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[2,3]-Wittig rearrangement of methyl β-pyrrolidinyl-γ-allyloxy-(*E*)-2-butenoate. Expeditious synthesis of 5-alkenyl-4-pyrrolidin-1-yl-5*H*-furan-2-ones ☆

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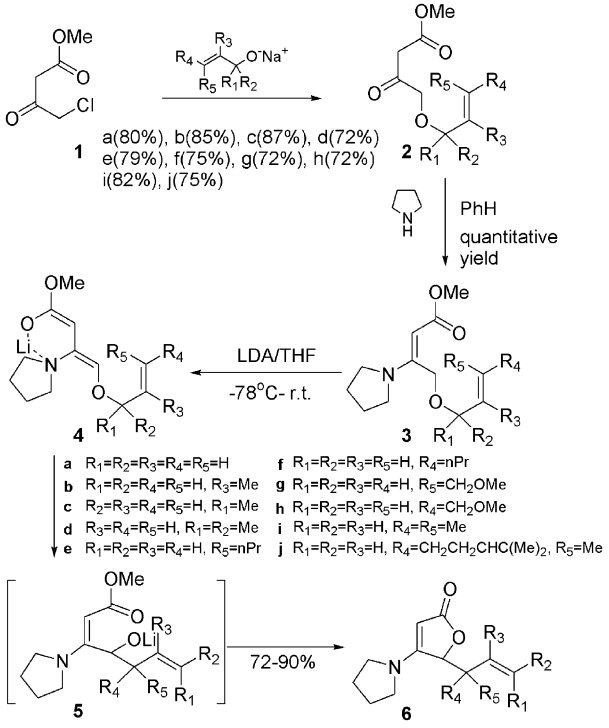
Abstract—Dienolates of various γ-allyloxy substituted methyl β-pyrrolidinyl (*E*)-2-butenoate undergo a [2,3]-Wittig rearrangement to generate various 5-alkenyl-4-pyrrolidin-1-yl-5*H*-furan-2-one type compounds.

5-Substituted 4-pyrrolidin-1-yl-5*H*-furan-2-ones **6** are important synthetic intermediates for natural product synthesis,[1] because they are amenable to chemical transformations in generating useful α,β-unsaturated γ-lactones and tetronic acids.[2,3] It has been shown that compound **6** could be obtained by the alkylation of enolates, which are derived from 4-pyrrolidin-1-yl-5*H*-furan-2-ones.[1c] Herein, we would like to report a new synthetic route for the synthesis of **6** involving the [2,3]-Wittig rearrangement of γ-allyloxy-β-pyrrolidinyl-2-butenoate dienolates **4** and the subsequent cyclization of the resulting alkoxides **5**.[4] This method not only provides the synthesis of simple C_5 allylated products but also offers the possibility to construct compounds with more sophisticated C_5-substitutions.

We commenced the reaction studies with the synthesis of γ-allyloxy substituted compounds **3a**–**j**. Ketoesters **2a**–**j** were first synthesized by the reaction of various allyl-oxides with methyl 4-chloroacetoacetate in 68–85% yields, respectively.[5] Subsequent condensation of **2a**–**j** with pyrrolidine utilizing Dean–Stark apparatus provided **3a**–**j** in almost quantitative yields (Scheme 1).

When simple substituted compounds **3a**–**d** ($R_4 = R_5 = H$) were treated with 2.5 equiv of LDA at



Scheme 1.

Keywords: [2,3]-Wittig rearrangement.
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−78 °C and then warmed to room temperature over a period of 4 h, a clean conversion of dienolates **4a–d** to compounds **6a–d** via [2,3]-Wittig rearrangement were achieved in moderate to good yields without the complication of [3,3]-sigmatropic rearrangement.[6] Meanwhile, product **6c** was found to have exclusively (*E*)-crotyl substitution (Table 1).

