ORGANIC LETTERS

2009
Vol. 11, No. 18
4224−4227

Asymmetric [3,3]- and [1,3]-Sigmatropic Rearrangements of γ-Allyloxy Vinylogous Urethanes

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Received July 22, 2009

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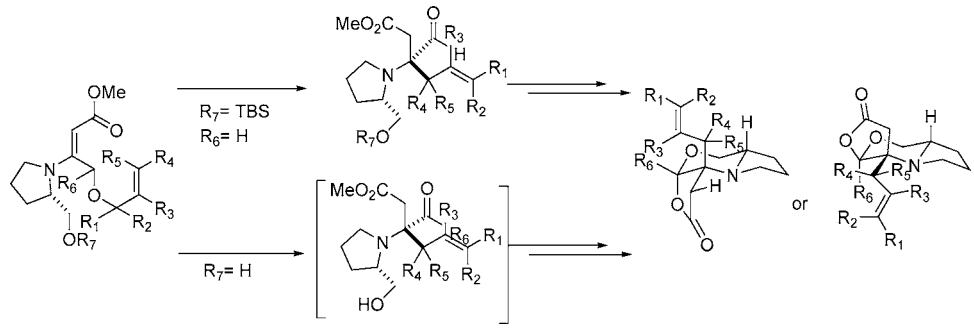
Publication Date (Web): August 25, 2009 | doi: 10.1021/ol901679h

ABSTRACT



Vinylogous urethanes derived from condensation of prolinol or prolinol *tert*-butyldimethylsilyl ether with 4-allyloxyketoester were found to undergo a thermal [3,3]-sigmatropic rearrangement, providing compounds with N-substituted quaternary carbon centers. Cyclizations (subsequently or in situ) of the rearranged products generated hexahydro-3,4-dioxa-8a-aza-as-indacen-2-ones. Various terminally substituted allyloxy ketoesters and arylmethoxy ketoesters were found to generate tricyclic compounds via [1,3]-sigmatropic rearrangement. Finally, tricyclic lactones were transformed successfully into lactams.

During the course of our investigation into [2,3]-Wittig rearrangements utilizing γ-allyloxy vinylogous urethanes **3** as starting material, trace amounts of aldehyde **4** were detected during the condensation of pyrrolidine with ketoesters **2**.[1] The aldehyde was presumably generated via a [3,3]-sigmatropic rearrangement pathway (the Claisen rearrangement) between the isomerized double bond and the allyloxyl moiety.[2] [3,3]-Sigmatropic rearrangement of a similar system **5**, generated by catalytic aminomercuriation of propagyl allyl ether, was previously reported by Barluenga.[3] More recent rearrangement studies of **6** and **7** reported, respectively, by Kazmaier and Hruby led to the syntheses of syn- and anti-β-substituted γ,δ-unsaturated amino acids (Figure 1).[4,5]

We envisioned that the rearrangement of the system **3** would constitute a general protocol for the construction of a chiral N-substituted quaternary carbon center if a chiral pyrrolidine was involved.[6] Therefore, syntheses of chiral

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(1) Li, Y.-J.; Lee, P.-T.; Yang, C.-M.; Chang, Y.-K.; Weng, Y. -C.; Liu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 1865.

(2) For reviews of the Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev* **1988**, *88*, 1423. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (c) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. (d) Nubbemeyer, U. *Synthesis* **2003**, 961.

(3) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Org. Chem.* **1987**, *52*, 5190.

(4) (a) Kazmaier, U. *Angew. Chem., Int. Ed.* **1994**, *33*, 998. (b) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 2012. (c) Kazmaier, U.; Maier, S. *J. Org. Chem.* **1999**, *64*, 4574. (d) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850.

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10.1021/ol901679h CCC: $40.75 © 2009 American Chemical Society
Published on Web 08/25/2009

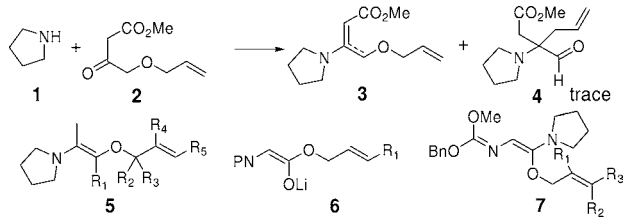


Figure 1. 3 and other known enol ether enamine systems.

