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Synthesis of Orthogonally Protected *S,S*-2,6-Diaminopimelic Acid via Olefin Cross-Metathesis

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Abstract: A short synthesis of orthogonally protected *S,S*-diaminopimelic acid, DAP, via a selective cross-metathesis between *S*-allyl glycine and *S*-vinyl glycine followed by hydrogenation is reported. By analogy, the *S,S*-diaminosuberic acid, DAS, is produced by self-metathesis of *S*-allyl glycine, and the self-metathesis of *S*-vinyl glycine is described.

Keywords: Cross-metathesis, diaminopimelic acid, Grubbs catalyst

The preparation of diamino dicarboxylic acids or bis(amino acids) has drawn considerable attention because of their ability to covalently link peptides. Shown in Fig. 1 are three bis(amino acids) with four, three, and two intervening methylenes. 2,7-Diaminosuberic acid (DAS) **1** represents the oxidatively stable carbon analogue of cystine and has demonstrated utility as the linchpin of two cyclic nonapeptides with hematoregulatory and oxytocin antagonistic activities.[1] *S,S*-2,6-Diaminopimelic acid (DAP) **2** is an intermediate in the biosynthesis of L-lysine via *meso*-DAP, which is a component of the peptidoglycan of most bacteria.[2] The truncated 2,5-diaminoadipic acid (DAA) **3** is also of interest as a mimic of these biochemically important diamino dicarboxylic acids.

These compounds have been prepared by nonstereoselective means[3] and several stereoselective methods. For example, by taking advantage of the

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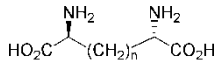


1 DAS n = 4
2 DAP n = 3
3 DAA n = 2

Figure 1. Diamino dicarboxylic acids.

resident chirality of natural amino acids, Kolbe electrolysis of protected glutamates and aspartates produces low yields of DAS and DAA in only one step,[4] but this procedure is limited to an even number of linking methylenes and symmetrically protected bis(amino acids). In contrast, *de novo* formation of the α-carbon stereochemistry of diamino dicarboxylic acids has been achieved by asymmetric hydrogenations of the enamide following Wittig olefination[5] or following Suzuki coupling.[6] Also, stereoselective glycinyl enolate alkylations[7] and epoxide opening of azides[8] have been reported to yield various bis(amino acid) derivatives.

Ruthenium-catalyzed metathesis reactions have been employed to furnish diamino dicarboxylic acid products. The first report entailed a ring-closing metathesis (RCM) of allyl glycines using the first-generation Grubbs ruthenium catalyst to form DAS-linked cyclic peptides.[9] Other RCM reactions have been utilized to form DAS peptides[10] and protected DAS derivatives.[11] A ring-closing alkyne metathesis for symmetrically protected DAS derivatives has also been described,[12] and recently a RCM reaction for the preparation of orthogonally protected *meso*-DAP was published.[13] To date, there has been only one report of a direct self-metathesis reaction to produce diamino dicarboxylic acids,[14] and surprisingly no cross-metathesis reactions have been exploited to form the *S,S*-diaminopimelic acid, DAP.

During our synthetic studies of carbon-linked glycosyl amino acids by a cross-metathesis methodology,[15] we encountered the ready production of the self-metathesis by-products from the starting *S*-allyl glycine **4** and *S*-vinyl glycine **5** precursors (Fig. 2). Here, we report the use of the allyl glycine and vinyl glycine self-metathesis reaction to yield DAS and DAA derivatives, respectively, and the successful cross-metathesis between allyl and vinyl glycines for DAP analogues.

Because allyl glycine **4** is considered a type 1, highly reactive, metathesis partner according to criteria suggested by Grubbs,[16] it was expected that its self-metathesis product would be isolated upon refluxing in dichloromethane in the presence of 15 mol% of the N-hetereocyclic Grubbs second-generation catalyst. We obtained a 71% yield of the symmetrical product **6**.

