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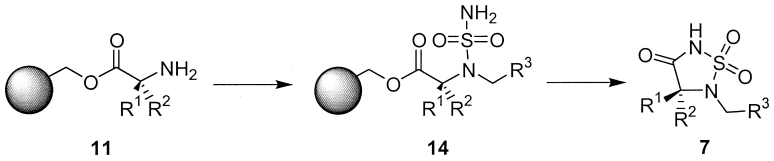

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Synthesis of a Sulfahydantoin Library[1]

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A five-step solid-phase synthesis of sulfahydantoins from α-amino acids and aldehydes was developed. The synthetic method allows the use of hindered amino acids, including Val, Phg, and Aib, and use of aromatic aldehydes substituted with electron-withdrawing and -donating groups. Some limitations were encountered with amino acids with reactive side chains. A small but diverse library of compounds was produced for biological testing.

Introduction

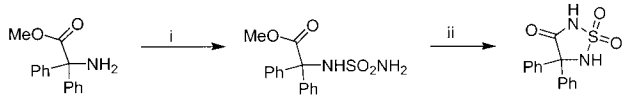
Combinatorial chemistry has its roots in peptide synthesis.[2−4] Furthermore, many heterocyclic libraries have incorporated amino acid building blocks.[5−7] The first example of a sulfahydantoin (1,2,5-thiadiazolidin-3-one 1,1-dioxide), compound **1**, was described in the literature in 1965,[8] and since then a number of groups have reported on the synthesis[9−15] of this heterocycle, usually from amino acid precursors, and the biological activity of the compounds prepared.[14,16−23] Sulfahydantoins substituted at the 2-position have received significant attention recently as serine protease inhibitors.[16−21] Our interest was drawn to 2-unsubstituted sulfahydantoins as a potentially fertile area for the discovery of plant systemic crop protection chemicals. By analogy with the artificial sweetener saccharin (**2**) and other acylsulfonamides, we anticipated that the proton at the 2-position of the sulfahydantoin would have a pK_a comparable to that of a carboxylic acid.[24−26] It is well established that compounds with pK_as in the range of carboxylic acids and with log *P* values less than 3 are transported from the leaves to the growing points of plants via the phloem.[27,28] Such mobility is a highly desirable property in new crop protection chemicals.[29]

Synthesis Design and Chemistry Development. Examination of the literature suggested that the route to **1** used by Timberlake and co-workers[9] (Scheme 1) could be generalized to work with other amino acid esters in addition to diphenylglycine and that it might be adapted to solid phase simply by replacing the methyl ester in **3** with an analogous resin-bound ester (cf. **11**, Scheme 3). An additional site of diversity could be introduced by reductive alkylation of the α-amino acid nitrogen ($N - 5$) in a resin-bound version of **11** with various aldehydes prior to treatment with sulfamoyl chloride, which is used to introduce the SO_2NH_2 moiety. Finally cyclitive cleavage of the sulfahydantoin from the resin was anticipated to give high-purity products.[30]

Prior to initiating development of the proposed chemistry on solid phase, 4,5-disubstituted sulfahydantoin **7a** was prepared in solution to demonstrate the general feasibility of the route described above and to provide intermediates and a final compound as spectroscopic standards (Scheme 2). Thus, phenylalanine ethyl ester was reductively alkylated with 4-methoxybenzaldehyde in the presence of sodium cyanoborohydride to afford **5**. Sulfamoyl chloride was prepared by reaction of chlorosulfonyl isocyanate and formic acid[31] and reacted with **5** to give the expected sulfamide **6**. Alternatively, treatment of **5** with $SO_2(NH_2)_2$ in refluxing dioxane also gave **6**.[32] Cyclization was effected with sodium methoxide in methanol at room temperature to provide **7a**. The pK_a of this compound was determined to be 3.5,[33] in accordance with our expectations.

Development of the chemistry on solid phase began with loading Fmoc-protected phenylalanine **9a** onto Wang resin (**8W**) using diisopropylcarbodiimide (DIC) and 4-dimethy-

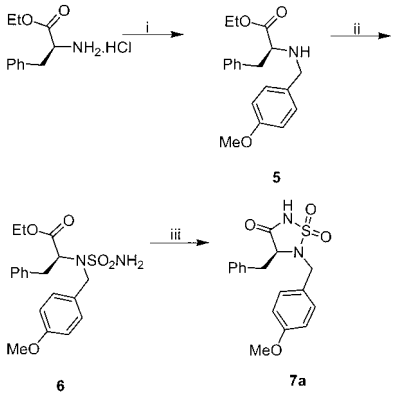
Scheme 1. Timberlake et al. Synthesis of a Sulfahydantoin[8,a]



3 4 1

[a] (i) NH_2SO_2Cl, Et_3N, THF. (ii) NaH, THF.

Scheme 2. Solution-Phase Synthesis of **7a**[a]



5 6 7a

[a] (i) 4-$MeOC_6H_4CHO$, NaOAc, $NaCNBH_3$, MeOH. (ii) H_2NSO_2Cl, Et_3N, CH_2Cl_2. (iii) NaOMe, MeOH.

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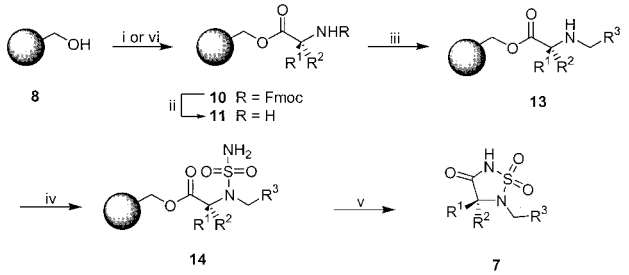
Scheme 3. Solid-Phase Synthesis of Sulfahydantoins[a]

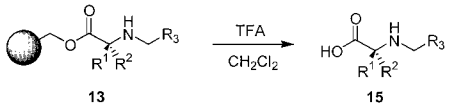


A Resin = AB-MBHA, **W** Resin = Wang resin
a R^1 = $PhCH_2$, R^2 = H, R^3 = 4-$MeOC_6H_4$
b R^1 = $PhCH_2$, R^2 = H, R^3 = Et
c R^1 = $PhCH_2$, R^2 = H, R^3 = 3-pyridyl
d R^1 = $PhCH_2$, R^2 = H, R^3 = 2,4-diCl-C_6H_3
e R^1 = Me, R^2 = Me, R^3 = 4-$MeOC_6H_4$
f R^1 = (S)-1-methylpropyl, R^2 = H, R^3 = 4-$MeOC_6H_4$
g R^1 = H, R^2 = (S)-1-methylpropyl, R^3 = 4-$MeOC_6H_4$

[a] (i) Fmoc−$NHCR^1R^2CO_2H$, (**9**, 3 equiv), DIC (3 equiv), DMAP (0.3 equiv), CH_2Cl_2/DMF (5:1), 2 h, room temp. (ii) Piperidine/DMF (1:4), 20 min, room temp. (iii) R^3CHO, (**12**, 11 equiv), HOAc (2 equiv), CH_2Cl_2/$(MeO)_3CH$ (1:1), 5 h, room temp, then $NaCNBH_3$ (11 equiv), CH_2Cl_2/$(MeO)_3CH$ (1:1), 3 × 2 h, room temp. (iv) H_2NSO_2Cl (**3**, 6 equiv), 2,4,6-collidine (10 equiv), CH_2Cl_2, 4 h, room temp. (v) DBU, CH_2Cl_2, 5h, room temp. (vi) Fmoc−$NHCR^1R^2CO_2H$, 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide, *N*-methylimidazole, CH_2Cl_2.