When R_4 or R_5 mono-substituted compounds **3e–h** were used in the reaction studies, ratios of *syn* and *anti* diastereomers were obtained, respectively, as shown in Table 1.

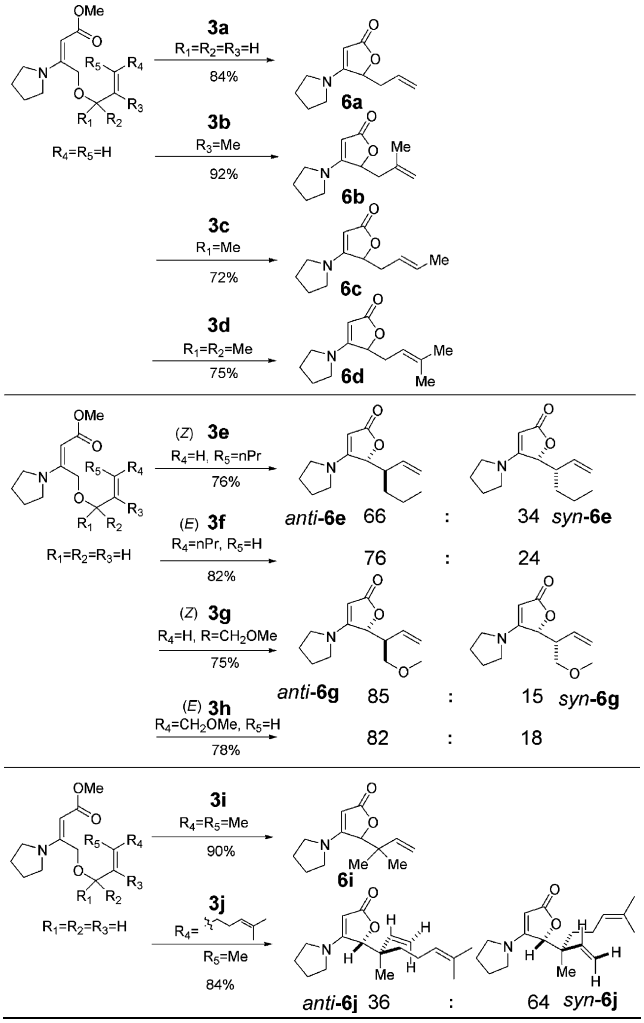
Rearrangement of **3e** and **3f** gave both *anti*-**6e** and *syn*-**6e** totally in 75% and 78% yields, respectively. The stereochemistry of the major product *anti*-**6e** was determined by single-crystal X-ray analysis as shown in Figure 1.[7] The outcome of the stereochemistry of the reactions of **3e** and **3f** were explained by possible transition states as shown in Scheme 2. When **3e** with a (*Z*)-allyloxy substitution was used in the reaction, via **7A** as the preferred transition state, **9C** was obtained as the major product ($R_Z = n$-Pr). On the other hand, when **3f** with (*E*)-substitution was used in the reaction, since **7A′** suffer less steric interactions between R_E group and the *pseudo*-equatorial H of the pyrrolidine ring,[8] **9C′** was obtained as the major product ($R_E = n$-Pr). Under the circumstances, though **3e** and **3f** are different both in nature by the configuration of the double bond and the different preference in the reaction transition state, they reacted to generate *anti*-**6e** as the same preferred product. The ^{1}H NMR signal of the H_a of *endo*-vinyl group of *anti*-**6e** at 5.55 ppm, relative to the signal of H_a of *exo*-vinyl group of *syn*-**6e** at 5.91 ppm, suggested an up-field shielding of H_a by a neighboring carbonyl group in *anti*-**6e** as shown in Figure 2.

