Asymmetric Synthesis of Differentially Protected 2,7-Diaminosuberic Acid, a Ring-Closure Metathesis Approach

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An efficient and versatile method has been developed for the synthesis of a selectively protected 2,7-diaminosuberic acid derivative. A Grubbs ring-closure olefin metathesis reaction was used as a key step on an allylglycine-derived template.

The disulfide bonds of cystine-containing peptides (**1**) constitute an important determinant of peptide hormone secondary structure and protein secondary and tertiary structure. However, the disulfide linkage is chemically and metabolically labile to reducing environments and nucleophilic and basic agents. Thus, isosteric dicarba analogues of cystine peptides (**2**), where the sulfur atoms have been replaced by methylene groups, have been synthesized and utilized to improve the chemical stability of biologically active peptides such as analogues of calcitonin,[1] oxytocin,[2−4] and somatostatin.[5−7]

The constituent amino acid of these dicarba cystine analogues is (2*S*,7*S*)-2,7-diaminosuberic acid (**3**, Figure 1). Despite the simplicity of this structure, the two amino and carboxyl groups must be differentially protected for convenient manipulation during solution- and/or solid-phase peptide synthesis. Previously described syntheses of 2,7-diaminosuberic acid typically involve Kolbe dimerization of two glutamic acid units. This approach is useful for the synthesis of symmetrical compounds, although it has also been used to prepare differentially protected 2,7-diaminosuberic acid[8] by the dimerization of two differently protected glutamic acids. As expected, this procedure yields a statistical mixture of two undesired symmetric dimers and one desired unsymmetrical dimer, which must separated.

It would be quite useful for additional applications of this cystine replacement, if there were more flexible methods for the unambiguous preparation of this building block that would also be amenable to the preparation of the *R*,*R*, *S*,*R*, and *R*,*S*-diastereomers. We have previously reported[9] such a solution to this problem for the preparation of the related 2,6-diaminopimelic acid derivatives in differentially protected form. Recently, Grubbs and co-workers[10] reported the elegant use of ring-closing olefin metathesis on allylglycine-containing peptides to construct rigidified amino acids and peptide systems. Since the specific sequence and attendant conformation of linear peptide substrates can often have a profound effect on the efficiency of macrocyclization, there still exists a need for alternative methods and building blocks for making 2,7-diaminosuberic acid-containing cyclic peptides. In this paper, we report an alternative method for the synthesis of selectively protected 2,7-diaminosuberic acid with defined stereochemistry. The methodology, which is based on the Grubbs approach,[10] is readily applicable to synthesizing other stereoisomers and could, in principle, be expanded to include homologues with additional methylene units spanning the glycyl substructures.

As shown in Scheme 1, *N*-(*tert*-butyloxycarbonyl)allylglycine was synthesized via enolate alkylation of **4** (95% yield of **5** as a single diastereomer) followed by dissolving metal reduction.[11] Condensation of the acid with 1,2-benzenedimethanol (**7**) afforded the benzyl ester **8** (85%). Activation with *p*-nitrophenyl carbonate gave **9**, which was condensed with the TFA salt of allylglycine phenyl ester (**10**, prepared from **6** in 75% yield by formation of the phenyl ester (PhOH, DCC) and TFA removal of the BOC group) to afford **11** in 86% yield. Ring-closure olefin metathesis according to Grubbs[10] furnished the macrocycle **12** in >80% yield. Finally, catalytic hydrogenation of **12** concomitantly saturated the olefin and cleaved both of the benzyl ester linkages, providing the differentially protected 2,7-diaminosuberic acid derivative **13** in high yield.

Some related observations on similar approaches that we examined are worthy of note. Initially, we examined the ring-closure olefin metathesis of the *t*-BOC-(*S*)-allylgly-(*S*)-allylgly-OPh substrate **14**. Unfortunately, no cyclization products were observed (Scheme 2). This is presumably due to the preference for the amide linkage to adopt the more thermodynamically stable s-trans conformation. We also examined the cyclization of the corresponding 1,3-benzenedimethanol substrate (**16**) and the 1,4-benzenedimethanol substrate (**18**). Compound **16** cyclized to provide the desired macrocycle **17**, in similar

