1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (12 mg, 0.06 mmol) then stirred at room temperature for 4 h, quenched with water (0.5 mL), and diluted with 20% dimethylformamide in toluene (15 mL). The aqueous layer was separated, Celite (1 g) was added to the organic layer, and the mixture was concentrated in vacuo. The resulting Celite mixture was placed on top of a column of silica gel and flash chromatographed, eluting with 10% dimethylformamide in toluene to give a yellow powder (21 mg, 56%): ^{1}H NMR (DMF-d_7, 300 MHz, ppm) 13.05 (s, 1 H), 11.40 (s, 1 H), 11.34 (s, 1 H), 11.10 (s, 1 H), 8.34 (s, 1 H), 8.23 (d, 1 H, J = 8.1), 7.92 (d, 1 H, J = 8.4), 7.69 (s, 1 H), 7.40 (t, 1 H, J = 8.1), 7.40 (t, 1 H, J = 8.1), 7.24 (s, 1 H), 7.20 (s, 1 H), 6.98 (bs, 2 H), 4.82 (t, 2 H, J = 8.7), 4.70 (d, 1 H, J = 8.7), 3.8–4.3 (m, partially obscured by residual water, including 4.22, t, J = 8.7; 4.1, dd, J = 1.8 and 8.7; 3.99, s, 3 H; 3.93, s, 3 H), 3.46 (t, 1 H, J = 9.3), 3.36 (t, 1 H, J = 9.3); UV (1% DMF in methanol) 358 nm (ϵ = 53 400); FABMS m/e (relative intensity) 737 (M + H_2, 0.5), 736 (M + H_1, 0.4), 279 (15), 202 (50), 177 (17), 167 (13), 135 (17), 118 (21), 103 (22), 91 (100); FABHRMS, the spectra was too weak for a peak match; $[\alpha]^{23}_D$ = +54.9° (c = 0.133, DMF). A portion of this yellow powder (14 mg, 0.019 mmol) was dissolved in acetonitrile/water/triethylamine (3:1:1, 10 mL), stirred at room temperature for 1 h, diluted with ethyl acetate (50 mL), washed with water (3 × 20 mL), dried (sodium sulfate), concentrated in vacuo, adsorbing the crude material on Celite (1 g), and flash chromatographed, eluting with 20% DMF in toluene to give **13** (12 mg, 94%) as a yellowish brown solid: ^{1}H NMR (DMF-d_7, 300 MHz, ppm) 13.08 (s, 1 H), 11.64 (s, 1 H), 11.37 (s, 1 H), 11.22 (s, 1 H), 8.10 (d, 1 H, J = 7.8), 7.62 (t, 1 H, J = 8.7), 7.47 (t, 1 H, J = 8.7), 7.29 (s, 1 H), 7.28 (d, 1 H, J = 7.8), 7.20 (s, 1 H), 7.00 (s, 2 H), 6.93 (s, 1 H), 4.80 (t, 2 H, J = 10.2), 4.68 (dd, 1 H, J = 6.0 and 10.2), 4.54 (d, 1 H, J = 10.2), 4.22 (t, 2 H, J = 10.2), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.3–3.5 (m, 5 H), 1.82 (d, 2 H, J = 6.2); UV (1% DMF in methanol) 367 nm (ϵ = 32 100); FABMS m/e (relative intensity) 701 (M + H, 4), 504 (4), 436 (4), 411 (6), 274 (6), 198 (17), 73 (100); FABHRMS m/e 701.2399 (M + H) ($C_{38}H_{33}N_6O_8$ requires 701.2360); $[\alpha]^{23}_D$ = +37.3° (c = 0.166, DMF).

Acknowledgment. We thank Professor K. Barry Sharpless for useful discussions and preprints concerning improved ligands for the asymmetric dihydroxylation reaction. We thank L. H. Li and T. F. DeKoning for the biological evaluation of **13** and **17**.

Supplementary Material Available: Copies of ^{1}H NMR spectra (10 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.

Synthesis of Hypusine and Other Polyamines Using Dibenzyltriazones for Amino Protection

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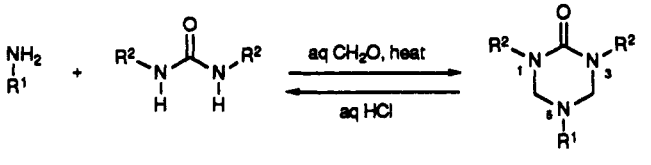
The use of 1,3-dibenzyl-5-substituted-hexahydro-2-oxo-1,3,5-triazine ("dibenzyltriazone") as a protecting group for primary amino is described. Optimized conditions for formation and hydrolysis of dibenzyltriazones, as well as a variety of transformations (reduction, oxidation, hydroxyl modification, C–C bond formation) compatible with this protecting group, are presented. N-Protected amino aldehydes such as **46**, **47**, and **94** are particularly valuable building blocks, as demonstrated by the syntheses of hypusine (**86**), deoxyhypusine (**85**), spermidine (**74**), and two unsaturated spermidine analogues **81** and **84**.

The synthesis of polyfunctional amino acids, amino alcohols, and polyamines typically requires the use of an amino protecting group so that functional group manipulations can be carried out at other sites.[1] Whereas commonly used protecting groups like benzyloxycarbonyl (Z), *tert*-butoxycarbonyl (BOC), or phthaloyl are suitable in many cases, we have encountered some applications where interfering side reactions involving the NH of –NHBOC or –NHZ, or the C=O of phthaloyl, rule out their use. To address the need for a simple amino protecting group that blocks both NH positions, and does not contain an electrophilic carbonyl or nucleophilic nitrogen, we have explored the chemistry of 1,3,5-tri-*N*-substituted hexahydro-2-oxo-1,3,5-triazines ("triazones"), **3**.[2-4] Triazones **3** may be formed from a primary amine **1**, an *N*,*N*′-disubstituted urea **2**, and aqueous formaldehyde, and are hydrolyzed by aqueous hydrochloric acid at room temperature. At higher temperature, mild acid (pH ~3–5) causes hydrolysis if an amine is added as a formaldehyde scavenger. Triazones also show good compatibility with a variety of functional group conversions and carbon–carbon bond forming reactions. In this paper, we describe (1) our progress optimizing triazone formation and hydrolysis, (2) the synthesis and properties of some triazone-containing polyfunctional building blocks, and (3) the use of triazones for the synthesis of the mysterious triamino hydroxy acid hypusine (**86**), its formal biosynthetic precursor 6-deoxyhypusine (**85**), and some unsaturated spermidines **81** and **84** designed to help elucidate hypusine biosynthesis.



Optimization of Triazone Formation. Although the earlier studies[2] indicated that triazones **3** could serve as useful amino protecting groups, the quandary of choosing

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp 309–405. (b) Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 3.1, pp 635–645.

(2) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109.

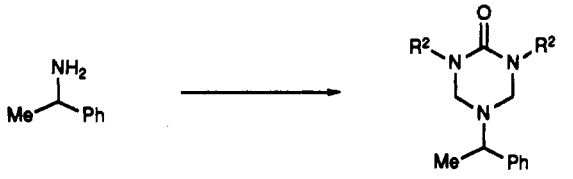
(3) Petersen, H. *Synthesis* **1973**, 243.

(4) (a) Larsen, B. R.; Nicolaisen, F. M.; Nielsen, J. T. *J. Mol. Struct.* **1976**, *32*, 247. (b) Hardies, D. E.; Krass, D. K. U.S. Patent 4150220, 1979; *Chem. Abstr.* **1979**, *91*, P57062e. (c) Hardies, D. E. U.S. Patent 4152516, 1979; *Chem. Abstr.* **1979**, *91*, P57063f.

0022-3263/92/1957-6239$03.00/0

the appropriate urea N-substituent (R^2 in **2** and **3**) remained. These studies pointed to "dimethyltriazones" (**3**, R^2 = Me) and "dibenzyltriazones" (**3**, $R^2 = CH_2Ph$) as the leading candidates. Whereas the former form in higher yields, and hydrolyze more quickly, the latter exhibit better mobility on silica gel and solubility in organic solvents. Because the anticipated applications involved polyfunctional triazones whose solubility properties would be crucial to their use in multistep syntheses, the dibenzyltriazone group was deemed more suitable, although this required further improvement of the procedures for triazone formation and hydrolysis.

Formation of the dimethyl- and dibenzyltriazones (**5a** and **5b**, respectively) from α-methylbenzylamine (**4**) under several different reaction conditions is shown below.



4

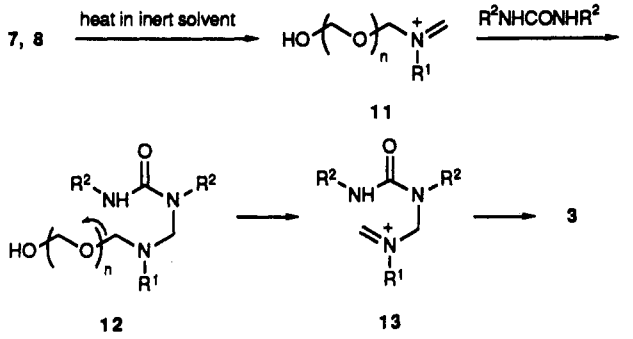
5a: R_2 = Me
5b: $R_2 = CH_2Ph$

Method	Reaction Conditions	Yield
"Lit"	N,N-dimethylurea, aq CH_2O, iPr_2EtN, EtOH, reflux	98% (**5a**)
"Lit"	N,N-dibenzylurea, aq CH_2O, i-Pr_2EtN, EtOH, reflux	<20% (**5b**)
"A"	N,N-dibenzylurea, aq CH_2O, dioxane, i-Pr_2EtN, then add toluene, 84→100 °C with water separation	32% (**5b**)
"B"	(1) aq CH_2O, i-Pr_2EtN, then add toluene and concentrate to a residue (2) N,N-dibenzylurea, EtOAc, reflux	94% (**5b**)

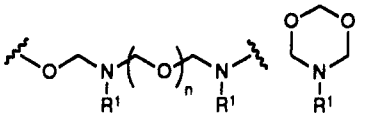
N,N'-Dimethylurea was obtained commercially, whereas N,N'-dibenzylurea was prepared from benzylisocyanate and benzylamine (see Experimental Section). Diisopropylethylamine was added in each case to neutralize the reaction mixture (commercial formalin contains varying amounts of formic acid). The procedure modeled after literature precedent[5] gave excellent yields of **5a** but dismal amounts of **5b**. The low yield of **5b** could be attributed to the fact that N,N'-dibenzylurea is a more sterically demanding nucleophile than N,N'-dimethylurea. Use of the formaldehyde precursors *sym*-trioxane or paraformaldehyde instead of aqueous formaldehyde did not increase the yield of **5b**. Some improvement was realized, however, with the addition of toluene during the course of the reaction and removal of the toluene–water azeotrope until no more water was produced (referred to as method A). Thus, water apparently promotes the formation of the formaldehyde-containing electrophilic species, but inhibits N–C–N bond formation. The yield rose dramatically when the amine was treated with excess neutralized aqueous formaldehyde *alone* (no urea), followed by azeotropic concentration of the reaction mixture to a dry residue and *subsequent* treatment of this amine–formaldehyde adduct with dibenzylurea in refluxing ethyl acetate (referred to as method B). This two-step procedure effectively separates the amine–formaldehyde condensation step (favored in aqueous solution) from the Mannich-like combination of the resulting adduct with the urea (favored in anhydrous solvent). The second step can also be carried out in tetrahydrofuran or toluene solution, depending upon the reaction temperature necessary.

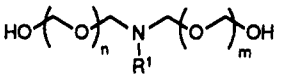
(5) Clemons, D. H.; Emmons, W. D. *J. Org. Chem.* **1961**, *26*, 767.

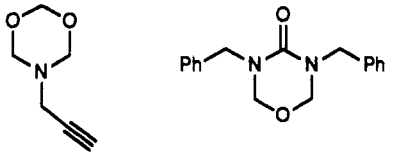
Scheme I. "Working Mechanism" for Triazone Formation



What is the nature of the amine–formaldehyde adduct? Formaldehyde might combine with a primary amine under these conditions to give an imine–formaldehyde copolymer (represented schematically by **6**), a cyclized 3:1 adduct (the *sym*-dioxazine **7**), or an oligomeric set of formaldehyde adducts **8**.[6,7] ^1H NMR and TLC analysis of the residues







obtained by concentration as in method B indicates that several compounds are present (there are many methylene singlets at δ 4.0–5.2). In one experiment, the attempted formation of a dibenzyltriazone derivative from propargylamine, the *sym*-dioxazinane **9** was isolated upon chromatography of the concentrated residue. When **9** was heated at reflux with an equimolar amount of N,N'-dibenzylurea in tetrahydrofuran, ethyl acetate, or toluene solution, the dibenzyltriazone of propargylamine (**15**) was isolated in high yield in each case.

As formalin solutions can contain varying amounts of formic acid, tertiary amine (diisopropylethylamine or triethylamine) was added to assure a pH of slightly greater than 7, even in cases where the primary amine was used as the free base. Without this neutralization, the (otherwise slow) formation of formaldehyde–urea adducts[3] can occur as a side reaction when using either method A or B. For example, the cyclized 2:1 formaldehyde–dibenzylurea adduct,[3] oxadiazinone **10**, was isolated from two incompletely neutralized reaction mixtures. Heating an equimolar solution of **10** and phenethylamine in ethyl acetate at reflux gave no observable triazone product after 16 h; therefore, *10 does not serve as a precursor to triazones*

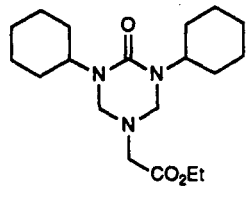
(6) Reaction of primary amines with formaldehyde: (a) Wagner, E. C. *J. Org. Chem.* **1954**, *19*, 1862. (b) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489. (c) Farrar, W. V. *Rec. Chem. Progr.* **1968**, *29*, 85.

(7) Dioxazinone formation: (a) Bergmann, M.; Jacobsohn, M.; Schotte, H. *Z. Phys. Chem.* **1924**, *131*, 18. (b) Bergmann, M.; Miekeley, M. *Ber.* **1924**, *57B*, 662.

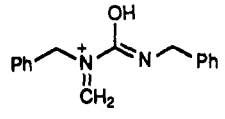
under these conditions. Its formation is deleterious to the amine protection reaction because dibenzylurea is thereby unproductively consumed.

A "working mechanism" for triazone formation that is consistent with these observations is shown in Scheme I. The amine–formaldehyde adducts 7 and 8 can lead upon heating to an iminium species 11, which can react with the nitrogen atom of dialkylurea to form the first N–C–N bond (see 12). Thermal generation of a second iminium electrophile 13 triggers ring closure to give the triazone product 3. An analogous process could also convert the imine–formaldehyde copolymer 6 to triazone 3. Triazone formation is thus a Mannich process wherein the urea serves as the nucleophile, and the mechanism does not require *N*-(hydroxymethyl)urea intermediates.

Many aliphatic and aryl amines, unsaturated amines, nonvicinal amino alcohols, and amino esters have now been converted to their dibenzyltriazone derivatives using the simpler toluene azeotrope method (A) or the two-step method (B) involving prior formation of the amine–formaldehyde adduct. The products, which were isolated by silica gel chromatography or by direct crystallization, are displayed in Table I ("DBT" represents the dibenzyltriazone ring). Method A is particularly good for amino esters, but fails to give good yields in many other cases. On the other hand, method B, which can be carried out at lower temperature, is much more generally successful for the amines examined. The triazone synthesis does not work well for *vicinal* amino alcohols, *vicinal* diols, and α-amino acids, probably because the amine–formaldehyde adducts in these cases are too stable to react with dibenzylurea (these triazones can be prepared efficiently by indirect methods described in the next section). The weakly nucleophilic substrates cytosine and 2-aminopyridine did not form dibenzyltriazones under these conditions. By using method B, glycine ethyl ester could be converted to its *N*(1),*N*(3)-di*cyclohexyl*triazone derivative **37** in 72% yield, whereas the bulky cyclohexyl groups prevent *N*,*N*′-dicyclohexylurea from forming triazones under other conditions.



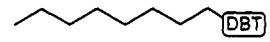
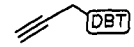
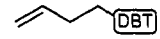
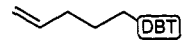
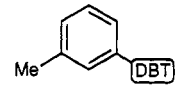
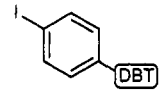
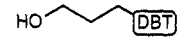
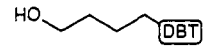
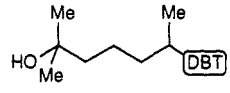
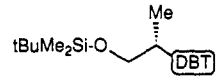
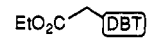
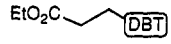
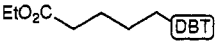
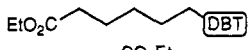
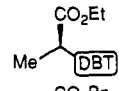
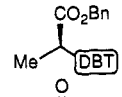
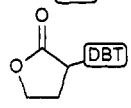
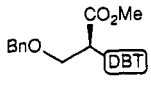
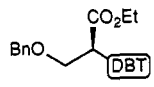
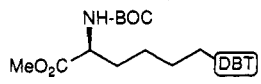
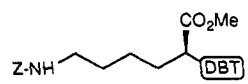
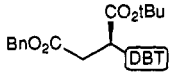
37



38

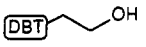
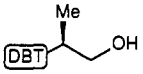
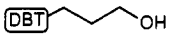
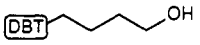
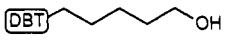
Dibenzyltriazones are not only easily extracted and chromatographed but also nonhygroscopic and readily characterized by elemental analysis and by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy. In general, the triazone ring methylene protons resonate at δ 4.06–4.18, the benzylic methylene protons at δ 4.51–4.57, and the aromatic protons at δ 7.32 in deuteriochloroform solution. Dibenzyltriazones derived from arylamines (**18** and **19**, Table I) show ring methylenes at δ 4.56. When a stereogenic center is present, as for α-amino acid derivatives, the ring methylenes and benzylic methylenes are typically split into AB quartets. ^{13}C NMR spectra of dibenzyltriazones show benzylic methylene carbons at δ 48.3–48.6 and ring methylene carbons at δ 63.2–65.6. The carbonyl carbon appears as a weak resonance at δ 155.2–155.4. The IR spectra of dibenzyltriazones contain a strong amide I band in the region 1645–1610 cm^{-1}. Protected amino alcohols capable of intramolecular hydrogen bonding absorb toward the lower end of this range. Dibenzyltriazones exhibit intense m/z (M + 1) peaks in their direct chemical ionization or

Table I. Synthesis of Dibenzyltriazones from Primary Amines[a,b]

product no.	structure	yield (method)
14		91% (B)
15		0% (A) 89% (B)
16		78% (B)
17		90% (A)
18		71% (B)
19		62% (B)
20		30% (A) 90% (B)
21		56% (A) 79% (B)
22		93% (B)
23		78% (B)
24		88% (B)
25		87% (A) 90% (B)
26		70% (A) 79% (B)
27		76% (A) 90% (B)
28		75% (A)
29		87% (A) 90% (B)
30		80% (B)
31		65% (B)
32		94% (B)
33		98% (B)
34		78% (B)
35		77% (B)
36		84% (B)

[a] DBT refers to the amino group protected as its dibenzyltriazone. [b] For conditions A and B see **4** → **5b** in text.

Table II. $LiBH_4$ Reduction of Protected Amino Esters[a,b]

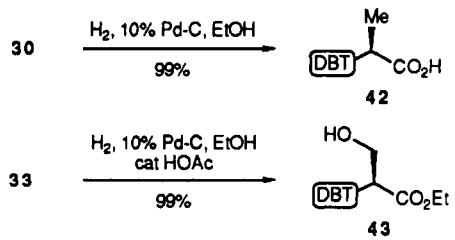
starting material	product	no.	yield
24		39	92%
29		40	94%
25		20	80%
26		21	85%
27		41	79%

[a] Reductions were carried out in THF solution between 48 °C and reflux. [b] DBT refers to the amino group protected as its dibenzyltriazone.

fast atom bombardment mass spectra, and in most cases this is the base peak of the spectrum. Fragmentation of the heterocycle usually results in smaller peaks at m/z 253 ($C_{16}H_{17}N_2O$, corresponding to structure **38**) and M − 253.

