Solid-Phase Synthesis: Intramolecular Azomethine Ylide Cycloaddition (→Proline) and Carbanilide Cyclization (→Hydantoin) Reactions

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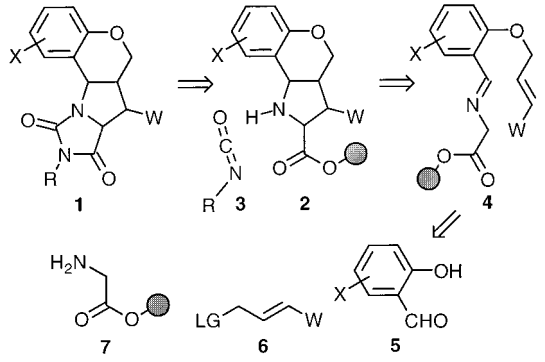
An efficient, diastereoselective route to 2,5,6,7-tetrasubstituted-1*H*-pyrrolo[1,2-*c*]imidazoles has been developed using solid-phase intramolecular azomethine ylide cycloaddition and carbanilide cyclization chemistries. To successfully execute this eight-step protocol in the solid phase, it was necessary to insert a spacer moiety between the resin and glycinate functional group. Experiments addressing the stereoselectivity of the 1,3-dipolar cycloaddition step as well as the cyclative release step are also presented.

Introduction

There is enormous interest in the development of solid-phase synthetic approaches to small molecules, particularly those which embrace polyfunctional heterocyclic targets.[2] As part of our solid-phase synthetic methods program, we have an interest in developing synthetic strategies and chemistries applicable to a combinatorial approach to hydantoin-containing heterocycles.[3] The hydantoin moiety imparts a broad range of biological activity including antiviral, antibacterial, antifungal, and herbicidal activity.[4] In preliminary solution studies, we have developed a novel route to hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazole derivatives by tandem azomethine ylide cycloaddition (→proline) and carbanilide cyclization (→hydantoin) chemistry. This chemistry delivers polycyclic hydantoin-containing targets with stereoselective control of four contiguous pyrolidine stereocenters.[5]

Here we disclose modifications in this solution chemistry which accommodate a solid-phase (SP) synthetic approach built around a cyclative release strategy[6] which encompasses intramolecular azomethine ylide cycloaddition[7] and carbanilide cyclization[8] steps. As outlined in Scheme 1, this strategy unfolds by elaborating a polymer-bound glycine ester to a SP hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole precursor where the starting SP-glycine ester

Scheme 1. Solid-Phase Approach to 1



(**7**) is now adorned with Cα- and N-substituents (see **2**). A variety of R-groups can then be introduced in the condensation of **2** with isocyanate **3**, setting the stage for heterocyclization with concomitant resin release of polyheterocyclic target **1**. Various substituents at positions "X" and "W" are incorporated in the elaboration of salicylaldehydes (**5**; "X") and alkylating agents (**6**; "W") to imino ester **4** which then delivers the azomethine ylide intermediate which leads to pyrrolidine **2**. This retrosynthetic analysis hinges on the tautomerization of an amino ester derived Schiff base intermediate (**4**) to a Grigg-type azomethine ylide (i.e., ©−CH=NCH$_2$CO$_2$R′ → ©−CH=N$^+$(H)C$^-$HCO$_2$R′; © = remainder of solid or solution compound)[9] with subsequent intramolecular 1,3-dipolar cycloaddition across an electron-deficient dipolarophile.[10,11]

Results and Discussion

Solution-Phase Chemistry. A two-stage solution-phase route to hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole **1** was examined first. In parallel with Grigg's studies,[9]

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(1) 1996−7 Fulbright Fellowship, University of California, Davis, CA 95616.

(2) (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385 (b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135 (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 557.

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(8) (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403 (b) Read, W. T. *J. Am. Chem. Soc.* **1922**, *44*, 1766.

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(10) For a recent intermolecular example, see: Tsuge, O.; Kanemasa, S.; Yoshioda, M. *J. Org. Chem.* **1988**, *53*, 1384.

(11) For a recent intramolecular example, see: Overman, L. E.; Tellew, J. E. *J. Org. Chem.* **1996**, *61*, 8338.

