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Ring Closing Metathesis in Organic Synthesis: Evolution of a High Speed, Solid Phase Method for the Preparation of β-Turn Mimetics.

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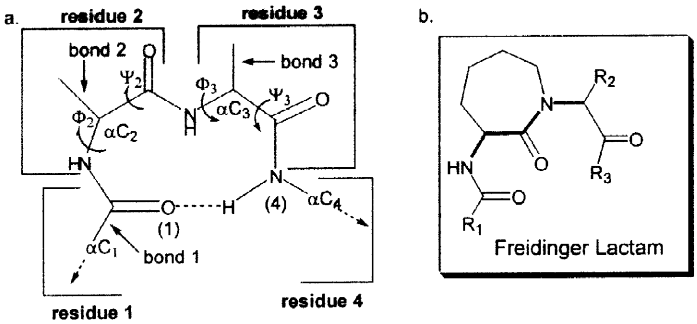
Abstract: Complimentary solid phase syntheses of the Freidinger lactam class of β-turn mimetics have been developed using ring closing metathesis as both the key carbon-carbon bond forming step and the cyclative cleavage mechanism. Solid phase variants of the Fukuyama-Mitsunobu process were utilized as part of a rapid three-step sequence to construct immobilized lactam precursors. An alternative solid phase process is offered which utilizes an Ugi/ring closing metathesis reaction tandem to deliver the desired compounds in two synthetic operations.

In vivo modulation of disease-relevant protein-protein interactions is a contemporary challenge for the pharmaceutical industry.[1] While a handful of biologically active proteins have become commercial successes (e.g. erythropoietin [EPO], granulocyte colony-stimulating factor [G-CSF], and the interferons [IFNs]),[2] general application of protein therapeutics has been severely limited do to their poor physiochemical properties, rapid clearance, rapid degradation, antigenicity, and systemic toxicity. In this regard, the industry must position itself to more readily identify low molecular weight lead compounds which either interfere with or augment macromolecular interactions. This critical need is further underscored when considering the enormous number of new therapeutic targets which will be identified over the next several years due to advances in cDNA microarray[3] and functional genomics techniques.[4]

The three fundamental motifs utilized by nature for protein assembly are α-helices, β-sheets, and reverse turns. Of these, reverse turns, including β-turns (Figure 1a) have been identified to play critical roles in molecular recognition.[5]

Figure 1



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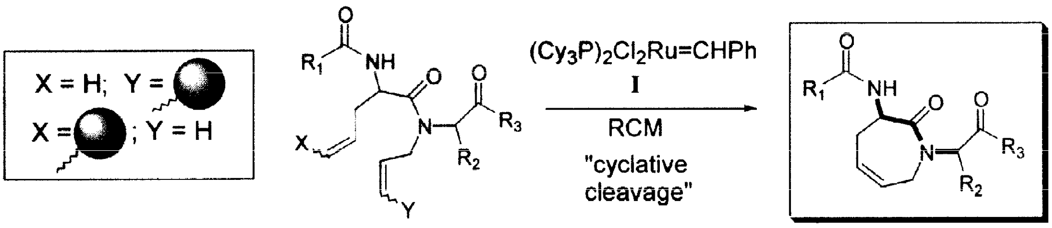
The β-turn is therefore an attractive motif for intervention by low molecular weight, conformationally constrained peptidomimetic scaffolds.[6] Information gleaned through receptor binding or enzyme inhibition assays using constrained analogs of biologically active peptides often leads to a greater understanding of the receptor-bound conformation of the endogenous, bioactive ligand. In addition, conformationally constrained "small molecule" peptide mimics often display metabolic profiles superior to their acyclic congeners and may therefore constitute attractive *in vivo* probes for proof of concept and target validation experiments. Thus, as part of a continuing program directed towards the modulation of selected protein-protein interactions, we set out to develop high-speed, combinatorial entries into the important Freidinger lactam[7] class of β-turn mimetics (Figure 1b).

