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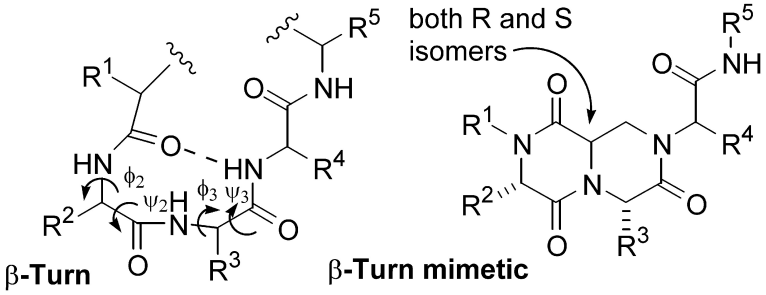

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Solid-Supported Synthesis of Putative Peptide β-Turn Mimetics via Ugi Reaction for Diketopiperazine Formation

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The scope and limitations of the solid-supported synthesis of a bicyclic diketopiperazine, an internal, putative peptide β-turn mimetic, are presented. The 4CC multicomponent Ugi reaction of α-*N*-Boc-diaminopropionic acid resin ester (an amine input), optically active α-bromoacid, aldehyde, and isocyanide is the key step in the proposed synthetic protocol. Application of cyclitive cleavage as the final step led to desired products in high purity.

Introduction

The design and synthesis of protein secondary structure mimetics have been a very active area of research.[1] Mimicry of the peptide reverse turn is a frequently reported target, and there is a continuing debate on the relevance, accuracy, and conformational compatibility of β-turn mimetics with the secondary structural elements that are to be imitated.[2] Considering that a significant percentage of medicinal chemistry is related to mimicking protein secondary structures, libraries of peptide β-turn mimetics would be a valuable addition to any corporate compound collection for both thematic and diversity-based screening.

The β-turn is a common feature in biologically active peptides and is defined as any tetrapeptide sequence with a 10-membered intramolecularly H-bonded ring, in which the Cα(i) to Cα($i + 3$) distance varies from 4 to 7 Å. Contingent upon the dihedral angle values for ϕ_2, ψ_2, ϕ_3, and ψ_3, there are at least 14 types of β-turn structures described in the literature.[3] These model conformers have been developed for linear, short peptides. In natural proteins, turn fragments can adopt an even larger variety of conformations due to stabilization provided by the remaining portion of the molecule.

There has been much discussion in the literature on what constitutes a β-turn mimetic and how different types of mimetics are to be characterized.[4] The varied approaches and scaffolds presented can be roughly classified into three broad classes, which are illustrated in Figure 1. Structure **1** represents the incorporation of a rigid scaffold template into an attached cyclic peptide. The rigid template serves to stabilize the attached cyclic peptide into a β-turn conformation. This type of structure has been earlier classified as an "external β-turn mimetic". Notable examples of this type of β-turn mimetic are those presented by DeGrado, Burgess,

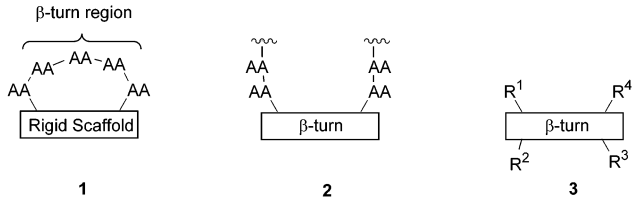

Figure 1.

and others.[4,5] Structure **2** illustrates a rigid scaffold, which, when incorporated into a peptide or pseudo-peptide chain, causes a reversal of the chain.[6] These are often incorporated to induce β-sheet formation. In strictest terms, these structures themselves adopt a β-turn conformation (vide supra), but quite often they lack substitution at the important $i + 1$ and $i + 2$ residues of the turn region or the means to introduce significant diversity at these positions. Structure **3** represents a scaffold that is able to display side chains in trajectories mimicking a peptide reverse turn (i.e., "an internal β-turn mimetic"; see ref 5). These scaffolds are quite often bicyclic, heterocyclic structures such as those presented by Kahn[7] or medium ring molecules such as those presented by Ellman.[8] There is a wealth of examples for each of these types of approaches as well as intermediate examples, which are not easily classified by these three categories. Any particular approach has benefits and limitations, which must be considered when approaching a particular target. For further discussion on the combinatorial syntheses of β-turn mimetic libraries, several recent reviews are available.[9]

