# Thio-Claisen Rearrangements. An Asymmetric Synthesis of 4,4-Disubstituted Cyclohexenones with Vicinal Quaternary and Tertiary Stereocenters

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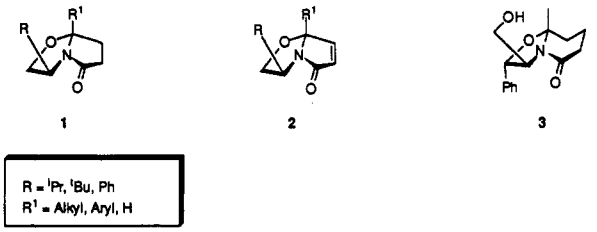
The thio-Claisen rearrangement, although potentially a powerful synthetic tool, has garnered relatively little attention when compared to its well-known oxygen analog.[1] As a result of our studies using chiral bicyclic lactams **1-3** to reach a host of chiral, nonracemic compounds,[2,3] we envisioned utilizing the O-Claisen

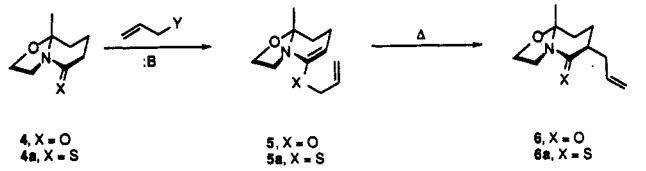



**1** **2** **3**

rearrangement starting with chiral lactams **4** and effecting an O-alkylation to **5**, which would then have the potential to undergo a [3,3] shift to form a new stereogenic center as in **6** (Scheme 1). Based on our previous successes with derivatives such as **6**, we felt that we could access a wide range of chiral, nonracemic cyclohexenones (*vide infra*).[4] However, all attempts to transform **4** into its O-allyl derivative **5** met with very poor yields and mixtures of C- and O-allyl products. We therefore considered the "thio version" of this process (**4a** → **5a** → **6a**) in the hope that S-alkylation of these lactams would proceed more efficiently. We can now report that this indeed was the case, and we describe our results leading to the title compounds in high enantiomeric purity. As mentioned above, the thio-Claisen rearrangement has received only sparse attention,[1] and only recently has there been a report of the stereoselectivity associated with this process.[5]

We transformed the readily obtainable and enantiomerically pure chiral bicyclic lactam **7**[4b] into its methyl ether (KH, THF, MeI) (Scheme 2) and then introduced the $\alpha$-methyl group (LDA, THF, −78 °C, MeI) to afford the monomethyl derivative **9** (88%) as a 1.2:1 mixture of $\alpha/\beta$-methyl diastereomers. This lack of selectivity was unimportant since the S-alkylation step (**10** → **11**) would render this center planar and provide a quaternary center after the thio-Claisen step had been performed. The lactam **9** was smoothly converted to the thiolactam **10** using the Belleau reagent (1 h, toluene, 110 °C, 98%).[6] The rearrangements were performed by first forming the thioenolate of **10** (2.0 equiv of LDA, THF, 0 °C) and then adding the allylic halide. The mixture of S-allyl derivatives **11** was quenched with an aqueous sodium