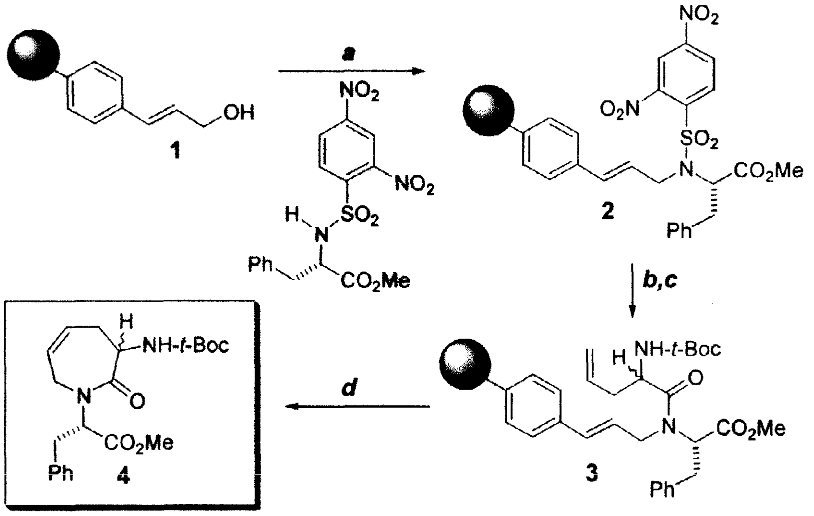
Inspired by reports from Grubbs' laboratories,[8] we envisioned that the desired lactams would be available from the corresponding acyclic dienes *via* ring closing metathesis (RCM) (Scheme 1).[9] Furthermore, if the diene precursors were attached to a solid support *via* one of the terminal olefin residues, the olefin methathesis reaction could serve as a cyclative cleavage mechanism in the formation of the desired products.[10-15] The olefin functionality in this scenario would, in turn, serve as an extremely robust "traceless linker."[13] The fact that metal carbene complexes such as **I** and related substances were developed and successfully utilized as ROMP (Ring Opening Metathesis Polymerization) catalysts[15] supported the intended solid phase application.

Scheme 1



Towards this end, the immobilized diene **3** (Scheme 2) was constructed in order to test the outlined reaction manifold. Starting with Frechet's cinnamyl alcohol resin **1**,[16] we employed a solid phase variant of the Fukuyama amine synthesis[17] for the crucial loading step. In practice, the 2,4-dinitrobenzenesulfonamide of phenylalanine methyl ester was subjected to the THF swollen resin **1** in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD).[18] After shaking for several hours, the immobilized sulfonamide **2** was treated with *n*-butylamine (10 equiv.; 1.0M in dichloromethane) at room temperature to affect sulfonamide cleavage. After one hour, the resin was washed, suspended in dichloromethane and acylated with racemic *t*-Boc-allyl glycine to give the penultimate, immobilized diene **3**. Treatment of the resin with 5 mol% **I** (based on loading)[19] in dichloromethane at room temperature afforded no detectable products (TLC, mass spec.) after 6h. However, utilization of 1,2-dichloroethane and heating at 80°C for 6h gave the desired lactam **4** in >90% purity[20a] as a 1:1 mixture of diastereomers (16% overall from **2**).

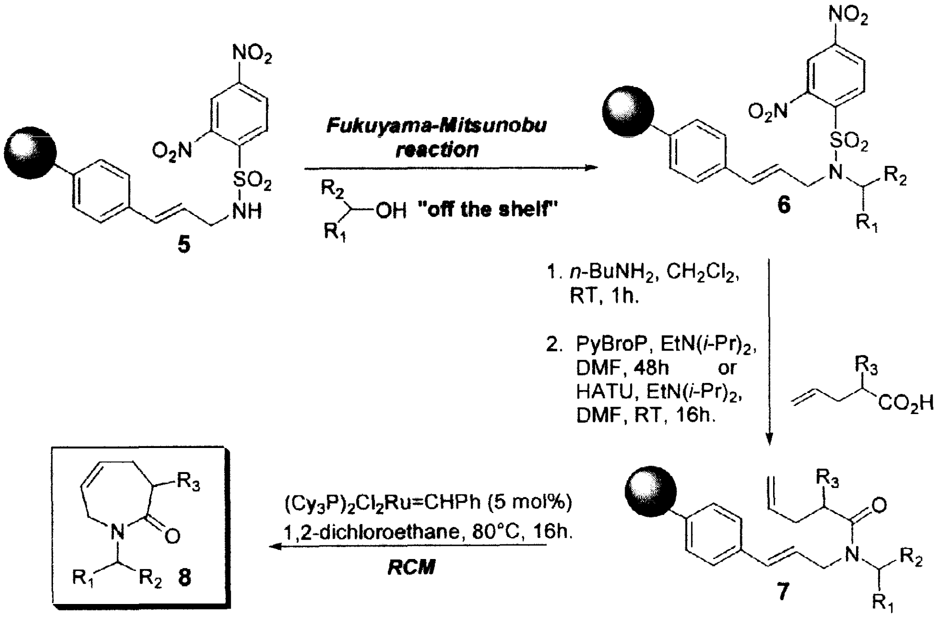
Scheme 2



(*a*) phenylalanine methyl ester-2,4-dinitrobenzenesulfonamide, DEAD, PPh_3, THF, RT, 16h, 69%. (*b*) *n*-$BuNH_2$, CH_2Cl_2, RT, 2h. (*c*) (±)-*N*-*t*-Boc-allyl glycine, 1-methyl-2-chloropyridinium iodide, EtN(*i*-Pr)$_2$, CH_2Cl_2, reflux, 16h. (*d*) catalyst **I** (5 mol % based on loading), 1,2-dichloroethane, 80°C, 16h, 16% from **2**.

