Here? *CRC Crit. Rev. Bioeng.* **1978**, 149–177.

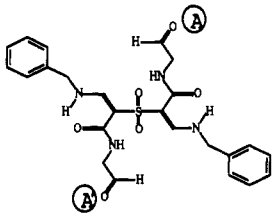
(3) Bunn, H. F.; Esham, W. T.; Bull, R. W. *J. Exp. Med.* **1969**, *129*, 909.

(4) (a) Sirwardane, U.; Chu, S. C.; Hosmane, N. S.; Bertha, C. M.; Hosmane, R. S. *Acta Crystallogr.* **1988**, *C44*, 104. (b) Siriwardane, U.; Chu, S. C.; Hosmane, N. S.; Bertha, C. M.; Hosmane, R. S. *Acta Crystallogr.* **1987**, *C43*, 1823. (c) Bertha, C. M. The Design and Synthesis of Cross-Linking Reagents for Hemoglobin Modification. Ph.D. Thesis submitted to the University of Maryland Graduate School, Baltimore, 1992.

0022-3263/92/1957-5868$03.00/0

modifying hemoglobins to be used as blood substitutes.[2,5] The tether length, however, was adequate to cross-link the two dissimilar subunits (α_1 to β_1 or α_2 to β_2). The X-ray data of 1 revealed that the distance between its two reactive centers (A–A′) was only 4.85 Å. The X-ray data of 2 showed a bond length of 1.3 Å for each of the two enamine CH–N bonds. Therefore, adding 2 × 1.3 Å to the A–A′ distance of 4.85 Å gives 7.4 Å as the approximate distance between the two approaching amino groups of amino acid nucleophiles reacting with 1. This distance is somewhat short considering that the shortest distance, as revealed by X-ray of hemoglobin,[6] between the two ε-amino groups of Lys 82 β_1 and Lys 82 β_2 lining the periphery of the 2,3-DPG pocket (β-cleft) ranges from 9.3 Å in the deoxy form to 10.7 Å in the oxy form. The second drawback of these reagents is their practically rigid configurational (*E,E*) and conformational (anti) stereochemistry at the cross-linking sites at ambient temperatures, leaving little flexibility for proper alignment of the bridging arms for optimal interactions with biomacromolecules.

We now report the synthesis of two new bifunctional reagents 3 and 4 which are designed to eliminate the above two problems of distance and rigidity associated with reagents 1 and 2. While reagent 3 incorporates bis-



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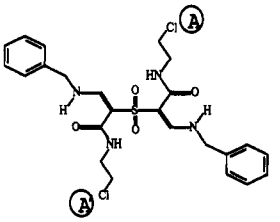
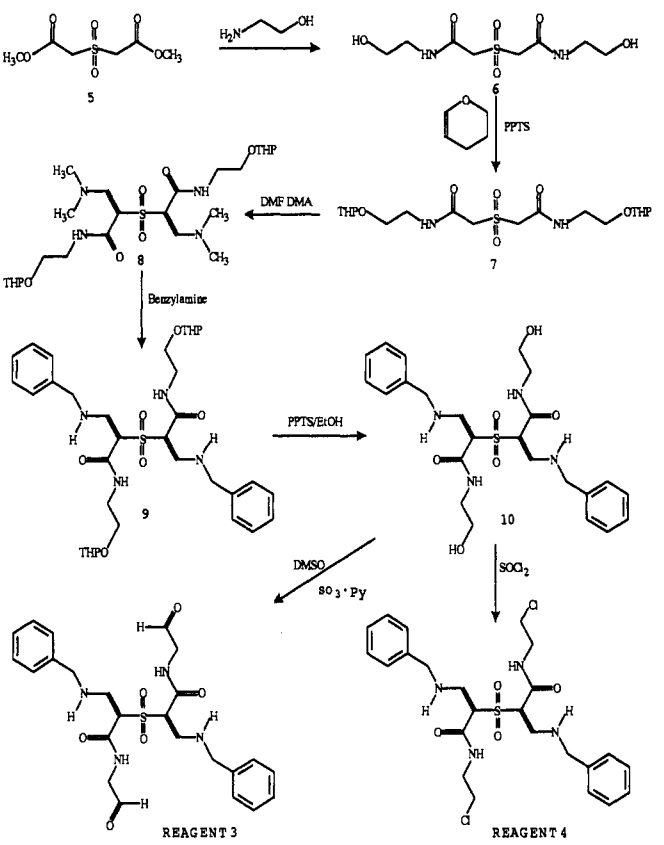


4

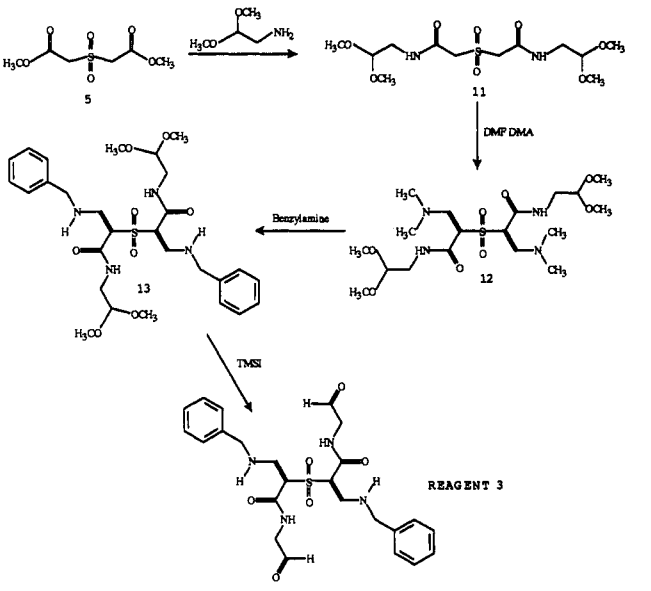
aldehydic groups as the cross-linking sites, reagent 4 possesses bis(alkyl halide) moieties to serve the same purpose. Reagent 4 has an added advantage over 3 in that it eliminates the usual reduction step required after the formation of the 3–Schiff base which is otherwise reversible.[7] Both reagents have an estimated[8] average tether length (A–A′) ranging from 9.2 to 9.9 Å. This length should be adequate to bridge the two β-82 lysine residues of human deoxy- as well as oxyhemoglobins considering that the amino groups in the β-cleft are capable of moving about somewhat in solution.[9] The bis(benzylamine) arms of 3 and 4 are designed for future additional manipulations of their hydrophobic as well as hydrophilic interactions (by appropriate substitutions on the phenyl ring) with the amino acids surrounding the β-cleft.

