Nucleophilic Opening of Chiral Bis(aziridines): A Route to Enantiomerically Pure α-Amino Aldehydes or Acids and Polysubstituted Piperidines

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α-Amino aldehydes or acids can be obtained by nucleophilic opening of suitably protected chiral bis(aziridines) derived from D-mannitol. Nucleophiles consist of a wide range of organometallic and heteronucleophilic reagents. Reaction orientation toward bis-opening (route to enantiomerically pure α-amino aldehydes or acids) or toward heterocyclization (route to chiral, polysubstituted piperidines) is influenced, notably, by the nature of the N-protecting group, the nucleophile, and by Lewis acids.

Many nonclassical α-amino acids exhibit biological activity.[1] α-(Acylamino) and α-[(alkoxycarbonyl)amino] aldehydes are potential inhibitors toward some classes of proteolytic enzymes;[2] furthermore, α-amino aldehydes are versatile chiral intermediates for the synthesis of biologically active compounds.[3] In connection with our interest in developing a convenient method for the preparation of unusual α-amino acids and suitably N-protected α-amino aldehydes as chiral synthons for the synthesis of asymmetric products such as fatty acid metabolite analogues,[4] we have studied the possibility of synthetizing α-amino aldehydes or α-amino acids from *N,N'*-disubstituted bis(aziridines) derived from D-mannitol, a naturally occurring chiral compound.

We have recently published the synthesis of two chiral diastereoisomeric bis(aziridines) A and B from D-mannitol[5] and preliminary results concerning their nucleophilic opening.[6] We report here the obtention of enantiomerically pure α-amino aldehydes or acids via these bis(aziridines) according to Scheme I as well as a systematic study of the ability of various nucleophiles to effect nucleophilic opening of the aziridine rings, the key step in the synthesis.

We describe in this paper a study of the reactivity of three different N-protected and activated bis(aziridines) A (I, Y = Ts; II, Y = $COOCH_2Ph$; III, Y = CH_2Ph) toward a number of carbon nucleophiles (Table I) and heteronucleophiles (Table II). Such N protections are of practical use in peptide synthesis and were chosen in order to resist acetonide hydrolysis. Tosyl, benzyloxycarbonyl, and benzyl nitrogen substituents confer a decreasing reactivity toward the nucleophilic opening of the aziridine ring. For *N*-benzylaziridine, electrophilic assistance is indispensable.

Nucleophilic opening of bis(aziridines) A led to an intermediate amide C, which is the precursor of three different compounds (Scheme II): (i) the symmetrical diamino compound a, resulting from regiospecific opening of both C-1 and C-6 of bis(aziridine), (ii) the aminopiperidine b, formed when C-1–N cleavage is followed by intramolecular opening by the intermediate amide of the second aziridine ring, and (iii) the monosubstituted derivative c. The compounds obtained depend strongly on the nature of the nucleophile, the substitution pattern at the nitrogen of the aziridine, and the presence or not of Lewis acid.

N,N'-Ditosyl bis(aziridine) AI was quite susceptible to ring-opening by carbon nucleophiles. Lithium organocuprates lead to regiospecific bis opening of AI, forming diamino derivatives a in high yields. Derivatives **1** and **2** were submitted to acetal hydrolysis followed by oxidative cleavage with either a $NaIO_4$·CrO_3 mixture (R = CH_3) or $Pb(OAc)_4$ (R = nBu) in order to prove the validity of the method for the obtention of enantiomerically pure compounds. Enantiomerically pure (*S*)-*N*-tosyl-α-aminobutyric acid (**5a**) and (*S*)-*N*-tosyl-α-aminoheptanal (**6**) were thus obtained (Scheme III). We have used this α-amino aldehyde **6** as a chiral intermediate for the synthesis of 13(*S*)-*N*-tosylamino 9(*Z*),11(*E*)-octadecadienoic acid.[4] (*R*)-*N*-tosyl-α-aminoheptanal (**6'**) was synthetized independently starting from *N,N'*-ditosyl bis(aziridine) BI according to the same pathway as for the *S* enantiomer **6**.

We were able to perform the symmetrical substitution of AI with saturated, vinylic, and allylic groups in good yields using a variety of organometallic species (Table I, entries 1, 2, 4, and 5). During organometallic aziridine ring opening, heterocyclization was not observed in THF or Et_2O, but when reacted with lithium heptynide in the presence of HMPA, aziridine AI led to the 2-alkylpiperidine heterocyclization compound **10** (entry 6).

Reaction of lithium dialkylcuprate with *N,N'*-bis(benzyloxycarbonyl) bis(aziridine) AII gave the disubstituted derivative a in a moderate yield (entries 7 and 8). This could be due to a partial decomposition of the intermediate metallic amide, since some benzylic alcohol is recovered from the reaction.

Regiospecific ring opening addition of (dimethylcopper)lithium to the poorly reactive *N,N'*-dibenzyl bis(aziridine) AIII promoted by BF_3·Et_2O led to the monoalkylated derivative c (entry 9). The monosubstituted derivative **13** isolated after protonation spontaneously cyclizes to the corresponding piperidine **b**.[7]

The reactivity of bis(aziridines) AI, AII, and AIII toward various heteronucleophiles such as halides, azides, or sulfides was studied in aprotic solvents. Nucleophilic

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(7) The isomerization of the *N*-benzyl monoalkylated derivative c in piperidine b is clean but slow at room temperature (2 months for completion) but it is accelerated by its stirring in a CH_2Cl_2 suspension of silica gel (20 h).

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Scheme I

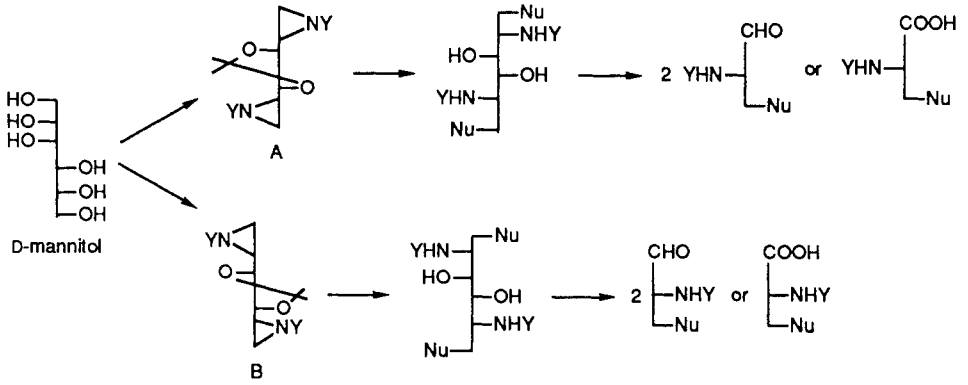


Table I. Reactions of Bis(aziridines) A with Carbon Nucleophiles

entry	aziridine	organometallic reagent	reaction conditions temp[a]/time/solvent	yield, % a	b	c	rc[b]
1[5a]	AI	$(CH_3)_2CuLi$ (2 equiv)	−78 → −30 °C/2 h, then −30 °C/2 h/THF	85 (1)			
2	AI	$(nBu)_2CuLi$ (2 equiv)	−78 → −30 °C/2 h, then −30 °C/2 h/THF	95 (2)			
3	AI	$(CH_2{=}CH)_2CuLi$ (4 equiv)	−78 → −40 °C/3 h, then −40 → −10 °C/2 h Et_2O–THF (2:1)			23 (7)	77
4	AI	$(CH_2{=}CH)_2CuCNLi_2$ (4 equiv)	−78 → 0 °C/1 h/THF	80 (8)			
5	AI	$CH_2{=}CHCH_2MgBr$ (4 equiv)	0 → 20 °C/1 h/Et_2O	75 (9)			
6	AI	$nC_5H_{11}C{\equiv}C\text{-}Li$ (4 equiv)	rt/5 h/THF–HMPA (10:1)		60 (10)		
7[5a]	AII	$(CH_3)_2CuLi$ (2 equiv)	−78 → −30 °C/2 h, then −30 °C/2 h/THF	46 (11)			
8	AII	$(nBu)_2CuLi$ (2 equiv)	−78 → −45 °C/1 h, then −45 °C/3 h/THF	59 (12)			
9[5a]	AIII	$(CH_3)_2CuLi{\cdot}BF_3$ (5 equiv)	−78 → 0 °C/4 h, then 0 → 20 °C/2 h/THF			50 (13)	50

[a] rt = room temperature. [b] rc = recovered material.