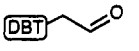
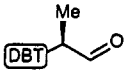
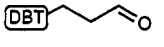
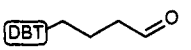
Functional Group Tranformations in the Presence of Dibenzyltriazones. Reductions. One of the attributes expected of dibenzyltriazones is stability to reducing conditions. Dibenzyltriazone-protected amino esters were reduced to the corresponding alcohols in good yields using lithium borohydride in tetrahydrofuran solution at reflux, as displayed in Table II. Inasmuch as direct dibenzyltriazone formation is difficult for vicinal amino alcohols like ethanolamine and alaninol, reduction of the corresponding esters to the alcohols (**39** and **40**, respectively) represents the better route to these compounds. Although dibenzyltriazones were found to be unstable toward lithium aluminum hydride (room temperature, tetrahydrofuran solution), they survive diisobutylaluminum hydride and sodium borohydride. Phthalimides, in contrast, are more easily reduced.[8]

Hydrogenolysis of benzyl groups can be carried out in the presence of dibenzyltriazones, and this provides a useful route to *N*-protected amino acids and amino alcohols. For example, dibenzyltriazone-protected alanine benzyl ester (**30**) smoothly gave the corresponding carboxylic acid **42** upon hydrogenolysis. Likewise, dibenzyltriazone-protected serine ethyl ester (**43**) was prepared by hydrogenolysis of the *O*-benzyl group of **33**. A catalytic amount of acetic acid was added to increase the reaction rate, but this had no effect on the triazone ring. The triazone *N*-benzyl groups are also unaffected under these conditions.



Oxidations. *N*-Protected amino aldehydes are important building blocks for use in carbon–carbon bond-forming reactions.[9] Oxidation of several dibenzyltriazone-protected amino alcohols using the Swern conditions[10] was found to provide a satisfactory route to the corresponding aldehydes, as shown in Table III. Pyridinium chlorochromate (with molecular sieves present) was also successful for *N*-protected 4-aminobutyraldehyde **47**. All of the dibenzyltriazone-protected amino aldehydes proved to be stable to storage at 0 °C and to silica gel chromatography. The 4-aminobutyraldehyde derivative **47** is particularly noteworthy, in that we were unable to prepare the corresponding BOC- and Z-protected 4-aminobutyraldehydes by oxidation of the alcohol, presumably because of *N*-cyclization. The use of **46** and **47** in polyamine synthesis is described in a later section.

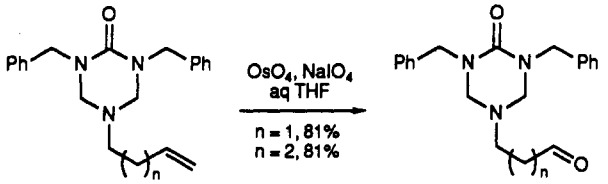
Table III. Oxidation of Protected Amino Alcohols[a,b]

starting material	product	no.	yield
39		44	86%
40		45	95%
20		46	96%
21		47	97% 91%[c]

[a] Oxidations were carried out under Swern conditions except as noted. [b] DBT refers to the amino group protected as its dibenzyltriazone. [c] This oxidation was carried out using PCC and molecular sieves.

The dibenzyltriazone-protected alaninal **45** was also shown to be configurationally stable, even after chromatography on silica gel. Reduction of freshly prepared and chromatographed **45** back to the alcohol **40** using sodium borohydride in ethanol solution afforded material with *ee* >99.5%, according to 400-MHz ^1H NMR analysis of the (*S*)-Mosher ester.[11,12] A sample of **45** that had been stored at 0 °C for 2 weeks similarly showed no racemization. The N-protected alaninal **45** is thus among the most configurationally stable of such derivatives[9,13,14] and should prove useful for a variety of applications.

An alternative route to the dibenzyltriazone-protected amino aldehydes **46** and **47** is provided by oxidative cleavage of the corresponding alkenes (**16** and **17**, respectively) with osmium tetraoxide and sodium periodate. For **16** → **46**, the intermediate diol was also prepared separately,[15] characterized, and then oxidized further to the aldehyde (see Experimental Section).



16, n = 1
17, n = 2

46, n = 1
47, n = 2

Triazones can react at *N*(5) with strongly electrophilic oxidizing reagents.[16] The dibenzyltriazone ring (of **20**) was stable to ethanolic hydrogen peroxide for 2 h at room

(8) (a) Dasgupta, F.; Garegg, P. J. *J. Carbohydr. Chem.* **1988**, *7*, 701. (b) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093. (c) For a clever reversible phthalmide modification, see: Astleford, B.; Weigel, L. O. *Tetrahedron Lett.* **1991**, *32*, 3301.

(9) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(10) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(11) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 125–152.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

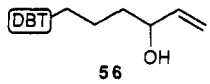
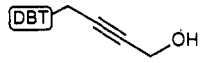
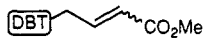
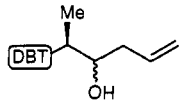
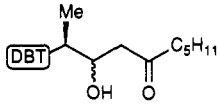
(13) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(14) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(15) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

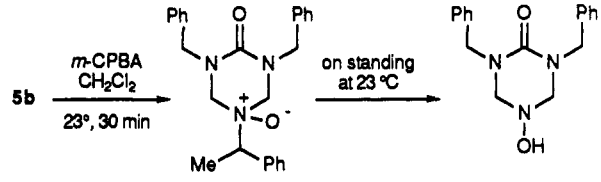
(16) Review of amine oxidations: Rosenblatt, D. H.; Burrows, E. P. In *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; John Wiley and Sons: Chichester, 1982; Suppl. F, Part 2, pp 1085–1149.

Table IV. Carbon–Carbon Bond Forming Reactions[a,b]

st matl	reactn condns	product	yield
47	CH_2=CHMgBr, THF, -10 °C, then aq NH_4Cl	 **56**	75%
15	*n*-BuLi, THF, -78 °C, then $(CH2O)_x$, -78→23 °C	 **57**	79%
44	Ph_3P=$CHCO_2Me$, benzene, reflux	 **58** (10:1 E/Z)	87%
45	CH_2=$CHCH_2MgBr$, THF, -78 °C, then aq NH_4Cl	 **59** (1:2 anti/syn)	62%
45	CH_2=$CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, -78 °C	**59** (1:3 anti/syn)	55%
45	CH_2=$CHCH_2SnBu_3$, BF_3·OEt_2, CH_2Cl_2, 0 °C	**59** (3:1 anti/syn)	80%
45	$C_5H_{11}C(OSiMe_3)$=CH_2, $SnCl_4$, CH_2Cl_2, -78 °C	 **60** (1:10 anti/syn)	57%
45	$C_5H_{11}C(OSiMe_3)$=CH_2, BF_3·OEt_2, CH_2Cl_2, -78 °C	**60** (1:1 anti/syn)	62%

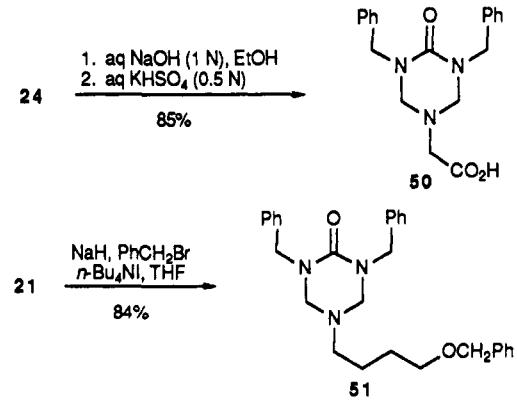
[a] DBT refers to the amino group protected as its dibenzyltriazone. [b] Product isomer ratios were determined by ^1H NMR analysis.

temperature, but destruction of the triazone ring of **5b** (by oxidation and/or hydrolysis) occurred in the presence of aqueous ceric ammonium nitrate and destruction of the triazone ring of **16** occurred in the presence of *N*-bromosuccinimide/water, according to ^1H NMR analysis of the crude reaction mixtures. Treatment of **5b** with *m*-chloroperoxybenzoic acid resulted in rapid oxidation to the triazone *N*-oxide **48**, which then underwent Cope elimination at room temperature to afford the hydroxylamine **49**. Compound **49**, which contains a fully protected hydroxylamine nitrogen, represents a potential precursor to *O*-alkylated hydroxylamines and to electrophilic ammonia equivalents.

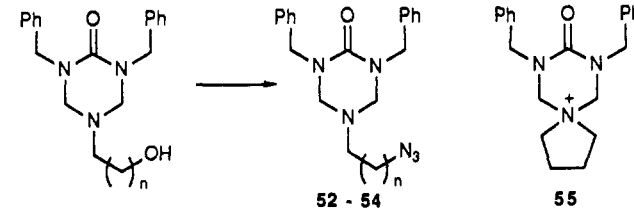


48 **49**

Basic and Acidic Conditions. Solutions of dibenzyltriazones were routinely washed with aqueous sodium bicarbonate, carbonate, and hydroxide solutions during workup without detectable damage to the triazone ring. Protected amino esters, such as the glycine derivative **24**, can be saponified to the corresponding carboxylic acids (e.g., **50**) in good yield, and this represents a good route to this class of compounds. The stability of dibenzyltriazones to strong bases like sodium hydride allows *O*-alkylation in the manner shown for **21** → **51**. Other types of hydroxyl modification, such as acetylation (acetic anhydride, pyridine), silylation (*t*-$BuMe_2SiCl$, DMF, imidazole), and alkylation ($MeOCH_2CH_2OCH_2Cl$, *i*-Pr_2EtN, CH_2Cl_2) have been successfully carried out using the mild bases indicated. Two-step conversion of the hydroxyl to



azido in the series of protected amino alcohols **39**, **20**, **21**, **41** proceeds well through the corresponding tosylate or mesylate in three cases but fails for the protected 4-aminobutanol **21** (only very polar material was produced from attempted mesylation). This may be attributed to the instability of the derived mesylate, which features a leaving group well-positioned for rapid *N*-cyclization to a five-membered ring ammonium species **55**.



52 - 54 **55**

n	Alcohol	Conditions	Azide	Yield
1	**39**	TsCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, then NaN_3, DMF, 80 °C	**52**	70%
2	**20**	MsCl, *i*-Pr_2EtN, CH_2Cl_2, then NaN_3, DMF, 80 °C	**53**	87%
3	**21**	MsCl, *i*-Pr_2EtN, CH_2Cl_2	-	-
4	**41**	MsCl, Et_3N, CH_2Cl_2; then NaN_3, DMF, 80 °C	**54**	71%

Dibenzyltriazones are hydrolyzed by prolonged exposure to aqueous acid, and this forms the basis for regeneration of the free amine, as described in a later section. Short-term exposure to dilute aqueous acid, however, does not cause hydrolysis. Reactions involving dibenzyltriazone-protected amines could be quenched with saturated aqueous ammonium chloride or extracted using 0.5 N aqueous potassium hydrogen sulfate (see **50**), without damage to the protecting group. Anhydrous acids by themselves probably protonate, but do not cleave, dibenzyltriazones. Thus, *N*-protected serine ester **43** was stable to an anhydrous dichloromethane solution of *p*-toluenesulfonic acid for 3 days at 23 °C. Similarly, the anhydrous Lewis acids titanium tetrachloride, tin tetrachloride, and boron trifluoride etherate probably coordinate with the protecting group carbonyl but do not cause deprotection below room temperature.

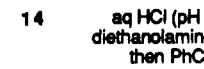
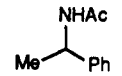
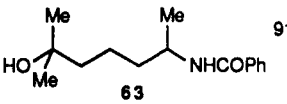
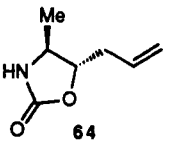
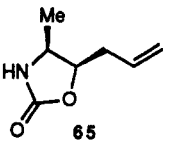
Carbon–Carbon Bond Formation. Dibenzyltriazones are stable to some common methods for carbon–carbon bond formation, as shown in Table IV. Vinylmagnesium bromide, as an example, reacted with the dibenzyltriazone-protected aminobutyraldehyde **47** to give allylic alcohol **56** in good yield. The propargylamine derivative **15** was metalated at the sp-carbon using *n*-butyllithium at low temperature, and the resulting carbanion was quenched with paraformaldehyde to afford the alcohol **57**. Chain extension of dibenzyltriazone-protected aminoacetaldehyde **44** occurred in the expected fashion with methyl (triphenylphosphoranylidene)acetate, providing the

interesting four-carbon building block **58**.

The dibenzyltriazone-protected *S*-alaninal **45**, which is configurationally stable under normal conditions of isolation and storage, was subjected to some typical organometallic addition reactions (Table IV) to establish the nature and extent of diastereoselection.[17,18] Allylmagnesium bromide addition, and also titanium tetrachloride-mediated allyltrimethylsilane addition, took place with a slight preference for the syn (threo) diastereoisomer **59-*syn***. Under the influence of boron trifluoride etherate, allyltributylstannane addition gave a good yield of a mixture enriched in **59-*anti***, corresponding to modest Cram's rule type stereoselection. This latter stereoselectivity is comparable to most other *N*-protected α-amino aldehydes, although *N,N*-dibenzylaminoacetaldehyde is markedly better with an allyltitanium nucleophile.[18] Structures of the adducts **59** were established by hydrolyzing each to the amino alcohol as described in the next section and then comparing the derived *cis*- and *trans*-oxazolidinones with the known compounds.[19] Addition of 2-[(trimethylsilyl)oxy]heptene[20] to **45** gave the syn (erythro) aldol diastereoisomer **60-*syn*** as the major product (10:1) with tin tetrachloride as the Lewis acid. The comparable boron trifluoride etherate-promoted addition to **45** was nonstereoselective, and boron,[21] lithium,[22] and titanium[23] enolates gave low yields of adduct.

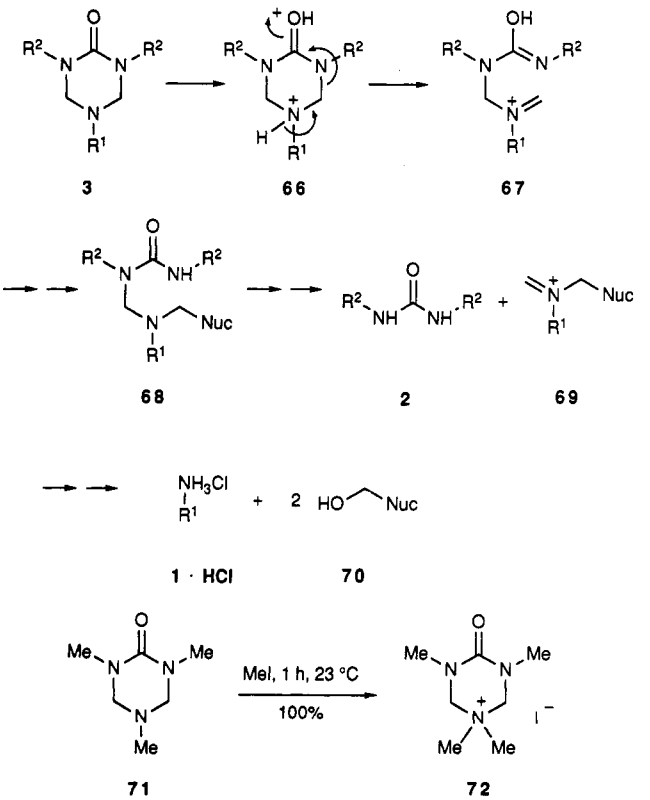
Hydrolysis of Dibenzyltriazones. Earlier studies[2] of di*methyl*triazone hydrolysis indicated that treatment of the triazone with concentrated aqueous hydrochloric acid at 23 °C, or with saturated aqueous ammonium chloride (pH ~ 5) at about 70 °C, led to cleavage of the heterocycle and formation of the primary amine and dimethylurea. In the latter case, formaldehyde was presumably consumed by reaction with ammonia. Di*benzyl*triazones, on the other hand, were found to be much less reactive under the latter conditions, and the rate of hydrolysis and yield of product varied greatly with the structure of the amine. Concentrated aqueous hydrochloric acid caused hydrolysis of dibenzyltriazones at 23 °C. Milder conditions for hydrolysis of dibenzyltriazones feature aqueous hydrochloric acid at pH ~ 3 and a *secondary* amine to act as formaldehyde scavenger. The nature of the secondary amine can be varied to facilitate isolation of the amine product. Thus, dibenzyltriazones of lipophilic primary amines are hydrolyzed in 1–2 h by using equal volumes of 20% aqueous diethanolamine (titrated to pH ~3 with concentrated hydrochloric acid) and methanol at 65 °C. Hydrolyses are followed by TLC for disappearance of starting material, and extractive workup of the basified reaction mixture provides essentially pure amine (dibenzylurea can also be recovered). The diethanolamine and its formaldehyde adduct remain in the aqueous solution. For water-soluble amines, a volatile secondary amine such as diethylamine or piperidine can be used as the formaldehyde scavenger. The reaction mixture is concentrated and washed with dichloromethane to remove dibenzylurea. The aqueous solution is basified with solid sodium hydroxide and then concentrated and purified if necessary by using silica gel or ion-exchange resin. Table V shows

Table V. Hydrolysis of Dibenzyltriazones[a,b]

st. martl	reactn condns	product	yield
14	aq HCl (pH 3), MeOH, diethanolamine, reflux, 1 h, then PhCOCl, pyr	 **61**	82%
5b	aq HCl (pH 3), MeOH, diethylamine, reflux, 1 h, then Ac_2O, pyr	 **62**	83%
22	aq HCl (pH 3), MeOH, diethylamine, reflux, 1 h, then PhCOCl, pyr	 **63**	91%
59-syn	aq HCl (pH 3), MeOH, diethanolamine, reflux, 2 h, then $COCl_2$, *i*-Pr_2EtN, CH_2Cl_2	 **64**	74%
59-anti	aq HCl (pH 3), MeOH, diethanolamine, reflux, 2 h, then $COCl_2$, *i*-Pr_2EtN, CH_2Cl_2	 **65**	78%

[a] For details of workup procedure, see Experimental Section. [b] Hydrolysis products can also be isolated as the free amines.

Scheme II. "Working Mechanism" for Triazone Hydrolysis



the hydrolysis of several dibenzyltriazones using the new conditions. The products were obtained in pure form as the free amines, according to ^1H NMR analysis, but isolated as derivatives to avoid carbon dioxide and water uptake, and, in the cases of **64** and **65**, to determine stereochemistry.[19] No evidence of $HOCH_2NHR$ or similar signals, as might result from incomplete formaldehyde scavenging, was seen.

The mechanism of acidic hydrolysis of triazones can be assumed to resemble the reverse of the mechanism for

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(18) Reetz, M. T.; Drewes, M. W.; Schmidt, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
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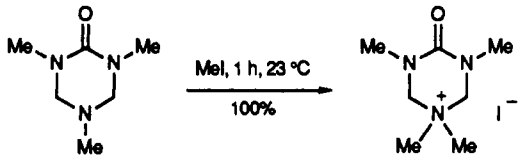
(22) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459.
(23) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.

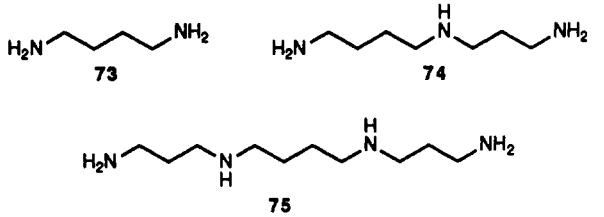
formation (Scheme I), in that iminium intermediates are involved, rather than dialkylurea–formaldehyde adducts. Scheme II shows a "working mechanism" for triazone hydrolysis (3 → 1) in the presence of a formaldehyde scavenger ("Nuc"). Protonation at $N(5)$ of 3 is probably not sufficient to initiate triazone cleavage, as no reaction occurs at pH ~5 at room temperature. Furthermore, the dimethyltriazone of methylamine (71) has been quaternized with iodomethane to give 72, and the latter is stable in aqueous solution at room temperature. Protonation of



71 72

the urea oxygen, however, directs electron flow (see 66) for cleavage of the (urea nitrogen)–carbon bond, and the resulting iminium species 67 is analogous to 13, the penultimate structure in Scheme I. The secondary amine (or water or methanol) can then act as the formaldehyde scavenger (= "Nuc") and trap 67 to prevent back-reaction. A similar cleavage of the second (urea nitrogen)–carbon bond leads to dialkylurea 2 and, ultimately, the desired amine 1 as its hydrochloride and the trapped formaldehyde species 70. We have never observed a dialkylurea–formaldehyde adduct (such as 10) as a product of a triazone hydrolysis.

