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A dual metathesis route to oligomeric sulfonamides

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Abstract—A strategy employing both ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP) as routes to synthesizing oligomeric sulfonamides is described. Amino acid-derived α,β-unsaturated γ-sultams, containing either *exo*-cyclic or γ-*endo*-cyclic stereogenic centers, are generated via RCM. These sultams undergo stereoselective Diels–Alder reactions to yield *endo*-norbornenyl sulfonamides as the major diastereomers. Subsequent ROMP rapidly produces sulfonamide-based oligomers.

Sulfonamides have long been valued for their chemical and biological utility.[1] Numerous pharmaceutical agents contain sulfonamides as key functional groups[2] due to their desirable physical properties, including hydrolytic stability, electron-withdrawing ability, and mild acidity. These properties have also been exploited in the construction of robust auxiliaries,[3] catalysts,[4] ligands,[5] and protecting groups.[6] A number of reports have recently emerged utilizing the sulfonamide group in the construction of novel biopolymers,[7,8] polymer-bound reagents,[9] and other interesting materials.[10] Our interest in the synthesis of phosphorus and sulfur heterocycles has led us to investigate a dual metathesis approach to sulfonamide oligomers, on which we now report.

Previous routes to polymeric sulfonamides have been limited to traditional modes of polymerization or post-polymerization functionalization. Ring-opening metathesis polymerization (ROMP)[11] provides an attractive route to the construction of oligomeric sulfonamides. ROMP has been used to produce highly functionalized polymers of controllable length, including a number of interesting bio-oligomeric scaffolds using either Schrock molybdenum-based alkylidenes[12] or Grubbs ruthenium-based alkylidenes.[13] These diverse scaffolds include oligomers based on sugars,[14] amino acids,[15] antibiotics,[16] and nucleic acids.[17] In addition, a number of interesting ROMP reagents have also been reported.[18] The use of ROMP to produce sulfonamide oligomers, however, has been limited.[19]

The strategy employed herein (Fig. 1) focuses on amino acid-derived norbornenyl sulfonamides **5**–**8**, formed from a ring-closing metathesis (RCM) reaction/Diels–Alder sequence. Sulfonamides with either *exo*-cyclic (**5**–**7**) or γ-*endo*-cyclic (**8**) stereogenic centers can be formed with this method. A subsequent ROMP yields sulfonamide oligomers (**1**–**4**). This flexible approach unites the chemical stability of sulfonamides with the synthetic versatility of metathesis.

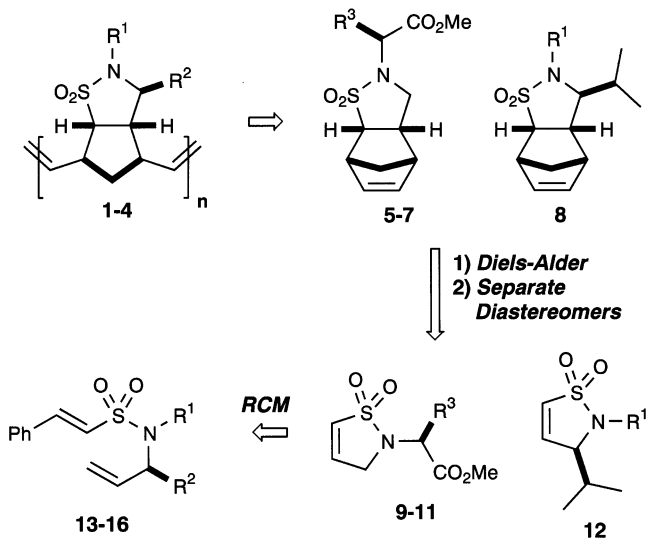

Figure 1. RCM/ROMP strategy.

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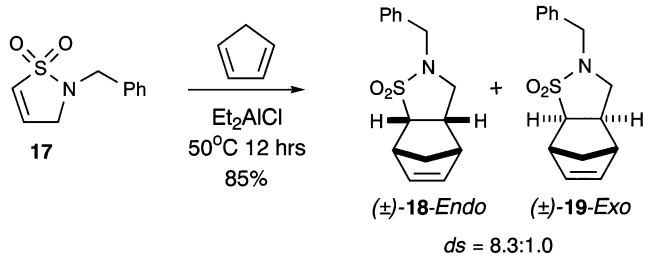
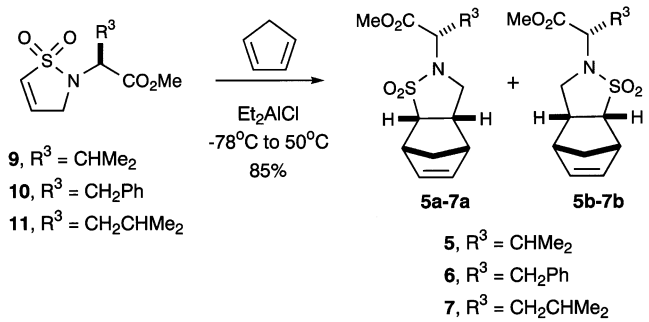


Scheme 1.

