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 (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 20% DMF in toluene to give a yellow powder (21 mg, 56%).³¹H NMR (DMF-d₇, 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), 7.92 (d, 1 H, J = 8.4), 7.30 (d, 1 H, J = 8.1), 7.13 (t, 1 H, J = 8.1), 7.04 (t, 1 H, J = 8.1), 7.04 (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) 358 nm (ε = 53 400); FABMS m/e (relative intensity) 785 (M + H)₂, 784 (M + H), 779 (M + H), 783 (M + H), 755 (M + H), 752 (M + H), 735 (M + H), 723 (M + H), 711 (M + H); FABHRMS m/e 701.2399 (M + H) (Found: 701.2394); [α]⁺D = +37.3° (c = 0.165, 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: ¹H NMR (DMF-d₇, 300 MHz, ppm) 13.08 (s, 1 H), 11.84 (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 (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) 387 nm (ε = 32 100); FABMS m/e (relative intensity) 701 (M + H), 504 (4), 436 (4), 411 (6), 274 (6), 196 (17), 123 (100); FABHRMS m/e 701.2398 (M + H) (Found: 701.2394); [α]⁺D = +37.3° (c = 0.165, 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 ¹H 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.

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Synthesis of Hypusine and Other Polyamines Using Dibenzyltriazones for Amino Protection

Spencer Knapp,* Jeffrey J. Hale, Margarita Bastos, Audrey Molina, and Kuang Yu Chen*

Department of Chemistry, Rutgers The State University of New Jersey, New Brunswick, New Jersey 08903

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The use of 1,3-dibenzy1-5-substituted-hexahydro-2-oxo-1,3,5-triazine ("triazone") 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 54 are particularly valuable building blocks, as demonstrated by the syntheses of hypusine (86), deoxyhypusine (88), 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 -NH₂, 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 ³⁻⁴ Triazones 3 may be formed from a primary amine 1, an Nₓ₂ di-

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(b) Petersen, H. Synthesis 1973, 243.

Optimization of Triazole Formation. Although the earlier studies² indicated that triazones 3 could serve as useful amino protecting groups, the quandary of choosing...
the appropriate urea N-substituent (R² in 2 and 3) remained. These studies pointed to "dimethyltriazones" (3, R² = Me) and "dibenzyltriazones" (3, R² = CH₂Ph) 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.

\[
\begin{align*}
\text{Method} & \quad \text{Reaction Conditions} & \quad \text{Yield} \\
\text{"Lit"} & \quad N,N'-dimethylurea, aq CH₃O₂, iPr₂EtN, EOH, reflux & \quad 96\% (5a) \\
\text{"Lit"} & \quad N,N'-dibenzylurea, aq CH₃O₂, iPr₂EtN, EOH, reflux & \quad <20\% (5b) \\
\text{"A"} & \quad N,N'-dibenzylurea, aq CH₂O₂, dioxane, iPr₂EtN, then add toluene, 84-100 °C with water separation & \quad 32\% (5b) \\
\text{"B"} & \quad (1) \text{aq CH₂O₂, iPr₂EtN, then add toluene and concentrate to a residue} & \quad 94\% (5b) \\
& \quad (2) N,N'-dibenzylurea, EtOAc, reflux &
\end{align*}
\]

N,N'-Dimethylurea was obtained commercially, whereas N,N'-dibenzylurea was prepared from benzylisocyanate and benzylamine (see Experimental Section). Diisopropylethyamine was added in each case to neutralize the reaction mixture. Commercial formalin contains varying amounts of formic acid. The procedure modeled after literature precedent 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 azetropic 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 may also be carried out in tetrahydrofuran or toluene solution, depending upon the reaction temperature necessary.

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. The nature of the amine–formaldehyde adduct 6 is suggested by 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 (diisopropylethyamine 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 can occur as a side reaction when using either method A or B. For example, the cyclized 2:1 formaldehyde–dibenzylurea adduct, 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.

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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 dibenzyltriazones 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* refers to 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 N1,N3-dicyclohexyltriazone derivative 37 in 72% yield, whereas the bulky cyclohexyl groups prevent N,N'-dicyclohexylurea from forming triazones under other conditions.

![Scheme I](image)

**Table I. Synthesis of Dibenzyltriazones from Primary Amines**

<table>
<thead>
<tr>
<th>product no.</th>
<th>structure</th>
<th>yield (method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td><img src="image" alt="Structure 1" /></td>
<td>91% (B)</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 2" /></td>
<td>0% (A)</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Structure 3" /></td>
<td>78% (B)</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Structure 4" /></td>
<td>90% (B)</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Structure 5" /></td>
<td>71% (B)</td>
</tr>
<tr>
<td>19</td>
<td><img src="image" alt="Structure 6" /></td>
<td>62% (B)</td>
</tr>
<tr>
<td>20</td>
<td><img src="image" alt="Structure 7" /></td>
<td>30% (A)</td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Structure 8" /></td>
<td>55% (A)</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Structure 9" /></td>
<td>93% (B)</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Structure 10" /></td>
<td>78% (B)</td>
</tr>
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<td>24</td>
<td><img src="image" alt="Structure 11" /></td>
<td>88% (B)</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="Structure 12" /></td>
<td>87% (A)</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Structure 13" /></td>
<td>70% (A)</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Structure 14" /></td>
<td>76% (A)</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Structure 15" /></td>
<td>90% (B)</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Structure 16" /></td>
<td>87% (A)</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Structure 17" /></td>
<td>90% (B)</td>
</tr>
<tr>
<td>31</td>
<td><img src="image" alt="Structure 18" /></td>
<td>65% (B)</td>
</tr>
<tr>
<td>32</td>
<td><img src="image" alt="Structure 19" /></td>
<td>94% (B)</td>
</tr>
<tr>
<td>33</td>
<td><img src="image" alt="Structure 20" /></td>
<td>98% (B)</td>
</tr>
<tr>
<td>34</td>
<td><img src="image" alt="Structure 21" /></td>
<td>78% (B)</td>
</tr>
<tr>
<td>35</td>
<td><img src="image" alt="Structure 22" /></td>
<td>77% (B)</td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Structure 23" /></td>
<td>84% (B)</td>
</tr>
</tbody>
</table>