The starting material for the synthesis of both 3 and 4 (Scheme I) is dimethyl 2,2′-sulfonyldiacetate (5)[10] which

Scheme I



Scheme II



was reacted with ethanolamine to provide the corresponding bis(amide–alcohol) 6 in 94% yield. The hydroxyl groups of 6 were protected with tetrahydropyranyl (THP) groups by treatment with dihydropyran/pyridinium *p*-toluenesulfonate (PPTS),[11] giving 7 in 95% yield. The latter, upon treatment with dimethylformamide dimethyl acetal (DMF DMA), yielded the bis(enamine) 8 in 75% yield. The treatment of 8 with benzylamine afforded 9 (74%), which is consistent with our earlier observations[1c] that the disubstituted enamines undergo facile amine-exchange reactions with primary amines to produce ther-

(5) For a few recent examples of hemoglobin cross-linking, see: (a) Reference 1a. (b) Manning, L. R.; Morgan, S.; Beavis, R. C.; Chait, B. T.; Manning, J. M.; Hess, J. R.; Cross, M.; Currell, D. L.; Marini, M. A.; Winslow, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 3329. (c) Yang, T.; Olsen, K. W. *Biochem. Biophys. Res. Commun.* **1991**, *174*, 518. (d) Fronticelli, C.; Bucci, E.; Razynska, A.; Sznajder, J.; Urbaitis, B.; Gryczynski, Z. *Eur. J. Biochem.* **1990**, *193*, 331. (e) Keipert, P. E.; Adeniran, A. J.; Kwong, S.; Benesch, R. E. *Transfusion* **1989**, *29*, 768.

(6) (a) Fermi, G. *J. Mol. Biol.* **1975**, *97*, 237. (b) Shaanan, B. *J. Mol. Biol.* **1983**, *171*, 31. (c) Fermi, G.; Perutz, M. F.; Shaanan, B.; Fourme, R. *J. Mol. Biol.* **1984**, *175*, 159.

(7) Acharya, A. S.; Manning, J. M. *Proc. Natl.* Acad. *U.S.A.* **1983**, *80*, 3590.

(8) The tether lengths of 3 and 4 were estimated via energy minimization, using ALCHEMYII, a force-field based molecular modeling software by Tripos Associates, St. Louis, Missouri, 1988.

(9) Benesch and co-workers have reported that the amino terminus Val 1 β can move as much as 3 Å inside the 2,3-DPG pocket of deoxyhemoglobin, see: Benesch, R.; Benesch, R. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1976**, *35*, 342.

(10) McCormick, J. E.; McElhinney, R. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1335.

(11) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

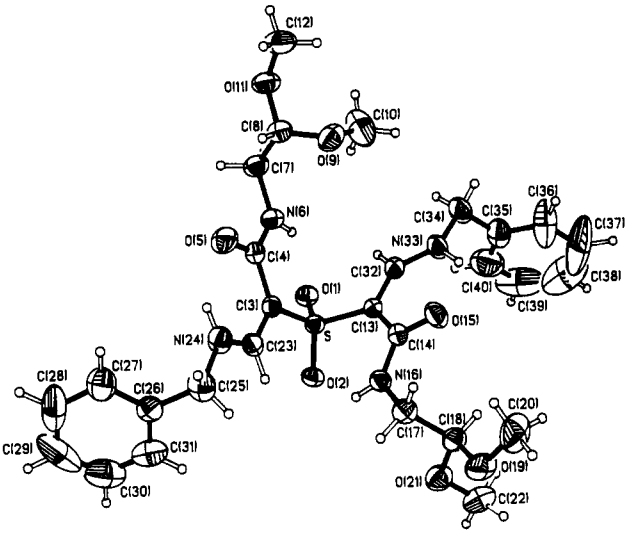


Figure 1. ORTEP view of 13 showing atom numbering scheme.

modynamically more stable enamines. Deprotection of the THP groups of 9 with alcoholic PPTS gave 10 in 85% yield. While oxidation of 10 using Me_2SO/SO_3–pyridine complex[12] provided reagent 3 (35%), treatment of 10 with thionyl chloride gave reagent 4 (81%). Reagent 3 is a white foam, whereas reagent 4 is a white crystalline solid. Both compounds were fully characterized by usual spectroscopic and microanalytical data.

Reagent 3 was also synthesized by a more efficient approach (Scheme II) involving fewer steps and higher yields. The reaction of the bis(ester) 5 with aminoacetaldehyde dimethyl acetal gave the bis(amide) 11 in 94% yield, which was subsequently reacted with DMF DMA to produce the bis(enamine–amide) 12 in 91% yield. Enamine exchange of 12 with benzylamine gave 13 in 96% yield. Finally, deacetalization of 13 with trimethylsilyl iodide (TMSI) afforded 3 in 79% yield. Preliminary indication of potential utility of 3 as a cross-linking reagent was provided by its facile reactions with benzylamine and phenylhydrazine forming the corresponding bis(Schiff base) and bis(hydrazone) in nearly quantitative yields.

