Evaluation of Solution and Solid-Phase Approaches to the Synthesis of Libraries of α,α-Disubstituted-α-acylaminoketones

ARTICLE *in* JOURNAL OF COMBINATORIAL CHEMISTRY · NOVEMBER 2005

Impact Factor: 4.93 · DOI: 10.1021/cc0500396 · Source: PubMed

Evaluation of Solution and Solid-Phase Approaches to the Synthesis of Libraries of α,α-Disubstituted-α-acylaminoketones

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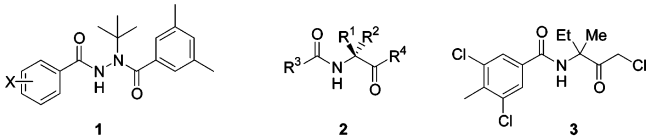
Received March 24, 2005

Solid phase, solution, and hybrid approaches to the synthesis of small focused libraries of α,α-disubstituted-α-acylaminoketones have been explored. Solution and hybrid approaches that used support-bound reagents and scavenger resins were the most productive.

Introduction

The insect moulting hormone ecdysone exerts its effects primarily by activation of the ecdysone receptor (EcR), which is a nuclear hormone receptor.[1] Nonsteroidal agonists of EcR have been of interest since the mid-1980s as insect control agents, and the two diacylhydrazines **1a** and **1b** (Figure 1) have been commercialized for this purpose, whereas **1c** has been reported to be under development.[2] More recently, systems to control gene expression in engineered non-insect cells using ecdysone agonist **1d** and related analogues have been described.[3,4] As part of an effort to discover non-diacylhydrazine-based classes of ecdysone agonists for use as ligands to control gene expression, we became interested in α,α-disubstituted-α-(acylamino)ketones of general structure **2** in which the *N-tert*-butyl group of the diacylhydrazines **1** is replaced with a disubstituted sp^3 carbon.[5] Our initial goal was to determine whether compounds of general structure **2** were competent ecdysone agonists and, based on the structure−activity relationship (SAR) of the diacylhydrazines **1**, we anticipated that R^3 and R^4 in **2** would typically be substituted phenyl groups. When a lead compound of general structure **2** was discovered, the goal of the project became optimization of the potency. For both the lead discovery and lead optimization phases of our project, we planned to prepare small libraries of analogues (ca. 5−50 members) as individual pure compounds, in quantities of ≥2 mg, although the possibility of much larger libraries was not excluded. In the course of this work, we have used both solid-phase and solution approaches to prepare **2**. The purpose of this paper is to compare the advantages and disadvantages of the various methodologies that have been used.



a X = 4-Et
b X = 2-Me-3-MeO
c X = 2-Me-3,4-OCH_2CH_2O-
d X = 2-Et-3-MeO

Figure 1.

Substantial numbers of α-acylaminoketones have been described in the literature, many as peptidomimetic inhibitors of proteases.[6] These compounds are typically monosubstituted at the α-position (**2**, R^1 = amino acid side chain, R^2 = H), and R^4 is often an electron-withdrawing group that increases the electrophilicity of the ketone carbonyl. Various methods, including solid-phase methods,[7−11] have been applied to the synthesis of compounds of general structure **2**.[12] Fewer α,α-disubstituted examples of **2** have been reported, although the commercial fungicide zoxamide (**3**) falls into this class.[13]

The advantages of solid-phase synthesis over solution synthesis for compound library preparation have been widely discussed.[14] The split and mix implementation of solid-phase synthesis allows economical generation of very large libraries of compounds as mixtures.[15] A major advantage of solid-phase synthesis is that reactions can be driven to completion by the use of excess reagents and multiple reaction cycles. Excess reagents and byproducts can then be removed by simple filtration, an operation that can readily be automated and run in parallel on multiple reactions. In favorable cases, at the end of the synthetic sequence, the desired product is cleaved in pure form from the solid support. On the other hand, the use of excess reagents is costly and limits the scale at which reactions can be conducted. Furthermore, monitor-

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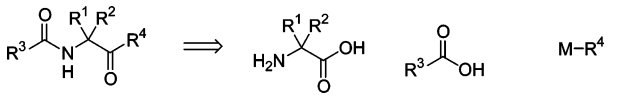
10.1021/cc0500396 CCC: $30.25
Published on Web 10/05/2005

Scheme 1. Retrosynthesis of α-Acylamino-α,α-disubstituted Ketones (**2**)



2 **4** **5** **6**

ing the progress of reactions on a solid support requires either specialized equipment (e.g., magic angle spinning nuclear magnetic resonance (MAS NMR) and photoacoustic annihilation spectrometry−Fourier transform infrared spectroscopy (PAS−FTIR)) or tedious cleavage of intermediates from the solid support, followed by analysis by standard solution-phase techniques (e.g., liquid chromatography−mass spectrometry (LC-MS), NMR). These factors often render development of a new sequence on a solid support time-consuming.

The scope of solution chemistry is broad and constitutes the vast bulk of the literature of organic chemistry. Solution-phase chemistry is not amenable to the production of the very large libraries that are available by solid-phase split and mix. Few reactions proceed to completion in quantitative yield in solution,[16] and the use of large excesses of reagents often is not a viable option. On the other hand, solution synthesis is more economical and reactions can be conducted on a larger scale. The use of resin-bound and other phase-tagged reagents and scavengers in solution-phase chemistry has become widespread in the past five years and has brought the possibility of at least partial purification of product by filtration to solution chemistry.[17] Instrumentation to analyze reaction mixtures and separate desired products are widely available and increasingly automated.

The advantages of solid-phase synthesis have made it the method of choice for peptides and oligonucleotides. However, it must be recognized that a huge investment has been made over many years to optimize the conditions and protecting groups to give complete reaction under mild conditions for these two classes of biopolymers. No single class of druglike small molecule compares in importance to peptides and oligonucleotides, so the investment of resources in method development on solid phase for any given class has been proportionally smaller.

Below, we describe several approaches to the synthesis of libraries of **2**. Our screening systems were not applicable to one-compound−one-bead libraries prepared by the split and mix methodology, one of the major strengths of solid-phase synthesis. Nonetheless, the approaches investigated include solid-phase methods as well as solution chemistry and hybrids of the two. All were based on the retrosynthetic analysis shown in Scheme 1, in which the target compounds are derived from three building blocks: α,α-disubstituted amino acids (**4**), carboxylic acids (**5**), and organometallic reagents (**6**) (M = Li, MgX). Very large numbers of carboxylic acids **5** and certain α,α-disubstituted amino acids **4** and Grignard reagents **6** are commercially available, allowing, in principle, the preparation of a large number of diverse compounds. Building blocks **4**, **5**, and **6** that have been used in this study are depicted in Figures 2−4. The Fmoc and Boc derivatives of **4**, **11**, and **24**, respectively, follow the same Chemset numbering scheme as **4** (Figure 2). Chemset numbering of the final compounds **2** was standardized as **2**{building block **4**, building block **5**, building block **6**}, to maintain consistent compound numbering for all analogues, regardless of the order of assembly of the building blocks that were used.

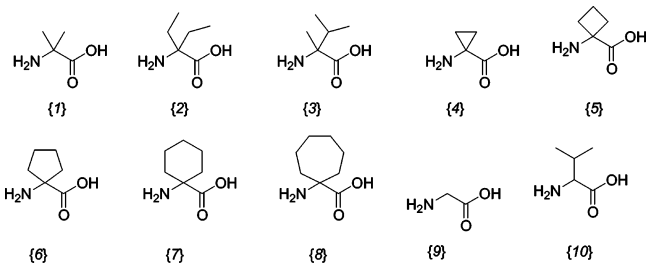


Figure 2. Amino acid building blocks (**4**). The corresponding Fmoc-protected amino acids **11** and Boc-protected amino acids (**24**) follow the same Chemset numbering scheme.

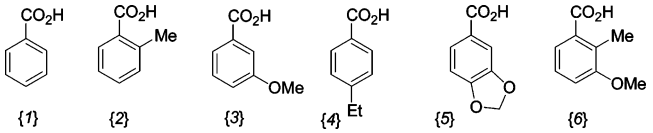


Figure 3. Carboxylic acid (**5**) building blocks.

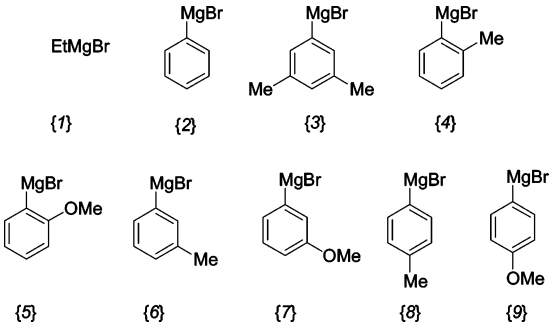


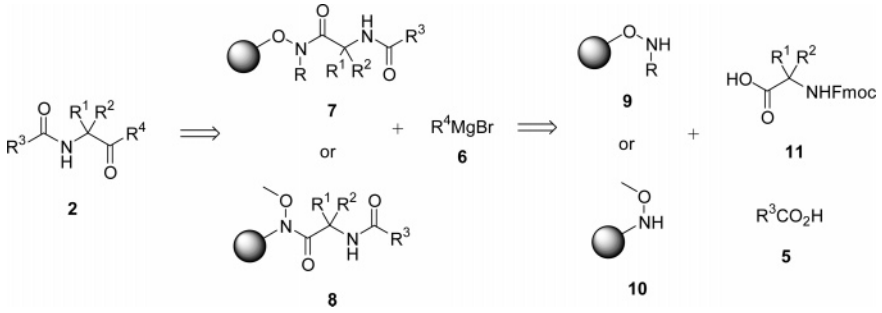
Figure 4. Grignard reagents (**6**).

Method 1. Solid-Phase Approach Using Solid-Supported Weinreb Amides as Key Intermediates

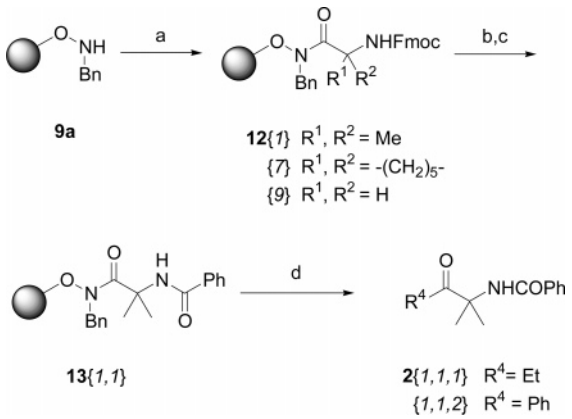
The first method we investigated was based on liberation of the desired compound **2** by cleavage of a resin-bound Weinreb amide **7** or **8** with a Grignard reagent **6** (Scheme 2).[5d] Several examples of the preparation of ketones from Weinreb amides on a solid phase have been reported,[18] and during the course of our work, O'Donnell et al.[7a] described preparation of a library of α-monosubstituted-α-acylaminoketones by a similar approach. Resin-bound Weinreb amides **7** or **8** could reasonably be assembled from *N*-protected α,α-disubstituted amino acids **11**, carboxylic acids **5** and resins **9** or **10**, respectively. However, the use of α,α-disubstituted amino acids could be problematic,[19] because of the steric bulk of the two α-alkyl substituents. In fact, O'Donnell et al.[7a] reported that the reaction between resin-bound intermediates similar to **8** and bulky Grignard reagents occurred in low yields, and, in the case of *t*-BuMgBr, the desired ketone was not detected.

Despite these potential difficulties, we decided to explore the synthesis of the desired α-acylamino ketones **2** by means of the approach depicted in Scheme 2, using either benzyloxyamino resin **9a** (R = Bn) reported by Salvino et al.[18a]

Scheme 2. Retrosynthesis of the Solid-Phase Approach to α-Acylamino-α,α-disubstituted Ketones (**2**)



Scheme 3[a]



[a] a = FmocNHCR^{1}R^{2}CO$_2$H (**11**{*1*}, 10 equiv), DIC (5 equiv), CH_2Cl_2/DMF (7:3), 3 d, rt; b = piperidine/DMF (1:4), 20 min, rt; c = $PhCO_2H$ (**5**{*1*}, 10 equiv), DIC (10 equiv), HOAt (10 equiv), 5 h, rt; and d = R^{4}MgBr (**6**, 10 equiv), THF(anhydrous), 18 h, rt.

or the commercially available Weinreb amide resin **10** developed by Martinez et al.[20]

N-benzylhydroxylamine resin **9a** (Scheme 3) was prepared from Wang resin via a reported literature procedure,[7a] and the intermediates were characterized by PAS−FTIR. Prior to use, resin **9a** was characterized by both PAS−FTIR and cleavage of a portion with TFA/CH_2Cl_2 (1:1) to afford C_6H_5-CH_2NHOH. Attachment of the α,α-disubstituted amino acid moiety onto the resin **9a** was performed using Fmoc-Aib-OH, (FmocNH−C(CH$_3$)$_2$−OH, **11**{*1*}), as a prototypical α,α-disubstituted amino acid, and the extent of conversion of **9a** to **12**{*1*} was estimated by PAS−FTIR.[21] Several standard peptide coupling conditions were explored; however, even the use of the most-reactive derivatives HATU/HOAt gave low conversion (20−30%) to amide **12**{*1*} (Table 1, entries 1−3, 5, and 6). The amino acid fluoride derivative afforded slightly better yields when generated in situ[22] (Table 1**,** entry 7, 40%), or preformed from **11**{*1*} and DAST[23] (Table 1**,** Entry 8, 42%). The best results for the attachment of **11**{*1*} onto resin **9a** were obtained by the in situ generation of the symmetrical anhydride of **11**{*1*}.[24] In this way, an 83% conversion was achieved (Table 1, entry 9). Subjecting the resin to a second cycle of coupling increased the conversion level up to 91% (Table 1**,** entry 10).

Removal of the Fmoc-protecting group from **12**{*1*} was followed by acylation of the free amino group with benzoic acid **5**{*1*} to afford **13**{*1,1*} (Scheme 3), which exhibited satisfactory PAS−FTIR spectra. Treatment of **13**{*1,1*} with an excess of EtMgBr **6**{*1*} afforded **2**{*1,1,1*} in 60% yield, based on the initial functionalization of the resin. This chemistry was successfully extended to aromatic Grignard reagents. Thus, reaction of **13**{*1,1*}, with an excess of PhMgBr **6**{*2*}, afforded **2**{*1,1,2*} in 31% yield. Biphenyl, which is a byproduct derived from dimerization of the Grignard reagent,[25] was also detected in the crude product. PAS−FTIR analysis of **13**{*1,1*}**,** after the Grignard reaction, showed that amide carbonyl groups were still present on the resin, indicating incomplete reaction. The importance of achieving high levels of conversion of **9a** to **12** was underscored by the unsatisfactory results that were obtained with incompletely derivatized samples of **12**{*1*}. Free *N*-benzylhydroxylamine groups in **9a** that had failed to react with **11**{*1*} were subsequently acylated with benzoic acid **5**{*1*} in step c to afford **14** (Scheme 4), which reacted with PhMgBr **6**{*2*} to give benzophenone **15** as the major product and the desired **2**{*1,1,2*} as a minor component.

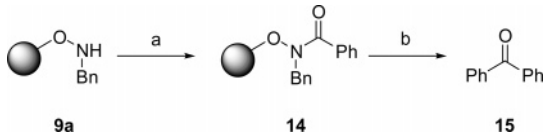
Despite the success ultimately achieved in preparing **2**{*1,1,1*} and **2**{*1,1,2*} from **11**{*1*} using this reaction sequence, attempts to extend it to more-hindered Fmoc-protected α,α-disubstituted amino acids (**11**) were not encouraging. The reaction of Fmoc-protected 1-aminocyclohexane-1-carboxylic acid **11**{*7*} with **9a** gave only 37% conversion to **12**{*7*} under the best conditions identified for **11**{*1*}. In view of these difficulties, we decided to attempt the same sequence on Weinreb resin **10** (Scheme 5) in the hope that the methoxylamine moiety in **10** would be more reactive than the benzyloxamino group in **9a**. Commercially available resin **16** was deprotected to **10** and treated with Fmoc-Aib-OH **11**{*1*} to give a 66% conversion to **17**{*1*}. Removal of the Fmoc group gave **18**{*1*}, which was coupled with benzoic acid **5**{*1*} to yield **19**{*1,1*}. Treatment of 19-{*1,1*} with excess of EtMgBr **6**{*1*} provided **2**{*1,1,1*} in 51% yield. A small amount of ethyl phenyl ketone was detected in the crude product. Treatment of **19**{*1,1*} with excess PhMgBr **6**{*2*} afforded **2**{*1,1,2*} in 36% yield. As before, biphenyl and benzophenone **15** were present in the crude product. The use of methoxyamino resin **10** did not offer any improvement over benzyloxyamino resin **9a**. Although we obtained the target compounds **2**{*1,1,1*} and **2**{*1,1,2*} from this sequence, the low purity of the crude products, and the presence of typical Grignard side-products in the cleavage solution made this route less than ideal for library production.