Recently, we reported the solid-phase synthesis of bicyclic diketopiperazines **4** and **5** (Figure 2).[10] This interesting class of compounds adopts a conformation similar to the type I β-turn motif and has tremendous potential to be used as an early stage drug discovery tool to map protein−protein or protein−peptide interactions. Recently, Below[11] and Kahn[12] reported syntheses of structurally similar bicyclic diketopiperazines. An improved synthesis of diaminopropionic acid was recently presented by the Merck research group.[13]

* To whom correspondence should be addressed. E-mail: golebiowski.a@pg.com.

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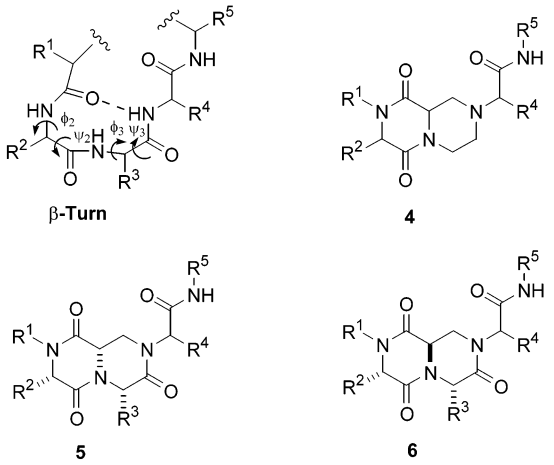
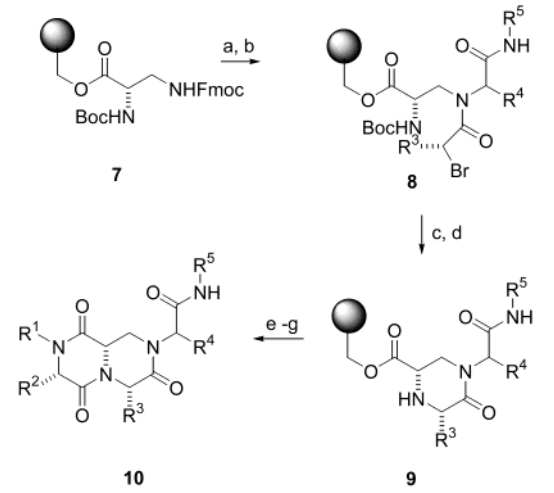


Figure 2.

Scheme 1[a]



[a] Reagents and conditions: (a) 25% piperidine, DMF, 30 min; (b) aldehyde (5 equiv), isocyanide (5 equiv), *R*-(+)-2-bromoalkyl acid, MeOH/$CHCl_3$ (1:4; v/v), room temp, 2 × 2 h; (c) 25% TFA in DCM; (d) 10% DIPEA, DCM, room temp, 18 h; (e) Boc-amino acid, NMM, isobutyl chloroformate, THF/DMF; (f) 25% TFA, DCM; (g) 2 M AcOH, ^{i}PrOH, 60 °C, 18 h.

Another approach using diaminopropionic acid in the solid-phase synthesis of pyridones and pyridopyrazines as a peptidomimetic scaffold has been reported by Creighton and co-workers.[14] Herein, we report the detailed experimental procedures for the solid-supported synthesis of internal β-turn mimetics **5** and **6** as well as studies on the scope and limitation of the proposed synthetic protocol.