As mentioned above, it is important that the designed cross-linking reagents possess appropriate stereochemical features to enable them to position themselves properly within the DPG pocket of hemoglobin. In this regard, it became necessary to know the configurational and conformational characteristics of the newly synthesized reagents or their immediate precursors. This information would also aid in our contemplated molecular modeling using X-ray coordinates of human hemoglobin.[13] To this end, the single-crystal X-ray diffraction analysis of 13 was carried out. The X-ray data revealed that an *E* configuration was present for each half molecule on either side of the central sulfonyl group, while the conformational relationship of each half with respect to the other was anti, as depicted in Figure 1. The distance between the two acetal methine carbons, representing the approximate span between the reactive centers of reagents 3 and 4, was 9.18 Å as computed from fractional coordinates and unit cell measurements of 13. The presence of two intramolecular hydrogen bonds, one on each side of the sulfonyl moiety, between the enamine NH and the amide C=O was apparent based on the calculated O···H distances which were 1.95 and 2.0 Å, respectively, well below the van der Waals internuclear distance of ~2.4 Å. The X-ray data also supported the existence of two other hydrogen bonds between the sulfonyl oxygens and the amide NHs with an O···H distance of 2.02 and 2.17 Å, respectively. The torsion angles defining the location of the first carbon atoms of the substituents on the enamine nitrogens with respect to the double bonds are near planarity (180° or 0°), indicating that the lone pair of electrons of enamine Ns are delocalized into their respective π systems consisting of the propenamide and the sulfone. This is also supported by the bond angles about the enamine nitrogens which are close to 120° and by the enamine C–N bond lengths of ~1.3 Å.

Further exploration of the full potential of reagents 3 and 4 as biomacromolecular cross-linking reagents is currently in progress.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 80, 300, or 500 and 125 MHz, respectively. Apparent multiplicity is designated by the abbreviation, ap = apparent). The multiplicity of ^{13}C NMR peaks is based on ^1H decoupled off-resonance spectra. Electron impact (EI) mass spectra were recorded at 70 eV. The high-resolution FAB mass spectra were recorded at the Mass Spectral Facility, Department of Biochemistry, Michigan State University, East Lansing, MI. Melting points are uncorrected. X-ray crystal structure analyses were performed at the Department of Chemistry, Southern Methodist University, Dallas, Texas. The ^1H NMR chemical shifts were referred to Me_4Si as an internal standard. Flash column chromatography was performed as described by Still et al.[14] Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} (0.2-mm thickness). Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. Anhydrous solvents were prepared as follows: MeOH was distilled from CaH_2 and was stored over molecular sieves (type 3A); acetonitrile was distilled from P_2O_5 and was stored over molecular sieves (type 3A); DMF and Me_2SO were dried over CaO (s) and then distilled at reduced pressure from CaH_2 and were subsequently stored over molecular sieves (type 3A); methylene chloride was distilled from CaH_2 and was stored over molecular sieves (type 3A); and diethyl ether was distilled from Na (s) and bezophenone. All starting materials were purchased from Aldrich Chemical Co. All solvents were reagent grade and were purchased from VWR Scientific with the exception of ethyl acetate which was purchased from Aldrich Chemical Co.

2,2′-Sulfonylbis[*N*-(2-hydroxyethyl)acetamide] (6). A mixture of 5 (5.00 g, 23.8 mmol) and ethanolamine (5.0 mL, 82.8 mmol) in MeOH (25.0 mL) was stirred at room temperature. The mixture became almost homogeneous until a white solid began to crystallize out of the solution. The reaction mixture was stirred for 4 h, after which time the precipitated white solid was filtered out by vacuum filtration and was washed with MeOH. After drying, the yield was 5.94–6.07 g (93–95%). The compound was recrystallized from MeOH to give colorless crystals: mp 165–166 °C; ^1H NMR (Me_2SO-d_6) δ 8.38 (br, 2 H, ex. w/D_2O, 2 amide NH), 4.74 (t, 2 H, J = 5.0 Hz, ex. w/D_2O, 2 OH), 4.25 (s, 4 H, 2 SO_2CH_2), 3.42 (ap q, 4 H, J = 5.5 Hz, t w/D_2O, J = 5.5 Hz, 2 CH_2O), 3.17 (ap q, 4 H, J = 5.5 Hz, m w/D_2O, 2 NCH_2); IR (KBr) 3280 (amide NH), 3000, 2945, 2885, 1656 (C=O), 1550, 1432, 1410, 1328, 1292, 1212, 1140, 1055, 937, 910 cm^{-1}; MS (CI w/*i*-C_4H_{10}) m/z 269 (MH^+: 9.6), 251 ($MH^+ - H_2O$: 1.3), 182 ($MH^+ - C_3H_5NO_2$: 18), 88 ($HO(CH_2)_2NHCO^+$: 100). Anal. Calcd for $C_8H_{16}N_2O_6S$: C, 35.82; H, 6.01; N, 10.44; S, 11.95. Found: C, 35.93; H, 6.03; N, 10.42; S, 11.89.

2,2′-Sulfonylbis[*N*-[2-(tetrahydropyranyloxy)ethyl]acetamide] (7). A mixture of 6 (4.00 g, 14.9 mmol), 3,4-dihydro-2*H*-pyran (5.00 mL, 54.8 mmol), and pyridinium *p*-toluenesulfonate (PPTS)[11] (0.80 g, 3.2 mmol) in anhydrous

(12) For reviews on activated Me_2SO oxidations: (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. (b) Tidwell, T. T. *Synthesis* **1990**, 857–870.

(13) The X-ray coordinates of human deoxy- and oxyhemoglobins are available from the Brookhaven National Laboratory, Upton, Long Island, NY.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

methylene chloride (150 mL) was stirred at room temperature for 17 h. The colorless solution was evaporated to dryness onto flash silica gel (40–63 μm, 15 g). This residue was suspended in chloroform, and the resulting slurry was loaded onto a flash chromatography column packed with flash silica gel (40–63 μm, 90 g) in chloroform. The column was eluted with chloroform/acetone (2:1). The appropriate iodine-absorbing fractions were collected, combined, and then evaporated on a rotary evaporator, leaving a colorless oil. The oil was dried in a vacuum oven at 70–80 °C. Typical yields ranged from 5.85 to 6.18 g (90–95%): ^{1}H NMR (Me_2SO-d_6) δ 8.43 (t, 2 H, J = 5.2 Hz, ex. w/D_2O, 2 NH), 4.57 (t, 2 H, J = 3.3 Hz, 2 acetal CH), 4.25 (s, 4 H, ex. w/D_2O, 2 SO_2CH_2), 3.75 (m, 2 H), 3.63 (ap quintet, 2 H, J = 5.2 Hz), 3.41 (m, 4 H), 3.30 (m, 4 H), 1.73 (m, 2 H), 1.62 (dt, 2 H, J = 9.2, 2.3 Hz), 1.47 (m, 8 H); IR (KBr) 3330, 3080, 2942, 2873, 1665 (amide C=O), 1550, 1327, 1120, 1073, 1032 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 437 (MH^+, 3.0), 353 ($MH^+ - C_5H_8O$, 21), 269 ($MH^+ - 2C_5H_8O$, 35), 104 (100). Anal. Calcd for $C_{18}H_{32}N_2O_8S$: C, 49.53; H, 7.39; N, 6.42; S, 7.34. Found: C, 49.43; H, 7.39; N, 6.36; S, 7.42.