laminopyridine (DMAP) to afford **10Wa** (Scheme 3). Initial trials using DMF as solvent resulted in incomplete loading. Complete coupling to the resin, as indicated by MAS NMR, was achieved by switching to CH_2Cl_2/DMF (5:1) and repeating the process twice. Removal of the Fmoc protecting group with piperidine in DMF gave **11Wa.** The procedure of Szardenings et al.,[34] which uses $NaCNBH_3$ as reducing agent and $(MeO)_3CH$ as solvent and dehydrating agent, and the procedure of Gordon et al.,[35] which employs $NaBH(OAc)_3$ as reducing agent, were explored to effect reductive alkylation of the amino group with 4-methoxybenzaldehyde (**12a**, Scheme 3). A modification of the former procedure using CH_2Cl_2/$(MeO)_3CH$ (1:1) as solvent and three successive additions of $NaCNBH_3$ gave the best results in our hands. Treatment of the resulting resin-bound *N*-benzylamino acid **13Wa** with sulfamoyl chloride in CH_2Cl_2 in the presence of 2,4,6-collidine provided the desired resin-bound sulfamide **14Wa**. The infrared S═O and N−H stretches expected for **14Wa** could not be detected by FTIR using the DRIFTS technique;[36] however, elemental analysis showed the expected amount of sulfur in the resin. Examination of the resin by the more sensitive PAS FTIR[37,38] revealed the presence of the expected S═O stretches. Initial attempts to effect cyclitive cleavage[30] of sulfahydantoin **7a** from **14Wa** employed sodium methoxide in a mixture of methanol and THF. Encouragingly, this procedure afforded traces of the desired product detectable by electrospray ionization (ESI) mass spectroscopy in negative ion mode. Sodium hydroxide in aqueous methanol, triethylamine in CH_2Cl_2, and DBU in CH_2Cl_2 were explored as alternative bases, and the last gave the best results. Several approaches to remove DBU from the crude product were investigated, and the most satisfactory proved to be treatment with an excess of the strongly acidic ion-exchange resin Amberlyst A-15, which produced **7a** in 23% overall yield, based on the initial functionalization of the resin, and 76% purity as shown by HPLC.

Scheme 4. Cleavage



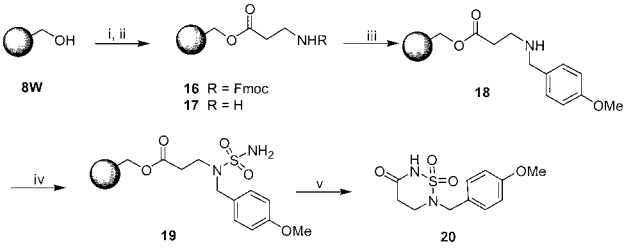
f R^1 = (S)-1-methylpropyl, R^2 = H, R^3 = 4-$MeOC_6H_4$
g R^1 = H, R^2 = (S)-1-methylpropyl, R^3 = 4-$MeOC_6H_4$

The procedure described above was repeated using MBHA-AB resin (**8A**) with very similar results; **7a** was produced in 26% yield and 75% purity. The transformation of **13Wa** to **14Wa** can also be effected with $(NH_2)_2SO_2$ in diglyme at 150 °C for 48 h;[32] however, these conditions are not convenient for library production and were not pursued further.

The final stage of chemistry development was designed to give a preliminary indication of the scope of the procedure described above. The reductive alkylation of **11Aa** was run with propionaldehyde (**12b**), pyridine-3-carboxaldehyde (**12c**), and 2,4-dichlorobenzaldehyde (**12d**) to determine whether aliphatic aldehydes, basic functional groups, and ortho-substituted aldehydes would be workable. Little or none of the expected products **7b** and **7c** were obtained when aldehydes **12b** and **12c** were used; however, the ortho-substituted aldehyde **12d** worked well to afford **7d** in 27% yield and 82% purity. The sequence was run with Fmoc-protected α,α-dimethylglycine (Aib) (**9e**) to afford the expected sulfahydantoin product **1e** in 16% yield and 100% purity, demonstrating that α,α-disubstituted amino acids could be included in library production. We attributed the modest yields to incomplete reaction in the reductive amination step and partial compound retention on the Amberlyte resin.

It was of interest to gauge the extent of racemization in this reaction sequence. To this end, Fmoc-protected isoleucine was loaded onto MBHA-AB resin (**8A**) using the conditions described above to afford **10Af**. A portion of the resin was treated with TFA, and the cleavage product was analyzed by 500 MHz ^{1}H NMR. Comparison of the spectrum of this material with those of the parent Fmoc−isoleucine (**9f**) and Fmoc−D-alloisoleucine (**9g**) indicated that ca. 7% racemization at the α-carbon of the amino acid had occurred.[39] The resin-bound Fmoc−isoleucine (**10Af**) was then deprotected to afford **11Af**, which was reductively alkylated with 4-methoxybenzaldehyde (**12a**). Cleavage of a sample of resin **13Af** with TFA (Scheme 4) and examination of the liberated *N*-(4-methoxybenzyl)amino acid **15f** by 500 MHz ^{1}H NMR indicated that no additional racemization had occurred during deprotection or reductive alkylation. The resin-bound intermediate **13Af** was carried on to afford mainly the sulfahydantoin **7f**, which by 500 MHz ^{1}H NMR contained ca. 6.5% of the diastereomer **7g**, indicating that possibly no further racemization had occurred in the sulfamide formation or cyclitive cleavage steps. The same set of experiments was carried out starting with Fmoc−D-alloisoleucine to afford **7g**. In this case no racemization could be detected in the **9g** cleaved from **10Ag**, in the cleavage product from **13Ag**, or in the sulfahydantoin **7g**. Switching the coupling reagents from DIC/DMAP to 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide/*N*-methylimidazole[40] and

Scheme 5. 1,2,6-Thiadiazin-3-one Synthesis[a]



[a] (i) Fmoc−NHCR[1]R[2]CO_2H, (**9**, 3 equiv), DIC (3 equiv), DMAP (0.3 equiv), CH_2Cl_2/DMF (5:1), 2 h, room temp. (ii) Piperidine/DMF (1:4), 20 min, room temp. (iii) R^3CHO, (**12**, 11 equiv), HOAc (2 equiv), CH_2Cl_2/$(MeO)_3CH$ (1:1), 5 h, room temp, then $NaCNBH_3$ (11 equiv), CH_2Cl_2/$(MeO)_3CH$ (1:1), 3 × 2 h, room temp. (iv) H_2NSO_2Cl (**3**, 6 equiv), 2,4,6-collidine (10 equiv), CH_2Cl_2, 48 h, room temp. (v) DBU, CH_2Cl_2, 5 h, room temp. (vi) 2,4,6-Mesitylenesulfonyl-3-nitro-1,2,4-triazolide, *N*-methylimidazole, CH_2Cl_2.

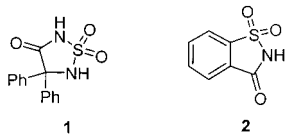


Figure 1. Compounds **1** and **2**.

using Fmoc−Ile-OH (**9f**) decreased the extent of racemization in the final product to ca. 2%. These conditions would be useful if the enantiomeric purity of the sulfahydantoins were of concern. In general the optical purity of the sulfahydantoin products can be expected to reflect the level of racemization experienced when loading Fmoc−amino acids onto hydroxymethyl resins.[39,41]

The chemistry was extended to the homologous six-membered ring heterocycle, the dihydro-2H-1,2,6-thiadiazin-3(4H)-one 1,1-dioxide system (Scheme 5).[22,39,42] By use of the conditions described above, Fmoc−β-alanine was loaded onto MBHA-AB resin (**8A**) to afford **16**, which was deprotected to **17**. Reductive alkylation with 4-methoxybenzaldehyde afforded **18**, which was converted to resin-bound sulfamide **19** by treatment with **3.** Resin-bound intermediates **16**−**19** were characterized by PAS FTIR.[37,38] The crude product from treatment of **19** with DBU for 48 h was analyzed by LC−MS, which indicated the presence of the desired product **20** as the major component of the mixture; however, a significant amount of an unidentified material, $m/z = 237$, was also present. Thus, the conditions developed for the sulfahydantions would require further optimization to be considered a useful synthesis of dihydro-2H-1,2,6-thiadiazin-3(4H)-one 1,1-dioxides.