Results and Discussion

α-*N*-Boc-β-*N*-Fmoc-L-diaminopropionic acid (product **7**) was attached to Merrifield's hydroxymethyl resin using Mitsunobu conditions. Standard Fmoc-group deprotection exposed an amine group, which was applied as one of the inputs in the solid-phase Ugi reaction (Scheme 1).[15] Optically active *R*-(+)-2-bromoalkyl acid,[16] aldehyde, and isocyanide were used in excess (5 equiv) to drive the reaction to completion. Boc group removal followed by base-catalyzed cyclization afforded resin-bound product **9**. The second ring system was elaborated via Boc-amino acid coupling. We surveyed several coupling procedures, and the mixed anhydride method was found to be the optimum. The penultimate step involved Boc group deprotection before heating in 2 M acetic acid/2-propanol to effect release of the product **10** from the resin. As expected, the application of a cyclitive cleavage step[17] led to crude product with a relatively high level of purity (50−90% pure, HPLC/UV detector).

The diastereoselectivity of the Ugi reaction was not high, and as a consequence, product **10** was isolated as a (1:1 to 1:2) mixture of diastereoisomers (**10a** and **10b**) at the R^4 center. However, it should be pointed out that the presented method allows control of all the remaining chiral centers. Both enantiomers of diaminopropionic acid are readily available from L- and D-asparagine. Optically active α-bromo acids are readily prepared from related α-amino acids. The bromine displacement occurs via an S_N2 mechanism with inversion of configuration on the R^3 stereocenter. No significant epimerization of the remaining R^2 chiral center was observed. Substituents R^4 and R^5 are not conformationally constrained, but they are presented at the right distance and position from the remaining R^1, R^2, and R^3 side chains.

Tables 1−5 summarize the influence of the selected substrate inputs as well as the chirality of the central bridging carbon (derived from starting diaminopropionic acid) on the yield and purity of the final product. Most common *N*-Boc-α-amino acids can be used as the R1/R2 input. The application of cyclic amino acids (entries 14−16) did not result in substantial premature cleavage, affording final products in comparable yields. We tested seven different α-bromo acids (R3 input). All of them could be used as one of the Ugi reaction inputs, but α-bromo acids derived from L-phenylalanine and β-*O*-benzyl-L-aspartic acid are less stable and expectedly led to lower overall yield. Aliphatic aldehydes (input R4) worked better then aromatic ones, most likely owing to the higher reactivity of the intermediate imine. A similar observation was reported earlier by Szardenings and co-workers for the application of the Ugi reaction for the solid-supported diketopiperazine synthesis.[18] R5 input is the major limitation of the proposed synthetic high-throughput protocol, since only a few of the commercially available isocyanides are tolerable to work with on this scale. The use of a "universal isocyanide" could potentially help alleviate this problem.[19]

The central chiral carbon atom, derived from diaminopropionic acid, can be used to slightly modify the space orientation of the crucial R^2 and R^3 amino acid side chains (see also modeling studies section) for biological interactions.

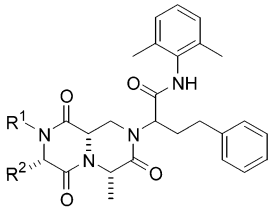
By use of the above-described synthetic protocol, several epimeric, bicyclic diketopiperazines **29**−**33** were prepared. α-*N*-Boc-β-*N*-Fmoc-D-diaminopropionic acid (prepared from the relatively inexpensive D-asparagine) was used as a substrate. Besides slightly lower yields, no significant synthetic differences were observed.

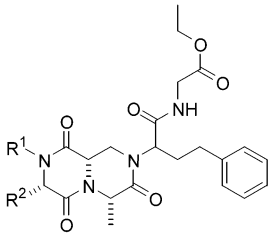
Modeling

Simulated annealing was performed using SYBYL 6.7.2 (Tripos Inc., St. Louis, MO) and the MMFF force field on both epimers of structure **34** (Figure 3) to determine their propensity to adopt a β-turn.