Gratified by these results, we set out to address one of the limitations of this approach, namely the absence of commercially available 2,4-dinitrobenzenesulfonamides. As shown in Scheme 3, we explored an alternative reaction paradigm utilizing the nucleophilic resin component **5** in the initial Fukuyama-Mitsunobu[18,19] loading step. We anticipated the described umpolung approach would allow us to leverage both

Scheme 3.



the enormous pool of commercially available alcohols and the versatility of the Fukuyama-Mitsunobu procedure[17,18] to render a more practical, high-speed entry into the desired peptidomimetic class. Thus, alkylation of the 2,4-dinitrobenzenesulfonamide resin **5** with an alcohol input using Fukuyama-Mitsunobu conditions[17,18] gave the intermediate resin-bound sulfonamide **6**. Sulfonamide cleavage followed by acylation with an ω-unsaturated pentenoic acid derivative afforded intermediate **7**. Finally, ring closing metathesis[8,9] (RCM) with concomitant substrate cleavage provided the desired lactams **8**.

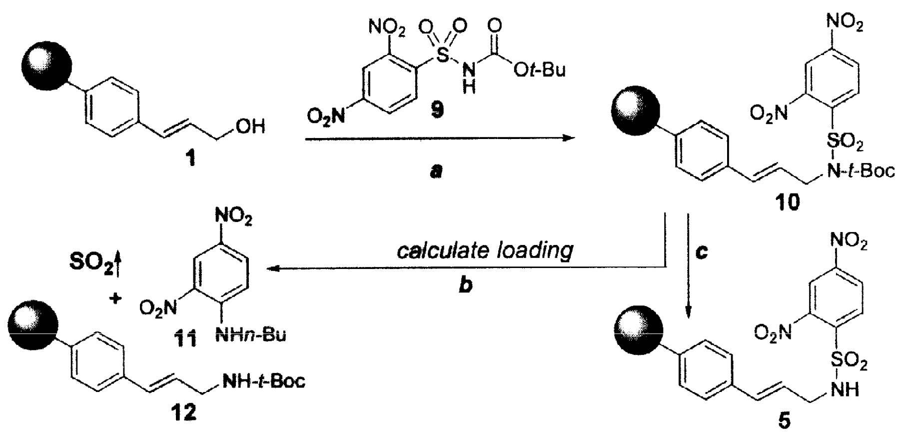
As shown in Table 1, the sequence is general with respect to the alcohol component. Thus, both primary and secondary substrates, including α-hydroxy esters serving as amino acid precursors (entry 7)[21] afforded the desired products in good overall yield and in excellent purity.[20a,b] In addition to the use of *t*-Boc-allyl glycine as the ω-unsaturated carboxylic acid input, α-(C)-substituted-4-pentenoic acids were successfully employed (entries 8-10).

Table 1. Synthesis of Freidinger lactams **8** *via* Scheme 3:

Entry	R_1	R_2	R_3	overall %yield of (8)
1	Ph	H	NH*t*-Boc	36
2	3-CF_3Ph	H	NH*t*-Boc	31
3	3-ClPh	H	NH*t*-Boc	31
4	4-MeOPh	H	NH*t*-Boc	30
5	*n*-Pr	H	NH*t*-Boc	34
6	Me	Me	NH*t*-Boc	29
7	Ph	CO_2Me	NH*t*-Boc	23
8	Ph	H	$(C_6H_{11})\text{-}CH_2CH_2$	34
9	Ph	H	*i*-Pr	35
10	Ph	H	Ph	15

The 2,4-dinitrobenzenesulfonamide resin **5** was prepared according to Scheme 4. Alkylation of *trans*-cinnamyl alcohol resin **1**[16] with the *t*-Boc protected 2,4-dinitrobenzenesulfonamide **9**[17] gave resin **10**. Loading was conveniently assessed at this stage *via* sulfonamide cleavage and gravimetric analysis of the resulting *N*-(*n*-butyl)-2,4-dinitroaniline **11**. Subsequent treatment of **10** with trifluoroacetic acid gave the desired cinnamylamine-2,4-dinitrobenzenesulfonamide resin **5** in multigram quantities and in excellent overall yield.[22]