We recently reported a rapid and flexible RCM strategy to prepare a variety of cyclic sulfonamides (sultams) **9**–**11** (Scheme 2) and **17** (Scheme 1).[20] Further exploration of the reactivity of these sultams revealed they underwent facile Diels–Alder reactions with cyclopentadiene under Lewis acid catalysis with good *endo*:*exo* selectivity (Scheme 1). Although there are many examples of Diels–Alder reactions with vinyl sulfonates,[21] there are relatively few examples with vinyl sulfonamides.[22] Furthermore, examples with sultams were unknown until recently, when Chan, Lee and co-workers reported that $Ti(OEt)_4$ catalyzed the reaction of a number of dienes with sultams.[23] Their reactions were reported to occur over a period of 4–9 days with excellent *endo*:*exo* selectivity (they report from 10:1 to complete *endo* selectivity).

Our initial Diels–Alder reactions were carried out with the benzylamine-derived sultam **17** and the results of these reactions led us to investigate the amino acid-derived systems **9**–**11** (Scheme 2). Not surprisingly, the sultam diastereofacial selectivity imparted by the external stereogenic center was poor, although the *endo*:*exo* diastereoselectivity was good (Table 1). The two *endo* diasteromers **5**–**6a**,**b** were readily separated via column chromatography on large scale, and X-ray crystallography allowed for the unambiguous assignment of the *endo* diastereomers **5**–**6a**,**b** (Fig. 2).[24]



Scheme 2.

Table 1.

Substrate	*Endo* (a:b)	*Exo*[a] (c:d)
9	8.4 (1.07:1)[b]	1.0 (1.4:1.0)[b]
10	9.8 (1.0:1.3)[c]	1.00[c]
11	8.2 (1.41:1.0)[b,d]	1.00[b]

[a] Absolute configurations of the *exo* diastereomers have not been determined.
[b] Ratios determined by GC analysis.
[c] Ratios determined by ^1H NMR analysis of olefinic protons.
[d] Absolute configurations of the leucine *endo* diastereomers have not been determined.

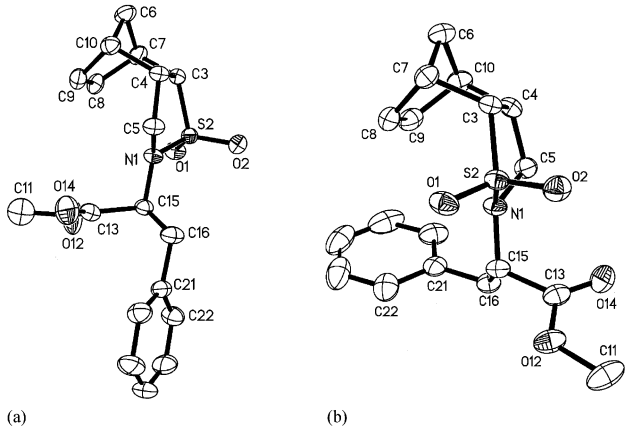


Figure 2. X-Ray crystal structure of **6a** and **6b**, respectively.

ROMPs were then carried out on both diastereomeric mixtures as well as on individual *endo* diastereomers of sulfonamides **5**, **6**, and **7** using 1–20 mol% of the Grubbs benzylidene catalyst and quenching with ethyl vinyl ether.[25] These reactions cleanly produced an array of oligomeric sulfonamides **1**–**3** as evident by GPC and MALDI-TOF analysis (Fig. 3). Both **5** and **6** were polymerized with 0.5 mol% of the second generation Grubbs catalyst to yield oligomers of approximately 200 repeating units. The PDI of poly-**5** and poly-**6** were 1.1 and 1.2, respectively, as determined by multiangle light scattering measurements. The resulting sulfonamide oligomers[26] are completely soluble in many organic solvents (tetrahydrofuran (THF), CH_2Cl_2, toluene, etc.), yet can be readily precipitated with methanol or pentane.