*DBT refers to the amino group protected as its dibenzyltriazone. For conditions A and B see 4 → 5b in text.*
**Table II. LiBH<sub>4</sub> Reduction of Protected Amino Esters**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>No.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>39</td>
<td>92%</td>
</tr>
<tr>
<td>29</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>40</td>
<td>94%</td>
</tr>
<tr>
<td>25</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>20</td>
<td>80%</td>
</tr>
<tr>
<td>26</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>21</td>
<td>85%</td>
</tr>
<tr>
<td>27</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>41</td>
<td>79%</td>
</tr>
</tbody>
</table>

*Reductions were carried out in THF solution between 48 °C and reflux. 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<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O, corresponding to structure 38) and M - 253.

**Functional Group Transformations 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.

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. Oxidation of several dibenzyltriazone-protected amino alcohols using the Swern conditions 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-aminobutyaldehyde 47. All of the dibenzyltriazone-protected amino aldehydes proved to be stable to storage at 0 °C and to silica gel chromatography. The 4-aminobutyaldehyde derivative 47 is particularly noteworthy, in that we were unable to prepare the corresponding Boc- and Z-protected 4-aminobutyaldehydes 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**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>No.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>44</td>
<td>96%</td>
</tr>
<tr>
<td>40</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>45</td>
<td>95%</td>
</tr>
<tr>
<td>20</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>46</td>
<td>96%</td>
</tr>
<tr>
<td>21</td>
<td>DBT&lt;sub&gt;OH&lt;/sub&gt;</td>
<td>47</td>
<td>97%</td>
</tr>
</tbody>
</table>

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

Table IV. Carbon–Carbon Bond Forming Reactions*\(^a\)

<table>
<thead>
<tr>
<th>st matl</th>
<th>reactn condns</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>CH(_2)=CHMeBr, THF, -10 °C, then aq NH(_4)Cl</td>
<td>DBT</td>
<td>75%</td>
</tr>
<tr>
<td>15</td>
<td>n-BuLi, THF, -78 °C, then (CH(_2))(_2)SO(_4), 78–23 °C</td>
<td>DBT</td>
<td>79%</td>
</tr>
<tr>
<td>44</td>
<td>Ph(_2)=CCHO(_2)Me, benzene, reflux</td>
<td>DBT</td>
<td>87%</td>
</tr>
<tr>
<td>45</td>
<td>CH(_2)=CHCH(_2)MeBr, THF, -78 °C, then aq NH(_4)Cl</td>
<td>DBT</td>
<td>62%</td>
</tr>
<tr>
<td>48</td>
<td>SnCl(_2), CH(_2)Cl(_2), -78 °C</td>
<td>MeOH</td>
<td>57%</td>
</tr>
</tbody>
</table>

*DBT refers to the amino group protected as its dibenzyltriazone. Product isomer ratios were determined by \(^1\)H NMR analysis.

- **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 (i-BuMe\(_3\)SiCl, DMF, imidazole), and alkylation (MeOCH\(_2\)CH\(_2\)OCH\(_2\)Cl, i-Pr\(_2\)EtN, CH\(_2\)Cl\(_2\)) 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.

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 dibenzyltriazene-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.** Dibenzyltriazines are stable to some common methods for carbon–carbon bond formation, as shown in Table IV. Vinylmagnesium bromide, as an example, reacted with the dibenzyltriazine-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 dibenzyltriazene-protected aminoacetalddehyde 44 occurred in the expected fashion with methyl (triphenylphosphoranylidyne)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 organo-metallic addition reactions (Table IV) to establish the nature and extent of diastereoselection.\(^{17,18}\) Alkylmagnesium bromide addition, and also titanium tetrachloride-mediated allyltrimethylsilane addition, took place with a slight preference for the syn (three) 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-dibenzylaminoaldehyde 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]heptane\(^{20}\) 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 Dibenzyliatrizones.** Earlier studies\(^{6}\) of dimethyltriazole hydrolysis indicated that treatment of the triazone with concentrated aqueous hydrochloric acid at 25 °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 dimethylenes. In the latter case, formaldehyde was presumably consumed by reaction with ammonia. Dibenzyliatrizones, 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 (dibenzyliurea 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 dibenzyliurea. 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 the hydrolysis of several dibenzyltriazones using the new conditions. The products were obtained in pure form as the free amines, according to \(^1\)H NMR analysis, but isolated as derivatives to avoid carbon dioxide and water uptake, and, in the cases of 64 and 65, to determine stereochemistry.\(^{10}\) No evidence of HOCH\(_2\)NHR or similar signals, as might result from incomplete formaldehyde scavenging, was seen.