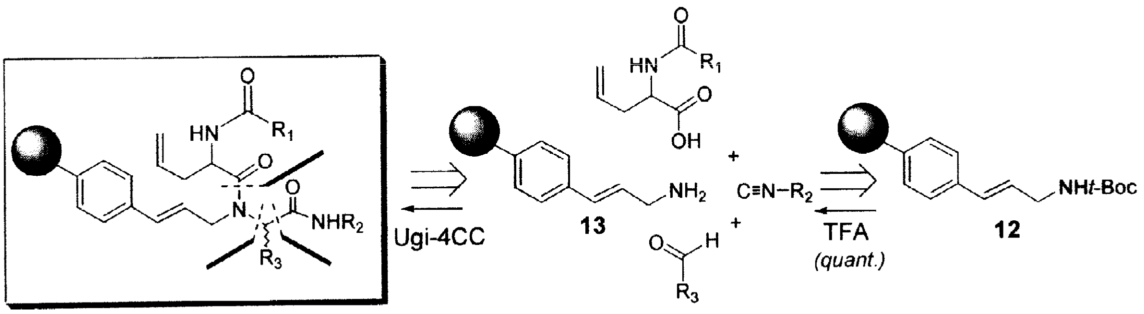
Scheme 4.



(*a*) DEAD, PPh_3, THF, RT, 16h. (*b*) *n*-$BuNH_2$, CH_2Cl_2, RT, 2h. (*c*) TFA, CH_2Cl_2, RT, 16h.

Next, we examined the possibility of substituting the three-step linear construction of immobilized lactam precursors **7** (Scheme 3) with a single multi-component coupling reaction.[23] If successful, this conclusive iteration would represent a complimentary, two-step solid phase synthesis. The concept derived precedent from the work of Armstrong and co-workers who previously reported successful implementation of Ugi four component coupling (4CC) chemistry[24] on solid support.[25] Retrosynthetic analysis according to Scheme 5 dictated the requirement for an unsaturated, immobilized amine component, an acylated allyl glycine component, and standard aldehyde and isonitrile inputs. The desired resin **13**, in turn, was prepared in multigram quantities *via* treatment of resin **12** (Scheme 4) with trifluoroacetic acid in dichloromethane (1:1), followed by rinsing with a solution of triethylamine in dichloromethane.

Scheme 5



With cinnamyl amine resin **13** in hand, it was screened for efficacy using *t*-Boc-allyl glycine, benzylisonitrile, and various aldehydes according to Scheme 6. The resulting immobilized dienes were washed, dried and suspended in 1,2-dichloroethane. Treatment with the RCM catalyst **I** (5 mol%)[26] at 80°C for 24h gave the desired lactams **14** as diastereomeric mixtures in moderate to good yields *after two synthetic operations*.

Scheme 6

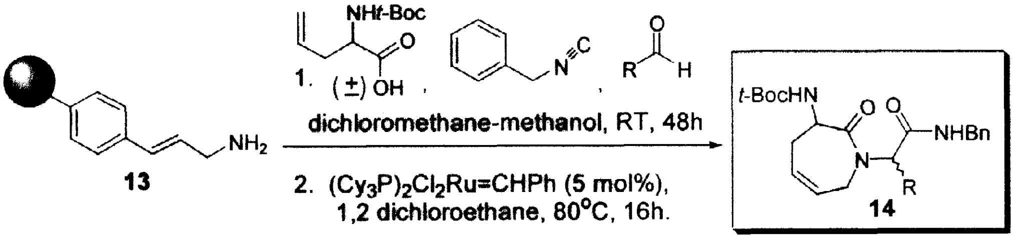
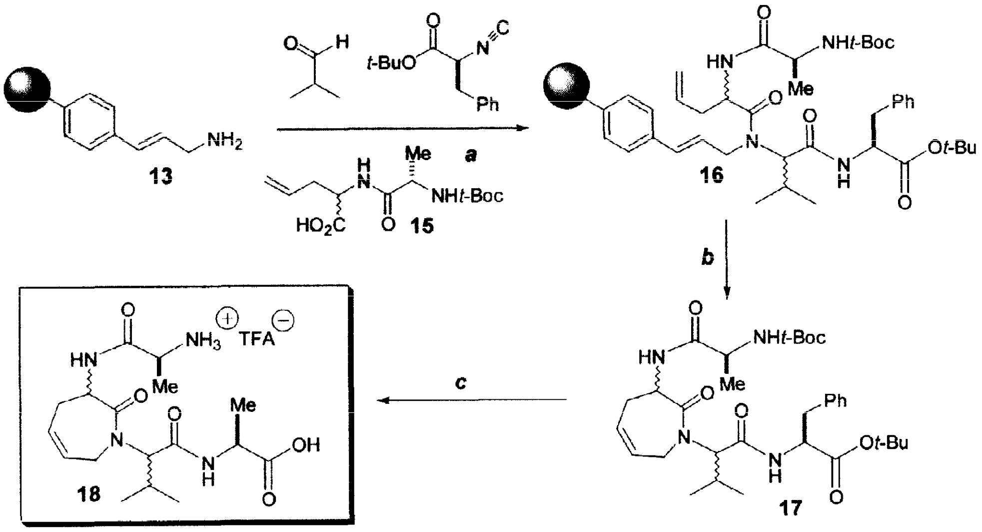


