Synthesis of Cyclic Amino Acid Derivatives via Ring Closing Metathesis on a Poly(ethylene glycol) Supported Substrate

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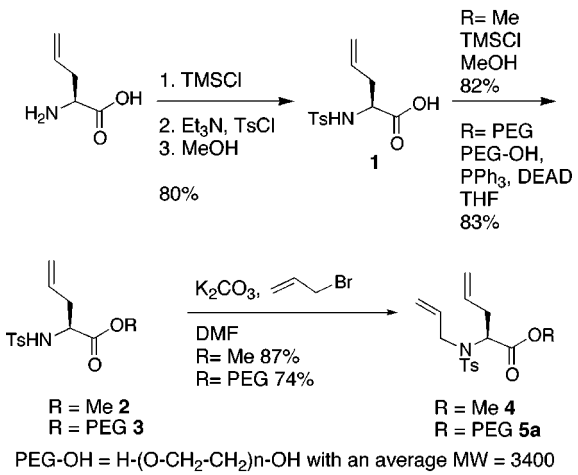
Liquid-phase organic synthesis where soluble polymers such as poly(ethylene glycol) (PEG) are used as polymeric support is a practical alternative to solid-phase organic synthesis (SPOS).[1] Recently we have developed several PEG-supported syntheses of amino acid derivatives[2] and we have studied the effect that can be induced by the polymer. Because of its polyoxygenated structure, the polymer exerts an influence on the reactivity of the supported reacting center as well as on the reagents or catalysts used during the course of the synthesis. We have shown that a synthesis of arylglycine using organozinc reagents could not be adapted on PEG because of the detrimental effect of the polymer.[2e] On the contrary, in the case of a Heck reaction used in the synthesis of glutamic acid analogues, PEG has an accelerating effect on the course of the reaction.[2c]

Ring closing metathesis (RCM) has emerged as a powerful tool in organic synthesis for generating cyclic structures via C−C bond formation.[3] Recently this reaction has been adapted to SPOS,[4] but to our knowledge, no reaction of RCM on soluble PEG has been published. In the following report, we present the results obtained in investigating the compatibility of RCM reaction conditions with the presence of PEG, and we describe the synthesis of various amino acid derivatives using this method.

Scheme 1



Since our interest lies in the synthesis of amino acids and peptidomimetics, we chose to adapt first the synthesis of a cyclic amino acid,[5] and we compared the results obtained with the molecule supported on PEG with the same reaction carried out in solution. Linear substrates **4** and **5a** were synthesized as described in Scheme 1.

Since it was preferable to obtain at each step of the synthesis on the soluble support complete conversion of the starting material to the expected product, we decided to use a tosyl group as a nitrogen-protecting group which also makes the amine proton more acidic for the alkylation reaction. Tosylation of commercially available (L)-allylglycine was adapted from a known procedure.[6] Esterification of **1** with MeOH in the presence of TMSCl yielded **2**, which was smoothly *N*-alkylated with allyl bromide in the presence of potassium carbonate to give **4**. Bifunctional poly(ethylene glycol) with an average mass of 3400 was used as the soluble support because it presents the right compromise between loading and good precipitation properties.[2b] Since the Ts group made allylglycine sensitive to racemization, we preferred to avoid classical coupling conditions and we chose a Mitsunobu reaction for anchoring the Ts allylglycine **1** on both of the hydroxyl groups of the PEG to give **3**.[7] Alkylation with allyl bromide in the presence of potassium carbonate yielded the PEG-supported *N*-allyl allylglycine **5a**.

Linear substrates **4** and **5a** were submitted to classical RCM reaction conditions using Grubbs' catalyst in various amounts (Scheme 2) and the results are presented in Table 1.

(1) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

(2) (a) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 821. (b) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Comb. Chem.* **2000**, *2*, 134. (c) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *C. R. Acad. Paris Sér. IIc* **1998**, *1*, 777. (d) Nouvet, A.; Binard, M.; Lamaty, F.; Martinez, J.; Lazaro, R. *Tetrahedron* **1999**, *55*, 4685. (e) Bouifraden, S.; Drouot, C.; El Hadrami, M.; Guenoun, F.; Lecointe, L.; Mai, N.; Paris, M.; Pothion, C.; Sadoune, M.; Sauvagnat, B.; Amblard, M.; Aubagnac, J. L.; Calmes, M.; Chevallet, P.; Daunis, J.; Enjalbal, C.; Fehrentz, J. A.; Lamaty, F.; Lavergne, J. P.; Lazaro, R.; Rolland, V.; Roumestant, M. L.; Viallefont, P.; Vidal Y.; Martinez, J. *Amino Acids* **1999**, *16*, 345.