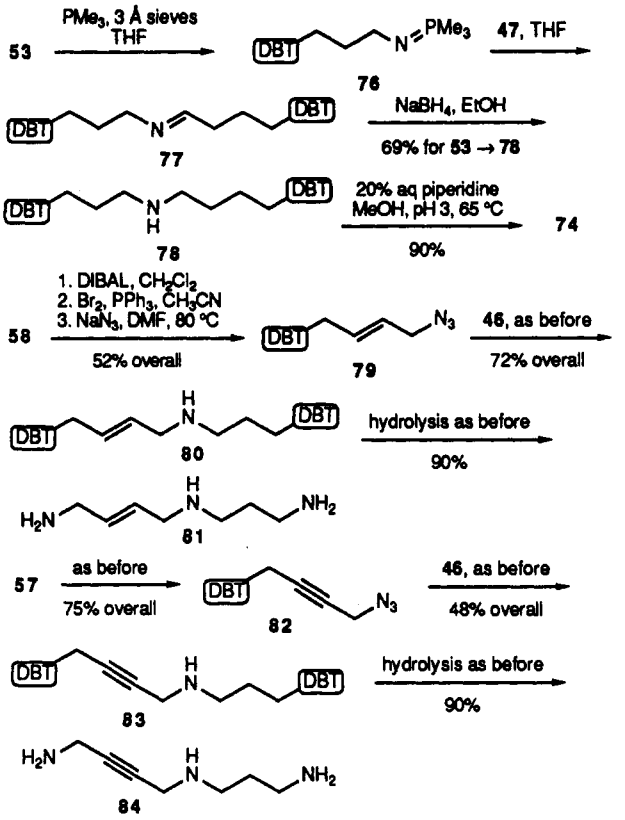
Synthesis of Spermidines. The naturally occurring polyamines putrescine (1,4-diaminobutane, 73), spermidine (4-aza-1,8-diaminooctane, 74), and spermine (4,9-diaza-1,12-diaminododecane, 75) are widely distributed in living systems, interact extensively with phospholipids, proteins, and nucleic acids, and exert a profound influence on biochemical processes.[24] The availability of synthetic polyamine analogues and specific inhibitors for polyamine metabolic enzymes should prove extremely useful for defining the role of polyamines more precisely in various biochemical processes,[25] and polyamine synthesis continues to be an active area.[26] 6,7-Unsaturated spermidines[27] were of particular interest to us as potential inhibitors of hypusine biosynthesis (see next section).



73 74 75

The stability of the dibenzyltriazone-protected aminopropanal 46 and aminobutanal 47 makes them well-suited

Scheme III. Synthesis of Spermidines



for the preparation of spermidine analogues. Golding's method[28] for the synthesis of secondary amines from aldehydes and azides by means of Staudinger and aza-Wittig reactions[29] was adapted for use with dibenzyltriazones (Scheme III). Reaction of the azide 53 with trimethylphosphine to form the iminophosphorane 76, aza-Wittig coupling of 76 with aldehyde 47, and reduction of the resulting imine 77 with sodium borohydride afforded the protected spermidine 78 in a one-pot procedure. The protected, unsaturated, spermidine analogues 80 and 83 were synthesized similarly (the unsaturated azides 79 and 82 were prepared from precursors 58 and 57 as illustrated in Scheme III). Deprotection following the general procedure gave in good yield the spermidines 74, 81, and 84, whose ^1H NMR spectra matched the published values.[27] Traces of nonaryl byproducts (1–3%), possibly chloromethyl ethers, were detected by NMR analysis in the hydrolysis of 84. They are not seen in the hydrolysis of singly-protected substrates, even for spermidine products.[2]

This method for polyamine synthesis potentially allows C–N bond formation at either side of a central nitrogen atom. A variety of functional groups and chain lengths should be tolerated, and tritium introduction should be possibly at several different sites.

Synthesis of Hypusine and Deoxyhypusine. In 1971 Shiba and co-workers isolated a new amino acid from bovine brain called hypusine (86).[30] The biosynthesis of 86 is now known to involve the posttranslational modification of a lysine residue on an 18 kDa protein first demonstrated in human peripheral lymphocytes[31] and in mouse

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(25) Pegg, A. E. *Cancer Res.* **1988**, *48*, 759.
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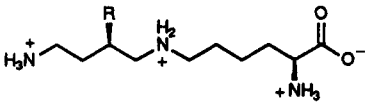
(27) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5044.
(28) Golding, B. G.; O'Sullivan, M. C.; Smith, L. L. *Tetrahedron Lett.* **1988**, *29*, 6651.
(29) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron Lett.* **1992**, *48*, 1353.
(30) Shiba, T.; Mizote, H.; Kaneko, T.; Nakajima, T.; Kakimoto, Y.; Sano, I. *Biochim. Biophys. Acta* **1971**, *244*, 523.
(31) Park, M. H.; Cooper, H. L.; Folk, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2869.

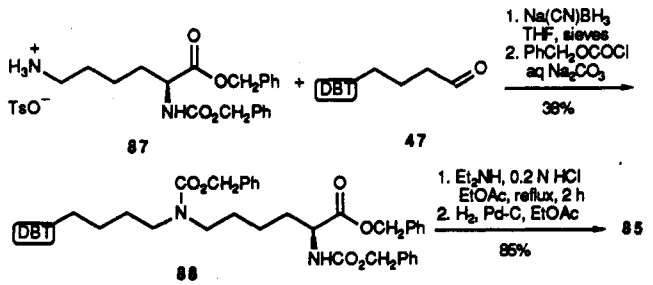
neuroblastoma cells.[32] The pathway for its formation consists of (1) attachment of an aminobutyl group from spermidine at the lysine ϵ-amino group and then (2) hydroxylation at C-9.[33] Hydrolysis of the modified 18 kDa protein gives free **86**. The intermediate modified amino acid is referred to as deoxyhypusine (**85**). The cellular functions of **85** and **86**, and the physiological significance of the modification of the 18 kDa protein, remain to be elucidated.[34]



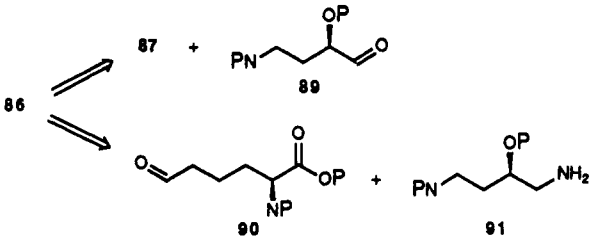
85: R = H (deoxyhypusine)
86: R = OH (hypusine)

We set out to synthesize quantities of **85** and **86** for use as probes of the enzyme system that modifies that 18 kDa protein, and to explore their biological function and fate. Both **85** and **86** have been synthesized,[30,35-37] although some ambiguity remains as to the degree of enantiomeric and diasteriomeric purity of the synthetic compounds. Our success with simple spermidine synthesis using dibenzyltriazone-containing building blocks suggested that the favorable characteristics of this protecting group might also be put to use for more complicated polyamine targets. The possibility of elaborating a lysine derivative to **85** and **86** was particularly attractive.

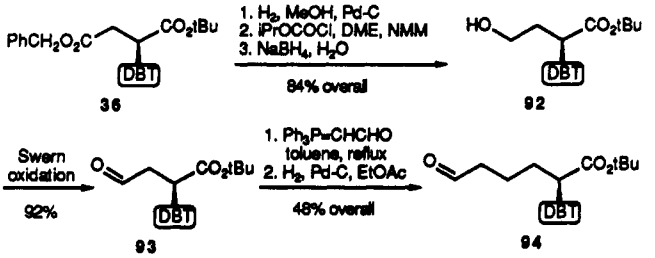
Reductive coupling of $N(\alpha)$-(benzyloxycarbonyl)lysine benzyl ester *p*-toluenesulfonate (**87**)[38] with our stable protected aminobutyraldehyde **47** gave a secondary amine that was converted to its Z-derivative **88** (to facilitate its purification and characterization). Deprotection of **88** was carried out in a one-pot operation by hydrolysis of the dibenzyltriazone ring (the other protecting groups are unaffected), followed by catalytic hydrogenolysis of the benzyl ester and benzyl carbamate. Deoxyhypusine **85** was isolated in 85% overall yield as the bis(hydrochloride salt.[30] Reversing the order of the deprotection steps also led to **85** in about the same yield. The $[\alpha]_D$ for **85**, which has not previously been reported, was found to be +17.41° (c = 0.85, 6 M HCl, 25 °C).



A reductive amination step analogous to that used for **85** was considered for the synthesis of hypusine (**86**), namely the coupling of a lysine derivative such as **87** and a resolved 4-amino-2-hydroxybutyraldehyde (**89**, **P** = protecting group). Alternatively, a lysine ϵ-aldehyde (**90**) could be coupled with a 2-hydroxy-1,4-butanediamine (**91**) to give the same target. The former approach has a potential shortcoming in that racemization of the aldehyde component could occur during its preparation or coupling. The latter approach also has a drawback: despite several attempts, no *isolable* lysine ϵ-aldehyde analogous to **90** had been prepared.[36,39] Although such compounds can apparently be generated for short periods in solution, they readily cyclize to afford a 1,4,5,6-tetrahydropyridine-5-carboxylate derivative. Such a cyclization might not occur if *both* NH positions of the α-amino group are blocked; thus, it was intriguing to examine the use of the dibenzyltriazone protecting group at the α-position to make and couple a lysine ϵ-aldehyde.



The synthesis of the required lysine ϵ-aldehyde **94** was achieved by chain extension of the aspartate derivative **36**. Hydrogenolysis of the benzyl ester of **36** and reduction through a mixed anhydride gave the homoserine derivative **92**. The enantiomeric purity of **92** was checked by converting it to the (*S*)-Mosher ester.[12] Examination of the signals due to the methoxy protons and the β-methylene protons in the ^{1}H NMR spectra of the (*S*)-Mosher ester (and for comparison the diasteriomeric mixture from derivatization of **92** with *racemic* Mosher acid chloride) showed it to have *ee* >99%. Swern oxidation of **92**, as for the protected amino aldehydes in Table III, afforded the aspartic semialdehyde **93**. These kinds of derivatives are potentially prone to elimination; nevertheless, **93** was chain-extended to an unsaturated aldehyde using (formylmethylene)triphenylphosphorane. Hydrogenation gave **94**, the first example of an isolable lysine ϵ-aldehyde. Aldehyde **94** was obtained in analytically pure form and could be stored in the freezer for weeks. The stability of **94** can be attributed to the lack of a reactive NH on the α-amino and to the reduced nucleophilicity and basicity of the triazone N(5) lone pair of electrons.



The four-carbon partner for coupling to **94** was prepared from D-asparagine (**95**). Reaction of **95** with nitrous acid according to Miyazawa[40] gave β-malamic acid, which was converted to its methyl ester **96** for convenience in purification and reduction. Treatment of **96** with diborane, followed by protection of the primary amino to its *tert*-butoxycarbonyl derivative, led to the aminobutanediol derivative **97** (attempts to protect the primary amino as the dibenzyltriazone derivative were unsuccessful). Conversion of the primary hydroxyl to amino was achieved by azide displacement of a monomethanesulfonate derivative. Following hydrogenation, the protected hydroxybutane-

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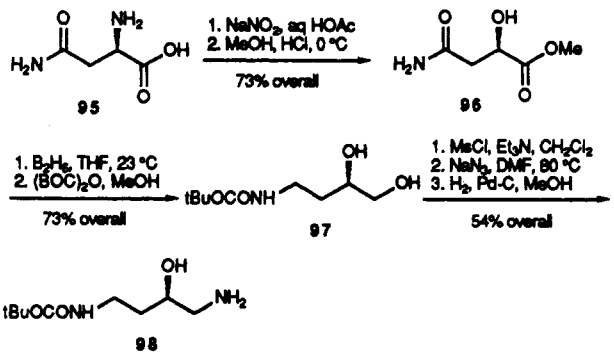
(36) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043.
(37) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048.
(38) Bezas, B.; Zervas, L. *J. Am. Chem. Soc.* **1961**, *83*, 719.
(39) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446.
(40) Miyazawa, T.; Akita, E.; Ito, T. *Agr. Biol. Chem.* **1976**, *40*, 1651.

diamine 98 was isolated in satisfactory yield. The enantiomeric purity of 97 was checked by conversion to its *O,O*-diacetyl derivative, and examination of the ^{1}H NMR spectrum in the presence of the chiral shift reagent tris-[(trifluoromethyl)hydroxymethylene-(−)-camphorato]europium(III).[41] Comparison of the acetate singlets with those of the corresponding racemic compound established the ee of 97 to be at least 90%.

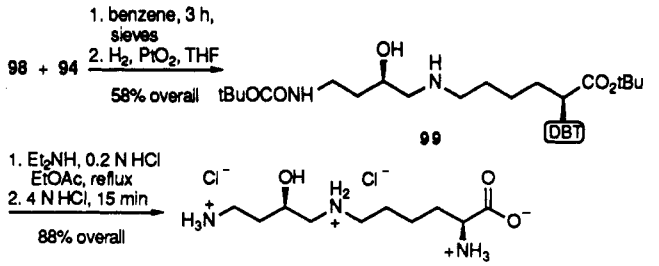


Reductive coupling of the lysine ε-aldehyde 94 and amine 98 was carried out by first stirring them in benzene solution in the presence of activated 4-Å molecular sieves. The benzene was removed, THF was added, and then the solution was hydrogenated over Adam's catalyst. Chromatography on silica gave the hypusine derivative 99. The protecting groups were removed in a one-pot operation: heating a mixture of 99, diethylamine, 0.2 N HCl, and ethyl acetate cleaved the dibenzyltriazone (TLC analysis); 4 N HCl was added, and the reaction was stirred at room temperature to hydrolyze the *tert*-butyl ester and carbamate. Hypusine (86) was isolated by chromatography on silica (1:2:1 dichloromethane/methanol/ammonium hydroxide as the eluant). An aqueous solution of 86 was brought to pH 5.2, causing precipitation of the bis(hydrochloride), mp 237–238 °C (lit.[35] mp 234–236 °C; lit.[36] mp 235–238 °C dec; lit.[37] mp 239–241 °C dec). The $[\alpha]_D$ (+7.8°, c = 0.52, 6 M HCl) of synthetic 86 is comparable to the reported values (+6.8°,[35] +9.9°,[35] +7.2°,[36] and +8.3°[37]), and the well-resolved 150-MHz ^{13}C NMR spectrum indicates that 86 was obtained as a single diastereomer.

The synthesis of hypusine demonstrates some of the advantages of the use of dibenzyltriazones as amino protecting groups in organic synthesis: (1) the dibenzyltriazone can be formed and cleaved under mild conditions in the presence of other functional groups and protecting groups, (2) the dibenzyltriazone survives a variety of reduction, oxidation, and C–C bond-forming reaction conditions, (3) the dibenzyltriazone bestows favorable solubility and chromatography characteristics on otherwise very polar synthetic intermediates, (4) *N*-protected α-amino esters (e.g., 92) are configurationally stable, and (5) *N*-protected amino aldehydes (e.g., 93 and 94) are stable and do not undergo elimination, cyclization, or self-condensation. The reactivity and formation/cleavage characteristics of dibenzyltriazones are complementary to those of other commonly used amino protecting groups, such as Z, BOC, and phthaloyl, and they can be recommended for applications to the synthesis of polyamines, amino alcohols, amino acids, and other similar targets.

Experimental Section

General.[42] Tetrahydrofuran (THF) was distilled from benzophenone ketyl and acetonitrile, dichloromethane (CH_2Cl_2), diisopropylethylamine (DIPEA), *N*-methylmorpholine, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dimethoxymethane (DME), and toluene from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. Organic solutions were dried over anhydrous magnesium sulfate. All air-sensitive reactions were run under an argon atmosphere. NMR values are given in ppm; J values are given in Hz. IR data are given in cm^{-1}.



Ethyl 4-aminobutyrate hydrochloride, ethyl 5-aminopentanoate hydrochloride, ethyl 6-aminohexanoate hydrochloride, and ethyl D-serinate hydrochloride were prepared by Fischer esterification of the amino acids (hydrochloric acid, ethanol, reflux, 16–20 h). Methyl *N*(α)-(*tert*-butoxycarbonyl)-*N*(ε)-(benzyloxycarbonyl)-L-lysinate,[43] *tert*-butyl *N*(α)-(*tert*-butoxycarbonyl)-*N*(ε)-(benzyloxycarbonyl)-L-lysinate,[44] benzyl *N*(α)-(benzyloxycarbonyl)-L-lysinate,[38] 4-aminobutene hydrochloride,[45] and *O*(γ)-benzyl *tert*-butyl aspartate[46] were prepared by the literature methods. "Formalin" refers to 37% aqueous formaldehyde solution.

***N,N'*-Dibenzylurea (2, R² = CH₂Ph).** A 1-L three-necked flask equipped with a thermometer, 50-mL addition funnel, calcium chloride drying tube, and magnetic stirbar was charged with a solution of 25 g (188 mmol) of benzyl isocyanate in 150 mL of CH_2Cl_2. The solution was cooled to below 5 °C, and then a solution of 20.1 g (188 mmol) of benzylamine in 25 mL of CH_2Cl_2 was added dropwise while the temperature was maintained below 10 °C. A precipitate formed immediately; CH_2Cl_2 was added during the reaction to facilitate stirring (total 250 mL). The reaction was allowed to stand at 5 °C for 30 min and then filtered. The resulting solid was washed with 200 mL of ice-cold CH_2Cl_2 and dried under vacuum (1 Torr, 23 °C, 3 h) to afford 39.2 g of dibenzylurea. The filtrate was concentrated in vacuo, and the resulting solid was suspended in 50 mL of ice-cold CH_2Cl_2, filtered, and dried under vacuum to yield an additional 5.3 g of dibenzylurea (99% total yield), mp 165–167 °C: ^{1}H NMR ($CDCl_3$/DMSO-d_6) 4.30 (d, 4 H, J = 5.8), 5.91–5.95 (m, 2 H), 7.26 (app s, 10 H); IR (KBr) 1626, 1579, 1454, 1267, 731, 696.

General Procedures for the Preparation of 5-Substituted 1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazones. Method A. The primary amine or primary amine salt (1 equiv) was combined with dibenzylurea (1 equiv), formalin (0.5–1.0 mL per mmol of amine), and dioxane or THF (0.25–0.5 mL per mmol of amine). The resulting mixture was neutralized with DIPEA (1–2 equiv). Toluene (5–10 mL per mmol of amine) was added, the reaction flask was fitted with a short-path distillation apparatus, and the reaction was stirred and heated, causing liquid to distill from the reaction mixture. When the temperature of the distillate reached 100 °C, heating was stopped, and then the reaction was cooled and concentrated. The residue was partitioned between EtOAc (10 mL per mmol of amine) and water (5 mL per mmol of amine). The organic layer was dried, concentrated, and purified by crystallization or chromatography.

Method B. The primary amine or primary amine salt was combined with formalin (0.5–1.0 mL per mmol of amine), and the resulting mixture was neutralized with DIPEA (1–2 equiv) and stirred for 10 min. Toluene (10 mL per mL of formaldehyde

(41) Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2273.

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solution) was added, and the mixture was concentrated on a rotary evaporator. The amine–formaldehyde adduct was dried to constant weight (1 Torr, 23 °C, 30 min). The dried amine–formaldehyde adduct, dibenzylurea (1 equiv), and an appropriate solvent (EtOAc, THF, or toluene; 5 mL per mmol of amine) were combined and heated at reflux. Disappearance of the dibenzylurea was monitored by TLC. After 1–2 h, the reaction was cooled, diluted with solvent (10–15 mL per mmol), washed with water (5 mL per mmol), dried, and concentrated. The crude product was purified by crystallization or chromatography.