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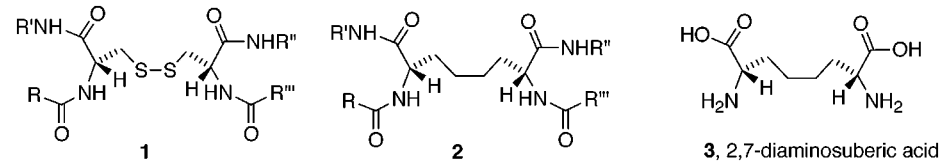
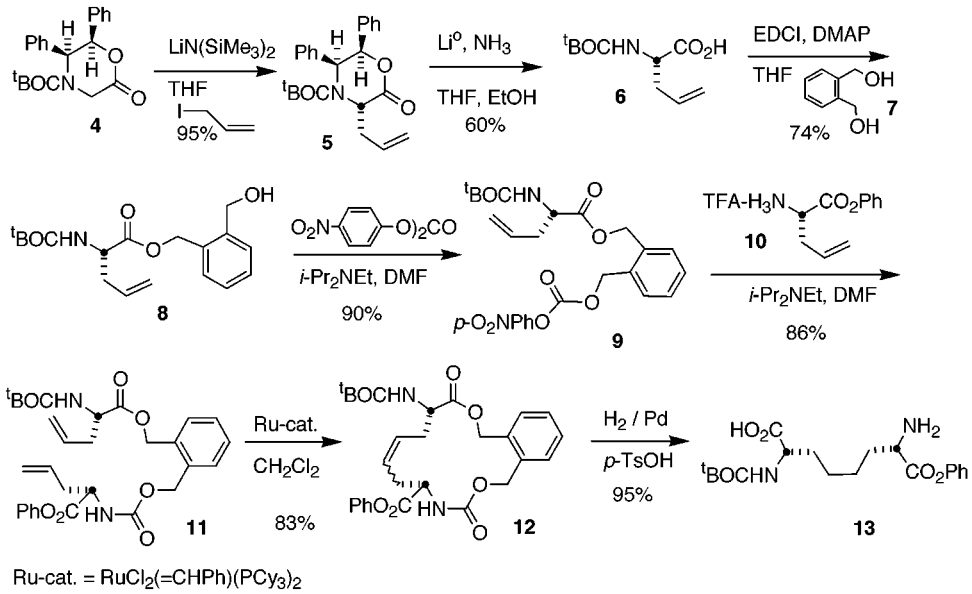
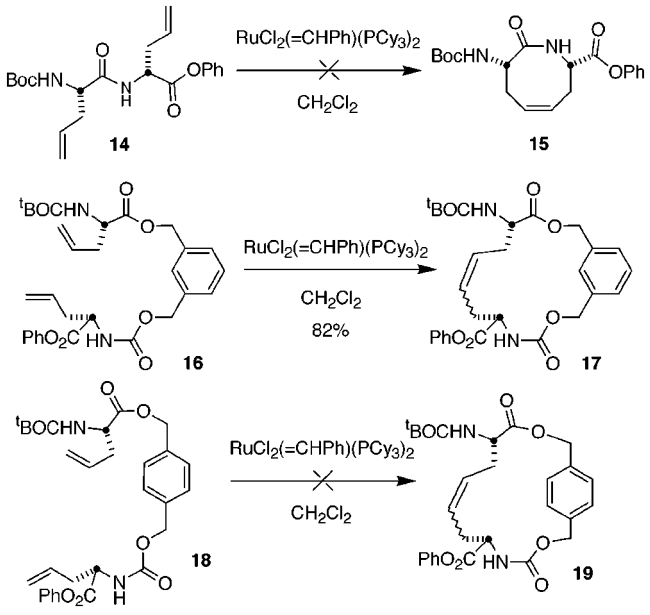


Figure 1.

Scheme 1



Scheme 2



yield (82%) to that obtained with **11**. The 1,4-disubstituted substrate **18** failed to give any detectable cyclization product. It is thus clear from these observations and related ones from the literature that the conformational space accessible to the olefin metathesis substrate is a critical aspect for a successful cyclization.

In summary, selectively protected 2,7-diaminosuberic acid derivative **13** of high optical purity has been prepared efficiently from *N*-(*tert*-butyloxycarbonyl)-(*S*)-allylglycine.[12] The protecting groups of **13** can be readily manipulated and should prove useful for both solution-phase and solid-phase cyclic peptide synthesis. Other C−C bond-coupling reactions besides olefin metathesis are under examination via the general strategy employed herein. Efforts to extend this methodology are being pursued in this laboratory and will be reported in due course.

Experimental Section

General Methods. For general experimental considerations and conditions, please refer to ref 11. Compound **6** was prepared according to ref 11. The purity of all new compounds reported was >95% as ascertained by homogeneity on TLC and by ^{1}H NMR (see the Supporting Information).