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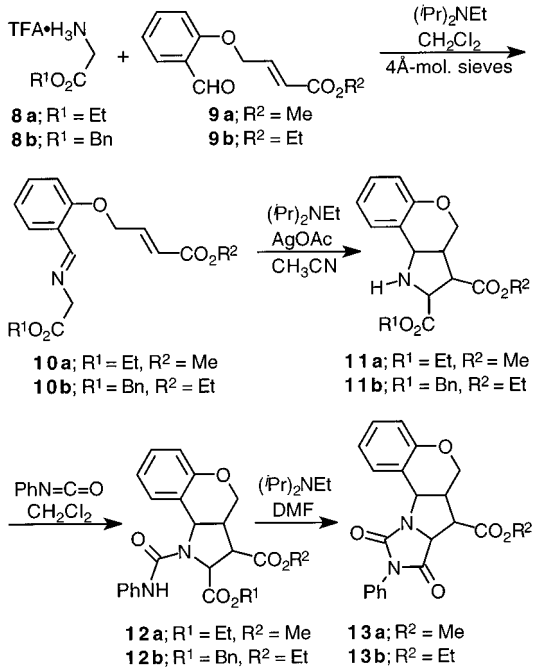
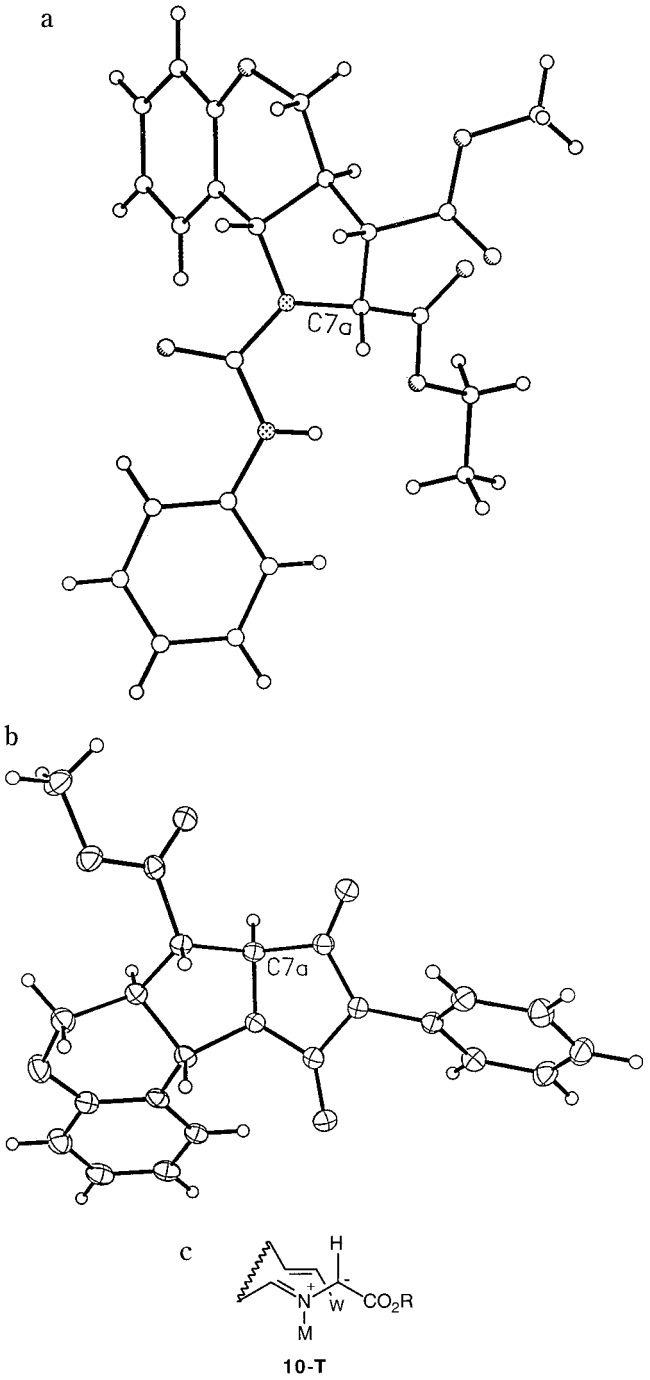
Scheme 2. Solution-Phase Route for 8 → 11 → 13



condensation of the TFA salt of glycine esters (**8**) with *O*-alkylated salicylaldehyde derivatives (**9**) delivered benzylideneglycinates (**10**) in ~80% yield (Scheme 2). Given the obvious steric constraints, it is not surprising that these benzylideneglycinates are obtained as one diastereomerically pure Schiff base isomer (presumably the *E*-isomer) as evidenced by a one-proton singlet at 7.98 ppm (CH=N) and a two-proton singlet at 4.41 ppm (NCH_2) in the ^{1}H NMR spectra. Treating these crude benzylideneglycinates at room temperature with silver acetate and *N*,*N*-diisopropylethylamine in acetonitrile (3 h) followed by aqueous ammonium chloride workup delivered cycloadducts **11a** (79% yield) and **11b** (87% yield). We were pleased to find that, to the limits of ^{1}H NMR detection, each cycloadduct (**11**) was obtained as a single diastereomer. However, since these four stereogenic centers occur on a five-membered ring, we were reluctant to make coupling-constant-based relative stereochemical assignments at this stage.

Treatment of proline derivatives **11** with phenyl isocyanate in dichloromethane at room temperature for 2 h resulted in urea formation, giving **12a** (83% yield) and **12b** (85% yield). Upon heating (90 °C) DMF solutions of **12** in the presence of *N*,*N*-diisopropylethylamine, hexahydro-1*H*-pyrrolo[1,2-*c*]imidazoles **13a** (82% yield) and **13b** (95% yield) were obtained as single isomers. The overall yield for this four-step process was excellent (**8b** → **13b** in 56% overall yield).

The relative stereochemical assignments for the four contiguous pyrrolidine stereogenic centers in **13a** were established at this point by single-crystal X-ray analysis (see crystallographic projection of **13a** in Figure 1). However, the stereochemistry at C7a−H (pyrroloimidazole numbering) was not that expected from endo-like transition state **10-T**. These stereochemical results are consistent with endo-like cycloaddition of a *trans*,*anti*-azomethine ylide followed by base-mediated C7a−H epimerization (C7a−Hβ → C7a−Hα) to deliver the thermodynamically preferred *trans*,*anti*,*trans*-pyrrolidine stereochemistry found in **13a**. Indeed, X-ray quality crystals



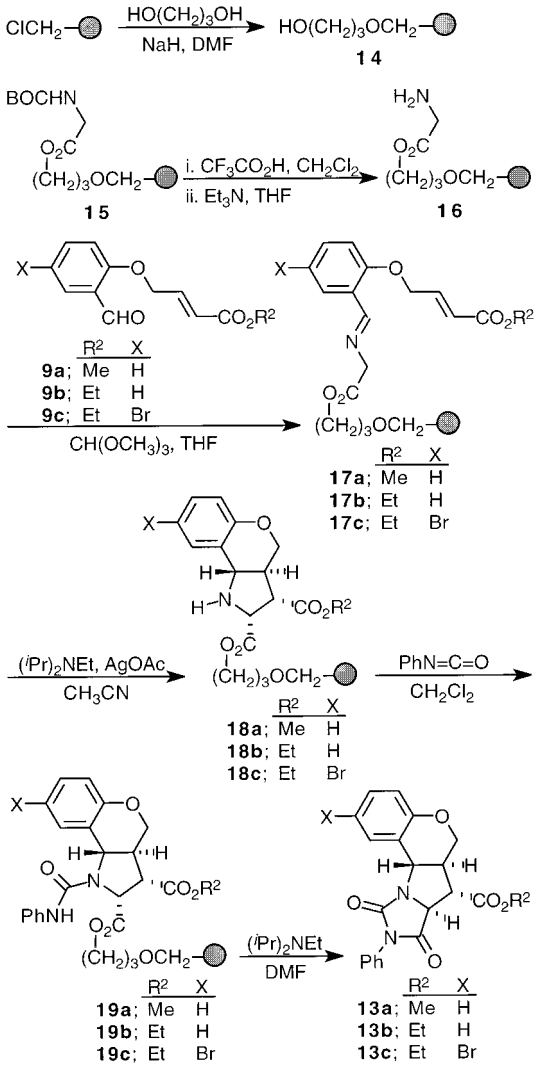
10-T

Figure 1. X-ray crystallographic presentations of (a) **12a** and (b) **13a** as well as (c) the preferred endo-like transition state (**10-T**) for **10** → **11**.

of urea **12a** have been obtained and analyzed by single-crystal X-ray analysis (see the crystallographic projection **12a** in Figure 1) showing that the stereochemistry of C7a here is opposite to that of **13a**. Taken together, these X-ray crystallographic studies establish that the 1,3-dipolar cycloaddition step (**10** → **11**) proceeds via an endo-like transition state followed by an epimerization at C7a during the carbanilide cyclization step (**12** → **13**).