(3) For reviews see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Ivin, K. J. *J. Mol. Catal. A: Chemical* **1998**, 1. (c) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chemical* **1998**, 29. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Fürstner, A. *Topics in Organomet. Chem.* **1998**, *1*, 1.

(4) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (b) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979. (c) Nicolaou, K. C.; Wissinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourioumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268. (d) van Maarseven, J. H.; Denhartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249. (e) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949. (f) Peters, J. U.; Blechert, S. *Synlett* **1997**, 348. (g) Piscopio, A. D.; Miller, J. F. Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143. (h) Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583. (i) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815. (j) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1998**, *39*, 2667. (k) Schurer, S. C.; Blechert, S. *Synlett* **1999**, 1879. (l) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (m) Reichwein, J. F.; Wels, B.; Krujitzer, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3684. (n) Knerr, L.; Schmidt, R. R. *Synlett* **1999**, 1802. (o) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189.

(5) For the synthesis by RCM of dehydropipecolic acid derivatives but with different *N*-protecting groups than Ts see: (a) reference 4a. (b) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (c) 4f.

(6) Nouvet, A.; Binard, M.; Lamaty, F.; Lazaro, R. *Lett. Pept. Sci.* **1999**, *6*, 239.

(7) Nouvet, A.; Lamaty, F.; Lazaro, R. *Tetrahedron Lett.* **1998**, *39*, 3469.

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Scheme 2

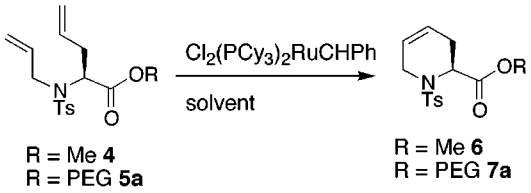


Table 1. Reaction Conditions for Ring Closing Metathesis of 4 and 5a

entry	linear substrate	cat. mol %	solvent	temp (°C)	reaction time (h)	conversion
1	**4**	10	CH_2Cl_2	20	0.17	100
2	**5a**	10	CH_2Cl_2	20	2	38
3	**5a**	10	CH_2Cl_2	20	>24	50
4	**5a**	30	CH_2Cl_2	40	2	82
5	**5a**	30	CH_2Cl_2	40	>24	90
6	**5a**	40	CH_2Cl_2	20	8	100
7	**5a**	10	toluene	110	8	45
8	**5a**	40	toluene	110	8	100
9	**5a**	7	H_2O	20	>24	20
10	**5a**	50	H_2O	20	24	100
11	**4**	10	a	b	0.17	100
12	**5a**	50	a	b	0.17	100

[a] The reaction was carried out in the absence of solvent under microwave. [b] Not measured.

Three reaction solvents for the reaction were chosen, CH_2Cl_2, toluene, and water, since PEG-bound molecules are soluble in all these solvents. The reaction was also carried out in the absence of solvent. Conversion of the starting material into the expected product was determined by ^{1}H NMR.

The reaction of **4** was complete within 10 min using 10 mol % of catalyst (entry 1). In sharp contrast, the reaction of **5a** under the same conditions reached only 38% conversion to **7a** (entry 2), clearly indicating a retarding effect due to the presence of the polymer. Increasing the reaction time to over 24 h slightly increased the conversion (entry 3). The use of a higher amount of catalyst and higher temperature (entry 4) did not give better conversion than 82%. It seems that after several hours of reaction the catalytic activity of the ruthenium catalyst decreased. Finally the best conditions we found were to use 40 mol % of catalyst at room temperature, then the reaction was complete within 8 h. In the case of toluene, 40 mol % of catalyst was needed also (entries 7 and 8). Using water as solvent[8] did not give better results (entry 9).