Table 2

Entry	R	% Yield (14)
1	*i*-Pr-	62
2	$PhCH_2CH_2$-	55
3	Ph-	21

Finally, we attempted the high speed synthesis of a four amino acid β-turn mimetic scaffold using the described, two-step manifold. Thus, treatment of the cinnamyl amine resin **13** with isobutyraldehyde, *t*-butyl 2-isocyano-3-phenyl propionate,[27] and the unsaturated *t*-Boc-protected dipeptide **15** gave the corresponding immobilized linear tetrapeptide **16**. RCM followed by trifluoroacetic acid treatment gave the desired lactam **18** as a mixture of diastereomers in 61% overall yield (>95% pure)[28] after trituration from ether.

Scheme 7



(*a*) CH_2Cl_2-MeOH, RT, 48h. (*b*) catalyst **I** (5 mol%), 1,2-dichloroethane, 80°C, 24h. (*c*) TFA, CH_2Cl_2, RT, 16h, 55% overall.

In conclusion, complimentary high-speed solid phase entries into the Freidinger lactam class of β-turn mimetics have been developed. The first and second generation approaches utilize novel, solid phase variants of the Fukuyama-Mitsunobu process and metathesis-promoted cyclative release as key steps. While the earlier methods utilize four-step linear sequences to access desired products, the described two-step (Ugi-RCM) approach procures its diversity, both constitutional and stereochemical, *via* a multi-component coupling process.

Acknowledgments. We thank Dr. Leszek Poppe and Mr. Stephan Gröger for their NMR assistance, Ms. Bhavana Shah and Ms. Anjali Bhide for their mass spectroscopy assistance.

Experimental

General Methods: All ^{1}H NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer. The following abbreviations were used to explain multiplicites: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; b, broad. IR spectra were recorded using a Nicolet FT-IR spectrometer using KBr. Low resolution mass spectra were obtained on a PE-SCIEX API-150 mass spectrometer under electrospray ionization conditions. High resolution mass spectra were recorded on a VG 7070EQ mass spectrometer under FAB or EI conditions (University of Colorado). Thin layer chromatography, flash chromatography and filtrations were performed with E. Merck silica gel (230-400).

Synthesis of Compound (4): To a suspension of resin **1** (0.5-0.7 mmol/g) in THF at RT was added the sulfonamide (3 equiv.), triphenylphosphine (3 equiv.) and diethylazodicarboxylate (3 equiv.), all as 0.2 M solutions in THF. After shaking 16h at RT, the mixture was diluted with 1 part CH_2Cl_2, and *n*-butylamine (1.0 M sol. in CH_2Cl_2; 10 equiv.) was added. After shaking for 1h at RT, the resin was filtered, washed with CH_2Cl_2, MeOH and air dried. The resin was re-suspended in dichloromethane at RT and treated with *t*-Boc-allyl glycine (3 equiv.), EtN(*i*-Pr)$_2$ (3 equiv.), and 1-methyl-2-chloropyridinium iodide (3 equiv). After heating at 40°C for 16h, the resin was washed with DMF, dioxane-water, MeOH-water, MeOH, CH_2Cl_2, air dried and re-suspended in degassed 1,2-dichloroethane. $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.1 M in 1,2-dichloroethane) was then added (5 mol% based on 80% conversion)[26] and the mixture was heated at 80°C for 16h. Cooling, filtration through silica gel and solvent evaporation gave the desired lactam.