Table 1. Optimization of Loading Fmoc-Aib-OH **11**{*1*} onto Resin **9a**

entry	reagent(s)[a]	solvent[b]	time (days)	conversion[c]
1	**11**{*1*} (4), DIC (4), HOAt (4)	DMF	3	28
2	**11**{*1*} (4), DIC (4), HOAt (4)	DMF	2 × 3	32
3	**11**{*1*} (4), HATU (4), *i*-Pr_2NEt (8)	DMF	3	20
4	**11**{*1*} (5), EDC (5)	DMF	3	15
5	**11**{*1*} (5), EDC (5), HOAt (4.5)	DMF	3	30
6	**11**{*1*} (5), DIC (5), HOAt (5)/*i*-Pr_2NEt (5)	NMP	3	20
7	**11**{*1*} (5), TFFH (5), *i*-Pr_2NEt (10)	DMF	2	40
8	Fmoc-Aib-F (5)[d]	DCM	1	42
9	$(Fmoc\text{-}Aib)_2O$ (5)[e]	DCM/DMF (7:3)	3	83
10	$(Fmoc\text{-}Aib)_2O$ (5)	DCM/DMF (7:3)	2 × 3	91

[a] All reactions were performed at room temperature. Values in parentheses are equivalents. [b] DMF = dimethylformamide; DCM = dichloromethane. [c] The conversion was measured by photoacoustic infrared spectroscopy.[21] [d] Fmoc-Aib-F, an acid fluoride of **11**{*1*}, was prepared from **11**{*1*} and DAST.[23] [e] $(Fmoc\text{-}Aib)_2O$, which is a symmetrical anhydride of **11**{*1*}, was prepared immediately prior to use from **11**{*1*}.[25]

Scheme 4[a]



[a] a = $PhCO_2H$ (**5**{*1*}, 10 equiv), DIC (10 equiv), HOAt (10 equiv), 5 h, rt; b = PhMgBr (**6**{*2*}, 10 equiv), THF(anhydrous), 18 h, rt.

Method 2. Solid-Phase Approach Using Solid-Supported Thioesters as Key Intermediates

As an alternative to Weinreb amides, we explored the reaction of resin-bound amino acid thioesters with Grignard reagents as a possible path to α-acylaminoketones **2**. Reactions of thioesters with Grignard and other organometallic reagents to give ketones in solution[26] and on a solid phase[8,27] have been previously reported. Vlattas et al.[8] reported a solid-phase approach to C-terminal ketone peptides from thioester linkers and Grignard reagents. Thioesters are generally more reactive toward Grignard reagents than methoxyamides and potentially less sterically demanding. A suitably functionalized polymeric support **23** was easily prepared from *p*-MBHA resin **20**, using a three-step sequence that was described by Camarero et al.[28] (Scheme 6). Thiol resin **23** was quantitatively acylated with Boc-Aib-OH **24**{*1*}, to give **25**{*1*} (Scheme 7). Removal of the *N*-terminal Boc group to give **26**{*1*}, followed by aroylation with benzoic acid **5**{*1*}, afforded **27**{*1,1*}, which, with an excess of EtMgBr **6**{*1*} or PhMgBr **6**{*2*}, yielded the desired **2**{*1,1,1*} or **2**{*1,1,2*}, respectively, as minor products. The major reaction products in both cases were tertiary alcohols **28**{*1,1,1*} or **28**{*1,1,2*} derived from the reaction of **2**{*1,1,1*} or **2**{*1,1,2*} with an excess of the Grignard reagent (Scheme 7). In an attempt to minimize the formation of tertiary alcohols, the reaction was performed using a reduced excess of the Grignard reagent, shorter reaction times, and lower temperature. Thus, treatment of **27**{*1,1*} with 3 equiv of either EtMgBr or PhMgBr for 30 min at 0 °C lead again to mixtures of ketones **2** and tertiary alcohols **28** in a 1:1 ratio. This approach afforded the desired products but was of limited utility for library production, because of poor product purity.

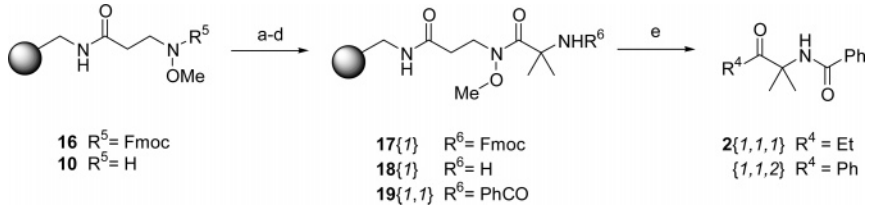
Method 3. Solution Phase Approach Using Solid-Supported Reagents and Weinreb Amides as Key Intermediates

We next attempted the preparation of α,α-disubstituted-α-acylaminoketones using the reaction of Weinreb amides of Boc-protected α,α-disubstituted-α-amino acid with Grignard reagents in solution. This reaction has been widely reported in the literature for the preparation of α-monosubstituted-α-amino acid derivatives;[29] however, very few reports include the preparation of α,α-disubstituted amino acid derivatives.[30] Boc-Val-OH, **24**{*10*} (a model compound for Boc-Aib-OH **24**{*1*}), was coupled with *N,O*-dimethylhydroxylamine to afford Boc-Val-NMeOMe **29**{*10*} (Scheme 8). Treatment of **29**{*10*} with excess PhMgBr (**6**{*2*}, 5 equiv) in THF solution at room temperature under an inert atmosphere of nitrogen for 8 h gave the expected Boc-protected α-aminoketone **30**{*10,2*} in 74% yield (Scheme 8). However, the reaction of *N*-Boc-Aib-NMeOMe **29**{*1*} with PhMgBr **6**{*2*} under same conditions did not yield the expected Boc-protected α-aminoketone **30**{*1,2*}, but, unexpectedly, did lead to two major products: α-acylaminoketone **2**{*1,1,2*} and α-aminoketone **31**{*1,2*}. The latter was isolated in 48% yield by precipitation of its trifluoroacetate salt with diethyl ether. Treatment of *N*-Boc-Aib-NMeOMe **29**{*1*} with EtMgBr **6**{*1*} similarly yielded **31**{*1,1*} and *N*-(1,1-dimethyl-2-oxobutyl)-propionamide (**2**, $R^1 = R^2 =$ Me, $R^3 = R^4 =$ Et).

The formation of **2**{*1,1,2*} and **31**{*1,2*} can be rationalized in two ways (Scheme 9). First, the addition of PhMgBr occurs at the Weinreb amide carbonyl to give the tetrahedral intemediate **32**. Nucleophilic addition of a second equivalent of PhMgBr to the carbamate carbonyl group of **32** would afford the tetrahedral intermediate **33**, which could unravel either by loss of *t*-butoxide anion (path a) to afford amide **2**{*1,1,2*}[31] or by loss of the anion of **31**{*1,2*} (path b). Alternatively, deprotonation of carbamate NH of **32** by 1 equiv of PhMgBr, followed by loss of the *t*-butoxide anion, would, in principle, give isocyanate **34**.[32] The addition of a second equivalent of PhMgBr to isocyanate **34**[33] would give **2**{*1,1,2*}, whereas reaction of the isocyanate with water during work up, followed by the loss of CO_2, would afford **31**{*1,2*}.

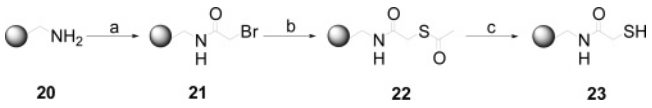
One of the factors that influences the outcome of Grignard additions in great measure is temperature.[34] Treatment of

Scheme 5[a]



[a] a = piperidine/DMF (1:4), 20 min, rt; b = Fmoc-Aib-OH (**11**{*1*}, 10 equiv), DIC (5 equiv), CH_2Cl_2/DMF (7:3), 3 days, rt; c = piperidine/DMF (1:4), 20 min, rt; d = $PhCO_2H$ (**5**{*1*}, 10 equiv), DIC (10 equiv), HOAt (10 equiv), 5 h, rt; and e = R^4MgBr (**6**, 10 equiv), THF(anh), 18 h, rt.

Scheme 6[a]



[a] a = $BrCH_2CO_2H$ (10 equiv), DCC (5 equiv), CH_2Cl_2, 2 h, rt; b = 10% solution of AcSH and *i*-Pr_2NEt in DMF, 2 × 20 min, rt; and c = 10% solution of β-mercaptoethanol and *i*-Pr_2NEt in DMF, 2 × 20 min, rt.

29{*1*} with 3 equiv of PhMgBr at −70 °C for 6 h, instead of at room temperature, did afford the desired Boc-protected aminoketone **30**{*1,2*} in 27% yield. The side products of this reaction were not identified. Alternatively, the use of less-reactive organometallic compounds such as organocopper reagents, could, in principle, minimize reaction with the Boc group.[35] Thus, the reaction of phenylthio ester **35**, the phenylthio ester analogue of **29**{*1*} (Scheme 10), and 3 equiv of $Ph_2CuMgBr$ (prepared in situ from PhMgBr and CuI) at −15 °C for 8 h yielded the desired **30**{*1,2*} in 21% yield. Starting material **35** was recovered and the presence of biphenyl was also detected. The reaction conversion was moderate and did not improve significantly using an excess of the organocuprate reagent.

The poor yields of the desired Boc-protected α-aminoketone **30**{*1,2*} encouraged us to take advantage of the serendipitous formation of α-aminoketone **31**{*1,2*}. A small demonstration library (library I) was prepared from **31**{*1,2*} and five benzoic acids **5**{*1*−*5*} (see Figure 3), using a catch-and-release strategy. The selection of benzoic acids was guided by knowledge of the SAR of the corresponding ring in the diacylhydrazines **1**. Polymer-supported active esters **37**{*1*−*5*}[36] were prepared from the corresponding benzoic acid, polymer-bound HOBt **36**, and DIC (Scheme 11). Acylations of **31**{*1,2*} were accomplished using 1.5 equiv of resins **37**{*1*−*5*}. LC−MS indicated that the main impurities in the crude products were unreacted aminoketone **31**{*1,2*} and the starting benzoic acids **5**{*1*−*5*}, which were readily removed by treatment with a weakly basic ion-exchange resin, followed by elution through a short column of silica gel to afford **2**{*1,1*−*5,2*} in good yields and acceptable purities (Table 2).

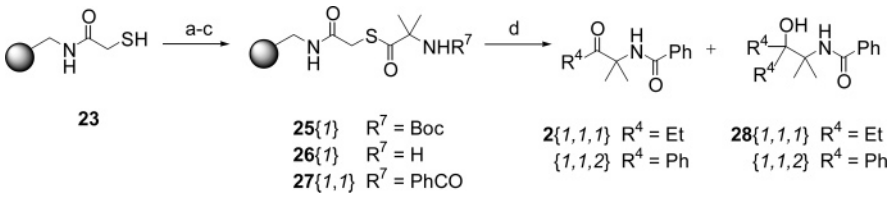
Attempts to extend this methodology to other α,α-disubstituted amino acids were less promising. For example, although the α-aminoketones **31**{*6,1*} or **31**{*6,2*} derived from Boc-protected 1-aminocyclopentanecarboxylic acid **24**{*6*} were detected in the crude reaction mixture, the trifluoroacetate salt did not precipitate from solution and could not be readily purified. Despite the successful production of the five-member demonstration library I, this approach was not pursued further.

Method 4. Combined Solution and Solid-Phase Approach Using Carbamate Linkers as Key Intermediates

We next investigated a solid-phase version of method 3 in which the Boc group is replaced with a carbamate linkage to a polymeric support.[5c] Porco et al. had previously reported some examples of this general approach.[18d] We speculated that a resin-bound carbamate linker might be less susceptible to react with a Grignard reagent than the Boc group of **29** (Scheme 12). Weinreb amide **29**{*1*} was deprotected to give aminoamide **38**{*1*}, which was incubated with *p*-nitrophenyl carbonate resin **39** to give resin-bound Weinreb amide **41**{*1*}. This intermediate exhibited a satisfactory PAS−FTIR spectrum. Similar results were obtained using (*N*-succinimidyl) carbonate resin **40** (see Scheme 12 and Table 3). To drive the reaction of **41**{*1*} with PhMgBr to high conversion, 15 equiv of Grignard reagent and a reaction time of 15 h proved to be necessary. Treatment of **42**{*1,2*} with TFA released α-aminoketone **31**{*1,2*} in 82% yield, based on the initial functionalization of Wang resin, and 13% of **38**{*1*}. In contrast to the corresponding solution phase reaction of **29**{*1*} with the previously described PhMgBr, we did not detect products of the reaction between PhMgBr and the carbamate linker of **41**{*1*}. The final conversion of **31**{*1,2*} to **2**{*1,1,2*} was accomplished using the polymer-supported active ester **37**, as described previously. Purification by treatment of the crude product with a weakly basic ion-exchange resin, followed by elution through a short column of silica gel, afforded **2**{*1,1,2*} in 86% yield and 89% purity by high-performance liquid chromatography (HPLC).

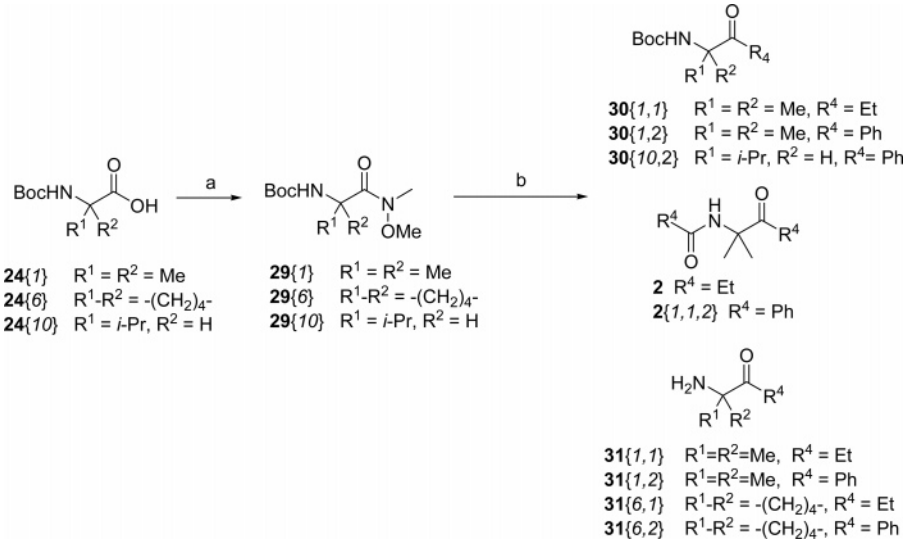
We used this methodology to produce a 25-member focused library (library II). The five α-aminoketone intermediates **31** shown in Table 4 were prepared from Boc amino acids **24**{*1*} and **24**{*6*} and Grignard reagents **6**{*1*}, **6**{*2*}, and **6**{*3*}. Good yields of the α-aminoketones **31** were obtained, especially when aromatic Grignard reagents **6**{*2*} and **6**{*3*} were used. The fully enumerated library of compounds derived from reaction of the five α-aminoketones **31** and resin-bound active esters **37**{*1*−*5*} was prepared. All compounds in library II were characterized by ^1H NMR and LC−MS. The yields and purities are shown in Table 5. On average, acceptable yields, in the range of 61−92%, were obtained in the acylation reaction. However, better yields were observed when the aromatic acid **5** did not have an ortho substituent, possibly because of the effect of steric hindrance. Purities were high (in the range of 82−97%) and demonstrate the excellent results that can be obtained using solid-supported reagents.