Table II. Reactions of Bis(aziridines) A with Heteronucleophiles

entry	aziridine	Nu	reagent	reaction conditions temp[a]/time/solvent	yield, % a	b	c	rc[b]
1	AI	F	$(nBu)_4NF$ (4 equiv)	rt/2 h/DMF		78 (14)		
2	AI	Br	$(nBu)_4NBr$ (4 equiv)	rt/2 h 30 min/DMF		50 (15)		40
3	AI	I	$(nBu)_4NI$ (4 equiv)	rt/4 h 30 min/DMF				100
4	AI	F	$LiBF_4$ (4 equiv)	rt/20 h/THF–CH_3CN			20 (16)	
5	AI	Br	$LiBr{\cdot}BF_3$ (4 equiv)	rt/4 h/THF	90 (17)			
6	AI	I	$LiI{\cdot}BF_3$ (4 equiv)	rt/1 h/THF	85 (18)			
7	AI	Br	Li_2NiBr_4 (1.6 equiv)	rt/10 min/THF	90 (17)			
8	AII	Br	Li_2NiBr_4 (1.6 equiv)	rt/15 h/THF	75 (19)			
9	AIII	Br	Li_2NiBr_4 (1.6 equiv)	−5 °C → rt/1 h/THF		65 (20)		
10	AI	Cl	Li_2CuCl_4 (1.6 equiv)	rt/4 days/THF	90 (21)			
11	AI	N_3	NaN_3 (4 equiv)	55 °C/2 h/DMF		80 (23)		
12	AII	N_3	NaN_3 (4 equiv)	65 °C/24 h/DMF		60 (24)		
13	AI	N_3	$NaN_3{\cdot}BF_3$ (4 equiv)	55 °C/2 h/DMF	85 (25)			
14	AII	N_3	$NaN_3{\cdot}BF_3$ (4 equiv)	65 °C/24 h/DMF	80 (26)			
15	AI	PhS	PhSNa (3 equiv)	rt/30 min/THF	90 (27)			
16	AIII	PhS	PhSNa (3 equiv)	65 °C/15 h/THF	10 (28)	50 (29)		20
17	AI	HS	$HSNa{\cdot}H_2O$ (1.5 equiv)	rt/6 h/THF	100 (30)			
18	AII	HS	$HSNa{\cdot}H_2O$ (4 equiv)	rt/15 h/DMF	80 (31)			

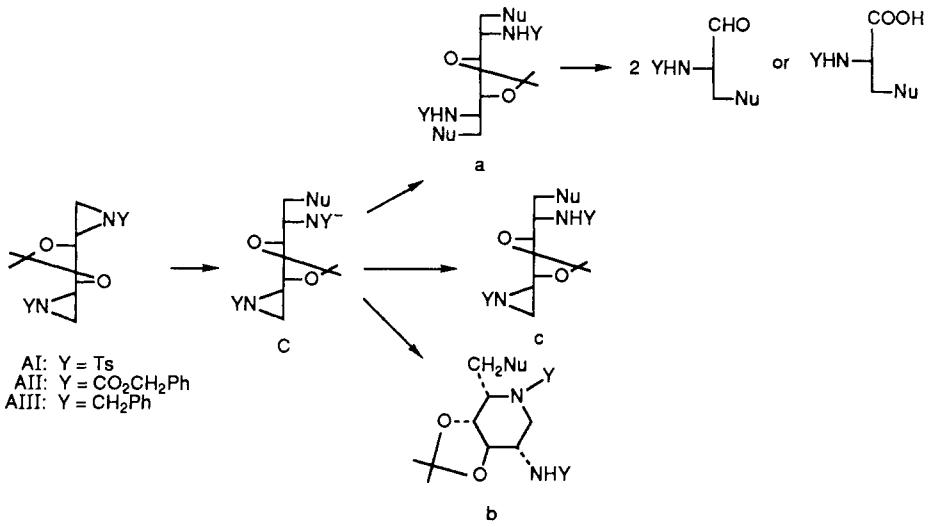
[a] rt = room temperature. [b] rc = recovered material.

opening is regiospecific and in most cases either the symmetrically substituted derivative a or the piperidine b was obtained (Table II).

Obtention of the halogenosubstituted derivatives a and b is an attractive project since it paves the way toward further transformations. Tetrabutylammonium halides are highly nucleophilic organic soluble reagents: when reacted with tetrabutylammonium fluoride, bis(aziridine) AI led to a good yield of piperidine **14** at room temperature (entry 1); for bromine substitution on AI longer reaction times were required (entry 2) but when AI was reacted with $(nBu)_4NI$ no reaction occurred (entry 3). Bromide and especially iodide ions are simultaneously reactive nucleophiles and good leaving groups: after rapid nucleophilic attack of AI leading to C, competition between piperidine b formation and re-formation of the aziridine ring occurs. For the obtention of disubstituted derivatives a heterocyclizations to b must be prevented. This was achieved in the presence of BF_3, since the negative charge of the intermediate amide C is partially masked.

Reaction of AI with lithium bromide or lithium iodide in the presence of a stoichiometric amount of $BF_3{\cdot}Et_2O$ (homogeneous medium) afforded the corresponding disubstituted derivatives in high yields (entries 5 and 6). Unfortunately, reaction of $LiBF_4$ with AI leads to a poor yield of derivative c (entry 4), forbidding the access to a fluoroalanine precursor. Dilithium tetrabromonickelate reacted under mild conditions with bis(aziridines) AI and AII, yielding a derivatives (entries 7 and 8); Li_2NiBr_4 was even able to perform ring-opening of nonactivated aziridine AIII, leading to piperidine **20** due to electrophilic assistance (entry 9). Less reactive dilithium tetrachlorocuprate afforded the dichloro derivative **21** from bis(aziridine) AI in an excellent yield (entry 10).[8]

Scheme II

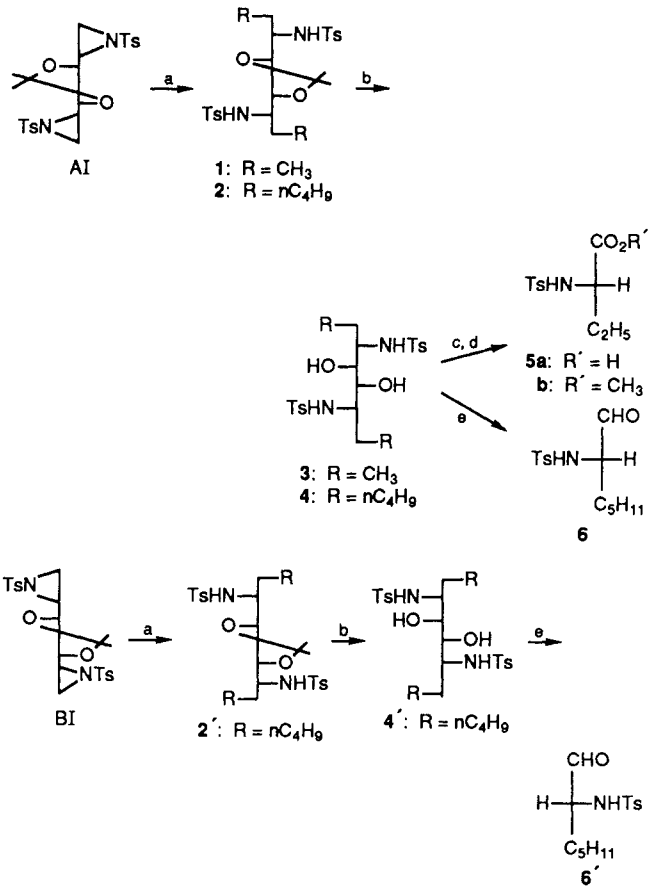


Bis(aziridines) AI and AII underwent ring-opening by sodium azide. Heating AI or AII with NaN_3 in DMF led to piperidines **23** and **24**, respectively (entries 11 and 12); addition of $BF_3{\cdot}Et_2O$ prevented heterocyclization and gave **25** and **26**, precursors of $N_\alpha N_\beta$ chemodifferentiated α,β-L-diaminopropionic acid (entries 13 and 14).

As expected sodium thiophenate underwent bissubstitution rapidly on bis(aziridine) AI, yielding a (entry 15) and monosubstitution with the nonactivated *N*-benzyl derivative AIII (entry 16). The monosubstituted derivative **29** led quantitatively to the piperidine **29′**.[7] Precursors of cysteine **30** (entry 17) and **31** (entry 18) are quantitatively obtained by reaction of sodium hydrosulfide hydrate with aziridines AI and AII, respectively.

