Pergamon

Tetrahedron Letters 39 (1998) 1689–1690

TETRAHEDRON LETTERS

Template-Promoted Dimerization of *C*-Allylglycine: A Convenient Synthesis of (*S,S*)-2,7-Diaminosuberic Acid

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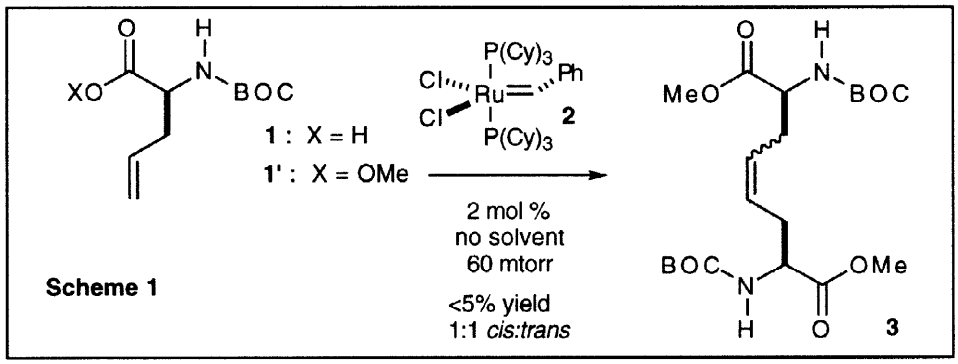
Received 5 November 1997; accepted 5 January 1998

Abstract: (*S,S*)-2,7-diaminosuberic acid can be synthesized in a convenient manner using an intramolecular ruthenium-catalyzed ring closing metathesis reaction of BOC-protected *C*-allylglycine anchored to a catechol template

In connection with our interest in using ruthenium-catalyzed ring-closing metathesis (RCM)[3,4] to constrain peptide secondary structures,[5] we desired a practical synthesis of optically active 2,7-diaminosuberic acid-related structures[6] (e.g., **3** and **7**) as surrogates for L-cystine (**4**). Our initial efforts examined an intermolecular metathesis reaction using ruthenium benzyl alkylidene **2** and protected (*S*)-*C*-allylglycine (**1'**). This unnatural amino acid is commercially available and also conveniently prepared in bulk by asymmetric synthesis[7] or by enzymatic resolution.[8,9] Although Ru-promoted intermolecular metathesis reactions have been described in systems with diverse functionality,[10] this reaction was unsuitable for BOC-protected *C*-allylglycine methyl ester (**1'**), even under forcing conditions (Scheme 1).

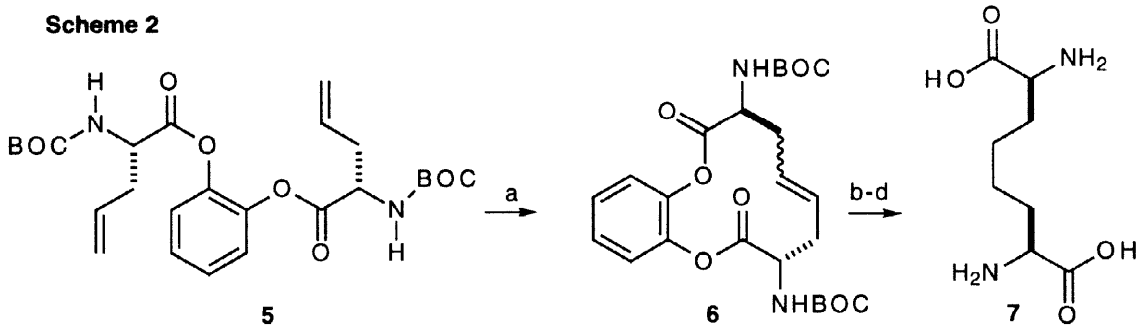


Scheme 1

To circumvent this problem, we have investigated intramolecular RCM reactions with (*S*)-**1** anchored to templates such as catechol (**5**, prepared via DCC coupling in 90% yield.) The RCM reaction proceeds cleanly and in 77-85% yield with slow addition of **2** (10-15 mol %) to a refluxing CH_2Cl_2 solution of **5** (0.1 M). HRMS analysis of the product (FAB, calcd for $C_{24}H_{33}N_2O_8$ 477.2236, found 477.2253) has confirmed the 12-membered ring structure **6**; ^1H NMR data is consistent with a 2:1 mixture of olefin isomers. Product **6** can be isolated in 65% yield by precipitation from hexane with the remainder recoverable by silica gel chromatography. Hydrogenation of **6** produced a single reduction product as judged by the ^1H NMR spectrum. The synthesis of bis-amino acid **7**[11] was completed with acid hydrolysis and conversion[6a] to the zwitterion.

0040-4039/98/$19.00
PII: S0040-4039(98)00126-9

Scheme 2



Reagents and Conditions: (a) 15 mol % **2** / CH_2Cl_2 / 45 °C, 85%; (b) H_2 / Pd-C / EtOAc / RT, 96%; (c) 3 N aq. HCl-dioxane (1:1) / 100 °C; (d) propylene oxide / EtOH / 80 °C, c-d 95%.

In conclusion, (*S*,*S*)-2,7-diaminosuberic acid can be synthesized from (*S*)-*C*-allylglycine in 3 steps from acyclic diene **5** in 77% overall yield using reactions that do not require chromatography. The procedure is suitable for preparing multigram quantities of **7**, and current investigations are directed at using the RCM approach to prepare differentially protected bis-amino acids for incorporation into peptide secondary structures.

Acknowledgments.

We thank Zeneca Pharmaceuticals for funding this research and the UC Riverside Mass Spectrometry Facility for their services. SJM thanks the NSF for a postdoctoral fellowship. DJO thanks Pomona College for provision of a Steele junior faculty leave. The authors thank Helen Blackwell for useful discussions.

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11. ^{1}H NMR (300 MHz, D_2O, HOD ref. 4.63 ppm): δ 3.53 ppm (2H, t, J = 6.1 Hz), 1.69 (4H, m), 1.24 (4H, m). $[\alpha]_D$ +33° (*c* 0.2, 6 N HCl) [lit.[6b] +41.8° (*c* 0.2, 6 N HCl)]. Efforts are currently underway to assess the enantiomeric purity of the product.