2,2′-Sulfonylbis[3-(dimethylamino)-(*E*,*E*)-*N*-[2-(tetrahydropyranyloxy)ethyl]propenamide] (8). A solution of 7 (2.98 g, 6.83 mmol) and 90% DMF DMA (7.0 mL, 47 mmol) in anhydrous acetonitrile (75.0 mL) was stirred at room temperature for 42 h. The solution became gradually more yellow with time. The yellow solution was evaporated on a rotary evaporator and then on a Kügelrohr distillation apparatus, leaving a yellow oil. The oil was dissolved in a minimum amount of chloroform, and this solution was loaded in three portions onto a chloroform-equilibrated SiO_2 Chromatotron plate (4-mm thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform/MeOH (9:1) which eluted the product as a wide short-wave UV absorbing band. The combined fractions were evaporated, producing an almost colorless oil. The oil began to crystallize later, and complete crystallization took place after the compound was placed in a vacuum desiccator overnight. The off-white solid weighed 2.80 g (75%). A small portion was cold recrystallized from THF/petroleum ether, giving an analytical sample in the form of colorless crystals: mp 102–104 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.59 (t, 2 H, ex. w/D_2O, 2 amide NH), 7.06 (s, 2 H, 2 = CH), 4.55 (br, 2 H, 2 acetal CH), 3.5 (m, 12 H, 2 NCH_2CH_2O and 2 OCH_2), 2.92 (s, 12 H, 2 $N(Me)_2$), 1.5 (br, 12 H, 2 $CH_2CH_2CH_2$); IR (KBr) 3390 (amide NH), 2940, 2863, 1640 (C=O), 1596 (C=C), 1515, 1427, 1378, 1268, 1125, 1100, 1070, 1032, 653 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 547 (MH^+, 44), 463 ($MH^+ - C_5H_8O$, 100), 379 ($MH^+ - 2C_5H_8O$, 75), 85 ($C_5H_9O^+$, 23); UV λ_{max} (MeOH) 290.5 nm. Anal. Calcd for $C_{24}H_{42}N_4O_8S$: C, 52.73; H, 7.74; N, 10.25; S, 5.86. Found: C, 52.62; H, 7.78; N, 10.22; S. 5.81.

2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-[2-(tetrahydropyranyloxy)ethyl]propenamide] (9). Method A. A solution of 8 (628 mg, 1.149 mmol) and benzylamine, distilled under reduced pressure from Zn dust (3.0 mL, 27.5 mmol), was stirred at room temperature for 20 h. The solution was evaporated on a Kügelrohr distillation apparatus, giving an almost colorless oil. The oil was dissolved in a minimum amount of chloroform, and this solution was loaded onto a chloroform-equilibrated SiO_2 Chromatotron plate (4-mm thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform/acetone (19:1) which eluted the product as a large short-wave UV absorbing band. The fraction was evaporated, yielding a colorless thick oil that was dried further in a vacuum desiccator, giving 569 mg (74%): ^{1}H NMR (Me_2SO-d_6) δ 9.59 (dt, 2 H, J = 13.8, 6 Hz, ex. w/D_2O, 2 enamine NH), 7.90 (d, 2 H, J = 13.4 Hz, s w/D_2O, 2 enamine = CH), 7.32 (m, 12 H, 2 H ex. w/D_2O, 2 amide NH and 2 phenyl), 4.53 (m, 6 H, br, s w/D_2O, 2 acetal CH and 2 benzylic CH_2), 3.5 (m, 12 H, 2 NCH_2CH_2O and 2 OCH_2 of 2 THP), 1.50 (m, 12 H, 2 $CH_2CH_2CH_2$); IR (KBr) 3375 (amide NH), 2940, 2865, 1630 (C=O), 1600 (C=C), 1525, 1450, 1410, 1366, 1332, 1278, 1233, 1200, 1180, 1160, 1125, 1073, 1028, 985, 900, 870, 777, 750, 735, 700, 640 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 671 (MH^+, 12), 587 ($MH^+ - C_5H_8O$, 45), 503 ($MH^+ - 2C_5H_8O$, 69), 85 ($C_5H_9O^+$, 100); UV λ_{max} (MeOH) 290 nm. Anal. Calcd for $C_{34}H_{46}N_4O_8S$: C, 60.88; H, 6.91; N, 8.35; S, 4.78. Found: C, 60.77; H, 6.96; N, 8.26; S, 4.72.

Method B. A solution of 7 (3.02 g, 6.92 mmol) and DMF DMA (6.0 mL, 40.6 mmol) in anhydrous acetonitrile (60.0 mL) was stirred at room temperature for 93 h. The solution was evaporated on a rotary evaporator, yielding a yellow oil. Benzylamine (4.0 mL) was added to this oil, and the resultant solution was stirred at room temperature under dry conditions for 24 h. The solution was evaporated on a Kügelrohr distillation apparatus, resulting in a yellow oil. This oil was dissolved in chloroform and was evaporated onto flash silica gel (40–63 μm, 12 g). Chloroform was added to the resultant residue, and the slurry was loaded onto a flash chromatography column packed with flash silica gel (40–63 μm, 80 g) in chloroform. The column was eluted with chloroform. The appropriate short-wave UV absorbing fractions were collected, combined, and evaporated on a rotary evaporator, yielding a slightly yellow oil. The oil was further dried in a vacuum oven at 70–80 °C. The yield was 2.41 g (52% for two steps). The ^{1}H NMR of the compound was superimposable upon that of the compound obtained by method A above.