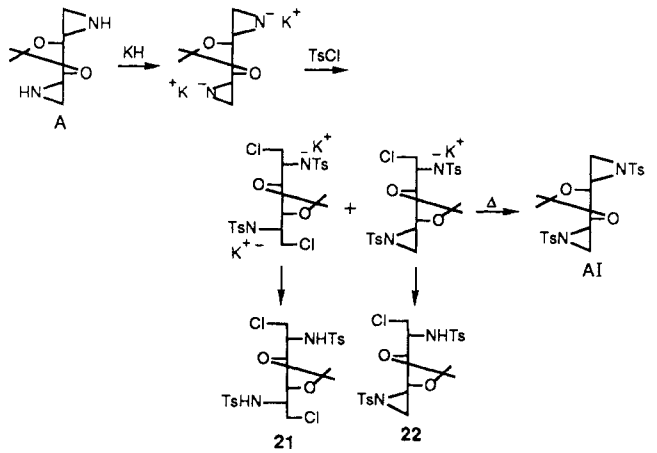
Symmetrical, regiospecific opening of chiral bis(aziridines) derived from D-mannitol provides a flexible route to optically pure α-amino acids or aldehydes, carrying various functionalities that are capable of undergoing subsequent modifications. Nonsymmetrical opening leads to chiral functionalized piperidines, which are close in structure to potent antineoplastic piperidine alkaloids[9] and glycosidase inhibitors.[10]

Scheme III[a]



[a] R = CH_3: (a) see Table I, entry 1; (b) TFA–H_2O, 0 °C, 4 h; (c) $NaIO_4$–CrO_3, AcOH–H_2O, room temperature, 3 h; (d) CH_2N_2, ether, 0 °C. R = nC_4H_9: (a) see Table I, entry 2; (b) TFA–H_2O, 0 °C, 1 h; (e) $Pb(OAc)_4$, CH_2Cl_2, −20 °C, 15 min.

(8) We have noticed that in the course of N–H bis(aziridine) tosylation by reaction of bis(aziridine potassium salt) with tosyl chloride, competitive formation of some mono- and dichlorosubstituted derivatives **22** and **21** can sometimes be observed. The formation of these byproducts is favored by mild reaction conditions and completely avoided by warming the reaction mixture after tosyl chloride condensation. Furthermore **21** or **22** is totally converted to *N*-tosyl aziridine AI on heating in the presence of potassium hydride. We propose the following reactional pathway for the N–H bis(aziridine) tosylation:



Experimental Section

Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately prior to use. Hexamethyl-

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phosphoramide (HMPA) and dichloromethane were distilled from CaH_2 and stored under an argon atmosphere. ^1H NMR spectra were recorded on a Varian EM 390 (90 MHz) or a Bruker AM 250 (250 MHz) instrument with tetramethylsilane as the internal standard. Chemical shifts are reported in δ (peak multiplicity, number of protons, coupling constant if appropriate in hertz, proton concerned). For cyclic compounds proton attribution was determined in most cases by 2D chemical shift correlated spectroscopy (COSY). ^{13}C NMR spectra were obtained on a Bruker AM 250 instrument. Infrared spectra were obtained with a Perkin-Elmer 783 spectrophotometer. Optical rotations were obtained with the indicated solvent and concentration in a 1-dm cell by using a Perkin-Elmer 241-C polarimeter. All reactions were carried out under an inert atmosphere of argon and were monitored by thin layer chromatography with E. Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with E. Merck Kieselgel 60 (230–400-mesh ASTM) silica.[11] The chemical names are given following IUPAC rules for carbohydrate derivatives.

1,2,5,6-Tetradeoxy-1,6-dimethyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (1): mp 198 °C; $[\alpha]^{20}_D$ −62° (*c* 1.0, CH_2Cl_2).

1,2,5,6-Tetradeoxy-1,6-dibutyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (2). To a suspension of cuprous iodide (1.165 g, 6.1 mmol) in THF (6.3 mL) at −40 °C was added dropwise a hexane solution of *n*-butyllithium (7.6 mL, 1.6 M solution, 12.2 mmol). After being stirred for 30 min at this temperature, the heterogeneous mixture was recooled to −60 °C and the *N,N'*-ditosyl bis(aziridine) AI (0.75 g, 1.52 mmol) in THF (16 mL) was introduced. After addition was complete, the temperature was increased to −30 °C over 2 h and stirring was continued for an additional 2 h at this temperature. The reaction was then quenched with a mixture composed of 10% concentrated NH_4OH/saturated aqueous NH_4Cl solution (20 mL) and allowed to stir at room temperature for 30 min. The resulting mixture was then filtered through Celite and extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (20% ethyl acetate in cyclohexane) gave **2** as white crystals (882 mg, 95% yield): mp 102 °C; $[\alpha]^{20}_D$ −60° (*c* 1.1, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.40 (m, 22 H, nBu, H_1), 1.37 (s, 6 H, $C(CH_3)_2$), 2.39 (s, 6 H, $C_6H_4CH_3$), 3.32 (dt, 2 H, $J_{2,1}$ = 7 Hz, $J_{2,NH}$ = 10 Hz, H_2), 3.99 (s, 2 H, H_3), 4.64 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.28, 7.74 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{31}H_{48}N_2O_6S_2$: C, 61.15; H, 7.94; N, 4.60. Found: C, 61.19; H, 8.04; N, 4.76.

1,2,5,6-Tetradeoxy-1,6-dibutyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-D-mannitol (2'). Bis opening of *N,N'*-ditosyl bis(aziridine) BI by dibutylcuprate was performed by using the same conditions as for AI, described previously, giving colorless oil **2'**: $[\alpha]^{20}_D$ +44° (*c* 1.0, CH_2Cl_2); IR (neat) cm^{-1} 3280 (NH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.64–1.36 (m, 22 H, nBu, H_1), 1.30 (s, 6 H, $C(CH_3)_2$), 2.38 (s, 6 H, $C_6H_4CH_3$), 3.39 (m, 2 H, H_2), 3.95 (m, 2 H, H_3), 4.99 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.28, 7.74 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4).

1,2,5,6-Tetradeoxy-1,6-dimethyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (3). A solution of **1** (210 mg, 0.4 mmol) in trifluoroacetic acid (3 mL) and water (0.3 mL) was stirred at 0 °C for 4 h. After addition of water (5 mL) the mixture was extracted with CH_2Cl_2 (2 × 6 mL). The organic extracts were washed with water and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (100% ethyl acetate) afforded **3** as white crystals (190 mg, 98% yield): mp 124 °C; $[\alpha]^{20}_D$ −104° (*c* 1.0, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 0.60 (t, 6 H, CH_3), 1.06–1.32 (m, 4 H, H_1), 2.35 (s, 6 H, $C_6H_4CH_3$), 3.47 (m, 2 H, H_2), 3.83 (s, 2 H, H_3), 6.13 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.22, 7.77 (AB, 8 H, C_6H_4). Anal. Calcd for $C_{22}H_{32}N_2O_6S_2$: C, 54.52; H, 6.65; N, 5.78. Found: C, 54.09; H, 6.63; N, 5.58.

1,2,5,6-Tetradeoxy-1,6-dibutyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (4). A solution of **2** (792 mg, 1.3 mmol) in trifluoroacetic acid (9.3 mL) and water (1 mL) was stirred at 0 °C for 1 h. After addition of water (8 mL) the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with 3% aqueous $NaHCO_3$ and then with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (50% ethyl acetate in cyclohexane) gave **4** as white crystals (740 mg, 92% yield): mp 140 °C; $[\alpha]^{20}_D$ −83° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3470 (OH), 3170 (NH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.54–1.35 (m, 22 H, nBu, H_1), 2.34 (s, 6 H, C_6H_4-CH_3), 3.55 (br s, 2 H, H_2), 3.81 (br s, 2 H, H_3), 6.50 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.23, 7.80 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13; H, 7.79; N, 4.92. Found: C, 59.29; H, 7.74; N, 4.96.

1,2,5,6-Tetradeoxy-1,6-dibutyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-D-mannitol (4'). Desacetalization of **2'** was carried out under identical conditions as for **2**, described beforehand, giving colorless oil **4'**: $[\alpha]^{20}_D$ +33° (*c* 1.0, CH_2Cl_2); IR (neat) cm^{-1} 3480 (OH), 3280 (NH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.55–1.60 (m, 22 H, nBu, H_1), 2.40 (s, 6 H, $C_6H_4CH_3$), 3.25 (m, 2 H, H_2), 3.73 (d, 2 H, $J_{3,2}$ = 6.5 Hz, H_3), 5.45 (d, 2 H, $J_{NH,2}$ = 9.5 Hz, NH), 7.27, 7.77 (AB, 8 H, J_{AB} = 9 Hz, C_6H_4).