5-(1(*S*)-Phenylethyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (5b). Method B was used to convert 131 mg (1 mmol) of (*S*)-phenethylamine to **5b**. The formaldehyde adduct from the reaction of the amine and 1.0 mL of formalin was combined with 240 mg (1.0 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 1 h. Chromatography on 15 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 361 mg (94%) of **5b** as an oil: $[\alpha]$ −15.8° (c = 0.5); ^{1}H NMR 0.98 (d, 3 H, J = 6.6), 3.83 (q, 1 H, J = 6.6), 4.03 and 4.24 (AB q, 4 H, J = 11.0), 4.42 and 4.57 (AB q, 4 H, J = 15.0), 6.93–6.97 (m, 2 H), 7.25–7.29 (m, 3 H), 7.30 (app s, 10 H); CI-MS 386 $(M + 1)^+$. Anal. Calcd for $C_{25}H_{27}N_3O$: C, 77.89; H, 7.06; N, 10.90. Found: C, 77.61; H, 6.95; N, 10.71.

5-(Prop-2-ynyl)-1,3,5-dioxazinane (9). A mixture of 0.21 mL (3.0 mmol) of propargylamine, 3 mL of formalin, 720 mg of dibenzylurea, and 20 mL of EtOAc was stirred and heated at 60 °C for 48 h. TLC indicated incomplete consumption of dibenzylurea. Additional propargylamine (0.07 mL, 1 mmol) was added, the bath temperature was raised to 70 °C, and the reaction was stirred for 24 h. The mixture was cooled and then partitioned between 20 mL of EtOAc and 10 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with 10 mL of brine, dried, and concentrated. Chromatography on 25 g of silica with 3:2 petroleum ether/ether as the eluant afforded 258 mg of the dioxazinane **9** and 458 mg of the dibenzyltriazone **15** (R_f's 0.85 and 0.15, respectively). For **9**: ^{1}H NMR 2.28 (t, 1 H, J = 2), 3.90 (d, 2 H, J = 2), 4.75 (s, 4 H), 5.16 (s, 2 H).

3,5-Dibenzyl-4-oxo-1,3,5-oxadiazinane (10). L-Serine ethyl ester hydrochloride (1 mmol) was subjected to dibenzyltriaone formation by method B, except that no DIPEA was added to neutralize the acid in the reaction mixture. Chromatography with 1:1 petroleum ether/ether as the eluant gave 0.270 mg of the oxidiazinanone **10** as an oil: ^{1}H NMR 4.59 (s, 4 H), 4.74 (s, 4 H), 7.20–7.41 (m, 10 H). The same product was obtained (9% yield) from the attempted conversion of 1 mmol of L-alanine ethyl ester hydrochloride to its dibenzyltriazone derivative by using method A, but adding only 1.0 equiv of DIPEA. No **10** is seen by TLC in reaction mixtures that have been brought above pH 7 by addition of DIPEA.

5-Octyl-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (14). Method B was used to convert 129 mg (1.0 mmol) of octylamine to **14**. The formaldehyde adduct obtained from the reaction of the amine and 1.0 mL of formalin was combined with 240 mg (1.0 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 1 h. Chromatography on 10 g of silica with 2:1 petroleum ether/ethyl ether as the eluant afforded 358 mg (91%) of **14** as an oil: ^{1}H NMR 0.88 (t, 3 H, J = 6.8), 1.05–1.25 (m, 12 H), 2.42 (t, 2 H, J = 6.4), 4.09 (s, 4 H), 4.55 (s, 4 H), 7.32 (app s, 10 H); ^{13}C NMR 14.1, 22.6, 26.9, 27.7, 29.1, 29.2, 31.7, 48.5, 50.7, 65.6, 127.3, 128.1, 128.5, 138.3, 155.4; FAB-MS 394 $(M + 1)^+$. Anal. Calcd for $C_{25}H_{35}N_3O$: C, 76.30; H, 8.96; N, 10.68. Found: C, 76.08; H, 9.14; N, 10.73.

5-(3-Propynyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (15). Method B was used to convert 110 mg (2.0 mmol) of propargylamine to **15**. The formaldehyde adduct obtained from the reaction of the amine and 1.0 mL of formalin was combined with 480 mg (2.0 mmol) of dibenzylurea and 10 mL of THF and heated at reflux for 20 h. Crystallization from 25 mL of 3:1 petroleum ether/ethyl ether afforded 587 mg (89%) of **15**, mp 82–84 °C: ^{1}H NMR 2.14 (t, 1 H, J = 2.4), 3.33 (d, 2 H, J = 2.4), 4.21 (s, 4 H), 4.56 (s, 4 H), 7.33 (app s, 10 H); IR (KBr) 2881, 1629; CI-MS 320 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.09; H, 6.63; N, 12.99.

5-(But-3-enyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (16). (A) By Protection of 4-Aminobutene. Method B, with 568.8 mg (2.37 mmol) of dibenzylurea, 260.4 mg (2.42 mmol) of 4-aminobutene hydrochloride, 1.0 mL (13.3 mmol) of formalin, and 440.0 μL (2.53 mmol) of DIPEA, was used to prepare **16**. Chromatography with 2:3 EtOAc/hexanes as the eluant gave **16** as an oil in 78% yield: ^{1}H NMR 1.82 (dt, 2 H, J = 7.2, 6.8), 2.53 (t, 2 H, J = 7.2), 4.09 (s, 4 H), 4.54 (s, 4 H), 4.82–4.90 (m, 1 H), 4.89 (d, 1 H, J = 16.0), 5.49–5.60 (m, 1 H), 7.32 (app s, 10 H); FAB-MS 336 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 74.97; H, 7.35; N, 12.29.

(B) From Aldehyde 46. A suspension of 536 mg (1.5 mmol) of methyltriphenylphosphonium bromide in 10 mL of THF was cooled with an ice/methanol bath for 10 min and then treated with 1.5 mL of a 1.6 N n-butyllithium solution in hexanes. The resulting yellow solution was stirred at 23 °C for 30 min, cooled in an ice/ethanol bath for 10 min, and then treated with a solution of 296 mg (0.88 mmol) of aldehyde **46** in 5 mL of THF. The cooling bath was removed, and the resulting mixture was stirred at 23 °C for 1.5 h. The reaction was quenched by adding 0.5 mL of MeOH, and the quenched reaction mixture was partitioned between 25 mL of ethyl ether and 5 mL of water. The organic layer was separated and dried. The aqueous layer was extracted with 20 mL of ethyl ether; the extract was dried and combined with the original organic layer. The combined organic layer was concentrated. Chromatography on 15 g of silica with 4:1:1 petroleum ether/ethyl ether/CH_2Cl_2 as the eluant afforded 220 mg (75%) of **16**.

5-(Pent-4-enyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (17). Protection of 5-aminopentene by method B as for **16**, and chromatography with 1:1 ether/petroleum ether as the eluant, gave **17** as an oil in 90% yield: ^{1}H NMR 1.14 (quintet, 2 H, J = 7), 1.81–1.87 (m, 2 H), 2.42–2.45 (t, 2 H, J = 7), 4.09 (s, 4 H), 4.53 (s, 4 H), 4.87–4.90 (app d, 2 H), 5.57–5.64 (m, 1 H), 7.26–7.36 (m, 10 H); ^{13}C NMR 26.85, 31.00, 48.45, 50.11, 65.57, 114.20, 127.30, 128.10, 128.52, 137.91, 138.31, 155.31. Anal. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.27; H, 7.96; N, 11.93.

5-(3-Methylphenyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (18). Method B was used to convert 107 mg (1.0 mmol) of m-toluidine to **18**. The formaldehyde adduct obtained from the reaction of the amine and 1.0 mL of formalin was combined with 240 mg (1.0 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 1 h. Chromatography on 10 g of silica with 2:1 petroleum ether/ethyl ether as the eluant afforded 262 mg (71%) of **18** as a solid, mp 98–101 °C: ^{1}H NMR 2.11 (s, 3 H), 4.57 (s, 4 H), 4.61 (s, 4 H), 6.40 (s, 1 H), 6.47 (d, 1 H, J = 7.8), 6.74 (d, 1 H, J = 7.2), 6.99 (app t, 1 H, J = 7.8), 7.26 (app s, 10 H); FAB-MS 372 $(M + 1)^+$. Anal. Calcd for $C_{24}H_{25}N_3O$: C, 77.60; H, 6.78; N, 11.31. Found: C, 77.42; H, 6.69; N, 11.16.

5-(4-Iodophenyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (19). Method B was used to convert 110 mg (0.5 mmol) of 4-iodoaniline to **19**. The formaldehyde adduct obtained from the reaction of the amine and 0.5 mL of formalin was combined with 120 mg (0.5 mmol) of dibenzylurea and 5 mL of EtOAc and heated at reflux for 1.5 h. Chromatography on 10 g of silica with 2:1 and then 1:1 petroleum ether/ethyl ether as the eluant afforded 153 mg (62%) of **19** as a solid, mp 97–99 °C: ^{1}H NMR 4.56 (s, 4 H), 4.57 (s, 4 H), 6.30 (d, 2 H, J = 9.0), 7.20–7.32 (m, 2 H), 7.27 (app s, 10 H); FAB-MS 483 $(M + 1)^+$. Anal. Calcd for $C_{23}H_{22}IN_3O$: C, 57.15; H, 4.59; N, 8.69; I, 26.26. Found: C, 57.31; H, 4.77; N, 8.48; I, 26.08.

5-(3-Hydroxypropyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (20). (A) By Protection of 3-Aminopropanol. Method B was used to convert 75 mg (1.0 mmol) of 3-amino-1-propanol to **20**. The formaldehyde adduct from the reaction of the amine and 1.0 mL of formalin was combined with 240 mg (1.0 mmol) of dibenzylurea and 5.0 mL of toluene and heated at reflux for 20 h. Chromatography on 15 g of silica with ethyl ether as the eluant afforded 310 mg (90%) of **20** that slowly solidified on standing, mp 71–72 °C: ^{1}H NMR 1.24–1.36 (m, 2 H), 2.63 (t, 2 H, J = 6.2), 2.84 (br s, 1 H), 3.55 (t, 2 H, J = 5.4), 4.11 (s, 4 H), 4.55 (s, 4 H), 7.32 (app s, 10 H); CI-MS 340 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.82; H, 7.40; N, 12.72.

(B) By Reduction of 25. Reduction of **25** as for **39** gave **20** in 80% yield.

5-(4-Hydroxybutyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (21). (A) By Protection of 4-Aminobutanol. Method B was used to convert 270 mg (3.0 mmol) of 4-aminobutanol to

21. The formaldehyde adduct from the reaction of the amine and 2 mL of formalin was combined with 720 mg (3.0 mmol) of dibenzylurea and 20 mL of EtOAc and heated at reflux for 20 h. Crystallization from 30 mL of 1:1 ethyl ether/petroleum ether afforded 839 mg (79%) of **21**, mp 103–105 °C: ^{1}H NMR 1.06–1.21 (m, 2 H), 1.32–1.45 (m, 2 H), 2.30 (br s, 1 H), 2.47 (t, 2 H, J = 6.8), 3.44 (t, 2 H, J = 6.5), 4.11 (s, 4 H), 4.56 (s, 4 H), 7.33 (app s, 10 H); CI-MS 354 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.42; H, 7.74; N, 11.77.

(B) By Reduction of 26. Reduction of **26** as for **39** gave **21** in 85% yield.

5-(2-Hydroxy-2-methyl-6-heptyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (22). Method B was used to convert 182 mg (1.0 mmol) of 6-amino-2-methyl-2-heptanol hydrochloride to **22**. The formaldehyde adduct from the reaction of the amine salt, 1.0 mL of formalin, and 180 μL (1.0 mmol) of DIPEA was combined with 240 mg (1.0 mmol) of dibenzylurea and 10 mL of toluene and heated at reflux for 20 h. Chromatography on 10 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 326 mg (93%) of **22** as an oil: ^{1}H NMR 0.81 (d, 3 H, J = 6.4), 0.98–1.26 (m, 6 H), 1.16 (s, 6 H), 2.72–2.76 (m, 1 H), 4.15 and 4.19 (AB q, 4 H, J = 11.6) 4.43 and 4.65 (AB q, 4 H, J = 14.8), 7.33 (app s, 10 H); ^{13}C NMR 17.6, 20.2, 29.1, 29.4, 35.0, 43.8, 48.6, 52.8, 63.2, 70.8, 127.3, 128.3, 128.5, 138.3, 157.9; FAB-MS 410 $(M + 1)^+$.

5-[1-[(*tert*-Butyldimethylsilyl)oxy]-2(*S*)-propyl]-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (23). A solution of 188 mg (2.5 mmol) of L-alaninol, 0.87 mL (5.0 mmol) of DIPEA, and 15 mg (0.13 mmol, 0.05 equiv) of 4-(dimethylamino)pyridine in 50 mL of CH_2Cl_2 at 0 °C was treated with 1.15 mL (5.0 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. The solution was stirred at 0 °C for 15 min and then concentrated. The resulting crude triflate salt was converted to **23** by using method B. The formaldehyde adduct from the reaction of the salt and 2 mL of formalin was combined with 600 mg (2.5 mmol) of dibenzylurea and 20 mL of EtOAc and heated at reflux for 1.5 h. Chromatography on 30 g of silica with 3:2 petroleum ether/ethyl ether as the eluant afforded 884 mg (78%) of **23** as an oil: $[\alpha]$ −13.1° (c = 0.5); ^{1}H NMR −0.05 (s, 6 H), 0.84 (s, 9 H), 0.86 (d, 2 H, J = 6.8), 2.82–2.90 (m, 1 H), 3.26 and 3.39 (two dd, 1 H each, J = 5.2, 10.4), 4.19 (app s, 4 H), 4.54 (app s, 4 H), 7.32 (app s, 10 H). Anal. Calcd for $C_{26}H_{39}N_3O_2Si$: C, 68.83; H, 8.66; N, 9.26. Found: C, 68.83; H, 8.62; N, 9.31.

Ethyl 2-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-acetate (24). Method B was used to convert 1.40 g (10 mmol) of ethyl glycinate hydrochloride to **24**. The formaldehyde adduct [obtained from reaction of the salt with 5 mL of formalin and 3.0 mL (17.2 mmol) of DIPEA] was combined with 2.40 g (10.0 mmol) of dibenzylurea and 50 mL of EtOAc and heated at reflux for 1 h. Crystallization from 50 mL of 2:1 petroleum ether/ethyl ether afforded 3.22 g (88%) of **24**, mp 91–93 °C: ^{1}H NMR 1.16 (t, 3 H, J = 7.2), 3.25 (s, 2 H), 4.00 (q, 2 H, J = 7.2), 4.18 (s, 4 H), 4.53 (s, 4 H), 7.32 (app s, 10 H); CI-MS 368 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.84; H, 6.86; N, 11.44. Found: C, 68.77; H, 6.90; N, 11.38.

Ethyl 3-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-propionate (25). Method A was used to convert 770 mg (5.0 mmol) of ethyl β-alaninate hydrochloride to **25**. The amine salt was combined with 1.20 g (5.0 mmol) of dibenzylurea, 5.0 mL of formalin, 0.9 mL (5.0 mmol) of DIPEA, and 50 mL of toluene. Chromatography on 50 g of silica with 3:2 ethyl ether/petroleum ether as the eluant afforded 1.66 g (87%) of **25** as an oil: ^{1}H NMR 1.20 (t, 3 H, J = 7.0), 2.05 (t, 2 H, J = 6.8), 2.78 (t, 2 H, J = 6.8), 4.06 (q, 2 H, J = 7.0), 4.08 (s, 4 H), 4.55 (s, 4 H), 7.32 (app s, 10 H); CI-MS 382 $(M + 1)^+$. Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.05; H, 7.19; 10.72. Method B (as for **16**) gave 90% yield of **25**.

Ethyl 4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-butyrate (26). Method A was used to convert 840 mg (5.0 mmol) of ethyl 4-aminobutyrate hydrochloride to **26** as for **25**. Chromatography on 50 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 1.38 g (70%) of **26** as an oil: ^{1}H NMR 1.20 (t, 3 H, J = 7.0), 1.33–1.47 (m, 2 H), 2.11 (t, 2 H, J = 7.3), 2.46 (t, 2 H, J = 6.9), 4.05 (q, 2 H, J = 7.0), 4.06 (s, 4 H), 4.53 (s, 4 H), 7.31 (app s, 10 H); CI-MS 396 $(M + 1)^+$. Anal. Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 70.04; H, 7.41; N, 10.60. Method B (as for **16**) gave 79% yield of **26**.

Ethyl 5-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-pentanoate (27). Method A was used to convert 91 mg (0.5 mmol) of ethyl 5-aminopentanoate hydrochloride to **27**. The amine salt was combined with 120 mg (0.5 mmol) of dibenzylurea, 0.5 mL of formalin, 90 μL (0.5 mmol) of DIPEA, 0.5 mL of dioxane, and 10 mL of toluene. Chromatography on 5 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 156 mg (76%) of **27** as an oil: ^{1}H NMR 0.97–1.11 (m, 2 H), 1.23 (t, 3 H, J = 7.0), 1.34–1.48 (m, 2 H), 2.11 (t, 2 H, J = 7.4), 2.43 (t, 2 H, J = 7.2), 4.07 (s, 4 H), 4.09 (t, 2 H, J = 7.0), 4.54 (s, 4 H), 7.32 (app s, 10 H); CI-MS 410 $(M + 1)^+$. Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.63; H, 7.69; N, 10.32. Method B (as for **16**) gave 90% yield of **27**.

Ethyl 6-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-hexanoate (28). Method A was used to convert 98 mg (0.5 mmol) of ethyl 6-aminohexanoate hydrochloride to 11. The amine salt was combined with 120 mg (0.5 mmol) of dibenzylurea, 0.5 mL of formalin, 90 μL (0.5 mmol) of DIPEA, and 10 mL of toluene. Chromatography on 5 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 158 mg (75%) of **28** as an oil: ^{1}H NMR 0.98–1.12 (m, 4 H), 1.25 (t, 3 H, J = 7.2), 1.38–1.50 (m, 2 H), 2.18 (t, 2 H, J = 7.4), 2.42 (t, 2 H, J = 7.2), 4.07 (s, 4 H), 4.11 (q, 2 H, J = 7.2), 4.54 (s, 4 H), 7.32 (app s, 10 H); ^{13}C NMR 14.1, 24.4, 26.3, 27.1, 34.0, 48.3, 50.3, 60.4, 65.3, 127.5, 128.0, 128.4, 138.1, 155.2, 173.4; FAB-MS 424 $(M + 1)^+$. Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.93; H, 7.75; N, 9.92.

Ethyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)propionate (29). Method B was used to convert 306 mg (2.0 mmol) of ethyl L-alaninate hydrochloride to **29**. The formaldehyde adduct obtained from the reaction of the amine salt, 1.5 mL of formalin, and 0.35 mL (2.0 mmol) of DIPEA was combined with 480 mg (2.0 mmol) of dibenzylurea and 15 mL of EtOAc and heated at reflux for 1 h. Chromatography on 20 g of silica with 20:1 CH_2Cl_2/ethyl ether as the eluant afforded 684 mg (90%) of **29** as an oil: $[\alpha]$ −38.4° (c = 0.25); ^{1}H NMR 0.98 (d, 3 H, J = 6.8), 1.15 (t, 3 H, J = 7.2), 3.54 (q, 1 H, J = 6.8), 3.93 and 4.05 (two dd, 1 H each, J = 10.4, 7.2), 4.15 and 4.25 (AB q, 4 H, J = 12.0), 4.49 and 4.55 (AB q, 4 H, J = 15.2), 7.32 (app s, 10 H); FAB-MS 382 $(M + 1)^+$. Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 68.99; H, 7.09; N, 10.98.

Benzyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)propionate (30). Method B was used to convert 262 mg (0.75 mmol) of benzyl L-alaninate *p*-toluenesulfonate to **30**. The formaldehyde adduct obtained from the reaction of the amine salt, 1.0 mL of formalin, and 130 μL (0.75 mmol) of DIPEA was combined with 180 mg (0.75 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 1 h. Chromatography on 7.5 g of silica with 3:2 petroleum ether/ethyl ether as the eluant afforded 265 mg (80%) of **30** as an oil: $[\alpha]$ −45.2° (c = 0.4); ^{1}H NMR 0.99 (d, 3 H, J = 6.8), 3.60 (q, 1 H, J = 6.8), 4.13 and 4.23 (AB q, 4 H, J = 12.0), 4.37 and 4.57 (AB q, 4 H, J = 14.8), 4.91 and 5.08 (AB q, 2 H, J = 12.0), 7.24–7.38 (m, 15 H); FAB-MS 444 $(M + 1)^+$. Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.12; H, 6.59; N, 9.47. Found: C, 73.29; H, 6.75; N, 9.29.

α-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-γ-butyrolactone (31). Method B was used to convert 137 mg (0.75 mmol) of α-amino-γ-butyrolactone hydrobromide to **31**. The formaldehyde adduct obtained from the reaction of the amine salt, 1.0 mL of formalin, and 130 μL (0.75 mmol) of DIPEA was combined with 180 mg (0.75 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 1 h. Chromatography on 7.5 g of silica with 3:2 ethyl ether/petroleum ether as the eluant afforded 178 mg (65%) **31** as a solid, mp 137–139 °C: ^{1}H NMR 1.47–1.54 (m, 1 H), 1.77–1.88 (m, 1 H), 3.50 (dd, 1 H, J = 11.2, 7.6), 3.85 (ddd, 1 H, J = 10.4, 9.2, 6.0), 4.11 (m, 1 H), 4.10 and 4.67 (AB q, 4 H, J = 11.2), 4.22 and 4.84 (AB q, 4 H, J = 14.8), 7.35 (app s, 10 H); IR (KBr) 1778, 1641; FAB-MS 366 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.99; H, 6.42; N, 11.80.

Methyl 3-(Benzyloxy)-2(*S*)-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)propionate (32). Two mL of trifluoroacetic acid was added slowly to a solution of 539.0 mg (1.74 mmol) of methyl *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serinate in 10 mL of dry CH_2Cl_2 at 0 °C. The solution was allowed to warm to room temperature and then concentrated to a residue. Protection using

method B as for 16 and chromatography with 1:2 EtOAc/petroleum ether as the eluant gave 734.6 mg (94% yield) of **32**: ^{1}H NMR 3.22 (dd, 1 H, J = 10.4), 3.38 (dd, 1 H, J = 10.4), 3.50 (s, 3 H), 3.53 (t, 1 H, J = 4), 4.12–4.32 (m, 6 H), 4.36 (d, 2 H, J = 15), 4.49 (d, 2 H, J = 15), 7.17–7.33 (m, 15 H); ^{13}C NMR 48.39, 51.94, 60.95, 63.92, 67.58, 72.95, 127.21, 127.75, 128.13, 128.42, 137.08, 155.09, 171.02. Anal. Calcd for $C_{28}H_{31}N_3O_4$: C, 71.01; H, 6.60; N, 8.87. Found: C, 70.95; H, 6.58; N, 8.71.

Ethyl 3-(Benzyloxy)-2(*S*)-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)propionate (33). Method B was used to convert 519 mg (2.0 mmol) of ethyl *O*-benzyl-L-serinate hydrochloride to **33**. The formaldehyde adduct obtained from the reaction of the amine salt, 1.5 mL of formalin, and 0.4 mL (2.3 mmol) of DIPEA was combined with 480 mg (2.0 mmol) of dibenzylurea and 20 mL of EtOAc and heated at reflux for 1 h. Chromatography on 40 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 954 mg (98%) of **33** as an oil: [α] −18.6° (c = 1.6); ^{1}H NMR 1.13 (t, 3 H, J = 6.8), 3.26 and 3.44 (two dd, 1 H each, J = 10.0, 4.0), 3.55 (t, 1 H, J = 4.0), 3.95 and 4.05 (two dq, 1 H each, J = 10.4, 6.8), 4.17 and 4.26 (AB q, 4 H, J = 12.0), 4.24 and 4.34 (AB q, 2 H, J = 12.4), 4.42 and 4.50 (AB q, 4 H, J = 14.8), 7.19–7.33 (m, 15 H); FAB-MS 488 $(M + 1)^+$.

Methyl 2(*S*)-[(*tert*-Butoxycarbonyl)amino]-6-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)hexanoate (34). A solution of 95 mg (0.25 mmol) of methyl $N(\alpha)$-(*tert*-butoxycarbonyl)-$N(\epsilon)$-(benzyloxycarbonyl)-L-lysinate[43] in 5 mL of methanol was treated with 5 drops of glacial acetic acid and 10 mg of 10% palladium-on-activated-carbon catalyst, and the resulting mixture was stirred under an atmosphere of hydrogen. After 45 min, the mixture was filtered through Celite and concentrated. The resulting crude acetate salt was converted to **34** by using method B. The formaldehyde adduct obtained from the reaction of the salt, 0.5 mL of formalin, and 50 μL (0.25 mmol) of DIPEA was combined with 60 mg (0.25 mmol) of dibenzylurea and 10 mL of EtOAc and heated at reflux for 20 h. Chromatography on 7.5 g of silica with 1:1 and then 2:1 ethyl ether/petroleum ether as the eluant afforded 102 mg (78%) of **34** as an oil: [α] +8.9° (c = 0.9); ^{1}H NMR 1.01–1.11 (m, 6 H), 1.45 (s, 9 H), 2.39 (t, 2 H, J = 8.0), 3.72 (s, 3 H), 4.07 (s, 4 H), 4.18–4.26 (m, 1 H), 4.54 (s, 4 H), 4.98 (d, 1 H, J = 7.0), 7.33 (app s, 10 H); ^{13}C NMR 22.6, 27.1, 28.2, 32.3, 48.4, 50.2, 52.1, 53.2, 65.4, 79.8, 127.3, 128.1, 128.5, 138.2, 155.2, 173.2; IR (neat) 1743, 1711, 1631; FAB-MS 525 $(M + 1)^+$. Anal. Calcd for $C_{29}H_{40}N_4O_5$: C, 66.39; H, 7.68; N, 10.68. Found: C, 66.21; H, 7.82, N, 10.56.

Methyl 6-[(Benzyloxycarbonyl)amino]-2(*S*)-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)hexanoate (35). A solution of 100 mg (0.26 mmol) of methyl $N(\alpha)$-(*tert*-butoxycarbonyl)-$N(\epsilon)$-(benzyloxycarbonyl)-L-lysinate[43] in 3 mL of 2:1 CH_2Cl_2/trifluoroacetic acid was stirred for 45 min at 23 °C and then concentrated. The resulting crude trifluoroacetate salt was converted to **35** by using method B. The formaldehyde adduct obtained from reaction of the salt, 0.5 mL of formalin, and 50 μL (0.25 mmol) of DIPEA was combined with 63 mg (0.26 mmol) of dibenzylurea and 5 mL of EtOAc and heated at reflux for 2 h. Chromatography on 5 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 106 mg (72%) of **35** as an oil: [α] −21.5° (c = 0.5); ^{1}H NMR 1.03–1.28 (m, 6 H), 3.05 (dt, 2 H, J = 6.8, 5.6), 3.39 (t, 1 H, J = 6.4), 3.52 (s, 3 H), 4.13 and 4.19 (AB q, 4 H, J = 12.0), 4.36 and 4.65 (AB q, 4 H, J = 14.8), 4.67 (br s, 1 H), 5.09 (s, 2 H), 7.25–7.36 (m, 15 H); ^{13}C NMR 22.1, 29.4, 29.6, 40.5, 48.6, 51.9, 61.3, 63.6, 66.5, 127.4, 127.7, 127.8, 128.1, 128.2, 128.5, 137.9, 155.3, 156.2, 172.9; FAB-MS 559 $(M + 1)^+$. Anal. Calcd for $C_{32}H_{38}N_4O_5$: C, 68.80; H, 6.86; N, 10.02. Found: C, 68.72; H, 6.89; N, 9.91.

1-*O*-*tert*-Butyl 4-*O*-Benzyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)succinate (36). Protection of *tert*-butyl benzyl aspartate by method B gave **36** as an oil in 84% yield: ^{1}H NMR 1.39 (s, 9 H), 2.48 and 2.59 (two dd, 1 H each, J = 16, 7), 3.74–3.80 (dd, 1 H, J = 8, 6), 4.16 and 4.19 (two d, 2 H each, J = 15), 4.32–4.37 (d, 2 H, J = 15), 4.70–4.73 (d, 2 H, J = 15), 5.05 and 5.10 (two d, 1 H each, J = 20), 7.2–7.4 (m, 15 H). Anal. Calcd for $C_{32}H_{37}N_3O_5$: C, 70.70; H, 6.86; N, 7.73. Found: C, 71.19; H, 6.58; N, 7.51.

Ethyl 2-(1,3-Dicyclohexylhexahydro-2-oxo-1,3,5-triazin-5-yl)acetate (37). Method B was used to convert 70 mg (0.5 mmol) of ethyl glycinate hydrochloride to **37**. The formaldehyde adduct obtained from the reaction of the amine salt, 180 μL (1.0 mmol) of DIPEA, and 1.0 mL of formalin was combined with 112 mg (0.5 mmol) of N,N'-dicyclohexylurea and 5 mL of EtOAc and heated at reflux for 2 h. Chromatography on 5 g of silica with 3:2 ethyl ether/petroleum ether as the eluant afforded 125 mg (71%) of **37** as a solid, mp 65–66 °C: ^{1}H NMR 1.02–1.78 (m, 20 H), 1.28 (t, 3 H, J = 7.2), 3.40 (s, 2 H), 4.19 (s, 4 H), 4.20–4.28 (m, 2 H) 4.22 (q, 2 H, J = 7.2); FAB-MS 352 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{33}N_3O_3$: C, 64.93; H, 9.46; N, 11.95. Found: C, 64.60; H, 9.85; N, 11.73.

General Procedure for Preparation of Mosher Esters. (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were prepared from (±)-α-methoxy-α-(trifluoromethyl)-phenylacetonitrile according to the procedure of Mosher.[12] The resolved acids were converted to their sodium salts by dissolving each in methanol (5 mL per mmol of salt) and titrating with 1.0 N sodium hydroxide. The solutions were concentrated, and then the resulting solids were suspended in ethyl ether (5 mL per mmol), filtered, and dried (1 Torr, 1 h). The Mosher acid sodium salts are nonhygroscopic solids and can be stored indefinitely without taking special precautions.

In a typical procedure to prepare a Mosher ester, 75 mg (0.29 mmol) of sodium (*S*)-α-methoxy-α-(trifluoromethyl)acetate was combined with 2 mL of oxalyl chloride and heated at gentle reflux for 16 h. The mixture was cooled, diluted with 5 mL of anhydrous ethyl ether, and filtered, and the filtrate was concentrated. The resulting oil exhibited a strong absorption in the IR at 1790 cm^{-1} and was used without further purification.

A solution of 33 mg (0.1 mmol) of the protected alaninol **40**, 50 μL (0.29 mmol) of DIPEA, 12 mg (0.1 mmol) of 4-(dimethylamino)pyridine, and the crude acid chloride in 3 mL of CH_2Cl_2 was heated at reflux for 1 h. The solution was cooled and partitioned between 10 mL of ethyl ether and 5 mL of water. The organic layer was dried, concentrated, and chromatographed on 4 g of silica with 2:1 petroleum ether/ethyl ether as the eluant to afford 40 mg of the (*S*)-Mosher ester of **40** for NMR analysis.

5-(2-Hydroxyethyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (39). A solution of 1.25 g (3.4 mmol) of ester **24** and 110 mg (5.0 mmol) of lithium borohydride in 15 mL of THF was heated at reflux for 1 h. The solution was cooled in an ice bath and quenched with 5 mL of saturated aqueous sodium bicarbonate. The mixture was diluted with 30 mL of EtOAc and 5 mL of water, and the layers were separated. The aqueous layer was extracted with 20 mL of EtOAc. The combined organic layer was washed with 15 mL of brine, dried, and concentrated. Chromatography on 25 g of silica gel with ethyl ether as the eluant afforded 1.01 g (92%) of **39** as an oil: ^{1}H NMR 2.09 (br s, 1 H), 2.61 (t, 2 H, J = 5.0), 3.25–3.32 (m, 2 H), 4.12 (s, 4 H), 4.57 (s, 4 H), 7.34 (app s, 10 H); CI-MS 326 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.23; H, 7.04; N, 12.80.

5-(1-Hydroxy-2(*S*)-propyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (40). A solution of 160 mg (0.42 mmol) of ester **29** and 25 mg (1.15 mmol) of lithium borohydride in 5 mL of THF was heated at reflux for 2 h. Workup as for **39** and chromatography on 7.5 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 134 mg (94%) of **40**, which slowly solidified on standing, mp 68–70 °C: [α] +7.1° (c = 1.5); ^{1}H NMR 0.86 (d, 3 H, J = 6.8), 1.94 (br s, 1 H), 2.80–2.89 (m, 2 H), 3.11–3.28 (m, 2 H), 4.15 and 4.20 (AB q, 4 H, J = 12.0), 4.42 and 4.66 (AB q, 4 H, J = 15.0), 7.33 (app s, 10 H); ^{13}C NMR 15.0, 48.6, 55.5, 63.3, 64.2, 127.4, 128.3, 128.6, 137.9, 155.8; CI-MS 340 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.50; H, 7.38; N, 12.32.

5-(5-Hydroxypentyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (41). Reduction of **27** as for **39** gave **41** in 79% yield, mp 79–80 °C: ^{1}H NMR 1.07–1.42 (m, 2 H), 1.36–1.40 (m, 2 H), 2.44 (t, 2 H, J = 7), 3.53 (t, 2 H, J = 6), 4.09 (s, 4 H), 4.55 (s, 4 H), 7.26–7.34 (m, 10 H). Anal. Calcd for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 71.35; H, 8.05; N, 11.09.

2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-propionic Acid (42). A solution of 275 mg (0.62 mmol) of ester **30** in 10 mL of absolute ethanol was treated with 25 mg of 10% palladium-on-activated-carbon catalyst and stirred under a hydrogen atmosphere for 4 h. The mixture was filtered through Celite and concentrated. The residue was triturated with ethyl

ether, and then the resulting solid was filtered and dried under high vacuum (1 Torr, 23 °C, 3 h) to give 216 mg (99%) of **42**, mp 128–129 °C: $[\alpha]$ −35.4° (c = 0.5); ^{1}H NMR 1.06 (d, 3 H, J = 6.8), 3.55 (q, 1 H, J = 6.8), 4.17 and 4.24 (AB q, 4 H, J = 12.0), 4.44 and 4.60 (AB q, 4 H, J = 15.2), 7.30 (app s, 10 H); IR (KBr) 3400, 1718, 1643; FAB-MS 354 (M + 1)$^+$. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.99; H, 6.42; N, 11.80.

Ethyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-3-hydroxypropionate (43). A solution of 200 mg (0.41 mmol) of benzyl ether **33** in 10 mL of absolute ethanol was treated with 20 mg of 10% palladium-on-activated-carbon catalyst and 10 drops of glacial acetic acid and stirred under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through Celite and concentrated. The residue was dissolved in 25 mL of EtOAc and washed with 15 mL of saturated aqueous sodium bicarbonate and 10 mL of brine. The solution was dried, concentrated, and chromatographed on 7.5 g of silica with 2:1 ethyl ether/petroleum ether as the eluant to afford 154 mg (95%) of **43** as a solid, mp 97–98 °C: $[\alpha]$−59.2° (c = 0.6); ^{1}H NMR 1.21 (t, 3 H, J = 7.2), 2.04 (t, 1 H, J = 5.8), 3.46–3.64 (m, 3 H), 4.01 and 4.13 (two dd, 1 H each, J = 14.4, 7.2), 4.24 (app s, 4 H), 4.40 and 4.65 (AB q, 4 H, J = 15.2), 7.32 (app s, 10 H); FAB-MS 398 (M + 1)$^+$. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.62; H, 6.73; N, 10.35.

General Procedure for Swern Oxidation of Dibenzyltriazone-Protected Amino Alcohols. A dried three-necked flask equipped with a septum, thermometer, and calcium chloride drying tube was charged with a solution of oxalyl chloride (2 equiv) in CH_2Cl_2 (5 mL per mmol of alcohol). The solution was cooled to below −60 °C, and then a solution of DMSO (3 equiv) in CH_2Cl_2 (1 mL per mmol of DMSO) was added via syringe at such a rate that the temperature was maintained below −50 °C. A solution of the alcohol (1 equiv) in CH_2Cl_2 (3 mL per mmol of alcohol) was slowly added via syringe while the temperature was maintained below −50 °C. The solution was stirred for 20 min, and then DIPEA (10 equiv) was added while the temperature was maintained below −50 °C. The resulting mixture was allowed to warm to 0 °C. The reaction was quenched with 0.5 N aqueous potassium bisulfate (15 equiv), and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried, and concentrated. Chromatography on silica afforded the pure dibenzyltriazone-protected amino aldehyde.

2-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)acetaldehyde (44). The general Swern procedure, with 0.52 mL (6.0 mmol) of oxalyl chloride, 0.64 mL (9.0 mmol) of DMSO, 5.2 mL (30.0 mmol) of DIPEA, and 90 mL of 0.5 N aqueous potassium bisulfate, was used to convert 975 mg (3.0 mmol) of **39** to **44**. Chromatography on 30 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 823 mg (86%) of **44** as an oil: ^{1}H NMR 3.33 (s, 2 H), 4.14 (s, 4 H), 4.53 (s, 4 H), 7.32 (app s, 10 H), 9.34 (s, 1 H); IR (neat) 1731, 1638.

2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-propionaldehyde (45). The general Swern procedure, with 0.26 mL (3.0 mmol) of oxalyl chloride, 0.32 mL (4.5 mmol) of DMSO, 2.60 mL of DIPEA, and 50 mL of 0.5 N aqueous potassium bisulfate, was used to convert 510 mg (1.5 mmol) of alaninol **40** to **45**. Chromatography on 20 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 438 mg (87%) of **45** as an oil: ^{1}H NMR 0.86 (d, 2 H, J = 7.2), 3.32 (dq, 1 H, J = 7.2, 2.2), 4.13 and 4.22 (AB q, 4 H, J = 12.0), 4.48 and 4.55 (AB q, 4 H, J = 14.8), 7.32 (app s, 10 H), 9.24 (d, 1 H, J = 2.2); IR (neat) 1732, 1632.

Configurational Stability of Alaninal 45. A stirred solution of 45 mg (0.13 mmol) of **45** in 3 mL of absolute ethanol was treated with 20 mg of sodium borohydride at 0 °C. The mixture was stirred for 20 min and then quenched with 2 mL of saturated aqueous sodium bicarbonate. The reaction mixture was concentrated and the residue partitioned between 10 mL of EtOAc and 3 mL of water. The organic layer was dried and concentrated. Chromatography on silica afforded 43 mg of alcohol **40**, which was converted to its (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate derivative by using the general procedure.

3-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-propionaldehyde (46). (A) By Swern Oxidation. The general Swern procedure, with 0.18 mL (2.0 mmol) of oxalyl chloride, 0.22 mL (3.0 mmol) of DMSO, 1.70 mL (10.0 mmol) of DIPEA, and 30 mL of 0.5 N aqueous potassium bisulfate, was used to convert 339 mg (1.0 mmol) of **20** to **46**. Chromatography on 10 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 325 mg (96%) of **46** as an oil: ^{1}H NMR 2.11 (dt, 2 H, J = 6.6, 1.8), 2.79 (t, 2 H, J = 6.6), 4.07 (s, 4 H), 4.55 (s, 4 H), 7.33 (app s, 10 H), 9.50 (t, 1 H, J = 1.8); IR (neat) 1723, 1621. Aldehyde **46** was also characterized as its oxime, mp 158–160 °C. Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.18; H, 6.86; N, 15.90. Found: C, 67.88; H, 6.87; N, 15.55.