The cyclization was also carried out under microwave activation[9] (entries 11 and 12). Ruthenium catalyst (50 mol %) was needed for cyclizing **5a** in the absence of solvent, but in this case, the reaction time was dramatically reduced [from 8 h (entry 6) to 10 min (entry 12)]. Cyclization took place also in the absence of PEG, since **4** in the presence of 10 mol % of the ruthenium catalyst and in the absence of solvent yielded 91% of isolated **5** (entry 11). To our knowledge these are the first examples of microwave-assisted RCM using Grubbs' catalyst.[10]

The presence of the oxygen atoms of the PEG did not seem at first to be a problem, since polyethers and crown ethers have been synthesized by RCM.[11] Even the presence of glycol ethers did not change significantly the catalyst turnover number in the metathesis of styrene.[11a] It is known that the presence of functional groups such as esters and ethers could be necessary for a RCM to proceed. Nevertheless, in certain cases, the coordination of these groups on the metal carbene may generate unproductive chelate complexes.[12] In the case of **4**, the reaction time was short, indicating that the presence of tosyl amino and methyl ester functions did not interfere negatively with the reaction. During the RCM of **5a**, it seemed that the metal carbene was sequestered by the PEG oxygens. To confirm the fact that the mere presence of the oxygens of the PEG could inhibit this reaction, a RCM of **4** was performed in the presence of 0.5 equiv of PEG−OMe (3400) (MeO−$(CH_2CH_2O)_m$−Me) obtained by methylation of the corresponding PEG−OH (3400). Surprisingly, the reaction proceeded to completion within 15 min. So it seemed that the main factor for the slowing down of the reaction was not the presence of the oxygens in the reaction mixture (even if they interfere) but the fact that the linear substrate was anchored on the polymer. This limitation was also described in SPOS in the case of a PEG/polystyrene support where the cyclization of a tetrapeptide required a higher amount of catalyst to reach only 60% conversion.[4a] Figure 1 depicts two possible unproductive chelates that may be present in our case. Once the metal carbene has reacted with either one of the olefins of the linear substrate, it produces a metallacycle or a new metal carbene that instead of reacting with the second olefin, could be chelated by the polymer, which is in the right position to generate a strong complex.

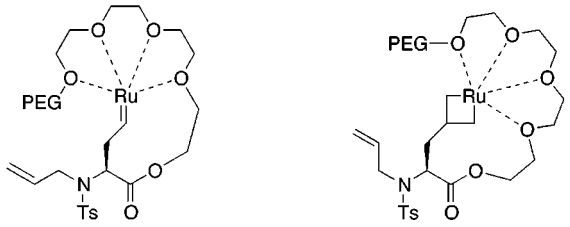


Figure 1. Two possible unproductive chelates that may be present in our case.

One can find in the literature examples of additives which could be employed to alleviate this problem. A Lewis acid such as Ti(OPr-*i*)$_4$[13] has been used to avoid unproductive complexes, while olefins such as 1-octene[4d] or styrene[4f] have been employed to promote the reactivation of the catalyst. When Ti(OPr-*i*)$_4$ (3 equiv) was used in our case, the conversion was higher (70% with 20 mol % catalyst) than in the absence of the Lewis acid, but full conversion was not reached. When the reaction was carried out with 2 equiv of 1-octene, it was possible to cut by half the amount of catalyst used (20 mol %), but so far we were not able to drop further this amount, even when employing a larger quantity of 1-octene. Styrene did not give better results. In this case, the presence of

(8) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904.

(9) Blettner, C.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885.

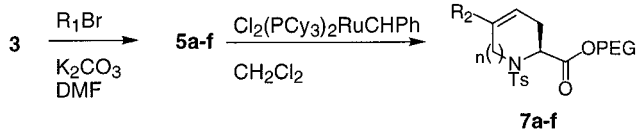
(10) For a metathesis polymerization under microwave activation, see: Dhanalakshmi, K.; Sundararajan, G. *Polym. Bull.* **1997**, *39*, 333.

(11) (a) König, B.; Horn, C. *Synlett* **1996**, 1013. (b) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101. (c) Rodríguez, R. M.; Morales, E. A.; Delgado, C. G.; Espínola, C. G.; Alvarez, E.; Pérez, R.; Martín, J. D. *Org. Lett.* **1999**, *1*, 725.

(12) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(13) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187. (c) Ramachandran, P. A.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583.