2(*S*)-[*N*-(*p*-Tolylsulfonyl)amino]butyric Acid (5a). To a solution of diol **3** (130 mg, 0.268 mmol) in acid acetic (0.4 mL) was added a solution of chromic anhydride (54 mg, 0.54 mmol) and sodium periodate (116 mg, 0.542 mmol) in 80% aqueous acetic acid (2 mL). The resulting mixture was stirred at room temperature for 3 h, afterwhich water (5 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with a 0.1 N sodium thiosulfate solution (5 mL) followed by brine, dried over magnesium sulfate, and evaporated. Flash chromatography of the residue on silica gel (40% ethyl acetate in cyclohexane) afforded **5a** as white crystals (130 mg, 75% yield): mp 118 °C (CH_2Cl_2/pentane 1/3); ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, 3 H, CH_3), 1.60–1.95 (m, 2 H, CH_2), 2.41 (s, 3 H, $C_6H_4CH_3$), 3.91 (m, 1 H, H_2), 5.10 (d, 1 H, $J_{NH,2}$ = 7.5 Hz, NH), 7.30, 7.75 (AB, 4 H, C_6H_4).

Methyl 2(*S*)-[*N*-(*p*-Tolylsulfonyl)amino]butanoate (5b). To a solution of **5a** (15 mg, 0.058 mmol) in ether (5 mL) was added dropwise an ethereal solution of diazomethane at 0 °C until persistance of the yellow coloration. Evaporation gave **5b** quantitatively as white crystals: mp 68 °C; $[\alpha]^{20}_D$ −26° (*c* 0.7, EtOH) (lit.[12] $[\alpha]^{20}_D$ −22° (*c* 1.0, EtOH)): ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (dd, 3 H, $J_{4,3}$ = 7 Hz, $J_{4,3'}$ = 7.5 Hz, H_4), 1.55–1.85 (m, 2 H, CH_2), 2.40 (s, 3 H, $C_6H_4CH_3$), 3.50 (s, 3 H, OCH_3), 3.87 (m, 1 H, H_2), 5.10 (d, 1 H, $J_{NH,2}$ = 10 Hz, NH), 7.26, 7.75 (AB, 4 H, C_6H_4).

2(*S*)-[*N*-(*p*-Tolylsulfonyl)amino]heptanal (6). To a solution of diol **4** (227.6 mg, 0.4 mmol) in CH_2Cl_2 (6 mL) was added lead tetraacetate (213 mg, 0.48 mmol) at −20 °C. After being stirred for 15 min, the reaction mixture was rapidly filtered through a small silica gel column (ether elution). Evaporation of the solvent gave aldehyde **6** quantitatively (226 mg) as a colorless oil, which was not further purified, due to its relative instability: ^1H NMR (250 MHz, $CDCl_3$) δ 0.70–1.70 (m, 11 H, C_5H_{11}), 2.40 (s, 3 H, $C_6H_4CH_3$), 3.85 (m, 1 H, H_2), 5.24 (d, 1 H, $J_{NH,2}$ = 7.5 Hz, NH), 7.27, 7.71 (AB, 4 H, J_{AB} = 7.5 Hz, C_6H_4), 9.39 (s, 1 H, H_1).

2(*R*)-[*N*-(*p*-Tolylsulfonyl)amino]heptanal (6'). **6'** was synthetized starting from diol **4'** according to the same conditions as for **4**. The enantiomeric purity of aldehyde **6** was proved by ^1H NMR spectroscopy (250 MHz) using tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium [Eu(tfc)$_3$] as a chiral shift reagent. A 50–50 mixture of the 2(*R*)- and 2-(*S*)-[*N*-(*p*-tolylsulfonyl)amino]heptanals **6'** and **6** showed two distinct aldehyde signals in the presence of 2 equiv of Eu(tfc)$_3$ ($\Delta\Delta\delta$ 0.03 ppm), whereas the aldehyde signal of **6** always appeared as a single peak.

1,2,5,6-Tetradeoxy-1-vinyl-2-[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-5,6-[*N*-(*p*-tolylsulfonyl)imino]-L-iditol (7). Vinyllithium, prepared at −78 °C from vinyl bromide (342 mg, 3.2 mmol) and a pentane solution of *tert*-butyllithium (3.76 mL, 1.7 M solution, 6.4 mmol) in ether

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(0.25 mL), was added via cannula to a suspension of CuI (305 mg, 1.6 mmol) in ether (5 mL) at −40 °C. After the mixture was stirred for 1 h at this temperature (dark green tint), AI (98.4 mg, 0.2 mmol) in THF (2 mL) was added at −60 °C. The solution was warmed to −10 °C over 2 h, stirred at that temperature for 1 h, and quenched in the usual fashion. Standard workup followed by flash chromatography on silica gel (30% ethyl acetate in cyclohexane) gave **7** as a colorless oil (24 mg, 23% yield) and the starting material AI (75.7 mg, 77%). **7**: IR (neat) cm^{-1} 3230 (NH), 1640 (CH=CH_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (s, 3 H, $C(CH_3)_2$), 1.32 (s, 3 H, $C(CH_3)_2$), 2.02 (t, 2 H, H_1), 2.39 (d, 1 H, $J_{6trans,5}$ = 4.5 Hz, H_{6trans}), 2.41 (s, 6 H, $C_6H_4CH_3$), 2.58 (d, 1 H, $J_{6cis,5}$ = 7 Hz, H_{6cis}), 2.83 (m, 1 H, H_5), 3.28 (m, 1 H, H_2), 3.75 (dd, 1 H, $J_{3,4}$ = 8 Hz, $J_{3,2}$ = 1.5 Hz, H_3), 4.03 (dd, 1 H, $J_{4,3}$ = 8 Hz, $J_{4,5}$ = 4 Hz, H_4), 4.66 (d, 1 H, $J_{NH,2}$ = 9.5 Hz, NH), 4.76–4.90 (m, 2 H, $H_{2'}$), 5.26–5.50 (m, 1 H, $H_{1'}$), 7.30, 7.33, 7.61, 7.82 (2 AB, 8 H, J_{AB} = 8 Hz, C_6H_4).

1,2,5,6-Tetradeoxy-1,6-divinyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (8). Vinyllithium prepared at −78 °C from vinyl bromide (342 mg, 3.2 mmol) and a pentane solution of *tert*-butyllithium (3.76 mL, 1.7 M solution, 6.4 mmol) in ether (0.25 mL), was added via cannula to a suspension of CuCN (144 mg, 1.6 mmol) in dry THF (1.6 mL). The heterogeneous mixture was vigourously stirred and allowed to warm gradually to 0 °C until complete dissolution resulted, giving a tan-brown coloration, and recooled to −78 °C. AI was then introduced as a solution in THF (2 mL), the mixture was warmed to 0 °C over 1 h, and the reaction was quenched in the usual fashion. Standard extractive workup followed by flash chromatography on silica gel (20% ethyl acetate in cyclohexane) gave **8** as white crystals (87.8 mg, 80% yield): mp 149–150 °C; $[\alpha]^{20}_D$ −54° (*c* 1.22, CH_2Cl_2); IR (KBr) cm^{-1} 3260 (NH), 1640 (CH=CH_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 6 H, $C(CH_3)_2$), 2.05 (t, 4 H, $J_{1,1'}$ = 6.5 Hz, H_1), 2.40 (s, 6 H, $C_6H_4CH_3$), 3.39 (dt, 2 H, $J_{2,1}$ = 6.5 Hz, $J_{2,NH}$ = 10 Hz, H_2), 3.91 (s, 2 H, H_3), 4.71 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 4.73–4.85 (m, 4 H, $H_{2'}$), 5.30–5.50 (m, 2 H, $H_{1'}$), 7.28–7.72 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4); ^{13}C NMR (250 MHz, $CDCl_3$) δ 21.4 ($C_6H_4CH_3$), 27.0 ($C(C_3)_2$), 38.5 (C_1), 51.2 (C_2), 78.0 (C_3), 108.6 ($C(CH_3)_2$), 118.3 ($C_{2'}$), 133.4 ($C_{1'}$), 127.1, 129.6, 138.5, 143.4 (C_6H_4). Anal. Calcd for $C_{27}H_{36}N_2O_6S_2$: C, 59.10; H, 6.61; N, 5.10 Found: C, 58.96; H, 6.69; N, 4.90.