**Scheme II. "Working Mechanism" for Triazone Hydrolysis**

![Diagram](https://example.com/diagram.png)

<table>
<thead>
<tr>
<th>st. matl</th>
<th>react cond</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>aq HCl (pH 3), MeOH, diethanolamine, reflux 1 h, then POCOCl, pyr</td>
<td>PhCONH$_2$C$_2$H$_5$</td>
<td>82%</td>
</tr>
<tr>
<td>5b</td>
<td>aq HCl (pH 3), MeOH, diethanolamine, reflux 1 h, then AgOC$_2$H$_5$, pyr</td>
<td>NHAc</td>
<td>83%</td>
</tr>
<tr>
<td>22</td>
<td>aq HCl (pH 3), MeOH, diethanolamine, reflux 2 h, then COC$_2$H$_5$, l-Pr$_2$EN, CH$_2$Cl$_2$</td>
<td>NHCOPh</td>
<td>91%</td>
</tr>
<tr>
<td>59-syn</td>
<td>aq HCl (pH 3), MeOH, diethanolamine, reflux 2 h, then POCOCl, pyr</td>
<td>HOCH$_2$NHMe, R</td>
<td>74%</td>
</tr>
<tr>
<td>59-anti</td>
<td>aq HCl (pH 3), MeOH, diethanolamine, reflux 2 h, then COC$_2$H$_5$, l-Pr$_2$EN, CH$_2$Cl$_2$</td>
<td>NHCOPh</td>
<td>76%</td>
</tr>
</tbody>
</table>

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

Synthesis of Hypusine

formation (Scheme I), in that iminium intermediates are involved, rather than dialkylurea-formaldehyde adducts. Scheme II shows a "working mechanism" for triazine hydrolysis (3 → 1) in the presence of a formaldehyde scavenger ("Nuc"). Protonation at N(6) of 3 is probably not sufficient to initiate triazine 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 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 dialkyurea and, ultimately, the desired amine 1 as its hydrochloride and the trapped formaldehyde species 70. We have never observed a dialkyurea–formaldehyde adduct (such as 10) as a product of a triazine hydrolysis.

Synthesis of Spermidines. The naturally occurring polyamines putrescine (1,4-diaminobutane, 78), spermidine (4-aza-1,5-diaminooctane, 74), and spermine (4,9-diazaoctanedodecane, 75) are widely distributed in living systems, interact extensively with phospholipids, proteins, and nucleic acids, and exert a profound influence on biochemical processes. 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, and polyamine synthesis continues to be an active area. Unsatuated spermidines were of particular interest to us as potential inhibitors of hypusine biosynthesis (see next section).

![Scheme III. Synthesis of Spermidines](image)

The stability of the dibenzyltriazone-protected aminopropanal 46 and aminobutanal 47 makes them well-suited for the preparation of spermidine analogues. Golding's method for the synthesis of secondary amines from aldehydes and azides by means of Staudinger and aza-Wittig reactions 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. 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.

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). 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 and in mouse...
The pathway for its formation consists of (1) attachment of an aminobutyl group from spermidine at the lysine e-amino group and then (2) hydroxylation at C-9. 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 physiologic significance of the modification of the 18 kDa protein, remain to be elucidated.

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, although some ambiguity remains as to the degree of enantiomeric and diastereomeric 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(α)-(benzoyloxybenzyl)lysine benzyl ester p-toluenesulfonate (87) 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).

Reversing the order of the deprotection steps also led to 85 in about the same yield. The [α]D for 85, which has not previously been reported, was found to be +17.41° (c = 0.85, 6 M HCl, 25 °C).

A reductiveamination 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 e-aldehyde (90) could be coupled with a 2-hydroxy-1,4-butanediolamine (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 e-aldehyde analogous to 90 had been prepared. Although such compounds can apparently be generated for short periods in solution, they readily cyclize to afford a 1,4,5,6-tetrahydroxyazine-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 e-aldehyde.

The synthesis of the required lysine e-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. Examination of the signals due to the methoxy protons and the β-methylene protons in the 1H NMR spectra of the (S)-Mosher ester (and for comparison the diastereomeric mixture from de-rivatization of 92 with racemic methylsulfonyl 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)triphosphorane. Hydrogenation gave 94, the first example of an isolable lysine e-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 triazole 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 gave β-malic acid, which was converted to its methyl ester 96 for convenience in purification and reduction. Treatment of 96 with diborate, 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 dibenzyltriazole derivative were unsuccessful). Conversion of the primary hydroxyl to amino was achieved by azide displacement of a monomethanesulfonate derivative. Following hydrogenation, the protected hydroxybutane-
diamine 98 was isolated in satisfactory yield. The enantio-meric purity of 97 was checked by conversion to its O,O-diaceetyl derivative, and examination of the $^1$H NMR spectrum in the presence of the chiral shift reagent tris[(trifluoromethyl)hydroxymethylene-(-)]camphorato]europium(III).\textsuperscript{41} Comparison of the ace-tate singlets with those of the corresponding racemic compound established the ee of 97 to be at least 90%.

\[
\begin{align*}
\text{HN} & \quad \text{OH} \\
\text{N} & \quad \text{OH} \\
\text{1. NeH2O, HzOAc} \quad \text{2. MeOH, HCl, 0°C} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{OH} \\
\text{N} & \quad \text{OH} \\
\text{1. BuLi, THF, 23°C} \quad \text{2. (Boc)2O, MeOH} \\
\text{18BuOCONH} \quad \text{97} \\
\text{54% overall} \\
\end{align*}
\]