Allylglycine Phenyl Ester (10). To a stirred solution of **6** (402 mg, 1.87 mmol), phenol (176 mg, 1.87 mmol), and pyridine (0.15 mL, 1.87 mmol) in THF (8 mL) at −20 °C was added DCC (386 mg, 1.87 mmol). The mixture was stirred at room temperature overnight. A few drops of AcOH was added, and 0.5 h later, the precipitate was removed by filtration. The filtrate was washed with 3% citric acid, 5% sodium bicarbonate, and brine. The organic solution was dried and concentrated to give *N*-(*tert*-butyloxycarbonyl)allylglycine phenyl ester (520 mg, 95%) as a colorless oil; this substance was used directly without further purification for the next step. To a solution of this compound (520 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added trifluoroacetic acid (5 mL). The mixture was stirred at 0 °C for 2.5 h. The mixture was concentrated under reduced pressure at 0 °C to an oil. Ether was added to the oil, and the mixture was concentrated again. The residue was triturated with 1:1 ether/petroleum ether at −30 °C, filtered, and washed with 1:1 ether/petroleum ether to give **10** (430 mg, 79%) as white solid: ^{1}H NMR (300 MHz, DMSO-d_6, vs TMS) δ 2.75 (2H, apparent t, J = 6.2 Hz), 4.46 (1H, t, J

(12) After completion of this work, we learned that Prof. John C. Vederas (University of Alberta) and co-workers have independently developed an olefin metathesis route to the selectively protected 2,7-diaminosuberic acid system. We thank Prof. Vederas for sharing his data with us prior to publication. *J. Org. Chem.* **1998**, *63*, 2133.

= 6.2 Hz), 5.20−5.40 (2H, m), 5.80−6.00 (1H, m), 7.10−7.50 (5H, m), 8.60 (3H, bs); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.43, 51.72, 120.3, 121.3, 126.5, 129.8, 131.1, 149.6, 167.9; IR (KBr pellet) 2927, 1762, 1667 cm^{-1}; $[\alpha]^{25}_D$ +4.6° (*c* 2.4, CH_2Cl_2); HRMS calcd for $C_{11}H_{14}NO_2$ (M + H$^+$) 192.1024, found 192.1017.

Compound 8. EDCI (240 mg, 1.25 mmol) was added to solution of *N*-(*tert*-butyloxycarbonyl)allylglycine (**6**)[12] (200 mg, 0.93 mmol), 1,2-benzenedimethanol (500 mg, 3.63 mmol), and DMAP (14.7 mg, 0.12 mmol) in CH_2Cl_2 (16 mL) at 0 °C. The solution was stirred at 0 °C for 3 h and at room temperature overnight. The mixture was concentrated, and the residue was purified by column chromatography (silica gel, 1:1 hexanes/EtOAc then EtOAc) to give **8** (230 mg, 74%) as colorless oil (400 mg of 1,2-benzenedimethanol was also recovered): ^{1}H NMR (300 MHz, DMSO-d_6, vs TMS) δ 1.41 (9H, s), 2.22 (1H, bs), 2.40−2.62 (2H, m), 4.30−4.42 (1H, dd, *J* = 7.7, 6 Hz), 4.75 (2H, ABq, *J* = 12.5 Hz), 4.95−5.20 (3H, m), 5.29 (2H, ABq, *J* = 12.5 Hz), 5.55−5.70 (1H, m), 7.30−7.50 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.38, 36.58, 53.16, 62.68, 64.92, 80.23, 119.4, 128.1, 128.9, 129.1, 129.9, 132.3, 133.3, 139.6, 155.5, 172.1; IR (NaCl, neat) 3375, 3080, 2978, 1698 cm^{-1}; $[\alpha]^{25}_D$ −8.0° (*c* 4.8, CH_2Cl_2); HRMS calcd for $C_{18}H_{26}NO_5$ (M + H$^+$) 336.1811, found 336.1802.