Scheme 7[a]



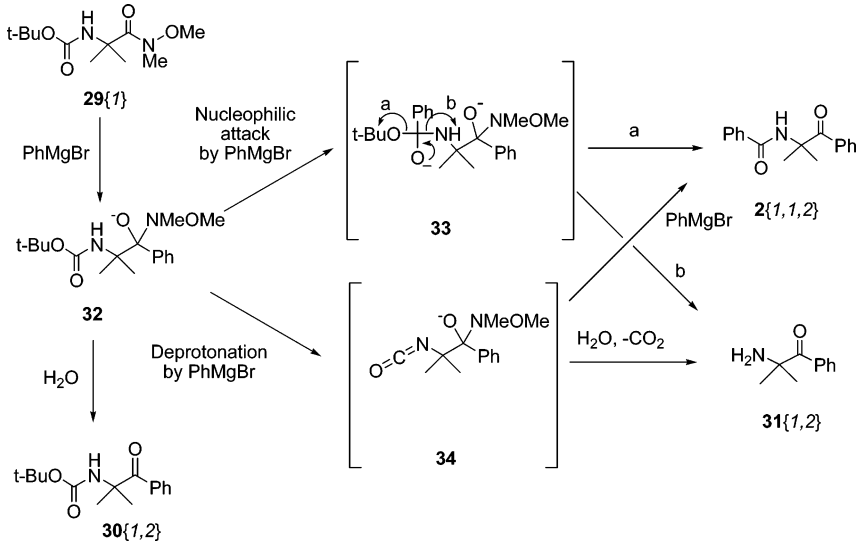
[a] a = Boc-Aib-OH (**24**{*1*}, 10 equiv), HATU (10 equiv), *i*-Pr_2NEt (20 equiv), DMF, 2 h, rt; b = TFA/ CH_2Cl_2 (4:6, v/v), 20 min, rt; c = $PhCO_2H$ (**5**{*1*}, 10 equiv), DIC (10 equiv), HOBt (10 equiv), 2 h, rt; and d = R^4MgBr (**6**, 10 equiv), THF(anhydrous), 12 h, rt.

Scheme 8[a]



[a] a = MeNHOMe·HCl (1.2 equiv), EDC (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), CH_2Cl_2, 24 h, rt; b = R^4MgBr (**6**{*2*}, 5 equiv), THF (anhydrous) (see text for time and temperature).

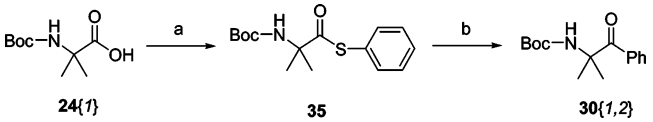
Scheme 9. Possible Mechanisms for the Formation of **2**{*1,1,2*} and **31**{*1,2*}



Method 5. Solution-Phase Approach Using Azlactones as Key Intermediates

Finally, we explored purely solution-phase approaches to the preparation of a focused library of α-acylaminoketones **2** (library III) modeled on the commercial insecticidal diacylhydrazine ecdysone agonist **1b.**[2,5b] In this library, the three amino acids **4**{*2*}, **4**{*3*}, and **4**{*6*} (see Figure 2) provided variation at R^1 and R^2. R^3 was fixed as 2-methyl-3-methoxyphenyl, derived from **5**{*6*}. Finally, R^4 was chosen to be phenyl substituted with methyl and methoxy groups at the 2-, 3-, and 4-positions of the phenyl ring, as well as with the 3,5-dimethyl pattern, which is present in **1b**.

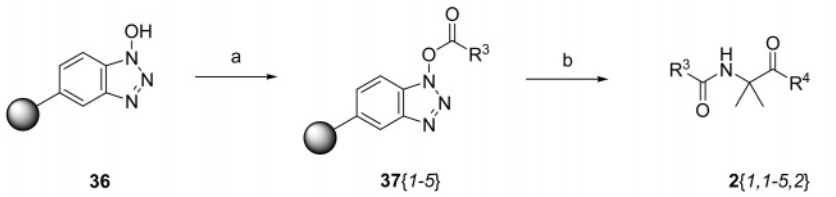
Scheme 10[a]



[a] a = Thiophenol (1.2 equiv), DCC (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), CH_2Cl_2, 16 h, rt; b = $Ph_2CuMgBr$ (3 equiv), THF (anhydrous), 8 h, −15 °C.

Initially, a synthetic route (Scheme 13, method 5A) was

Scheme 11[a]



[a] a = R^3CO_2H (**5**{*1*−*5*}, 5 equiv), DIC (5 equiv), DMAP (1 equiv), DMF−CH_2Cl_2 (1:1), 5 h, rt; b = **31**{*1,2*} (0.7 equiv), *i*-Pr_2NEt (1 equiv), CH_2Cl_2, 16 h, rt.

Table 2. Yields and Purities of Library I

benzoic acid	product	yield (%)[a]	purity (%)[b]
5{*1*}	**2**{*1,1,2*}	86	92
5{*2*}	**2**{*1,2,2*}	78	78
5{*3*}	**2**{*1,3,2*}	83	83
5{*4*}	**2**{*1,4,2*}	88	88
5{*5*}	**2**{*1,5,2*}	91	90

[a] Yields were calculated based on starting α-aminoketone **30**{*1,2*} TFA salt. [b] Purities were calculated based on integration of the HPLC trace at 220 nm.

investigated in which reaction of a Grignard reagent with Weinreb amide **44** was the key step. Commercially available α,α-disubstituted amino acids **4**{*2*}, **4**{*3*}, and **4**{*6*} were cyclized to the corresponding azlactones **43**{*2,6*}, **43**{*3,6*}, and **43**{*6,6*} by treatment with 2.5 equiv of the acid chloride of 2-methyl-3-methoxybenzoic acid **5**{*6*} in pyridine. The key Weinreb amide intermediates **44** were generated by opening the azlactone rings of **43** with *N,O*-dimethylhydroxylamine in the presence of pyridine.[37] Treatment of **44**{*6,6*} with 3-methoxy-phenylmagnesium bromide **6**{*7*} in THF at room temperature afforded the desired α-acylaminoketone **2**{*6,6,7*} in 63% yield. However, when the Grignard reaction was performed with the more sterically congested Weinreb amide **44**{*3,6*} under similar conditions, the major product was *N*-(hydroxymethyl)-*N*-methylamide **45**{*3,6*} and little of the desired ketone **2**{*3,6,7*} was present in the crude reaction mixture. Compounds such as **45** have previously been reported in reactions of hindered Weinreb amides and Grignard reagents.[38]

To circumvent the limitations of Grignard reactions with Weinreb amides, an alternative synthetic route (Scheme 13, method 5B) in which the ketone is generated by the addition of a Grignard reagent to an aldehyde, followed by oxidation, was used. The key aldehyde intermediates **46**{*2,6*}, **46**{*3,6*}, and **46**{*6,6*} were generated by reduction of the previously prepared azlactones **43**{*2,6*}, **43**{*3,6*}, and **43**{*6,6*} to primary alcohols, followed by oxidation with Dess−Martin periodinane.[39] Aldehydes **46**{*2,6*}, **46**{*3,6*}, and **46**{*6,6*} were reacted with eight different phenylmagnesium bromides **6**{*2*−*9*} in THF at low temperature to afford 24 secondary alcohols, which were oxidized, once again, with the Dess−Martin periodinane, to afford 23 of the desired 24 α-acylaminoketones **2** of library III (Table 6). Isolated yields of **2** from **46** were in the range of 9−60%.

Because the most potent compounds found in library III were those derived from 1-aminocyclopentane-1-carboxylic acid, follow-up library IV (Table 7) was prepared to explore the effect of the ring size on ecdysone agonist activity.[5a] The synthesis was performed using methods 5A and 5B (Scheme 13). Method 5A afforded the desired cyclopropane **2**{*4,6,3*} and cyclobutane **2**{*5,6,3*} products in yields of 68% and 66%, respectively; however, less-satisfactory results were obtained using this method for cyclohexane **2**{*7,6,3*}. Method 5B was determined to be more satisfactory for the preparation of cyclohexanes **2**{*7,6,3*} and **2**{*7,6,5*}, as well as cycloheptanes **2**{*8,6,3*} and **2**{*8,6,5*}.

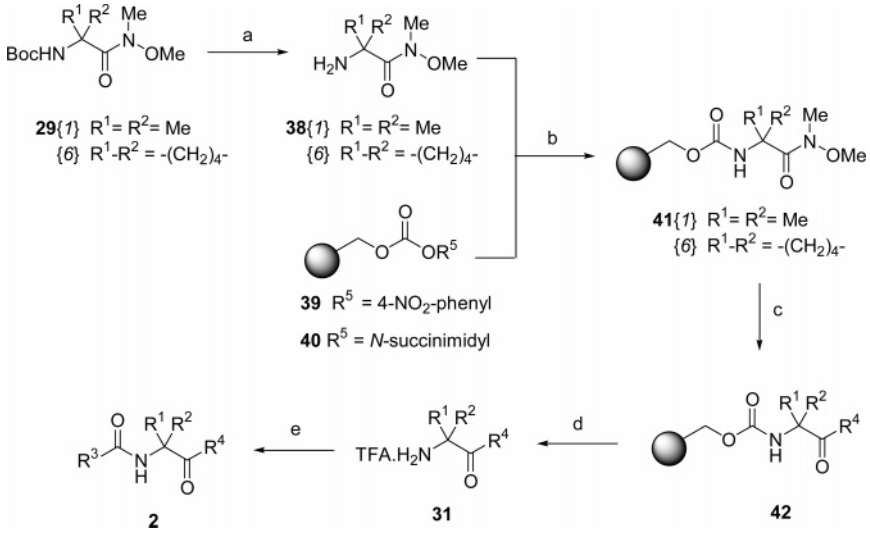
Weinreb amides **44** and aldehydes **46** were prepared in bulk using traditional solution-chemistry techniques, including flash chromatography. The diversification of these intermediates to the target compounds **2** was expedited by the use of more recently introduced techniques. Reaction workups were expedited using Varian Chem-Elut cartridges.[17c] Unreacted aldehydes **46** were efficiently removed from the final products by incubation with PS-$TsNHNH_2$ tosylhydrazide resin.[40] Fractionation of crude products on silica gel solid phase extraction (SPE) cartridges by elution with a series of solvent mixtures of increasing polarity generally afforded products of adequate purity (>85%) for screening in at least one fraction.

Biological Activity

The compounds prepared as ecdysone agonists were assayed in a cell-based assay system in which a *β*-galactosidase reporter gene is under the control of the ecdysone receptor from *Bombyx mori* (BmEcR).[41,42] Initially, the compounds were tested at a concentration of 33 *μ*M and the ratio of *β*-galactosidase expression was compared to a dimethylsulfoxide (DMSO) control. Compounds that performed well in this assay were typically re-tested in a dose response assay in which diacylhydrazine **1d** was used as a positive control. The results from the dose response assay were reported as EC_{50} (the dose affording 50% of the maximum *β*-galactosidase expression caused by the test compound) and efficacy (the ratio of the ratio of the maximum level of *β*-galactosidase expression with the test compound to the maximum level with **1d**).

None of the members of the five-compound demonstration library I based on amino acid **4**{*1*} were active at a concentration of 33 *μ*M. Two members of library II were active: **2**{*6,4,2*} and **2**{*6,4,3*} (see Figure 5) caused 133- and 1027-fold induction of the *β*-galactosidase expression over the DMSO control, respectively. The complete assay results of libraries III and IV have been reported previously.[5a,5b] In library III, the most potent and efficacious compound was **2**{*6,6,3*} (EC_{50} = 1.9 *μ*M, efficacy = 0.85), whereas, in library IV, **2**{*7,6,3*} (EC_{50} = 1.41 *μ*M, efficacy = 0.99) and **2**{*7,6,5*} (EC_{50} = 0.98 *μ*M, efficacy = 0.84) were the most active compounds.

Scheme 12[a]



[a] a = TFA−CH_2Cl_2 (1:1), 25 °C, 20 min; b = **37** (10 equiv), *i*-Pr_2NEt (15 equiv), NMP, 60 °C, 16 h; c = R^4MgBr (**6**, 15 equiv), THF, 25 °C, 4 h followed by HOAc−CH_2Cl_2 (9:1); d = TFA−H_2O (95:5); and e = **37** (1.5 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2.

Table 3. Yields and Purities of α-aminoketone **31**{*1*} Using *p*-Nitrophenyl and (*N*-Succinimidyl) Carbonate Resins

resin	temperature (°C)	yield[a,b] (%)	purity (%)[c]
39	25	72	91
39	60	82	90
40	25	76	92
40	60	70	85

[a] 10 equiv of **38**{*1*}. Isolated as trifluoroacetate (TFA) salt. [b] Yield was calculated based on the initial functionalization of the resin. [c] Purity confirmed by integration of the HPLC trace at 220 nm.

Generally, the SAR trends of R^3 and R^4 in **2** paralleled those observed in the diacylhydrazines **1**. Joining R^1 and R^2 in **2** to form a cyclohexane ring was the optimum replacement found for the *N*-*tert*-butyl group in **1**. The best compound discovered from the four libraries described was **2**{*7,6,3*}in library IV; however, it was less potent than the analogous diacylhydrazine **1b**. Nonetheless, the rigid cyclohexane moiety of **2** may offer some advantage as an alternative platform for tailored exploration of the hydrophobic pocket normally occupied by the *tert*-butyl group of **1**.

Conclusions

We have investigated several approaches to the synthesis of libraries of α,α-disubstituted-α-acylaminoketones of general structure **2**, which is a new class of ecdysone agonists. The approaches explored included pure solid-phase synthesis (methods 1 and 2), traditional solution chemistry (methods 5A and 5B), and approaches that combined features of both solid-phase and solution chemistry (methods 3 and 4). We were unable to fully realize the advantages of solid-phase synthesis in method 1, because the loading of the amino acid **4** onto the resin could not be driven to completion, which led to the formation of impurities in the final products. Furthermore, the crude cleavage products from the resin in both methods 1 and 2 required chromatographic purification, eliminating a nominal advantage of solid-phase synthesis over solution synthesis. More promising results were obtained with methods 3 and 4, which were hybrid approaches that relied on strategic combinations of solution chemistry, solid-phase steps, and a resin-bound reagent. The solution approaches (methods 5A and 5B) were able to produce the desired compounds in larger amounts and with less investment in method development and smaller quantities of reagents; however, laborious chromatographic purification was required after most steps.

Four of the approaches (methods 1, 3, 4, and 5A) relied on reaction of a Weinreb amide with a Grignard reagent to form the ketone of **2**. This reaction proved troublesome when applied to such amides derived from α,α-disubstituted-α-amino acids, especially those with bulky α-substituents.[7a] Replacement of the Weinreb amide with an aldehyde in solution (method 5B) solved this problem at the expense of additional synthetic steps. This approach was not attempted on the solid phase.

For the small focused libraries prepared in this study, solution chemistry was able to deliver target compounds with a smaller investment in chemistry development than solid-phase approaches. The use of polymer-supported reagents and scavengers facilitated the solution approaches. For the much-larger libraries contemplated for chemical genetic experiments, the investment in chemistry development is warranted, and solid-phase split and mix synthesis remains the method of choice.[14a,43]

Experimental Section

Abbreviations. The following abbreviations are used: Aib, α-aminoisobutyric acid; Boc, *tert*-butoxycarbonyl; d, days; DAST, diethylaminosulfur trifluoride; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DIC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-(dimethyl-amino)pyridine; DMF, *N*,*N*-dimethylformamide; DSC, disuccinimidyl carbonate; EcR, ecdysone receptor; EDC, eq, equivalents; 1-ethyl-3-(3′-(dimethylamino)-propyl)carbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate; HOAc, acetic acid; HOAt,

Table 4. Yields and Purities of α-aminoketones **31**[a]

product α-aminoketone	R^1, R^2	R^4	yield[b]	purity of **31** (% of recovered **38**)[c]
31{*1,1*}	Me, Me	Et	82	85 (9)
31{*1,3*}	Me, Me	3,5-diMe-Ph	76	89[d] (9)
31{*6,1*}	$-(CH_2)_4-$	Et	80	80 (12)
31{*6,2*}	$-(CH_2)_4-$	Ph	94	92[d] (5)
31{*6,3*}	$-(CH_2)_4-$	3,5-diMe-Ph	86	94[d] (3)

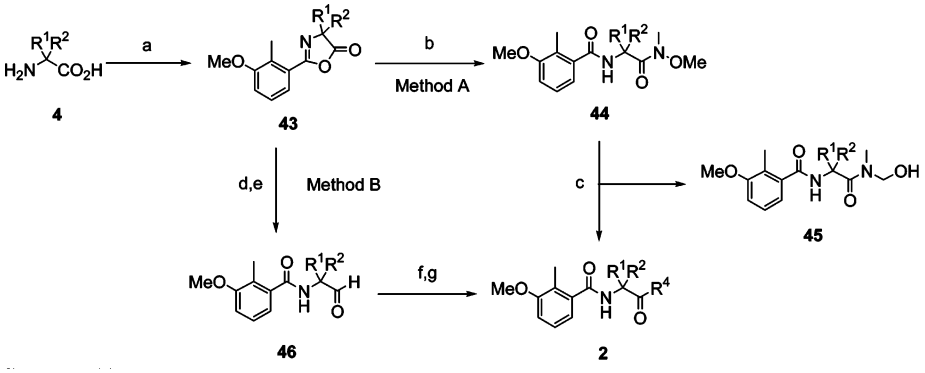
[a] Isolated as TFA salts. [b] Yield was calculated based on the initial functionalization of the resin. [c] Purity was calculated by integration of the appropriate peaks in the ^{1}H NMR spectra. [d] Purity confirmed by integration of the HPLC trace at 220 nm.