In a distance-dependent dielectric, the structures were heated to 2000 K in 2000 fs and subsequently annealed to

Table 1. Influence of the Amino Acid Input (R1 and R2) on Yield and Purity of the Crude Product

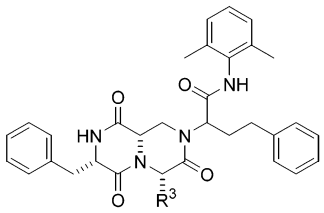


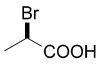
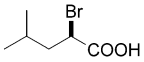
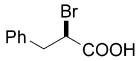
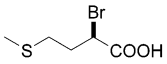
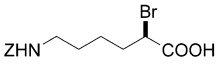
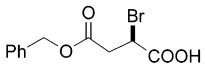
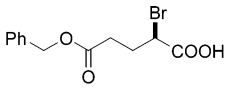


Entry	R1 / R2	Crude yield[a]	Purity[b]
11	Boc-Phe-OH	48%, 43 mg,	77%
12	Boc-Ala-OH	37% 27 mg,	76%
13	Boc-Asp-(O-Bzl)-OH	28%, 26 mg,	57%
14	Boc-Pro-OH	47% 36 mg,	80%
15	Boc-Hyp(Bzl)-OH	43% 39 mg,	88%
16	Boc-Thz-OH	39% 36 mg,	88%

[a] Crude yield (% and mg), 200 mg of resin **7**. [b] By HPLC (UV, 215 nm).

Table 2. Influence of the α-Bromo Acid Input (R3) on Yield and Purity of the Crude Product



Entry	R3	Crude yield[a]	Purity[b]
11		48% 43 mg,	77%
17		42% 39 mg,	61%
18		24%, 23 mg,	60%
19		47%, 41 mg,	53%
20		52% 60 mg,	52%
21		47% 36 mg,	63%
22		28%, 26 mg,	61%

[a] Crude yield (% and mg), 200 mg of resin **7**. [b] By HPLC (UV, 215 nm).

300 K in 10 000 fs. This approach was repeated 100 times for each epimer to allow increased sampling of the conformational space. Each annealed conformation was then subjected to energy minimization. The structures that lie within 6 kcal/mol of the lowest energy conformation of each epimer were analyzed further. Root-mean-square deviations (rmsd) were calculated between Cα(i), C(i), Cα(i + 1), Cα(i + 2), Cβ(i + 2), N(i + 3), and Cα(i + 3) of ideal types I and II β-turns and the corresponding atoms in the two epimers (i.e., O1, C2, C3, C4, C5, C6, N7, C8). The average rmsd between a type I β-turn and the *R* and *S* isomers

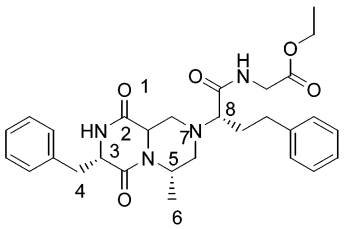
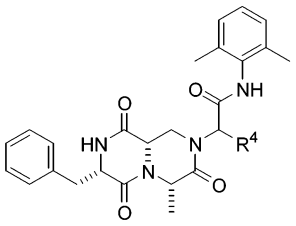
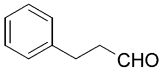
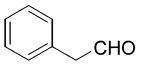
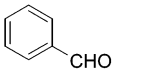
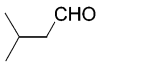


Figure 3. Structure **34**.

of structure **34** were 0.56 ± 0.1 Å and 0.48 ± 0.03 Å, respectively. The rmsd values were more substantial between

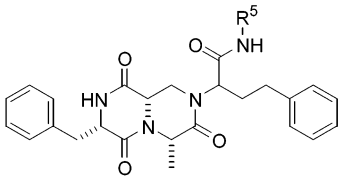
Table 3. Influence of the Aldehyde Input (R4) on Yield and Purity of the Crude Product

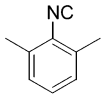
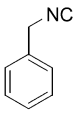
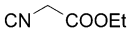
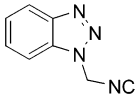


Entry	R4	Crude yield[a]	Purity[b]
11		48% 43 mg,	77%
23		37% 31 mg,	59%
24		18%, 15 mg,	24%
25		53%, 41 mg,	78%

[a] Crude yield (% and mg), 200 mg of resin **7**. [b] By HPLC (UV, 215 nm).