2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2-hydroxyethyl)propenamide] (10). Method A. A solution of 9 (2.41 g, 3.59 mmol) and PPTS[11] (227 mg, 0.904 mmol) in ethanol (60 mL) was heated to 55 °C (oil bath temperature) for 20.5 h. The colorless reaction solution was evaporated, leaving a white solid. This solid was dissolved in a minimum amount of chloroform/MeOH (5:1). The colorless solution was evaporated to dryness onto flash silica gel (40–63 μm, 6 g). This residue was suspended in chloroform, and the resulting slurry was loaded onto a flash chromatography column packed with flash silica gel (40–63 μm, 60 g) in chloroform. The column was eluted with chloroform/MeOH (29:1). The appropriate short-wave UV absorbing fractions were collected, combined, and evaporated on a rotary evaporator, leaving a white solid that weighed 1.80 g after drying in a vacuum desiccator overnight. The solid was recrystallized from chloroform, yielding a white solid that weighed 1.54 g (85%) after thorough drying, mp 165–166 °C: ^{1}H NMR (Me_2SO-d_6) δ 9.57 (dt, 2 H, J = 13.6, 6 Hz, ex. w/D_2O, 2 enamine NH), 7.89 (d, 2 H, J = 13.5 Hz, s w/D_2O, 2 = CH), 7.32 (m, 12 H, 2 H ex. w/D_2O, 2 amide NH and 2 phenyl), 4.76 (t, 2 H, J = 4.9 Hz, ex. w/D_2O, 2 OH), 4.50 (d, 4 H, J = 6.1 Hz, s w/D_2O, 2 benzylic CH_2), 3.42 (m, 4 H, 2 OCH_2), 3.20 (m, 4 H, 2 amide NCH_2); IR (KBr) 3400 (amide NH), 1628 (C=O), 1521, 1350, 1273, 1233, 1126 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 503 (MH^+, 100); UV λ_{max} (MeOH) 290 nm. Anal. Calcd for $C_{24}H_{30}N_4O_6S$: C, 57.36; H, 6.02; N, 11.15; S. 6.38. Found: C, 57.45; H, 6.04; N, 11.11; S, 6.45.

Method B. A solution of 8 (2.24 g, 4.10 mmol) in benzylamine (5.0 mL, 46 mmol) was allowed to stand at room temperature for 16 h. The excess benzylamine was distilled using a Kügelrohr apparatus, yielding a yellow oil. This oil was dissolved in reagent-grade ethanol (60.0 mL). PPTS[11] (1.03 g, 4.10 mmol) was added, and the resulting solution was heated to 55–60 °C with an oil bath for 64.5 h. The solution was allowed to cool and was evaporated on a rotary evaporator, producing a yellow oil. The oil was dissolved in chloroform (25 mL), and this solution was evaporated onto flash silica gel (40–63 μm, 7.0 g). This residue was suspended in chloroform, and the resulting slurry was loaded onto a flash chromatography column packed with flash silica gel (40–63 μm, 70 g) in chloroform. The column was eluted with chlorform/MeOH (29:1). The appropriate short-wave UV absorbing fractions were collected, pooled, and evaporated on a rotary evaporator, leaving a white solid. The solid was cold recrystallized from chloroform/petroleum ether. The fluffy white solid was filtered and was dried in a drying pistol at 64 °C. The weight was 1.37 g (67% for two steps), and the mp was 164.5–165 °C.

2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2-oxoethyl)-propenamide] (3). Method A. A solution of freshly sublimed I_2 (560 mg g, 2.21 mmol) in anhydrous methylene chloride (10.0 mL) was prepared. Hexamethyldisilane (0.42 mL, 2.05 mmol) was added to this, followed by 13 (248 mg, 0.42 mmol). The resulting dark brown solution was stirred at room temperature under a nitrogen atmosphere for 3 h. The excess TMSI was destroyed by adding 2% $NaHCO_3$ (5.0 mL). The mixture was diluted with methylene chloride (20 mL), and this mixture was washed with 10% $Na_2S_2O_5$ (20 mL). The aqueous layer was washed with methylene chloride (20 mL), and the organic layers were combined and were dried over Na_2SO_4 (s). After gravity filtration, the slightly yellow clear filtrate were concentrated on a rotary evaporator to about 5 mL. This solution was loaded onto a chloroform-equilibrated SiO_2 Chromatotron plate (2-mm

thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform/acetone (6:1) until the major fast moving short-wave UV absorbing compound (R_f in chloroform/acetone (6:1) was 0.15) had moved about halfway across the plate. The solvent was changed to a mixture of chloroform/acetone (4:1), and the compound was collected. This fraction was first evaporated on a rotary evaporator, yielding a white foam. The foam was dried in a vacuum desiccator overnight. The yield was 155 mg (74%): ^1H NMR (Me_2SO-d_6) δ 9.56 (dt, 2 H, J = 12.9, 6.3 Hz, ex. w/D_2O, 2 enamine NH), 9.40 (s, 2 H, 2 CHO), 8.06 (d, 2 H, J = 13.7 Hz, s w/D_2O, 2 =CH), 7.63 (t, 2 H, J = 4.5 Hz ex. w/D_2O, 2 amide NH), 7.31 (s, 10 H, 2 phenyl), 4.49 (d, 4 H, J = 6.1 Hz, s w/D_2O, 2 benzylic CH_2), 3.94 (d, 4 H, J = 5.2 Hz, s w/D_2O, 2 CH_2CO); IR (KBr) 3380 (amide NH), 1720 (CHO), 1628 (amide C=O), 1600 (C=C), 1524, 1449, 1363, 1273, 1230, 1127, 1082, 696, 1013, 696, 632 cm^{-1}; UV λ_{max} (MeOH) 289.0 nm. Anal. Calcd for $C_{24}H_{26}N_4O_6S$: C, 57.82; H, 5.26; N, 11.24; S, 6.43. Found: C, 57.88; H, 5.29; N, 11.16; S, 6.37.