Library Design. Desirable ranges of MW, calculated log *P*, and numbers of hydrogen bond donors, acceptors, and rotatable bonds for orally bioavailable drugs and for agrochemicals have been proposed.[44−46] The molecular weight and calculated log *P* values[47] for three representative sulfahydantoins are shown in Figure 2. The calculated log *P* results suggested that R^1, R^2, and R^3 in **7** (Scheme 3) should be selected to include hydrophobic groups roughly equivalent to two benzene rings to bring the log *P* of the library compounds into the 1−3 range considered most desirable. Furthermore, such compounds remain below the MW = 500 cutoff.

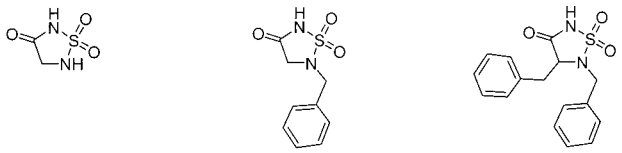


Figure 2. MW and calculated log *P* values (see ref 47) of representative sulfahydantoins.

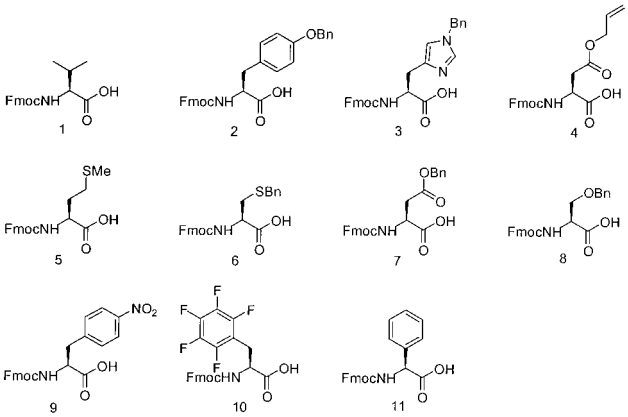


Figure 3. Amino acids **9** used for library production.

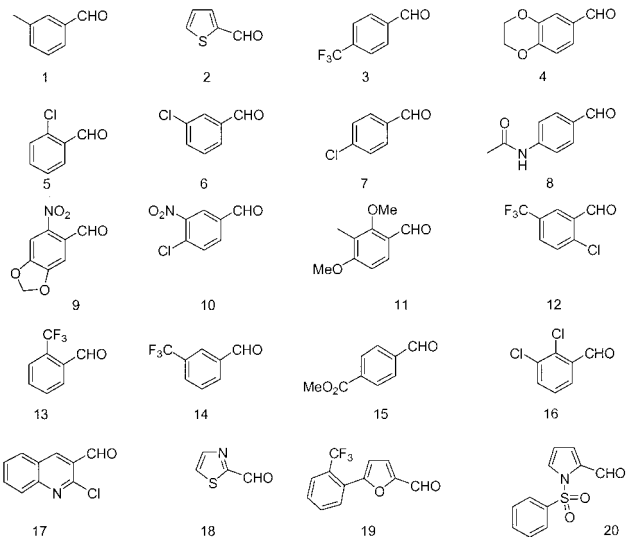


Figure 4. Aldehydes **12** used for library production.

Eleven commercially available Fmoc-protected amino acids **9**{*1*−*11*} with hydrophobic side chains were selected on the basis of price and diversity (Figure 3). Twenty aromatic and heteroaromatic aldehydes **12**{*1*−*20*} were selected to encompass a range of substituent types encountered in agrochemicals (Figure 4). A 96-compound synthesis library (Table 1) was selected from the virtual library of 220 sulfahydantoins attainable from the selected Fmoc−amino acids and aldehydes to demonstrate the concept. The MW, calculated log *P*,[47] hydrogen bond acceptor, and rotatable bond distributions of the 96 library members proposed for production are shown in Figures 5−8. These graphs indicate that the library lies within the space defined by Lipinski's Rule of 5[44] and is also within similar parameter ranges defined for agrochemicals.[46] Each compound has a single hydrogen bond donor, the acidic proton in the sulfahydantoin

Table 1. Library Yields[a] and Purities[b]

aldehyde **12**	Fmoc−amino acid **9** 1	2	3	4	5	6	7	8	9	10	11
1	$^{20}/_{86}$	$^{28}/_{68}$	$^{6}/_{85}$	$^{19}/_{37}$							
2	$^{11}/_{100}$	$^{22}/_{81}$	$^{4}/_{0}$	$^{5}/_{60}$							
3	$^{20}/_{90}$	$^{19}/_{68}$	$^{12}/_{80}$	$^{9}/_{57}$							
4	$^{31}/_{94}$	$^{34}/_{33}$	$^{5}/_{100}$	$^{8}/_{66}$							
5	$^{24}/_{96}$	$^{7}/_{100}$			$^{13}/_{87}$	$^{16}/_{90}$	$^{7}/_{80}$				
6	$^{24}/_{94}$	$^{14}/_{97}$			$^{38}/_{97}$	$^{28}/_{89}$	$^{5}/_{82}$				
7	$^{14}/_{42}$	$^{11}/_{0}$			$^{3}/_{0}$	$^{20}/_{10}$	$^{11}/_{50}$				
8	$^{18}/_{81}$	$^{8}/_{100}$			$^{17}/_{76}$	$^{13}/_{94}$	$^{22}/_{93}$				
9	$^{37}/_{90}$	$^{8}/_{87}$			$^{2}/_{28}$	$^{11}/_{70}$	$^{10}/_{41}$				
10	$^{21}/_{86}$	$^{6}/_{92}$			$^{2}/_{87}$	$^{14}/_{84}$	$^{8}/_{73}$				
11	$^{20}/_{0}$	$^{7}/_{92}$			$^{2}/_{93}$	$^{20}/_{65}$	$^{5}/_{82}$				
12	$^{16}/_{84}$	$^{14}/_{31}$			$^{3}/_{82}$	$^{6}/_{60}$	$^{6}/_{48}$				
13	$^{21}/_{90}$							$^{20}/_{81}$	$^{12}/_{68}$	$^{10}/_{0}$	$^{18}/_{88}$
14	$^{16}/_{96}$							$^{14}/_{79}$	$^{12}/_{61}$	$^{16}/_{0}$	$^{11}/_{70}$
15	$^{11}/_{88}$							$^{14}/_{64}$	$^{11}/_{59}$	$^{22}/_{0}$	$^{13}/_{78}$
16	$^{18}/_{93}$							$^{15}/_{46}$	$^{14}/_{63}$	$^{26}/_{0}$	$^{37}/_{88}$
17	$^{20}/_{94}$							$^{14}/_{70}$	$^{10}/_{25}$	$^{10}/_{0}$	$^{12}/_{82}$
18	$^{7}/_{0}$							$^{10}/_{0}$	$^{4}/_{0}$	$^{5}/_{0}$	$^{7}/_{0}$
19	$^{16}/_{88}$							$^{23}/_{64}$	$^{7}/_{63}$	$^{17}/_{0}$	$^{9}/_{75}$
20	$^{14}/_{95}$							$^{13}/_{74}$	$^{16}/_{83}$	$^{19}/_{0}$	$^{14}/_{89}$

[a] Yields were calculated on the basis of the weight of product and the initial functionalization of the resin and are shown in the upper left of each cell. [b] Purities were calculated on the basis of integration of the 214 nm UV absorption of the peak with the expected molecular ion. Purities are shown in the lower right of each cell.

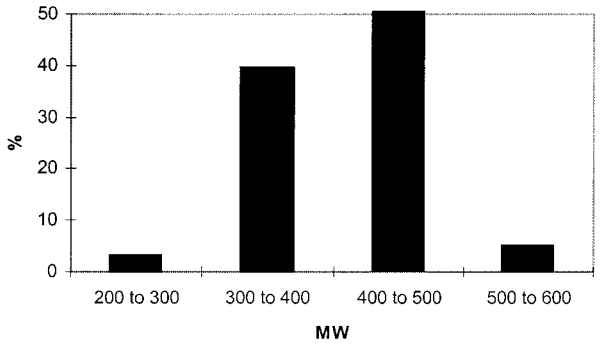


Figure 5. Molecular weight distribution of target library.