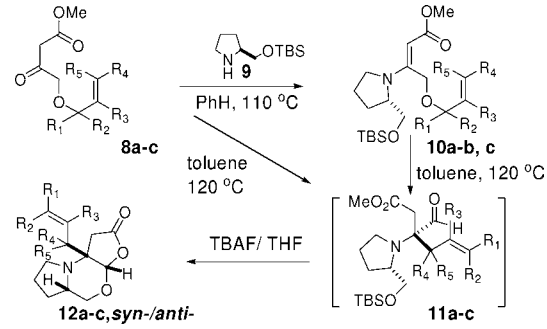
vinylogous urethanes incorporated with chiral pyrrolidine were commenced to investigate this rearrangement.

Compounds **10a**,**b** were first synthesized by condensation of ketoesters **8a**,**b** with prolinol *tert*-butyldimethylsilyl ether **9** in 98% and 95% yield, respectively. When **10a**,**b** were heated, using toluene as solvent, they provided inseparable diastereomeric aldehydes **11a**,**b**. While **10a**,**b** were stable enough to be isolated, attempts to isolate **10c** under the same conditions gave mixtures of **10c** and **11c**. It is conceivable that **11c** was generated due to the prolonged heating in the synthesis of **10c**. Therefore, **11c** was obtained simply by heating of **8c** with prolinol *tert*-butyldimethylsilyl ether **9** in toluene. Subsequent removal of the O-silyl protecting group of **11a**−**c** by tetra *n*-butylammonium fluoride (TBAF) resulted in the formation of *syn*- and *anti*-hexahydro-3,4-dioxa-8a-aza-as-indacen-2-ones **12a**−**c** in 87−89% yields (Table 1). The anti stereochemistry of the minor product **12a**-*anti* was confirmed by X-ray analysis (Figure 2).[7]

The success of this rearrangement was found to be highly influenced by the substitution on the allyl group. Having substituents on R_3, R_4, or R_5 generally led to the formation of polymerized products that would most likely have resulted from the decomposition of aldehydes.

To avoid the decomposition problem, prolinol was used as a surrogate to react with various 4-allyloxy substituted ketoesters. It is conceivable that the intramolecular trapping of the resulting aldehyde by the hydroxymethyl moiety to form hemiacetal together with the following cyclization to form a lactone would both efficiently protect the aldehyde from decomposition and provide thermodynamic stability for the forward rearrangement. Therefore, when L-prolinol was used to react with terminal unsubstituted allyloxy ketoesters ($R_4 = R_5 = H$), it provided tricyclic compounds in better yields than in prolinol *tert*-butyldimethylsilyl ether cases (Table 2). In entries 1 and 2, the rearrangement provided reasonable diastereoselectivities, whereas in entry 3 with cumbersome *gem*-dimethyl substitution the rearrangement succumbed to 2 to 1 selectivity. In entry 4, the internal vinylic

Table 1. Rearrangement of Various Alkene Substrates



entry	substrate	% yield of **10**	% yield of **11**[a]	% yield[b] of **12**(syn/anti)
1	$R_1=R_2=R_3=R_4=R_5=H$ (a)	98	68	**12a**-*syn* 87(89:11) **12a**-*anti*
2	$R_1=Me$, $R_2=R_3=R_4=R_5=H$ (b)	95	72	**12b**-*syn* 89(84:16) **12b**-*anti*
3	$R_1=R_2=Me$, $R_3=R_4=R_5=H$ (c)		72	**12c**-*syn* 87(72:28) **12c**-*anti*

[a] Mixtures of inseparable diastereomers. [b] Isolated yields.

methyl group seems to insert a synergistic effect with the chiral arm, therefore providing exclusively **14** in 90% yield.