Compound (4): (mixture of diastereomers) ^{1}H NMR ($CDCl_3$) δ 7.31-7.12 (m, 10H), 5.80-5.70 (m, 2H), 5.69-5.54 (m, 2H), 5.51 (dd, J = 10.5 Hz, 5.0 Hz, 1H), 5.36 (dd, J = 9.5 Hz, 6.5 Hz, 1H), 4.93-4.75 (m, 2H), 4.29-4.12 (m, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.63-3.29 (m, 2H), 3.04 (dd, J = 14.1 Hz, 9.5 Hz, 1H), 2.94 (dd, J = 14.1 Hz, 10.5 Hz, 1H), 2.70-2.55 (m, 2H), 2.55-2.46 (m, 2H), 2.29-2.13 (m, 2H), 1.91-1.17 (m, 2H), 1.45 (s, 9H), 1.44 (s, 9H). MS (electrospray): m/z 406.3 $(M+NH_4)^+$, 100%; 389.2 $(M+H)^+$ 60%.

Representative experimental for the solid phase synthesis of (8): To a suspension of resin **5** (0.5-0.7 mmol/g) in THF at RT was added the alcohol (3 equiv.), triphenylphosphine (3 equiv.) and diisopropylazodicarboxylate (3 equiv), all as 0.2 M solutions in THF. After shaking 16h at RT, the mixture was diluted with 1 part CH_2Cl_2, and *n*-butylamine (1.0 M sol. in CH_2Cl_2; 10 equiv.) was added. After shaking for 1h at RT, the resin was filtered, washed with CH_2Cl_2, MeOH and air dried. The resin was re-suspended in DMF at RT and treated with *t*-Boc-allyl glycine (3 equiv.), EtN(*i*-Pr)$_2$ (3 equiv.), and HATU ([O-(7-azabenztriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]) or PyBroP (bromo-tris(pyrrolidino)phosphonium hexafluorophosphate) (3 equiv.), all as 0.1 M solutions in DMF. After shaking 16h at RT (48h when PyBroP was used), the resin was washed with DMF, MeOH-water, MeOH, CH_2Cl_2, air dried and re-suspended in degassed 1,2-dichloroethane. $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.1 M in 1,2-dichloroethane) was then added (5 mol% based on 80% conversion)[26] and the mixture was heated at 80°C for 16h. Cooling, filtration through silica gel and solvent evaporation gave the desired lactam.

Table 1; entry 1: ^{1}H NMR (CDCl$_3$) δ 7.45-7.14 (m, 5H), 5.91 (bd, J = 7.3 Hz 1H), 5.78-5.71 (m, 1H), 5.67-5.60 (m, 1H), 4.99-4.97 (m, 1H), 4.70 (ABq, J_{AB} = 15Hz, $\Delta\nu_{AB}$ = 49.8, 2H), 4.37-4.30 (m, 1H), 3.38 (m, 1H), 2.35-2.26 (m, 1H), 1.49 (s, 9H). m/z 334.1 (M+NH$_4$)$^+$, 20%; 317.4 (M+H)$^+$ 100%.

Table 1; entry 2: ^{1}H NMR (CDCl$_3$) δ 7.59 (m, 4H), 5.82 (bd, J = 7.2 Hz, 1H), 5.80-5.72 (m, 1H), 5.68-5.59 (m, 1H), 5.68-5.59 (m, 1H), 5.10-5.02 (m, 1H), 4.73 (ABq, JAB = 15.0 Hz, $\Delta\nu$AB = 37.8, 2H), 4.41-4.35 (m, 1H), 3.35 (m, 1H), 2.78-2.70 (m, 1H), 2.35-2.22 (m, 1H), 1.45 (s, 9H). HRMS (EI) (M+H)$^+$ calc. for: 385.1739, found: 385.1723.

Table 1; entry 3: ^{1}H NMR (CDCl$_3$) δ 7.25-7.20 (m, 3H), 7.15-7.088, (m, 1H), 5.87 (bd, J = 7.6 Hz, 1H), 5.79-5.73 (m, 1H), 5.69-5.61 (m, 1H), 5.00 (m, 1H), 4.65 (ABq, JAB = 15.0Hz, $\Delta\nu$AB = 33.5, 2H), 4.40-4.30 (m, 1H), 3.34 (m, 1H), 2.76-2.67 (m, 1H), 2.35-2.23 (m, 1H), 1.47 (s, 9H). HRMS (EI) (M+H)$^+$ calc. for: 351.1475, found: 351.1465.