Although not as reactive to the metathesis conditions as allyl glycine, the bis(trimethylsilylethyl) *S*-vinyl glycine **5** in the presence of the second-generation ruthenium catalyst affords self-metathesis product **7** in 62%

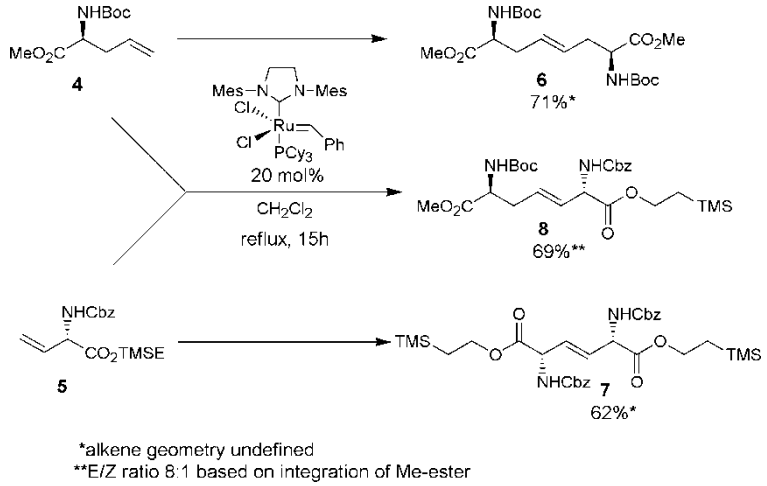


Figure 2. Self-metatheses and cross-metathesis reactions.

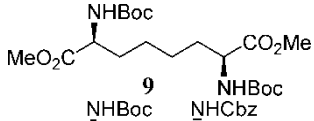
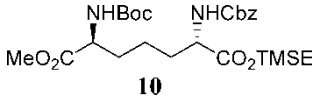
yield. This is in sharp contrast to results using $(Cy_3P)_2Cl_2Ru=CHPh$ as catalyst, in which no self-metathesis was observed, and a recent report by Schmittmann et al.[14b]

In view of this reactivity pattern, it seemed likely that a selective cross-metathesis may be achieved between the more reactive allyl glycine and the less reactive vinyl glycine. To this end, a 2 : 1 ratio of vinyl to allyl glycine was subjected to the cross-metathesis conditions, and a 69% yield of **8**, based on **4**, was collected after chromatography. The E-isomer was distinguishable by the 15.4-Hz coupling constant between the vinyl protons at postitions 3 and 4. This reaction also produced the readily separable ($\Delta Rf > 0.1$), less polar, vinyl glycine self-metathesis product **7** in 39% yield based on **5**.

Hydrogenation of each of the metathesis adducts **6, 7**, and **8** should lead to DAS, DAA, and DAP, respectively. As shown in Table 1, hydrogenation was successful for the production of the symmetrically protected *S,S*-DAS **9** and for the orthogonally protected *S,S*-DAP **10**. Production of **10** required the use of platinum on alumina to prevent hydrogenolysis of the Cbz-protecting group.

Attempts to hydrogenate the alkene of compound **7** led to mixtures. The rate of hydrogenation is impeded by the proximity of the protecting groups, and alkene isomerization to the α,β-unsaturated ester, presumably due to metal coordination, is observed; therefore, any hydrogenated product affords an uncontrolled mixture of diastereomers. Diimide reduction of **7** using tosylhydrazide and sodium acetate at 70°C also gave a thermal isomerization, whereas attempted diimide reductions at room temperature failed to reduce the alkene in our hands.[17]

Table 1. Hydrogenation of olefin metathesis adducts

Alkene	Catalyst/ reagent	Product	Yield (%)
6	Pd/C	 **9**	96
8	Pt/Al_2O_3	 **10**	92

In summary, the self-metathesis reactions of *S*-allyl and *S*-vinyl glycines produced alkenes in good yield. Taking advantage of the differential reactivity of these glycine derivatives led to a moderately selective cross-metathesis reaction using the second-generation Grubbs ruthenium catalyst. The cross-metathesis adduct **8** can be hydrogenated to yield an orthogonally protected *S,S*-diaminopimelic acid **10**. In principle, the *meso*-diaminopimelic acid can be produced through hydrogenation of the cross-metathesis product from *R*-allyl glycine[18] and *S*-vinyl glycine.

