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# Diastereoselectivity in the Carroll rearrangement of β-keto esters of tertiary allylic alcohols ☆

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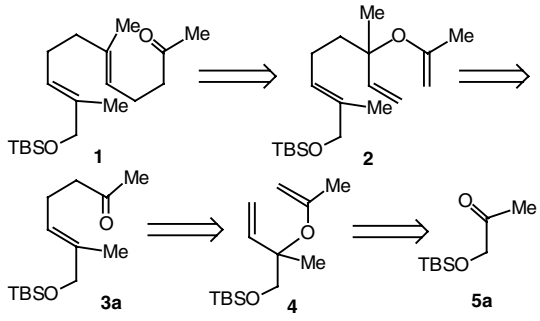
**Abstract**—Carroll rearrangement of β-keto esters derived from tertiary allylic alcohols, for example, **7**, under basic conditions followed by decarboxylation of the resulting β-keto acids yielded the expected γ,δ-unsaturated methyl ketones **8** with a range of olefin geometries from 100:0 to 1:1.8 *E*/*Z*, depending on the relative steric requirements of the two groups at the allylic center.

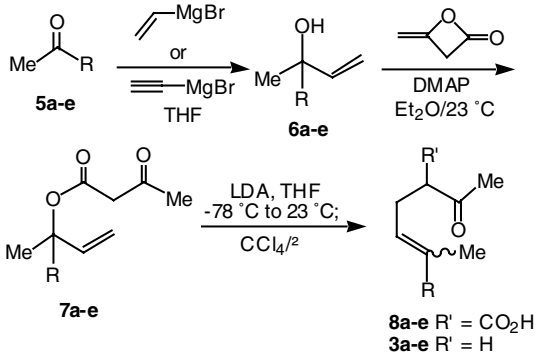

For a proposed synthesis of several biologically active polycyclic triterpene natural products, we investigated the use of the Carroll rearrangement[1] in order to achieve the desired olefin geometry in the 7-substituted 6-methyl-5-hepten-7-one subunit (Scheme 1). In particular, we hoped that the steric difference between a silyloxymethyl and a methyl group in an intermediate such as **4** would afford predominantly the *E*-olefin geometry in the Claisen rearrangement product **3a**. Likewise, we hoped for a similar selectivity in the rearrangement of **2** to give **1**.




**Scheme 1.**

We report herein the results of the Carroll rearrangement of β-keto esters of a series of tertiary allylic alcohols with alkyl groups of differing sizes. Although the yields of the rearrangement process are low, we have demonstrated the ability to access both geometries with varying functionality on the olefins.

Preparation of the substrates **7a**–**e** for the Carroll rearrangement was straightforward (Scheme 2).[2] The two silyloxy derivatives **5ab** were obtained in good yield from reaction of either TBSOTf or TIPSOTf with commercially available acetol and triethylamine or pyridine. Subsequent treatment with vinylmagnesium




**Scheme 2.**

*Keywords*: Carroll rearrangement; [3,3]-sigmatropic rearrangement; steric effects; electronic effects.

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**Table 1.** Formation and Carroll rearrangement of β-keto esters **7a–e**

| R | | Yield (%) | | Yield (%) | | Yield (%) | $E/Z$ ratio |
|---|---|---|---|---|---|---|---|
| $CH_2OTBS$ | **6a** | 70 | **7a** | 88 | **3a** | 36 | 2.1:1 |
| $CH_2OTIPS$ | **6b** | 100 | **7b** | 67 | **3b** | 53 | 1.4:1 |
| $CH(OMe)_2$ | **6c** | 99 | **7c** | 75 | **3c**[a] | 86 | 100:0 |
| $CH{=}CMe_2$ | **6d** | 100 | **7d** | 100 | **3d** | 38[b] | 3:1[c] |
| C≡CH | **6e** | 93 | **7e** | 68 | **3e** | 13 | 1:1.8 |

[a] Acidification of the aqueous layer to retrieve acid **8c**, even to a pH of 5, caused the dimethyl acetal to be completely converted to the corresponding aldehyde.

[b] The reported yield is for the inseparable mixture of products where both the dimethylvinyl and vinyl substituents participated in the rearrangement. See text.