1,2,5,6-Tetradeoxy-1,6-diallyl-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (9). An ether solution of allylmagnesium bromide (1.78 mL, 0.9 M solution, 1.6 mmol) was slowly added to a stirring solution of AI (98.4 mg, 0.2 mmol) in ether (2 mL) at 0 °C. The mixture was progressively warmed to 20 °C for 1 h and then quenched at 0 °C by the addition of saturated aqueous ammonium chloride (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **9** as white crystals (86.5 mg, 75% yield): mp 155–156 °C; $[\alpha]^{20}_D$ −45° (*c* 1.0, CH_2Cl_2); IR (KBr) cm^{-1} 3250 (NH), 1640 (HC=CH_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 6 H, $C(CH_3)_2$), 1.22–1.57 (m, 4 H, H_1), 1.78 (m, 4 H, $H_{1'}$), 2.38 (s, 6 H, $C_6H_4CH_3$), 3.30 (dt, 2 H, $J_{2,1}$ = 7 Hz, $J_{2,NH}$ = 10 Hz, H_2), 3.83 (s, 2 H, H_3), 4.77 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 4.80–4.92 (m, 4 H, $H_{3'}$), 5.46–5.65 (m, 2 H, $H_{2'}$), 7.28, 7.72 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4); ^{13}C NMR (250 MHz, $CDCl_3$) δ 21.5 ($C_6H_4CH_3$), 27.1 ($C(CH_3)_2$), 29.5 (C_1), 33.2 ($C_{1'}$), 51.4 (C_2), 77.8 (C_3), 108.6 ($C(CH_3)_2$), 114.9 ($C_{3'}$), 137.4 ($C_{2'}$), 126.8, 129.6, 138.5, 143.4 (C_6H_4). Anal. Calcd for $C_{29}H_{40}N_2O_6S_2$: C, 60.40; H, 6.99; N, 4.85. Found: C, 60.24; H, 7.05; N, 4.72.

1,2,5,6-Tetradeoxy-1-(1-heptynyl)-2,6-[*N*-(*p*-tolylsulfonyl)imino]-3,4-*O*-(1-methylethylidene)-5-[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (10). To a cold (0 °C) stirring solution of 1-heptyne (0.26 mL, 1.92 mmol) in THF (2 mL) was added a hexane solution of *n*-butyllithium (1.0 mL, 1.6 M solution, 1.6 mmol). After the mixture was stirred for 30 min at this temperature the *N,N'*-ditosyl bis(aziridine) AI (98.4 mg, 0.2 mmol) in THF (1.5 mL) was added, followed by the addition of HMPA (0.28 mL, 1.6 mmol). The reaction mixture was stirred for 5 h at room temperature, quenched at 0 °C by the addition of saturated aqueous ammonium chloride (5 mL), and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **10** as white crystals (70.6 mg, 60% yield): mp 94–95 °C; $[\alpha]^{20}_D$ +23.3° (*c* 1.0, CH_2Cl_2); IR (KBr) cm^{-1} 3180 (NH), 2250 (C≡C); ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, 3 H, CH_3), 1.15–1.58 (m, 12 H, $(CH_2)_3$, $C(CH_3)_2$), 1.98 (t, 2 H, $H_{3'}$), 2.40 (s, 3 H, $C_6H_4CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.20–2.60 (m, 2 H, H_1), 2.77 (dd, 1 H, $J_{6ax,6eq}$ = 14.5 Hz, $J_{6ax,5}$ = 10.5 Hz, H_{6ax}), 3.16 (m, 1 H, H_5), 3.31 (dd, 1 H, $J_{3,2}$ = 5.5 Hz, $J_{3,4}$ = 9 Hz, H_3), 3.54 (dd, 1 H, $J_{4,3}$ = 9 Hz, $J_{4,5}$ = 9 Hz, H_4), 4.10 (dd, 1 H, $J_{6eq,5}$ = 4.5 Hz, H_{6eq}), 4.62 (m, 1 H, H_2), 4.93 (br s, 1 H, NH), 7.27, 7.32, 7.78 (2 AB, 8 H, J_{AB} = 8 Hz, C_6H_4); ^{13}C NMR (250 MHz, $CDCl_3$) δ 13.9 (CH_3), 16.2, 18.8, 22.2 ($(CH_2)_3$), 21.6 ($C_6H_4CH_3$), 26.4, 26.6 ($C(CH_3)_2$), 28.5 ($C_{3'}$), 31.1 (C_1), 44.9 (C_6), 53.6, 54.8 (C_2, C_5), 75.7 ($C_{2'}$), 74.6, 76.2 (C_3, C_4), 83.0 ($C_{1'}$), 110.9 ($C(CH_3)_2$), 127.4, 129.6, 129.7, 137.5, 143.5, 143.8 (C_6H_4). Anal. Calcd for $C_{30}H_{40}N_2O_6S_2$: C, 61.20; H, 6.85; N, 4.76. Found: C, 61.17; H, 6.96; N, 4.68.

1,2,5,6-Tetradeoxy-1,6-dimethyl-2,5-bis[*N*-(benzyloxycarbonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (11): mp 103 °C; $[\alpha]^{20}_D$ −23° (*c* 1.05, CH_2Cl_2). Anal. Calcd for $C_{27}H_{36}N_2O_6$: C, 66.92; H, 7.48; N, 5.78. Found: C, 66.82; H, 7.54; N, 5.63.

1,2,5,6-Tetradeoxy-1,6-dibutyl-2,5-bis[*N*-(benzyloxycarbonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (12). To a suspension of cuprous iodide (228.5 mg, 1.2 mmol) in THF (1.25 mL) at −40 °C was added dropwise a hexane solution of *n*-butyllithium (1.5 mL, 1.6 M solution, 2.4 mmol). After being stirred for 30 min at this temperature, the heterogeneous mixture was recooled to −65 °C and the *N,N'*-bis(benzyloxycarbonyl) bis(aziridine) AII (135.6 mg, 0.3 mmol) in THF (3 mL) was added. After addition was complete, the temperature was increased to −45 °C over 1 h and stirring was continued for an additional 3 h at this temperature. The reaction was quenched and worked up as described previously for **2**. Flash chromatography of the residue on silica gel (15% ethyl acetate in cyclohexane) gave **12** as white crystals (100 mg, 59% yield): mp 75 °C; $[\alpha]^{20}_D$ −9° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH), 1700 (C=O); ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.60 (m, 2 H, nBu, H_1), 1.33 (s, 6 H, $C(CH_3)_2$), 3.52–3.84 (m, 4 H, H_2, H_3), 4.90 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 5.10, 5.14 (AB, 4 H, J_{AB} = 12 Hz, NCH_2), 7.32 (m, 10 H, C_6H_5). Anal. Calcd for $C_{33}H_{48}N_2O_6$: C, 69.68; H, 8.50; N, 4.92. Found: C, 69.50; H, 8.58; N, 4.98.

1,2,5,6-Tetradeoxy-1-methyl-2-(*N*-benzylamino)-3,4-*O*-(1-methylethylidene)-5,6-(*N*-benzylimino)-L-iditol (13): ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (dd, 3 H, CH_3), 1.20–1.85 (m, 12 H, $C(CH_3)_2$), H_1, H_2), 2.40 (m, 1 H, H_5), 3.33–3.60 (AB, 2 H, J_{AB} = 13 Hz, NCH_2), 3.65–3.88 (AB, 2 H, J_{AB} = 13 Hz, NCH_2), 3.84 (m, 2 H, H_3, H_4), 7.20–7.50 (m, 10 H, C_6H_5). Anal. Calcd for $C_{24}H_{32}O_2N_2$: C, 75.75; H, 8.47; N, 7.36. Found: C, 74.97; H, 8.41; N, 7.26.

13 isomerized spontaneously at room temperature in 2 months into piperidine **13'**.

1,2,5,6-Tetradeoxy-1-methyl-2,6-(*N*-benzylimino)-3,4-*O*-(1-methylethylidene)-5-(*N*-benzylamino)-L-iditol (13'): $[\alpha]^{20}_D$ −37° (*c* 1.0, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.39 (s, 3 H, $C(CH_3)_2$), 1.46 (s, 3 H, $C(CH_3)_2$), 1.48–1.62 (m, 2 H, H_1), 2.31 (dd, 1 H, $J_{6ax,5}$ = 10 Hz, $J_{6ax,6eq}$ = 13 Hz, H_{6ax}), 2.80 (dd, 1 H, $J_{6eq,5}$ = 4 Hz, H_{6eq}), 2.92–3.12 (m, 2 H, H_2, H_5), 3.55 (dd, 1 H, $J_{4,5}$ = 10 Hz, $J_{4,3}$ = 9 Hz, H_4), 3.65–3.85 (m, 6 H, H_3, NCH_2, NH), 7.20–7.40 (m, 10 H, C_6H_5).