Compound 9. To a solution of **8** (220 mg, 0.66 mmol) and bis(4-nitrophenyl) carbonate (500 mg, 1.64 mmol) in DMF (8 mL) was added diisopropylethylamine (128 mg, 0.99 mmol). The yellow solution was stirred overnight and poured into EtOAc (40 mL). The organic layer was washed with 0.01 N KOH until the aqueous layer was no longer yellow, and the organic layer was then washed with brine twice, dried, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3:1 hexanes/EtOAc) to give **9** (300 mg, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s), 2.40−2.55 (2H, m), 4.38−4.48 (1H, dd, *J* = 7.7, 6 Hz), 5.00−5.15 (3H, m), 5.33 (2H, ABq, *J* = 12.5 Hz), 5.42 (2H, s), 5.58−5.75 (1H, m), 7.30−7.50 (6H, m), 8.25−8.30 (2H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.46, 36.82, 53.14, 64.53, 68.53, 80.19, 119.5, 121.9, 125.5, 129.3, 129.8, 130.5, 130.5, 132.3, 133.1, 134.6, 145.6, 152.5, 155.7, 172.0; IR (NaCl, neat) 3400, 3081, 2978, 1766, 1716, 1525, 1348 cm^{-1}; $[\alpha]^{25}_D$ −6.9° (*c* 5.8, CH_2Cl_2); HRMS calcd for $C_{25}H_{29}N_2O_{99}$ (M + H$^+$) 501.1873, found 501.1858.

Compound 11. To a solution of **9** (200 mg, 0.4 mmol) and compound **10** (134 mg, 0.44 mmol) in DMF (3 mL) was added diisopropylethylamine (0.175 mL, 0.99 mmol). The yellow solution was stirred overnight and poured into EtOAc (40 mL). The organic layer was washed twice with 3% citric acid and with 0.01 N KOH until the aqueous phase was no longer yellow. The mixture was then washed with brine twice, dried over anhydrous Na_2SO_4, and concentrated to give **11** (190 mg, 86%) as a colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6, vs TMS) δ 1.42 (9H, s), 2.40−2.62 (2H, m), 2.65−2.72 (2H, m), 4.35−4.48 (1H, dd, *J* = 7.8, 6 Hz), 4.60−4.72 (1H, dd, *J* = 7.6, 6.3 Hz), 5.00−5.10 (3H, m), 5.15−5.30 (6H, m), 5.58−5.90 (3H, m), 7.00−7.45 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.46, 36.80, 36.83, 53.10, 53.77, 64.75, 64.77, 80.14, 119.4, 119.9, 121.5, 126.3, 128.9, 129.1, 129.7, 130.2, 130.3, 132.1, 132.4, 134.2, 135.1, 150.6, 155.4, 155.8, 170.6, 172.0; IR (NaCl, neat) 3346, 3076, 2979, 1716 cm^{-1}; $[\alpha]^{25}_D$ −3.5° (*c* 5.2, CH_2Cl_2); HRMS calcd for $C_{30}H_{37}N_2O_8$ (M + H$^+$) 553.2550, found 553.2581.

Compound 12. The Ru catalyst[10] $RuCl_2(=CHPh)(PCy_3)_2$ (81 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) was added via gastight syringe to a solution of **11** (135 mg, 0.24 mmol) in CH_2Cl_2 (70 mL, degassed and dried). The solution was stirred at 43 °C for 66 h. The resulting mixture was concentrated, and the residue was purified by column chromatography (silica gel, 3:1 hexanes/EtOAc) to give **12** (106 mg, 83%) as an off-white solid (13 mg of **11** was recovered). ^{1}H NMR revealed two geometrical isomers exist in 1:1 ratio; these isomers were not separated but used directly for the next step as a mixture (the NMR data is included in the Supporting Information): IR (KBr, pellet) 3340, 2977, 1718, 1506 cm^{-1}; $[\alpha]^{25}_D$ −29° (*c* 1.36, CH_2Cl_2); HRMS calcd for $C_{28}H_{33}N_2O_8$ (M + H$^+$) 525.2237, found 525.2254.

Compound 13. A mixture of **12** (15 mg, 0.029 mmol), *p*-TsOH (5.7 mg, 0.03 mmol), and Pd/C (10%) (4 mg) in 2-propanol (2 mL) and THF (0.1 mL) was stirred at room temperature under 1 atm of H_2 for 2.5 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give **13** (15 mg 95%) as an off-white solid: ^{1}H NMR (300 MHz, methanol-d_4) δ 1.44 (9H, s), 1.45−2.15 (8H, m), 2.37 (3H, s), 4.05−4.15 (1H, m), 4.30−4.40 (1H, m), 7.10−7.50 (7H, m), 7.71 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 21.45, 25.56, 26.51, 28.88, 31.56, 32.75, 54.25, 122.5, 127.1, 127.9, 130.0, 130.9, 141.8, 143.7, 151.7, 169.7; IR (KBr) 3422, 2977, 1718 cm^{-1}; $[\alpha]^{25}_D$ +17.5° (*c* 1, methanol-d_4); HRMS calcd for $C_{19}H_{29}N_2O_6$ (M + H$^+$) 381.2026, found 381.2040.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8**−**13** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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