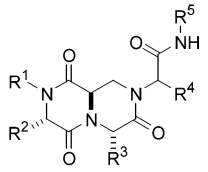
Table 4. Influence of the Isocyanide Input (R5) on Yield and Purity of the Crude Product

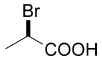
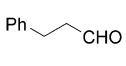
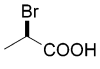
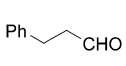
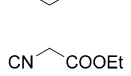
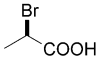
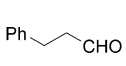
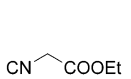
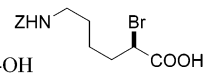
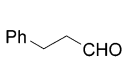
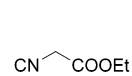
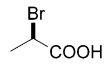
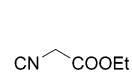


Entry	R5	Crude yield[a]	Purity[b]
11		48% 43 mg,	77%
26		54% 45 mg,	88%
27		55%, 45 mg,	73%
28		54%, 49 mg,	62%

[a] Crude yield (% and mg), 200 mg of resin **7**. [b] By HPLC (UV, 215 nm).

Table 5. Selected Examples of Putative β-Turn Mimetic **6**



Entry	R1 and R2	R3	R4	R5	Crude Yield	Purity
29	Boc-Phe-OH				40% 34 mg,	73%
30	Boc-ProOH				48% 36 mg,	79%
31	Boc-Phe-OH				32 % 26 mg,	64%
32	Boc-Phe-OH				25% 28 mg,	63%
33	Boc-Phe-OH				33% 25 mg,	70%

[a] Crude yield (% and mg), 200 mg of resin **7**. [b] By HPLC (UV, 215 nm).

Table 6. Calculated Average Torsion Angles (in deg) for the *S* and *R* Epimers[a]

	$\phi 2$	$\psi 2$	$\phi 3$	$\psi 3$
R	6 ± 17	-6 ± 17	-149 ± 14	-7 ± 12
S	-36 ± 6	35 ± 6	-164 ± 5	-27 ± 3
NMR[a]	−22	−13	157	−35

[a] Experimental values of the torsion angles of structure **34** obtained by NMR.

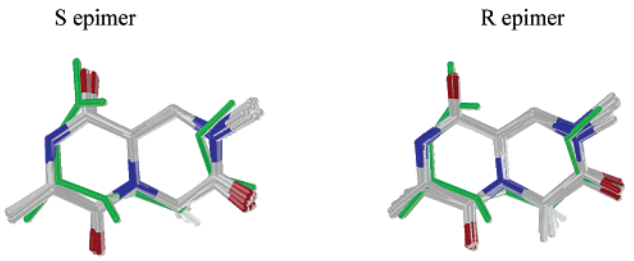


Figure 4. Annealed conformations of both epimers superimposed onto an ideal type I β-turn (in green).

a type II β-turn and the *R* and *S* isomers (0.65 ± 0.1 Å and 0.75 ± 0.1 Å, respectively), which suggests that structure **34** is more likely to adopt a type I β-turn.

Furthermore, the average torsion angles defining the putative β-turn in the two epimers of structure **34** were calculated and are presented in Table 6. On average, the torsion angles of the *R* (*S*) isomer deviate by 39° (47°) from an ideal β I turn and by 80° (60°) from an ideal β II turn. The NMR structure deviates by an average of 51° from an ideal β I turn and by 68° from an ideal β II turn. These data further suggest that structure **34** will more closely fit a type I β-turn as illustrated in Figure 4.

Conclusions

The design and synthesis of novel, internal, putative β-turn mimetics were demonstrated. Both L- and D-diaminopropionic acid can be used as a starting material, leading to two (complementary) epimeric series of β-turn mimetics. Most natural amino acid side chains can be displayed at R2, R3, and R4 positions. The application of solid-supported synthetic protocol, combined with Ugi 4CC multicomponent reaction, leads to convenient and rapid synthesis of the final compounds. Additionally, incorporation of the cyclitative cleavage as the final step gave final crude compounds at 50−90% purity level, suitable in many cases for the initial screening without an additional purification step.