1,2,5,6-Tetradeoxy-1-fluoro-2,6-[*N*-(*p*-tolylsulfonyl)imino]-3,4-*O*-(1-methylethylidene)-5-[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (14). To a solution of tetrabutylammonium fluoride (727 mg, 0.8 mmol, 1.1 mM on silica gel) in DMF (1 mL) at room temperature was added the *N,N'*-ditosyl bis(aziridine) AI (49.2 mg, 0.1 mmol) in DMF (1 mL). The reaction mixture was stirred for 2 h, quenched by the addition of water (3 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **14** as white crystals (40 mg, 78% yield): mp 163 °C; $[\alpha]^{20}_D$ +22° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3270 (NH), 1090 (CF); ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 3 H, $C(CH_3)_2$), 1.28 (s, 3 H, $C(CH_3)_2$), 2.41 (s, 6 H, $C_6H_4CH_3$), 2.83 (dd, 1 H, $J_{6ax,5}$ = 11 Hz, $J_{6ax,6eq}$ = 14.5

Hz, H_{6ax}), 3.14 (m, 1 H, H_5), 3.24 (dd, 1 H, $J_{3,4}$ = 9.5 Hz, H_3), 3.55 (dd, 1 H, $J_{4,5}$ = 9.5 Hz, H_4), 4.10 (*ABX*, 1 H, $J_{1',2}$ = 7 Hz, $H_{1'}$), 4.14 (*ABX*, 1 H, $J_{1,2}$ = 5 Hz, $J_{1,1'}$ = 14 Hz, H_1), 4.48 (dd, 1 H, $J_{6eq,5}$ = 4 Hz, H_{6eq}), 4.68 (m, 1 H, H_2), 5.05 (d, 1 H, $J_{NH,5}$ = 5.5 Hz, NH), 7.29, 7.66, 7.74 (2 AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{23}H_{29}N_2O_6FS_2$: C, 53.89; H, 5.70; N, 5.46. Found: C, 54.02; H, 5.61; N, 5.42.

1,2,5,6-Tetradeoxy-1-bromo-2,6-[*N*-(*p*-tolylsulfonyl)imino]-3,4-*O*-(1-methylethylidene)-5-[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (15). To a solution of tetrabutylammonium bromide (257 mg, 0.8 mmol) in DMF (1 mL) at room temperature was added the *N,N'*-ditosyl bis(aziridine) AI (49.2 mg, 0.1 mmol) in DMF (1 mL). The reaction mixture was stirred for 2 h 30 min and then quenched, worked up, and purified as for **14**, giving **15** (28.6 mg, 50% yield) and the starting material AI (40 mg, 40%). **15**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (s, 3 H, $C(CH_3)_2$), 1.28 (s, 3 H, $C(CH_3)_2$), 2.41 (s, 3 H, $C_6H_4CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.80 (dd, 1 H, H_{6ax}), 2.96–3.60 (m, 5 H, H_1, H_3, H_4, H_5), 4.20 (m, 1 H, H_{6eq}), 4.71 (m, 1 H, H_2), 5.05 (br s, 1 H, NH), 7.26, 7.65, 7.71 (2 AB, 8 H, C_6H_4).

1,2,5,6-Tetradeoxy-1-fluoro-2-[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-5,6-[*N*-(*p*-tolylsulfonyl)imino]-L-iditol (16). To a solution of *N,N'*-ditosyl bis(aziridine) AI (49.2 mg, 0.1 mmol) in THF (1 mL) at room temperature was added an acetonitrile solution of lithium tetrafluoroborate (0.8 mL, 1 M solution, 0.8 mmol). The reaction mixture was stirred for 20 h, quenched at 0 °C by the addition of water (2 mL), and extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product obtained quantitatively, contained according to ^{1}H NMR (90 MHz) about 80% of AI and 20% of **16**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.25 (s, 3 H, $C(CH_3)_2$), 1.35 (s, 3 H, $C(CH_3)_2$), 2.30 (d, 1 H, $J_{6trans,5}$ = 4 Hz, H_{6trans}), 2.45 (s, 6 H, $C_6H_4CH_3$), 2.60 (d, 1 H, $J_{6cis,5}$ = 7 Hz, H_{6cis}), 2.80 (m, 1 H, H_5), 3.15–3.60 (m, 3 H, H_1, H_2), 3.90 (m, 2 H, H_3, H_4), 4.90 (d, 1 H, $J_{NH,2}$ = 10 Hz, NH), 7.35, 7.70, 7.80 (2 AB, 8 H, J_{AB} = 7 Hz, C_6H_4).

1,2,5,6-Tetradeoxy-1,6-dibromo-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (17) (Entry 5, Table II). To a suspension of lithium bromide (70 mg, 0.8 mmol) in THF (1 mL) at room temperature was added the *N,N'*-ditosyl bis(aziridine) AI (49.2 mg, 0.1 mmol) in THF (1.5 mL) followed by boran trifluoride etherate (0.1 mL, 0.8 mmol). The reaction mixture was stirred for 4 h, quenched at 0 °C by the addition of water (3 mL), and extracted with ether (3 × 5 mL). The combined extracts were washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **17** as white crystals (59 mg, 90% yield): mp 166 °C; $[\alpha]^{20}_D$ −23° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 6 H, $C(CH_3)_2$), 2.40 (s, 6 H, $C_6H_4CH_3$), 3.20 (d, 4 H, $J_{1,2}$ = 6.5 Hz, H_1), 3.54 (dt, 2 H, H_2), 4.04 (s, 2 H, H_3), 5.00 (d, 2 H, $J_{NH,2}$ = 9.5 Hz, NH), 7.32, 7.81 (AB, 8 H, C_6H_4). Anal. Calcd for $C_{23}H_{30}N_2O_6S_2Br_2$: C, 42.22; H, 4.62; N, 4.28. Found: C, 42.86; H, 4.58; N, 4.33.

1,2,5,6-Tetradeoxy-1,6-diiodo-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (18). To a suspension of lithium iodide (107 mg, 0.8 mmol) in THF (1 mL) at room temperature was added AI (49.2 mg, 0.1 mmol) in THF (1.5 mL) followed by boran trifluoride etherate (0.1 mL, 0.8 mmol). The reaction mixture was stirred for 1 h at 20 °C, quenched, and worked up as described above. Flash chromatography of the residue on silica gel (25% ethyl acetate in cyclohexane) gave **18** as white crystals (63.5 mg, 85% yield): mp 169–170 °C; $[\alpha]^{20}_D$ −32° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 6 H, $C(CH_3)_2$), 2.41 (s, 6 H, $C_6H_4CH_3$), 3.02 (*ABX*, 2 H, $J_{1,1'}$ = 11 Hz, $J_{1',2}$ = 6.5 Hz, $H_{1'}$), 3.03 (*ABX*, 2 H, $J_{1,2}$ = 6.5 Hz, H_1), 3.50 (dt, 2 H, H_2), 4.04 (s, 2 H, H_3), 4.98 (d, 2 H, $J_{NH,2}$ = 9.5 Hz, NH), 7.31, 7.77 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{23}H_{30}N_2O_6S_2I_2$: C, 36.91; H, 4.04; N, 3.74. Found: C, 37.29; H, 4.12; N, 3.70.

1,2,5,6-Tetradeoxy-1,6-dibromo-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (17) (Entry 7, Table II). To a solution of *N,N'*-ditosyl bis(aziridine) AI (49.2 mg, 0.1 mmol) in THF (1 mL) at room temperature was added a THF solution of dilithium tetrabromonickelate[13] (0.8 mL, 0.4 M solution, 0.32 mmol). After being stirred for 10 min, the reaction mixture was quenched by the addition of phosphate buffer KH_2PO_4/K_2HPO_4 (4 mL, 1 M) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **17** as white crystals (60 mg, 90% yield).

1,2,5,6-Tetradeoxy-1,6-dibromo-2,5-bis[*N*-(benzyloxycarbonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (19). To a solution of *N,N'*-bis(benzyloxycarbonyl) bis(aziridine) AII (45.2 mg, 0.1 mmol) in THF (1 mL) at room temperature was added a THF solution of dilithium tetrabromonickelate[13] (0.8 mL, 0.4 M solution, 0.32 mmol). The reaction mixture was stirred for 15 h and then quenched and worked up as described above. Flash chromatography of the residue on silica gel (15% ethyl acetate in cyclohexane) gave **19** as white crystals (46 mg, 75% yield): mp 88 °C; $[\alpha]^{20}_D$ −15° (*c* 1.24, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (s, 6 H, $C(CH_3)_2$), 3.25–3.50 (m, 4 H, H_1), 3.90–4.20 (m, 4 H, H_2, H_3), 5.05–5.20 (m, 6 H, $CH_2C_6H_5$, NH), 7.35 (m, 10 H, C_6H_5). Anal. Calcd for $C_{25}H_{30}N_2O_6Br_2$: C, 48.87; H, 4.92; N, 4.56. Found: C, 48.91; H, 4.98; N, 4.49.