Table 5. Yields and Purities of Compounds of Library II

	5{*1*}[b]		**5**{*2*}		**5**{*3*}		**5**{*4*}		**5**{*5*}	
α-amino-ketone[a]	library compd[c]	yield and purity (%)	library compd[c]	yield and purity (%)	library compd[c]	yield and purity (%)	library compd[c]	yield and purity (%)	library compd[c]	yield and purity (%)
31{*1,1*}	**2**{*1,1,1*}	87[d] (83)[e]	**2**{*1,2,1*}	61 (82)	**2**{*1,3,1*}	78 (89)	**2**{*1,4,1*}	76 (82)	**2**{*1,5,1*}	83 (91)
31{*1,3*}	**2**{*1,1,3*}	90 (95)	**2**{*1,2,3*}	76 (90)	**2**{*1,3,3*}	80 (85)	**2**{*1,4,3*}	92 (92)	**2**{*1,5,3*}	81 (86)
31{*6,1*}	**2**{*6,1,1*}	82 (96)	**2**{*6,2,1*}	65 (87)	**2**{*6,3,1*}	70 (88)	**2**{*6,4,1*}	69 (92)	**2**{*6,5,1*}	73 (87)
31{*6,2*}	**2**{*6,1,2*}	76 (95)	**2**{*6,2,2*}	74 (92)	**2**{*6,3,2*}	83 (92)	**2**{*6,4,2*}	84 (84)	**2**{*6,5,2*}	77 (82)
31{*6,3*}	**2**{6,*1,3*}	89 (94)	**2**{*6,2,3*}	74 (92)	**2**{*6,3,3*}	87 (95)	**2**{*6,4,3*}	88 (96)	**2**{*6,5,3*}	84 (97)

[a] See Table 4 for R^1, R^2, and R^4 substituent definitions. [b] Carboxylic acid building block used. (See Figure 3.) [c] Library compound number. [d] Yields were calculated based on starting α-aminoketone TFA salt. [e] Purities were calculated based on integration of the HPLC trace at 220 nm.

Scheme 13[a]



[a] a = 2-Me,3-MeO−PhCOCl (2.5 equiv), pyridine, rt; b = MeNHOMe·HCl, pyridine, CH_2Cl_2, rt; c = R^4MgBr (**6**, 4 equiv), THF, rt, 5 h; d = $NaBH_4$, THF, rt; e = Dess−Martin periodinane, CH_2Cl_2, rt; f = R^4MgBr (**6**, 4 equiv), THF, −70 °C → rt; and g = Dess−Martin periodinane, CH_2Cl_2, rt.

Table 6. Yields for Library III[a,b]

	Yield (%)		
Grignard reagent	**46**{*2,6*}	aldehyde **46**{*3,6*}	**46**{6,*6*}
6{*2*}	42	38	46
6{*3*}	29	19	60
6{*4*}	19	26	41
6{*5*}	20	35	39
6{*6*}	16	34	29
6{*7*}	47	35	41
6{*8*}	28	9	36
6{*9*}	56	*c*	22

[a] Yields are for the two steps from aldehyde **46** to library compound **2** and represent a lower limit, because mixed fractions were discarded. [b] Purities were estimated to be >85% based on inspection of the ^{1}H NMR spectra. [c] Desired compound not isolated from reaction mixture.

1-hydroxy-7-azabenzotriazole; HOBt, 1-hydroxybenzotriazole; *i*-Pr_2Net, *N*,*N*-diisopropylethylamine; MBHA, *p*-methylbenzhydrylamine; NMM, *N*-methyl-morpholine; NMP, *N*-methylpyrrolidin-2-one; PAS−FTIR, photoacoustic Fourier transform infrared spectroscopy; rt, room temperature; TFA, trifluoroacetic acid; TFFH, tetramethylfluoroformamidinium hexafluorophosphate; and THF, tetrahydrofuran.

General. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. MBHA, Wang, and Fmoc−Weinreb resins were obtained from Novabiochem. Fmoc−amino acids were obtained from Advanced Chemtech, Boc-Aib-OH was obtained from Novabiochem, and 1-amino-cyclopentanecarboxylic acid was obtained from Aldrich. Solvents were removed on a rotary evaporator at 20−50 mm Hg. Solution ^{1}H NMR and ^{13}C NMR spectroscopy was performed on a Bruker DPX300 or Varian XL200. Magic angle spinning ^{1}H NMR spectra were obtained from an NMR analysis system (Bruker DMX400). Photoacoustic FTIR spectra were obtained on a Bio-Rad FTS 6000 step-scan spectrometer. LC−MS analyses were performed 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 or Waters Separation Module 2690 Alliance coupled to a VG platform (Fisons). The data were acquired and processed using Micromass MassLynx v3.2 with OpenLynx. HPLC analyses were performed using various equipment (Hewlett−Packard HP Series 1050, Shimadzu LC-6A, or Waters 600E).

Table 7. Synthetic Methods and Yields for Library IV

target compound	R^1-R^2	R^3	R^4	method[a]	yield[b] (%)
2{*4,6,3*}	$-(CH_2)_2-$	2-Me-3-MeO-Ph	3,5-diMe-Ph	5A	68
2{*5,6,3*}	$-(CH_2)_3-$	2-Me-3-MeO-Ph	3,5-diMe-Ph	5A	66
2{*7,6,3*}	$-(CH_2)_5-$	2-Me-3-MeO-Ph	3,5-diMe-Ph	5B	44[c]
2{*8,6,3*}	$-(CH_2)_6-$	2-Me-3-MeO-Ph	3,5-diMe-Ph	5B	28
2{*7,6,5*}	$-(CH_2)_5-$	2-Me-3-MeO-Ph	2-MeO-Ph	5B	34
2{*8,6,5*}	$-(CH_2)_6-$	2-Me-3-MeO-Ph	2-MeO-Ph	5B	18

[a] See Scheme 13. [b] Yields for method 5A are based on Weinreb amide **44** (one step). Yields for method 5B are based on aldehyde **46** (two steps). [c] Yield using method 5A was 25%.

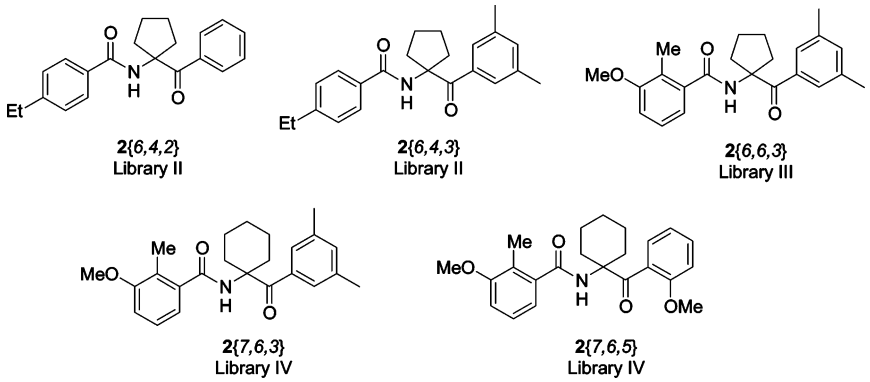


Figure 5. Selected biologically active library compounds.

General Methods. The following experimental procedures are representative.

1. Preparation of Fmoc-Aib-N(Bn)-O-Wang Resin (12{*1*}). Fmoc-Aib-OH (**11**{*1*}, 1.95 g, 6 mmol, 10 equiv) and DIC (0.45 mL, 3 mmol, 5 eq) were dissolved in 3 mL of CH_2Cl_2/DMF (7:3). The mixture was stirred at room temperature for 10 min, the resulting precipitate (*N*,*N*′-diisopropylurea) was removed by filtration, and the filtrate was added to *N*-benzylhydroxylamine resin **9a** (0.50 g, 0.60 mmol, 1.2 mmol/g). The mixture was shaken at room temperature for 3 d and drained. The resin was washed with DMF (10 × 5 mL) and CH_2Cl_2 (10 × 5 mL) and then dried at reduced pressure to afford **12**{*1*} (0.73 g, 0.6 mmol, 0.82 mmol/g). PAS−FTIR Fmoc carbamate C═O stretch, 1727 cm^{-1}; amide C═O stretch, 1676 cm^{-1}. The conversion was 83%, as determined by PAS−FTIR.

2. Preparation of Ph-CO-Aib-N-(Bn)-O-Wang Resin (13{*1,1*}). Resin **12**{*1*} (0.73 g, 0.6 mmol, 0.82 mmol/g) was suspended in 20% piperidine in DMF (7 mL), and the reaction mixture was stirred for 20 min. The solution was drained, and the resin was washed thoroughly with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL). A solution of benzoic acid (0.732 g, 6 mmol, 10 equiv), HOAt (0.815 g, 6 mmol, 10 equiv) and DIC (0.91 mL, 6 mmol, 10 equiv) in 3 mL of DMF was added and the mixture was shaken for 5 h. The resin was filtered and washed with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL) and then dried at reduced pressure to afford **13**{*1,1*} (0.69 g, 0.6 mmol, 0.87 mmol/g). PAS−FTIR amide bound to the solid support C═O stretch, 1670 cm^{-1}; benzamide C═O stretch, 1655 cm^{-1}.

3. Preparation of Fmoc-Aib-Weinreb Resin (17{*1*}). Commercially available Fmoc-Weinreb resin **16** was treated with a solution of 20% piperidine in DMF for 20 min to yield resin **10**. Independently, Fmoc-Aib-OH (**11**{*1*}, 0.62 g, 1.89 mmol, 10 equiv) and DIC (0.15 mL, 0.94 mmol, 5 equiv) were dissolved in 7:3 CH_2Cl_2/DMF (2 mL). The mixture was stirred at room temperature for 10 min, the resulting precipitate (*N*,*N*′-diisopropylurea) was removed by filtration, and the filtrate was added to the previously prepared Weinreb amide resin **10**. The mixture was shaken at room temperature for 3 d. The resin was drained, washed with DMF (10 × 5 mL) and CH_2Cl_2 (10 × 5 mL), and finally dried under reduced pressure to afford **17**{*1*} (0.31 g, 0.19 mmol, 0.6 mmol/g). PAS−FTIR Fmoc carbamate C═O stretch, 1726 cm^{-1}; amide C═O stretch, 1632 cm^{-1}; resin amide C═O stretch, 1678 cm^{-1}. The conversion was 66%, as determined by PAS−FTIR.

4. Preparation of Ph-CO-Aib-Weinreb Resin (19{*1,1*}). Removal of the Fmoc-protecting group from resin **17**{*1*} (0.31 g, 0.19 mmol, 0.6 mmol/g) and acylation of the free amino group with benzoic acid **5**{*1*} was performed using the same experimental procedure as that previously described for resin **13**{*1,1*} to obtain resin **19**{*1,1*} (0.3 g, 0.19 mmol, 0.62 mmol/g). PAS−FTIR resin amide C═O stretch, 1678 cm^{-1}; amide bound to the solid support C═O stretch, 1631 cm^{-1}; benzamide C═O stretch, 1653 cm^{-1}.

5. General Procedure for Cleavage of Products from the Resins. The Grignard reagent (1 M solution in THF, R^4MgBr **6**, 10 equiv) was added to a suspension of the Weinreb amide derivative anchored to the resin, in anhydrous THF (2 mL) under an atmosphere of argon. The reaction mixture was shaken for 18 h and quenched by addition of 1 M aq HCl:THF (1:1) until the pH of the resulting solution was ∼3. The reaction mixture was agitated for 30 min and drained into a vial. The resin was washed with THF (3 × 2 mL). The combined filtrates were evaporated to dryness, and the residue was eluted through a silica gel solid-phase extraction cartridge with CH_2Cl_2 (2 × 2 mL). The eluate was concentrated to yield the crude product, which was purified by flash chromatography, using hexane:ethyl acetate

(1:1) as the solvent. The appropriate fractions were pooled and evaporated to give the desired product.

***N*-(1,1-Dimethyl-2-oxo-butyl)-benzamide (2{*1,1,1*}).** 60%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, J = 7.4 Hz, 3H), 1.63 (s, 6H), 2.65 (q, J = 7.2 Hz, 2H), 7.23 (sa, 1H), 7.4−7.58 (aromatic H's, 3H), 7.80 (dd, J = 8.2, 1.6 Hz, 2H). MS (ESI, positive ion): m/z 220.1 $(M+1)^+$.

***N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-benzamide(2{*1,1,2*}).** 31%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 6H), 6.84 (bs, 1H), 7.30−7.57 (aromatic H's, 8H), 7.88 (dd, J = 8, 1.6 Hz, 2H). MS (ESI, positive ion): m/z 268.3 $(M+1)^+$.

6. Preparation of Mercaptoacetamide Resin (23). Bromoacetic acid (1.94 g, 14 mmol, 10 equiv), and DIC (1.08 mL, 7 mmol, 5 equiv) were dissolved in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 10 min, the resulting precipitate (*N*,*N*′-diisopropylurea) was removed by filtration, and the filtrate was added to MBHA resin **20** (2 g, 1.4 mmol, 0.7 mmol/g). The mixture was shaken at room temperature for 2 h. The resin was filtered and washed with CH_2Cl_2 (10 × 5 mL) and DMF (10 × 5 mL) to afford **21**. A negative ninhydrin test of the resin indicated that the coupling of bromoacetic acid was quantitative. Resin **21** was treated with 15 mL of a 10% mixture of thioacetic acid and *i*-Pr_2NEt in DMF (2 × 20 min); the resin was drained and then washed with DMF (10 × 5 mL) to obtain resin **22**, which was treated with 15 mL of a 10% mixture of β-mercaptoethanol and *i*-Pr_2NEt in DMF (2 × 20 min). The solution was removed, and the resin was washed with DMF (10 × 5 mL) and CH_2Cl_2 (10 × 5 mL) to afford resin **23**. An aliquot of resin **23** was submitted to a qualitative Ellmann test, in which a very intense reddish coloration was observed, which indicated the presence of free thiol groups on the solid support.

7. Preparation of Boc-Aib-S-CH_2-CO-MBHA Resin (25{*1*}). Boc-Aib-OH (0.71 g, 3.5 mmol, 10 equiv), HATU (1.33 g, 3.5 mmol, 10 equiv) and *i*-Pr_2NEt (1.19 mL, 7 mmol, 20 equiv) in DMF were added to mercaptoacetamide resin **23** (0.7 mmol/g, 0.5 g, 0.35 mmol) and shaken for 2 h. The solution was drained, and the resin was washed with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL). An aliquot of resin **25**{*1*} was submitted to a qualitative Ellmann test, in which a yellow pale coloration was observed, which indicated the absence of free thiol groups on the solid support.

8. Preparation of Ph-CO-Aib-S-CH_2-CO-MBHA Resin (27{*1,1*}). Resin **25**{*1*} (0.35 mmol) was suspended in a 40% TFA solution in CH_2Cl_2 (7 mL), and the reaction mixture was stirred for 20 min. The solution was drained, and the resin was washed thoroughly with CH_2Cl_2 (5 × 5 mL), 5% *i*-Pr_2NEt in CH_2Cl_2 (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and DMF (5 × 5 mL). Benzoic acid (0.43 g, 3.5 mmol, 10 equiv), HOBt (0.54 g, 3.5 mmol, 10 equiv), and DIC (0.54 mL, 3.5 mmol, 10 equiv) in 3 mL of DMF was added to the resulting resin, and the reaction mixture was shaken for 5 h. After the liquid was drained, the resin was washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and MeOH (5 × 5 mL) and dried overnight under reduced pressure to afford resin **27**{*1,1*} (0.67 g, 0.35 mmol, 0.52 mmol/g).

9. General Procedure for Cleavage of Products from Resin 27{*1,1*}. The following experimental procedure is representative. Resin **27**{*1,1*} (0.1 g, 0.052 mmol, 0.52 mmol/g) was suspended in freshly distilled, dry THF (2 mL) under an atmosphere of argon, treated with EtMgBr (1M solution in THF, 0.52 mL, 0.52 mmol, 10 equiv), and shaken for 12 h. The resin was first washed with dry THF (2 × 2 mL), to remove the excess Grignard reagent and other possible impurities that will be present in the reaction mixture, and the filtrates were collected in a vial (fraction 1). A tetrahedral intermediate, which theoretically still remains attached to the resin, was then decomposed with HOAc-THF (1:3, v/v, 2 × 2 mL), and the filtrates were collected in a different vial (fraction 2). Both fractions were analyzed by LC−MS, and the following results were obtained.