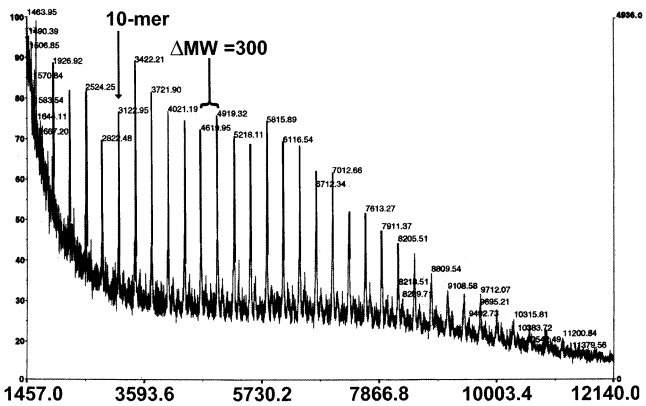
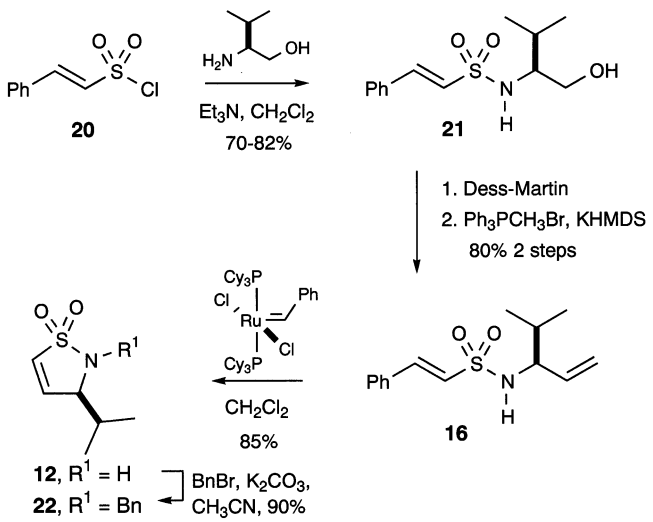


Figure 3. MALDI-TOF analysis of oligomeric **5** produced using 10 mol% of catalyst.

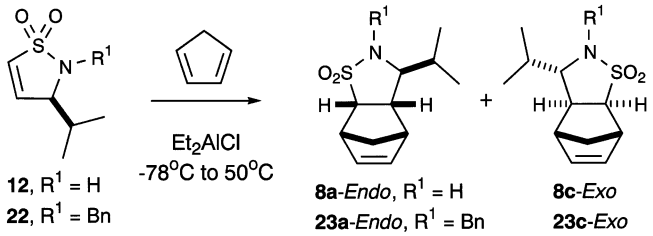
Further expansion of this RCM/ROMP approach prompted the synthesis of α,β-unsaturated γ-sultams **12**, **22** bearing an internal stereogenic center at the γ-position (Scheme 3). Previous results of cycloadditions with butenolides[27] led us to believe that the internal center in sultam **12** would enhance the diastereofacial selectivity of the Diels–Alder reaction. In addition, the resulting sultam would have a free N–H for further manipulation.

The valine-derived vinyl sultam **12** was synthesized from β-styrenesulfonyl chloride **20**[28] (Scheme 3). Slow addition of a solution of the sulfonyl chloride in CH_2Cl_2 to a solution of valinol in CH_2Cl_2 in the presence of Et_3N at 0°C afforded the addition product **21** in good yield. The main side product was a 2:1 (sulfonyl:valinol) adduct as determined by mass spectroscopy. The bis-sulfonylated product was formed in amounts dependent on the rate of RSO_2Cl addition as well as the concentration of the reaction mixture. The formation of this 2:1 adduct could be avoided by TBS-protection of the valinol-OH prior to RSO_2Cl addition. Swern or Dess Martin oxidation of **21** followed by a Wittig reaction afforded the RCM template **16** in good yield. The RCM reaction of **16** afforded the cyclic sulfonamide **12**. Though sluggish, the reaction proceeded cleanly and the product was isolated in good yield. Subsequent benzylation of sultam **12** resulted in **22**.



Scheme 3.

Sultams **12** and **22** underwent cycloaddition with cyclopentadiene under Lewis acid catalysis (Scheme 4). These reactions proceeded with complete facial selectivity arising from the approach of the cyclopentadiene *anti* to the isopropyl group. Interestingly, the yield and *endo*:*exo* ratio obtained were strongly temperature dependant, as shown in Table 2. The *endo* adducts **8a** and **23a** were formed as the major diastereomers in each case, with X-ray crystallography providing unambiguous proof of the stereochemistry for **8a** (Fig. 4). The *exo* isomers **8c** and **23c**, also arising from the approach of the cyclopentadiene *anti* to the isopropyl group, were tentatively assigned the structures shown in Scheme 4. It was also found that, whereas **8a** and **8c** ($R^1 = H$) were nearly impossible to separate cleanly, **23a** and **23c** ($R^1 = Bn$) could be readily separated via column chromatography.