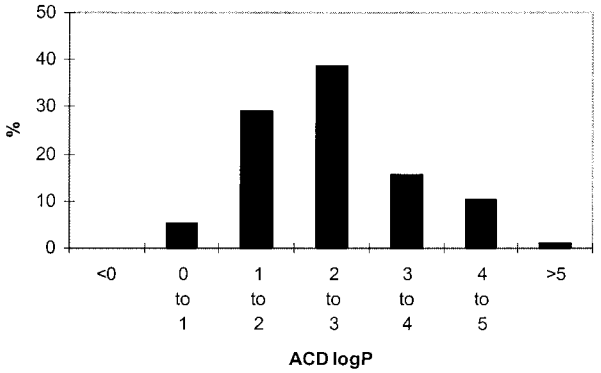


Figure 6. ACD log *P* Distribution of proposed library compounds (see ref 47).

ring, with the exception of library members derived from aldehyde **12**{*8*}, which have two hydrogen bond donors.

Library Production. An ACT496 with a 40-well block was used for library production. The first production run of 16 reactions employed the four Fmoc−amino acids **9**{*1*−*4*}, the four aldehydes **12**{*1*−*4*}, and MBHA-AB resin **8A** as solid support. Because of the loading of the resin (1.12 mmol g^{-1}) and the desire to produce 20−50 mg of product, each reaction was run in two wells. The second production run of 40 reactions used the five Fmoc−amino acids **9**{*1,2,5*−*7*}, the eight aldehydes **12**{*5*−*12*}, and high-loading Wang resin (1.7 mmol g^{-1}) as solid support. The third run also used Wang resin with the five Fmoc−amino acids **9**{*1,8*−*11*} and the eight aldehydes **12**{*13*−*20*}. The yields and purities of the library compounds produced are presented in Table 1. Of 96 library members targeted for production, 80 were detected in the crude products by LC−MS. Twelve of the 16 failures occurred with the amino acid **9**{*10*} and the aldehyde **12**{*18*}. Forty-six of the 80 compounds were isolated in ≥80% purity, and a further 21 were isolated in 60−80% purity. The yields of the 46 compounds isolated in >80% purity ranged from a low of 2% to a high of 38%. The first library production run on MBHA-AB resin gave better results on the whole than the second and third runs on Wang resin; however, given that the two resins gave essentially identical results when used to prepare **7a** during chemistry development, it seems more likely that the amino acids and aldehydes employed in runs 2 and 3 were responsible for poorer results. The best yields obtained correspond to an average yield of 83% per step over five steps. It is unclear from the data collected which step or steps are responsible for the rather low yields observed in a number of cases; however, resin loading and Fmoc deprotection are well-developed reactions that are expected to proceed efficiently. Thus, suspicion falls on the reductive alkylation, sulfamidation, cyclitive cleavage, and purification steps.

Sulfahydantoins derived from Fmoc−valine **9**{*1*} were produced in the best yields and purities. Not surprisingly, lower yields and purities were often encountered when the

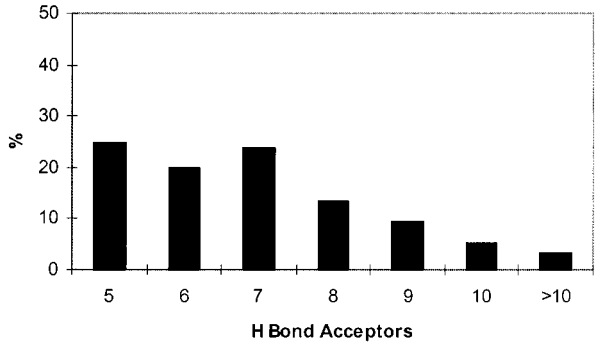


Figure 7. Hydrogen bond acceptor distribution of proposed library compounds.

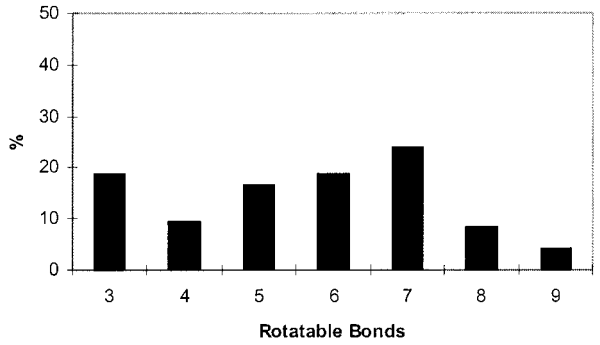
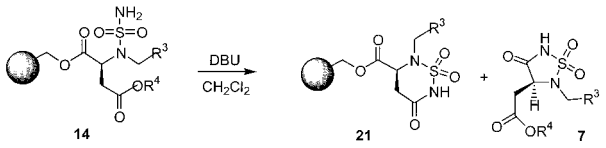


Figure 8. Rotatable bond distribution of proposed library compounds.

Scheme 6



Resin = MBHA-AB or Wang, R^4 = allyl or benzyl

Fmoc−amino acid **9** had a side chain with potentially reactive functionality. For example, the products derived from Fmoc−Asp(allyl)-OH **9**{4} and Fmoc−Asp(benzyl)-OH **9**{7} were generally obtained in rather poor yields and in slightly inferior purities compared to the corresponding products derived from Fmoc−Val-OH **9**{*1*}. It is possible that a portion of the resin-bound sulfamide intermediate **14**{*4*,*x*} or **14**{*7*,*x*} follows the nonproductive pathway leading to formation of a resin-bound 1,2,6-thiadiazin-3-one **21** (Scheme 6). The poor yields and purities of the sulfahydantoins derived from Fmoc−His(Bn)-OH **9**{*3*} may be due to loss of these basic compounds during Amberlyst A15 treatment. None of the expected products was observed when Fmoc−pentafluorophenylalanine **9**{*10*} was used; however, six of the eight crude products contained a significant (>50%) peak, which LC−MS indicated had a molecular ion 72 Da lower than the desired product. This corresponds to the formal reduction of four fluorines to hydrogen and may plausibly have occurred during treatment with excess sodium cyanoborohydride. No attempt was made to determine the regiochemistry of the putative monofluorophenyl product.

Among the aldehydes employed, thiazole-2-carboxaldehyde **12**{*18*} failed to give any of the desired products. The reasons for this failure were not investigated. More surprisingly 4-chlorobenzaldehyde **12**{*7*} gave poor results (low purity) despite being well within the scope of chemistry development. This was attributed to machine and/or human error. These factors may have also been responsible for some other unexpected failures such as **7**{*1*,*11*}.

The presence of the open-chain acid **22** (Figure 9) was detected by LC−MS as a minor (1−5%) component of many of the sulfahydantoin products. The formation of this byproduct can be attributed to base-catalyzed hydrolysis of **19**{*x*, *y*} by adventitious water in the DBU/CH_2Cl_2 mixture used to effect cyclitive cleavage. In a single instance (the attempt to produce **7**{*3*,*2*}) the open-chain acid **22**{*3*,*2*} was the major product isolated. The reasons for this are unclear.

Conclusions

A procedure has been described that allowed the production of a small but diverse library of sulfahydantoins. The products were formed in acceptable purity, albeit low yield. The synthetic method was demonstrated to be compatible with hindered amino acids including phenyl glycine, valine, and isoleucine. Furthermore, it allowed the use of aromatic aldehydes bearing both electron-donating and -withdrawing substituents but not with aliphatic aldehydes. The level of biological activity in whole organism fungicide, herbicide, and insecticide screens did not warrant synthesis of additional library members.

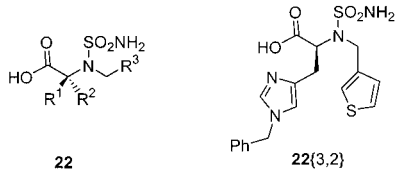


Figure 9. Compounds **22** and **22**{*3*,*2*}.