LC Conditions. Reversed phase column Nucleosil C_{18} (250 × 4.6 mm, 10 μm), linear gradient 10% B → 100% B in 30 min (A: 0.045% TFA in H_2O, B: 0.036% TFA in CH_3CN), flow 1 mL/min, and UV detection at 220 nm.

Fraction 1: *N*-(1,1-Dimethyl-2-oxo-butyl)-benzamide 2{*1,1,1*}. t_R = 17.2 min (UV purity: 19%, MS (ESI, positive ion): m/z 220.0 $(M+1)^+$).

***N*-(2-Ethyl-2-hydroxy-1,1-dimethyl-butyl)-benzamide 28-{*1,1,1*}.** t_R = 20.4 min (UV purity: 72%, MS (ESI, positive ion): m/z 250.0 $(M+1)^+$).

Fraction 2: *N*-(1,1-Dimethyl-2-oxo-butyl)-benzamide 2{*1,1,1*}. t_R = 17.1 min (UV purity: 18%, MS (ESI, positive ion): m/z 220.1 $(M+1)^+$).

***N*-(2-Ethyl-2-hydroxy-1,1-dimethyl-butyl)-benzamide 28-{*1,1,1*}.** t_R = 20.4 min (UV purity: 54%, MS (ESI, positive ion): m/z 250.2 $(M+1)^+$).

[1-(Methoxy-methyl-carbamoyl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester (29{*10*}). To a solution of Boc-Val-OH **24**{*10*} (2 g, 9.2 mmol) in CH_2Cl_2 (15 mL) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (2.12 g, 11.05 mmol, 1.2 equiv), and the resulting mixture was stirred for 10 min. A solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.08 g, 11.05 mmol, 1.2 equiv) and *i*-Pr_2NEt (1.88 mL, 11.05 mmol, 1.2 equiv) in CH_2Cl_2 was added to the resulting mixture, shaken at room temperature for 16 h, and evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed sequentially with 10% aqueous citric acid (3 × 100 mL), 10% aqueous $NaHCO_3$ (3 × 100 mL), and brine (2 × 100 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford Boc-Val-N(OMe)Me as a white solid (**29**{*10*}, 1.63 g, 68%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.36 (s, 9H), 1.93 (m, 1H), 3.22 (s, 3H), 3.14 (s, 3H), 3.70 (s, 3H), 4.48 (m, 1H), 5.11 (d, J = 7 Hz, 3H). MS (ESI, positive ion): m/z 260.3 $(M+1)^+$.

11. (1-Benzoyl-2-methyl-propyl)-carbamic acid *tert*-butyl ester (30{*10,2*}). To a stirred solution of Boc-Val-N(OMe)Me **29**{*10*} (0.50 g, 1.92 mmol) in dry THF under an atmosphere of argon at −20 °C was added PhMgBr (1M solution in THF, 9.6 mL, 9.6 mmol, 5 equiv), and then the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was poured into a cooled (0 °C) 5% HCl solution in ethanol and partitioned between Et_2O/CH_2Cl_2 (1:1, v/v, 50 mL) and brine (50 mL). The

organic phase was washed with brine (2 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a colorless oil (1.32 g). Flash chromatography on silica gel (hexanes−ethyl acetate, 70:30) afforded the desired product **30**{*10,2*} (0.41 g, 74%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75 (d, J = 7 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 2.15 (m, 1H), 5.18 (m, 1H), 5.45 (d, J = 7.2 Hz, 1H), 7.35−7.60 (aromatic H's, 3H), 7.94 (d, J = 8 Hz, 2H). MS (ESI, positive ion): m/z 277.2 $(M+1)^+$ and biphenyl (0.85 g, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34−7.60 (aromatic H's, 6H), 7.57 (dd, J = 8.2, 1.4 Hz, 4H).

12. [1-(Methoxy-methyl-carbamoyl)-1-methyl-ethyl]-carbamic acid *tert*-butyl ester (29{*1*}). Following the experimental procedure described for Boc-Val-N(OMe)Me **29**{*10*} and using Boc-Aib-OH **24**{*1*} (2 g, 9.84 mmol), Boc-Aib-N(OMe)Me was isolated as a white solid (**29**{*1*}, 1.48 g, 61%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 6H), 1.58 (s, 9H), 3.22 (s, 3H), 3.68 (s, 3H), 6.90 (bs, 1H). MS (ESI, positive ion): m/z 247.0 $(M+1)^+$.

13. 2-Amino-2-methyl-1-phenyl-propan-1-one (31{*1,2*}). PhMgBr (**6**{*2*}, 1 M solution in THF, 6.1 mL, 6.1 mmol, 5 equiv) was added to a stirred cooled (−20 °C) solution of Boc-Aib-N(OMe)Me **29**{*1*} (0.30 g, 1.22 mmol) in dry THF under argon, warmed to room temperature, and stirred for 5 h. The reaction mixture was concentrated under reduced pressure to give a yellow oil (0.4 g), which was diluted in solution of TFA in Et_2O (40 mL). Subsequent centrifugation of the precipitate gave the TFA salt of 2-amino-2-methyl-1-phenyl-propan-1-one **31**{*1,2*} as a white solid (0.09 g, 48%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86 (s, 6H), 7.4−7.6 (aromatic H's, 3H), 7.96 (d, J = 8 Hz, 2H). MS (ESI, positive ion): m/z 164.0 $(M+1)^+$. From the organic phase was also isolated *N*-(1,1-dimethyl-2-oxo-2-phenyl-ethyl)-benzamide (**2**{*1,1,2*}, 0.07 g, 21%) as a white solid, and biphenyl (0.08 g).

14. *N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-benzamide (2{*1,1,2*}). Hydroxybenzotriazole resin **36** (0.1 g, 0.184 mmol) was treated with benzoic acid (0.11 g, 0.92 mmol, 5 equiv), DIC (0.142 mL, 0.92 mmol, 5 equiv) and DMAP (0.02 g, 0.184 mmol, 1 equiv) in DMF−CH_2Cl_2 (1:1) and shaken for 5 h. The mixture was filtered and the resin was washed with DMF (10 × 5 mL) and CH_2Cl_2 (10 × 5 mL) to give **37**{*1*}. A solution of **31**{*1,2*} (0.02 g, 0.13 mmol, 1 equiv) and *i*-Pr_2NEt (0.03 mL, 0.184 mmol, 1.5 equiv) in CH_2Cl_2 was added to a suspension of **37**{*1*} (0.184 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL). The resulting mixture was agitated for 16 h and drained into a vial. The filtrate was treated with a weakly basic ion-exchange resin Amberlite IRA-95 (1 g, 4.7 mmol/g, 25 equiv) for 16 h (to remove any excess of benzoic acid). Filtration and elution of the corresponding filtrate through a short column of silica gel (hexane/ethyl acetate 50:50) removed unreacted amine yielded *N*-(1,1-dimethyl-2-oxo-2-phenyl-ethyl)-benzamide (**2**{*1,1,2*}), 0.03 g, 86%) as a white solid.

The next examples were synthesized following the same procedure.

15. *N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-2-methyl-benzamide (2{*1,2,2*}). 78% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 6H), 2.12 (s, 3H), 6.62 (bs, 1H), 7.10−7.54 (aromatic H's, 7H), 7.96 (d, J = 8.2 Hz, 2H). MS (ESI, positive ion): m/z 282.6 $(M+1)^+$.

16. *N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-3-methoxy-benzamide (2{*1,3,2*}). 83% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.81 (s, 6H), 3.80 (s, 3H), 7.04 (m, 1H), 7.16 (bs, 1H), 7.25−7.50 (aromatic H's, 3H), 7.96 (d, J = 8.2 Hz, 2H). MS (ESI, positive ion): m/z 298.3 $(M+1)^+$.

17. *N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-4-ethyl-benzamide (2{*1,4,2*}). 88% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (t, J = 7.4 Hz, 3H), 1.81(s, 6H), 2.66 (q, J = 7.4 Hz, 2H), 7.06 (bs, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.30−7.50 (aromatic H's, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8 Hz, 2H). MS (ESI, positive ion): m/z 296.3 $(M+1)^+$.

18. Benzo[1,3]dioxole-4-carboxylic acid (1,1-dimethyl-2-oxo-2-phenyl-ethyl)-amide (2{*1,5,2*}). 91% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 (s, 6H), 5.96 (s, 2H), 6.53 (bs, 1H), 6.72 (d, J = 8.2 Hz, 1H), 7.30−7.40 (aromatic H's, 5H), 7.94 (dd, J = 8, 1.4 Hz, 2H). MS (ESI, positive ion): m/z 312.3 $(M+1)^+$.

19. 2-Amino-2-methyl-pentan-3-one (31{*1,1*}). EtMgBr (1 M solution in THF, 6.1 mL, 6.1 mmol, 5 equiv) was added to a stirred cooled (−20 °C) solution of Boc-Aib-N(OMe)-Me **29**{*1*} (0.30 g, 1.22 mmol) in dry THF (15 mL) under an argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 5 h. Workup as described in the preparation of **31**{*1,2*} yielded a colorless oil residue (0.32 g), which was diluted in Et_2O (40 mL). Subsequent centrifugation afforded 2-amino-2-methyl-pentan-3-one (**31**{*1,1*}, 0.04 g, 26%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02 (t, J = 7 Hz, 3H), 1.72 (s, 6H), 2.78 (q, J = 7.2 Hz, 2H). MS (ESI, positive ion): m/z 115.9 $(M+1)^+$. From the organic phase was also isolated *N*-(1,1-dimethyl-2-oxo-butyl)-propionamide as a white solid (0.08 g, 37%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, J = 7 Hz, 3H), 1.15 (t, J = 7.6 Hz, 3H), 1.51 (s, 6H), 2.22 (q, J = 7.2 Hz, 2H), 2.56 (q, J = 7.4 Hz, 2H), 6.39 (bs, 1H). MS (ESI, positive ion): m/z 172.1 $(M+1)^+$.

20. 1-*tert*-Butoxycarbonylamino-cyclopentanecarboxylic acid (24{*6*}). To a suspension of 1-aminocyclopentane-carboxylic acid **4**{*6*} (2 g, 15.48 mmol) in 20 mL of *t*-BuOH: H_2O (1:1, v/v) was added 1 M aqueous solution of NaOH to bring the pH to 9, followed by the addition of Boc_2O (10.15 g, 46.45 mmol, 3 equiv) and 5 mL of dioxane. The reaction mixture was stirred at room temperature, keeping the pH at 9 via further addition of 1 M aqueous solution of NaOH. After the reaction was completed, the mixture was washed with hexane (2 × 150 mL). The aqueous layer was cooled to 0 °C, acidified to pH 2 with 1 M HCl, and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 1-*tert*-butoxycarbonylamino-cyclopentanecarboxylic acid **24**{*6*} as a white solid (2.56 g, 72% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.81 (m, 4H), 1.94 (m, 2H), 2.21 (m, 2H), 6.65 (bs, 1H), 11.15 (bs, 1H). MS (ESI, positive ion): m/z 230.2 $(M+1)^+$.

21. [1-(Methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-butyl ester (29 {*6*}). Following the experimental procedure described for Boc-Val-N(OMe)Me (**29**{*10*})

and using 1-*tert*-butoxycarbonylamino-cyclopentanecarboxylic acid **24**{*6*} (1 g, 4.36 mmol), [1-(methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-butyl ester was isolated as a white solid (**29**{*6*}, 1.48 g, 61% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 1.80 (m, 4H), 1.89 (m, 2H), 2.13 (m, 2H), 3.28 (s, 3H), 3.83 (s, 3H), 7.14 (bs, 1H). MS (ESI, positive ion): *m*/*z* 273.2 $(M+1)^+$.

22. 1-(1-Amino-cyclopentyl)-propan-1-one (31{*6,1*}). Following the experimental procedure described for 2-amino-2-methyl-pentan-3-one (**31**{*1,1*}) and using [1-(methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-butyl ester (**29**{*6*}) (0.30 g, 1.1 mmol), 1-(1-amino-cyclopentyl)-propan-1-one was isolated as a white solid (**31**{*6,1*}, 0.04 g, 12% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, J = 7.2 Hz, 3H), 2.09 (m, 4H), 2.21 (m, 2H), 2.42 (m, 2H), 2.75 (q, J = 7.2 Hz, 2H). MS (ESI, positive ion): *m*/*z* 142.1 $(M+1)^+$. *N*-(1-propionyl-cyclopentyl)-propionamide also is obtained as a white solid (0.06 g, 28% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, J = 7.4 Hz, 3H), 1.16 (t, J = 7.6 Hz, 3H), 1.83 (m, 4H), 2.06 (m, 2H), 2.31 (m, 2H), 2.32 (q, J = 7.2 Hz, 2H), 2.64 (q, J = 7.4 Hz, 2H), 6.65 (bs, 1H). MS (ESI, positive ion): *m*/*z* 198.3 $(M+1)^+$.

23. (1-Amino-cyclopentyl)-phenyl-methanone (31{*6,2*}). Following the experimental procedure described for 2-amino-2-methyl-pentan-3-one **31**{*1,2*} and using [1-(methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-butyl ester **29**{*6*} (0.30 g, 1.1 mmol) and PhMgBr (1 M solution in THF), (1-amino-cyclopentyl)-phenyl-methanone was isolated as a white solid (**31**{*6,2*}, 0.03 g, 15% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.18 (m, 4H), 2.40 (m, 2H), 2.68 (m, 2H), 7.50−7.72 (aromatic H's, 3H), 7.96 (d, J = 8.4 Hz, 2H). MS (ESI, positive ion): *m*/*z* 190.1 $(M+1)^+$. In addition, *N*-(1-benzoyl-cyclopentyl)-benzamide is obtained as a white solid (**2**{*6,1,2*}, 0.07 g, 23% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 (m, 4H), 2.12 (m, 2H), 2.64 (m, 2H), 7.05−7.60 (aromatic H's, 8H), 7.93 (d, J = 8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 294.5 $(M+1)^+$.

24. (1,1-Dimethyl-2-oxo-butyl)-carbamic acid *tert*-butyl ester (30{*1,1*}). EtMgBr (1 M solution in THF, 2.44 mL, 2.44 mmol, 3 equiv) was added to a stirred cooled (−78 °C) solution of Boc-Aib-N(OMe)Me **29**{*1*} (0.20 g, 0.81 mmol) in dry THF (10 mL) under an argon atmosphere. The reaction mixture was stirred at −78 °C for 3 h. Workup as described in the preparation of **30**{*10,2*} yielded a colorless oil residue (0.26 g), which was purified by silica gel chromatography (hexanes−ethyl acetate, 70:30), afforded (1,1-dimethyl-2-oxo-butyl)-carbamic acid *tert*-butyl ester as a white solid (**30**{*1,1*}, 0.04 g, 21% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, J = 7.2 Hz, 3H), 1.52 (s, 9H), 1.64 (s, 6H), 2.54 (q, J = 7.4 Hz, 2H), 6.45 (bs, 1H). MS (ESI, positive ion): *m*/*z* 216.0 $(M+1)^+$.

25. (1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (30{*1,2*}). PhMgBr (1 M solution in THF, 2.44 mL, 2.44 mmol, 3 equiv) was added to a stirred cooled (−78 °C) solution of Boc-Aib-N(OMe)Me **29**{*1*} (0.20 g, 0.81 mmol) in dry THF (10 mL) under an argon atmosphere and stirred at −78 °C for 3 h. Workup as described in the preparation of **30**{*10,2*} yielded a colorless oil residue (0.30 g), which was purified by silica gel chromatography (hexanes−ethyl acetate, 70:30) to yield (1,1-dimethyl-2-oxo-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester as a white solid (**30**{*1,2*}, 0.06 g, 27% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (s, 9H), 1.80 (s, 6H), 6.72 (bs, 1H), 7.30−7.60 (aromatic H's, 3H), 7.96 (d, J = 8.2 Hz, 2H). MS (ESI, positive ion): *m*/*z* 264.2 $(M+1)^+$.