When terminally substituted propenoxy ketoesters **15a**−**c** were used in the rearrangement studies (Table 3), **15a** (R_4 = Pr) provided [3,3]-rearranged product **16**-*syn* in 65% yield. Although absolute stereochemistries of the resulting propyl group were not yet determined, 300 MHz ^{1}H NMR in D-chloroform indicated that the ratios of diastereomers were approximately 2/1. When bulkier substituted **15b** (R_4 = Ph) and **15c** ($R_4 = R_5$ = Me) were used in the rearrangement studies, **15b** provided **17a**-*syn* and **17b**-*syn*/*anti* in 73% yield and in 5:75:20 ratio. In comparison to the propyl substitution on **16**-*syn*, phenyl substitution on **17a**-*syn* turned out to be

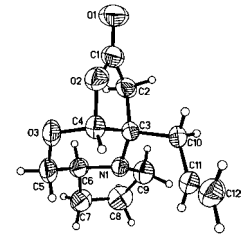


Figure 2. X-ray crystallographic structure (ellipsoid: 50% probability) of **12a**-*anti*.

(6) For recent reviews regarding synthesis of N-substituted quaternary carbon, see :(a) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.

(7) CCDC 678877 & CCDC 678876 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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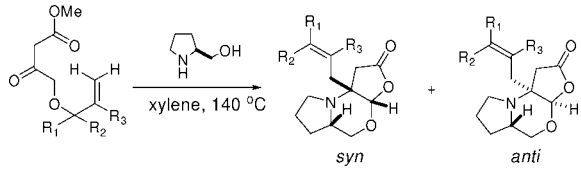
Table 2. Rearrangement of Various Alkene Substrates



entry	substrate	products[a] (yield)	(syn/anti) ratio[b]
1	$R_1 = R_2 = R_3 = H$, **8a**	84	**12a** (5:1)
2	$R_1 = Me$, $R_2 = R_3 = H$, **8b**	81	**12b** (9:1)
3	$R_1 = R_2 = Me$, $R_3 = H$, **8c**	80	**12c** (2:1)
4	$R_3 = Me$, $R_1 = R_2 = H$, **13**	90	**14** (syn only)

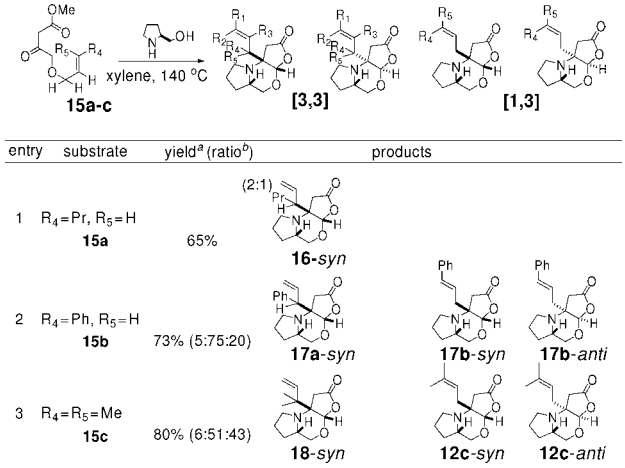
[a] Isolated yields. [b] Integration from ^{1}H NMR signals.

stereospecific. Nevertheless, the absolute stereochemistry could not be determined. Ketoester **15c** rearranged to **18a**-*syn* and **12c**-*syn*/*anti* in 80% yield and in 6:51:43 ratio. Products **17b**-*syn*/*anti* and **12c**-*syn*/*anti* were presumably generated via a previously unforeseen [1,3]-sigmatropic rearrangement pathway (Table 3).[8]

Temperature-dependent rearrangement of **15c** under different solvents was studied as shown in Table 4. Although reaction for 1 h provided about a 3:2 ratio of [3,3]- to [1,3]-sigmatropic rearrangement products in benzene, it provided exclusively the [1,3]-rearranged product when DMF was used as refluxing solvent (Table 4).