Solid-Phase Chemistry. With these results in hand, we focused our attention on adapting the chemistry of Scheme 2 to a solid-phase format. Given the relative expense of Merrifield's resin (chloromethylated styrene/2% divinyl benzene copolymer) versus more elaborate linker-modified polystyrene resins, our initial thought

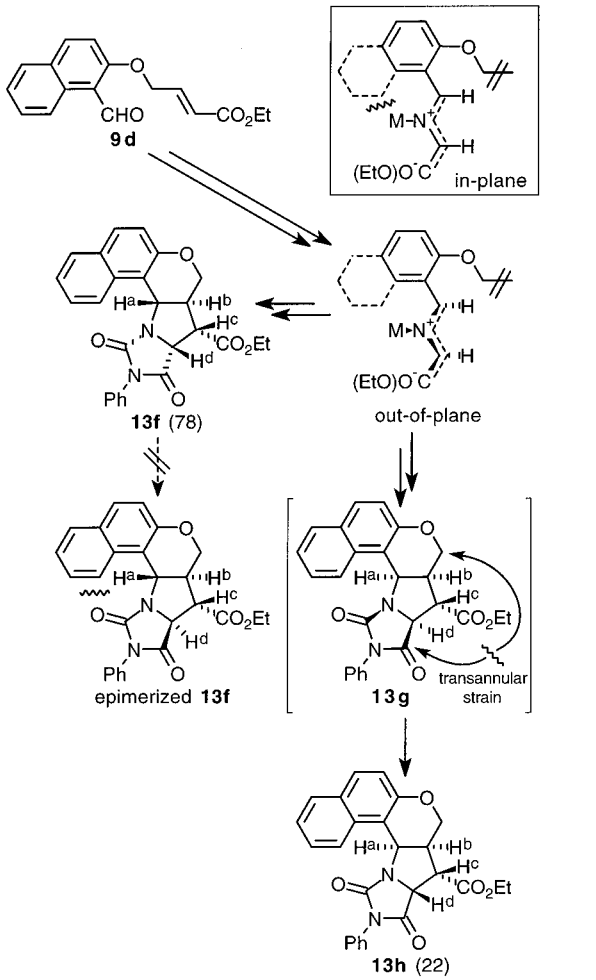
Scheme 3. Solid-Phase Route to 13



was to tether BOC-protected glycine to the polystyrene support by direct attachment (i.e., ®−CH_2Cl → ®−$CH_2O_2CCH_2NHBOC$ where ® = polymer).[12] This transformation was successful as judged by FT-IR analysis [1750 ($CH_2O_2CCH_2$) and 1719 (NHBOC) cm^{-1}], but the subsequent solid-phase elaboration and cyclative release of our pyrroloimidazole target proved altogether inadequate, as **13** was obtained in only trace amounts. While the cause for this solid-phase nonperformance was concealed by resin-imposed analytical limitations, inspection of the remaining four transformations (see Scheme 2) suggested that two steps (namely, **10** → **11** and **11** → **12**) might be particularly sensitive to resin-based steric constraints.

On the basis of the observations by Tietze et al.,[13] we decided to address this issue of resin-based steric limitations by inserting a spacer between the resin support and the glycine moiety, as we felt our cyclative release bias limited our options to varying the "spacer" part of the polymer−spacer−glycinate triad. Our decision was to

Scheme 4. 13 from 2-Hydroxy-1-naphthaldehyde



elaborate the "CH_2 spacer" of ®−**CH_2**O_2CCH_2NH−Boc to the "$CH_2OCH_2CH_2CH_2$ spacer"[13] of ®−**$CH_2OCH_2CH_2$-CH_2**O_2CCH_2NH−Boc. Treating Merrifield resin with excess 1,3-propanediol and sodium hydride in DMF resulted in *O*-alkylation to give resin **14** (3462 cm^{-1}). Esterfication of **14** with Boc-protected glycine with DCC/DMAP afforded polymer-bound Boc-glycinate **15,** which displayed two carbonyl functionalities in the FT-IR (1752 and 1722 cm^{-1}), providing strong evidence for conversion of Merrifield resin to **15**. Removal of the Boc group by trifluoroacetic acid (TFA/CH_2Cl_2 1:1) treatment followed by washing with triethylamine (50% Et_3N/THF) gave polymer-bound glycinate **16**, which displayed amine and carbonyl functional groups in the FT-IR (3396 and 1740 cm^{-1}). After attempts with $CaCl_2$, $MgSO_4$, Al_2O_3, and 4 Å molecular sieves as dehydrating agents, we concluded that triethyl orthoformate-mediated condensation of **9** with solid-phase amino ester **16** to give **17** was the most practical,[14] as the other desiccants proved difficult to remove from the polymer-bound condensation product. We observed two diagnostic peaks in the FT-IR of **17**: a composite carbonyl (i.e., the two ester carbonyls were not resolved) at 1729 cm^{-1} and an imine at 1639 cm^{-1}.

1,3-Dipolar cyclization of **17**, mediated by silver acetate and *N,N*-diisopropylethylamine in acetonitrile at room temperature, gave solid-phase proline derivative **18** as evidenced by disappearance of the 1639 cm^{-1} C=N peak

(12) For related ® −CH_2Cl → ®−$CH_2OC(=O)R'$, see: (a) Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661. (b) Kurth, M. J.; Ahlberg Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang, R.; Nakatsu, T.; Green, C. *J. Org. Chem.* **1994**, *59*, 5862.

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(14) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029.