**Scheme 1**

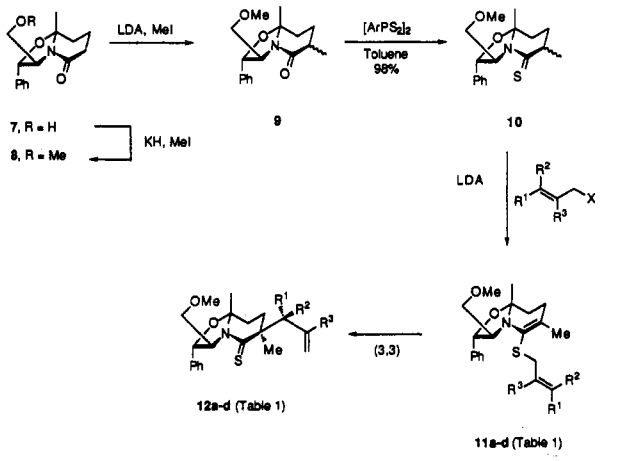



**4**, X = O
**4a**, X = S

**5**, X = O
**5a**, X = S

**6**, X = O
**6a**, X = S

**Scheme 2**




**7**, R = H
**8**, R = Me

**9**

**10**

**12a-d** (Table 1)

**11a-d** (Table 1)

**Table 1.** Diastereoselective Thio-Claisen Rearrangements (**11** → **12**)

| | allyl halide | | | | | | |
|---|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | $R^3$ | X | $T$ (°C)[a] | yield of **12** (%) | dr[b] |
| a | H | H | Me | Cl | 25 | 71 | 3:1 |
| b | Me | H | H | Br | 25 | 79 | 91:9 |
| c | Ph | H | H | Br | 140 | 48 | >99:1 |
| d | Me | Me | H | Br | 140 | 68 | >99:1 |

[a] Rearrangements at room temperature were carried out in THF; at 140 °C, xylene was the solvent employed. [b] Diastereomeric ratios determined by capillary GLC and 300-MHz NMR integration of the benzylic proton in the oxazolidine ring.

bicarbonate solution and without purification was either stirred at ambient temperatures or heated in an appropriate solvent for 12 h (Table 1). The diastereomeric ratios (Table 1) were determined by either NMR or gas chromatography, and the stereochemistry of the rearrangement was confirmed by single crystal X-ray determination of **12b** obtained from the crotyl thioether **11b**. The X-ray study clearly indicated that the allyl groups in **11** had entered the exo($\beta$) face of the bicyclic system (**12**), in contrast to our earlier studies, wherein enolate-based quaternary alkylation on the amide **1** preferred the endo($\alpha$) face.[4] The rearrangement to the $\beta$-face in **12** appears to depend upon several factors yet to be determined but, nevertheless, adds versatility to the stereochemical outcome using these chiral lactams since this thermal thio-Claisen reaction leads to the opposite stereoisomer.

From the examples depicted in the table, it is clear that the stereoselectivity is a function of the substitution pattern of the allylic halide. Poor selectivity was observed in entry a with methallyl chloride, although the rearrangement was facile at room temperature. On the other hand, crotyl bromide addition (entry b), while also undergoing rearrangement at room temperature, gave a much higher selectivity in spite of the presence of an isomeric impurity.[7] The use of cinnamyl bromide, geometrically pure, gave excellent stereoselectivity on rearrangement, although heating to 140 °C (xylenes) was required. Similarly, $\beta,\beta$-dimethylallyl bromide (entry d) proceeded with excellent selec-

(1) (a) Tamaru, Y.; Harada, T.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1980**, *102*, 2392. (b) Tamaru, Y.; Harada, T.; Yoshida, Z.-i. *Tetrahedron Lett.* **1978**, *19*, 2167. (c) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084. (d) Metzner, P. *Synthesis* **1992**, 1185 (a review on thiocarbonyls).

(2) For a recent review on this subject, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.

(3) For more recent studies utilizing **1** and **2**, see: (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (b) Meyers, A. I.; Snyder L. *J. Org. Chem.* **1993**, *58*, 36.

(4) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936. (b) Meyers, A. I.; Berney, D. *Org. Syn.* **1990**, *69*, 55.

(5) (a) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232. (b) Beslin, P.; Perrio, S. *Tetrahedron* **1992**, *48*, 4135. (c) Beslin, P.; Perrio, S. *Tetrahedron* **1991**, *47*, 6275.

(6) (a) Barrett, A. G. M.; Lee, A. C. *J. Org. Chem.* **1992**, *57*, 2818. (b) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815.

(7) The 91:9 ratio for the crotyl derivative, **11b** going to **12b**, was found to be a result of 4.5% *cis*-crotyl bromide present in the *trans*-isomer utilized.