1,2,5,6-Tetradeoxy-1-bromo-2,6-(*N*-benzylimino)-3,4-*O*-(1-methylethylidene)-5-(*N*-benzylamino)-L-iditol (20). To a solution of *N,N'*-dibenzyl bis(aziridine) AIII (72.8 mg, 0.2 mmol) in THF (2 mL) at −5 °C was added dropwise a THF solution of dilithium tetrabromonickelate[13] (1.6 mL, 0.4 M solution, 0.64 mmol). After being stirred for 10 min, the solution was warmed to 20 °C, stirred at this temperature for 1 h, and quenched in the usual fashion. Standard workup followed by flash chromatography on silica gel (30% ethyl acetate in cyclohexane) gave **20** as a colorless oil (73.5 mg, 65% yield): $[\alpha]^{20}_D$ −71° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (s, 3 H, $C(CH_3)_2$), 1.45 (s, 3 H, $C(CH_3)_2$), 2.32 (dd, 1 H, $J_{6ax,6eq}$ = 13 Hz, $J_{6ax,5}$ = 10 Hz, H_{6ax}), 2.85 (dd, 1 H, $J_{6eq,5}$ = 4.5 Hz, H_{6eq}), 2.95 (m, 1 H, H_5), 3.42 (dd, 1 H, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H_4), 3.57 (d, 2 H, $J_{1,2}$ = 5 Hz, H_1), 3.60–3.80 (m, 5 H, H_2, H_3, $NHCH_2$), 3.82, 4.07 (AB, 2 H, J_{AB} = 13 Hz, NCH_2), 7.10–7.40 (m, 10 H, C_6H_5).

1,2,5,6-Tetradeoxy-1,6-dichloro-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (21). To a solution of AI (98.4 mg, 0.2 mmol) in THF (2 mL) at room temperature was added a THF solution of dilithium tetrachlorocuprate[14] (1.28 mL, 0.5 M solution, 0.64 mmol). After being stirred for 4 days, the reaction mixture was quenched in the usual fashion. Standard workup followed by flash chromatography on silica gel (30% ethyl acetate in cyclohexane) gave **21** as white crystals (102 mg, 90% yield): mp 172 °C; $[\alpha]^{20}_D$ −27° (*c* 1.05, CH_2Cl_2); IR (Nujol) cm^{-1} 3290 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 6 H, $C(CH_3)_2$), 2.41 (s, 6 H, $C_6H_4CH_3$), 3.20–3.60 (m, 6 H, H_1, H_2), 4.00 (s, 2 H, H_3), 5.05 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.28, 7.75 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{23}H_{30}N_2O_6S_2Cl_2$: C, 48.85; H, 5.34; N, 4.95. Found: C, 49.02; H, 5.33; N, 4.94.

1,2,5,6-Tetradeoxy-1-azido-2,6-[*N*-(*p*-tolylsulfonyl)imino]-3,4-*O*-(1-methylethylidene)-5-[*N*-(*p*-tolylsulfonyl)amino]-L-iditol (23). To a suspension of sodium azide (52 mg, 0.8 mmol) in DMF (1 mL) at room temperature was added bis(aziridine) AI (49.2 mg, 0.1 mmol) in DMF (1 mL). The reaction mixture was stirred for 2 h at 55 °C, quenched by the addition of water (3 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **23** as white crystals (43 mg, 80% yield): mp 152 °C; $[\alpha]^{20}_D$ +23° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH), 2100 (N_3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, $C(CH_3)_2$), 2.41 (s, 3 H, $C_6H_4CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.72 (dd, 1 H, $J_{6ax,5}$ = 10.5 Hz, $J_{6ax,6eq}$ = 14.5 Hz, H_{6ax}), 3.07–3.56 (m, 5 H, H_1, H_3, H_4, H_5), 4.11 (dd, 1 H, $J_{6eq,5}$ = 4.5 Hz, H_{6eq}), 4.56 (m, 1 H, H_2), 5.31 (d, 1 H, $J_{NH,5}$ = 5.5 Hz, NH), 7.30, 7.31, 7.70, 7.75 (2 AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for

(13) Dawe, R. D.; Molinski, T. F.; Turner, J. V. *Tetrahedron Lett.* **1984**, *25*, 2061.

(14) Ciaccio, J. A.; Addess, K. J.; Bell, T. W. *Tetrahedron Lett.* **1986**, *27*, 3697.

$C_{23}H_{29}N_5O_6S_2$: C, 51.57; H, 5.45; N, 13.07. Found: C, 50.83; H, 5.42; N, 12.47.

1,2,5,6-Tetradeoxy-1-azido-2,6-[*N*-(benzyloxycarbonyl)imino]-3,4-*O*-(1-methylethylidene)-5-[*N*-(benzyloxycarbonyl)amino]-L-iditol (24). To a suspension of sodium azide (52 mg, 0.8 mmol) in DMF (1 mL) containing 2 drops of water at room temperature was added the *N,N'*-bis(benzyloxycarbonyl) bis(aziridine) AII (45.2 mg, 0.1 mmol) in DMF (1 mL). The reaction mixture was stirred at 24 h at 65 °C and then quenched, worked up, and purified as for **23**, giving **24** (30 mg, 60% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 6 H, $C(CH_3)_2$), 2.72 (m, 1 H, H_{6ax}), 3.32–3.86 (m, 5 H, H_1, H_3, H_4, H_5), 4.62 (m, 1 H, H_{6eq}), 4.89–5.45 (m, 6 H, $CH_2C_6H_5$, NH, H_2), 7.20–7.50 (m, 10 H, C_6H_5).

1,2,5,6-Tetradeoxy-1,6-diazido-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (25). To a suspension of sodium azide (211 mg, 3.25 mmol) in DMF (4 mL) at room temperature was added AI (200 mg, 0.4 mmol) in DMF (4 mL) followed by boron trifluoride etherate (0.4 mL, 3.2 mmol). The reaction mixture was stirred for 2 h at 55 °C, quenched at 0 °C by the addition of water (12 mL), and extracted with ether (3 × 15 mL). The combined extracts were washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **25** as white crystals (200 mg, 85% yield): mp 97 °C; $[\alpha]^{20}_D$ +21° (*c* 1.12, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH, 2100 (N_3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (s, 6 H, $C(CH_3)_2$), 2.41 (s, 6 H, $C_6H_4CH_3$), 3.15 (*AB*X, 2 H, $J_{1,1'}$ = 12.5 Hz, $J_{1',2}$ = 6.5 Hz, $H_{1'}$), 3.20 (*AB*X, 2 H, $J_{1,2}$ = 6.5 Hz, H_1), 3.46 (dt, 2 H, H_2), 3.90 (s, 2 H, H_3), 4.97 (d, 2 H, $J_{NH,2}$ = 9.5 Hz, NH), 7.32, 7.76 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{23}H_{30}N_8O_6S_2$: C, 47.74; H, 5.22; N, 19.36. Found: C, 47.69; H, 5.26; N; 19.29.

1,2,5,6-Tetradeoxy-1,6-diazido-2,5-bis[*N*-(benzyloxycarbonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (26). To a suspension of sodium azide (52 mg, 0.8 mmol) in DMF (1 mL) at room temperature was added AII (45.2 mg, 0.1 mmol) in DMF (1 mL) followed by boron trifluoride etherate (0.1 mL, 0.8 mmol). The reaction mixture was stirred for 24 h at 65 °C and then quenched, worked up, and purified as for **25**, giving **26** (43 mg, 80% yield): $[\alpha]^{20}_D$ +24° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH), 2100 (N_3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 6 H, $C(CH_3)_2$), 3.24–3.28 (m, 4 H, H_1), 3.74 (s, 2 H, H_3), 3.98 (m, 2 H, H_2), 5.02–5.20 (m, 6 H, $CH_2C_6H_5$, NH), 7.34 (m, 10 H, C_6H_5).