Reducive coupling of the lysine $\epsilon$-aldehyde 94 and amine 98 was carried out by first stirring them in benzene solution in the presence of activated 4-A 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, diethy lamine, 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 227–228 °C (lit.\textsuperscript{35} mp 234–236 °C; lit.\textsuperscript{36} mp 235–238 °C dec; lit.\textsuperscript{37} mp 239–241 °C dec). The [\(\alpha\)]\textsubscript{D} (+7.8\textdegree, c = 0.52, 6 M HCl) of synthetic 86 is comparable to the reported values (+6.8\textdegree\textsuperscript{36} +9.9\textdegree\textsuperscript{35} +7.2\textdegree\textsuperscript{36} and +8.3\textdegree\textsuperscript{37}), and the well-resolved 150-MHz $^1$H 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 $\epsilon$-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.\textsuperscript{42} Tetrahydrofuran (THF) was distilled from benzophenone ketyl and acetonitrile, dichloromethane (CH$_2$Cl$_2$), diisopropylpropylethylamine (DIPEA), N-methylmorpholine, N,N-di- methylformamide (DMF), dimethyl sulfoxide (DMSO), dimethoxyxane (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-amino pentanoate hydrochloride, ethyl 6-aminohexanoate hydrochloride, and ethyl 3,5-diaminoacetone hydrochloride were prepared by Fischer esterification of the amino acids (hydrochloric acid, ethanol, reflux, 16–20 h). Methyl N-[(tert-butoxycarbonyl)-N-(benzyloxycarbonyl)-L-lysinate,\textsuperscript{43} tert-butyl N-[(tert-butoxycarbonyl)-N-(benzyloxycarbonyl)-L-lysinate,\textsuperscript{44} benzyl N-[(benzyloxycarbonyl)-L-lysinate,\textsuperscript{45} 4-amino butenone hydrochloride,\textsuperscript{45} and O-(5-benzyl tert-buty1 aspartate\textsuperscript{46} were prepared by the literature methods. "Formalin" refers to 37% aqueous formaldehyde solution.

$^{N,N}$-Dibenzylurea (2, R$^2$ = CH$_3$Ph). A 1-L three-necked flask equipped with a thermometer, 50-mL addition funnel, calcium chloride drying tube, and magnetic stir bar was charged with a solution of 25 g (186 mmol) of benzyl isocyanate in 150 mL of CH$_2$Cl$_2$. The solution was cooled to below 6 °C, and then a solution of 201 g (188 mmol) of benzylamine in 25 mL of CH$_2$Cl$_2$ was added dropwise while the temperature was maintained below 15 °C. A precipitate formed immediately; CH$_2$Cl$_2$ was added during the reaction to facilitate stirring (total 250 mL). The reaction was allowed to stand at 5 °C for 50 min and then filtered. The resulting solid was washed with 200 mL of ice-cold CH$_2$Cl$_2$ and dried under vacuum (1 Torr, 23 °C, 3 h) to afford 39.2 g of dibenzyl urea. The filtrate was concentrated in vacuo, and the resulting solid was suspended in 250 mL of ice-cold CH$_2$Cl$_2$, 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, 4H, J = 5.8), 5.31–5.35 (m, 2H), 7.26 (app s, 10H); IR (KBr) 1625, 1579, 1454, 1267, 731, 739, 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), forminal (0.5–1.0 mL per mmol of amine), and dioxygen or THF (0.55–0.5 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).
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 for 1 h. TLC of the diluted reaction mixture 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)-Phenethyl)-1,3-dibenzyhexahydro-2-oxo-1,3,5-triazine (5b). Method B was used to convert 151 mg (1 mmol) of (S)-phenylethylamine 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 ether/petroleum ether afforded 587 mg (91%) of dibenzylurea, and 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/CH2Cl2 as the eluant afforded 220 mg (75%) of 5b.

(5-Pent-4-enyl)-1,3-dibenzyhexahydro-2-oxo-1,3,5-triazine (17). Protection of 5-aminopentene by method B as for 16, and with chromatography with 1:1 ether/petroleum ether as the eluant, gave 17 as an oil in 90% yield: 'H NMR 1.14 (m, 2 H), 1.50-1.55 (m, 4 H), 1.97 (s, 3 H), 2.42-2.48 (t, 2 H, J = 7.5), 2.70-2.75 (m, 2 H), 3.79 (d, 2 H), 4.61 (s, 4 H), 5.52 (d, 1 H), 6.08 (d, 1 H), 7.20-7.24 (m, 5 H), 7.25-7.30 (m, 5 H). Anal. Calcd for C21H21N3O: C, 77.60; H, 7.42; N, 15.10. Found: C, 77.62; H, 7.45; N, 15.13.

5-(4-Methylphenyl)-1,3-dibenzyhexahydro-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: 'H NMR 1.11 (s, 3 H), 3.67 (s, 4 H), 4.76 (s, 4 H), 5.39 (d, 1 H), 6.74 (d, 1 H), 7.20 (app 8, 10 H); CI-MS 350 (M+1). Anal. Calcd for C21H21N3O: C, 75.76; H, 7.25; N, 11.34. Found: C, 75.77; H, 7.26; N, 11.38.

5-(4-Phenylphenyl)-1,3-dibenzyhexahydro-2-oxo-1,3,5-triazine (19). Method B was used to convert 110 mg (0.5 mmol) of 4-iodocinnoline 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 petroleum ether/ethyl ether as the eluant afforded 262 mg (82%) of 19 as a solid, mp 97-99 °C: 'H NMR 1.14 (s, 3 H), 5.49 (s, 4 H), 7.49 (d, 1 H, J = 7.5), 7.64 (d, 1 H, J = 7.3), 7.35 (app 8, 10 H), 7.35 (app 8, 10 H); CI-MS 352 (M+1). Anal. Calcd for C21H21N3O: C, 77.60; H, 7.49; N, 11.34. Found: C, 77.62; H, 7.48; N, 11.34.