Method B. A three-neck flask fitted with a condenser and a thermometer was removed from an oven. A septum was loosely fitted to the remaining neck, and the apparatus was cooled under a stream of nitrogen gas. Freshly sublimed I_2 (s) (1.20 g, 4.73 mmol) was added, and the septum was closed. Next, hexamethyldisilane (1.00 mL, 4.88 mmol) was added and this mixture was heated to 60 °C, at which point an exothermic reaction ensued and the temperature rose quickly to 100 °C. The purple-brown solution was held at reflux for 30 min, and it gradually became colorless. The fresh TMSI solution was allowed to cool to room temperature, and it was subsequently diluted with dry methylene chloride (10 mL). The compound 13 (620 mg, 1.05 mmol) was added, and the resultant slightly cloudy yellow solution was allowed to stir at ambient temperature for 1 h. The excess TMSI was quenched with 2% $NaHCO_3$ (15 mL). This mixture was poured into a separatory funnel, and methylene chloride (40 mL) and 10% $Na_2S_2O_5$ (40 mL) were added. After vigorous shaking of the mixture, the methylene chloride layer was removed and was dried over anhydrous Na_2SO_4 (s). After gravity filtration, the filtrate was evaporated, giving a slightly yellow oil. The oil was dissolved in a minimum amount of chloroform, and this solution was loaded onto a chloroform-equilibrated SiO_2 Chromatotron plate (2-mm thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform/methanol (19:1) until the major fast-moving short-wave UV absorbing compound (R_f in chloroform/methanol (19:1) was 0.29) was eluted and collected. This fraction was first evaporated on a rotary evaporator, yielding a white foam. The foam was dried in a vacuum desiccator overnight. The yield was 412.9 mg (79%). The ^1H NMR of the foam was identical to that of the compound prepared by method A above.

Method C. To a stirred solution of anhydrous 10 (253 mg, 0.50 mmol) and anhydrous triethylamine (1.20 mL, 8.61 mmol) in anhydrous dimethyl sulfoxide (3.0 mL, 42.3 mmol) was added a solution of sulfur trioxide–pyridine complex (dried in vacuum over P_2O_5) (1.33 g, 8.38 mmol) in anhydrous dimethyl sulfoxide (3.0 mL, 42.3 mmol). The reaction mixture was stirred at room temperature for 30 min and was subsequently poured into an ice-cold mixture of 0.5 g of Celite in distilled water (30 mL). The resultant residue was filtered out, using a sintered glass funnel with a 0.5-g pad of Celite. The filtered residue mixed with Celite was dried in a vacuum desiccator for 1 h over P_2O_5. The residue was triturated with chloroform, and this mixture was filtered in vacuo. The filtrate was loaded onto a chloroform-equilibrated SiO_2 Chromatotron plate (2-mm thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform/acetone (6:1) which eluted the product short-wave UV absorbing band. The appropriate fractions were evaporated, which produced a slightly yellow oil that was dried further in a vacuum desiccator, 88.4 mg (35%). The ^1H NMR of the oil was identical to that of the compound prepared by method A or B above.

A Bis(phenylhydrazone) Derivative of Reagent 3. The reagent was dissolved in 3 mL of acetonitrile, and then a solution of phenylhydrazine hydrochloride (0.5 g, 3.5 mmol) and sodium acetate trihydrate (0.80 g, 5.9 mmol) in 5.0 mL of water was added. The solution was stirred vigorously. After a few min, a pale yellow precipitate appeared. The mixture was stirred for 1 h, and then the precipitate was filtered from the solution and dried in a vacuum desiccator over P_2O_5 (s). The yield was 84%: mp 121–123 °C dec; ^1H NMR (Me_2SO-d_6) δ 9.88 (s, 2 H, ex. w/D_2O, 2 hydrazone NH), 9.55 (dt, 2 H, J = 13.5, 6 Hz, ex. w/D_2O, 2 enamine NH), 8.02 (d, 2 H, J = 13.6 Hz, s w/D_2O, 2 enamine = CH), 7.83 (br, 2 H, ex. w/D_2O, 2 amide NH), 7.15 (m, 20 H, 4 phenyl), 6.69 (m, 2 H, 2 hydrazone = CH), 4.24 (d, 4 H, J = 5.9 Hz, s w/D_2O, 2 benzylic CH_2), 3.90 (m, 4 H, 2 CH_2 on 2 amide N); IR (KBr) 1630 (C=O), 1600 (C=C), 1520 cm^{-1}; UV λ_{max} (MeOH) 287.5 nm. Anal. Calcd for $C_{36}H_{36}N_8O_4S$: C, 63.70; H, 5.64; N, 16.51; S. 4.72. Found: C, 63.63; H, 5.66; N, 16.45; S. 4.77.

A Bis(Schiff Base) of Reagent 3 with Benzylamine. A solution of 3 (102.5 mg, 0.21 mmol) and benzylamine (50 μL, 0.46 mmol) in dry acetonitrile (2.50 mL) was allowed to stand in a flask with type 3A molecular sieves (570 mg) for 18 h. The solution was filtered to remove the insoluble material, the filtrate was evaporated on a rotary evaporator, and the resultant off-white foam was further dried in a vacuum desiccator for 2 days. Spectral data indicated quantitative conversion to the product: ^1H NMR (Me_2SO-d_6) δ 9.49 (dt, 2 H, J = 13.8, 5.9 Hz, ex. w/D_2O, 2 enamine NH), 8.17 (t, 2 H, J = 3.4 Hz, ex. w/D_2O, 2 amide NH), 7.80 (d, 2 H, J = 13.2 Hz, s w/D_2O, 2 = CH of 2 enamine), 7.72 (t, 2 H, J = 1.5 Hz, 2 = CH of 2 Schiff base), 7.27 (m, 20 H, 4 phenyl), 4.52 (s, 4 H, 2 = NCH_2), 3.99 (m, 4 H, J = 1.5 Hz, 2 CH_2 next to 2 amide N), 3.87 (d, 4 H, J = 6.3 Hz, s w/D_2O, 2 CH_2 next to 2 enamine N); IR (KBr) 3360, 3050, 3020, 2910, 2860, 1621 (amide C=O), 1600 (C=C and phenyl), 1507 (phenyl) 1443, 1360, 1320, 1280, 1227, 1125, 1076, 1020, 730, 690, 625 cm^{-1}; UV λ_{max} (MeOH) 289.5 nm; ^{13}C NMR (Me_2SO-d_6) δ 165.13 (2 amide C=O), 158.56, 156.37 (4 methine C), 138.69, 137.33 (2 ipso C of phenyl), 128.50, 128.46, 127.85, 127.52, 127.08, 126.61 (phenyl CH), 100.01 (2 C α to S), 63.59, 52.36, 43.61 (6 CH_2); HRMS (FAB) calcd for $C_{38}H_{41}N_6O_4S$ (M + H^+) 677.2910, found m/z 677.2941.