Scheme 4.

Table 2.

Entry	Temperature (°C)	*Endo* (a:b)[a]	*Exo* (c:d)[a]	Conversion (%)
12	−78	N.a.	N.a.	0
12	−25	11.1 (>99:1)	1 (>99:1)	8
12	25	5.1 (>99:1)	1 (>99:1)	25
12	50	5.1–6.9 (>99:1)	1 (>99:1)	99
12	77–80	3.5 (>99:1)	1 (>99:1)	99
22	50	4.6 (>99:1)	1 (>99:1)	99

[a] Ratios determined by gas chromatography (GC) analysis.

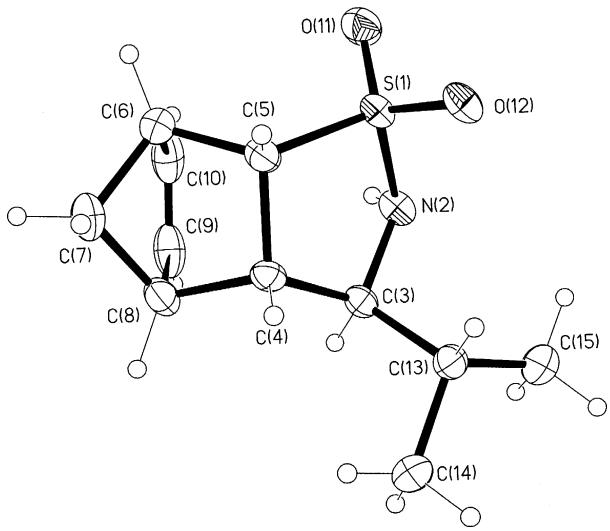


Figure 4. X-Ray crystal structure of **8a**.

The mixture of **8a** and **8c** was treated with Grubbs benzylidene catalyst[25] and the resulting polymer (**4a**) was analyzed by MALDI-TOF mass spectroscopy, showing again an array of oligomeric sulfonamides. Compound **23a** could also be treated with Grubbs benzylidene catalyst to produce polymer **4b**.

In conclusion, it has been shown that amino acid-derived α,β-unsaturated γ-sultams, generated via RCM, undergo selective Diels–Alder reactions to produce norbornenyl sulfonamides. These entities efficiently undergo ROMP, yielding oligomeric sulfonamides.

Acknowledgements

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24. X-Ray structures of the valine-derived sulfonamide *endo* diastereomers **5a** and **5b** are also available upon request. The absolute configurations of the leucine-derived *endo* diastereomers **7a**,**b** have not been unambiguously determined.
25. Polymerizations were monitored via thin layer chromatography (TLC) and considered complete when all monomer had been consumed resulting in the appearance of a lone baseline spot.
26. ^{1}H NMR data for **5b**: (400 MHz, $CDCl_3$) 6.33 (dd, 1H, $J=5.6$, 2.9 Hz), 6.27 (dd, 1H, $J=5.5$, 2.9 Hz), 3.75 (dd, 1H, $J=9.4$, 3.9 Hz), 3.71 (s, 3H), 3.67 (dd, 1H, $J=9.9$, 8.6 Hz), 3.52 (d, 1H, $J=10.5$ Hz), 3.41 (bs, 1H), 3.17–3.14 (ddd, 1H, $J=9.0$, 4.0, 1.4 Hz), 3.10 (bs, 1H), 2.87 (dd, 1H, $J=10.1$, 1.3 Hz), 1.95–1.89 (m, 1H), 1.61 (bd, 1H, $J=8.9$ Hz), 1.38 (d, 1H, $J=8.9$ Hz), 0.95 (d, 3H, $J=6.6$ Hz), 0.87 (d, 3H, $J=6.6$ Hz); ^{1}H NMR of oligomeric **5b**: (500 MHz, $CDCl_3$) 6.15–6.09 (m, 0.25H), 6.04 (dd, 0.75H, $J=15.1$, 7.5 Hz), 5.58 (dd, 1H, $J=15.2$, 7.3 Hz), 3.8 (m, 1H), 3.71 (s, 3H), 3.58 (m, 1H), 3.47 (m, 1H), 3.22 (m, 2H), 2.95–2.75 (m, 2H), 2.15–1.85 (m, 3H), 1.02 (bd, 3H, $J=6.4$ Hz), 0.94 (bd, 3H, $J=6.3$ Hz).
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