5-(3-Hydroxypropyl)-1,3-dibenzyhexahydro-2-oxo-1,3,5-triazine (20). (A) By Protection of 5-Aminopropano. Method B was used to convert 75 mg (1.0 mmol) of 5-aminopropano 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: '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 = 4.4), 4.11 (s, 4 H), 4.50 (d, 1 H, J = 7.5), 7.20-7.25 (m, 5 H), 7.32 (app 8, 10 H), 7.32 (app 8, 10 H); CI-MS 340 (M+1). Anal. Calcd for C21H21N3O: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.82; H, 7.40; N, 12.72.
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 188 mg (79%) of 1,3,5-triazine (26). Method B was used to convert 182 mg (1.0 mmol) of 6-amino-2-ethyl-2-heptanol hydrochloride to 22. The formaldehyde adduct from the reaction of the amine and 1.0 mL of formalin, and 180 mL (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: 

\[ \text{H NMR 0.81 (d, 3 H, J = 6.4), 0.98-1.26 (m, 6 H, 1.6), 2.72-2.76 (m, 3 H, 4.15, and 4.19 (AB, q, J = 11.6) 4.43 and 4.65 (AB, q, J = 14.6).} \]

7.52 (app, 10 H). Found: C 70.89; H 7.75; N 9.92. 

**Ethyl 2-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yi)propionate (29).** Method B was used to convert 306 mg (2.0 mmol) of ethyl L-alanine hydrochloride to 29. The formaldehyde adduct obtained from the reaction of the amine and 1.0 mL of formalin, and 0.35 mL (2.0 mmol) of DIPEA was combined with 490 mg (2.5 mmol) of dibenzylurea and 15 mL of EtOAc and heated at reflux for 1 h. Chromatography on 20 g of silica with 2:1 CH2Cl2/ethyl ether as the eluant afforded 864 mg (90%) of 29 as an oil: 

\[ \text{H NMR 0.99 (d, 3 H, J = 6.8), 2.29-2.90 (m, 1 H), 3.26 and 3.39 (two dd, 1 H each, J = 5.1, 10.4), 4.19 (app, 4 H), 4.54 (app, 4 H), 7.32 (app, 10 H).} \]


**Ethyl 2-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yi)acetate (24).** Method B was used to convert 1.40 g (10 mmol) of ethyl glycinate hydrochloride to 24. The formaldehyde adduct obtained from the reaction of the salt with 5 mL of formalin, and 15 mL (0.15 mmol) of DIPEA, and 50 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 277 mg (80%) of 24 as an oil: 

\[ \text{H NMR 1.15 (t, 3 H, J = 7.2), 3.45 (q, 4 H, J = 6.8), 4.05 and 4.23 (two dd, 1 H each, J = 10.4, 7.2, 7.45 (app, 10 H).} \]

Found: C 70.89; H 7.75; N 9.92. 

**Ethyl 3-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yi)propionate (25).** Method A was used to convert 770 mg (5.0 mmol) of ethyl 8-benzaldehyde 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: 

\[ \text{H NMR 1.20 (t, 3 H, J = 7.0), 2.05 (t, 2 H, J = 6.8), 2.79 (2 H, J = 6.8), 4.06 (q, 2 H, J = 7.0), 4.08 (d, 2 H, J = 6.8), 4.53 (3 H, J = 4.4, J = 11.2, 7.55 (app, 10 H); CI-MS 382 (M+1)*.} \]

Anal. Calcd for C27H26N6O3: C 76.84; H 6.86; N 11.44. Found: C 76.87; H 6.83; N 11.36.

**Ethyl 4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yi)butyrate (26).** Method A was used to convert 840 mg (5.0 mmol) of ethyl 4-aminobutyrate hydrochloride to 26. Chromatography on 50 g of silica with 3:2 ethyl ether/petroleum ether as the eluant afforded 1.38 g (70%) of 26 as an oil: 

\[ \text{H NMR 1.20 (t, 3 H, J = 7.0), 1.33-1.47 (m, 2 H), 2.11 (t, 2 H, J = 7.0), 2.46 (t, 2 H, J = 6.9); 4.05 (q, 2 H, J = 7.0), 4.06 (s, 4 H, 4.53 (s, 4 H), 7.31 (app, s, 10 H); CI-MS 396 (M+1)*.} \]


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method B as for 16 and chromatography with 1:2 EtOAc/petroleum ether as the eluent gave 734.6 mg (94% yield) of 32: H NMR 3.23 (dd, 1 H, J = 10.4), 3.38 (dd, 1 H, J = 10.4), 3.50 (s, 3 H), 3.56 (d, 1 H, J = 4), 4.12-4.22 (m, 2 H), 4.36 (s, 3 H), 4.70-4.73 (d, 2 H, J = 15), 4.83 (d, 2 H, J = 15), 7.17-7.33 (m, 15 H), 18.32; 13C 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 C32H31N3O4: C, 66.8; H, 7.7; Found: C, 67.0; H, 7.4.

Ethyl 3-(Benzylloxy)-2-(S)-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)propanoate (33). Method B was used to convert 31 mg (2.0 mmol) of ethyl O-benzyl-
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ether, and then the resulting solid was filtered and dried under high vacuum (1 Torr, 25 °C, 3 h) to give 216 mg (99%) of 42, mp 128–129 °C: [α]20 = −36.4° (c = 0.5); 1H 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 4.45 (AB q, 4 H, J = 16.4), 7.35 (app s, 10 H); IR (KBr) 1718, 1643; FAB-MS 354 (M+ - 1). Anal. Calcd for C22H27N303: C, 68.18; H, 6.68; N, 15.90. Found: C, 67.88; H, 6.87; N, 15.55.

treated with ether. The organic layer was washed with 5 mL of water, dried, and concentrated. Chromatography on 5 g of silica gel with 1:1 ethyl ether/petroleum ether as the eluant afforded 52 mg (87%) of 5 as an oil: 1H NMR 1.22-1.33 (m, 2 H), 2.50 (t, 2 H, J = 7.0), 3.08 (s, 2 H, J = 6.8), 4.07 (s, 2 H), 4.55 (s, 4 H), 7.33 (app s, 10 H); IR (neat) 2997, 1640; CI-MS 365 (M + 1)\(^{+}\). Anal. Calcd for C\(_{24}\)H\(_{22}\)NO\(_{3}\): C, 65.91; H, 6.64; N, 23.06.

