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Ring-closing metathesis to a divergent endocyclic sulfonamide template

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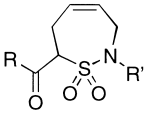
Abstract

The efficient synthesis of a novel endocyclic sulfonamide template via a ring-closing metathesis methodology is reported. A solid-supported variant of the Grubbs catalyst is shown to be effective and the suitability of the template for both combinatorial derivatization and potential incorporation into peptidomimetics is demonstrated. © 2000 Published by Elsevier Science Ltd.

The sulfonamide moiety is a common constituent of combinatorial small molecule libraries due to its relative ease of derivatization and ubiquitous biological activity. The motif is a direct isostere of the amide bond and it favorably displays significantly different physical characteristics.[1] The tetrahedral sulfonamide can provide a hydrolytically stable analogue of the transition state adduct formed during the enzymatic hydrolysis of an amide linkage in a peptide.[2] In addition, the SO_2NH junction may alter the conformation of a peptide.[3] Cyclic, conformationally constrained amino acids (i.e. proline,[4] Freidinger lactams,[5] sugar amino acids[6]) can alter or induce a short peptide's specific secondary structure. The incorporation of a sulfonamide into novel peptidomimetics has thus received attention[7] and cyclic sulfonamide moieties may provide an area of further interest.

As part of a program to develop highly functionalized templates for combinatorial derivatization we report the synthesis of a novel, endocyclic sulfonamide template **1** via a ring-closing metathesis (RCM) reaction.



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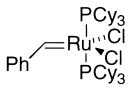

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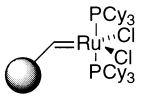

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The scope and functional group tolerance of the principal RCM catalysts developed by Schrock and Grubbs has been extensively investigated and reviewed.[8] However, there are few

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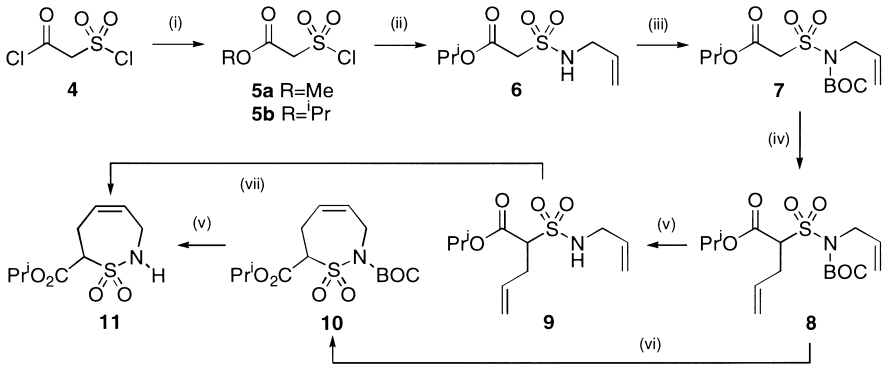
examples for RCM of substrates bearing a sulfonamide.[9] The Grubbs ruthenium catalyst **2** is commercially available and particularly robust.† However, its use often requires repeated chromatography of products to remove ruthenium residues and it is non-recyclable from the reaction mixture. Recently, Barrett addressed these issues by developing a polystyrene bound analogue **3**.[10] We chose to compare the effectiveness of the catalysts **2** and **3** for endocyclic sulfonamide metathesis.



Scheme 1. (i) MeOH or ^{i}PrOH, Et_2O, 0°C; (ii) **5b**, allylamine, CH_2Cl_2, 0°C; (iii) BOC_2O, DMAP, Et_3N, CH_2Cl_2; (iv) allyl bromide, K_2CO_3, DMF; (v) TFA/CH_2Cl_2; (vi) 5 mol% **2** or **3**, DCE, 80°C; (vii) 5 mol% **2** or **3**, DCE

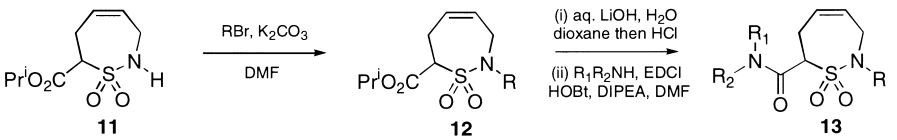
The synthetic strategy towards template **1** necessitated both introduction of an allyl group α to the carbonyl and formation of an *N*-allyl sulfonamide from the commercially available chlorosulfonylacetyl chloride **4** (Scheme 1). Reaction of the acid chloride **4** with 1 equivalent of methanol or isopropyl alcohol in ether at 0°C gave the esters **5a** and **5b**, respectively, in quantitative yield. Treatment of the methyl ester **5a** with a secondary or hindered amine afforded selective reaction with the sulfonyl chloride.[11] However, reaction with allylamine yielded complex mixtures. In contrast, the bulky isopropyl ester **5b** reacted with allylamine to give the sulfonamide **6** (91%) in excellent yield. The nitrogen of sulfonamide **6** was protected as its *tert*-butyloxycarbonyl (BOC) derivative **7** (92%) upon treatment with BOC_2O and triethylamine in the presence of 4,4-dimethylaminopyridine in dichloromethane. Subsequent mono-*C*-allylation α to the sulfone motif of **7** was effected with allyl bromide in DMF in the presence of potassium carbonate to give the racemic RCM substrate mixture **8** in 93% yield.