Experimental Section

Abbreviations. Those used for amino acids follow the rules of the IUPAC-IUB Commission of Biochemical Nomenclature in *J. Biol. Chem.* **1972**, *247*, 977−983. Amino acid symbols denote the L-configuration unless indicated otherwise. The following additional abbreviations are used: AB, 3-(4-(hydroxymethyl)phenoxy)propionyl (alkoxybenzyl); DBU, 1,8-diazbicyclo[5,4,0]undec-7-ene; DIC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DRIFTS, diffuse reflectance infrared Fourier transform spectroscopy; ESI, electrospray ionization; MBHA, *p*-methylbenzhydrylamine; MeCN, acetonitrile; PAS FTIR, photoacoustic Fourier transform infrared spectroscopy; TFA, trifluoroacetic acid.

General. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. MBHA and Wang resins were obtained from Novabiochem and Polymer Labs. Fmoc−amino acids were obtained from Advanced Chemtech, Fluka, Aldrich, Bachem, or Novabiochem. Solvents were removed on a rotary evaporator at 20−50 mmHg or on a Genevac HT-12 evaporator at 1−2 mmHg. Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Solution ^{1}H NMR spectroscopy was performed on a Bruker DPX300, Varian XL200, or Varian VXR-500S. Solution ^{13}C and ^{19}F NMR were performed on a Bruker DPX300. Solution infrared spectra were recorded on a Perkin-Elmer model BMC spectrophotometer or a Mattson Genesis-II FTIR. DRIFTS IR spectra were acquired on a Applied Systems MonitIR FTIR spectrometer equipped with a Spectra Tech DRIFTS accessory. Photoacoustic FTIR spectra were obtained on a Bio-Rad FTS 6000 step−scan spectrometer. GC−MS spectra were obtained on a Hewlett-Packard 5970 GC−MS. LC−MS were run using a Hewlett-Packard HP1100 series binary pump, autosampler, and vacuum degasser coupled to a Hewlett-Packard HP1050 VWD detector and Micromass (Fisons) Quattro I SQ. The data were acquired and processed using Micromass MassLynx v3.2 with OpenLynx. HPLC were run on a Hewlett-Packard HP series 1050. Elemental analyses were performed by Robertson-Microlit Labs. A higher loading MBHA-AB resin (1.12 mmol/g) was used for library production to increase compound productivity.

Solution-Phase Synthesis of 4S-Phenylmethyl-5-(4-methoxyphenylmethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7a). A slurry of L-phenylalanine ethyl ester hydrochloride (5.01 g, 21.8 mmol), 4-methoxybenzaldehyde (**12a**, 2.7 mL, 21.8 mmol), and sodium acetate (1.78 g, 21.7 mmol) in methanol (50 mL) was stirred at room temperature for 0.5 h, and solid sodium cyanoborohydride (4.1 g, 65.2 mmol) was added. Vigorous gas evolution occurred. The mixture was stirred overnight at room temperature and

evaporated to dryness under reduced pressure. The residue was suspended in 5% aqueous NaOH (50 mL) and extracted with ethyl acetate (2 × 150 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure to afford an oil (7.96 g). The crude product was taken up in ethyl acetate (150 mL) and extracted with 5% aqueous HCl (2 × 50 mL). The combined aqueous extracts were neutralized by cautious addition of solid K_2CO_3, cooled to <5 °C in an ice bath, and treated with 50% aqueous NaOH (2 mL). The mixture was extracted with ethyl acetate (3 × 100 mL). These ethyl acetate extracts were combined, dried over $MgSO_4$, and concentrated in vacuo to afford *N*-(4-methoxybenzyl)phenylalanine ethyl ester (**5**, 6.37 g, 93%).[48] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.5 Hz, 3H), 2.93 (d, J = 7 Hz, 2H) 3.50 (t, J = 7 Hz, 1H), 3.58 (d, J = 15.5 Hz, 1H), 3.73 (d, J = 15.5 Hz, 1H), 3.79 (s, 3H), 4.10 (q, J = 7.5 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 7.15−7.3 (m, 5H). IR (neat): 1729 cm^{-1}.

A stirred solution of chlorosulfonyl isocyanate (0.5 mL, 5.7 mmol) in CH_2Cl_2 (5 mL) was cooled to <5 °C in an ice bath, and formic acid (0.22 mL, 5.8 mmol) was added dropwise over 2 min. The ice bath was allowed to expire, and the mixture was stirred overnight at room temperature. The mixture was recooled to <5 °C in an ice bath, and a solution of **5** (1.43 g, 4.6 mmol) and triethylamine (1 mL, 7.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 20 min. The ice bath was allowed to expire, and the mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (150 mL), washed with 5% aqueous HCl (2 × 50 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure left crude product (1.98 g). Flash chromatography on silica gel (50 g), eluting successively with 150 mL portions of 0, 20, 40, 60, 80, and 100% ether in hexanes, afforded **6** (1.11 g, 62%) as a white solid, mp 103−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, J = 7.2 Hz, 3H), 3.22 (m, 2H), 3.79 (s, 3H), 4.04 (d, J = 15 Hz, 1H), 4.14 (m, 2H), 4.19 (d, J = 15 Hz, 1H), 4.31 (t, J = 7.5 Hz, 1H), 4.78 (br s, 2H), 6.73 (d, J = 8.5 Hz, 2H), 7.04 (d, 2H, J = 8.5 Hz), 7.1−7.22 (m, 5H). IR (solid state, DRIFTS): 3398, 3298, 1740, 1358, 1158 cm^{-1}.

To a stirred solution of **6** (0.49 g, 1.25 mmol) in methanol (10 mL) was added 25% sodium methoxide in methanol (0.43 g, 2.0 mmol). The mixture was stirred at room temperature for 1 day and concentrated under reduced pressure. The residue was taken up in water (50 mL) and washed with ether (50 mL). The aqueous layer was acidified to pH ≤ 1 with concentrated HCl (ca. 1 mL) and extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 4S-phenylmethyl-5-(4-methoxyphenylmethyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**7a**, 0.39 g, 90%) as a broad melting white solid, mp 110−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (m, 2H), 3.79 (s, 3H), 3.93 (d, J = 14.5 Hz, 1H), 4.08 (dd, J = 5.3, 7.9 Hz, 1H), 4.33 (d, J = 14.5 Hz, 1H), 6.79 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.13 (s, 2H), 7.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.8, 50.7, 55.7, 65.7, 114.6, 125.3, 128.8, 129.1, 130.1, 131.0, 135.6, 160.1, 169.1. IR ($CDCl_3$): 3360, 1735, 1330, 1160 cm^{-1}. MS (ESI, negative ion): m/z 345 $(M - 1)^-$.

Sulfamoyl Chloride. Chlorosulfonyl isocyanate (1.489 g, 10.5 mmol) was stirred, cooled to 5 °C, and treated with anhydrous formic acid (0.484 g, 10.5 mmol). The mixture was stirred at room temperature until gas evolution ceased to afford sulfamoyl chloride as a liquid, which was used immediately.[32]

MBHA-AB Resin (8A). MBHA resin (0.60 g, 0.42 mmol) was preswollen in DMF. A solution of 3-(4-(hydroxymethyl)-phenoxy)propionic acid (0.25 g, 1.26 mmol, 3 equiv) and DIC (0.19 mL, 1.26 mmol, 3 equiv) in DMF (10 mL) was added, and the mixture was gently stirred for 12 h. The resin was filtered, washed sequentially with DMF, CH_2Cl_2, and MeOH, and dried.

Solid-Phase Synthesis Protocol. The general procedure developed for solid-phase synthesis is described below for compound **7f**. In subsequent experimental procedures the same conditions and ratios of reagents were employed and only deviations from this general procedure are noted.

5-(4-Methoxyphenylmethyl)-4S-(2S-methylpropyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7f). Resin Loading. Fmoc−Ile-OH (**9f**, 0.20 g, 0.6 mmol, 3 equiv), DMAP (0.008 g, 0.06 mmol, 0.3 equiv), and DIC (0.093 mL, 0.6 mmol, 3 equiv), in CH_2Cl_2/DMF (5:1) (3 mL), were added to **8A** (0.35 g, 0.201 mmol). The reaction was shaken for 1 h and drained. The resin was washed with CH_2Cl_2 (5 × 5 mL) and DMF (5 ×5 mL). This overall process was repeated to afford **10Af**.

