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A Second Generation Solid Phase Approach to Freidinger Lactams: Application of Fukuyama's Amine Synthesis and Cyclative Release *via* Ring Closing Metathesis

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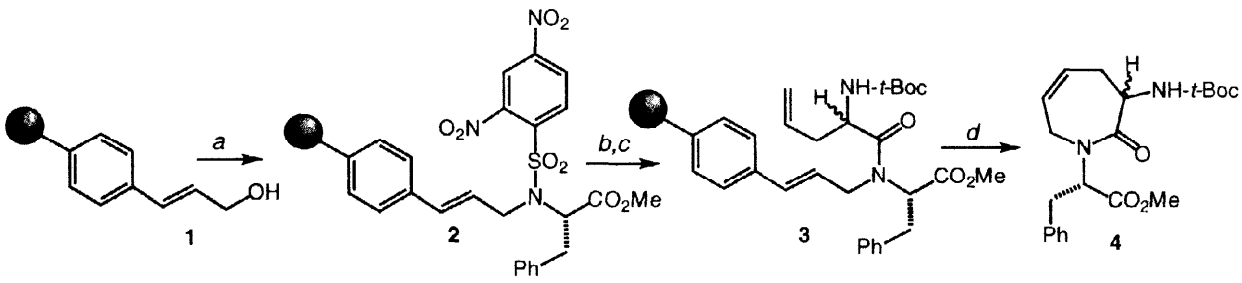
Abstract: A high-speed solid phase synthesis of Freidinger lactams was accomplished using a novel variant of Fukuyama's amine synthesis and ring closing metathesis-promoted cyclative cleavage as key steps.

In a previous communication,[1] we reported an efficient solid phase approach[2,3] to the synthesis of Freidinger lactams **4**[4,5] utilizing the Fukuyama modification of the Mitsunobu reaction[6,7] and ring closing metathesis[8] (cyclative cleavage event) as key steps according to Scheme 1. While the approach is adequate with regard to

Scheme 1



(*a*) (S)-phenylalanine methyl ester-2,4-dinitrobenzenesulfonamide, DEAD, PPh_3, THF, RT, 16h, 69%.[9] (*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*) $(Cy_3P)_2Cl_2Ru$=CHPh (5 mol% based on loading),[9] 1,2-dichloroethane, 80°C,16h,16% from **1**.

technical ease, overall chemical yields and purity of the desired products, the absence of commercially available 2,4-dinitrobenzenesulfonamides prompted us to explore an alternative reaction paradigm utilizing a nucleophilic resin component in the initial Fukuyama-Mitsunobu loading step (Scheme 2). We anticipated the described umpolung approach would allow us to leverage both the enormous pool of commercially available alcohols and the versatility of the Fukuyama-Mitsunobu procedure to render a more practical high-speed entry into this important peptidomimetic class. Thus, alkylation of the 2,4-dinitrobenzenesulfonamide resin **5** with an alcohol input using Fukuyama-Mitsunobu conditions[6] 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] (RCM) with concomitant substrate cleavage provided the desired lactam **8**.

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Scheme 2.