26. 2-*tert*-Butoxycarbonylamino-2-methyl-thiopropionic acid *S*-phenyl ester (35). A solution of Boc-Aib-OH **24**{*1*} (2 g, 9.84 mmol), DCC (2.44 g, 11.81 mmol, 1.2 equiv), thiophenol (1.3 g, 11.81 mmol, 1.2 equiv) and *i*-Pr_2NEt (2.01 mL, 11.81 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL) was stirred overnight at room temperature. The reaction was filtered to remove *N*,*N*′-dicyclohexylurea, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with 10% aqueous citric acid (3 × 100 mL), 10% aqueous $NaHCO_3$ (3 × 100 mL), and brine (2 × 100 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil (2.43 g), which was purified by silica gel chromatography (hexanes−ethyl acetate, 80:20) to yield 2-*tert*-butoxycarbonylamino-2-methyl-thiopropionic acid *S*-phenyl ester (**35**, 2.02 g, 70%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.53 (s, 6H), 7.39 (s, 5H). MS (ESI, positive ion): *m*/*z* 296.7 $(M+1)^+$.

27. (1,1-Dimethyl-2-oxo-butyl)-carbamic acid *tert*-butyl ester (30{*1,1*}). EtMgBr (1M solution in THF, 4.06 mL, 4.06 mmol, 6 equiv) was added to a suspension of CuI (0.39 g, 2.03 mmol, 3 equiv) in dry THF (10 mL) under a nitrogen atmosphere at −78 °C, and the resulting mixture warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to −78 °C, and a solution of 2-*tert*-butoxycarbonylamino-2-methyl-thiopropionic acid *S*-phenyl ester (**35**) (0.20 g, 0.68 mmol) in dry THF (10 mL) was added. The mixture was stirred at −15 °C for 8 h. The excess of the organocopper reagent was removed by addition of saturated aqueous ammonium chloride (30 mL), and the mixture was extracted with diethyl ether (2 × 50 mL). The organic phase was washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a colorless oil crude (0.34 g), which was purified by silica gel chromatography (hexanes−ethyl acetate, 80:20) to yield (1,1-dimethyl-2-oxo-butyl)-carbamic acid *tert*-butyl ester as a white solid (**30**{*1,1*}, 0.05 g, 32% yield).

28. 1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (30{*1,2*}). PhMgBr (1 M solution in THF, 4.06 mL, 4.06 mmol, 6 equiv) was added to a suspension of CuI (0.39 g, 2.03 mmol, 3 equiv) in dry THF (10 mL) under a nitrogen atmosphere at −78 °C. The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to −78 °C, and 2-*tert*-butoxycarbonylamino-2-methyl-thiopropionic acid *S*-phenyl ester (**35**) (0.20 g, 0.68 mmol) in dry THF (10 mL) was added and stirred at −15 °C for 8 h. The excess of the organocopper reagent was removed via an addition of saturated aqueous ammonium chloride (30 mL) and extraction with diethyl ether (2 × 50 mL). The organic phase was washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a colorless oil, which was purified by silica gel chromatography (hexanes−ethyl acetate, 80:

20) to afford (1,1-dimethyl-2-oxo-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester **30**{*1,2*} as a white solid (0.05 g, 28% yield).

29. [1-(Methoxy-methyl-carbamoyl)-1-methyl-ethyl]-carbamic acid *tert*-butyl ester (29{*1*}). DCC (6.09 g, 29.53 mmol, 1.2 equiv) was added to a stirred mixture of Boc-Aib-OH (5 g, 24.61 mmol, 1 equiv), MeNHOMe.HCl (2.88 g, 29.53 mmol, 1.2 equiv), DMAP (3.61 g, 29.53 mmol, 1.2 equiv), *i*-Pr_2NEt (5.02 mL, 29.53 mmol, 1.2 equiv), and CH_2Cl_2 (100 mL). The resulting mixture was stirred at room temperature for 5 days. The mixture was filtered to remove precipitated *N*,*N*′-dicyclohexylurea, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), washed with 10% aqueous citric acid (3 × 200 mL), 10% aqueous $NaHCO_3$ (3 × 200 mL), and saturated aqueous sodium chloride (3 × 200 mL), and then dried over $MgSO_4$. Removal of the solvent gave the crude product, which was purified by column chromatography (hexane/ethyl acetate 60:40) to afford **29**{*1*}, (4.85 g, 80% yield) as a white solid.

30. 2-Amino-*N*-methoxy-2,*N*-dimethyl-propionamide (38{*1*}). Boc-protected Weinreb amide **29**{*1*} (1.1 g, 4.47 mmol) was dissolved in a 50% solution of TFA in CH_2Cl_2 (50 mL) and stirred for 20 min. Removal of the solvent yielded 2-amino-*N*-methoxy-2,*N*-dimethyl-propionamide (**38**{*1*}, 1.15 g, quantitative yield) as its TFA salt. ^{1}H NMR (200 MHz, CD_3OD): δ 1.63 (s, 6H), 3.25 (s, 3H), 3.78 (s, 3H). MS (ESI, positive ion): *m*/*z* 147.3 $(M+1)^+$.

31. Preparation of the Activated *p*-nitrophenyl Carbonate Resin (39). *N*-methylmorpholine (0.94 mL, 8.6 mmol, 10 equiv), *p*-nitrophenyl chloroformate (0.87 g, 4.3 mmol, 5 equiv), and CH_2Cl_2 (2 mL) were added to a suspension of Wang resin (1 g, 0.86 mmol, 0.86 mmol/g) in CH_2Cl_2 (5 mL) under argon at 0 °C. The reaction mixture was shaken at room temperature for 6 h. The solution was drained and the resin was washed sequentially with CH_2Cl_2 (5 × 5 mL), DMF (5 × 5 mL), and MeOH (5 × 5 mL), and dried overnight under reduced pressure to afford resin **39** (1.13 g, 0.86 mmol, 0.76 mmol/g). PAS−FTIR carbonate C═O stretch, 1770 cm^{-1}.

32. Preparation of the Activated *N*-succinimidyl Carbonate Resin (40). DSC (1.10 g, 4.3 mmol, 10 equiv) and DMAP (0.05 g, 0.43 mmol, 1 equiv) previously dissolved in DMF (2 mL) were added to a suspension of Wang resin (0.50 g, 0.43 mmol, 0.86 mmol/g) in DMF (3 mL) under an argon atmosphere. The reaction mixture was shaken at room temperature for 1 h, and then the solution was filtered; the resin was washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and MeOH (5 × 5 mL), and then dried overnight under reduced pressure to give resin **40** (0.57 g, 0.43 mmol, 0.75 mmol/g). PAS−FTIR carbonate C═O stretch, 1770 cm^{-1}.

33. Preparation of Wang-CO-Aib-N(OMe)Me Resin (41{*1*}). To a suspension of resin **39** (1.13 g, 0.86 mmol) in NMP (5 mL) were added **38**{*1*} (1.15 g, 4.42 mmol, 5 equiv) and *i*-Pr_2NEt (2.2 mL, 12.9 mmol, 15 equiv), the reaction mixture was heated at 60 °C for 16 h, the resin was filtered and washed sequentially with NMP (5 × 10 mL), DMF (5 × 10 mL), and CH_2Cl_2 (5 × 10 mL), and then dried under vacuum overnight to leave resin **41**{*1*} (1.16 g, 0.86 mmol, 0.74 mmol/g). PAS−FTIR carbamate C═O stretch, 1727 cm^{-1}; amide C═O stretch, 1646 cm^{-1}.

34. Preparation of Resin 42{*1,2*}. PhMgBr (1 M solution in THF, 12.9 mL, 12.9 mmol, 15 equiv) was added to a suspension of resin **41**{*1*} (0.86 mmol) in dry THF (5 mL) under argon atmosphere. The mixture was stirred for 4 h, and the resin was washed with THF (5 × 10 mL), DMF−H_2O (5 × 10 mL), and CH_2Cl_2 (5 × 10 mL), followed by HOAc−CH_2Cl_2 (9:1) and CH_2Cl_2 (5 × 10 mL), and then dried overnight under vacuum to afford resin **42**{*1,2*}. PAS−FTIR carbamate C═O stretch, 1734 cm^{-1}; ketone C═O stretch, 1718 cm^{-1}.

35. 2-Amino-2-methyl-1-phenyl-propan-1-one (31{*1,2*}). Resin **42**{*1,2*} was treated with 90:10 TFA/H_2O (5 mL) for 2 h. The mixture was filtered, and the filtrate was evaporated to afford 2-amino-2-methyl-1-phenyl-propan-1-one (**31**{*1,2*}), 0.19 g, 81%) as its TFA salt.

36. *N*-(1,1-Dimethyl-2-oxo-2-phenyl-ethyl)-benzamide (2{*1,1,2*}). Prepared following the experimental procedure previously described, using polymer-supported active ester **37**{*2*} as an acylating agent (0.196 mmol, 1.5 equiv), and 2-amino-2-methyl-1-phenyl-propan-1-one **(31**{*1,2*}**)** (0.04 g, 0.131 mmol, 1 equiv) in the presence of *i*-Pr_2NEt (0.033 mL, 0.196 mmol, 1.5 equiv) yielded the expected compound as a white solid (0.03 g, 87% yield).

37. 2-Amino-2-methyl-pentan-3-one (31{*1,1*}). EtMgBr (1 M solution in THF, 12.9 mL, 12.9 mmol, 15 equiv) was added to a suspension of resin **41**{*1*} (1.20 g, 0.86 mmol, 0.72 mmol/g) in dry THF (5 mL) under argon atmosphere and stirred for 4 h. The resin was washed with THF (5 × 10 mL), DMF−H_2O (5 × 10 mL), and CH_2Cl_2 (5 × 10 mL), followed by HOAc−CH_2Cl_2 (9:1) and CH_2Cl_2 (5 × 10 mL), and then dried overnight under vacuum to afford resin **42**{*1,1*}. This resin was treated with 90:10 TFA/H_2O (10 mL) for 2 h. The mixture was filtered, and the filtrate was evaporated to yield 2-amino-2-methyl-pentan-3-one (**31**{*1,1*}, 0.19 g, 82% yield) as its TFA salt. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 1.04 (t, J = 6.8 Hz, 3H), 1.71 (s, 6H), 2.77 (q, J = 7 Hz, 2H), 8.97 (bs, 1H). MS (ESI, positive ion): *m*/*z* 115.9 $(M+1)^+$.

38. 2-Amino-1-(3,5-dimethyl-phenyl)-2-methyl-propan-1-one (31{*1,3*}). Using the previously described preparation procedure, resin **41**{*1*} (1.20 g, 0.86 mmol, 0.72 mmol/g), and 3,5-dimethylphenylmagnesium bromide (**6**{*3*},1M solution in THF, 12.9 mmol, 15 eq) afforded 2-amino-1-(3,5-dimethyl-phenyl)-2-methyl-propan-1-one (**31**{*1,3*}, 0.23 g, 76% yield) as its TFA salt. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 1.95 (s, 6H), 2.38 (s, 6H), 7.32 (s, 1H), 7.61 (s, 2H). MS (ESI, positive ion): *m*/*z* 192.1$(M+1)^+$.

39. [1-(Methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-Butyl Ester (29{*6*}). Following the experimental procedure described for **29**{*1*} and using 1-*tert*-butoxycarbonylamino-cyclopentanecarboxylic acid **24**{*6*} (5 g, 21.81 mmol), MeNHOMe.HCl (2.55 g, 26.17 mmol, 1.2 equiv), DMAP (3.20 g, 26.17 mmol, 1.2 equiv), *i*-Pr_2NEt (4.45 mL, 26.17 mmol, 1.2 equiv), and DCC (5.4 g, 26.17 mmol, 1.2 equiv) yielded [1-(methoxy-methyl-carbamoyl)-cyclopentyl]-carbamic acid *tert*-butyl ester as a white solid (**29**{*6*}, 4.46 g, 75% yield).

40. 1-Amino-cyclopentanecarboxylic acid methoxy-methyl-amide (38{*6*}). Following the experimental procedure described for **38**{*1*} and using **29**{*6*} (4.46 g, 16.38 mmol), 1-amino-cyclopentanecarboxylic acid methoxy-methyl-amide was isolated quantitatively as its TFA salt (**38**{*6*}, 4.69 g). ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 1.98 (m, 4H), 2.09 (m, 2H), 2.32 (m, 2H), 3.30 (s, 3H), 3.85 (s, 3H). MS (ESI, positive ion): *m*/*z* 173.2 $(M+1)^+$.

41. Preparation of Resin 41{*6*}. Following the experimental procedure described for **41**{*1*} and using resin **39** (3.4 g, 2.58 mmol), **38**{*6*} (3.7 g, 12.9 mmol, 5 equiv) and *i*-Pr_2NEt (6.6 mL, 38.7 mmol, 15 equiv) yielded resin **41**{*6*} (3.54 g, 2.58 mmol, 0.73 mmol/g).

42. 1-(1-amino-cyclopentyl)-propan-1-one (31{*6,1*}) Following the experimental procedure described for **31**{*1,1*} and using EtMgBr (1 M solution in THF, 12.9 mL, 12.9 mmol, 15 equiv), 1-(1-amino-cyclopentyl)-propan-1-one was isolated as the corresponding TFA salt (**31**{*6,1*}), 0.22 g, 80% yield). ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 1.07 (t, J = 7.4 Hz, 3H), 2.06 (m, 4H), 2.18 (m, 2H), 2.40 (m, 2H), 2.74 (q, J = 7 Hz, 2H), 8.23 (bs, 1H). MS (ESI, positive ion): *m*/*z* 142.3 $(M+1)^+$.

43. (1-Amino-cyclopentyl)-phenyl-methanone (31{*6,2*}). Following the experimental procedure described for **31**{*1,2*} and using resin **41**{*6*} (1.18 g, 0.86 mmol, 0.73 mmol/g) and PhMgBr (1 M solution in THF, 12.9 mL, 12.9 mmol, 15 equiv), (1-amino-cyclopentyl)-phenyl-methanone was isolated as its TFA salt (**31**{*6,2*}, 0.24 g, 94% yield). ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 2.20 (m, 4H), 2.39 (m, 2H), 2.68 (m, 2H), 7.51−7.69 (aromatic H's, 3H), 7.95 (dd, J = 8.8, 1.4 Hz, 2H), 8.54 (bs, 1H). MS (ESI, positive ion): *m*/*z* 190.2 $(M+1)^+$.

44. (1-Amino-cyclopentyl)-(3,5-dimethyl-phenyl)-methanone (31{*6,3*}). Following the experimental procedure described for **31**{*1,3*} and using resin **41**{*6*} (1.18 g, 0.86 mmol, 0.73 mmol/g) and 3,5-dimethylphenylmagnesium bromide (1 M solution in THF, 12.9 mmol, 15 equiv), (1-amino-cyclopentyl)-(3,5-dimethyl-phenyl)-methanone was isolated as its TFA salt (**31**{*6,3*}, 0.25 g, 86% yield). ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 2.19 (m, 4H), 2.34(m, 2H), 2.36 (s, 6H), 2.70 (m, 2H), 7.33 (s, 1H), 7.53 (s, 2H), 8.63 (bs, 1H). MS (ESI, positive ion): *m*/*z* 218.2 $(M+1)^+$.

Library Production. The synthesis of the complete library was performed following the experimental procedure described previously for *N*-(1,1-dimethyl-2-oxo-2-phenyl-ethyl)-benzamide **2**{*1,1,2*}, starting from α-aminoketones **31**{*1,1*}, **31**{*1,3*}, **31**{*6,1*−*3*} (1 equiv), using polymer-supported active esters **37**{*1*−*5*} as acylating agents (1.5 equiv), and *i*-Pr_2NEt (1.5 equiv) to afford the expected α-acylamino-α,α-disubstitutedketones. The products were analyzed by LC−MS on a C18 column (250 × 4.6 mm, 10 μm) with a flow rate of 1 mL/min and a mobile phase gradient using two solvents (for solvent A, 0.045% TFA in H_2O; for solvent B, 0.036% TFA in MeCN), starting at 10% solvent B and changing linearly to 100% solvent B. Ultraviolet (UV) absorption was monitored at 220 nm. The product peaks were identified by mass spectroscopy, using electrospray ionization in positive mode. Purities were calculated on the basis of integration of the UV absorption at 220 nm. All compounds were also characterized by ^{1}H NMR.

1. *N*-(1,1-Dimethyl-2-oxo-butyl)-benzamide (2{*1,1,1*}). 87% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3H), 1.57 (s, 6H), 2.63 (q, J = 7 Hz, 2H), 7.21 (bs, 1H), 7.38−7.56 (aromatic H's, 3H), 7.79 (dd, J = 8, 1.8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 220.2 $(M+1)^+$.

2. *N*-(1,1-Dimethyl-2-oxo-butyl)-2-methyl-benzamide (2{*1,2,1*}). 61% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, J = 7.4 Hz, 3H), 1.62 (s, 6H), 2.44 (s, 3H), 2.64 (q, J = 7.4 Hz, 2H), 6.63 (bs, 1H), 7.19−7.41 (aromatic H's, 4H). MS (ESI, positive ion): *m*/*z* 234.1 $(M+1)^+$.

