Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3651-3652, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0655-H

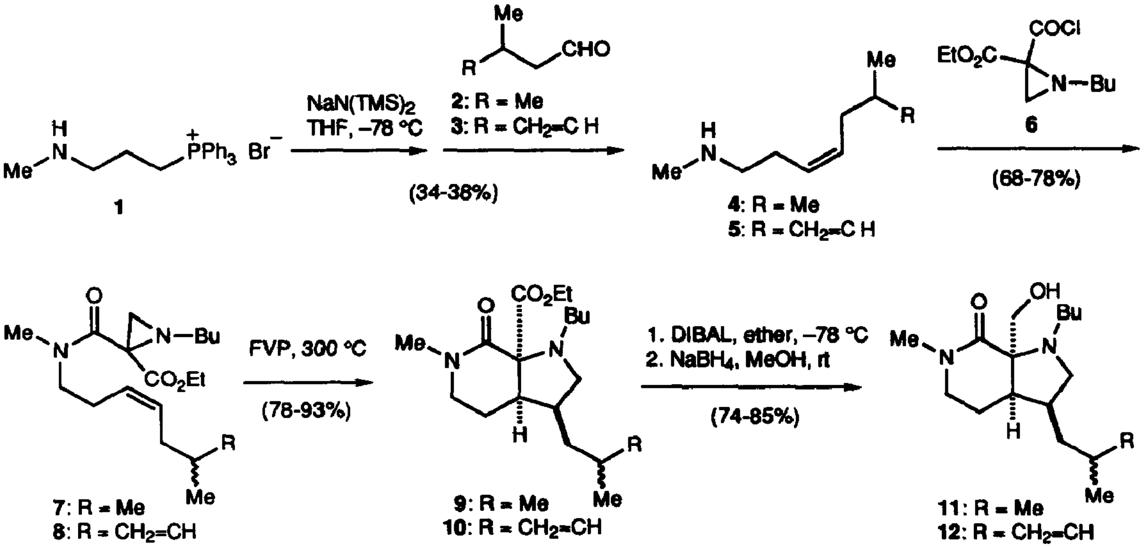
An Unusual Isomerization Under Lawesson Thiation Conditions.

Matthew J. Sharp and Clayton H. Heathcock*
Department of Chemistry, University of California, Berkeley, CA 94720

Abstract: Treatment of lactam esters **9** and **10** under Lawesson thiation conditions caused epimerization of a remote stereocenter, providing diastereomeric lactam esters **13** and **14**.

In connection with our synthetic approach to the marine natural product sarain A,[1] we synthesized the bicyclic lactam esters **9** and **10** as shown in Scheme 1. The synthetic protocol used began with aminophosphonium salt **1** and aldehydes **2** and **3** and was based on that previously reported for the preparation of related compounds.[2]

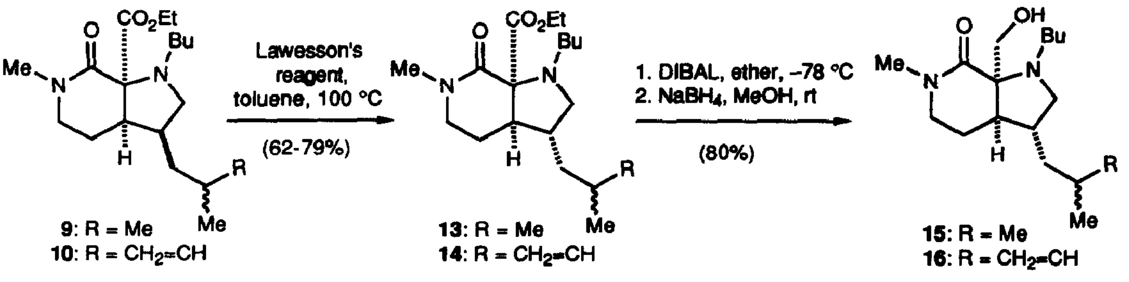
Scheme 1



The complete stereostructure of **9** was determined by single crystal x-ray analysis of derivative **11**, mp 84-85 °C. The relative configuration of **10** at the three ring stereocenters is assumed to be the same, by analogy.

In an attempt to activate the lactam carbonyl for addition reactions, **9** and **10** were treated under standard Lawesson thiation conditions.[3] Much to our surprise, no thiation was observed in either case. Instead, diastereomeric lactam esters **13** and **14** were obtained in good yield (Scheme 2). Reduction of the primary products **13** and **14** gave primary alcohols **15** and **16**.

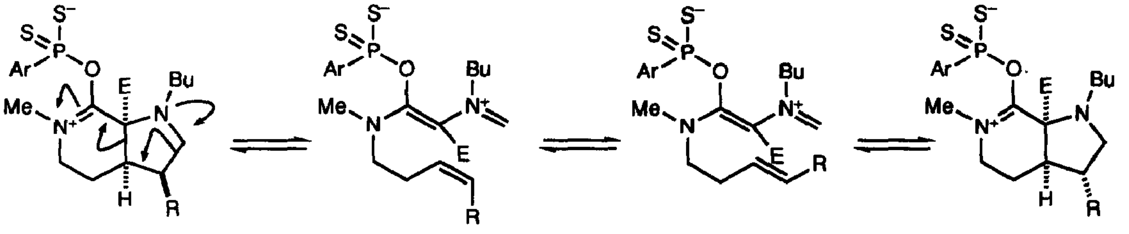
Scheme 2



The relative configurations of these diastereomeric reaction products were determined by nuclear Overhauser enhancement studies on lactam esters **9** and **13**. Molecular mechanics calculations[4] show that the lowest energy conformation of **13** is about 2.8 kcal mole^{-1} lower in energy than that of **9**.

The seemingly inexplicable isomerization might involve a 1,3-dipolar cycloreversion, as shown in Scheme 3 (E = CO_2Et). One must then postulate that some unknown sulfur radical species causes cis-trans isomerization the double bond. Normal 1,3-dipolar cycloaddition would give the observed product.[5]

Scheme 3



The failure of **13** and **14** to undergo thiation might be due to the sterically-hindered nature of the lactam carbonyl.

Acknowledgements. This work was supported by a research grant from the National Institutes of Health (GM 46057).

References and Notes.

1. (a) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863. (b) Cimio, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519.
2. Henke, B. H.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056.
3. Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.
4. Calculations were carried out with Macromodel using the MM2* force field and the TNCG minimization method. Global minimizations were carried out on simplified versions of **9** and **13** in which the ethoxycarbonyl and butyl groups were replaced by methyl groups.
5. The following control experiment established that Lawesson's reagent is essential for the observed isomerization: Compound **9** was heated in toluene (110 °C) for 6 h in the presence of 0.3 mole-equivalents of diphenyl disulfide. The ^1H NMR spectrum of the recovered material showed no detectable conversion to **13**.

(*Received in USA* 19 *January* 1994; *revised* 25 *March* 1994; *accepted* 31 *March* 1994)