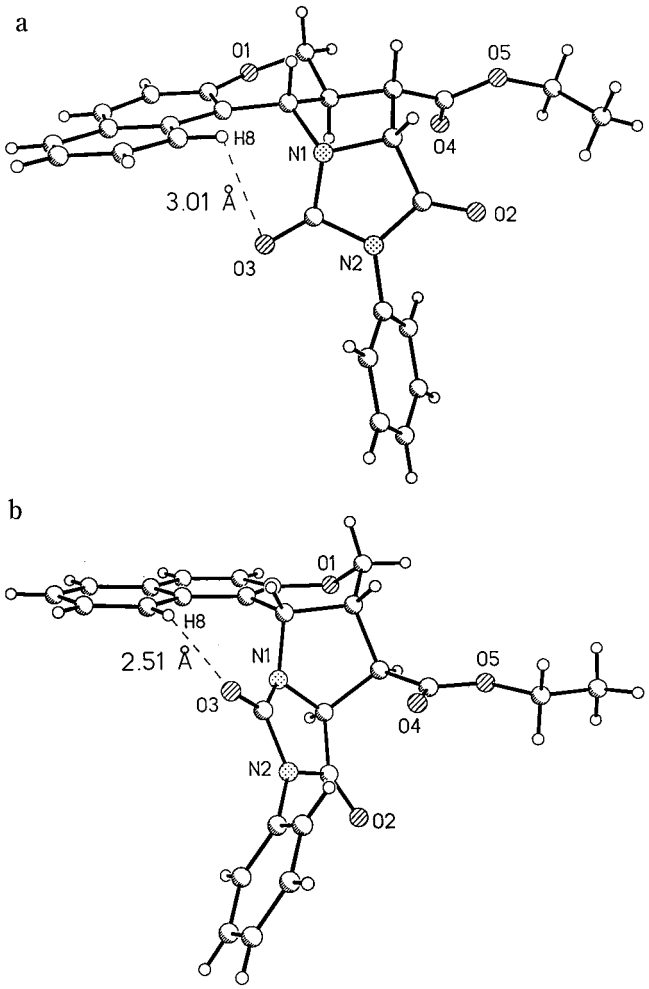
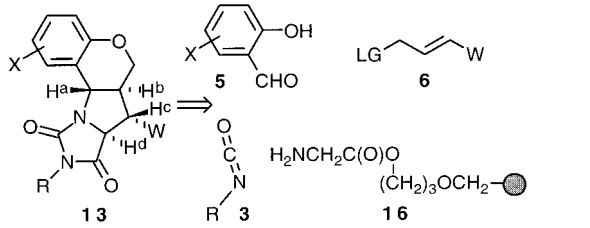


Figure 2. X-ray crystallographic presentations of (a) **13f** and (b) **13h**.

and appearance of secondary amine (3455 cm^{-1}) and ester (1743 cm^{-1}) peaks in the FT-IR spectrum. Treatment of **18** with phenyl isocyanate in dichloromethane at room temperature for 12 h resulted in urea formation, giving carbanilide **19** (FT-IR urea peak at 1680 cm^{-1}). Finally, hydantoin formation with concomitant release of product was affected by heating (110 °C) a DMF solution of **19** with *N,N*-diisopropylethylamine. Pyrroloimidazole **13a** was obtained in good yield (98 mg; 13% overall yield, translating to ~77% yield per step in this eight-step sequence). The relative stereochemistry at the four contiguous pyrrolidine stereogenic centers in **13a** and **13b** were identical for both solution- and solid-phase routes (as judged by mp, ^{1}H NMR, and ^{13}C NMR). On the basis of our solution studies, we presume that base-mediated epimerization of C7a−Hβ → C7a−Hα occurs in the final solid-phase step (**19** → **13**). Employing 5-bromosalicylaldehyde in place of salicylaldehyde leads to **9c,** which delivers **13c** (**16** + **9c**), a bromo analogue of **13b**.

Interestingly, use of 2-hydroxy-1-naphthaldehyde (**16** + **9d**) results in a different stereochemical arrangement about the pyrrolidine ring (Scheme 4). With this substrate, the major product (**13f**) is obtained with trans,anti,cis-stereochemistry (**13a**−**c** have trans,anti,trans-stereochemistry) and a minor product (**13h**) is obtained with cis,anti,cis-stereochemistry (see Figure 2). We believe two separate issues are involved in determining the stereochemistry of **9d** → **13f**/**h**. First, salicylaldehyde

Table 1. Diversity Potential in the Preparation of 13



product	X	W	R	yield (%)[a]
13a	H	CO_2Me	C_6H_5	13
13b	H	CO_2Et	C_6H_5	14
13c	4-Br	CO_2Et	C_6H_5	10
13d	H	CO_2Me	C_6H_4-4-Cl	9
13e	H	CO_2Me	$(CH_2)_3CH_3$	6
13f[b]/**h**[c]	-−C_4H_4−[d]	CO_2Et	C_6H_5	15[e]

[a] Overall yield for eight steps. [b] $H^a/H^b/H^c/H^d$ configuration of **13f** is trans,anti,cis. [c] $H^a/H^b/H^c/H^d$ configuration of **13h** is cis,anti,cis. [d] That is, derived from 2-hydroxy-1-naphthaldehyde. [e] **13f**:**13h** is 78:22.

(**9a**−**c**) derived azomethine ylides can adapt an "in-plane" (conjugated) conformation which leads to the observed trans,anti,cis-intermediate (**18a**−**c**) by endo addition. In contrast, the 2-hydroxy-1-naphthaldehyde-derived azomethine ylide is forced "out-of-plane", where favored endo addition again delivers a trans,anti,cis-intermediate while competing exo addition leads to a cis,anti,trans-intermediate. Second, *N*-acylation and carbanilide cyclization delivers **13f** as the major product *without* H^d-epimerization and **13h** as the minor product *after* H^d-epimerization of hypothetical intermediate **13g**. We believe the naphthalene ring prevents **13f** H^d-epimerization because this structural change would bring O3 of the hydantoin ring into close proximity with H8 of the naphthalene ring (see Figure 2a). Epimerization **13g** → **13h** relieves transannular strain without placing O3 of the hydantoin ring into close proximity with H8 of the naphthalene ring (see Figure 2b).