Experimental Section

Materials. α-Bromo acids were obtained according to the Ellman procedure.[16] Both enantiomers of diaminopropionic acid were synthesized using the Merck research group procedure.[13] All reagents and solvents were obtained from commercial suppliers and used without further purification. Resin and amino acids were purchased from Novabiochem or Advanced ChemTech. ^{1}H and ^{13}C NMR spectra were recorded on Varian at 300 or 600 MHz using $CDCl_3$ as the solvent. All the LC−MS data were performed on a Micromass Platform 2. Analytical RP-HPLC was recorded on Thermo Quest spectra system P4000 using a Polaris C18 reversed-phase column. RP-HPLC preparative purification was performed on a Rainin Dynamax SD-1 purification system using an Intersil ODS-3 column (20 mm × 250 mm, 9.0 mL/min flow rate). All the HRMS data were provided by Nebraska Center for Mass Spectrometry. All the reactions were performed in PTFE tubes using a Quest 210 apparatus manufactured by Argonaut Technologies.

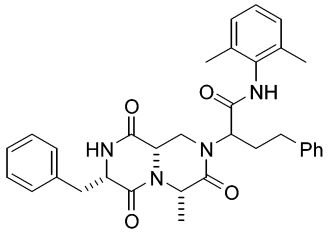
Compound 7. Merrifield-OH resin (20 g, 22.6 mmol, Novabiochem) was swelled in 1:1 tetrahydrofuran (THF)/dichloromethane (DCM). To this was added triphenylphosphine (29.6 g, 113 mmol) and α-*N*-Boc-*β*-*N*-Fmoc-L-diaminopropionic acid (48.1 g, 113 mmol), and the slurrry was cooled to 0 °C under argon. To this gently agitated solution was added diethyl azodicarboxylate (19.66 g, 113 mmol) slowly over a period of 10 min. This reaction mixture was kept at 0 °C for 1 h and then was allowed to gradually warm to room temperature while agitating overnight. The resin was filtered and washed with THF/DCM 1:1 (5×), and the reaction was repeated in an identical manner except that it was allowed to agitate for 48 h. The off-white resin was filtered, washed with THF (5×) and DCM (5×), and then washed with alternating DCM and methanol (MTH) (six each). The resin was vacuum-dried for 18 h. Yield: 27.1 g (93%). CHN: %N, 2.263 (obsd), 2.5 (calcd). IR (cm^{-1}): 1731, 1716, 1695.

Compound 9. α-*N*-Boc-*β*-*N*-Fmoc-L-diaminopropionic Merifield-PS resin ester (0.2 g, 0.15 mmol) was rinsed three times with DCM and then treated with a solution of 25% piperidine in *N*,*N*-dimethylformamide (DMF). The reaction mixture was allowed to agitate for 45 min. The resin was filtered and washed liberally with DMF (6×) followed by MeOH (3×), DCM (3×), and alternating MeOH and DCM washes (3× each). (Ninhydrin testing[20] of this resin gave a strong positive result.) The deprotected resin was rinsed a final time with a 4:1 solution of chloroform (CHL)/MeOH. Resin **7** was swelled in 4:1 CHL/MTH (20−25 mL), and to this was added an aldehyde (5 equiv, 0.75 mmol). The resin was agitated for 10 min before addition of isocyanide (5 equiv, 0.75 mmol) followed by *R*-(+)-bromo acid (5 equiv, 0.75 mmol). The resin mixture was agitated for 2.5 h before filtering and washing with 4:1 CHL/MeOH (5×). The reaction was repeated in an identical manner for 3.5 h. The resin was filtered and washed with 4:1 CHL/MeOH (5×) followed by alternating DCM and MeOH washes (3× each). Ninhydrin testing of this resin was negative. Resin **8** was treated with 25% trifluoroacetic acid (TFA) in DCM for 1 h, then filtered and washed with DCM (6×) followed by alternating DCM and MeOH (3× each) washes. The Boc deprotected resin was swelled in 10% diisopropylethylamine (DiPEA) in DCM and agitated for 18 h, then filtered and washed with DMF (3×) followed by alternating DCM and MeOH (3× each) washes, affording resin **9**.