EXPERIMENTAL

(*S*)-Allyl glycine **4** and (*S*)-vinyl glycine **5** were prepared according to the literature procedures.[14] All NMR spectral assignments were determined on a Bruker Avance spectrometer by ^1H (400 MHz) and ^{13}C (100 MHz) attached proton tests, Correlation Spectroscopy (COSY), and Heteronuclear Multiple Quantum Correlation Spectroscopy (HMQC) two-dimensional techniques in $CDCl_3$. Mass spectra were recorded on a Bruker Daltonics Autoflex MALDI-ToF using α-cyano-4-hydroxycinnamic acid as the matrix. Spectral data for compound **6** (4b and 13) and hydrogenation product **9** (8) are in agreement with literature values.

Dimethyl (2*S*, 7*S*)-Bis-(*tert*-butoxycarbonyl)amino-4-octenedioate 6. A solution of *S*-allyl glycine **4** (105 mg, 0.458 mmol) in dichloromethane (6 mL) was bubbled with Ar for 5 min, and then cannulated into a flask containing 15 mol% of the Grubbs II catalyst (29 mg, 0.034 mmol). The dark solution was refluxed overnight (16 h). The reaction mixture was concentrated onto SiO_2 followed by flash column chromatography using 20% EtOAc/hexanes ($R_f = 0.47$ in 30% EtOAc/hex) to yield a light brown oil, 90 mg (71% yield). ^1H NMR: δ 5.42 (bs, 2H, H-4 and H-5), 5.13 (bd, $J = 7.7$ Hz, 2H, 2NH), 4.35 (m, 2H, H-2 and H-7), 3.75 (s, 6H), 2.47 (m, 4H, H-3 and H-6), 1.45 (s, 18H).

Bis(2-trimethylsilylethyl) (2*S*, 5*S*)-2,5-bis[(phenylmethoxycarbonyl) Expeamino]-3-hexenedioate 7. A solution of *S*-vinyl glycine **5** (150 mg, 0.427 mmol) in dichloromethane (3 mL) was bubbled with Ar for 5 min, and then cannulated into a flask containing the Grubbs II catalyst (36 mg, 0.043 mmol). The dark solution was refluxed overnight (18 h). The reaction mixture was concentrated onto SiO_2 followed by flash column chromatography using 10–20% EtOAc/hexanes ($R_f = 0.30$ in 20% EtOAc/hex) to yield a light brown oil, 93 mg (62% yield). ^{1}H NMR: δ 7.4 (m, 10H, $2C_6H_5$), 5.87 (bs, 2H, H-3 and H-4), 5.42 (bs, 2H, 2NH), 5.14 (s, 4H, 2PhCH_2), 4.95 (bd, $J = 7.2$ Hz, 2H, H-2 and H-5), 4.25 (bdt, $J = 8.8$ and 12.1 Hz, 4H), 1.03 (bt, $J = 8.8$ Hz, 4H), 0.07 (s, 18H). ^{13}C NMR δ 170.1, 155.4, 136.1, 128.5, 128.2, 128.1, 127.8, 67.2, 64.6, 55.1 (C-2 and C-5), 17.3, −1.5 ppm. MALDI-ToF MS: m/z = 665.3 ($M^+ + Na$), 681.2 ($M^+ + K$). HRMS calcd. for $C_{32}H_{46}N_2O_8Si_2Na$ 665.2690; found 665.2698.