(B) By Oxidative Cleavage. A solution of 75 mg (0.22 mmol) of alkene **16** in 2 mL of 2:1:1 acetone/2-methyl-2-propanol/water was treated with 20 μL of a 0.1 N osmium tetraoxide solution in water. The resulting dark brown solution was treated with 40 mg (0.34 mmol) of 4-methylmorpholine *N*-oxide and stirred for 2 h. The reaction was quenched with 50 mg of sodium bisulfite, and the volatiles were removed. The residue was partitioned between 20 mL of EtOAc and 3 mL of water. The organic layer was separated, dried, and concentrated. Chromatography on 4 g of silica with 40:1 CH_2Cl_2/methanol as the eluant afforded 78 mg (94%) of the diol as a solid, mp 112–113 °C: ^{1}H NMR 1.18–1.26 (m, 2 H), 2.20 (t, 1 H, J = 5.6), 2.47–2.54 (m, 1 H), 2.78–2.84 (m, 1 H), 3.27–3.33 (m, 1 H), 3.42–3.47 (m, 1 H), 3.59 (d, 1 H, J = 2.8), 3.60–3.68 (m, 1 H), 4.07 and 4.14 (AB q, 4 H, J = 12.0), 4.52 and 4.57 (AB q, 4 H, J = 15.2), 7.32 (app s, 10 H); FAB-MS 370 (M + 1)$^+$. Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.03; H, 7.12; N, 11.09.

A solution of 45 mg (0.12 mmol) of the diol and 32 mg (0.15 mmol) of sodium metaperiodate in 2 mL of 4:1 THF/water was stirred for 10 min. The reaction mixture was partitioned between 15 mL of ethyl ether and 5 mL of water. The aqueous layer was extracted with another 5 mL of ethyl ether. The combined organic layer was dried and concentrated. Chromatography on 3 g of silica gel with 2:1 ethyl ether/petroleum ether as the eluant afforded 34 mg (82%) of **46**.

Aldehyde **46** was also prepared by a one-pot oxidative cleavage of alkene **16**. Osmium tetraoxide (5.0 mg, 0.020 mmol) was added to a solution of 1.24 mmol of **16** in 15 mL THF and 5 mL of water. The reaction mixture was stirred for 5 min, during which time the solution turned dark brown. Sodium periodate (846.3 mg, 3.96 mmol) was then added slowly. TLC analysis showed that the reaction was complete in 10–15 min. The reaction mixture was filtered through Celite and concentrated. The residue was diluted with EtOAc, washed with water (2 × 7.5 mL), dried, and chromatograhed with 2:1 ether/petroleum ether as the eluant to give 337 mg of **46** (81%).

4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)butyraldehyde (47). (A) By Swern Oxidation. The general Swern procedure, with 100 μL (1.14 mmol) of oxalyl chloride, 120 μL (1.70 mmol) of DMSO, 1.0 mL (5.6 mmol) of DIPEA, and 15 mL of 0.5 N aqueous potassium bisulfate, was used to convert 200 mg (0.57 mmol) of **21** to **47**. Chromatography on 10 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 191 mg (96%) of **47** as an oil: ^{1}H NMR 1.37–1.44 (m, 2 H), 2.24 (td, 2 H, J = 6.8, 1.6), 2.45 (t, 2 H, J = 7.2), 4.06 (s, 4 H), 4.54 (s, 4 H), 7.32 (app s, 10 H), 9.54 (br s, 1 H): IR (neat) 1721, 1626. Aldehyde **47** was also characterized as its oxime, mp 128–130 °C. Anal. Calcd for $C_{21}H_{28}N_4O_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 68.74; H, 7.21; N, 15.03.

Aldehyde **47** was also prepared by oxidation with pyridinium chlorochromate.[47] Alcohol **21** (294.5 mg, 0.84 mmol) was added to a suspension of 414.3 mg (1.92 mmol) of pyridinium chlorochromate and 120 mg of 4-Å activated molecular sieves in 5 mL of CH_2Cl_2. The reaction mixture was stirred for 4 h and then filtered through Celite. Chromatography afforded 269 mg (91% yield) of **47**.

(B) By Oxidative Cleavage. Oxidative cleavage of 1.24 mmol of alkene **17** according to the one-pot procedure for **46**, and then chromatography with 2:1 ether–petroleum ether as the eluant, gave **47** in 81% yield.

1,3-Dibenzylhexahydro-5-hydroxy-2-oxo-1,3,5-triazine (49). A solution of 150 mg (0.4 mmol) of dibenzyltriazone **5b** in 3 mL of CH_2Cl_2 was treated with 62 mg (0.6 mmol) of *m*-chloroper-

(47) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

oxybenzoic acid. After 15 min, TLC analysis showed consumption of **5b** and formation of a new product (presumably the *N*-oxide **48**) with R_f 0.11 (with 19:1 CH_2Cl_2/methanol as the eluant). The reaction mixture was partitioned between 20 mL of ether and 10 mL of a 1 N aqueous sodium hydroxide, and then the organic layer was washed with brine, dried, and concentrated. TLC analysis of the reaction mixture at this point showed the presence of a second product at R_f 0.18. Chromatography on 7.5 g of silica with 30:1 CH_2Cl_2/methanol as the eluant afforded 46 mg of the higher R_f product and 82 mg of the lower R_f product. The two products were dried in vacuo at 23 °C for 12 h, whereupon TLC analysis indicated that the lower R_f product had been converted to the higher R_f product. The two products were combined, triturated with petroleum ether, and dried in vacuo to afford 103 mg (87%) of the hydroxylamine **49**, mp 144–146 °C: ^{1}H NMR 4.08 and 4.36 (AB q, 4 H, J = 11.5), 4.48 and 4.66 (AB q, 4 H, J = 15.4), 6.35 (s, 1 H), 7.23–7.32 (m, 10 H); IR 3263, 1613. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.60; H, 6.43; N, 14.26.

2-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)acetic Acid (50). A stirred solution of 150 mg (0.41 mmol) of ester **24** in 5 mL of absolute ethanol was treated with 1.0 mL of 1.0 N aqueous sodium hydroxide at 0 °C. After 15 min, the solution was concentrated, and the residue was partitioned between 15 mL of EtOAc and 5 mL of 0.5 N aqueous potassium bisulfate. The aqueous layer was extracted with an additional 10 mL of EtOAc. The combined organic layer was washed with 5 mL of brine, dried, and concentrated. The resulting solid was suspended in 5 mL of ethyl ether, filtered, and dried under high vacuum (1 Torr, 23 °C, 3 h) to afford 115 mg (82%) of **50**, mp 159–162 °C: ^{1}NMR 3.29 (s, 2 H), 4.19 (s, 4 H), 4.53 (s, 4 H), 7.30 (app s, 10 H); FAB-MS 340 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.99; H, 6.36; N, 12.16.

5-[4-(Benzyloxy)-1-butyl]-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (51). An oven-dried, 100-mL three-necked flask equipped with a stopper, septum, and argon balloon was charged with a solution of 150 mg (0.43 mmol) of alcohol **21** in 8 mL of THF. The solution was treated with 20 mg (0.48 mmol, 1.1 equiv) of 60% sodium hydride dispersion in mineral oil, 8 mg (0.02 mmol, 0.05 equiv) of tetrabutylammonium iodide, and 56 μL (0.48 mmol, 1.1 equiv) of benzyl bromide, and the resulting mixture was stirred for 20 h. The reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with 20 mL of ethyl ether. The organic layer was washed with 5 mL of brine, dried, and concentrated. Chromatography on 7.5 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 158 mg (84%) of **51** as an oil: ^{1}H NMR 1.11–1.19 (m, 2 H), 1.38–1.44 (m, 2 H), 2.44 (t, 2 H, J = 7.2), 3.30 (t, 2 H, J = 6.4), 4.07 (s, 4 H), 4.43 (s, 2 H), 4.53 (s, 4 H), 7.23–7.35 (m, 15 H); FAB-MS 444 $(M + 1)^+$.

5-(2-Azidoethyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (52). A solution of 125 mg (0.39 mmol) of alcohol **39**, 35 mg (0.29 mmol, 0.75 equiv) of 4-(dimethylamino)pyridine, and 200 μL (1.15 mmol, 3 equiv) of DIPEA in 5 mL of CH_2Cl_2 was treated with 88 mg (0.46 mmol, 1.2 equiv) of *p*-toluenesulfonyl chloride at 0 °C and then stirred at 23 °C for 6 h. The reaction was partitioned between 15 mL of ethyl ether and 5 mL of water, and the organic layer was dried and concentrated. Chromatography on 5 g of silica with 3:2 ethyl ether/petroleum ether as the eluant afforded 144 mg (78%) of the stable tosylate as an oil: ^{1}H NMR 2.43 (s, 3 H), 2.66 (t, 2 H, J = 5.4), 3.74 (t, 2 H, J = 5.4), 3.99 (s, 4 H), 4.50 (s, 4 H), 7.25–7.32 (m, 12 H), 7.67 (app d, 2 H, J = 8.2); ^{13}C NMR 21.6, 48.4, 49.6, 65.9, 67.9, 127.4, 127.8, 128.0, 128.6, 129.7, 132.8, 137.9, 144.8, 155.1. Anal. Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76; S, 6.69. Found: C, 64.96; H, 6.22; N, 8.58; S, 6.71.

A mixture of 110 mg (0.23 mmol) of the tosylate, 35 mg (0.23 mmol) of sodium iodide, 75 mg (1.15 mmol, 5 equiv) of sodium azide, and 1.5 mL of DMF was stirred at 80 °C for 4 h. The mixture was cooled and concentrated, and the residue was partitioned between 15 mL of ethyl ether and 5 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with water (2 × 5 mL), dried, and concentrated. Chromatography on 5 g of silica with 1:1 ethyl ether/petroleum ether as the eluant afforded 72 mg (90%) of **52** as an oil: ^{1}H NMR 2.61 (t, 2 H, J = 5.8), 2.93 (t, 2 H, J = 5.8), 4.11 (s, 4 H), 4.55 (s, 4 H), 7.33 (app s, 10 H); IR (neat) 2102, 1639; FAB-MS 351 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{22}N_6O$: C, 65.12; H, 6.33; N, 23.98. Found: C, 65.41; H, 6.38; N, 23.70.

5-(3-Azidopropyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (53). A stirred solution of 100 mg (0.29 mmol) of alcohol **20** and 250 μL (1.47 mmol, 5 equiv) of DIPEA in 5 mL of CH_2Cl_2 was treated with 110 μL (1.47 mmol, 5 equiv) of methanesulfonyl chloride at 0 °C. After 10 min, the reaction mixture was partitioned between 15 mL of ethyl ether and 5 mL of water. The organic layer was dried and concentrated to give the crude mesylate, which was immediately combined with 96 mg (1.47 mmol) of sodium azide and 1.5 mL of DMF and stirred at 80 °C for 1.25 h. The reaction was cooled and concentrated, and the residue was partitioned between 15 mL of ethyl ether and 5 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with water (3 × 5 mL), dried, and concentrated. Chromatography on 5 g of silica gel with 1:1 ethyl ether/petroleum ether as the eluant afforded 92 mg (87%) of **53** as an oil: ^{1}H NMR 1.22–1.33 (m, 2 H), 2.50 (t, 2 H, J = 7.0), 3.08 (t, 2 H, J = 6.6), 4.07 (s, 4 H), 4.55 (s, 4 H), 7.33 (app s, 10 H); IR (neat) 2097, 1640; CI-MS 365 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{24}N_6O$: C, 65.91; H, 6.64; N, 23.06. Found: C, 65.73; H, 6.73; N, 23.02.

5-(5-Azidopentyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (54). Compound **54** was prepared from alcohol **41** by the same procedure used for the preparation of **53**. Chromatography with 2:3 ether/petroleum ether as eluant gave **54** as an oil in 71% yield: ^{1}H NMR 0.90–1.04 (m, 2 H), 1.09–1.16 (m, 2 H), 1.37–1.42 (m, 2 H), 2.42 (t, 2 H, J = 7), 3.15 (t, 2 H, J = 7, 4.08 (s, 4 H), 4.54 (s, 4 H), 7.26 (br s, 10 H); IR 2096, 1639.

5-(4-Hydroxyhex-5-enyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (56). An oven-dried, 50-mL three-necked flask equipped with a stopper, septum, and argon balloon was charged with 4.0 mL of a 1.0 N solution of vinylmagnesium bromide in THF. The Grignard solution was cooled with an ice/ethanol bath for 15 min and then treated with a solution of 215 mg (0.64 mmol) of aldehyde **47** in 5 mL of THF. After 15 min, the reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate. The mixture was extracted with 25 mL of ethyl ether; the organic extract was washed with 5 mL of brine, dried, and concentrated. Chromatography on 10 g of silica with 2:1 ethyl ether/petroleum ether as the eluant afforded 182 mg (75%) of **56** as an oil: ^{1}H NMR 1.04–1.21 (m, 2 H), 1.31–1.42 (m, 2 H), 2.44 (t, 2 H, J = 6.8), 2.92 (br s, 1 H), 3.85–3.97 (m, 1 H), 4.07 (s, 4 H), 4.53 (s, 4 H), 5.03 (dt, 1 H, J = 12, 0.5), 5.10 (dt, 1 H, J = 18, 0.5), 5.72 (ddd, J = 18, 12, 7, 1 H), 7.31 (app s, 10 H); ^{13}C NMR 23.3, 34.6, 48.5, 50.5, 65.2, 72.2, 114.2, 127.3, 128.1, 128.5, 138.0, 141.0, 155.1.

5-(4-Hydroxybut-2-ynyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (57). An oven-dried, 100-mL three-necked flask equipped with a stopper, septum, and argon balloon was charged with a solution of 225 mg (0.71 mmol) of alkyne **15** in 6 mL of THF. The solution was stirred and cooled with a dry ice/acetone bath for 20 min, treated with 0.35 mL (1.05 equiv) of a 2.1 N *n*-butyllithium solution in hexanes, and then stirred for 10 min. The stopper of the reaction flask was removed, and 100 mg of paraformaldehyde was added as a moderate flow of argon was maintained over the solution. The stopper was replaced, and the reaction was warmed to 23 °C and stirred for 3.5 h. The reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with 15 mL of ethyl ether. The organic layer was washed with 5 mL of brine and dried. The combined aqueous layer was back-extracted with 15 mL of ethyl ether, which was dried and combined with the original organic layer, and the combined organic layer was concentrated. Chromatography on 10 g of silica with 4:1 ethyl ether/petroleum ether as the eluant afforded 196 mg (79%) of **57**, which slowly solidified on standing, mp 101–102 °C: ^{1}H NMR 2.14 (t, 1 H, J = 6.0), 3.37 (t, 2 H, J = 2.0), 4.09 (dt, 2 H, J = 6.0, 2.0), 4.19 (s, 4 H), 4.57 (s, 4 H), 7.33 (app s, 10 H); CI-MS 350 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.94; H, 6.66; N, 12.00.

Methyl 4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-2(*E*)-butenoate (58). A solution of 380 mg (1.18 mmol) of aldehyde **44** and 500 mg (1.50 mmol) of methyl (triphenylphosphoranylidene)acetate in 10 mL of benzene was heated at reflux for 1 h and then cooled and concentrated. Chromatography on 35 g of silica with 40:1 ethyl ether/CH_2Cl_2 as the eluant afforded 386 mg (87%) of ester **58** as a 10:1 *E*/*Z* mixture of isomers: ^{1}H NMR (*E* isomer in mixture) 3.18 (dd, 2 H, J = 6.0, 1.6), 3.70

(s, 3 H), 4.08 (s, 4 H), 4.53 (s, 4 H), 5.45 (dt, 1 H, J = 15.6, 1.6), 6.63 (dt, 1 H, J = 15.6, 6.0), 7.33 (app s, 10 H); CI-MS 380 (M + 1)$^+$. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.57; H, 6.65; N, 10.89.

5(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-(*R*,*S*)-hydroxyhexene (59). (A) By Grignard Reaction. An oven-dried, 50-mL three-necked flask equipped with a stopper, septum, and argon balloon was charged with 3 mL of a 1 N solution of allylmagnesium bromide in ethyl ether. The stirred Grignard solution was cooled with a dry ice/acetone bath for 15 min. A solution of 130 mg (0.39 mmol) of aldehyde **45** in 2 mL of ethyl ether was added slowly, and then the bath was removed and the mixture was stirred for 20 min. The reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate and then extracted with 20 mL of ethyl ether. The ether extract was washed with 5 mL of brine, dried, and concentrated. Chromatography on 5 g of silica with 2:1 and then 1:2 petroleum ether/ethyl ether as the eluant afforded 61 mg of **59-*syn*** and 31 mg of **59-*anti*** (R_f's 0.50 and 0.28, respectively, with ether as the eluant), both as oils (62% total). For **59-*syn***: ^{1}H NMR 0.90 (d, 3 H, J = 6.8), 1.91–1.99 (m, 1 H), 2.20–2.26 (m, 1 H), 2.52 (dq, 1 H, J = 7.6, 7.2), 2.97 (br s, 1 H), 3.17 (td, 1 H, J = 7.6, 3.6), 4.06 and 4.19 (AB q, 4 H, J = 12.0), 4.40 and 4.67 (AB q, 4 H, J = 15.2), 5.00–5.01 (m, 1 H), 5.04 (app s, 1 H), 5.71–5.81 (m, 1 H), 7.32 (app s, 10 H); FAB-MS 380 (M + 1)$^+$. For **59-*anti***: ^{1}H NMR 0.77 (d, 3 H, J = 6.8), 1.76–1.83 (m, 1 H), 2.02–2.09 (m, 1 H), 2.13 (br m, 1 H), 2.68 (qd, 1 H, J = 6.8, 2.8), 3.30–3.34 (m, 1 H), 4.18 and 4.21 (AB q, 4 H, J = 12.0), 4.27 and 4.77 (AB q, 4 H, J = 14.8), 4.98–5.00 (m, 1 H), 5.02–5.03 (m, 1 H), 5.46–5.54 (m, 1 H), 7.32 (app s, 10 H); FAB-MS 380 (M + 1)$^+$.

(B) By Allyltrimethylsilane Addition. A solution of 50 mg (0.15 mmol) of aldehyde **45** in 0.5 mL of CH_2Cl_2 was cooled with a dry ice/acetone bath for 15 min and then treated with 0.5 mL of a 1.0 N titanium tetrachloride solution in CH_2Cl_2. A thick precipitate formed. Allyltrimethylsilane (0.06 mL, 0.40 mmol) was added, and the resulting mixture was maintained at −78 °C for 1 h. The reaction was quenched and extracted as before. Chromatography on 4 g of silica with 20:1 and then 10:1 CH_2Cl_2/acetonitrile as the eluant afforded 14 mg of **45** and 22 mg of a 3:1 mixture (^{1}H NMR analysis) of **59-*syn*** and **59-*anti*** (total 55%, based on consumed **45**).

(C) By Allylstannane Addition. A solution of 105 mg (0.31 mmol) of **45** in 0.35 mL of CH_2Cl_2 was cooled with a dry ice/acetone bath for 15 min and then treated with 0.20 mL (1.6 mmol, 5.2 equiv) of boron trifluoride etherate and 0.31 mL (1.0 mmol, 3.2 equiv) of allyltributylstannane. The solution was stirred at −78 °C for 1 h and then 0 °C for 16 h. The reaction was quenched, extracted, and chromatographed as in A to afford 96 mg (80%) of a 1:3 mixture (^{1}H NMR analysis) of **59-*syn*** and **59-*anti***.