Fmoc Removal. 10Af was suspended in 20% piperidine in DMF (5 mL), and the reaction mixture was stirred for 20 min. The solution was drained, and the resin was washed with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL) to afford **11Af**.

Reductive Alkylation. To a suspension of **11Af** (250 mg, 0.145 mmol) in a mixture of $(MeO)_3CH/CH_2Cl_2$ (1:1) (3 mL), 4-methoxybenzaldehyde (**12a**, 0.395 mL, 3.25 mmol, 22.4 equiv) and HOAc (0.017 mL, 0.29 mmol, 2 equiv) were added, and the mixture was shaken for 3 h. The solution was drained and washed with CH_2Cl_2 (3 × 5 mL), followed by the addition of $NaCNBH_3$ (205 mg, 3.25 mmol, 22.4 equiv) in $(MeO)_3CH/CH_2Cl_2$ (1:1). After 2 h the solution was drained and the resin was washed with methanol (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). Treatment with $NaCNBH_3$ in $(MeO)_3CH/CH_2Cl_2$ was repeated two additional times to afford **13Af**.

Sulfamide Preparation. To a suspension of **13Af** (150 mg, 0.087 mmol) in CH_2Cl_2 (4 mL) was added sulfamoyl chloride (0.06 g, 0.52 mmol, 6 equiv). The mixture was stirred for 30 min, and collidine (0.115 mL, 0.87 mmol, 10 equiv) was added. After 4 h of agitation, the resin was rinsed with CH_2Cl_2 (3 × 5 mL) to afford **14Af**.

Cyclitive Cleavage. Resin-bound sulfamide **14Af** was treated with 1 M DBU in CH_2Cl_2 (0.87 mL, 0.87 mmol, 10 equiv). After 4 h, the resin was filtered and washed with CH_2Cl_2 (3 × 5 mL). The combined filtrates were evaporated to dryness. The residue was dissolved in ethyl acetate, washed with 5% aqueous HCl, dried with $MgSO_4$, and concentrated under vacuum. The crude material was purified by medium-pressure liquid chromatography (MPLC) using

a convex gradient containing from 0% to 30% of a solution of 0.05% TFA in MeCN in 0.05% of TFA in water at a flow rate of 150 mL/h and UV detection at 220 nm to yield **7f** (10 mg, 43%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.5$ Hz, 3H), 0.99 (d, $J = 7$ Hz, 3H), 1.43 (m, 1H), 1.52 (m, 1H), 1.76 (m, 1H), 3.79 (s, 3H), 3.86 (d, $J = 3.5$ Hz, 1H), 4.29 (d, $J = 15$ Hz, 1H), 4.45 (d, $J = 15$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H). Integration of the CH_2CH_3 triplets at 0.81 ppm (**7f**) and at 0.86 ppm (**7g**) indicated that 7.2% racemization had occurred.

4S-Phenylmethyl-5-(4-methoxyphenylmethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7a). Use of Fmoc−Phe-OH (**9a**) and 4-methoxybenzaldehyde (**12a**) afforded **7a** in 26% yield and 75% purity. Using Wang resin in place of MBHA-AB resin afforded **7a** in 23% yield and 76% purity. ^{1}H NMR and MS spectra were identical to those enumerated above for material obtained by solution synthesis.

5-(2,4-Dichlorophenylmethyl)-4S-phenylmethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7d). Use of Fmoc−Phe-OH (**9a**) and with 2,4-dichlorobenzaldehyde (**12d**) afforded **7d.** Yield: 27%. Purity: 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (m, 2H), 4.64 (d, $J = 15.5$ Hz, 1H), 4.18 (dd, $J = 4.2$, 7.9 Hz, 1H), 4.60 (d, $J = 15.5$ Hz, 1H), 6.9−7.4 (8H). MS (ESI, negative ion): m/z 383 $(M - 1)^-$.

4,4-Dimethyl-5-(4-methoxyphenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7e). Use of Fmoc−Aib-OH (**9e**) and 4-methoxybenzaldehyde (**12a**) afforded **7e.** Yield: 16%. Purity: 100%. MS (ESI, negative ion): m/z 283 $(M - 1)^-$.

5-(4-Methoxyphenyl)methyl-4R-(2S-methylpropyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (7g). Use of Fmoc−D-allo-Ile-OH (**9g**) and 4-methoxybenzaldehyde (**12a**) afforded **7g**, which was purified by MPLC as described in the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, $J = 8$ Hz, 3H), 1.02 (d, $J = 7$ Hz, 3H), 1.22 (m, 1H), 1.58 (m, 1H), 1.84 (m, 1H), 3.79 (s, 3H), 3.88 (d, $J = 3$ Hz, 1H), 4.33 (d, $J = 15$ Hz, 1H), 4.45 (d, $J = 15$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H). No evidence for the presence of **7f**, which would result from racemization, was detected by ^{1}H NMR.

Characterization of Resin-Bound Intermediates. The following resin-bound intermediates from the preparation of **7a** on Wang resin were characterized by PAS FTIR. **10Wa**: 3410, 1735, 1510 cm^{-1}. **11Wa**: 3380, 3310, 1735 cm^{-1}. **13Wa**: 1735, 1255, 1040 cm^{-1}. **14Wa**: 1735, 1386, 1093 cm^{-1}.

Cleavage of Resin-Bound Intermediate 10Af for Racemization Study. Resin **10Af** (100 mg) was treated with 95% TFA in CH_2Cl_2 (2 mL) for 90 min. The resin was filtered and washed with TFA. After concentration of the combined filtrates, the crude material was purified by MPLC using a convex gradient containing from 5% to 40% of a solution of 0.05% TFA in MeCN in 0.05% of TFA in water at a flow rate of 150 mL/h and UV detection at 220 nm to yield **9f** (15 mg, 88%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, $J = 7$ Hz, 3H), 0.96 (d, $J = 6.5$ Hz, 3H), 1.15 (m, 1H), 1.47 (m, 1H), 1.94 (m, 1H), 4.21 (t, $J = 6.5$ Hz, 1H), 4.37 (dd, $J = 5$, 9 Hz, 1H), 4.40 (d, $J = 7$ Hz, 2H), 5.28 (d, $J = 9$ Hz, 1H), 7.29 (t, $J = 7$ Hz, 2H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.57 (dd, $J = 3.5$, 7 Hz, 2H), 7.74 (d, $J = 7$ Hz, 2H). On the basis of integration of signals at 5.28 (**9f**) and 5.20 ppm (**9g**), 6.8% racemization had occurred.

Cleavage of Resin-Bound Intermediate 10Ag for Racemization Study. A portion of **10Ag** was treated as described for **10Af** above to afford recovered **9g**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, $J = 7$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H), 1.23 (m, 1H), 1.44 (m, 1H), 2.00 (m, 1H), 4.22 (t, $J = 7$ Hz, 1H), 4.40 (d, $J = 7$ Hz, 2H), 4.49 (dd, $J = 3$, 9 Hz, 1H), 5.20 (d, $J = 9$ Hz, 1H), 7.29 (t, $J = 7$ Hz, 2H), 7.38 (t, $J = 7$ Hz, 2H), 7.58 (dd, $J = 4$, 7 Hz, 2H), 7.74 (d, $J = 7$ Hz, 2H). None of the diastereomer **9f** that would result from racemization was detected by ^{1}H NMR.

Cleavage of Resin-Bound Intermediate 13Af for Racemization Study. A portion of resin **13Af** (100 mg) was treated as described above for **10Af** to yield **15f** (7 mg, 55%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 0.83 (t, $J = 7.5$ Hz, 3H), 0.87 (d, $J = 6.5$ Hz, 3H), 1.30 (m, 1H), 1.48 (m, 1H), 1.98 (m, 1H), 3.57 (m, 1H), 3.73 (s, 3H), 3.98 (d, $J = 13$ Hz, 1H), 4.14 (d, $J = 13$ Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 7.32 (d, $J = 8.5$ Hz, 2H). The extent of racemization, based on integration of the peaks at 0.83 and 0.87 ppm in **15f** vs those at 0.70 and 0.94 ppm in **15g**, was 6.5%.