With the examples delineated in Table 1, this solid-phase approach to **13** accommodates three-component product diversity from reagents **3** (i.e., "R"), **5** (i.e., "X"), and **6** (i.e., "W"). A number of reaction protocols for the cyclative release step (solution-phase **12** → **13** and solid-phase **19** → **13**) were evaluated. We discovered that excess triethylamine in DMF (90 °C) mediates hydantoin formation with concomitant C7a−H epimerization such that release of substrate from the solid-phase generates **13** with trans,anti,trans-stereochemistry.

Finally, the results presented in Scheme 3 validate our decision to employ a spacer ("$CH_2OCH_2CH_2CH_2$") as our glycinate starting material (**16**; ®−**$CH_2OCH_2CH_2CH_2$**$O_2CCH_2NH_2$). Our results are consistent with polymer-induced steric encumbrance in addressing the glycinate moiety. We believe two transformations, **17** → **18** and **19** → **13**, are particularly sensitive to steric constraints and benefit from switching to glycinate **16**.

Summary

In conclusion, we have developed a novel route to hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole derivatives by solid-phase azomethine ylide cycloaddition (→proline) and carbanilide cyclization (→hydantoin) chemistry. As discussed above, the key to successfully executing this eight-step protocol was insertion of a spacer moiety between the solid-phase support and glycinate functional group.

Other experiments address the stereoselectivity of the 1,3-dipolar cycloaddition step as well as the cyclative release step.

Experimental Section

General. All chemicals were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merk, 70−230 mesh). NMR spectra (^{1}H at 300 MHz; ^{13}C at 75 MHz) were recorded in $CDCl_3$ solvent, and chemical shifts are expressed in ppm relative to internal TMS. Single-crystal X-ray structure determinations were obtained through the X-ray Crystallography Facility, Department of Chemistry, University of California, Davis, CA Concentration refers to rotoevaporation.

Solution-Phase Procedures. **General Procedure for the Preparation of Salicylaldehyde Ethers [Specific for 9b]**. To an ice-cold suspension of sodium hydride (180.2 mg, 7.51 mmol) in DMF (20 mL) was added salicylic aldehyde (610.0 mg, 5.00 mmol). After 20 min, ethyl 4-bromocrotonate (1.41 g, 5.5 mmol) was added and the mixture was stirred at ambient temperature for 1 h. The reaction was quenched with water (30 mL) and extracted with ether (25 mL × 3), and the combined organic solution was washed with brine, dried (Na_2SO_4), and concentrated. The resulting oily compound was purified by flash column chromatography (EtOAc/hexane 1:4) to give **9b** (950 mg, 4.06 mmol) as a colorless oil in 81% yield.

9a:[9b] yield = 75%; IR (KBr) 1727 and 1686 cm^{-1}; ^{1}H NMR δ 10.53 (s, 1H), 7.86 (d, 1H, J = 6 Hz), 7.53 (m, 1H), 7.13−6.91 (m, 3H), 6.23 (d, 1H, J = 15 Hz), 4.83 (m, 2H), 3.75 (s, 3H); ^{13}C NMR δ 189.68, 166.71, 160.75, 141.98, 136.38, 129.48, 125.91, 122.85, 122.07, 113.22, 67.55, 52.31.

9b:[9b] yield = 81%; IR (KBr) 1718 and 1687 cm^{-1}; ^{1}H NMR δ 10.52 (s, 1H), 7.83 (d, 1H, J = 6 Hz), 7.54 (m, 1H, 7.11−6.90 (m, 3H), 6.18 (d, 1H, J = 15 Hz), 4.80 (m, 2H), 4.20 (q, 2H, J = 7 Hz), 1.31 (t, 3H, J = 7 Hz); ^{13}C NMR δ 189.64, 166.23, 160.75, 141.61, 136.33, 129.34, 125.83, 123.22, 121.97, 113.19, 67.52, 61.17, 14.70.

9c: yield = 80%; IR (KBr) 1719 and 1685 cm^{-1}; ^{1}H NMR δ 10.44 (s, 1H), 7.93 (d, 1H, J = 3 Hz), 7.63 (dd, 1H, J = 3, 9 Hz), 7.07 (dt, 1H, J = 3, 15 Hz), 6.85 (d, 1H, J = 9 Hz), 6.18 (d, 1H, J = 15 Hz), 4.81 (m, 2H), 4.22 (q, 2H, J = 7 Hz), 1.31 (t, 3H, J = 7 Hz); ^{13}C NMR δ 187.63, 165.26, 158.83, 140.37, 137.96, 130.90, 126.11, 122.56, 114.53, 113.88, 67.20, 60.44, 13.95. Anal. Calcd for $C_{13}H_{13}BrO_4$: C, 49.86; H, 4.18. Found: C, 49.79; H, 4.21.

9d:[9b] yield = 78%; IR (KBr) 1718 and 1671 cm^{-1}; ^{1}H NMR δ 10.98 (s, 1H), 9.25 (d, 1H, J = 9 Hz), 8.05 (d, 1H, J = 9 Hz), 7.77 (d, 1H, J = 6 Hz), 7.64 (t, 1H, J = 6 Hz), 7.43 (t, 1H, J = 6 Hz), 7.25−7.11 (m, 2H), 6.22 (dt, 1H, J = 3, 15 Hz), 4.95 (m, 2H), 4.23 (q, 2H, J = 7 Hz), 1.31 (t, 3H, J = 7 Hz); ^{13}C NMR δ 191.86, 166.25, 162.81, 141.58, 138.02, 132.17, 130.58, 129.57, 128.80, 125.74, 125.69, 123.54, 118.12, 113.97, 68.61, 61.32, 14.78. Anal. Calcd $C_{17}H_{16}O_4$: C, 71.82; H, 5.62. Found: C, 71.78; H, 5.75.

General Procedure for the Preparation Schiff Base Intermediates [Specific for 10b]. A mixture of glycine benzyl ester trifluoroacetate (**8b**; 1.02 g, 3.6 mmol) and *N*,*N*-diisopropylethylamine (0.61 mL, 3.66 mmol) in dry CH_2Cl_2 (30.0 mL) was stirred at ambient temperature for 15 min. Aldehyde **9b** (860.0 mg, 3.66 mmol) and activated 4 Å molecular sieves (3.0 g) were added, and stirring was continued at ambient temperature for 15 h. The mixture was filtered and the filtrate was washed with water (30 mL × 2) and brine, dried (Na_2SO_4), and concentrated. The resulting yellow oil (**10b**; 1.15 g, 80% yield) was used without further purification due to its moisture sensitivity.