Table 2. Examples of RCM for the Synthesis of Cyclic Amino Acid Derivatives



7a-f

entry	R_1	5	cat. mol %	n	R_2	yield of 7 (%)
1	allyl	**a**	20[a]	1	H	92
2	PhCH=CHCH$_2$	**b**	40	1	H	86
3	H$_2$C=CH(CH$_3$)	**c**	40	1	CH$_3$	95
4	H$_2$C=CH(CH$_2$)$_2$	**d**	40	2	H	90
5	H$_2$C=CH(CH$_2$)$_3$	**e**	40	3	H	82
6	H$_2$C≡C−CH$_2$	**f**	40[a]	1	CH=CH$_2$	80

[a] 2 equiv of 1-octene was used.

an allyl-substituted olefin could displace the complex to a more reactive form. But this process seemed somewhat limited, since 20 mol % of catalyst was still needed.

Table 2 presents different examples of ruthenium-catalyzed cyclizations which led to the synthesis of amino acid derivatives. PEG supported (L)-allylglycine **3** was readily alkylated with different bromides to yield linear substrates **5a**−**f**, which were cyclized to **7a**−**f**. First it has to be noted that **5b** (entry 2) yields the same final product as **5a**. We chose a cinnamyl substituent on the nitrogen with the idea of being able to decrease the amount of ruthenium catalyst by stabilizing the metal carbene generated during the reaction.[8] Nevertheless, 40 mol % was needed for the cyclization to reach completion. A methyl substitutent on the olefin did not hamper the cyclization (entry 3). By varying the chain length on R_1, 7- and 8-membered rings **7d** and **7e** could be obtained in good yields. We checked also the formation of the novel 8-membered ring starting from the methyl ester analogue of **5e**. The cyclization in the absence of PEG proceeded smoothly in 15 min in the presence of 10 mol % of ruthenium catalyst. Finally, enyne metathesis[14] could also be performed on the PEG-supported substrate **5f**; however, a higher amount of catalyst was needed in this case.

To release the Ts amino acid from the polymer, a racemization free acidic hydrolysis was performed (in refluxing 6 N HCl for 4 h), and the free acids were obtained in good yields.

In conclusion, we have presented here the first examples of RCM on a soluble PEG-supported substrate. Although a relatively high amount of catalyst was needed, this method allows for the efficient synthesis of optically active cyclic amino acid derivatives with various ring sizes. Further investigation to improve the catalytic efficiency of this reaction is under study in our laboratory.

Experimental Section

General. All reagents including poly(ethylene glycol) 3400 were obtained from Aldrich Chemical Co. and used without purification. ^{1}H- and ^{13}C NMR analyses were performed, respectively, with 200 and 400 MHz NMR spectrometers. Infrared spectra were recorded by diffuse reflectance as a microcup of KBr or by transmittance in KBr salt plates. Mass spectra (electrospray ionization mode, ESIMS) were recorded on a quadrupole mass spectrometer fitted with an electrospray interface.

Microwave-assisted reactions were performed in a domestic microwave at a power of 850 W.

The HPLC analyses were carried out at a wavelength of 214 nm, using a reversed phase Nucleosil C18 column (5 μm, 250 × 10 mm) with a flow rate of 1 mL/min (eluents: solvent A, 0.1% TFA in H_2O; solvent B, 0.1% TFA in CH_3CN). The chiral HPLC analyses were carried out at a wavelength of 230 nm, using a Chiralcel OD column, (5 μm, 250 × 4.6 mm) with a flow rate of 1 mL/min (eluent: hexane/2-propanol/TFA (92/8/0.4)).

Optical rotations were recorded on a polarimeter at 589 nm and reported as α_D (concentration in grams/100 mL of solvent).