Cleavage of Resin-Bound Intermediate 13Ag for Racemization Study. A portion of **13Ag** was treated as described above for **10Af** to afford **15g**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (t, $J = 7$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H), 1.23 (m, 1H), 1.29 (m, 1H), 2.03 (m, 1H), 3.47 (m, 1H), 3.75 (s, 3H), 3.93 (d, $J = 14$ Hz, 1H), 4.21 (d, $J = 13.5$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 2H), 7.34 (d, $J = 8$ Hz, 2H). None of the diastereomer **15f** that would result from racemization was detected by NMR.

Low Racemization Loading of 9f onto MBHA-AB Resin. A solution of Fmoc−Ile-OH (**9f**, 0.2 g, 0.6 mmol, 3 equiv) and *N*-methylimidazole (0.036 mL, 0.453 mmol, 2.25 equiv) in dry CH_2Cl_2 (2 mL) was added by syringe to 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide (0.264 g, 0.604 mmol, 3 equiv) in dry CH_2Cl_2 (1 mL). The resulting solution was added to MBHA-AB resin **(8A,** 0.35 g, 0.201 mmol), and the mixture was shaken for 90 min. The resin was washed with CH_2Cl_2 (5 × 5 mL) and DMF (5 × 5 mL) to afford **10Af**. A portion of **10Af** (100 mg) was agitated with 95% TFA in CH_2Cl_2 (2 mL) for 90 min. The resin was filtered and washed with TFA. After concentration of the combined filtrates, the crude material was purified by MPLC using a convex gradient containing from 5% to 40% of a solution of 0.05% TFA in MeCN in 0.05% of TFA in water at a flow rate of 150 mL/h and UV detection at 220 nm to yield **9f** (16 mg, 92%) as a colorless solid. Inspection of the CH_2CH_3 triplets at 0.69 and 0.97 ppm in the 500 MHz ^{1}H NMR spectrum of **9f** indicated that 2% of racemization had occurred. Conversion of **10Af** prepared in this fashion to **7f**, using the general procedure, afforded **7f** containing ca. 2% of **7g**.

Library Production Run 1. The general procedure was run in an ACT496 with a 40-well block. Each well was loaded with MBHA-AB resin (**8A**, 200 mg, 1.12 mmol g^{-1},

0.224 mmol). Reagents were added by the robot from stock solutions with the exception of DIC and sulfamoyl chloride, which were added as neat liquids. Each reaction was run in two wells, and the products from both were combined for purification. In place of purification by MPLC, each combined crude product was taken up in 5% aqueous HCl (4 mL) and applied to a solid-phase extraction cartridge (Supelclean LC-18, 1 g size). The cartridge was washed with water (4 mL) and then with methanol (4 mL). The methanol eluate was evaporated, and yields were calculated on the basis of the weight of product and the initial functionalization of the resin (Table 1). The products were analyzed by LC−MS using a C18 column with a flow rate of 0.8 mL/min and a mobile phase gradient starting at H_2O/MeCN/HOAc (85:15:0.1), changing linearly to MeCN/HOAc (100:0.1) over 4 min and holding at MeCN/HOAc (100:0.01) for 1.5 min. UV absorption was monitored at 214 nm. The product peaks were identified by mass spectroscopy using the electrospray ionization in negative ion mode. Purities were calculated on the basis of integration of the UV absorption at 214 nm and are also shown in Table 1. The following products were characterized by ^{1}H NMR.

5-(3-Methylphenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,1*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 2.10 (m, 1H), 2.36 (s, 3H), 3.80 (d, J = 3.6 Hz, 1H), 4.39 (d, J = 15.8 Hz, 1H), 4.48 (d, J = 15.8 Hz, 1H), 7.15−7.30 (3H).

5-(3-Thienyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,2*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 2.15 (m, 1H), 3.78 (d, 3.6 Hz, 1H), 4.44 (d, J = 16.5 Hz, 1H), 4.50 (d, J = 16.5 Hz, 1H), 7.17 (m, 1H), 7.33 (m, 2H).

5-(4-(Trifluoromethyl)phenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,3*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 2.19 (m, 1H), 3.86 (d, J = 3.4 Hz, 1H), 4.45 (d, J = 15.7 Hz, 1H), 4.60 (d, J = 15.7 Hz, d), 7.56 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, d). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 17.9, 29.5, 50.3, 70.9, 125.9, 127.5 (q), 128.7, 130.7 (q), 138.5, 168.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.9

5-(3,4-(Ethylenedioxy)phenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,4*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 2.12 (m, 1H), 3.80 (d, J = 3.5 Hz, 1H), 4.23 (s, 4H), 4.24 (d, J = 15.6 Hz, 1H), 4.41 (d, J = 15.6 Hz, d), 6.78−6.90 (3H).

Library Production Runs 2 and 3. The procedure described for library production run 1 was followed except that Wang resin **8W** (300 mg, 1.7 mmol g^{-1}, 0.51 mmol) was employed; each reaction was run in only a single well of the ACT496 40-well block, and a different purification procedure was adopted. The crude product solution was drained from the resin, shaken with Amberlyst-A15 (2.6 g, 4.8 mmol g^{-1}, 12.5 mmol, 5 equiv) for 4 h and filtered. The filtrate was evaporated under reduced pressure to afford **7**. Analysis, yields, and purities were determined as described for library production run 1 and are shown in Table 1. The following compounds were also characterized by ^{1}H NMR.

5-(2-Chlorophenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,5*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 2.18 (m, 1H), 3.90 (d, J = 4.0 Hz, 1H), 4.40 (d, J = 15.7 Hz, 1H), 4.82 (d, J = 15.7 Hz, 1H), 7.30−7.65 (4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 18.3, 30.8, 48.7, 71.9, 127.5, 129.9 (double height), 130.6, 132.0, 133.7, 166.8.

5-(3-Chlorophenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,6*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 2.15 (m, 1H), 3.83 (d, J = 3.5 Hz, 1H), 4.42 (d, J = 15 Hz, 1H), 4.47 (d, J = 15 Hz, 1H), 7.33 (m, 3H), 7.4 (s, 1H).

5-(4-Acetamidophenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,8*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 7.1 Hz, 3H), 2.18 (m, 1H), 2.19 (s, 3H), 3.81 (d, J = 6 Hz, 1H), 4.40 (d, J = 15 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H).

4S-Isopropyl-5-(4,5-methylenedioxy-2-nitrophenyl)-methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,9*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 2.23 (m, 1H), 4.03 (d, J = 3.2 Hz, 1H), 4.61 (d, J = 17.4 Hz, 1H), 5.11 (d, J = 17.4 Hz, 1H), 6.16 (m, 2H), 7.33 (s, 1H), 7.59 (s, 1H).

5-(4-Chloro-3-nitrophenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,10*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 2.18 (m, 1H), 3.90 (d, J = 3.2 Hz, 1H), 4.34 (d, J = 16 Hz, 1H), 4.64 (d, J = 16 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.95 (s, 1H).

5-(2-Chloro-5-(trifluoromethyl)phenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,12*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (m, 3H), 1.02 (m, 3H), 2.11 (m, 1H), 3.92 (m, 1H), 4.26 (d, J = 15.8 Hz, 1H), 4.88 (d, J = 16 Hz, 1H), 7.49 (m, 2H), 7.98 (s, 1H).

5-(2,3-Dichlorophenyl)methyl-4S-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*1,16*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 2.18 (m, 1H), 3.94 (d, J = 3.6 Hz, 1H), 4.36 (d, J = 16.3 Hz, 1H), 4.89 (d, J = 16.3 Hz, 1H), 7.28 (m, 1H), 7.47 (d, J = 8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 18.1, 30.8, 49.7, 72.7, 127.7, 128.2, 130.4, 131.6, 133.6, 134.9, 167.6.

5-(2-Chlorophenyl)methyl-4S-((4-phenylmethoxy)phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,5*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (m, 2H), 4.18 (d, J = 15.4 Hz, 1H), 4.20 (1H, m), 4.64 (d, J = 15.4 Hz, 1H), 4.98 (s, 2H), 6.70−7.80 (13H).