10a:[9b] yield = 83%; ^{1}H NMR δ 8.77 (s, 1H), 8.03 (m, 1H), 7.41−6.84 (m, 4H), 6.18 (m, 1H), 4.77 (m, 2H), 4.42 (s, 2H), 4.24 (m, 2H, J = 7 Hz), 3.77 (s, 3H), 1.30 (t, 3H, J = 7 Hz).

10b:[9b] yield = 80%; ^{1}H NMR δ 8.70 (s, 1H), 7.98 (m, 1H), 7.33−6.77 (m, 9H), 6.08 (dt, 1H, J = 16 Hz, 2.1 Hz), 5.15 (s, 2H), 4.68 (m, 2H), 4.41 (s, 2H), 4.15 (q, 2H, J = 7 Hz), 1.23 (t, 3H, J = 7 Hz).

General Procedure for Azomethine Ylide Cycloaddition [Specific for 11b]. A mixture of **10b** (1.43 g, 3.6 mmol), silver acetate (0.90 g, 5.4 mmol), and DIPEA (0.46 g, 3.6 mmol) in dry acetonitrile (20.0 mL) was stirred at ambient temperature for 3 h and then quenched with aqueous ammonium chloride. The mixture was extracted with ether (20 mL × 3), washed with brine, and dried (Na_2SO_4). Concentration gave an oil which was purified by flash column chromatography (EtOAc/hexane 1:4) to give **11b** (1.21 g, 3.29 mmol) in 87% yield.

11a:[9b] yield = 79%; mp 115−116 °C; IR (KBr) 1740 cm^{-1}; ^{1}H NMR δ 7.31−7.15 (m, 2H), 6.93−6.83 (m, 2H), 4.58 (dd, 1H, J = 10 Hz, 4.2 Hz) 4.38 (d, 1H, J = 10 Hz), 4.30−4.10 (m, 3H), 3.77 (d, 1H, J = 11.4 Hz), 3.70 (s, 3H), 3.08 (t, 1H, J = 11.4 Hz), 2.50 (b−s, 1H), 2.39 (m, 1H), 1.27 (t, 3H, J = 7 Hz); ^{13}C NMR δ 171.62, 171.10, 153.14, 128.72, 124.55, 124.44, 120.37, 116.11, 69.15, 63.86, 61.70, 60.40, 52.06, 50.34, 46.91, 14.05. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.82; H, 6.22; N, 4.59.

11b:[9b] yield = 87%; IR (KBr) 1736 cm^{-1}; ^{1}H NMR δ 7.40−6.68 (m, 9H), 5.22 (dd, 2H, J = 12.0, 12.0 Hz), 4.99 (d, 1H, J = 6.6 Hz), 4.37 (d, 1H, J = 9.3 Hz), 4.02(dd, 1H, J = 9.3, 3.6 Hz), 3.88 (d, 1H, J = 7.2 Hz), 3.65−3.49 (m, 3H), 2.97 (m, 1H), 0.65 (t, 3H, J = 6.0 Hz); ^{13}C NMR δ 173.33, 172.19, 155.58, 135.81, 128.64, 128.56, 128.33, 128.16, 125.84, 125.45, 120.91, 110.53, 68.14, 66.89, 63.51, 61.14, 60.34, 52.26, 47.77, 13.65.

General Procedure for Urea Formation [Specific for 12b]. To a solution of **11b** (1.27 g, 3.33 mmol) in dry CH_2Cl_2 (30.0 mL) was added phenyl isocyanate (476.5 mg, 4.01 mmol), and the mixture was stirred at ambient temperature for 2 h. The solvent was removed by rotary evaporation and the oily residue was triturated with ether to give **12b** (1.4 g, 2.79 mmol) as a colorless oil in 85% yield.

12a: yield = 83%; mp 205−206 °C; IR (KBr) 1735, 1673, 1602, 1542, 1216, 754 cm^{-1}; ^{1}H NMR δ 8.12 (s, 1H), 7.50−6.81 (m, 9H), 4.93 (d, 1H, J = 9 Hz), 4.85 (dd, 1H, J = 3 Hz), 4.67 (d, 1H, J = 12 Hz), 4.2 (m, 5H), 3.75 (s, 3H), 3.05 (m, 2H), 1.33 (t, 3H, J = 7 Hz); ^{13}C NMR δ 170.06, 169.26, 157.02, 152.82, 138.54, 128.96, 128.22, 125.98, 124.71, 123.29, 120.16, 119.18, 115.81, 69.70, 64.31, 62.56, 60.27, 52.17, 46.35, 41.41, 13.87. Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.86; H, 5.66; N, 6.61. X-ray crystal structure **12a** shown in Figure 1.

12b: yield = 85%; mp 177−178 °C; IR (KBr) 3371, 3064, 3033, 1741(s), 1675(s), 1600, 1539, 11189, 756 cm^{-1}; ^{1}H NMR δ 7.99 (s, 1H), 7.41−6.85 (m, 14H), 5.32 and 5.16 (AB-q, 2H, J = 12 Hz), 5.01 (d, 1H, J = 7.2 Hz), 4.90 (dd, 1H, J = 10, 4 Hz), 4.75 (d, 1H, J = 10 Hz), 4.30 (t, 1H, J = 10 Hz), 4.01 (m, 2H), 3.17 (m, 2H), 1.18 (t, 3H, J = 7 Hz); ^{13}C NMR δ 169.67, 168.76, 157.12, 152.90, 138.44, 134.18, 129.10, 129.00, 128.93, 128.88, 128.33, 128.70, 128.34, 126.00, 124.77, 123.33, 120.23, 119.17, 115.95, 69.90, 68.32, 64.53, 61.40, 60.60, 46.72, 41.48, 13.94. Anal. Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.15; H, 5.59; N, 5.55.