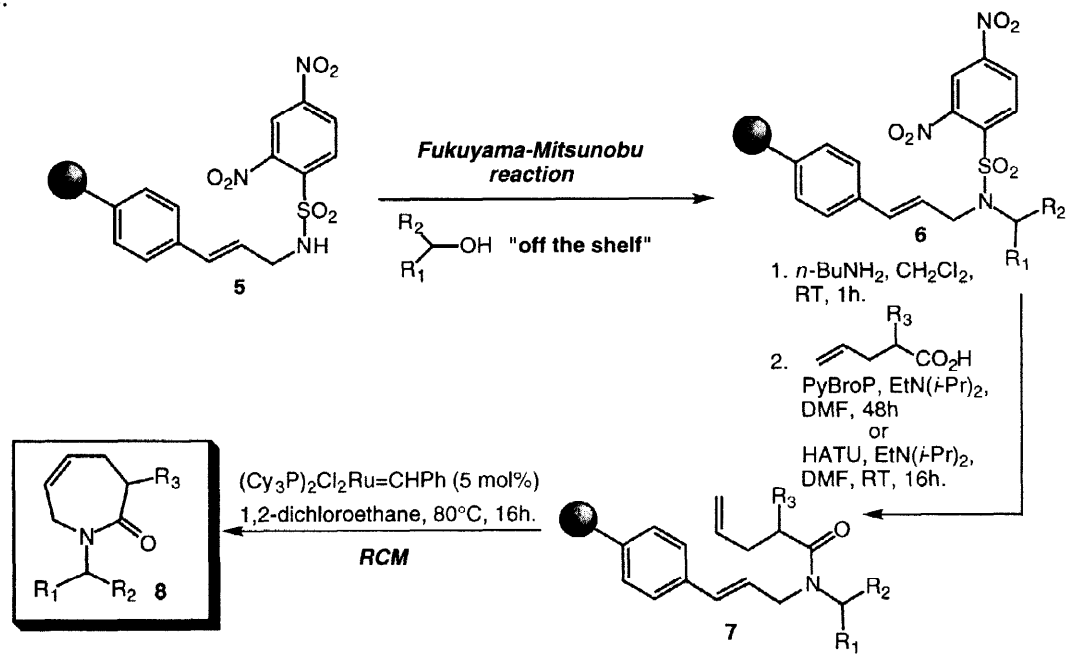


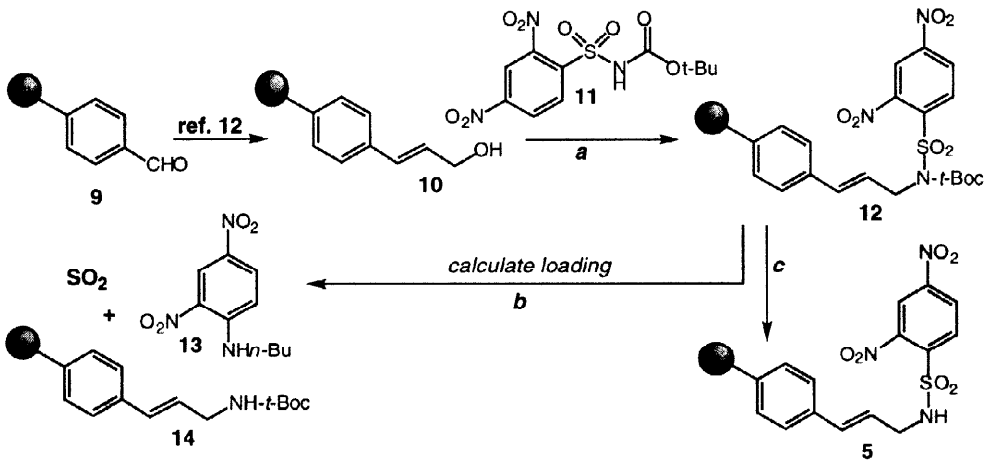
Table 1. Synthesis of Freidinger lactams **8** *via* Scheme 2:

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[10]	Ph	CO_2Me	NH*t*-Boc	23
8	Ph	H	(C_6H_{11})-CH_2CH_2	34
9	Ph	H	*i*-Pr	35
10	Ph	H	Ph	15

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) afforded the desired products in good overall yield and in excellent purity.[11] 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).

The 2,4-dinitrobenzenesulfonamide resin **5** was prepared according to Scheme 3. Alkylation of the known *trans*-cinnamyl alcohol resin **10**[12] with the *t*-Boc-protected 2,4-dinitrobenzenesulfonamide **11**[6] gave resin **12**. Loading was conveniently assessed at this stage *via* sulfonamide cleavage and gravimetric analysis of the resulting *N*-(*n*-Butyl)-2,4-dinitroaniline **13**. Subsequent treatment of **12** with trifluoroacetic acid gave the desired cinnamylamine-2,4-dinitrobenzenesulfonamide resin **5** in multigram quantities and in excellent overall yield.[13]

Scheme 3.



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

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 DIAD, 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[14] ([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)[15] and the mixture was heated at 80°C for 16h. Cooling, filtration through silica gel and solvent evaporation gave the desired lactam.

In conclusion, an efficient, high-speed solid phase approach to the synthesis of Freidinger lactams has been developed which utilizes a novel, solid phase variant of the Fukuyama-Mitsunobu process and metathesis-promoted substrate release as key steps. The method is underscored by its versatility, operational simplicity and its ability to employ readily available inputs.

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9. Based on recovered *N*-(*n*-Butyl)-2,4-dinitroaniline from sulfonamide removal with *n*-butylamine (assumes quantitative cleavage): see reference 6.

10. (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.

11. Purity levels ranged from 90-95% based on ^{1}H NMR analysis at 400 MHz. Detectable impurities incuded: diisopropylethylamine•HPF_6 (5-10%) when HATU was used despite rigorous washing of the resin following acylation, and tricyclohexylphosphine oxide < 5%.

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13. The amount of recovered of **13** indicated a quantitative conversion of **10** to **12** and I.R. analysis of of resin **5** following TFA treatment indicated a complete disappearance of the characteristic carbonyl stretch.

14. HATU and PyBroP gave similar yields. However, while the less reactive PyBroP required longer reaction times, desired products were obtained free of ammonium salts (see reference 11).

15. Based on solution phase model studies using *trans*-cinnamyl amine.