5-(3(*S*,*R*)-Hydroxy-5-oxo-2(*S*)-decyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (60). A solution of 50 mg (0.15 mmol) of **45** in 3 mL of CH_2Cl_2 was treated with 0.37 mL (2.5 equiv) of a tin tetrachloride solution in CH_2Cl_2 at −78 °C. After 10 min, a solution of 80 mg (0.43 mmol, 2.7 equiv) of 2-[(trimethylsilyl)oxy]-1-heptene in 0.5 mL of CH_2Cl_2 was added, and the resulting mixture was stirred at −78 °C for 3 h. The reaction was poured into a rapidly stirred mixture of 15 mL of ethyl ether and 10 mL of saturated aqueous ammonium chloride. The layers were separated; the organic layer was washed with 10 mL of saturated aqueous sodium bicarbonate and 10 mL of brine and then dried and concentrated. Chromatography on 5 g of silica with 9:1 CH_2Cl_2/ethyl ether as the eluant afforded 38 mg (57%) of **60-*syn*** and **60-*anti*** as a 10:1 mixture of diastereomers. A similar reaction was carried out with 45 μL (0.37 mmol) of boron trifluoride etherate as the Lewis acid. Chromatography afforded 42 mg (62%) of **60-*syn*** and **60-*anti*** as a 1:1 mixture. Careful chromatography of 80 mg of a 1:1 mixture of **60-*syn*** and **60-*anti*** on 7.5 g of silica with 3:2 hexanes/ethyl as the eluant afforded 40 mg each of **60-*syn*** and **60-*anti***. For **60-*syn***: ^{1}H NMR 0.87 (t, 3 H, J = 6.8), 0.88 (d, 3 H, J = 6.8), 1.20–1.31 (m, 4 H), 1.48–1.56 (m, 2 H), 2.36 (d, 2 H, J = 4.6), 2.37 (t, 2 H, J = 7.2), 2.62 (dq, 1 H, J = 6.6, 6.8), 2.98 (br s, 1 H), 3.66 (td, 1 H, J = 4.6, 6.6), 4.05 and 4.20 (AB q, 4 H, J = 12.0), 4.38 and 4.69 (AB q, 4 H, J = 14.8), 7.33 (app s, 10 H). For **60-*anti***: ^{1}H NMR 0.79 (d, 2 H, J = 6.8), 0.90 (t, 3 H, J = 7.2), 1.23–1.32 (m, 4 H), 1.54 (m, 2 H), 2.07 and 2.38 (two dd, 1 H each, J = 16.8, 6.0), 2.33 (t, 2 H, J = 6.8), 2.62 (qd, 1 H, J = 7.2, 3.2), 2.70 (br s, 1 H), 3.80–3.84 (m, 1 H), 4.17 and 4.22 (AB q, 4 H, J = 12.0), 4.39 and 4.67 (AB q, 4 H, J = 14.8), 7.33 (app s, 10 H).

General Procedure for the Hydrolysis of Dibenzyltriazones. A mixture of the dibenzyltriazone (1 equiv), 20% aqueous secondary amine solution (5 mL per mmol of dibenzyltriazone, titrated to pH 3 with concentrated aqueous hydrochloric acid), and methanol (5 mL per mmol of dibenzyltriazone) was heated at reflux. Disappearance of starting material was monitored by TLC. After 1–2 h, the reaction was cooled and the methanol removed in vacuo. The residue was partitioned between CH_2Cl_2 (10 mL per mmol of dibenzyltriazone) and 1.0 N aqueous hydrochloric acid (5 mL per mmol of dibenzyltriazone). The aqueous layer was extracted with a second portion of CH_2Cl_2 to completely remove dibenzylurea. The aqueous layer was then basified to pH >10 and extracted with three portions of CH_2Cl_2 (5 mL per mmol of dibenzyltriazone). The combined extract was concentrated to provide the primary amine.

Deprotection of Octylamine (as 61). Deprotection of 85 mg (0.22 mmol) of **14** following the general procedure with 20% aqueous diethanolamine afforded 23 mg (82%) of octylamine, which was characterized as its benzamide derivative, mp 42–44 °C (lit.[48] mp 43–45 °C): ^{1}H NMR 0.88 (t, 3 H, J = 6.8), 1.28–1.38 (m, 8 H), 1.58–1.66 (m, 2 H), 3.45 (td, 2 H, J = 7.2, 5.6), 6.91 (br s, 1 H), 7.40–7.51 (m, 3 H), 7.74–7.76 (m, 2 H).

Deprotection of Phenethylamine (as 62). Deprotection of 74 mg (0.19 mmol) of **5b** following the general procedure with 20% aqueous diethylamine afforded 19 mg (83%) of phenethylamine, which was characterized[49] as its acetamide: ^{1}H NMR 1.48 (d, 3 H, J = 6.8), 1.97 (s, 3 H), 5.09–5.19 (m, 1 H), 5.89 (br s, 1 H), 7.32 (app s, 5 H).

Deprotection of 6-Amino-2-methyl-2-heptanol (as 63). Deprotection of 65 mg (0.16 mmol) of **22** following the general procedure with 20% aqueous diethylamine afforded 21 mg (91%) of 6-amino-2-methyl-2-heptanol, which was characterized as its benzamide: ^{1}H NMR 1.20 (s, 3 H), 1.21 (s, 3 H), 1.25 (d, 3 H, J = 6.4), 1.43–1.61 (m, 6 H), 4.20–4.27 (m, 1 H), 5.91–5.93 (m, 1 H), 7.40–7.53 (m, 3 H), 7.74–7.83 (m, 2 H).

Deprotection of 5(*S*)-Amino-4(*S*)-hydroxyhexene (as 64). Deprotection of 130 mg (0.34 mmol) of **59-*syn*** following the general procedure with 20% aqueous diethanolamine afforded 31 mg (78%) of 5(*S*)-amino-4(*S*)-hydroxyhexene, which was characterized[19] as the *cis*-oxazolidinone **64**: ^{1}H NMR 1.20 (d, 3 H, J = 6.8), 2.32–2.39 (m, 1 H), 2.51–2.59 (m, 1 H), 3.94 (dt, 1 H, J = 13.2, 6.8), 4.61–4.66 (m, 1 H), 5.16 (dt, 1 H, J = 10.4, 1.6), 5.21 (t, 1 H, J = 1.6), 5.77–5.88 (m, 2 H).

Deprotection of 5(*S*)-Amino-4(*R*)-hydroxyhexene (as 65). Deprotection of 65 mg (0.18 mmol) of **59-*anti*** following the general procedure with 20% aqueous diethanolamine afforded 15 mg (74%) of 5(*S*)-amino-4(*R*)-hydroxyhexene, which was characterized[19] as the *trans*-oxazolidinone **65**: ^{1}H NMR 1.20 (d, 3 H, J = 6.0), 2.44–2.51 (m, 2 H), 3.63 (qd, 1 H, J = 6.0, 6.4), 4.17 (dt, 1 H, J = 6.4, 6.0), 5.17 (s, 1 H), 5.21 (dd, 1 H, J = 8.8, 1.2), 5.77–5.84 (m, 1 H), 5.84 (br s, 1 H); IR (neat) 1745.

Hexahydro-2-oxo-1,3,5,5-tetramethyl-1,3,5-triazinium Iodide (72). A mixture of 0.50 g (3.5 mmol) of hexahydro-2-oxo-1,3,5-trimethyl-1,3,5-triazine[2] (**71**) and 2.00 g (4 equiv) of iodomethane was stirred for 1 h. A precipitate formed immediately. Ether was added, and the precipitate was collected by filtration, giving 1.00 g (100%) of white solid, mp 162–164 °C: ^{1}H NMR (D_2O) 2.79 (s, 6 H), 3.15 (s, 6 H), 4.63 (s, 4 H); IR (KBr) 1672. Anal. Calcd for $C_7H_{16}IN_3O$: C, 29.49; H, 5.66; N, 14.74; I, 44.51. Found: C, 29.50; H, 5.56; N, 14.49; I, 44.78.

4-Aza-1,3-bis(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)octane (78). A mixture of 128 mg (0.35 mmol) of azide **53**, 5 mL of THF, 0.75 mL of 1.0 N solution of trimethylphosphine solution in THF, and 200 mg of activated 4-Å molecular sieves was stirred at 23 °C for 45 min. A solution of 125 mg (0.35 mmol) of aldehyde **47** in 5 mL of THF was added, and the resulting mixture was stirred for 30 min. The reaction mixture, which contained the imine **77**, was concentrated to a residue while the argon atmosphere was maintained. The residue was dissolved

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in 5 mL of absolute ethanol, and then 50 mg (1.32 mmol, 3.75 equiv) of sodium borohydride was added as a solid (under a stream of argon), and the resulting mixture was stirred at 23 °C for 20 h. The reaction was filtered, quenched with 2 mL of water, concentrated, and then partitioned between 20 mL of EtOAc and 10 mL of saturated aqueous sodium bicarbonate. The organic layer was dried and concentrated. Chromatography on 10 g of silica with 250:10:1 CH_2Cl_2/methanol/ammonium hydroxide as the eluant afforded 164 mg (69%) of the protected spermidine **78** as an oil: ^{1}H NMR 1.00–1.08 (m, 2 H), 1.17–1.26 (m, 4 H), 2.30 (t, 2 H, J = 7.2), 2.35 (t, 2 H, J = 6.8), 2.42 (t, 2 H, J = 7.2), 2.49 (t, 2 H, J = 7.2), 4.06 (s, 4 H), 4.08 (s, 4 H), 4.54 (s, 8 H), 7.31 (app s, 20 H); ^{13}C NMR 25.4, 27.2, 27.8, 47.5, 48.5, 48.8, 49.5, 50.4, 65.5, 127.2, 128.0, 128.5, 138.2, 155.2. Anal. Calcd for $C_{41}H_{51}N_7O_2$: C, 73.07; H, 7.63; N, 14.55. Found: C, 72.79; H, 7.58; N, 14.25.

5-(4-Azidobut-2(*E*)-enyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (79). An oven-dried 50-mL three-necked flask equipped with a septum, stopper, argon balloon, and magnetic stirbar was charged with 2.0 mL (1.3 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene and 5.0 mL of CH_2Cl_2. The reaction mixture was cooled with a dry ice/acetone bath for 20 min. A solution of 438 mg (1.16 mmol) of ester **58** in 5 mL of CH_2Cl_2 was slowly added via syringe, the cold bath was replaced with an ice bath, and then the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with 5 mL of 1.0 N aqueous sodium hydroxide and diluted with 15 mL of ethyl ether. The organic layer was washed with 5 mL of brine, dried, and concentrated. Crystallization of the product from 25 mL of 3:1 ethyl ether/petroleum ether afforded 256 mg (63%) of the allylic alcohol as a single stereoisomer, mp 140–142 °C: ^{1}H NMR 1.66 (t, 1 H, J = 5.4), 3.07 (d, 2 H, J = 6.4), 3.90 (m, 2 H), 4.09 (s, 4 H), 4.53 (s, 4 H), 5.11 (dt, 1 H, J = 15.6, 5.6), 5.43 (dt, 1 H, J = 15.6, 6.8), 7.33 (app s, 10 H); CI-MS 352 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.89; H, 7.19; N, 11.90.

A solution of 373 mg (1.42 mmol) of triphenylphosphine in 8 mL of acetonitrile was treated with bromine, added dropwise, until the solution was pale yellow. A few crystals of triphenylphosphine were added to consume the excess bromine. The solution was treated with 250 mg (0.71 mmol) of the above allylic alcohol, stirred for 10 min, and then concentrated. A solution of this crude allylic bromide and 238 mg (3.56 mmol, 5 equiv) of sodium azide in 4 mL of DMF was stirred at 80 °C for 3 h. The mixture was cooled and concentrated, and the residue was partitioned between 20 mL of ethyl ether and 10 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with water (2 × 10 mL), dried, and concentrated. Chromatography on 15 g of silica with 100:1 CH_2Cl_2/EtOAc as the eluant afforded 223 mg of **79** (82% yield, but slightly contaminated with the isomeric azide) as an oil: ^{1}H NMR 3.06 (d, 2 H, J = 6.6), 3.51 (d, 2 H, J = 5.2), 4.10 (s, 4 H), 4.53 (s, 4 H), 4.89 (dt, 1 H, J = 15.0, 6.6), 5.48 (dt, 1 H, J = 15.0, 5.2), 7.34 (app s, 10 H); CI-MS 377 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{24}N_6O$: C, 67.00; H, 6.43; N, 22.32. Found: C, 66.81; H, 6.40; N, 22.28.

4-Aza-1,3-bis(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)oct-6-ene (80). Coupling of 180 mg (0.48 mmol) of azide **79** and 170 mg (0.50 mmol) of aldehyde **46** was carried out by using a procedure identical to that used to prepare the parent protected spermidine **78**. Chromatography afforded 232 mg (72%) of **80** as an oil: ^{1}H NMR 1.18–1.26 (m, 2 H), 2.32 (t, 2 H, J = 7.2), 2.49 (t, 2 H, J = 6.8), 2.91 (d, 2 H, J = 6.0), 3.05 (d, 2 H, J = 6.8), 4.07 (s, 8 H), 4.52 (s, 4 H), 4.54 (s, 4 H), 5.05 (dt, 1 H, J = 15.4, 6.0), 5.30 (dt, 1 H, J = 15.4, 6.8), 7.32 (app s, 20 H); ^{13}C NMR 27.8, 47.0, 48.4, 50.8, 52.9, 65.0, 65.5, 127.3, 128.1, 128.5, 132.9, 138.2, 138.3, 155.3; CI-MS 672 $(M + 1)^+$.

5-(4-Azido-1-but-2-ynyl)-1,3-dibenzylhexahydro-2-oxo-1,3,5-triazine (82). A solution of 538 mg (2.05 mmol) of triphenylphosphine in 10 mL of acetonitrile was treated with bromine, added dropwise, until the solution was pale yellow. A few crystals of triphenylphosphine were added to consume the excess bromine. The solution was treated with 358 mg (1.03 mmol) of alcohol **57**, stirred for 10 min, and then concentrated. A mixture of the crude propargylic bromide, 345 mg (5.15 mmol, 5 equiv) of sodium azide, and 5 mL of DMF was heated at 80 °C for 5 h. The mixture was cooled, concentrated, and partitioned between 20 mL of ethyl ether and 10 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with 10 mL of brine, dried, and concentrated. Chromatography on 20 g of silica with 9:1 and then 4:1 chloroform/EtOAc as the eluant afforded 287 mg (75%) of azide **82** as an oil: ^{1}H NMR 3.82 (s, 2 H), 4.09 (s, 4 H), 4.22 (s, 2 H), 4.57 (s, 4 H), 7.27 (app s, 10 H); ^{13}C NMR 44.3, 45.1, 48.9, 65.5, 127.4, 127.9, 128.6, 137.6, 155.3; IR (neat) 2098, 1614.

4-Aza-1,8-bis(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)oct-6-yne (83). Coupling of 160 mg (0.43 mmol) of azide **82** and 150 mg (0.44 mmol) of aldehyde **46** was carried out by using a procedure identical to that used to prepare the parent protected spermidine **78**. Chromatography afforded 138 mg (48%) of **83** as an oil: ^{1}H NMR 1.16–1.24 (m, 2 H), 2.36 (t, 2 H, J = 6.8), 2.49 (t, 2 H, J = 7.0), 3.57 (s, 2 H), 3.76 (s, 2 H), 4.40 (s, 4 H), 4.05 (s, 4 H), 4.52 (s, 4 H), 4.54 (s, 4 H), 7.29 (app s, 10 H); ^{13}C NMR 27.5, 43.0, 45.1, 46.8, 48.5, 48.9, 65.4, 127.3, 127.6, 127.9, 128.5, 137.9, 139.8, 142.5, 155.2; IR (neat) 2237, 1633.

Spermidine (74), 6,7-Didehydrospermidine (81), and 6,6,7,7-Tetradehydrospermidine (84). The general procedure was used to separately hydrolyze 50–100-mg samples of **78**, **80**, and **83** (1.0 N aqueous hydrochloric acid/methanol or 20% aqueous piperidine at pH 3 were used). The reaction mixture was cooled and partioned between CH_2Cl_2 and 1.0 N aqueous hydrochloric acid (1 mL per 10 mg of starting material for both layers). The aqueous layer was concentrated. Ion-exchange chromatography of the residue on Dowex 50X8-400 ion-exchange resin (500 mg per 10 mg of starting material; the resin was prewashed with ethanol) with 100:0, 20:1, and then 4:1 ethanol/ammonium hydroxide as the eluant afforded the polyamines **74**, **81**, and **84**, respectively. Dried under high vacuum (1 Torr, 23 °C, 20 h), the products had spectral characteristics (^{1}H NMR, ^{13}C NMR, IR) matching those of an authentic sample (for **74**), or reported in the literature (for **81** and **84**).[27] In the 400-MHz ^{1}H NMR spectrum, **84** showed small singlets at 5.60 and 5.67, possibly $-OCH_2Cl$ impurities, amounting to about 1–2% each.

7-Aza-2(*S*),11-diaminoundecanoic Acid Dihydrochloride, Deoxyhypusine (85). Aqueous hydrochloric acid (1.0 mL of a 0.2 N solution) was added dropwise to a refluxing solution of 104.0 mg (0.15 mmol) of **88** and 64.9 mg (0.64 mmol) of diethylamine hydrochloride in 5 mL of EtOAc. The solution was cooled to 23 °C, and then 63.9 mg of 5% palladium-on-activated-carbon catalyst was added. The reaction mixture was stirred under a hydrogen atmosphere for 2 h. The reaction mixture was filtered through Celite and chromatographed with 1:2:1 CH_2Cl_2/methanol/ammonia as the eluant to give 27.4 mg (85% yield) of **85** as an oil: ^{1}H NMR (D_2O) 1.3–1.9 (m, 10 H), 2.8–3.0 (m, 6 H), 3.85 (t, 1 H, J = 7); ^{13}C NMR (150 MHz, D_2O) 23.96, 25.16, 26.39, 27.62, 32.23, 41.28, 49.26, 49.60, 56.85, 176.74; IR 3429, 1610; $[\alpha]$ +17.41° (c = 0.85, 6 N HCl).

7-Aza-2(*S*),11-diamino-9(*R*)-hydroxyundecanoic Acid Dihydrochloride, Hypusine (86). Aqueous hydrochloric acid (2 N, 1.2 mL) was added to a stired solution of 86.2 mg (0.13 mmol) of **99** and 97.9 mg (0.96 mmol) of diethylamine hydrochloride in 7 mL of EtOAc at 80 °C. The reaction mixture was cooled to 23 °C, 0.5 mL of 4 N aqueous hydrochloric acid was added, and then the solution was stirred overnight. The reaction mixture was concentrated, neutralized with 10% aqueous sodium bicarbonate, and then concentrated to dryness. The residue was chromatographed with 1:2:1 CH_2Cl_2/methanol/ammonia as the eluant to give 25.5 mg (83% yield) of hypusine (**86**) as the free base. The compound was dissolved in 0.5 mL of water, the pH was adjusted to 5.2, and the resulting white solid was collected by filtration and dried in vacuo to give 28.5 mg of **86·2HCl**, mp 237–238 °C: ^{1}H NMR (D_2O) 1.2–1.8 (m, 8 H), 2.8–3.0 (m, 6 H), 3.75 (t, 1 H, J = 6), 3.85 (app t, 1 H); ^{13}C NMR (150 MHz, D_2O) 24.01, 27.53, 32.42, 33.90, 38.92, 49.78, 54.57, 56.99, 67.29, 177.26; IR 3400, 1624; $[\alpha]$ +7.8° (c = 0.52, 6 N HCl) [lit.[35] $[\alpha]$ +6.8°, +9.9° (c = 0.12, 6 N HCl), lit.[36] $[\alpha]$ +7.2° (c = 0.25, 6 N HCl), lit.[37] $[\alpha]$ +8.3° (c = 0.96, 6 N HCl)].