When **3g** and **3h** were utilized in the reaction studies, *anti*-**6g** was obtained as the major product as shown in Table 1.[9]

With tri-substituted compounds **3i** and **3j** undergoing [2,3]-Wittig rearrangement, **6i** was obtained from the reaction of **3i** as the exclusive product without any [1,2]-rearrangement product being observed.[10] The reaction of **3j** provided *anti*-**6j** and *syn*-**6j** in 36/64 ratio totally in 84% yields.[11]

After having completed the rearrangement studies of linear allyloxy system **3a–j**, endocyclic alkene derived

Table 1. [2,3]-Wittig rearrangement of **3a–j**[a,b]



[a] All the experiments were conducted using THF as solvent. The chemical yields were indicated after purification by chromatography.

[b] Diastereomeric ratios were determined by ^{1}H NMR integration.

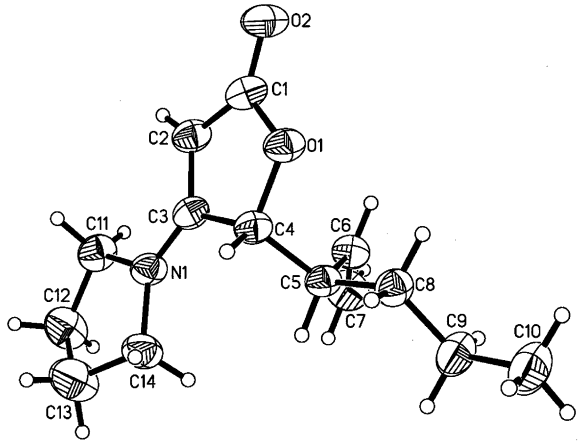
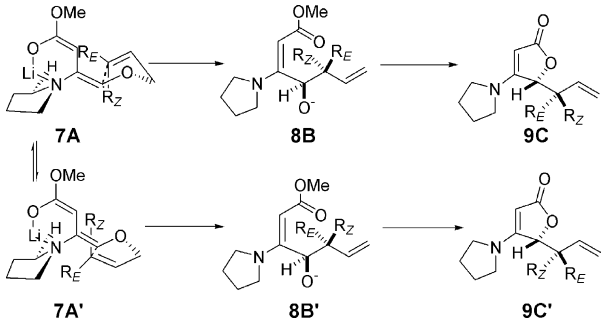


Figure 1. ORTEP drawing of *anti*-**6e**.



Scheme 2.

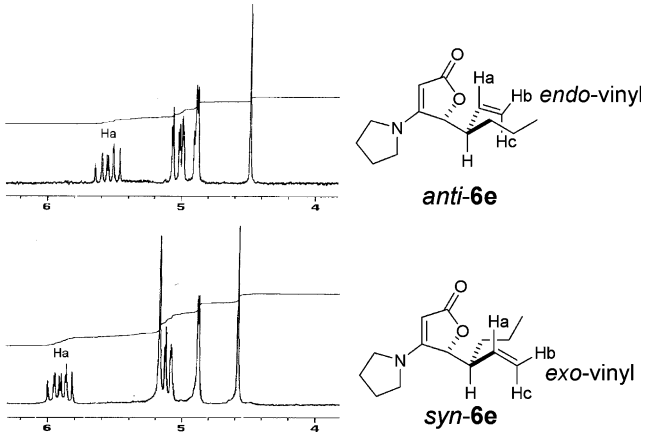
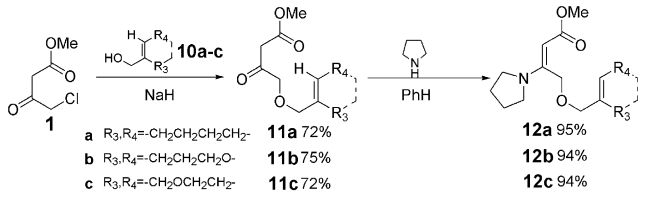
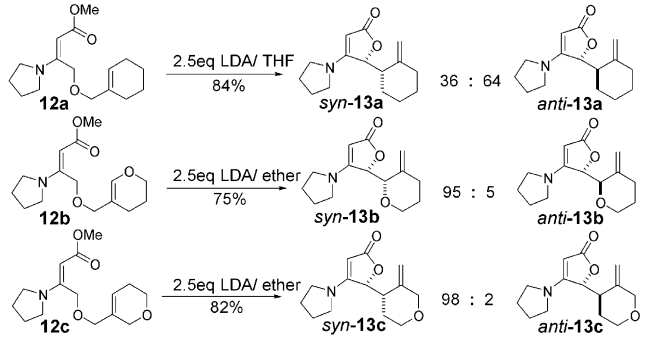