Table 1; entry 4: ^{1}H NMR (CDCl$_3$) δ 7.16 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 5.91 (bd, J = 6.5Hz, 1H), 5.77-5.67 (m, 1H), 5.66-5.57 (m, 1H), 4.96-4.92 (m, 1H), 4.60 (ABq, JAB = 14.8Hz, $\Delta\nu$AB = 33.5, 2H), 4.33-4.20 (m, 1H), 3.81 (s, 3H), 3.36 (m, 1H), 2.74-2.63 (m, 1H), 2.34-2.21 (m, 1H), 1.47 (s, 9H). HRMS (EI) (M+H)$^+$ calc. for: 346.1893, found: 346.1863.

Table 1; entry 5: ^{1}H NMR (CDCl$_3$) δ 5.87 (bd, J = 7.0Hz, 1H), 5.81-5.73 (m, 2H), 4.95-4.87 (m, 1H), 4.46-4.36 (m, 1H), 3.59 (dt, J = 13.4Hz, 7.3Hz, 2H), 3.41-3.37 (m, 1H), 3.38-3.29 (m, 1H), 2.71-2.62 (m, 1H), 2.28-2.17 (m, 1H), 1.46 (s, 9H), 1.36-1.26 (m, 2H), 0.94 (t, J = 7.3Hz, 3H). HRMS (EI) (M+H)$^+$ calc. for: 283.2021, found: 283.2036.

Table 1; entry 6: ^{1}H NMR (CDCl$_3$) δ 5.90 (bd, J = 6.5Hz, 1H), 5.81-5.70 (m, 2H), 4.97-4.87 (m, 2H), 4.15-4.05 (m, 1H), 3.44 (m, 1H), 2.71-2.63 (m, 1H), 2.27-2.17 (m, 1H), 1.47 (s, 9H), 1.11 (d, J = 6.0Hz), 1.10 (d, J = 6.0Hz). HRMS (EI) (M+H)$^+$ calc. for: 269.1865, found: 269.1857.

Table 1; entry 7: ^{1}H NMR (CDCl$_3$) δ 7.32-7.17 (m, 5H), 5.77 (bd, J = 6.4Hz, 1H), 5.64-5.57 (m, 2H), 4.89-4.81 (m, 1H), 4.28-4.12 (m, 1H), 3.75 (s, 3H), 3.41 (m, 1H), 2.98-2.91 (m, 1H), 2.55-2.47 (m, 1H), 1.92-1.80 (m, 1H), 1.44 (s, 9H). HRMS (EI) (M+H)$^+$ calc. for: 388.1998, found: 388.2014.

Table 1; entry 8: ^{1}H NMR (CDCl$_3$) δ 7.32-7.21 (m, 5H), 5.75-5.69 (m, 1H), 5.64-5.57 (m, 1H), 4.68 (s, 2H), 4.38-4.28 (m, 1H), 3.32 (m, 1H), 3.07-2.96 (m, 1H), 2.36-2.16 (m, 2H), 2.03-1.91 (m, 1H), 1.81-1.16 (m, 5H), 1.42-1.11 (m, 9H). HRMS (EI) (M+H)$^+$ calc. for: 311.2249, found: 311.2241.

Table 1; entry 9: ^{1}H NMR (CDCl$_3$) δ 7.41-7.16 (m, 5H), 5.79-5.72 (m, 1H), 5.66-5.59 (m, 1H), 4.67 (ABq, JAB= 15.3, $\Delta\nu$AB = 127, 2H), 4.36-4.26 (m, 1H), 3.35 (m, 1H), 2.82-2.75 (m, 1H), 2.24-2.13 (m, 1H), 1.05 (d, J = 6.4Hz, 3H), 1.02 (d, J = 6.4Hz, 3H). HRMS (EI) (M+H)$^+$ calc. for: 243.1623, found: 243.1625.

Table 1; entry 10: ^{1}H NMR (CDCl$_3$) δ 7.43-7.27 (m, 10H), 5.91-5.85 (m, 1H), 5.76-5.69 (m, 1H), 4.71 (s, 2H), 4.44 (dd, J = 12.0Hz, J = 3.7Hz, 1H), 4.33-4.26 (m, 1H), 3.49 (m, 1H), 2.99-2.88 (m, 1H), 2.67-2.59 (m, 1H). HRMS (EI) (M+H)$^+$ calc. for: 277.1467, found: 277.1455.

Preparation of Resin (5): To a suspension of resin **1** in THF at RT was added *t*-butyloxycarbonyl-2,4-dinitrobenzenesulfonamide (3 equiv.), triphenylphosphine (3 equiv.), and diisopropylazodicarboxylate (3 equiv.). After shaking for 12h, the resin is filtered and washed with THF, dichloromethane, methanol and dried to give **10**. Loading was calculated by treating an aliquot of the resin with excess *n*-butylamine in dichloromethane at RT. Filtration followed by evaporation gave the corresponding aniline **11** as a bright yellow solid (assumes quantitative conversion). To a suspension of resin **10** in dichloromethane at RT is added trifluoroacetic acid (equal part). After 12 h, the resin was filtered, washed with dichloromethane, methanol and dried to give **5**.