2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2-chloroethyl)propenamide] (4). A solution of 10 (108 mg, 0.21 mmol) in dry methylene chloride (5.0 mL) over excess anhydrous K_2CO_3 (s) (2.35 g, 17.0 mmol) was stirred under nitrogen while thionyl chloride (0.20 mL, 2.7 mmol) was added. The mixture was stirred at room temperature for 30 min and was then evaporated on a rotary evaporator. The resultant white residue was triturated with acetonitrile. The solid material was filtered out with vacuum filtration, and the filtrate was evaporated, giving a colorless glass. The glass was co-evaporated with ether, and this yielded a white solid residue which was dried in a vacuum desiccator overnight. The solid was dissolved in a minimum amount of chloroform, and this solution was loaded onto a chloroform-equilibrated SiO_2 Chromatotron plate (2-mm thickness, Kieselgel 60 GF_{254}). The plate was eluted with chloroform (6:1) which eluted the product short-wave UV absorbing band (R_f = 0.22 in chloroform/methanol (59:1)). The appropriate fractions were evaporated, which produced a white crystalline solid that was dried in a vacuum desiccator overnight. The yield was 94 mg (81%). An analytical sample was prepared by cold recrystallization from chloroform/petroleum ether, producing fluffy white crystals: mp 143–144 °C; ^1H NMR (Me_2SO-d_6) δ 9.61 (dt, 2 H, J = 13.8, 6.0 Hz, ex. w/D_2O, 2 enamine NH), 8.05 (d, 2 H, J = 13.5 Hz, s w/D_2O, 2 = CH), 7.37 (m, 12 H, 2 H ex. w/D_2O, 2 amide NH and 2 phenyl), 4.51 (d, 4 H, J = 6.3 Hz, s w/D_2O, 2 benzylic CH_2), 3.58 (t, 4 H, J = 6.3 Hz, 2 CH_2 Cl), 3.44 (ap q, 4 H, J = 6 Hz, t w/D_2O, J = 6 Hz, 2 amide NCH_2); IR (KBr) 3390 (amide NH), 1622 (amide C=O), 1593 (C=C), 1512, 1440, 1405, 1343, 1304, 1267, 1226, 1119, 1076, 1000, 770, 728, 693, 631 cm^{-1}; UV λ_{max} (MeOH) 289.5 nm. Anal. Calcd for $C_{24}H_{28}Cl_2N_4O_4S$: C, 53.43; H, 5.23; Cl, 13.14; N, 10.38; S, 5.94. Found: C, 53.59; H, 5.29; Cl, 13.21; N, 10.48; S. 6.07.

2,2′-Sulfonylbis[*N*-(2,2-dimethoxyethyl)acetamide] (11). Method A. A solution of 5 (210 mg, 1.00 mmol) and aminoacetaldehyde dimethyl acetal (2.0 mL, 18.4 mmol) was stirred at room temperature. After 1 h, a white solid began to come out of the solution and TLC showed no more starting material. The solution was stirred overnight, and the precipitated white solid was filtered out in vacuo and was rinsed with diethyl ether. A second crop was obtained by evaporating down the filtrate first on a rotary evaporator to remove diethyl ether and then on a Kügelrohr. The residue was a buff-colored solid. The solid was triturated with diethyl ether. After air-drying, the total yield from the first and second crops was 341 mg (96%). The two crops had the same R_f by TLC. A recrystallization from ethyl acetate–

petroleum ether (3:2) yielded white crystals: mp 141–142 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.41 (t, 2 H, J = 5 Hz, ex. w/D_2O, 2 NH), 4.35 (t, 2 H, J = 5.4 Hz, 2 acetal CH), 4.26 (s, 4 H, 2 SO_2CH_2), 3.28 (s, 12 H, 4 acetal methyl), 3.22 (m, 4 H, J = 5.4 Hz, d w/D_2O, 2 NCH_2); IR (KBr) 3270 (amide NH), 3100, 2990, 2930, 1670, 1650 (C=O), 1580, 1570, 1560, 1540, 1470, 1460, 1440, 1400, 1385, 1330, 1300, 1240, 1200, 1180, 1120, 1100, 1070, 1040 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 357 (MH^+: 1.0), 325 (MH^+ – MeOH: 100), 293 (MH^+ – 2MeOH: 29), 132 (O=$C^+NHCH_2CH(OCH_3)_2$: 25). Anal. Calcd for $C_{12}H_{24}N_2O_8S$: C, 40.44; H, 6.79; N, 7.86; S. 9.00. Found: C, 40.52; H, 6.82; N, 7.82; S, 9.09.

Method B. A solution of **5** (3.00 g, 14.3 mmol) and aminoacetaldehyde dimethyl acetal (5.3 mL, 48.6 mmol) in MeOH (60.0 mL) was heated to reflux for 99 h. After being cooled, a white solid crystallized out of the reaction solution. The solid was filtered out and was rinsed liberally with diethyl ether. The solid weighed 4.30 g and had a mp of 141.5–142.5 °C. A second and third crop were obtained after evaporation of the filtrate and trituration with diethyl ether. The total combined yield was 4.80 g (94%). A ^{1}H NMR of the product was identical to that isolated from method A above.