3. *N*-(1,1-Dimethyl-2-oxo-butyl)-3-methoxy-benzamide (2{*1,3,1*}). 78% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H), 1.64 (s, 6H), 2.62 (q, J = 7.4 Hz, 2H), 3.85 (s, 3H), 7.05 (m, 1H), 7.16 (bs, 1H), 7.28−7.39 (aromatic H's, 3H). MS (ESI, positive ion): *m*/*z* 250.2 $(M+1)^+$.

4. *N*-(1,1-Dimethyl-2-oxo-butyl)-4-ethyl-benzamide (2{*1,4,1*}). 76% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, J = 7.4 Hz, 3H), 1.24 (t, J = 7.8 Hz, 3H), 1.63 (s, 6H), 2.61 (q, J = 7.4 Hz, 2H), 2.69 (q, J = 7.8 Hz, 2H), 7.12 (bs, 1H), 7.26 (d, J = 8 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H). MS (ESI, positive ion): *m*/*z* 248.2 $(M+1)^+$.

5. Benzo[1,3]dioxole-5-carboxylic acid (1,1-dimethyl-2-oxo-butyl)-amide (2{*1,5,1*}). 83% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H), 1.62 (s, 6H), 2.61 (q, J = 7.4 Hz, 2H), 6.03 (s, 2H), 6.83 (d, J = 7.6 Hz, 1H), 7.03 (bs, 1H), 7.27−7.39 (aromatic H's, 2H). MS (ESI, positive ion): *m*/*z* 264.2 $(M+1)^+$.

6. *N*-[2-(3,5-Dimethyl-phenyl)-1,1-dimethyl-2-oxo-ethyl]-benzamide (2{*1,1,3*}). 90% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 (s, 6H), 2.32 (s, 6H), 7.11 (s, 1H), 7.36−7.51 (aromatic H's, 3H), 7.56 (s, 2H), 7.74 (dd, J = 7.8, 1.8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 296.2 $(M+1)^+$.

7. *N*-[2-(3,5-Dimethyl-phenyl)-1,1-dimethyl-2-oxo-ethyl]-2-methyl-benzamide (2{*1,2,3*}). 76% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 6H), 2.22 (s, 3H), 2.34 (s, 6H), 6.61 (bs, 1H), 7.14 (s, 1H), 7.16−7.38 (aromatic H's, 4H), 7.57 (s, 2H). MS (ESI, positive ion): *m*/*z* 310.3 $(M+1)^+$.

8. *N*-[2-(3,5-Dimethyl-phenyl)-1,1-dimethyl-2-oxo-ethyl]-3-methoxy-benzamide (2{*1,3,3*}). 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 (s, 6H), 2.33 (s, 6H), 3.83 (s, 3H), 7.02 (m, 1H), 7.12 (s, 1H), 7.27−7.38 (aromatic H's, 3H), 7.55 (s, 2H). MS (ESI, positive ion): *m*/*z* 326.3 $(M+1)^+$.

9. *N*-[2-(3,5-Dimethyl-phenyl)-1,1-dimethyl-2-oxo-ethyl]-4-ethyl-benzamide (2{*1,4,3*}). 92% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J = 7.6 Hz, 3H), 1.82 (s, 6H), 2.32 (s, 6H), 2.68 (q, J = 7.6 Hz, 2H), 7.1 (s, 1H), 7.23 (d, J = 8 Hz, 2H), 7.56 (s, 2H), 7.66 (d, J = 8.2 Hz, 2H). MS (ESI, positive ion): *m*/*z* 324.4 $(M+1)^+$.

10. Benzo[1,3]dioxole-5-carboxylic acid [2-(3,5-dimethyl-phenyl)-1,1-dimethyl-2-oxo-ethyl]-amide (2{*1,5,3*}). 81% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.81 (s, 6H), 2.32 (s, 6H), 6.01 (s, 2H), 6.81 (d, J = 8 Hz, 1H), 7.12 (s, 1H), 7.21−7.38 (aromatic H's, 2H), 7.54 (s, 2H). MS (ESI, positive ion): *m*/*z* 340.2 $(M+1)^+$.

11. *N*-(1-Propionyl-cyclopentyl)-benzamide (2{*6,1,1*}). 82% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, $J = 7.4$ Hz, 3H), 1.86 (m, 4H), 2.00 (m, 2H), 2.27 (m, 2H), 2.59 (q, $J = 7.4$ Hz, 2H), 6.72 (bs, 1H), 7.43−7.54 (aromatic H's, 3H), 7.78 (dd, $J = 8$, 1.8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 246.2 $(M+1)^+$.

12. 2-Methyl-*N*-(1-propionyl-cyclopentyl)-benzamide (2{*6,2,1*}). 65% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (t, $J = 7.2$ Hz, 3H), 1.86 (m, 4H), 1.97 (m, 2H), 2.23 (m, 2H), 2.46 (s, 3H), 2.66 (q, $J = 7$ Hz, 2H), 6.26 (bs, 1H), 7.20−7.41 (aromatic H's, 3H). MS (ESI, positive ion): *m*/*z* 260.3 $(M+1)^+$.

13. 3-Methoxy-*N*-(1-propionyl-cyclopentyl)-benzamide (2{*6,3,1*}). 70% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, $J = 7.4$ Hz, 3H), 1.86 (m, 4H), 1.97 (m, 2H), 2.23 (m, 2H), 2.59 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 6.70 (bs, 1H), 7.05 (m, 1H), 7.29−7.40 (aromatic H's, 3H). MS (ESI, positive ion): *m*/*z* 276.4 $(M+1)^+$.

14. 4-Ethyl-*N*-(1-propionyl-cyclopentyl)-benzamide (2-{*6,4,1*}). 69% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, $J = 7.4$ Hz, 3H), 1.25 (t, $J = 7.8$ Hz, 3H), 1.87 (m, 4H), 1.96 (m, 2H), 2.26 (m, 2H), 2.58 (q, $J = 7.4$ Hz, 2H), 2.70 (q, $J = 7.8$ Hz, 2H), 6.66 (bs, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8$ Hz, 2H). MS (ESI, positive ion): *m*/*z* 274.3 $(M+1)^+$.

15. Benzo[1,3]dioxole-5-carboxylic acid (1-propionyl-cyclopentyl)-amide (2{*6,5,1*}). 73% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, $J = 7.4$ Hz, 3H), 1.87 (m, 4H), 1.95 (m, 2H), 2.22 (m, 2H), 2.57 (q, $J = 7.4$ Hz, 2H), 6.03 (s, 2H), 6.57 (bs, 1H), 6.83 (d, $J = 8$ Hz, 1H), 7.27−7.38 (aromatic H's, 2H). MS (ESI, positive ion): *m*/*z* 290.3 $(M+1)^+$.

16. *N*-(1-Benzoyl-cyclopentyl)-benzamide (2{*6,1,2*}). 76% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 4H), 2.10 (m, 2H), 2.64 (m, 2H), 6.74 (bs, 1H), 7.31−7.58 (aromatic H's, 8H), 7.91 (dd, $J = 8$, 1.8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 294.2 $(M+1)^+$.

17. *N*-(1-Benzoyl-cyclopentyl)-2-methyl-benzamide (2-{*6,2,2*}). 74% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 4H), 1.95 (s, 3H), 2.08 (m, 2H), 2.62 (m, 2H), 6.41 (bs, 1H), 6.96−7.52 (aromatic H's, 7H), 7.87 (dd, $J = 8$, 1.6 Hz, 2H). MS (ESI, positive ion): *m*/*z* 308.3 $(M+1)^+$.

18. *N*-(1-Benzoyl-cyclopentyl)-3-methoxy-benzamide (2{*6,3,2*}). 83% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 4H), 2.09 (m, 2H), 2.63 (m, 2H), 3.75 (s, 3H), 6.70 (bs, 1H), 7.07 (m, 1H), 7.24−7.42 (aromatic H's, 3H), 7.90 (dd, $J = 8.2$, 1.6 Hz, 2H). MS (ESI, positive ion): *m*/*z* 324.3 $(M+1)^+$.

19. *N*-(1-Benzoyl-cyclopentyl)-4-ethyl-benzamide (2-{*6,4,2*}). 84% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, $J = 7.6$ Hz, 3H), 1.77(m, 4H), 2.03 (m, 2H), 2.56 (q, $J = 7.4$ Hz, 2H), 2.57 (m, 2H), 6.75 (bs, 1H), 7.07 (d, $J = 8.2$ Hz, 2H), 7.18−7.44 (aromatic H's, 3H), 7.41 (d, $J = 8$ Hz, 2H), 7.84 (dd, $J = 7.6$, 1.4 Hz, 2H). MS (ESI, positive ion): *m*/*z* 322.3 $(M+1)^+$.

20. Benzo[1,3]dioxole-5-carboxylic acid (1-benzoyl-cyclopentyl)-amide (2{*6,5,2*}). 77% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 4H), 2.07 (m, 2H), 2.62 (m, 2H), 5.98 (s, 2H), 6.51 (bs, 1H), 6.74 (d, $J = 8$ Hz, 1H), 7.28−7.38 (aromatic H's, 5H), 7.88 (dd, $J = 8.2$, 1.6 Hz, 2H). MS (ESI, positive ion): *m*/*z* 338.3 $(M+1)^+$.

21. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopentyl]-benzamide (2{*6,1,3*}). 89% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 4H), 2.10 (m, 2H), 2.29 (s, 6H), 2.61(m, 2H), 6.62 (bs, 1H), 7.04 (s, 1H), 7.30−7.46 (aromatic H's, 3H), 7.51 (s, 2H), 7.58 (dd, $J = 8.4$, 1.8 Hz, 2H). MS (ESI, positive ion): *m*/*z* 322.4 $(M+1)^+$.

22. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopentyl]-2-methyl-benzamide (2{*6,2,3*}). 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 (m, 4H), 2.05 (s, 3H), 2.12 (m, 2H), 2.32 (s, 6H), 2.60 (m, 2H), 6.32 (bs, 1H), 7.11 (s, 1H), 7.14−7.38 (aromatic H's, 4H), 7.48 (s, 2H). MS (ESI, positive ion): *m*/*z* 336.3 $(M+1)^+$.

23. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopentyl]-3-methoxy-benzamide (2{*6,3,3*}). 87% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 (m, 4H), 2.09 (m, 2H), 2.28 (s, 6H), 2.60 (m, 2H), 3.75 (s, 3H), 6.72 (bs, 1H), 6.96 (m, 1H), 7.04 (s, 1H), 7.07−7.38 (aromatic H's, 3H), 7.51 (s, 2H). MS (ESI, positive ion): *m*/*z* 352.3 $(M+1)^+$.

24. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopentyl]-4-ethyl-benzamide (2{*6,4,3*}). 88% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, $J = 7.8$ Hz, 3H), 1.82 (m, 4H), 2.10 (m, 2H), 2.27 (s, 6H), 2.62 (q, $J = 7.8$ Hz, 2H), 2.64 (m, 2H), 6.82 (bs, 1H), 7.02 (s, 1H), 7.12 (d, $J = 8$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.52 (s, 2H). MS (ESI, positive ion): *m*/*z* 350.4 $(M+1)^+$.

25. Benzo[1,3]dioxole-5-carboxylic acid [1-(3,5-dimethyl-benzoyl)-cyclopentyl]-amide (2{*6,5,3*}). 84% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 (m, 4H), 2.09 (m, 2H), 2.27 (s, 6H), 2.59 (m, 2H), 5.94 (s, 2H), 6.64 (d, $J = 8.2$ Hz, 1H), 6.83 (s, 1H), 6.98−7.09 (aromatic H's, 2H), 7.51 (s, 2H). MS (ESI, positive ion): *m*/*z* 366.3 $(M+1)^+$.

Method 5A. The following procedure for the preparation of **2**{*4,6,3*} is typical.

1. 5-(3-Methoxy-2-methyl-phenyl)-6-oxa-4-aza-spiro-[2.4]hept-4-en-7-one (43{*4,6*}). Solid 3-methoxy-2-methylbenzoyl chloride (4.35 g, 23.6 mmol) was added to a stirred solution of 1-aminocyclopropanecarboxylic acid (**4**{*4*}1.06 g, 10.5 mmol) in pyridine (20 mL) cooled to ~ 5 °C. The mixture was stirred at room temperature for 1 week and evaporated under reduced pressure to leave an oily solid. This material was taken up in 20% diethyl ether in hexanes (175 mL), washed with water (50 mL), 5% aqueous HCl (2 × 50 mL), and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to leave the title compound (1.90 g) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (m, 2H), 1.90 (m, 2H), 2.49 (s, 3H), 3.85 (s, 3H), 7.01 (d, 1H), 7.22 (t, 1H), 7.40 (d, 1H).

2. 3-Methoxy-*N*-[1-(methoxy-methyl-carbamoyl)-cyclopropyl]-2-methyl-benzamide (44{*4,6*}). A mixture of **43**-{*4,6*} (1.90 g, 8.2 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.96 g, 9.9 mmol), pyridine (0.80 mL, 9.9 mmol), and methylene chloride (30 mL) was stirred at room temperature for 1 week. The mixture was diluted with ethyl acetate (150 mL), washed with 5% aq HCl (2 × 50 mL) and saturated aqueous $NaHCO_3$ (2 × 50 mL) and dried. Removal of the solvent afforded crude product (2.54 g) as a

syrup. The crude product was purified by flash chromatography on a silica gel (75 g) column eluted sequentially with 0%, 20%, 40%, 60%, 80%, 100% diethyl ether in hexanes (200 mL of each) and ethyl acetate (500 mL) to afford **44**{*4,6*} (1.67 g, 69%) as a white solid (mp 173−175 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.53 (m, 2H), 2.23 (s, 3H), 3.22 (s, 3H), 3.69 (s, 3H), 3.82 (s, 3H), 6.67 (s, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 15.1, 33.6, 35.1, 55.6, 61.0, 111.4, 118.6, 124.9, 126.5, 137.4, 157.9, 170.3, 170.9. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.24; H, 6.75; N, 9.30.

3. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopropyl]-3-methoxy-2-methyl-benzamide (2{*4,6,3*}). A round-bottom flask was flushed with dry nitrogen and charged with a stirbar, **44**{*4,6*}- (73 mg, 0.25 mmol), and 3,5-dimethylphenylmagnesium bromide (1 M in THF, 1 mL, 1.0 mmol). The mixture was subjected to stirring for 5 h and poured into stirred saturated aqueous $NaHCO_3$ (6 mL). The mixture was added to a 20 mL ChemElut cartridge and allowed to stand for 5 min. The cartridge was eluted with CH_2Cl_2 (25 mL). The eluate was evaporated to dryness to afford crude product (67 mg) as a solid.

The crude product was applied to a 2-g silica cartridge and eluted with 25%, 50%, and 75% ethyl acetate in hexanes (10 mL of each) and ethyl acetate (3 × 10 mL), and six fractions were collected. Fractions 2, 3, and 4 were combined to afford **2**{*4,6,3*} (58 mg) as a white solid (mp 174−176 °C). ^{1}H NMR ($CDCl_3$): δ 1.31 (m, 2H), 1.83 (m, 2H), 1.93 (s, 3H), 2.32 (s, 6H), 3.79 (s, 3H), 6.47 (s, 1H), 6.56 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 7.10 (s, 1H), 7.33 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 11.9, 18.6, 21.2, 40.7, 55.6, 111.4, 118.1, 123.5, 125.1, 126.4, 133.1, 137.1, 137.7, 138.0, 157.9, 170.4, 202.3.

Spectral Data for Compounds Prepared by Method 5A: *N*-[1-(3,5-Dimethyl-benzoyl)-cyclobutyl]-3-methoxy-2-methyl-benzamide (2{*5,6,3*}). ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 3H), 2.03 (m, 2H), 2.31 (s, 6H), 2.34 (m, 2H), 3.04 (m, 2H), 3.76 (s, 3H), 6.55 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.84 (br s, 1H), 7.02 (t, J = 7.9 Hz), 7.10 (s, 1H), 7.39 (s, 2H).

Method 5B. The following procedure for the preparation of **2**{*3,6,6*} is typical.

1. 4-Isopropyl-2-(3-methoxy-2-methyl-phenyl)-4-methyl-4H-oxazol-5-one (43{*3,6*}). Solid 3-methoxy-2-methylbenzoyl chloride, derived from **5**{*6*} (8.31 g, 45 mmol), was added to a stirred suspension of (±)-α-methylvaline **4**{*3*} (2.62 g, 20 mmol) in pyridine (40 mL) that was cooled to ∼5 °C. The mixture was allowed to warm to room temperature, stirred for 1 week, evaporated under reduced pressure to remove pyridine, and taken up in diethyl ether (150 mL) and water (50 mL). The organic layer was separated, washed with 5% aq HCl (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and dried over $MgSO_4$. Removal of the solvent left **43**{*3,6*} (6.41 g, 122%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.51 (s, 3H), 2.12 (m, 1H), 2.50 (s, 3H), 3.85 (s, 3H), 7.02 (m, 1H), 7.24 (m, 1H), 7.40 (m, 1H).