1-Trimethylsilylethyl 7-methyl (2S,6S)-E-2-(phenylmethoxycarbonyl) amino-6-(*tert*-butoxycarbonyl)amino-3-heptenedioate 8. A solution of *S*-allyl glycine **4** (100 mg, 0.436 mmol) and *S*-vinyl glycine **5** (292 mg, 0.872 mmol) in dichloromethane (6 mL) was bubbled with Ar for 5 min, and then cannulated into a flask containing the Grubbs II catalyst (74 mg, 0.087 mmol). The dark solution was refluxed overnight (18 h). The reaction mixture was concentrated onto SiO_2 followed by flash column chromatography using 10–20% EtOAc/hexanes to yield a light brown oil, 161 mg (69% yield). $R_f = 0.19$ (20% EtOAc/hex). ^{1}H NMR: δ 7.3 (m, 5H, C_6H_5), 5.64 (dt, $J = 8.1$ and 15.4 Hz, 1H, H-4), 5.54 (dd, $J = 5.7$ and 15.4 Hz, 1H, H-3), 5.44 (bd, $J = 7.3$ Hz, 1H, NH-2), 5.06 (s, 2H, PhCH_2), 5.05 (overlapped, 1H, NH-6), 4.77 (bt, $J = 5.6$ Hz, 1H, H-2), 4.32 (m, 1H, H-6), 4.19 (bdt, $J = 8.8$ and 10.8 Hz, 2H), 3.66(s, 3H, OCH_3), 2.47 (m, 2H, H-5), 1.39 (s,9H, Boc), 1.04(bt, $J = 8.8$ Hz, 2H),0.00 (s, 9H). ^{13}C NMR δ 172.1, 170.5, 155.4, 155.1, 136.1, 128.6, 128.5, 128.2, 128.1, 128.1, 79.9, 67.0, 64.3, 55.6 (C-6), 52.8 (C-2), 52.2, 35.2 (C-5), 28.2, 17.2, −1.6 ppm. MALDI-ToF MS: m/z = 559.2 ($M^+ + Na$), 575.2 ($M^+ + K$). HRMS calcd. for $C_{26}H_{41}N_2O_8Si$ 537.2632; found 537.2627.

Dimethyl (2S,7S)-bis-(*tert*-butoxycarbonyl)aminooctanedioate 9. EtOAc (4 mL) was added to the alkene **6** (151 mg, 0.35 mmol) and 20% Pd/C (75 mg, 0.0 mmol), and the solution was degassed by evacuation and flushing with Ar (2×). An atmosphere of H_2 was introduced in a like manner. The reaction mixture was left under a balloon of hydrogen and filtered through a Celite pad after 12 h. Evaporation of solvent provided 145 mg (96% yield) of an oil. ^{1}H NMR: δ 5.05 (bd, $J = 8.0$ Hz, 2H, 2NH), 4.27 (bdt, $J = 7.7$, 5.5 Hz, 2H, H-2 and H-7), 3.73 (s, 6H), 1.76 (m, 2H, H-3a and H-6a), 1.61 (m, 2H, H-3b and H6b), 1.43 (s, 18H), 1.36 (m, 4H, H-4 and H-5).

1-Trimethylsilylethyl 7-methyl (2S, 6S)-2-(phenylmethoxycarbonyl) amino-6-(*tert*-butoxycarbonyl)aminoheptanedioate 10. EtOAc (2 mL) was added to the alkene **8** (95 mg, 0.18 mmol) and 5% Pt/Al_2O_3 (69 mg,

0.018 mmol), and the solution was degassed by evacuation and flushing with Ar (2×). An atmosphere of H_2 was introduced in a like manner. The reaction mixture was left under a balloon of hydrogen and filtered through a Celite pad after 16 h. Evaporation of solvent provided 88 mg (92% yield) of a dark oil. ^{1}H NMR: δ 7.3 (m, 5H, C_6H_5), 5.41 (bd, $J = 7.3$ Hz, 1H, NH), 5.13 (s overlapping bd, 3H, NH and PhCH_2), 4.25 (bm, 4H, H-2, H-6 and OCH_2), 3.74 (s, 3H, OCH_3) 1.8–1.6 (2 × bm, 4H, H-3 and H-5), 1.44 (bs, 11H, H-4 and Boc) 1.02 (bt, $J = 8.7$ Hz, 2H), 0.06 (s, 9H). ^{13}C NMR δ 173.1, 172.4, 156.0, 155.6, 136.2, 128.5, 128.1, 128.1, 79.9, 67.0, 63.9, 53.2 and 52.9 (C-2 and C-6), 52.3, 32.1 and 32.0 (C-3 and C-5), 28.3, 21.2 (C-4), 17.3, − 1.6 ppm. MALDI-ToF MS: m/z = 561.3 ($M^+ + Na$), 577.2 ($M^+ + K$). HRMS calcd. for $C_{26}H_{43}N_2O_8Si$ 539.2770; found 539.2797.

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