5-(5-Azido-pentyl)-1,3-dibenzo[b,f]azepino[2,3-c]azepine-2-oxo-1,3,5-triazine (84). Compound 54 was prepared from alcohol 41 by the same procedure used for the preparation of 83. Chromatography with 2:3 ether/petroleum ether as eluant gave 54 as an oil in 71% yield: 1H 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 = 7.1), 3.15 (t, 2 H, J = 7.0, 4.08 (s, 4 H), 4.54 (s, 4 H), 7.26 (br s, 10 H); IR 2966, 1639.

5-(4-Hydroxy-2-ethyl-5-oxo-1,3-dibenzo[b,f]azepino[2,3-c]azepine (84). An oven-dried, 50-mL three-necked flask equipped with a stopper, septum, and argon balloon was charged with a solution of ethyl alcohol in 15 mL of THF. The solution 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 5 mL of petroleum ether, dried, and concentrated. Chromatography on 5 g of silica gel with 1:1 ethyl ether/petroleum ether as the eluant afforded 182 mg (75%) of 55 as an oil: 1H 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 = 12.5, 5.10 (dt, 1 H, J = 18.0, 5.72 (dd, 1 H, J = 18, 12, 7, 7.1), 7.31 (app s, 10 H); 13C NMR 23.3, 34.6, 48.5, 50.5, 65.2, 72.2, 114.2, 127.3, 128.1, 128.5, 140.1, 150.1.

5-(3-Azido-pentyl)-1,3-dibenzo[b,f]azepino[2,3-c]azepine-2-oxo-1,3,5-triazine (82). A solution of 125 mg (0.39 mmol) of alcohol 39, 35 mg (0.29 mmol, 0.76 equiv) of 4-(dimethylamino)pyridine, and 200 mL (1.15 mmol, 3 equiv) of DIPPEA in 5 mL of CH\(_{2}\)Cl\(_2\) was treated with 88 mg (0.46 mmol, 1.2 equiv) of p-toluene sulfonamide at 0 °C. The mixture was washed with 5 mL of saturated aqueous sodium bicarbonate, the organic layer was washed with 5 mL of petroleum ether, dried, and concentrated. Chromatography on 5 g of silica gel with 3:2 ethyl ether/petroleum ether as the eluant afforded 158 mg of 52 as a solid: 1B NMR 6.6), 2.73-3.75 (m, 15 H); FAB-MS 444 (M + 1)\(^{+}\).

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. Chromatography on 5 g of silica gel with 1:1 ethyl ether/petroleum ether as the eluant afforded 72 mg (80%) of 51 as an oil: 1H 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), 5.35 (app s, 10 H); IR (neat) 2102, 1638; FAB-MS 531 (M + 1)\(^{+}\). Anal. Calcd for C\(_{24}\)H\(_{22}\)N\(_{2}\)O\(_{2}\): C, 65.12; H, 6.33; N, 23.98. Found: C, 65.41; H, 6.38; N, 23.70.
(a, 3 H), 4.06 (s, 4 H), 5.43 (s, 4 H), 5.15 (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_{66}H_{92}NO_{15}C_{6}: C, 69.84; H, 6.64; N, 11.07. Found: C, 69.57; H, 6.05; N, 10.93.

For 1,3-Trimethyl-2-oxo-1,3,5-triazin-5-yl)4-((R)-hydroxy-6-hexyloxyl)-1-propene: 5, 66% (10 mL per 35.9 mg of dibenzyltriamine) and 1.0 N aqueous hydrochloric acid (5 mL per 35.9 mg of dibenzyltriamine) 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_{2}Cl_{2} (10 mL per 35.9 mg of dibenzyltriamine) and water (5 mL per 35.9 mg of dibenzyltriamine). The combined extract was concentrated to provide the primary amine.

Deprotection of Octylamine (as 61). Deprotection of 65 mg (0.22 mmol) of 14 following the general procedure with 20% aqueous diethanolamine afforded 23 mg (92%) of octylamine, which was characterized as its benzamide derivative, mp 42-44 °C (lit, 66 mg 45-46 °C): 'H NMR 0.88 (3, 3 H, J = 6.8), 1.29-1.38 (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 diethanolamine afforded 19 mg (85%) of phenethylamine, which was characterized as its acetate: 'H NMR 1.48 (d, 3 H, J = 6.8), 1.97 (s, 3 H), 5.09-5.19 (m, 1 H), 5.59 (br s, 1 H), 7.32 (app s, 5 H).

Deprotection of 6-Amino-2-methyl-2-heptanolo (as 63). Deprotection of 65 mg (0.16 mmol) of 14 following the general procedure with 20% aqueous diethanolamine afforded 21 mg (91%) of 6-amino-2-methyl-2-heptanolo, which was characterized as its benzenamide: 'H NMR 1.20 (3, 3 H, J = 6.8), 1.25 (s, 3 H, J = 6.4), 1.43-1.51 (m, 6 H), 4.20-4.27 (m, 1 H), 6.91-6.93 (m, 3 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 as its oxazolidinone: 'H NMR 1.20 (d, 3 H, J = 6.8), 2.32-2.39 (m, 1 H), 2.51-2.69 (m, 1 H), 3.84 (dt, 1 H, J = 14.8, 6.0), 4.19 (dt, 1 H, J = 14.8, 5.6), 5.17 (d, 1 H, J = 10.4, 16.0), 5.21 (t, 1 H, J = 4.6, 17.6), 7.77-7.85 (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 as the trans-oxazolidinone: 'H NMR 1.20 (d, 3 H, J = 6.0), 2.44-2.51 (m, 2 H), 3.83 (qd, 1 H, J = 6.0, 4.4), 4.17 (dt, 1 H, J = 6.4, 6.0), 5.17 (d, 1 H, J = 8.0, 5.0), 5.21 (d, 1 H, J = 3.5, 13.2), 6.77-6.84 (m, 1 H), 5.24 (br s, 1 H); IR (neat) 2174.