(L)-*N*-Tosylallylglycine (1). To a suspension of allylglycine (0.570 g, 5.00 mmol) in 10 mL of CH_2Cl_2 at room temperature was added trimethylsilyl chloride (0.540 g 5.00 mmol). The mixture was heated under reflux for 2 h, and Et_3N (1.01 g, 10.0 mmol) was added, followed by addition of *p*-toluenesulfonyl chloride (0.950 g, 5.00 mmol) in 5 mL of CH_2Cl_2. The resulting mixture was vigorously stirred for 1 h at room temperature, then MeOH (0.640 g, 20.0 mmol) was added. Evaporation was followed by addition of water and K_2CO_3 in order to obtain pH = 8. The aqueous layer was washed with Et_2O and then acidified to pH = 1 with 1 N HCl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated to afford 1.06 g (79%) of the title compound: IR (KBr) 2945 (s), 1441 (m), 1347 (s), 1286 (s), 1244 (s) cm^{-1}; ^{1}H NMR (CD_3OD, Me_4Si) δ 2.30−2.55 (m, 5 H), 3.90 (dd, J_1 = 6.0 Hz, J_2 = 7.0 Hz, 1 H), 5.00−5.15 (m, 2 H), 5.60−5.85 (m, 1 H), 7.35 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (CD_3OD, Me_4Si) δ 20.46, 37.41, 56.03, 117.84, 127.22, 129.54, 132.95, 138.30, 143.65, 173.06; MS (electrospray) *m*/*z* 270 (M + H)$^+$, 539 (2M + H)$^+$.

Methyl (L)-*N*-Tosylallylglycinate (2). To a solution of **1** (1.00 g, 3.7 mmol) in 25 mL of MeOH was added trimethylsilyl chloride (1.00 mL, 7.9 mmol). The mixture was refluxed for 7 h and was concentrated after cooling to yield 1.00 g (95%) of the title compound: IR (CCl_4) 3274 (w), 2951 (m), 2352 (w), 1743 (s), 1349 (s) cm^{-1}; ^{1}H NMR (CD_3OD, Me_4Si) δ 2.30−2.50 (m, 5 H) 3.45 (s, 3 H), 3.95 (t, J = 7.0 Hz, 1 H), 5.00−5.15 (m, 2 H), 5.60−5.80 (m, 1 H), 7.40 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (CD_3OD, Me_4Si) δ 20.41, 37.24, 51.41, 56.15, 117.94, 127.22, 129.53, 132.77, 138.19, 143.73, 171.85; MS (electrospray) *m*/*z* 284 (M + H)$^+$, 567 (2M + H)$^+$, 589 (2M + Na)$^+$.

Poly(ethylene glycol) 3400 Di((L)-*N*-tosylallylglycinate) (3). To a solution of PEGOH (1.95 g, 0.574 mmol) in 15 mL of THF was added a solution of triphenylphosphine (0.63 g, 2.4 mmol) in 5 mL of THF. The mixture was stirred at room temperature for 1 h. A solution of DEAD (0.468 g,2.40 mmol) and **1** (0.650 g, 2.40 mmol) in 2 × 5 mL of THF was added to the mixture. The reaction was refluxed for 10 h. After cooling and evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and precipitated in Et_2O, and the product was filtered and dried in vacuo to yield 2.04 g (91%) of the title compound: IR (KBr) 2876 (s), 1743 (m), 1466 (m), 1095 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.40 (s, 6 H), 2.50 (t, J = 6.5 Hz, 4 H), 3.50−3.70 (large s, ∼310 H), 4.00−4.10 (m, 6 H), 5.00−5.15 (m, 4 H), 5.40 (d, J = 9.0 Hz, 2 H), 5.55−5.75 (m, 2 H), 7.30 (d, J = 8.5 Hz, 4 H), 7.75 (d, J = 8.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.91, 37.89, 55.62, 62.00, 64.84, 68.95, 70.67, 70.91, 72.89, 120.04, 127.73, 130.13, 131.81, 137.33, 143.88, 171.14.

Methyl (L)-*N*-Allyl-*N*′-tosylallylglycinate (4). To a solution of **2** (0.150 g, 0.500 mmol) in 10 mL of DMF were added K_2CO_3 (0.370 g, 2.70 mmol) and allyl bromide (0.085 g, 0.795 mmol). The mixture was stirred at room temperature for 10 h, then 10 mL of EtOAc and 10 mL of H_2O were added. The aqueous layer was washed twice with EtOAc. The combined organic phases were washed three times with H_2O, dried over $MgSO_4$, and concentrated to afford 0.150 g (88%) of the title compound: IR (CCl_4) 2950 (w), 2356 (w), 1743 (s), 1350 (s), 1165 (s) cm^{-1}; ^{1}H NMR (CD_3OD, Me_4Si) δ 2.45 (s, 3 H), 2.40−2.80 (m, 2 H), 3.50 (s, 3 H), 3.90 (dd, J_1 = 1.5 Hz, J_2 = 6.5 Hz, 2 H), 4.60 (dd, J_1 = 6.5 Hz, J_2 = 9.0 Hz, 1 H), 5.05−5.25 (m, 4 H), 5.60−5.90 (m, 2 H), 7.30 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.93, 34.86, 48.61, 52.34, 59.71, 118.03, 118.85, 127.95, 129.79, 133.65, 135.38, 137.53, 143.80, 171.36; MS (electrospray) *m*/*z* 324 (M + H)$^+$, 346 (M + Na)$^+$, 647 (2M + H)$^+$, 669 (2M + Na)$^+$.