Preparation of the Isobutylcarbonic Acid Mixed Anhydride of Boc-Phe-OH. Boc-amino acid (5equiv, 7.5 mmol) was dissolved in dry THF (2 mL) under an argon atmosphere and cooled to 0 °C using an ice bath while being magnetically stirred. To the cooled solution was added *N*-methylmorpholine (5.5 equiv, 8.3 mmol) followed by the *slow* addition of isobutyl chloroformate (4.25 equiv, 6.4 mmol) over a period of 10 min. A white precipitate was

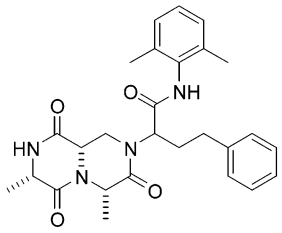
observed immediately. The heterogeneous solution was allowed to stir at 0 °C for 2 h and then for an additional 2 h at room temperature.

Compound 11.



11a and 11b. Resin **9** was swelled in DMF (0.5 mL), and to this was added the suspension in DMF of the mixed anhydride prepared previously. The reaction mixture was allowed to agitate overnight before filtering and washing with DMF (5×). The reaction was repeated in an identical manner except that it was allowed to agitate for 72 h. The resin was filtered and washed with DMF (5×) followed by alternating DCM and MeOH (3× each) washes. Resin **9d** was agitated with a solution of 25% TFA/DCM for 1 h. Resin **9e** was filtered and washed with alternating DCM and MeOH (5× each) followed by DCM (2×) and then taken up in a 2 M solution of acetic acid (AcOH) in 2-propanol (^{i}PrOH) and heated to 60 °C for 18 h. The resin was filtered and washed with alternating MeOH and DCM (2×), and the filtrate and washings were collected and combined before evaporating to dryness under reduced pressure. The crude products were purified by RP-HPLC (C_4 column, 55 min linear gradient start, 95% water with 0.1% TFA added/5% acetonitrile to 100% acetonitrile).

Compound 12.



12a. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.06−7.35 (m, 8H), 5.23 (t, 1H, J = 7.2 Hz), 4.84 (q, 1H, J = 7.2 Hz), 4.11 (dd, 1H, J = 3.9, 14.4 Hz), 4.00 (q, 1H, J = 6.6 Hz), 3.78 (dd, 1H, J = 3.0, 10.8 Hz), 3.54 (dd, 1H, J = 11.4, 14.4 Hz), 2.79−2.85 (m, 1H), 2.64−2.74 (m, 2H), 2.46−2.53 (m, 1H), 2.20 (s, 6H), 1.51 (d, 3H, J = 6.9 Hz), 1.46 (d, 3H, J = 6.9 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 170.4, 167.9, 167.6, 167.0, 140.7, 135.2, 133.3, 128.9, 128.7, 128.5, 127.8, 126.7, 56.6, 55.0, 53.3, 50.4, 41.0, 32.9, 29.9, 19.6, 18.8, 16.3. $[\alpha]_D$ +25.5° (c 0.65, $CHCl_3$). HRMS calcd for $C_{27}H_{33}N_4O_4$ 477.250 181, found 477.250 136.

12b. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.05−7.38 (m, 8H), 5.25 (dd, 1H, J = 6.3, 9.0 Hz), 4.84 (q, 1H, J = 6.9 Hz), 4.33−4.42 (m, 2H), 4.05 (q, 1H, J = 6.6 Hz), 3.57 (ddd, 1H, J = 3.9, 12.6, 15.3 Hz), 2.75 (t, 2H, J = 7.5 Hz), 2.38−2.48 (m, 1H), 2.23−2.34 (m, 1H), 2.19 (s, 6H), 1.52 (d, 3H, J = 6.9 Hz), 1.5 (d, 3H, J = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 170.3, 169.1, 167.8, 167.0, 140.2, 135.2, 133.2, 129.0, 128.6, 128.5, 127.8, 126.8, 56.2, 55.2, 53.9, 50.4, 42.1, 32.8, 31.0, 19.8, 18.7, 16.5. $[\alpha]_D$ −76.4° (c 0.61, $CHCl_3$). HRMS calcd for $C_{27}H_{33}N_4O_4$ 477.250 181, found 477.250 527.

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Supporting Information Available. Analytical data (^{1}H and ^{13}C NMR, $[\alpha]_D$, and HRMS) for products **13**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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