Exposure of the diolefin **8** to either ruthenium catalyst **2** or **3**[12] in 1,2-dichloroethane (0.04 M) at 80°C for 24 h resulted in conversion to the seven-membered cyclic product **10** (79 and 84%, respectively). The BOC group of **10** was easily removed upon treatment with TFA/dichloromethane to afford the endocyclic, divergent sulfonamide **11** (90%).[13] Alternatively, removal of the BOC protection from the acyclic substrate **8** prior to RCM using TFA/dichloromethane gave the diolefin **9** in 97% yield. In this case, RCM of **9** mediated by either **2** or **3**[12] in 1,2-dichloroethane (0.04 M) was extremely efficient, proceeding at room temperature in 30 min to afford the cyclic sulfonamide **11** in excellent yield (93 and 95%, respectively). This observation is in contrast with reported RCM reactions which indicate that the efficiency of the olefin metathesis improves with increased bulk at a developing endocyclic nitrogen center.[14] Consideration of the use of catalysts **2** and **3** showed that both were equally active in mediating endocyclic sulfonamide

† Ruthenium catalyst **2** is available from Strem Chemicals, Inc. at $60.00/g.

metathesis. However, the solid bound catalyst **3** was favorable since the crude metathesis products obtained via its use required only a single silica gel chromatographic purification to completely remove the characteristic color of ruthenium residue impurities. The use of **2**, particularly on a large scale typically required two or three chromatographic purifications to remove the brown ruthenium residue color. In addition, **3** could be regenerated for further use from the reaction mixture by simple filtration. However, in contrast to the reports of Barrett the recovered catalyst **3** was markedly less active.[10] RCM of **8** and **9** in the presence of regenerated **3** gave the products **10** and **11** in lower yields (46 and 54%, respectively, 95 and 99% over recovered starting material) than the reactions using fresh catalyst **3** (84 and 95%, respectively).

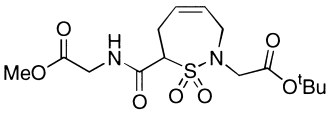
The diverse nature of the endocyclic sulfonamide template **11** and its suitability as a scaffold for combinatorial library generation was demonstrated through matrix derivatization of two of the three available functional groups (Scheme 2). Thus, mono-alkylation of the sulfonamide **11** with a set of alkyl bromides in DMF in the presence of potassium carbonate proceeded in good yield (83–95%) to afford the *N*-substituted derivatives **12**[15] (no *C*-alkylation was observed). Subsequent hydrolysis of esters **12** with aqueous lithium hydroxide in a mixture of water/dioxane followed by acidification with hydrochloric acid gave crude acids, which were coupled with a set of amines under standard peptide coupling conditions;[16] EDCI, HOBt, DIPEA in DMF. All 16 products **13** were obtained in $>95\%$ purity after HPLC purification.[17]



11 **12** **13**

Scheme 2. RBr = *tert*-butyl bromoacetate; 4-bromobenzylbromide; cyclopentyl bromide; 4-bromomethylbiphenyl R_1R_2NH = 2-aminothiazole; piperidine; glycine methyl ester; *N*,*N*,*N*′-trimethyl-ethylenediamine

Of particular interest was the glycine methyl ester-derived compound **14**.[18] The orthogonally protected ester groups of **14** should facilitate ready peptide formation at either *C*-terminus which highlights the potential ease with which **14** and thus the parent sulfonamide template **1** could be incorporated into a peptidomimetic.



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In summary, we have effected the efficient synthesis of a highly functionalized endocyclic sulfonamide template **11** via a RCM reaction and demonstrated its utility for both combinatorial library generation and potential peptidomimetic incorporation. In addition, use of the solid-supported ruthenium catalyst **3** was evaluated and shown to facilitate high yielding sulfonamide metathesis, simple purification of products and reasonable catalyst recovery. Application of this methodology to eight-membered ring analogues and further combinatorial library generation including automated approaches will be reported in due course.