(14) For a synthesis in solution of a vinyl dehydro pipecolic acid via enyne metathesis see: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

Poly(ethylene glycol)-3400 Di((L)-*N*-allyl-*N*′-tosylallylglycinate) (5a). Allyl bromide (0.073 g, 0.603 mmol) was added to **3** (0.784 g, 0.200 mmol) and potassium carbonate (0.273 g, 2.00 mmol) in 30 mL of DMF. The mixture was stirred vigorously for 8 h. The reaction was concentrated and dissolved in CH_2Cl_2, the base was filtered, and the filtrate precipitated in Et_2O. The product was filtered and dried in vacuo to yield 0.660 g (83%) of the title compound: IR (KBr) 2874 (s), 1739 (m), 1474 (m), 1345 (m), 1094 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.40 (s, 6 H), 2.45−2.80 (m, 4 H), 3.50−3.70 (large s, ∼310 H), 3.85−3.90 (m, 6 H), 4.65 (dd, $J_1 = 6.5$ Hz, $J_2 = 9.0$ Hz, 2 H), 5.05−5.20 (m, 8 H), 5.65−5.90 (m, 4 H), 7.25 (d, $J = 8.5$ Hz, 4 H), 7.1 (d, $J = 8.5$ Hz, 4 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.93, 34.95, 48.64, 59.82, 61.87, 64.46, 68.93, 70.51, 72.91, 117.99, 119.82, 124.74, 127.97, 129.81, 130.56, 133.67, 135.56, 170.82.

Methyl (L)-*N*-Tosyl-4,5-didehydropipecolate (6). Method a. The ruthenium catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (0.003 g, 0.004 mmol) was added to a solution of **4** (0.014 g, 0.043 mmol) in 15 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 10 min and purified on silica gel (30% EtOAc/hexane). The organic layer was dried and concentrated to afford 0.012 g (95%) of the title compound.

Method b. The ruthenium catalyst (0.003 g, 0.004 mmol) was added to a suspension of **4** (0.014 g, 0.043 mmol) in 15 mL of H_2O, and the mixture was vigorously stirred at room temperature for 24 h. The aqueous layer was washed twice with CH_2Cl_2, and the organic layers were combined, dried over $MgSO_4$, concentrated, and purified on silica gel (30% EtOAc/hexane) to afford 0.010 g (80%) of the title compound.

Method c. The ruthenium catalyst (0.003 g, 0.004 mmol) was added to **4** (0.014 g, 0.043 mmol), the mixture was activated under microwave (850 W) during 10 min. The residue was purified on silica gel (30% EtOAc/hexane) to afford 0.012 g (91%) of the title compound.

Method d. The ruthenium catalyst (0.003 g, 0.004 mmol) was added to a solution of **4** (0.014 g, 0.043 mmol) and PEGOMe (0.074 g, 0.022 mmol) in 15 mL of CH_2Cl_2, the mixture was stirred at room temperature for 15 min, purified on silica gel (30% EtOAc/hexane) and concentrated to afford 0.012 g (91%) of the title compound: IR (neat) 2949 (m), 1735 (s), 1341 (m), 1288 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.45 (s, 3 H), 2.55 (large s, 2 H), 3.50 (s, 3 H), 3.75−4.15 (m, 2 H), 4.90 (t, $J = 4.0$ Hz, 1 H), 5.60−5.70 (large s, 2 H), 7.30 (d, $J = 8.5$ Hz, 2 H), 7.70 (d, $J = 8.5$ Hz, 2 H);^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.97, 28.18, 42.57, 52.55, 52.99, 122.69, 123.81, 127.68, 129.88, 136.61, 143.78, 171.35; MS (electrospray) *m*/*z* 296 $(M + H)^+$, 318 $(M + Na)^+$, 334 $(M + K)^+$.