Benzyl 7-Aza-7-(benzyloxycarbonyl)-2(*S*)-[(benzyloxycarbonyl)amino]-11-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)undecanoate (88). A suspension of 364.0 mg (0.67 mmol) of benzyl $N(\alpha)$-(benzyloxycarbonyl)lysinate p-toluenesulfonate (**87**), 74.8 mg (0.71 mmol) of sodium carbonate, and 1 g of activated 4-Å molecular sieves in 5 mL of THF was stirred at 23 °C for 0.5 h. A solution of 238.3 mg (0.68 mmol) of aldehyde

47 in 15 mL of THF was added. The solution was stirred for 2 h, and then 16.38 mg (0.28 mmol) of solid sodium cyanoborohydride was added in one portion. The reaction mixture was stirred for 2 h, filtered through Celite, concentrated, and then partitioned between 20 mL of CH_2Cl_2 and 5 mL of water. The organic layer was washed with 2 × 5 mL of saturated aqueous sodium carbonate and dried. Chromatography with 200:15:1 CH_2Cl_2/methanol/ammonia as the eluant gave 250 mg (52% yield) of the coupled secondary amine. This product was dissolved in a mixture of 6 mL of THF and a solution of 50.1 mg (0.47 mmol) of sodium carbonate in 1 mL of water. Benzylchloroformate (90.0 μL, 0.63 mmol) was added, and the reaction mixture was stirred for 2 h. Concentration and chromatography with 3:2 EtOAc/petroleum ether as the eluant gave 220.1 mg (74% yield) of 88 as an oil: ^{1}H NMR 0.9–1.5 (m, 8 H), 2.3–2.45 (m, 2 H), 3.0–3.2 (m, 4 H), 4.05 (d, 4 H), 4.37–4.41 (m, 1 H), 4.5 (s, 4 H), 5.0–5.2 (m, 6 H), 5.56–5.61 (m, 1 H), 7.2–7.36 (m, 25 H); ^{13}C NMR 21.20, 22.19, 24.69, 25.32, 25.74, 27.17, 27.97, 31.51, 32.14, 46.29, 46.92, 48.31, 50.05, 53.71, 65.32, 66.78, 126.88, 127.17, 127.66, 127.71, 127.98, 128.12, 128.36, 135.18, 136.08, 136.70, 138.16, 155.12, 155.83, 172.07; IR 3422, 1722, 1635; FAB-MS 841 $(M + 1)^+$. Anal. Calcd for $C_{50}H_{57}N_5O_7$: C, 71.50; H, 6.84; N, 8.34. Found: C, 71.44; H, 6.56; N, 8.14.

***tert*-Butyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-hydroxybutyrate (92) and Mosher Ester Analysis.** A suspension of 330.2 mg (0.61 mmol) of aspartate **36** and 30.2 mg of 10% palladium-on-activated-carbon catalyst in 7 mL of methanol was stirred under an atmosphere of hydrogen for 20 min. The mixture was filtered through Celite and concentrated to give 262.7 mg (96% yield) of the aspartate half ester as a white solid, mp 47–48 °C: ^{1}H NMR 1.41 (s, 9 H), 2.51 (t, 2 H, J = 7), 3.74 (t, 1 H, J = 7), 4.20 (s, 4 H), 4.35 (d, 2 H, J = 15), 4.73 (d, 2 H, J = 15), 7.29–7.34 (m, 10 H); IR 1727, 1610. Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27. Found: C, 66.23; H, 6.84; N, 9.17. A solution of 1.88 g (4.14 mmol) of the aspartate half ester in 14 mL of DME was stirred at −20 °C. *N*-Methylmorpholine (460 μL, 4.18 mmol) was added, and then 540 μL (4.16 mmol) of isopropyl chloroformate was added slowly. After 5 min, the reaction was allowed to warm to 0 °C. A solution of 998.6 mg (26.28 mmol) of sodium borohydride in 1.5 mL of water was added, followed immediately by 2.5 mL of water. The reaction mixture was allowed to warm to 23 °C and then extracted with 30 mL of EtOAc. The organic layer was washed with 2 × 10 mL of water and then dried. Chromatography with 1:1 EtOAc/petroleum ether as the eluant afforded 1.41 g (87% yield) of the alcohol **92** as an oil: ^{1}H NMR 1.4 (s, 9 H), 1.55–1.65 (m, 2 H), 3.47–3.59 (m, 2 H), 4.18 (d, 2 H, J = 12), 4.23 (d, 2 H, J = 12), 4.38 (d, 2 H, J = 15), 4.69 (d, 2 H, J = 15), 7.27–7.35 (m, 10 H); IR 3439, 1723, 1639. Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 66.31; H, 7.57; N, 9.56. Found: C, 66.28; H, 7.61; N, 9.31.

Alcohol **92** (28.7 mg, 0.066 mmol) was converted to its (*S*)-Mosher ester by using the general procedure. Chromatography with 2:1 EtOAc/petroleum ether as the eluant gave 39.1 mg (88% yield) of the (*S*)-Mosher ester as an oil: ^{1}H NMR 1.40 (s, 9 H), 1.72–1.78 (m, 2 H), 3.36 (t, 2 H, J = 7), 3.48 (s, 3 H), 4.12 (s, 4 H), 4.15–4.25 (m, 1 H), 4.27–4.31 (d, 2 H, J = 15), 4.73 (d, 2 H, J = 15), 7.22–7.48 (m, 15 H); IR 1748, 1643. A corresponding epimeric mixture of (*R* and *S*)-Mosher esters was likewise prepared by starting with racemic Mosher acid. Comparison of the well-resolved CH_3O– singlets and the –CH_2O– triplets in the ^{1}H NMR spectra of both samples indicated that the ester of **92** contained no observable (<0.5%) diastereomer.

***tert*-Butyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-oxobutyrate (93).** Oxidation of alcohol **92** by using the general Swern procedure afforded aldehyde **93** as an oil in 92% yield: ^{1}H NMR 1.39 (s, 9 H), 2.35 and 2.54 (two dd, 1 H each, J = 17, 8), 3.76 (dd, 1 H, J = 8, 5), 4.18 (s, 4 H), 4.34 (d, 2 H, J = 15), 4.72 (d, 2 H, J = 15), 7.26–7.36 (m, 10 H), 9.50 (s, 1 H); IR 1724, 1643. Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.29; H, 7.31; N, 9.21.

***tert*-Butyl 2(*S*)-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-6-oxohexanoate (94).** A mixture of 140.3 mg (0.32 mmol) of aldehyde **93**, 375.8 mg (1.20 mmol) of (formylmethylene)triphenylphosphorane, and 5 mL of toluene was refluxed for 1 h, during which time the (formylmethylene)triphenylphosphorane dissolved and the solution turned dark red. The solvent was removed under reduced pressure and the residue chromatographed with 1:1 EtOAc/petroleum ether as the eluant to afford 90.7 mg (61% yield) of the unsaturated aldehyde as an oil: ^{1}H NMR 1.34 (s, 9 H), 2.13–2.30 (m, 2 H), 3.5 (t, 1 H, J = 6), 4.18 (s, 4 H), 4.30 (d, 2 H, J = 15), 4.75 (d, 2 H, J = 15), 5.84–5.90 (m, 1 H), 6.50–6.57 (m, 1 H), 7.27–7.37 (m, 10 H), 9.40 (d, 1 H, J = 8); IR 1731, 1690, 1642.

A suspension of 228.4 mg (0.49 mmol) of the unsaturated aldehyde and 51.5 mg of 10% palladium-on-activated-carbon catalyst in 5 mL of EtOAc was stirred under an atmosphere of hydrogen for 20 min. The reaction mixture was filtered through Celite and chromatographed with 2:3 EtOAc/petroleum ether as the eluant to afford 182.2 mg (79% yield) of aldehyde **94** as an oil: ^{1}H NMR 1.36–1.43 (m, 13 H), 2.20–2.25 (m, 2 H), 3.30 (t, 1 H, J = 6), 4.13 (d, 2 H, J = 12), 4.24 (d, 2 H, J = 16), 4.33 (d, 2 H, J = 15), 4.73 (d, 2 H, J = 15), 7.2–7.4 (m, 10 H), 9.65 (s, 1 H); IR 1725, 1645. Anal. Calcd for $C_{27}H_{35}N_3O_4$: C, 69.65; H, 7.58; N, 9.03. Found: C, 70.00; H, 7.72; N, 8.92.

3(*R*)-Hydroxy-3-carbomethoxypropanamide (96). A solution of 2.33 g (33.84 mmol) of sodium nitrite in 30 mL of water was added dropwise to a stirred solution of 2.24 g (16.92 mmol) of D-asparagine (**95**) in 150 mL of 20% aqueous acetic acid at 0 °C. The reaction mixture was stirred overnight at 0 °C and then allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 12 h and then concentrated under reduced preasure. The residue was dissolved in 30 mL of methanol and cooled to 0 °C. Hydrogen chloride gas was bubbled into the solution until the pH reached 1 (a white solid precipitated almost immediately). The reaction mixture was allowed to warm to room temperature, at which time TLC analysis showed that the reaction was complete. The reaction mixture was filtered through silica with THF as the eluant. Chromatography with 9:1 EtOAc/methanol as the eluant gave 1.82 g (73% yield) of **96** as a white solid, mp 67–68 °C: ^{1}H NMR 2.51–2.64 (m, 2 H), 3.59 (s, 3 H), 4.42 (t, 1 H, J = 6); IR 1735, 1666.

4-[(*tert*-Butoxycarbonyl)amino]-1,2(*R*)-butanediol (97) and Configurational Analysis of Its Diacetate Derivative. A 1 N solution of borane in THF (32.0 mL) was added to a stirred suspension of 977.1 mg (6.64 mmol) of amide ester **96** in 10 mL of THF at 23 °C. After 6 h, the excess diborane was quenched by the slow addition of 4 N aqueous hydrochloric acid. The reaction mixture was allowed to stir overnight, and then was concentrated, neutralized with 10% aqueous sodium hydroxide, concentrated to dryness under reduced pressure, and then redissolved in 20 mL of methanol. Di-*tert*-butyl dicarbonate (1.15 g, 5.28 mmol) was added, and the reaction mixture was stirred for 2 h. Concentration and chromatography with EtOAc as the eluant gave 993.0 mg (73% yield) of **97** as an oil: ^{1}H NMR 1.42 (s, 9 H), 1.48–1.55 (m, 2 H), 3.09–3.16 (m, 1 H), 3.40–3.50 (m, 2 H), 3.57–3.60 (m, 1 H), 3.70–3.78 (m, 1 H), 4.65 (br s, 1 H); IR 3380, 1688. Anal. Calcd for $C_9H_{19}N_4O$: C, 52.66; H, 9.33; N, 6.82. Found: C, 52.10; H, 9.73; N, 6.58.

A solution of 38.3 mg (0.19 mmol) of **97**, 3.2 mg (0.026 mmol) of 4-(dimethylamino)pyridine, and 150.0 μL (1.59 mmol) of acetic anhydride in 1.5 mL of pyridine was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the crude mixture purified by chromatography with 1:3 EtOAc/petroleum ether as the eluant to give 43.6 mg (81% yield) of the diacetate as an oil: ^{1}H NMR 1.43 (s, 9 H), 1.73–1.80 (m, 2 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.97–3.06 (m, 1 H), 3.28–3.35 (m, 1 H), 4.04–4.08 (m, 1 H), 4.21–4.24 (m, 1 H), 4.81 (br s, 1 H), 5.11–5.17 (m, 1 H); IR 3376, 1744, 1694.

Small portions (up to 1 equiv) of the chiral shift reagent tris[(trifluoromethyl)hydroxymethylene-(−)-camphorato]europium(III) were added to a deuteriochloroform solution of the diacetate, and the chemical shifts of the (complexed) acetate singlets were monitored in the ^{1}H NMR spectrum. For comparison, parallel complexation studies of the diacetate of *rac*-**97** [prepared by hydroxylation of 4-[(*tert*-butoxycarbonyl)amino]-butene] were also carried out. A signal for complexed acetate corresponding to less than 5% of the undesired 2*S*-enantiomer was observed.

1-Amino-4-[(*tert*-butoxylcarbonyl)amino]-2(*R*)-butanol (98). Diol **97** was converted to the primary azide by the same procedure used for **20** → **53**. Chromatography with 1:2 EtOAc/petroleum ether as the eluant gave the azide as an oil in 54%

yield: ^{1}H NMR 1.4 (s, 9 H), 1.54–1.59 (m, 2 H), 3.12–3.16 (m, 1 H), 3.29–3.31 (m, 2 H), 3.45–3.54 (m, 1 H), 3.74–3.85 (m, 2 H), 4.85 (br s, 1 H); IR 2102, 1688.

A suspension of 191.3 mg (0.83 mmol) of the azide and 32.9 mg of 10% palladium-on-activated-carbon catalyst in 5 mL of methanol was stirred under an atmosphere of hydrogen for 30 min. The reaction mixture was filtered through Celite and concentrated to afford 170.8 mg (100%) of **98** as a white solid, mp 81–83 °C: ^{1}H NMR 1.45 (s, 9 H), 1.46–1.60 (m, 2 H), 2.58–2.62 (m, 1 H), 2.72–2.78 (m, 1 H), 2.95 (br s, 1 H), 3.12–3.18 (m, 1 H), 3.34–3.40 (m, 1 H), 3.56–3.62 (m, 1 H), 5.28–5.34 (m, 1 H); IR 3372, 1691.

***tert*-Butyl 7-Aza-2(*S*)-[(*tert*-butoxycarbonyl)amino]-11-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)-9(*R*)-hydroxyundecanoate (99).** A suspension of 37.8 mg (0.081 mmol) of lysine ϵ-aldehyde **94**, 19.1 mg (0.093 mmol) of amino alcohol **98**, and 1 g of activated 4-Å molecular sieves in 5 mL of benzene was stirred at room temperature for 3 h and then filtered. The solvent was removed under reduced pressure, the residue was dissolved in 5 mL of THF, and then 7.6 mg of platinum oxide catalyst was added. The reaction mixture was hydrogenated at 23 °C and atmospheric pressure for 6 h. The reaction mixture was filtered through Celite and chromatographed with 200:20:1 CH_2Cl_2/methanol/ammonia as the eluant to give 30.6 mg (58% yield) of **99** as an oil: ^{1}H NMR 1.10–1.75 (m, 10 H), 1.36 and 1.43 (two s, 9 H each), 2.48–2.54 (m, 4 H), 2.68–2.74 (m, 2 H), 3.2–3.4 (m, 3 H), 3.70–3.78 (m, 1 H), 4.13 and 4.19 (AB q, 4 H, J = 12), 4.35 and 4.70 (two d, 1 H each, J = 15), 5.02–5.12 (m, 1 H), 7.26–7.36 (m, 10 H); IR 3328, 1710, 1635. Anal. Calcd for $C_{36}H_{55}N_5O_6$: C, 64.93; H, 8.33; N, 10.52. Found: C, 64.64; H, 8.60; N, 10.21.

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Registry No. **2** (R^2 = CH_2Ph), 1466-67-7; (*S*)-**4**, 2627-86-3; (*S*)-**5b**, 143565-19-9; **9**, 143565-20-2; **10**, 143565-21-3; **14**, 143565-22-4; **15**, 143565-23-5; **16**, 143565-24-6; **17**, 143565-25-7; **18**, 143565-26-8; **19**, 143565-27-9; **20**, 143565-28-0; **21**, 130750-01-5; **22**, 143565-29-1; **23**, 143565-30-4; **24**, 143565-31-5; **25**, 143565-32-6; **26**, 143565-33-7; **27**, 143565-34-8; **28**, 143565-35-9; **29**, 130750-08-2; **30**, 143565-36-0; **31**, 143591-06-4; **32**, 143565-37-1; **33**, 143565-38-2; **34**, 143565-39-3; **35**, 143565-40-6; **36**, 143565-41-7; **37**, 143565-42-8; **39**, 143565-43-9; **39** (tosylate), 143565-85-9; **40**, 143565-44-0; **40** (*S*-Mosher ester), 143565-83-7; **41**, 143565-45-1; **42**, 143565-46-2; **43**, 143565-47-3; **44**, 143565-48-4; **45**, 143565-49-5; **46**, 143565-50-8; **47**, 130750-14-0; **48**, 143591-07-5; **49**, 143565-51-9; **50**, 143565-52-0; **51**, 143565-53-1; **52**, 143565-54-2; **53**, 143565-55-3; **54**, 143565-56-4; **56**, 143565-57-5; **57**, 143565-58-6; (*E*)-**58**, 143565-59-7; (*Z*)-**58**, 143565-86-0; *syn*-**59**, 143565-60-0; *anti*-**59**, 143565-87-1; *syn*-**60**, 143565-61-1; *anti*-**60**, 143565-88-2; **61**, 2772-60-3; **62**, 19144-86-6; **63**, 34021-62-0; **64**, 143616-44-8; **65**, 143616-45-9; **71**, 18213-80-4; **72**, 130750-13-9; **74**, 124-20-9; **78**, 143565-69-9; **79**, 143565-70-2; **80**, 143565-71-3; **81**, 110319-65-8; **82**, 143565-72-4; **83**, 143565-73-5; **84**, 110319-63-6; **85**·2HCl, 143565-74-6; **86**·2HCl, 82310-93-8; **86** (free base), 34994-11-1; **87**, 5361-91-1; **88**, 143565-75-7; **92**, 143565-76-8; **92** (*R*-Mosher ester), 143565-65-5; **92** (*S*-Mosher ester), 143565-64-4; **93**, 143565-77-9; **94**, 143565-78-0; **95**, 2058-58-4; **96**, 143565-79-1; **97**, 143565-80-4; (±)-**97** (diacetate), 143616-46-0; **98**, 143565-81-5; **99**, 143565-82-6; BnNCO, 3173-56-6; $BnNH_2$, 100-46-9; $HC{\equiv}CCH_2NH_2$, 2450-71-7; H-Ser-OEt·HCl, 26348-61-8; $Ph_3P^+Me{\cdot}Br^-$, 1779-49-3; $CH_3(CH_2)_7NH_2$, 111-86-4; $H_2C{=}CHCH_2CH_2NH_2{\cdot}HCl$, 17875-18-2; $H_2C{=}CH(CH_2)_3NH_2$, 22537-07-1; (*E*)-$HOCH_2CH{=}CHCH_2$-DBT, 143565-62-2; (*S*)-$HOOCCH_2CH$(COOBu-*t*)-DBT, 143565-63-3; $Ph_3P{=}CHCHO$, 2136-75-6; $OHCCH{=}CHCH_2$-(*S*)-CH(COOBu-*t*)-DBT, 143565-66-6; (*R*)-$BocNHCH_2CH_2CH(OAc)CH_2OAc$, 143565-67-7; (*R*)-$BocNHCH_2CH_2CH(OH)CH_2N_3$, 143565-68-8; 3-$MeC_6H_4NH_2$, 108-44-1; 4-$IC_6H_4NH_2$, 540-37-4; $HO(CH_2)_3NH_2$, 156-87-6; $HO(CH_2)_4NH_2$, 13325-10-5; $HOCMe_2(CH_2)_3CH(NH_2)CH_3{\cdot}HCl$, 543-15-7; (*S*)-$HOCH_2CH(NH_2)CH_3$, 2749-11-3; H-Gly-OEt·HCl, 623-33-6; $EtO_2CCH_2CH_2NH_2{\cdot}HCl$, 4244-84-2; $EtO_2C(CH_2)_3NH_2{\cdot}HCl$, 6937-16-2; $EtO_2C(CH_2)_4NH_2{\cdot}HCl$, 29840-57-1; $EtO_2C(CH_2)_5NH_2{\cdot}HCl$, 3633-17-8; H-Ala-OEt·HCl, 1115-59-9; H-Ala-OBn·TsOH, 42854-62-6; Boc-Ser(Bn)-OMe, 80963-10-6; H-Ser(Bn)-OEt·HCl, 58178-57-7; Boc-Lys(Z)-OMe, 73548-77-3; H-Asp(OBn)-OBu-*t*, 94347-11-2; $HOCH_2CH(OH)CH_2CH_2$-DBT, 143565-84-8; $Ph_3P{=}CHCO_2Me$, 2605-67-6; $H_2C{=}CHCH_2MgBr$, 1730-25-2; $H_2C{=}CHCH_2SiMe_3$, 762-72-1; $H_2C{=}CHCH_2SnBu_3$, 24850-33-7; $C_5H_{11}C(OSiMe_3){=}CH_2$, 19980-26-8; *N*,*N*′-dicyclohexylurea, 2387-23-7; α-amino-γ-butyrolactone hydrobromide, 6305-38-0.

Supplementary Material Available: ^{13}C NMR spectrum of synthetic hypusine (**86**), ^{1}H NMR spectra of (*S*)-Mosher esters from the configurational study of **45**, ^{1}H NMR spectra of (*S*)- and (*RS*)-Mosher esters of **92**, and ^{1}H NMR spectra of the diacetate of **97** with added chiral shift reagent (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.