Preparation of Resin (13): To a suspension of resin **10** in dichloromethane at RT was added *n*-butylamine (10 equiv.). After stirring for 2h, the resin was filtered and washed with dichloromethane, THF, methanol and dried to give **12**. The resin was then re-suspended in dichloromethane at RT and trifluoroacetic acid (equal part) was added. After 12 h, the resin was filtered, washed with a 1% solution of triethylamine in dichloromethane, dichloromethane, methanol and dried to give **13**.

Representative experimental for the solid phase synthesis of (14): To a suspension of resin **13** in 1:1 dichloromethane-methanol was added racemic *t*-Boc-allyl glycine (5 equiv.), benzylisonitrile, (5 equiv.) and an aldehyde (5 equiv.). The mixture was shaken at RT for 48h at which time the resin was filtered, washed with dichloromethane, THF, methanol and dried. The resin was then suspended in degassed 1,2-dichloroethane, $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.1 M in 1,2-dichloroethane) (5 mol% based on 80% conversion)[27] added, and the mixture was heated at 80°C for 16h. Cooling, filtration through silica gel and solvent evaporation gave the desired lactam.

Table 2; entry 1: (mixture of diastereomers) ^1H NMR ($CDCl_3$) δ 7.37-7.17 (m, 5H), 6.28 (bs, 2H), 5.84-5.75 (m, 2H), 5.73-5.64 (m, 1H), 5.62-5.55 (m, 1H), 5.04-4.86 (m, 2H), 4.61-4.46 (m, 4H), 4.35-4.13 (m, 6H), 4.08-3.94 (m, 2H), 3.91-3.80 (m, 1H), 2.74-2.58 (m, 1H), 2.44-2.17 (m, 3H), 2.07-1.63 (m, 6H), 1.47 (bs, 9H), 1.46 (bs, 9H), 1.00 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.5Hz, 3H), 0.89 (d, J = 7.0Hz, 3H), 0.85 (d, J = 7.0Hz, 3H). m/z 434.4 $(M+NH_4)^+$, 100%; 416.6 $(M+H)^+$ 65%.

Table 2; entry 2: (mixture of diastereomers) ^1H NMR ($CDCl_3$) δ 7.42-7.08 (m, 20H), 6.31-6.17 (m, 2H), 5.84-5.53 (m, 6H), 5.18-5.04 (m, 4H), 5.06-4.95 (m, 2H), 4.86-4.77 (m, 2H), 4.55-4.34 (m, 2H), 4.29-4.10 (m, 2H), 4.04-3.94 (m, 2H), 3.74-3.56 (m, 2H), 2.78-2.51 (m, 4H), 2.44-2.23 (m, 2H), 2.10-1.88 (m, 2H), 1.48 (bs, 9H), 1.47 (bs, 9H). m/z 495.6 $(M+NH_4)^+$, 100%; 477.4 $(M+H)^+$ 65%.

Table 2; entry 3: (mixture of diastereomers) ^1H NMR ($CDCl_3$) δ 7.43-7.23 (m, 20H), 6.28 (bs, 1H), 6.11 (bs, 1H), 5.87-5.64 (m, 4H), 5.60-5.53 (m, 1H), 5.30-5.22 (m, 1H), 5.08-4.93 (m, 2H), 4.59-4.44 (m, 6H), 4.38-4.25 (m, 1H), 4.00-3.90 (m, 1H), 3.68-3.57 (m, 2H), 2.76-2.61 (m, 2H), 2.32-2.12 (m, 2H), 1.48 (bs, 9H), 1.47 (bs, 9H). m/z 467.8 $(M+NH_4)^+$, 100%; 449.6 $(M+H)^+$ 55%.

Preparation of Compound (18): The procedure for the synthesis of **14** was used. Following the ring closing metathesis step, the product was treated with a 1:1 solution of dichloromethane-trifluoroacetic acid for 16h. Compound **18** was obtained as a mixture of diastereomers after solvent evaporation and trituration from ether. MS (electrospray): (mixture of diastereomers) m/z 368.2 $(M+NH_4)^+$ 100%.

References and Notes

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21. (S)-Allyl glycine and (S)-methyl-2-hydroxy-3-phenyl propionate were used and a single diastereomeric product (**8**) was obtained, presumably with inversion of configuration during the loading step.
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