Figure 2.

allyloxy compounds **12a–c** were synthesized in 75–85% yields according to the precedent procedure and were utilized in rearrangement studies[12] (Scheme 3). Rearrangement of **12a** under standard procedure, using THF as solvent, generated 84% yield of *syn*-**13a** and *anti*-**13a** in 34/64 ratio.[13] When dihydropyran compounds **12b–c** were used, respectively, in the rearrangement studies



Scheme 3.



Scheme 4.

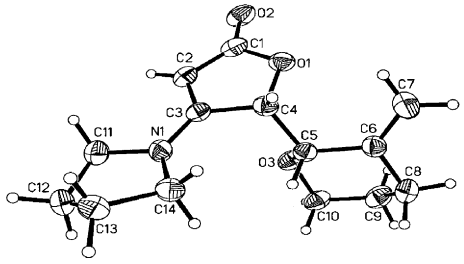


Figure 3. ORTEP drawings of *syn*-**13b** and *syn*-**13c**.

using diethyl ether and THF as reaction co-solvent (ethyl ether/THF, 4/1), excellent diastereoselectivities of 5-(tetrahydro-pyran-2-yl)-5*H*-furan-2-ones (*syn*-**13b**/*anti*-**13b**) and 5-(tetrahydro-pyran-4-yl)-5*H*-furan-2-ones (*syn*-**13c**/*anti*-**13c**) were obtained in 95/5 and 98/2 ratio, respectively (Scheme 4). The stereochemistry of major products *syn*-**13b** and *syn*-**13c** were analyzed by single crystal X-ray crystallography as shown in Figure 3.[14]

Transition states **14A** and **14B** relative to **14C**, with less steric interaction between dihydropyran and pyrrolidine-ring moiety, were proposed to account for the formation of major products *syn*-**13b** and *syn*-**13c**, respectively. Excellent diastereoselections of these two rearrangements of **12b** and **12c**, relative to the rearrangement of **12a**, suggest an important involvement of the lithium–oxygen chelation (Fig. 4).

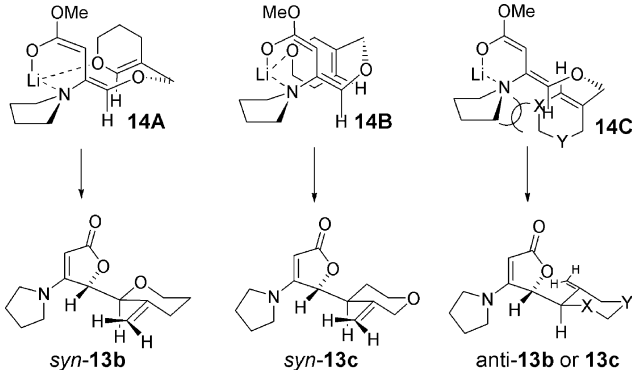


Figure 4.

In summary, we have shown that [2,3]-Wittig rearrangement of the dienolates derived from γ-allyoxy-β-pyrrolidinyl-2-butenoates is applicable to the efficient synthesis of sophisticated 5-substituted-4-pyrrolidin-1-yl-5H-furan-2-ones. Further studies on the asymmetric version of this reaction as well as the synthetic applications of the methodology are in progress in our laboratory.

Acknowledgements

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14. The crystal structure of compounds *syn*-**13b** and *syn*-**13c** have been deposited at the Cambridge Crystallographic Data Centre as CCDC 212546 and CCDC 212547.