Poly(ethylene glycol)-3400 Di((L)-*N*-tosyl-4,5-didehydropipecolate) (7a). Method a. The ruthenium catalyst (0.004 g, 0.005 mmol) was added to a solution of **5a** (0.050 g, 0.013 mmol) in 5 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 8 h and then precipitated in Et_2O twice. The product was filtered and dried in vacuo to yield 0.047 g (92%) of the title compound.

Method b. The ruthenium catalyst (0.012 g, 0.014 mmol) was added to a solution of **5b** (0.150 g, 0.036 mmol) in 15 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 8 h and then precipitated in Et_2O twice. The product was filtered and dried in vacuo to yield 0.120 g (86%) of the title compound.

Method c. The ruthenium catalyst (0.002 g, 0.003 mmol) was added to a solution of **5a** (0.050 g, 0.013 mmol) and 1-octene (0.003 g, 0.026 mmol) in 5 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 8 h and then precipitated in Et_2O twice. The product was filtered and dried in vacuo to yield 0.047 g (92%) of the title compound.

Method d. The ruthenium catalyst (0.005 g, 0.0065 mmol) was added to **5a** (0.050 g, 0.013 mmol), and the mixture was activated under microwave (850 W) for 10 min and then precipitated in Et_2O twice. The product was filtered and dried in vacuo to yield 0.047 g (92%) of the title compound.

Method e. The ruthenium catalyst (0.005 g, 0.007 mmol) was added to a solution of **5a** (0.050 g, 0.013 mmol) in 5 mL of water, and the mixture was vigorously stirred at room temperature for 24 h and then concentrated. The residue was dissolved in CH_2Cl_2 and then precipitated twice in Et_2O. The product was filtered and dried in vacuo to yield 0.040 g (81%) of the title compound: IR (KBr) 2359 (s), 1484 (w), 1349 (m), 1113 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.45 (s, 6 H), 2.55 (sl, 4 H), 3.50−3.70 (large s, ∼ 310 H), 4.90 (t, $J = 4.0$ Hz, 2 H), 5.70 (s, 4 H), 7.30 (d, $J = 8.5$ Hz, 4 H), 7.70 (d, $J = 8.5$ Hz, 4 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.93, 28.21, 42.52, 52.89, 64.43, 68.96, 70.92, 122.50, 123.86, 127.65, 129.85, 136.66, 143.64, 170.67.

(L)-*N*-Tosyl-4,5-didehydropipecolic Acid. A solution of **7a** (0.050 g, 0.013 mmol) in 2 mL of 6 N HCl was stirred at reflux for 4 h. The residue was concentrated and dissolved in CH_2Cl_2 and then precipitated in Et_2O. The poly(ethylene glycol) 3400 was filtered, the filtrate was washed with an aqueous solution of $NaHCO_3$, the aqueous layer was acidified to pH = 1 and washed with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to yield 0.005 g (68%)of the title compound: IR (neat) 2913 (m), 1724 (m), 1348 (m), 1323 (m), 1159 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.45 (s, 3 H), 2.60 (s, 2 H), 4.00 (dd, $J_1 = 18.0$ Hz, $J_2 = 30.0$ Hz, 2 H), 4.90 (dd, $J_1 = 5.0$ Hz, $J_2 = 8.5$ Hz, 1 H,), 5.70 (sl, 1H), 7.30 (d, $J = 8.0$ Hz, 2 H), 7.70 (d, $J =$ 8,5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.97, 27.84, 30.13, 42.44, 122.70, 123.87, 127.67, 129.97, 136.64, 144.06, 207.49; MS (electrospray) *m*/*z* 282 $(M + H)^+$, 304 $(M + Na)^+$, 585 $(2M + Na)^+$; HPLC $t_R = 20.74$ min; Chiral HPLC $t_R = 16.9$ min; $[\alpha]^{20}_D = -6.6$ (0.45, MeOH); HRMS calcd for $C_{13}H_{16}NO_4S$ (MH^+) 282.0800, found 282.0796.

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Supporting Information Available: Procedures for the preparation of **5b**−**f**, **7c**−**f**, and hydrolysis products from **7c**−**f**, and corresponding spectral data; ^{13}C NMR spectra of compounds **3**, **5b**−**f**, **7a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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