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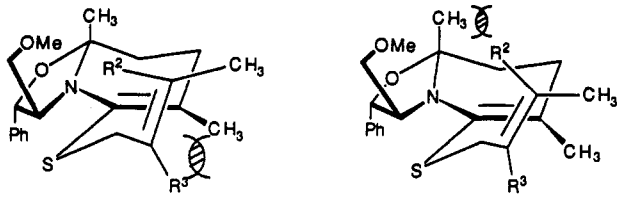


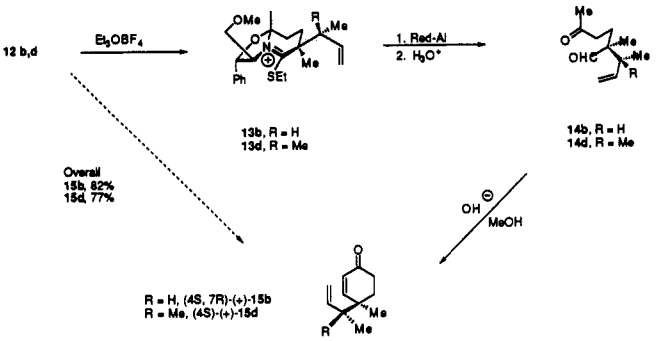
A, $R^3$ = alkyl, $R^2$ = H B, $R^3$ = H, $R^2$ = alkyl

**Figure 1.**

tivity. At present, we can suggest that the variations in rearrangement conditions, from 25 °C to 140 °C, may be the result of nonbonded interactions, as shown in Figure 1. In the thioenol ether **A**, the β-aminovinyl methyl group exhibits considerable interaction with the vinyl methyl group when $R^3$ = alkyl, thus allowing endo(α) entry to compete (~25%) in the rearrangement. Furthermore, when $R^2 = R^3 = H$, there appears to be little or no interaction with either the angular methyl group, or the aminovinyl methyl group and rearrangement proceeds at lower temperatures, as observed with the *trans*-crotyl derivative (entry b). In **B**, the effect of the substituent $R^2$ is seen (entry d) where β,β-dimethylallyl bromide was employed ($R^2 = CH_3$). The rearrangement required high temperatures to overcome the $R^2$–$CH_3$ interaction in **B**, but the absence of an alkyl substituent for $R^3$ allowed for the observed high stereoselectivity, leading to the exo(β) product.

To demonstrate the synthetic value of this highly selective thio-Claisen process, we were successful in transforming the rearranged products **12b,d** to cyclohexenones **15b,d** in high enantiomeric purity (Scheme 3). This was accomplished by treating the thio lactams **12b** or **d** with Meerwein reagent (1.2 equiv, $(CH_2Cl)_2$, 83 °C) to generate the thioiminium salts **13** which were reduced with Red-Al (1.05 equiv, 0 °C) to the thioaminal and directly hydrolyzed (3:2, EtOH:$H_2O$, $HClO_4$) to furnish the keto aldehydes **14**. The aldol cyclization was performed with dilute KOH in MeOH to provide the cyclohexenones in good yield (**15b**, 82%; **15d**, 77%). It is noteworthy that the latter cyclohexenone systems contain two vicinal quaternary

**Scheme 3**



centers (**15d**) or two vicinal stereogenic centers—one tertiary, the other quaternary.[8] This preliminary report will now set the stage for further studies involving more complex systems such as trichodiene or bazzanene,[9] compounds with vicinal stereogenic quaternary centers which have to date not been successfully reached in an asymmetric manner.

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**Supplementary Material Available:** General conditions, complete physical data, ($^1$H NMR spectra **15b**, **15d**), combustion analyses, ORTEP, X-ray structural data, and coordinates (**12b**) (15 pages). This material is contained in many 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.

(8) For other routes to enantiomerically pure adjacent quaternary and tertiary stereocenters, see: (a) Yamaguchi, M.; Hamada, M.; Nakashima, H.; Minami, T. *Tetrahedron Lett.* **1987**, *28*, 1785. (b) Knölker, H.-J.; Graf, R. *Tetrahedron Lett.* **1993**, *34*, 4765.

(9) The syntheses of trichodiene and bazzanene in racemic form have been reported, c.f.: Kraus, G. A.; Thomas, P. J. *J. Org. Chem.* **1986**, *51*, 503. Gilbert, J. C.; Weichman, B. E. *J. Org. Chem.* **1986**, *51*, 258 and earlier references to other syntheses cited by these authors. Recently, Gilbert reported a synthesis of trichodiene in enantiomerically enriched form (41% ee). Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255.