Experimental procedure for compound **11**: 1-Hexene (1.6 μl, 12.6 μmol) and catalyst **3** (90 mg, 5 mol%) were added to a stirred solution of compound **9** (66 mg, 0.25 mmol) in 1,2-dichloroethane (6 ml). The reaction mixture was stirred at room temperature for 30 min. TLC (ethyl acetate:hexane, 1:3) indicated complete conversion of the starting material (R_f 0.5) to a single

product (R_f 0.3). The catalyst was recovered by filtration (dichloromethane eluant) and the filtrate concentrated in vacuo. The slightly colored residue was purified by flash chromatography (ethyl acetate:hexane, 1:3) to yield **11** (56 mg, 95%) as a white solid.[13]

Acknowledgements

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12. Compound **3** was prepared as reported and its use in RCM was accompanied by the addition of 1-hexene to the reaction mixture to facilitate regeneration of the catalyst, as described in Ref. 10a. The loading of **3** was 1.4 mmol/g and had an active site composition of 10 mol%.
13. Selected data for **11**; δ_H ($CDCl_3$): 1.26–1.30 (6H, m, $CH(CH_3)_2$), 2.84 (2H, b-d, CH_2CHSO_2), 3.63–3.80 (2H, m, NCH_2), 4.06 (1H, m, CH_2CHSO_2), 4.90 (1H, b-s, NH), 5.08 (1H, sept, $CH(CH_3)_2$), 5.88, 6.03 (2H, 2×m, CH=CH); δ_C ($CDCl_3$): 21.8, 21.8 (2×q, $CH(CH_2)_2$), 26.3 (t, CH_2CHSO_2), 40.9 (t, NCH_2), 64.1 (d, CH_2CHSO_2), 70.5 (d, $CH(CH_3)_2$), 129.2, 132.8 (2×d, CH=CH), 166.0 (C=O); *m/z* (TIC): 234.2 ($M+H^+$), 251.0 ($M+NH_4^+$); HRMS+Na^+: 256.0615. $C_9H_{15}O_4NS$+Na requires: 256.0614.
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15. In the case of the less reactive cyclopentyl bromide the reaction was heated to 75°C to achieve completion. Selected data for **12**: (RBr = cyclopentyl bromide); δ_H ($CDCl_3$): 1.29 (6H, a-t, $CH(CH_3)_2$), 1.45–1.69 (6H, m, $CH_2CH_2CH_2CH_2$), 1.83–1.96 (2H, m, $CH_2CH_2CH_2CH_2$), 2.58, 2.89 (2H, 2×m, CH_2CHSO_2), 3.70–3.91 (3H, m, NCH_2CH, CH_2CHSO_2), 4.24 (1H, m, NCH), 5.09 (1H, sept, $CH(CH_3)_2$), 5.85–5.88 (2H, 2×m, CH=CH); δ_C

($CDCl_3$): 21.7, 21.8 (2×q, $CH(CH_3)_2$), 23.1, 23.4, 30.4, 31.2 (4×t, $CH_2CH_2CH_2CH_2$), 26.4 (t, CH_2CHSO_2), 41.3 (t, NCH_2), 59.4 (d, NCH), 67.8 (d, CH_2CHSO_2), 70.24 (d, $CH(CH_2)_2$), 128.4, 132.4 (2×d, CH=CH), 165.5 (s, C=O); *m*/*z* (TIC): 302.4 ($M+H^+$); HRMS+Na^+: 324.1239. $C_{14}H_{23}O_4NS$+Na requires: 324.1240.

16. The acid labile *tert*-butyl acetate-derived hydrolysis mixture was not subjected to acidification. The carboxylate salt was used in subsequent amidation.
17. Isolated yields of the matrix compounds **13** ranged from 18–85% for the three-step procedure from **11**.
18. Selected data for **14**: δ_H (CD_3OD): 1.48 (9H, s, $C(CH_3)_3$), 2.66, 2.80 (2H, 2×m, CH_2CHSO_2), 3.73 (3H, s, CO_2CH_3), 3.78–4.13 (7H, m, NCH_2CH, CH_2CHSO_2, $CH_2CO_2C(CH_3)_3$, $CH_2CO_2CH_3$), 5.98, 6.10 (2H, 2×m, CH=CH); δ_C (CD_3OD): 25.9 (t, CH_2CHSO_2), 27.1 (q, $C(CH_3)_3$), 41.0, 44.8, 49.5 (3×t, NCH_2, $CH_2CO_2C(CH_3)_3$, $CH_2CO_2CH_3$), 51.5 (t, CO_2CH_3), 65.4 (d, CH_2CHSO_2), 129.8, 132.1 (2×d, C=CH), 168.5, 170.2 (2×s, 2×C=O); *m*/*z* (TIC): 321.2 ($M+H^+-C(CH_3)_3$), 377.2 ($M+H^+$); HRMS-$C(CH_3)_3$+Na^+: 343.0582. $C_{15}H_{24}O_7N_2S$-$C(CH_3)_3$+Na requires: 343.0570.