General Procedure for Pyrroloimidazole Preparation [Specific for 13b]. A solution of urea **12b** (470.0 mg, 0.94 mmol) and DIPEA (15 mL, 9.4 mmol) in DMF (15.0 mL) was stirred at 90 °C for 15 h. The resulting mixture was diluted with 3 N aqueous HCl (2.0 mL) and extracted with ether (20 mL × 3). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The resulting crude oil (402.1 mg) was crystallized from ether to give **13b** (353.2 mg, 0.90 mmol) as a white solid in 95% yield.

13a: yield = 82%; mp 203−204 °C; IR (KBr) 1722, 1677, 1600, 1203 cm^{-1}; ^{1}H NMR δ 7.56−6.83 (m, 9H), 4.90 (d, 1H, J = 10 Hz), 4.60 (m, 2H), 4.36 (t, 1H, J = 10.5 Hz), 3.85 (s, 3H), 3.04 (m, 2H); ^{13}C NMR δ 170.04, 168.97, 160.69, 152.62, 131.54 129.30, 129.12, 128.46, 126.14, 125.73, 123.83, 120.77, 116.08, 67.99, 67.03, 62.06, 53.03, 47.47, 46.35. Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.29; H, 4.71; N, 7.40. X-ray crystall structure **13a** shown in Figure 1.

13b: yield = 95%; mp 197−198 °C; IR (KBr) 1724, 1649, 1599 cm^{-1}; ^1H NMR δ 7.48−6.75 (m, 9H), 4.82 (d, 1H, J = 10 Hz), 4.50 (m, 2H), 4.33−4.19 (m, 3H), 2.92 (m, 2H), 1.25 (t, 3H, J = 7 Hz); ^{13}C NMR δ 170.09, 168.47, 160.73, 152.56, 129.26, 129.18, 129.11, 128.43, 126.12, 125.71, 123.81, 120.72, 116.02, 68.03, 67.05, 62.17, 62.07, 47.46, 46.56, 14.16. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.34; H, 5.20; N, 7.21.

Solid-Phase Procedures. **Preparation of Resin 14**. Sodium hydride (264.0 mg, 11.0 mmol) was added to a solution of 1,3-propanediol (760.1 mg, 10.0 mmol) in cold (0 °C) DMF (50.0 mL). The solution was stirred at ambient temperature for 2 h and Merrifield resin (chloromethylated 2% vinylbenzene−styrene copolymer; 1.0 g, 2.0 mmol) was added. The resulting suspension was stirred for 48 h at 100 °C. Resin **14** was isolated by filtration, washed (sequentially with THF, DMF/H_2O 1:1, DMF, THF, CH_2Cl_2, and MeOH), and dried: IR (KBr), 3462(OH) cm^{-1}.

Preparation of Resin 15. Dicyclohexylcarbodiimide (DCC; 1.24 g, 6.0 mmol) and *N*,*N*-(dimethylamino)pyridine (DMAP; 122.2 mg, 1.0 mmol) were added to a suspension of Boc-glycine (1.05 g, 6.0 mmol) and resin **14** (1.00 g, 2.0 mmol) in dry CH_2Cl_2 (50.0 mL). The mixture was stirred for 24 h at ambient temperature and the resin isolated by filtration. Resin **15** was washed (CH_2Cl_2, THF, and MeOH) and dried: IR (KBr) 1753 (ester C=O), 1722 (Boc C=O) cm^{-1}.

Preparation of Resin 16. Trifluoroacetic acid (7.40 g, 5.0 mL, 65.0 mmol) was added to a suspension of **15** (1.0 g, 2.0 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C. After stirring of the mixture at 0 °C for 2 h, the resin was isolated by filtration to give the TFA salt (washed with CH_2Cl_2): IR (KBr) 3441 (NH_3^+), 1752 (ester C=O), 1679 ($CF_3CO_2^-$) cm^{-1}.

This TFA salt (1.0 g, 2.0 mmol) was added to a solution of triethylamine (5.0 mL) in dry THF (5.0 mL) at room temperature. After stirring for 15 min, the resin was isolated by filtration and washed with CH_2Cl_2 and dried to give **16**: IR (KBr) 3391($-NH_2$), 1739 (ester C=O) cm^{-1}.

General Procedure for the Preparation of Resin-Bound Benzylidene Glycinates 17. Salicylicaldehyde derivative **9a** (1.32 g, 6.0 mmol) was added to a stirred suspension of resin **16** (1.0 g, 2.0 mmol) in dry THF (10.0 mL) at ambient temperature. Trimethyl orthoformate (11.0 mL, 100.0 mmol) was added and stirring was continued for 24 h. The resulting resin was isolated by filtration, washed (THF, CH_2Cl_2, and MeOH), and dried. IR (KBr): **17a,** 1729 (ester C=O), 1639 (imine C=N) cm^{-1}; **17b,** 1723 (ester C=O), 1639 (imine C=N) cm^{-1}; **17c,** 1725 (ester C=O), 1646 (imine C=N) cm^{-1}; **17d,** 1731 (ester C=O), 1641 (imine C=N) cm^{-1}.

General Procedure for the Preparation of Resin-Bound 1,3-Dipolar Cycloadduct [Specific for 18a]. *N*,*N*-Diisopropylethylamine (722.0 mg, 6.0 mmol) was added to a suspension of resin **17a** (1.0 g, 2.0 mmol) in dry acetonitrile (30.0 mL) at ambient temperature. Silver acetate (1.0 g, 6.0 mmol) was added and stirring was continued for 48 h. The resin was isolated by filtration, washed (CH_3CN, 3 N aqueous HNO_3, THF, CH_2Cl_2, and MeOH), and dried. IR (KBr) showed a disappearance of the imine C=N peak: **18a,** 1741 (ester C=O) cm^{-1}; **18b,** 1739 (ester C=O) cm^{-1}; **18c,** 1735 (ester C=O) cm^{-1}; **18d,** 1733 (ester C=O) cm^{-1}.

General Procedure for the Preparation of Resin-Bound Urea [Specific for 19a]. Phenyl isocyanate (71.4 mg, 6.0 mmol) was added to a suspension of resin **18a** (1.0 g, 2.0 mmol) in dry CH_2Cl_2 at ambient temperature and the reaction mixture was stirred for 24 h. The resin was isolated by filtration, washed (CH_2Cl_2 and MeOH), and dried. IR (KBr) showed a disappearance of the imine C=N peak: **19a,** 1740 (ester C=O), 1680 (urea C=O) cm^{-1}; **19b,** 1734 (ester C=O), 1681 (urea C=O) cm^{-1}; **19c,** 1739 (ester C=O), 1681 (urea C=O) cm^{-1}; **19d,** 1747 (ester C=O), 1673 (urea C=O) cm^{-1}; **19e,** 1734 (ester C=O), 1687 (urea C=O) cm^{-1}; **19f,** 1734 (ester C=O), 1679 (urea C=O) cm^{-1}.