6-Hexyloxyl-1,3,5,5-tetramethyl-1,3,5-triazin-3-ylidene (72). A mixture of 0.50 g (3.5 mmol) of hexyloxyl-1,3,5,5-tetramethyl-1,3,5-triazin-3-ylidene (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: 'H NMR 1.59 (30.50H, J = 6.7, 2.96 (s, 3 H, J = 7.1), 3.16 (s, 6 H, J = 7.1), 4.86 (s, 6 H, J = 7.1), 6.03 (s, 1 H, J = 7.1), 3.24 and 3.26 (2 H, J = 7.3), 2.85 (m, 2 H, J = 7.1), 1.71-1.89 (m, 2 H, J = 7.1), 4.86 (s, 6 H, J = 7.1), 5.94 (s, 1 H, J = 7.1), 7.48-7.53 (m, 3 H, J = 7.1), 7.61-7.67 (m, 2 H).

4-Aza-1,3-bis(1,3-dibenzylhexyloxyl-2,3-oxa-1,3,5-triazin-5-yl)octane (78). A mixture of 128 mg (0.35 mmol) of azide 63, 5 mL of THF, 0.75 mL of 1.0 N solution of trimethylphosphine solution in THF, and 200 mg of activated 4-A molecular sieves was stirred at 23 °C for 45 min. A solution of 125 mg (0.36 mmol) of ethylene glycol in 5 mL of THF was added, and the reaction 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
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 portioned 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 25:10:1 CHCl₃/methanol/ammonium hydroxide as the eluant afforded 164 mg (69%) of the protected spermidine 78 as an oil: ¹H NMR 1.00-1.08 (m, 2 H), 1.17-1.26 (m, 2 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), 4.09 (s, 4 H), 4.54 (s, 5 H), 7.31 (dt, 1 H, J = 9.0, 3.8), 10.0 ppm (1 H). HRFABMS 485.4, 485.5, 485.4, 485.5, 485.4, 66.5, 66.6, 66.7, 66.8, 120.8, 128.5, 138.2, 165.2. Anal. Calcd for C₂₅H₂₃O₃N₄: C, 72.1; H, 6.7; N, 14.5. Found: C, 72.7; H, 6.8; N, 14.25.

5-(4-Azido-2-(E)-enyl)-1,3-benzylhexahydro-2-oxo-1,3,5-triazine (79). An oven-dried 50-mL three-neck flask equipped with a septum, stopper, argon balloon, and magnetic stirrer was charged with 2.0 mL (1.33 mmol) of a 1.5 M solution of disobutylaluminium hydride in toluene and 5.0 mL of CH₂Cl₂. 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 CH₂Cl₂ was slowly added via syringe, the cold bath was replaced with an ice bath, and then the reaction mixture was stirred at 5 °C for 1.5 h. The reaction was quenched with 5.0 mL of 1 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 a solid (69%) as a white solid, mp 57-58 °C, [α]₂₅ = 45.1, 48.9, 48.8, 65.5, 127.4, 127.5, 128.6, 137.6, 155.3; IR (neat) 2089, 1614.

4-Aza-1,8-bis(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)oct-6-ene (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 a oil: ¹H NMR 1.18-1.24 (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); ¹³C NMR 27.5, 43.0, 45.1, 46.1, 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, 1533.

Spermidine (74), 6,7-Didehydro spermidine (81), and 6,6,7,7-Tetradehydro spermidine (64). 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 partitioned between CH₂Cl₂ and 1 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 50WX-400 ion-exchange resin (500 mg per 10 mg of starting material; the resin was pre-washed with ethanol) with 1000 µL 20%, and then 4:1 ethanol/ammonium hydroxide as the eluant, afforded 91 mg (63%) of 81 and 84, respectively. Dried under high vacuum (1 Torr, 25 °C), the products had spectral characteristics (¹H NMR, ¹³C NMR, IR) matching those of an authentic sample (for 74), or reported in the literature (for 81 and 84). In the 400-MHz ¹H NMR spectrum, 84 showed small singlets at 5.60 and 5.67, possibly OCH₃Cl impurities, amounting to about 1-2% each.

4-Aza-2(S),11-dimethylundecanoic Acid Dihydrochloride, Dihydropyruvate (85). Aqueous hydrochloric acid (1.0 mL of a 0.2 N solution) was added dropwise to a refluxing solution of 10.4 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 CHCl₃/methanol/ammonia as the eluant to give 27.2 mg (87%) of 85 as an oil: ¹H NMR (D₂O) 1.3-1.9 (m, 10 H), 2.8-3.0 (m, 6 H), 3.85 (1 H, J = 7); ¹³C NMR (150 MHz, D₂O) 23.9, 25.6, 26.3, 27.6, 32.2, 41.28, 49.26, 49.60, 56.65, 78.74; IR 3429, 1610; [α]₂₅ +17.41° (c = 0.85, 6 N HCl).

4-Aza-2(S),11-dimino-9(R)-hydroxundecanoic Acid Dihydropyruvic Acid, Pyruvate (88). Aqueous hydrochloric acid (2 N, 1.2 mL) was added to a stirred solution of 98.2 mg (0.15 mmol) of 89 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 reaction mixture 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 CHCl₃/methanol/ammonium as the eluant to give 62 mg (85%) of the desired compound. 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 66-HCl, mp 237-238 °C: ¹H NMR (D₂O) 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); ¹³C NMR (150 MHz, D₂O) 24.01, 27.53, 28.22, 33.90, 38.92, 49.78, 54.57, 50.39, 67.28, 172.78; IR 3400, 1624; [α]₂₅ +17.9° (c = 0.62, 6 N HCl) [α]₂₅ +17.9° (c = 0.12, 6 N HCl); [α]₂₅ +17.9° (c = 0.26, 6 N HCl), [α]₂₅ +17.9° (c = 0.96, 6 N HCl).