2,2′-Sulfonylbis[3-(dimethylamino)-(*E*,*E*)-*N*-(2,2-dimethoxyethyl)propenamide] (12). A solution of **11** (3.00 g, 8.42 mmol) and 90–95% DMF DMA (12.0 mL, 81 mmol) in acetonitrile (100 mL) was stirred at room temperature for 31 h. The reaction solution became slightly yellow in color with time and was evaporated on a rotary evaporator, resulting in a yellow oil. The oil crystallized after some time. The crystalline mass was triturated with 15 mL of diethyl ether, and the resultant off-white solid was filtered and dried. The yield was 3.57 g (91%). An analytical sample was prepared by cold recrystallization from THF/petroleum ether: mp 87–89 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.51 (t, 2 H, J = 5.5 Hz, 2 amide NH), 7.07 (s, 2 H, 2 = CH), 4.36 (t, 2 H, J = 5.6 Hz, 2 acetal CH), 3.24 (m, 16 H, 2 NCH_2 and 4 acetal methyl), 2.89 (s, 12 H, 2 $N(Me)_2$); ^{13}C NMR (Me_2SO-d_6) δ 222.6, 162.7, 149.4, 103.4, 101.5, 52.7, 42.3; IR (KBr) 3380 (NH), 2920, 2825, 1635 (C=O), 1600 (C=C), 1520, 1430, 1385, 1270, 1190, 1120, 1065, 848, 749, 638 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 467 (MH^+: 29), 435 (MH^+ – MeOH: 16); UV λ_{max} (MeOH): 290.5 nm. Anal. Calcd for $C_{18}H_{34}N_4O_8S$: C, 46.34; H, 7.34; N, 12.01; S. 6.87. Found: C, 46.17; H, 7.40; N, 11.95; S. 6.84.

2,2′-Sulfonylbis[3-(benzylamino)-(*E*,*E*)-*N*-(2,2-dimethoxyethyl)propenamide] (13). A solution of **12** (1.00 g, 2.14 mmol) and benzylamine (2.0 mL, 18.3 mmol) in acetonitrile (10.0 mL) was stirred at room temperature for 3 h. The solution was evaporated on a rotary evaporator and then on a Kügelrohr distillation apparatus (45–50 °C), which yielded an almost colorless oil. Diethyl ether was added, and the oil crystallized after some time. The crystalline mass was triturated with diethyl ether, and the crystalline solid was filtered out by vacuum filtration and rinsed with diethyl ether/petroleum ether (1:1). The yield was 1.21 g (96%): mp 86–88 °C; ^{1}H NMR (Me_2SO-d_6) δ 9.58 (dt, 2 H, J = 13.4 5.9 Hz, ex. w/D_2O, 2 NH), 7.89 (d, 2 H, J = 13.6 Hz, s w/D_2O, 2 = CH), 7.3 (m, 12 H, 2 H, ex. w/D_2O, 2 amide NH and 2 phenyl), 4.51 (d, 4 H, J = 6.1 Hz, s w/D_2O, 2 benzylic CH_2), 4.37 (t, 2 H, J = 5.3 Hz, 2 acetal CH), 3.23 (m, 16 H, 2 NCH_2 and 4 acetal methyl); IR (KBr) 3380 (amide NH), 2940, 2835, 1633 (C=O), 1605, (C=C), 1530, 1452, 1367, 1354, 1315, 1278, 1200, 1130, 1085, 1020, 780, 740, 702, 640 cm^{-1}; MS (CI w/i-C_4H_{10}) m/z 591 (MH^+: 2.6), 559 (MH^+ – MeOH: 13); UV λ_{max} (MeOH) 289.5 nm. Anal. Calcd for $C_{28}H_{38}N_4O_8S$: C, 56.93; H, 6.48; N, 9.48; S. 5.43. Found: C, 56.98; H, 6.52; N, 9.46; S. 5.53.

Single-Crystal X-ray Analysis of 13. A colorless crystal of **13** was mounted on a Nicolet R3m/V diffractometer. Final unit cell parameters were obtained by a least-squares fit of the angles of 24 accurately centered reflections (16° < 2θ < 27°). Intensity data were collected in the range of 3.5° ≤ 2θ ≤ 50.0° at −43 °C using graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. The scan was θ/2θ; 6165 reflections were collected with 5701 unique with R_{int} = 0.011. Three standard reflections monitored after every 150 reflections did not show any significant change in intensity during the data collection. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct-methods with SHELXTL-Plus package.[15] Full-matrix least-squares refinement was performed. Scattering factors were taken from the *International Tables for X-ray Crystallography*.[16] Hydrogen atoms were placed at idealized positions without refinement. The weight had the form $\omega = [\sigma^2(F_o) + g(F_o)^2]^{-1}$ where g = 0.0009. The final cycles of refinement converged at $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.069$, $\omega R = [|\sum\omega(|F_o| - |F_c|)^2|/\sum \omega(F_o)^2]^{1/2} = 0.104$, GOF = 2.70 for 4187 observed reflections [$I > 3.0\sigma(I)$]. The maximum and minimum difference Fourier residuals were 1.06 and −0.37 e/Å^3, respectively.

Crystallographic Data for 13: $C_{28}H_{38}N_4O_8S$, M_r = 590.7, P_1, a = 10.536 (3) Å, b = 10.875 (3) Å, c = 14.197 (4) Å, α = 82.19 (2)°, β = 86.59 (2)°, γ = 87.84 (2)°, V = 1607 (1) Å^3, Z = 2, D_x = 1.22 g cm^{-3}, (Mo Kα) = 0.71073 Å, μ = 1.43 cm^{-1}. Final R = 0.069 for 4187 reflections [$I > 3.0\sigma(I)$].

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Supplementary Material Available: Tables of bond lengths, bond angles, torsion angles, and positional parameters (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Sheldrick, G. M. SHELXTL-Plus, Siemens Analytical X-Ray Instruments, Inc., 1990.
(16) *International Tables for X-ray Crystallography* Kynock Press: Birmingham, 1974; Vol. IV.