5-(3-Chlorophenyl)methyl-4S-((4-phenylmethoxy)phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,6*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (m, 2H), 4.11 (d, J = 5.1 Hz, 1H), 4.15 (d, J = 4.6 Hz, 1H), 4.31 (t, J = 4.2 Hz, 1H), 5.03 (s, 2H), 6.7−7.6 (aromatic H's, 13H).

5-(4-Acetamidophenyl)methyl-4S-((4-phenylmethoxy)-phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,8*}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H), 3.01 (m, 2H), 3.94 (d, J = 12.8 Hz, 1H), 4.00 (t, J = 3.5 Hz, 1H), 4.25 (d, J = 13.8 Hz, 1H), 5.01 (s, 2H), 6.86 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 3H), 7.37 (m, 7H), 7.89 (s, 1H).

5-(4,5-Methylenedioxy-2-nitrophenyl)methyl-4S-((4-phenylmethoxy(phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,9*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (m, 2H), 4.30 (m, 2H), 5.00 (m, 3H), 6.08 (d, J = 6.5 Hz, 2H), 6.75 (m, 2H), 6.96 (m, 3H), 7.36 (m, 4H), 7.40 (s, 1H), 7.42 (s, 1H).

5-(4-Chloro-3-nitrophenyl)methyl-4S-(4-(phenylmethoxy)phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,10*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (m, 1H), 3.23 (m, 1H), 4.04 (d, J = 15.4 Hz, 1H), 4.09 (t, J = 3.6 Hz, 1H), 4.25 (d, J = 15.1 Hz, 1H), 5.04 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.39 (m, 8H).

5-(2,4-Dimethoxy-3-methylphenyl)methyl-4S-(4-(phenylmethoxy)phenyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*2,11*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.98 (m, 2H), 3.62 (s, 3H), 3.81 (s, 3H), 4.21 (t, J = 6 Hz, 1H), 4.24 (d, J = 13.5 Hz, 1H), 4.37 (d, J = 13.7 Hz, 1H), 5.01 (s, 2H), 6.56 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.4 Hz, 1H), 7.41 (m, 5H).

5-(3-Chlorophenyl)methyl-4S-(2-methylthio)ethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*5,6*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.12 (m, 2H), 2.5 (m, 2H), 4.15 (t, J = 5.4 Hz, 1H), 4.28 (d, J = 15 Hz, 1H), 4.54 (d, J = 15 Hz, 1H), 7.34 (m, 3H), 7.43 (d, J = 9 Hz, 1H).

5-(4-Chloro-3-nitrophenyl)methyl-4S-(2-methylthio)-ethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*5,10*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.20 (m, 2H), 2.5 (m, 2H), 4.21 (t, J = 5.6 Hz, 1H), 4.38 (d, J = 16.7 Hz, 1H), 4.61 (d, J = 15.1 Hz, 1H), 7.53 (d, J = 10.2 Hz, 1H), 7.63 (m, 1H), 8.00 (s, 1H).

5-(2,4-Dimethoxy-3-methylphenyl)methyl-4S-(2-methylthio)ethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*5,11*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.15 (s, 3H), 2.43 (m, 2H), 3.02 (m, 2H), 3.75 (s, 3H), 3.83 (s, 3H), 4.15 (t, J = 5.4 Hz, 1H), 4.25 (d, J = 15 Hz, 1H), 4.55 (d, J = 15 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H).

5-(2-Chloro-5-(trifluoromethyl)phenyl)methyl-4S-(2-methylthio)ethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*5,12*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.15 (m, 2H), 2.45 (m, 2H), 4.22 (t, J = 5.4 Hz, 1H), 4.35 (d, J = 15 Hz, 1H), 4.84 (d, J = 15 Hz, 1H), 7.56 (m, 2H), 7.86 (s, 1H).

5-(2-Chlorophenyl)methyl-4S-(phenylmethylthio)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*6,5*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75 (dd, J = 14.5, 4.1 Hz, 1H), 2.88 (dd, J = 14.5, 4.6 Hz, 1H), 3.64 (d, J = 13.3 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 4.16 (t, J = 4.2 Hz, 1H), 4.41 (d, J = 15.5 Hz, 1H), 4.73 (d, J = 15.4 Hz, 1H), 7.30 (m, 8H), 7.59 (m, 1H).

5-(3-Chlorophenyl)methyl-4S-(phenylmethylthio)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*6,6*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (m, 2H), 3.67 (d, J = 15 Hz, 1H), 3.75 (d, J = 15 Hz, 1H), 4.04 (t, J = 6 Hz, 1H), 4.37 (s, 2H), 7.2−7.6 (aromatic H's, 9H).

5-(4-Acetamidophenyl)methyl-4S-(phenylmethylthio)-methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*6,8*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.70 (dd, J = 18, 6 Hz, 1H), 2.87 (dd, J = 15, 6 Hz, 1H), 3.69 (d, J = 13.3 Hz, 1H), 3.77 (d, J = 13.4 Hz, 1H), 4.04 (t, J = 4.2 Hz, 1H), 4.31 (d, J = 14.8 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 7.29 (m, 7H), 7.49 (d, J = 8.3 Hz, 2H).

5-(4,5-Methylenedioxy-2-nitrophenyl)methyl-4S-(phenylmethylthio)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*6,9*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (d, J = 5.5 Hz, 2H), 3.70 (s,2H), 4.11 (t, J = 4.5 Hz, 1H), 4.55 (d, J = 17.3 Hz, 1H), 5.00 (d, J = 17.3 Hz, 1H), 6.14 (m, 2H), 7.32 (m, 6H), 7.56 (s, 1H).

5-(4-Chloro-3-nitrophenyl)methyl-4S-(phenylmethylthio)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*6,10*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (dd, J = 14.5, 3.9 Hz, 1H), 2.92 (dd, J = 14.2, 5.6 Hz, 1H), 3.73 (s, 2H), 4.02 (t, J = 3 Hz, 1H), 4.30 (d, J = 15 Hz, 1H), 4.47 (d, J = 15 Hz, 1H), 7.29 (m, 1H), 7.53 (m, 1H), 7.89 (s, 1H).

5-(3-Chlorophenyl)methyl-4S-(phenylmethoxycarbonyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*7,6*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (m, 2H), 4.29 (d, J = 16.1 Hz, 1H), 4.53 (d, J = 16 Hz, 1H), 4.78 (t, J = 7.3 Hz, 1H), 5.07 (s, 2H), 7.34 (m, 9H).

5-(4-Acetamidophenyl)methyl-4S-(phenylmethoxycarbonyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*7,8*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.74 (dd, J = 18, 6 Hz, 1H), 2.91 (dd, J = 18, 9 Hz, 1H), 4.29 (d, J = 15 Hz, 1H), 4.36 (t, J = 3 Hz, 1H), 4.49 (d, J = 15 Hz, 1H), 5.04 (d, J = 15 Hz, 1H), 5.15 (d, J = 15 Hz, 1H), 7.34 (m, 7H), 7.46 (d, J = 7.7 Hz, 2H).

5-(4-Chloro-2-nitrophenyl)methyl-4S-(phenylmethoxycarbonyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*7,10*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (m, 2H), 4.32 (d, J = 16.7 Hz, 1H), 4.79 (t, J = 6.6 Hz, 1H), 5.06 (m, 3H), 7.36 (m, 5H), 7.55 (m, 2H), 7.92 (s, 1H).

5-(2,4-Dimethoxy-3-methylphenyl)methyl-4S-(phenylmethoxycarbonyl)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide 7{*7,11*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.73 (m, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 4.30 (m, 1H), 4.31 (d, J = 13.3 Hz, 1H), 4.52 (d, J = 14.4 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 5.13 (d, J = 12.2 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 7.34 (m, 6H).

6-(4-Methoxyphenylmethyl)-5,6-dihydro-2H-1,2,6-thiadiazin-3(4H)-one 1,1-Dioxide (20). The general procedure described above was followed using Fmoc−β-alanine with the exception that **19** was treated with DBU for 48 h. LC−MS of the crude product indicated the presence of 56% of **20**. MS (ESI, negative ion): m/z 269 $(M - 1)^-$ and 26% of an unidentified compound (m/z 237).

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