General Procedure for the Preparation of Pyrroloimidazoles [Specific for 13a]. *N*,*N*-Diisopropylethylamine (2.41 g, 20.0 mmol) was added to a suspension of resin **19a** (1.0 g, 2.0 mmol) in dry DMF (20.0 mL) at ambient temperature and the mixture was stirred at 100 °C for 36 h. After filtration, the resin was washed with CH_2Cl_2 (20 mL × 3) and EtOAc (20 mL × 3) and the combined filtrate was concentrated. Water (100 mL) was added to the resulting solution and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic solution was washed with water (30 mL × 3), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (EtOAc/hexanes 1:4) gave pyrroloimidazole **13a** (98.4 mg, 0.26 mmol) in 13% overall yield through eight steps from Merrifield resin.

13a: overall yield (eight steps) = 13%; mp 203−204 °C; IR (KBr), ^1H NMR, ^{13}C NMR, and EA as above.

13b: overall yield (eight steps) = 14%; mp 197−198 °C; IR (KBr), ^1H NMR, ^{13}C NMR, and EA as above.

13c: overall yield (eight steps) = 10%; mp 176−177 °C; IR ($CDCl_3$) 1725, 1475, 1400, 1193 cm^{-1}; ^1H NMR δ 7.66−7.25 (m, 7H), 6.71 (d, 1H, J = 9 Hz), 4.87 (d, 1H, J = 9 Hz), 4.54 (m, 2H), 4.32 (m, 3H), 2.97 (m, 2H), 1.32 (t, 3H, J = 7 Hz); ^{13}C NMR δ 169.82, 168.24, 160.64, 151.74, 132.12, 129.09, 128.85, 128.40, 125.82, 125.68, 117.91, 112.90, 68.16, 66.97, 63.02, 61.66, 47.21, 46.57, 14.11. Anal. Calcd for $C_{22}H_{19}BrN_2O_5$: C, 56.07; H, 4.06; N, 5.94. Found: C, 56.27; H, 4.19; N, 5.86.

13d: overall yield (eight steps) = 9%; mp 187−188 °C; IR ($CDCl_3$) 1723, 1496, 1397, 1202 cm^{-1}; ^1H NMR δ 7.58−6.83 (m, 8H), 4.92 (d, 1H, J = 10 Hz), 4.56 (m, 2H), 4.35 (t, 1H, J = 11 Hz), 3.85 (s, 3H), 3.01−3.08 (m, 2H); ^{13}C NMR δ 169.82, 168.88, 160.29, 152.63, 134.23, 130.09, 129.34, 126.82, 126.06, 123.70, 120.81, 116.15, 68.01, 67.02, 62.24, 53.03, 47.61, 46.48. Anal. Calcd for $C_{21}H_{17}ClN_2O_5$: C, 61.10; H, 4.15; N, 6.79. Found: C, 61.33; H, 4.22; N, 6.64.

13e: overall yield (eight steps) = 6%; IR ($CDCl_3$) 1714, 1440, 1414, 1214 cm^{-1}; ^1H NMR δ 7.45−6.73 (m, 4H), 4.67 (d, 1H, J = 10 Hz), 4.48 (dd, 1H, J = 10.4 Hz), 4.36 (d, 1H, J = 10.8 Hz), 4.25 (t, 1H, J = 9 Hz), 3.75 (s, 3H), 3.47 (dt, 2H, J = 7, 4 Hz), 2.84−2.77 (m, 2H), 1.62−1.52 (m, 2H), 1.32−1.27 (m, 2H), 0.94−0.85 (t, 3H, J = 7 Hz); ^{13}C NMR δ 171.51, 169.07, 162.17, 152.64, 129.22, 126.16, 123.97, 120.74, 116.02, 68.09, 67.20, 61.92, 52.68, 47.61, 46.36, 39.22, 29.92, 19.97, 13.55. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.42; H, 6.40; N, 7.52.

13f: overall yield (eight steps) = 11.7%; mp 199−200 °C; IR ($CDCl_3$) 1722, 1401, 1210 cm^{-1}; ^1H NMR δ 8.26−6.95 (m, 11H), 4.75 (d, 1H, J = 9 Hz), 4.50 (dd, 2H, J = 15, 6 Hz), 4.22−4.04 (m, 3H), 3.20 (dd, 1H, J = 9, 9 Hz), 3.01 (m, 1H); 1.23 (t, 3H, J = 6 Hz); ^{13}C NMR δ 169.72, 169.68, 157.74, 152.36, 133.12, 131.36, 130.35, 128.87, 128.66, 128.29, 128.04, 126.65, 126.21, 125.14, 123.84, 118.54, 111.44, 67.24, 64.54, 62.25, 61.09, 47.87, 46.36, 14.13. X-ray crystallographic data available; see Supporting Information.

13h: overall yield (eight steps) = 3.3%; mp 185−186 °C; IR ($CDCl_3$) 1721, 1472, 1404, 1226 cm^{-1}; ^1H NMR δ 8.35−6.96 (m, 11H), 6.01 (d, 1H, J = 9 Hz), 4.27−4.07 (m, 5H), 3.73 (t, 1H, J = 9 Hz), 3.25 (t, 1H, J = 6 Hz), 1.20 (t, 3H, J = 9 Hz); ^{13}C NMR δ 171.97, 170.32, 158.744, 154.12, 132.42, 131.82, 130.78, 130.03, 129.14, 128.57, 128.36, 127.44, 126.23, 124.42, 123.37, 118.65, 111.61, 68.16, 66.97, 62.02, 61.66, 47.21, 46.57, 14.11. X-ray crystallographic data available; see Supporting Information.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, and FT-IR spectra as well as X-ray crystallographic data for compounds **13f** and **13h**; X-ray crystallographic data for compounds **12a** and **13a** (10 pages). This material is contained in 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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