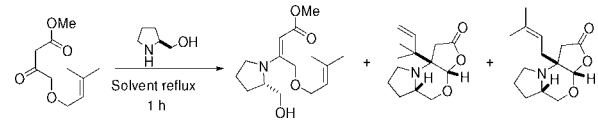
To clarify whether [1,3]-sigmatropic rearrangement should be involved in the simple allyl substituted case ($R_1 \sim R_5 =$ H), a deuterium-labeled compound **20** was subjected to the study.[9] Careful NMR analysis indicated that the compound underwent pure [3,3]-sigmatropic rearrangement to generate

Table 3. Rearrangement of R_4, R_5 Substituted Alkene Substrates



[a] Isolated yields. [b] Integration from ^{1}H NMR signals.

Table 4. Relative Product Composition of [3,3]- vs [1,3]-Sigmatropic Rearrangement under Different Solvents[a]



solvent	bp (°C)	**19** (%)	**18**-*syn* (%)	**12c**-*syn*/*anti* (%)
benzene	80	52	28	20
toluene	110	10	30	60
xylene	144		10	90
DMF	153			100

[a] Ratio determined by the integration from ^{1}H NMR signals.

exclusively compound **21** with no [1,3]-rearrangement (Figure 3).[10]

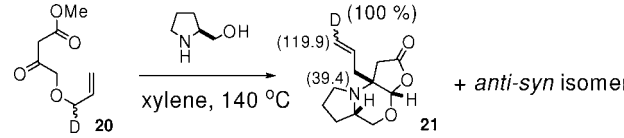
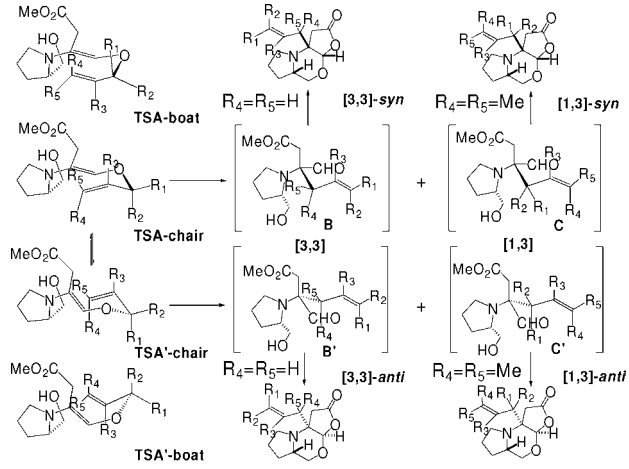


Figure 3. Deuterium labeling studies of rearrangement of **20**.

To account for the diastereoselectivity and the pathway preference between [3,3]- vs [1,3]-rearrangement products, Scheme 1 was depicted to briefly explain our observations.

Scheme 1. Reasoning for the syn/anti Ratio and [3,3]- vs [1,3]-Reaction Pathway



The chiral arm (CH_2OH) on the pyrrolidine was expected to hamper the approach of the allyloxy moiety from the

(8) Recent review of [1,3] O-to-C rearrangement, see: Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240.

(9) Deuterated compound **20** was obtained via the reduction of acrolein with sodium borodeuteride, follow by the reaction with methyl 4-bromoacetoacetate.

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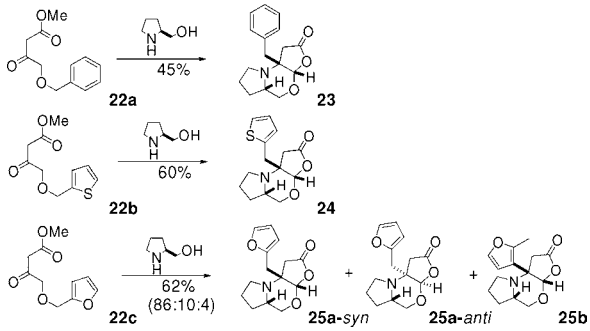
α-face in the TSA′ and therefore bias the reaction to proceed via TSA in favor of generating the syn product as the major diastereomer. Although moderate stereoselectivity of the resulting azaquaternary center was observed, stereoselectivity of the substitution on the neighboring allylic position ranged from nonselective (R_4 = Pr, Table 3, entry 1) to excellent (R_4 = Ph, Table 3, entry 2). Presumably, it depends on the degree of preferences between TSA-chair and TSA-boat. While the less hindered allyloxy moiety (Table 2, entries 1−4, and Table 3, entry 1) rearranged exclusively by the [3,3]-pathway, the more hindered case (Table 3, entries 2 and 3) was observed to rearrange mainly by the [1,3]-pathway. Presumably the steric interaction between the two reacting terminals prohibits the [3,3]-pathway.