2. *N*-(1-Formyl-1,2-dimethyl-propyl)-3-methoxy-2-methyl-benzamide (46{*3,6*}). Solid sodium borohydride (0.15 g, 4.0 mmol) was added to a stirred solution of **43**{*3,6*} (1.76 g, 6.7 mmol) in THF (30 mL) at room temperature. The mixture was stirred for 16 h. Removal of the solvent under reduced pressure left a white glassy solid, which was taken up in CH_2Cl_2 (150 mL), washed with 1% aqueous HCl (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and dried over $MgSO_4$. Removal of the solvent left crude primary alcohol (1.25 g, 69%) as a white solid (mp 142−145 °C). Dess−Martin periodinane solution (15 wt %, 2.4 mL, ∼1.1 mmol) was added to a stirred solution of crude primary alcohol (285 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred at room temperature for 4 h and poured into saturated aqueous $NaHCO_3$ (50 mL). Solid $Na_2S_2O_3$ (2.13 g, 8.6 mmol) was added, and the mixture was stirred for 0.5 h. The mixture was extracted with diethyl ether (150 mL). The diethyl ether extract was washed with saturated aqueous $NaHCO_3$ (50 mL) and then dried and evaporated under reduced pressure to afford **46**{*3,6*} (293 mg, 70% yield from **43**{*3,6*}) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.51 (s, 3H), 2.27 (s, 3H), 2.29 (m, 1H), 3.84 (s, 3H), 6.30 (br s, 1H), 6.91 (m, 1H), 6.96 (m, 1H), 7.18 (m, 1H), 9.60 (s, 1H).

3. *N*-[1,2-Dimethyl-1-(3-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*3,6,6*}). An oven-dried vial equipped with a stirbar was flushed with nitrogen, charged with a stock solution of **46**{*3,6*}in dry THF (1 mL of 0.5 M, 0.5 mmol), and cooled in dry ice/acetone. 3-Methylphenylmagnesium bromide in THF (1.0 M, 2 mL, 2.0 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), which was applied to a 10-mL ChemElut cartridge, allowed to stand for 5 min, and eluted with CH_2Cl_2 (25 mL). The eluate was evaporated to leave crude secondary alcohol (180 mg). Dess−Martin periodinane (1.4 mL, 15wt % in CH_2Cl_2, ∼0.65 mmol) was added to a stirred solution of crude secondary alcohol in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 6 h, diluted with saturated aqueous $NaHCO_3$ (5 mL) and treated with solid $Na_2S_2O_3$ (∼1 g, 6.3 mmol). The mixture was stirred for 0.5 h, applied to a 10-mL ChemElut cartridge, allowed to stand for 5 min, and eluted with CH_2Cl_2 (20 mL). The eluate was evaporated to leave crude ketone **2**{*3,6,6*} (95 mg). The crude ketone was taken up in CH_2Cl_2 (4 mL), treated with Argonaut PS-TsNHNH$_2$ resin (0.20 g, 2.9 mmol/g, 0.58 mmol), and allowed to stand for 6 h. The mixture was filtered and washed with CH_2Cl_2 and diethyl ether. The filtrate was evaporated to leave a solid that was fractionated on a 2-g silica cartridge eluted sequentially with 0%, 25%, 50%, 75%, and 100% diethyl ether in hexanes (10 mL of each). The fourth fraction (75% diethyl ether in hexanes) contained ketone **2**{*3,6,6*} (27 mg, 15%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.67 (s, 3H), 2.01 (s, 3H), 2.37 (s, 3H), 2.50 (m, 1H), 6.36 (br s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 7.12 (m, 1H), 7.40 (m, 2H), 7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1, 17.1, 17.4, 17.5, 21.5, 34.3, 55.6, 67.5, 111.3, 118.3, 125.0, 125.1, 126.5, 127.7, 129.2, 132.5, 136.7, 137.6, 137.9, 158.0,

168.9, 201.0. The third fraction (50% diethyl ether in hexanes) contained additional **2**{*3,6,6*} (34.5 mg, 20%) of lower purity.

Spectral Data for Compounds Prepared by Method 5B.

1. *N*-(1-Benzoyl-1-ethyl-propyl)-3-methoxy-2-methyl-benzamide (2{*2,6,2*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, $J = 7.4$ Hz, 6H), 2.16 (m, 1H), 2.22 (s, 3H), 2.86 (m, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 7.18 (m, 2H), 7.24 (m, 2H), 7.35 (m, 1H), 7.92 (d, $J = 7.4$ Hz, 2H).

2. *N*-[1-(3,5-Dimethyl-benzoyl)-1-ethyl-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,3*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, $J = 7.4$ Hz, 6H), 2.20 (m, 2H), 2.27 (s, 3H), 2.37 (s, 6H), 2.88 (m, 2H), 3.84 (s, 3H), 6.89 (d, $J = 8.2$ Hz, 1H), 6.99 (d, $J = 7.6$ Hz, 1H), 7.18 (m, 2H), 7.51 (s, 2H).

3. *N*-[1-Ethyl-1-(2-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,4*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.4$ Hz), 2.17 (s, 3H), 2.20 (m, 2H), 2.40 (s, 3H), 2.57 (m, 2H), 3.83 (s, 3H), 6.76 (br s, 1H), 6.68 (d, $J = 6.9$ Hz, 2H), 7.17 (m, 2H), 7.29 (m, 2H), 7.52 (d, $J = 7.8$ Hz, 1H).

4. *N*-[1-Ethyl-1-(2-methoxy-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,5*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.4$ Hz, 6H), 2.05 (m, 2H), 2.30 (s, 3H), 2.61 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 6.75 (m, 5H), 7.18 (t, $J = 8.0$ Hz, 1H), 7.26 (m, 1H), 7.40 (m, 1H).

5. *N*-[1-Ethyl-1-(3-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,6*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, $J = 7.5$ Hz, 6H), 2.20 (m, 2H), 2.25 (s, 3H), 2.41 (s, 3H), 2.88 (m, 2H), 3.84 (s, 3H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 7.19 (m, 2H), 7.36 (m, 2H), 7.70 (m, 2H).

6. *N*-[1-Ethyl-1-(3-methoxy-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,7*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, $J = 7.4$ Hz, 6H), 2.20 (m, 2H), 2.24 (s, 3H), 2.85 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 7.13 (m, 3H), 7.36 (t, $J = 8.1$ Hz, 1H), 7.43 (m, 1H), 7.52 (d, $J = 7.9$ Hz, 1H).

7. *N*-[1-Ethyl-1-(4-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,8*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, $J = 7.4$ Hz, 6H), 2.20 (m, 1H), 2.26 (s, 3H), 2.41 (s, 3H), 2.92 (m, 1H), 3.84 (s, 3H), 6.89 (d, $J = 8.2$ Hz, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 7.24 (m, 3H), 7.87 (d, $J = 8.3$ Hz, 2H).

8. *N*-[1-Ethyl-1-(4-methoxy-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*2,6,9*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, $J = 7.4$ Hz, 6H), 2.20 (m, 2H), 2.27 (s, 3H), 2.95 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.94 (m, 3H), 7.01 (d, $J = 7.0$ Hz, 1H), 7.18 (t, $J = 7.9$ Hz, 1H), 7.34 (br s, 1H), 8.03 (m, 2H).

9. *N*-(1-Benzoyl-1,2-dimethyl-propyl)-3-methoxy-2-methyl-benzamide (2{*3,6,2*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.67 (s, 3H), 1.97 (s, 3H), 2.54 (m, 1H), 3.80 (s, 3H), 6.40 (br s, 1H), 6.74 (d, $J = 7.9$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 7.11 (t, $J = 7.9$ Hz, 1H), 7.36 (m, 2H), 7.47 (m, 1H), 8.00 (m, 2H).

10. *N*-[1-(3,5-Dimethyl-benzoyl)-1,2-dimethyl-propyl]-3-methoxy-2-methyl-benzamide (2{*3,6,3*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 3H), 1.08 (d, 3H), 1.68 (s, 3H), 2.05 (s, 3H), 2.32 (s, 6H), 2.50 (m, 1H), 3.81 (s, 3H), 6.35 (s, 1H), 7.75 (d, 1H), 7.85 (d, 1H), 7.12 (m, 2H), 7.60 (s, 2H).

11. *N*-[1,2-Dimethyl-1-(2-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*3,6,4*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, $J = 6.9$ Hz, 3H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.73 (s, 3H), 1.97 (s, 3H), 2.48 (s, 3H), 2.52 (m, 1H), 3.79 (s, 3H), 6.14 (br s, 1H), 6.57 (d, $J = 7.5$ Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 7.10 (m, 2H), 7.26 (m, 2H), 7.49 (d, $J = 7.8$ Hz, 1H).

12. 3-Methoxy-*N*-[1-(2-methoxy-benzoyl)-1,2-dimethyl-propyl]-2-methyl-benzamide (2{*3,6,5*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.78 (s, 3H), 2.16 (s, 3H), 2.52 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 6.35 (br s, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.86 (m, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.11 (t, $J = 7.9$ Hz, 1H), 7.38 (m, 2H).

13. 3-Methoxy-*N*-[1-(3-methoxy-benzoyl)-1,2-dimethyl-propyl]-2-methyl-benzamide (2{*3,6,7*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.67 (s, 3H), 2.02 (s, 3H), 2.54 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 6.36 (br s, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 7.02 (m, 1H), 7.16 (m, 1H), 7.24 (m, 1H), 7.59 (m, 2H).

14. *N*-[1,2-Dimethyl-1-(4-methyl-benzoyl)-propyl]-3-methoxy-2-methyl-benzamide (2{*3,6,8*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.67 (s, 3H), 2.01 (s, 3H), 2.37 (s, 3H), 2.64 (m, 1H), 3.81 (s, 3H), 6.38 (br s, 1H), 6.79 (d, $J = 7.6$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 7.17 (m, 3H), 7.94 (d, $J = 8.2$ Hz, 2H).

15. *N*-(1-Benzoyl-cyclopentyl)-3-methoxy-2-methyl-benzamide (2{*6,6,2*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (s, 3H), 1.78 (m, 4H), 2.02 (m, 2H), 2.51 (m, 2H), 3.74 (s, 3H), 6.37 (d, 1H), 6.72 (d, 1H), 6.93 (t, 1H), 7.04 (s, 1H), 7.33 (m, 2H), 7.42 (m, 1H), 7.82 (m, 2H).

16. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclopentyl]-3-methoxy-2-methyl-benzamide (2{*6,6,3*}). Mp 130−132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (m, 4H), 1.85 (s, 3H), 2.06 (m, 2H), 2.31 (s, 6H), 2.58 (m, 2H), 3.77 (s, 3H), 6.46 (br s, 1H), 6.52 (d, $J = 7.6$ Hz, 1H), 6.79 (d, $J = 8.1$ Hz, 1H), 7.04 (t, $J = 7.9$ Hz, 1H), 7.10 (s, 1H), 7.46 (s, 2H)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 21.3, 24.9, 37.8, 55.6, 70.9, 111.2, 118.2, 124.8, 126.1, 126.3, 133.2, 136.7, 137.3, 137.4, 157.9, 169.0, 201.7. IR ($CDCl_3$): 3431, 1684, 1664 cm^{-1}. MS (ESI, +ve ion): *m/z* 366 (M + 1).

17. 3-Methoxy-2-methyl-*N*-[1-(2-methyl-benzoyl)-cyclopentyl]-benzamide (2{*6,6,4*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 1.82 (m, 4H), 2.14 (m, 2H), 2.47 (s, 3H), 2.55 (m, 2H), 3.75 (s, 3H), 6.30 (m, 2H), 6.76 (d, $J = 8.2$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 1H), 7.11 (m, 1H), 7.25 (m, 2H), 7.41 (d, $J = 7.6$ Hz, 1H).

18. 3-Methoxy-*N*-[1-(2-methoxy-benzoyl)-cyclopentyl]-2-methyl-benzamide (2{*6,6,5*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (m, 4H), 1.88 (s, 3H), 2.20 (m, 2H), 2.50 (m, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 6.28 (br s, 1H), 6.36 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.00 (m, 2H), 7.36 (m, 1H), 7.58 (m, 1H).

19. 3-Methoxy-2-methyl-*N*-[1-(3-methyl-benzoyl)-cyclopentyl]-benzamide (2{*6,6,6*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 1.84 (m, 4H), 2.05 (m, 2H), 2.37 (s, 3H), 2.62 (m, 2H), 3.78 (s, 3H), 6.35 (s, 1H), 6.63 (d, 1H), 6.80 (d, 1H), 7.04 (t, 1H), 7.24 (m, 2H), 7.62 (d, 1H), 7.69 (s, 1H).

20. 3-Methoxy-*N*-[1-(3-methoxy-benzoyl)-cyclopentyl]-2-methyl-benzamide (2{*6,6,7*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (m, 2H), 1.84 (s, 3H), 2.05 (m, 2H), 2.60 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 6.43 (br s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.4 (m, 2H), 7.26 (t, J = 8.0 Hz), 7.42 (m, 2H).

21. 3-Methoxy-2-methyl-*N*-[1-(4-methyl-benzoyl)-cyclopentyl]-benzamide (2{*6,6,8*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (s, 3H), 1.83 (m, 4H), 2.03 (m, 2H), 2.37 (s, 3H), 2.59 (m, 2H), 3.77 (s, 3H), 6.52 (d, 1H), 6.60 (br s, 1H), 6.78 (d, 1H), 7.01 (t, 1H), 7.15 (d, 2H), 7.78 (d, 2H).

22. 3-Methoxy-*N*-[1-(4-methoxy-benzoyl)-cyclopentyl]-2-methyl-benzamide (2{*6,6,9*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (m, 4H), 1.82 (s, 2H), 2.03 (m, 2H), 2.60 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 6.58 (d, J = 7.9 Hz, 1H), 6.64 (br s, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.04 (t, J = 7.9 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H).

23. *N*-[1-(3,5-Dimethyl-benzoyl)-cyclohexyl]-3-methoxy-2-methyl-benzamide (2{*7,6,3*}). Mp 161−163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.2−1.9 (8H), 1.96 (s, 3H), 2.05 (m, 2H), 2.31 (s, 6H), 3.80 (s, 3H), 6.25 (br s, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 7.08 (s, 1H), 7.14 (m, 1H), 7.51 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.9, 21.3, 21.7, 25.1, 35.4, 55.6, 64.0, 111.3, 118.2, 125.0, 125.8, 126.5, 133.0, 137.2, 137.3, 137.7, 158.0, 168.7, 203.1. IR ($CDCl_3$): 1680, 2939 cm^{-1}. MS (ESI positive ion): m/z 380 (M−1). Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.77; H, 7.94; N, 3.83.

24. *N*-[1-(3,5-Dimethyl-benzoyl)-cycloheptyl]-3-methoxy-2-methyl-benzamide (2{*8,6,3*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (m, 8H), 1.93 (s, 3H), 2.22 (m, 2H), 2.31 (s, 6H), 2.45 (m, 2H), 3.80 (s, 3H), 6.30 (br s, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 7.11 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H).

25. 3-Methoxy-*N*-[1-(2-methoxy-benzoyl)-cyclohexyl]-2-methyl-benzamide (2{*7,6,5*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20−2.00 (8H), 2.09 (s, 3H), 2.45 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 5.96 (br s, 1H), 6.70 (d, J = 7.5 Hz, 1H), 6.85 (m, 2H), 7.00 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.34 (m, 1H), 7.54 (dd, J = 7.5, 1.5 Hz, 1H).

26. 3-Methoxy-*N*-[1-(2-methoxy-benzoyl)-cycloheptyl]-2-methyl-benzamide (2{*8,6,5*}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (m, 8H), 2.07 (s, 3H), 3.300 (m, 4H), 3.78 (s, 3H), 3.81 (s, 3H), 6.03 (br s, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.9 Hz), 7.34 (m, 1H), 7.54 (m, 2H).

Acknowledgment. The work performed at the University of Barcelona was partially supported by the Universitat de Barcelona (MdelF), Ministerio de Educación y Ciencia, DGICYT (PB96-1490), and Generalitat de Catalunya. The work at RheoGene was supported by NIST Advanced Technology Project Grant No. 70NANB0H3012.

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CC0500396