1,2,5,6-Tetradeoxy-1,6-bis(phenylthio)-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (27). To a suspension of sodium hydride (28.8 mg, 1.2 mmol) in THF (3 mL) was added thiophenol (170 μL, 1.2 mmol). After being stirred for 30 min from 0 to 20 °C, the *N,N'*-ditosyl bis(aziridine) AI (98.4 mg, 0.2 mmol) in THF (3 mL) was added. The reaction mixture was stirred for 30 min, quenched by the addition of water (5 mL), and extracted with ether (3 × 8 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography on silica gel (30% ethyl acetate in cyclohexane) gave **27** as white crystals (128.4 mg, 90% yield): mp 124 °C; $[\alpha]^{20}_D$ −57°5 (*c* 1.4, CH_2Cl_2); IR (Nujol) cm^{-1} 3300 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (s, 6 H, $C(CH_3)_2$), 2.38 (s, 6 H, $C_6H_4CH_3$), 2.84 (*AB*X, 2 H, $J_{1,1'}$ = 14.5 Hz, H_1), 3.58 (m, 2 H, H_2), 4.20 (s, 2 H, H_3), 4.91 (d, 2 H, $J_{NH,2}$ = 10 Hz, NH), 7.12–7.24 (m, 14 H, C_6H_4, C_6H_5), 7.62 (AB, 4 H, J_{AB} = 7.5 Hz, C_6H_4). Anal. Calcd for $C_{35}H_{40}N_2O_6S_4$: C, 58.96; H, 5.65; N, 3.92. Found: C, 58.75; H, 5.71; N, 3.86.

1,2,5,6-Tetradeoxy-1,6-bis(phenylthio)-2,5-bis(*N*-benzylamino)-3,4-*O*-(1-methylethylidene)-L-iditol (28) and 1,2,5,6-Tetradeoxy-1-(phenylthio)-2-(*N*-benzylamino)-3,4-*O*-(1-methylethylidene)-5,6-(*N*-benzylimino)-L-iditol (29). To a suspension of sodium hydride (43.2 mg, 1.8 mmol) in DMF (4.5 mL) was added thiophenol (255 μL, 1.8 mmol). After being stirred for 30 min from 0 to 20 °C, the *N,N'*-dibenzyl bis(aziridine) AIII (109.2 mg, 0.3 mmol) in DMF (4.5 mL) was added. The reaction mixture was stirred for 15 h at 65 °C, quenched, and worked up as described above. Flash chromatography of the residue on silica gel (20% ethyl acetate in cyclohexane) gave **28** (17 mg, 10% yield), **29** (71 mg, 50% yield), and the starting material AIII (22 mg, 20%). **28**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 6 H, $C(CH_3)_2$), 2.75 (m, 2 H, H_2), 3.00 (*AB*X, 2 H, $J_{1,1'}$ = 13 Hz, $J_{1',2}$ = 7.5 Hz, $H_{1'}$), 3.15 (*AB*X, 2 H, $J_{1,2}$ = 5 Hz, H_1), 3.60–3.97 (m, 6 H, $CH_2C_6H_5$, NH), 4.43 (s, 2 H, H_3), 7.10–7.30 (m, 20 H, C_6H_5). **29**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, 1 H, $J_{6cis,5}$ = 6.5 Hz, H_{6cis}), 1.40 (s, 6 H, $C(CH_3)_2$), 1.60 (m, 1 H, H_5), 1.78 (br s, 1 H, H_{6trans}), 2.57 (m, 1 H, H_2), 2.97 (*AB*X, 1 H, $Jj_{1,1'}$ = 13 Hz, $J_{1',2}$ = 8 Hz, $H_{1'}$), 3.18 (*AB*X, 1 H, $J_{1,2}$ = 5 Hz, H_1), 3.19 (AB, 1 H, J_{AB} = 13.5 Hz, NCH_2), 3.62, 3.68 (AB', 2 H, $J_{AB'}$ = 13 Hz, $NHCH_2$), 3.77 (m, 1 H, NH), 3.81 (dd, 1 H, $J_{4,3}$ = 8 H, H_4), 3.87 (AB, 1 H, NCH_2), 4.13 (dd, 1 H, $J_{3,2}$ = 2.5 Hz, H_3), 7.10–7.40 (m, 15 H, C_6H_5).

29 isomerized spontaneously to **29'** after 2 months at room temperature.

2,6-(*N*-Benzylimino)-3,4-*O*-(1-methylethylidene)-5-(*N*-benzylamino)-L-iditol 29'. The stirring of a solution of **29** in CH_2Cl_2 (0.2 M) with silica gel gave **29'** after 24 h: $[\alpha]^{20}_D$ −56° (*c* 2.2, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.42 (s, 3 H, $C(CH_3)_2$), 1.46 (s, 3 H, $C(CH_3)_2$), 2.31 (dd, 1 H, $J_{6ax,6eq}$ = 13 Hz, $J_{6ax,5}$ = 10 Hz, H_{6ax}), 2.84 (dd, 1 H, $J_{6eq,5}$ = 5 Hz, H_{6eq}), 2.99 (m, 1 H, H_5), 31.0 (*AB*X, 1 H, $J_{1,1'}$ = 13 Hz, $J_{1',2}$ = 8 Hz, $H_{1'}$), 3.20 (*AB*X, 1 H, $J_{1,2}$ = 4 Hz, H_1), 3.40–3.85 (m, 7 H, H_2, H_3, H_4, NCH_2, $NHCH_2$), 3.94 (AB, 1 H, J_{AB} = 13.5 Hz, NCH_2), 7.10–7.40 (m, 15 H, C_6H_5).

1,2,5,6-Tetradeoxy-1,6-dithio-2,5-bis[*N*-(*p*-tolylsulfonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (30). To a solution of AI (49.2 mg, 0.1 mmol) in THF (1 mL) at 20 °C was added a solution of sodium hydrogen sulfide hydrate (15.3 mg, 0.3 mmol) in THF (1 mL). After being stirred for 6 h, the reaction mixture was quenched at 0 °C by the addition of saturated aqueous ammonium chloride (5 mL) and then acidified with 10% hydrochloric acid (pH = 2) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with 3% aqueous $NaHCO_3$ and then with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (40% ethyl acetate in cyclohexane) gave **30** as white crystals (56.7 mg, 100% yield): mp 232 °C; $[\alpha]^{20}_D$ +33° (*c* 0.54, CH_2Cl_2); IR (Nujol) cm^{-1} 3270 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (s, 6 H, $C(CH_3)_2$), 2.38 (s, 6 H, $C_6H_4CH_3$), 2.72 (*AB*X, 2 H, $J_{1,1'}$ = 15.5 Hz, $J_{1',2}$ = 6 Hz, $H_{1'}$), 2.94 (*AB*X, 2 H, $J_{1,2}$ = 5 Hz, H_1), 3.27 (m, 2 H, H_2), 3.73 (m, 2 H, H_3), 4.86 (d, 2 H, $J_{NH,2}$ = 4.5 Hz, NH), 7.26, 7.70 (AB, 8 H, J_{AB} = 8 Hz, C_6H_4). Anal. Calcd for $C_{23}H_{32}N_2O_6S_4$: C, 49.26; H, 5.75; N, 4.89. Found: C, 49.38; H, 5.85; N, 4.93.

1,2,5,6-Tetradeoxy-1,6-dithio-2,5-bis[*N*-(benzyloxycarbonyl)amino]-3,4-*O*-(1-methylethylidene)-L-iditol (31). To a solution of AII (45.2 mg, 0.1 mmol) in DMF (1 mL) at room temperature was added a solution of sodium hydrogen sulfide hydrate (41 mg, 0.8 mmol) in DMF (1 mL). After being stirred for 15 h, the reaction mixture was quenched and worked up as described above. Flash chromatography of the residue on silica gel (30% ethyl acetate in cyclohexane) gave **31** as white crystals (42.2 mg, 80% yield): mp 155 °C; $[\alpha]^{20}_D$ +78° (*c* 1.0, CH_2Cl_2); IR (Nujol) cm^{-1} 3330 (NH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (s, 6 H, $C(CH_3)_2$), 2.73 (*AB*X, 2 H, $J_{1,1'}$ = 14 Hz, $J_{1',2}$ = 7 Hz, $H_{1'}$), 2.98 (*AB*X, $J_{1,2}$ = 5 Hz, H_1), 3.82–4.04 (m, 4 H, H_2, H_3), 5.02–5.28 (m, 6 H, $CH_2C_6H_5$, NH), 7.32 (m, 10 H, C_6H_5). Anal. Calcd for $C_{25}H_{32}N_2O_6S_2$: C, 57.67; H, 6.19; N, 5.38. Found: C, 58.09; H, 6.24; N, 5.57.