Benzyl 7-Aza-7-(benzoyloxy)carbonyl-2(S)-( benzoyloxycarbonyl)camino-11-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)undecanoate (88). A suspension of 564.0 mg (0.67 mmol) of benzyl N(a)-(benzoyloxycarbonyl)lysinate p-toluenesulfinate (87), 74.5 mg of 10% palladium-on activated carbon, and 1 g of activated 4-A 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 alkalde...
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$_2$Cl$_2$ and 5 mL of water. The organic layer was then washed with CH$_2$Cl$_2$ for saturated aqueous sodium carbonate and dried. Chromatography with 200:1:1 CH$_2$Cl$_2$/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. Benzylchlorofomate (90.0 µL, 0.63 mmol) was added, and the reaction mixture was stirred for 30 min. A corresponding amount of racemic Mosher acid was then added, and the reaction mixture was allowed to 182.2 mg (79% yield) of aldehyde as an oil: $^1$H NMR 1.36–1.43 (m, 13 H), 2.0–2.25 (m, 2 H), 3.30 (t, 1 H, J = 6), 4.13 (d, 2 H, J = 12), 4.24 (d, 2 H, J = 18), 4.33 (d, 2 H, J = 15), 4.75 (d, 2 H, J = 16), 5.84–5.90 (m, 1 H), 6.50–6.57 (m, 1 H), 7.27–7.27 (m, 10 H), 9.40 (d, 1 H, J = 8); IR 1731, 1690, 1642.

A suspension of 228.6 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 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 pressure. 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 the 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) 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.

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 1.39 (s, 3 H), 2.13–2.30 (m, 2 H), 3.5 (t, 1 H, J = 6), 4.19 (s, 4 H), 4.30 (d, 2 H, J = 18), 4.76 (d, 2 H, J = 16), 5.84–5.90 (m, 1 H), 6.60–6.57 (m, 1 H), 7.27–7.27 (m, 10 H), 9.40 (d, 1 H, J = 8); IR 1731, 1690, 1642.

A solution of 2.32 g (53.84 mmol) of sodium nitrite in 50 mL of water was added dropwise to a stirred solution of 2.94 g (16.92 mmol) of D-asparagine (98) in 150 mL of 20% aqueous acetic acid at 0 °C. The mixture was allowed to warm to 0 °C and then filtered through Celite and chromatographed with 2:3 EtOAc/petroleum ether as the eluant to afford 2.94 g (17% yield) of aldehyde as an oil: $^1$H NMR 1.36–1.43 (m, 13 H), 2.0–2.25 (m, 2 H), 3.30 (t, 1 H, J = 6), 4.13 (d, 2 H, J = 12), 4.24 (d, 2 H, J = 18), 4.33 (d, 2 H, J = 15), 4.75 (d, 2 H, J = 15), 7.2–7.2 (m, 10 H), 9.65 (s, 1 H); IR 1725, 1645. Anal. Calcd for C$_{36}$H$_{36}$O$_6$N$_6$: C, 69.65; H, 7.58; N, 9.03. Found: C, 70.00; H, 7.72; N, 8.92.

8(R)-Hydroxy-3-carbomethoxypropamidine (96). A solution of 2.33 g (53.84 mmol) of sodium nitrite in 50 mL of water was added dropwise to a stirred solution of 2.94 g (16.92 mmol) of D-asparagine (98) 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 pressure. 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 the 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) 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.

A corresponding 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 re-dissolved in 20 mL of methanol. Di-tert-butyldicarbonate (1.15 g, 5.20 mmol) was added and the reaction mixture was stirred overnight 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 3590, 1688. Anal. Calcd for C$_{36}$H$_{36}$O$_6$N$_6$: C, 62.66; H, 7.58; N, 9.62. Found: C, 62.10; H, 7.93; N, 6.56.

A solution of 38.3 g (0.19 mmol) of 97, 3.2 g (0.026 mmol) of 4-(dimethylaminomethyl)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), 4.51–4.24 (m, 1 H), 4.81 (br s, 1 H), 5.13 (s, 1 H); IR 1717, 1717 (m, 1 H); IR 1547, 1572 (m, 1 H); IR 1531 (m, 1 H). Small portions (up to 1 equiv) of the chiral shift reagent tri(trifluoromethyl)hydroxymethyl(−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 (pre pared by hydrolysis of 4-([(tert-butyloxycarbonyl)amino]-butenone) were also carried out. A signal for complexed acetate corresponding to less than 5% of the undesired 2S-enantiomer was observed.

1-Amino-4-[(tert-butyloxycarbonyl)amino]-2(R)-butanol (98). Diol 97 was converted to the primary azide by the same procedure used for 26 → 53. Chromatography with 1:2 EtOAc/petroleum ether as the eluant gave the azide as an oil in 54%
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Supplementary Material Available: $^1$H NMR spectra of synthetic hypothins (86), $^1$H NMR spectra of ($S$)-Moah esters from the configurational study of 45; $^{13}$C NMR spectra of ($S$)- and ($R$)-Moah esters of 92, and $^3$H NMR spectra of the diastereot of 97 with added chiral shift reagent (4 pages). This material is contained in many libraries on microfiche, immediately follows microfiche, immediately follows microfiche, immediately follows microfiche, immediately follows microfiche.