After completion of the investigations on allyloxy systems, we turned our attention to the study of the substitution pattern when allyloxy double bonds are part of aromatic systems. Arylmethoxy-substituted ketoesters such as 1-benzyloxy, 1-thiophenomethoxy, and 1-furanomethoxy **22a**−**c** were first synthesized in 71−75% yields, respectively. Though the phenyl case provided 45% of [1,3]-rearranged tricyclic product **23**, thienyl and furanyl provided moderate yields of [1,3]-rearranged products **24** and **25a**-*syn*/*anti*.[11] Meanwhile, in the furanyl case, trace amounts of [3,3]-rearranged product **25b** were observed and carefully isolated (Scheme 2).

Scheme 2. Rearrangement of Arylmethoxy-Substituted Substrate



A single crystal of **25a**-*syn* was analyzed by X-ray crystallography to confirm its stereochemistry as well as the stereochemistries of all the other related *syn*-compounds[7] (Figure 4).

Finally, tricyclic lactones could be successfully converted to the lactams **26**−**30**, simply by reacting them with benzylamine and trifluoroacetic acid in toluene at reflux to generate 3-benzyl-octahydro-4-oxa-3,8a-diaza-as-indacen-2-ones in 80−90% yields (Scheme 3).

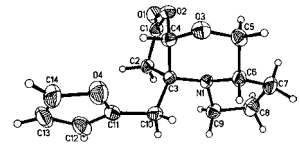


Figure 4. X-ray crystallographic structure (ellipsoid: 50% probability) of **25a**-*syn*

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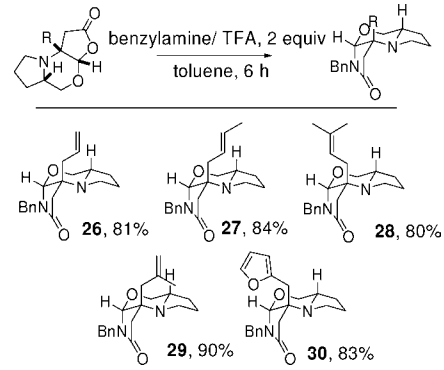
Scheme 3. Transformation of Tricyclic Lactones into Lactams



In summary, we have reported the studies of [3,3]- and [1,3]-sigmatropic rearrangements of the γ-allyloxy and arylmethoxy vinylogous urethane systems. A chiral N-substituted quaternary cabon center was successfully obtained, and tricyclic lactones can be transformed successfully into lactams. Further studies and their applications to natural product synthesis are currently in progress in our laboratory.

Acknowledgment. We thank the Taiwan National Science Council (NSC-94-2113-M-415-003) for generous financial support. Database service from the NCHC and partial support from the mass spectrometer facility provided by NCHU and support from the X-ray facility of NTU are also acknowledged.

Supporting Information Available: Full experimental details and characterization including ^{1}H and ^{13}C spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Proton-decoupled ^{13}C spectra showed a 1:1:1 triplet at 119.9 ppm for the terminal carbon of alkene (CH_2−CH═CHD) and a pure singlet at 39.4 ppm for the methylene carbon (CH_2−CH═CHD).

(11) [1,3]-Rearrangement involving the arylmethyl shift from oxygen to carbon, see: (a) Burger, K.; Gaa, K.; Geith, K.; Schierlinger, C. *Synthesis* **1989**, 850. (b) Shishido, K.; Shitara, E.; Fukumoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 5810.

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