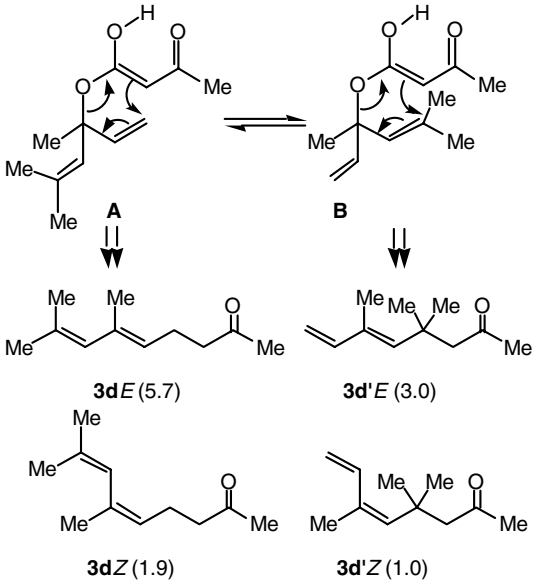
[c] See text for discussion.

bromide in THF provided **6ab** in 70% and 100% yields, respectively. The dimethyl acetal derivative **6c** was obtained from reaction of vinylmagnesium bromide and pyruvaldehyde dimethoxy acetal **5c** in THF in 99% yield. The dimethylvinyl derivative **6d** was obtained from reaction of vinylmagnesium bromide with mesityl oxide **5d** in THF in quantitative crude yield. Finally, the enyne substrate **6e** was obtained from reaction of methyl vinyl ketone with ethynylmagnesium bromide in THF in good yield.

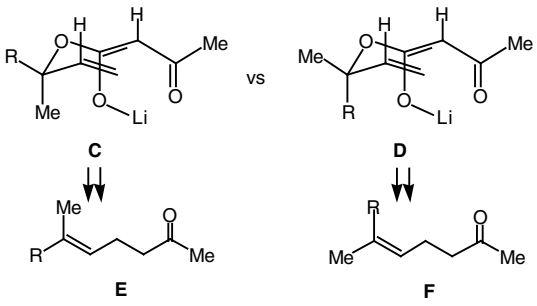
All of the tertiary alcohols **6a–e** were treated with diketene and catalytic DMAP in ether to afford the acetoacetates **7a–e** in good to excellent yields (Table 1). Treatment of the substrates **7a–e** with LDA in THF at −78 °C with subsequent warming to 23 °C furnished the Carroll rearrangement products, the β-keto acids **8a–e**, in good crude yields. These were generally not purified but immediately refluxed in $CCl_4$ to effect decarboxylation and give the ketones **3a–e** in poor to good yield. The dimethyl acetal of **8c** was hydrolyzed during the purification to give the aldehyde **3c**, which was somewhat unstable and therefore was reduced to the primary alcohol **9c** for further analysis. The acid sensitivity of **3c–e** made column chromatography partially responsible for the low yields, even on silica gel columns deactivated with triethylamine. The olefin geometries of **3a–e** were determined by assignment of the cross peaks in the NOESY spectra.

The rearrangement of the bis-vinyl substrate **7d** produced intriguing results, with a mixture of four compounds being isolated (Scheme 3). Careful proton NMR analysis with significant use of difference NOE allowed us to assign the mixture as shown below, namely: **3d*E***:**3d′*E***:**3d*Z***:**3d′*Z*** 5.7:3.0:1.9:1.0. Thus, the rearrangement takes place predominantly on the unsubstituted vinyl group via **A**, rather than via **B**, presumably due to steric hindrance, although the selectivity (roughly 2:1) is less than might have been anticipated. The $E/Z$ ratio was 3:1 in each case.

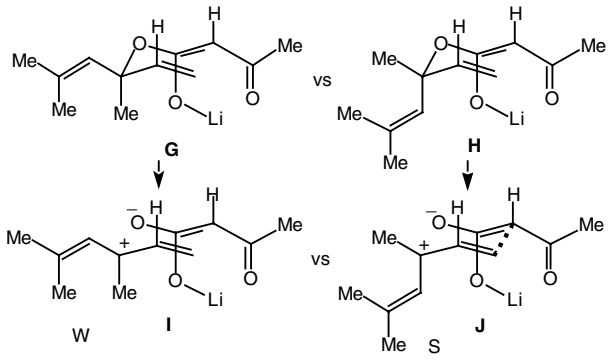
The stereochemistry resulting from the cyclizations was in accordance with the anticipated steric differences in all but one case. For the substrates **7a–c**, an $E$ alkene was expected due to the size difference between a methyl substituent and the R group. Bulky R groups would exhibit a preference for the equatorial position in the transition state, for example, **C** to give **E**, in order to avoid the pseudo 1,3-diaxial interactions that would result from an axial arrangement as in **D**, which would give **F** (Scheme 4). We see the size of the steric differences of the diaxial interactions reflected in the olefin ratios, with the most sterically demanding R group, the dimethoxymethyl group **7c**, having the highest $E/Z$ selectivity (essentially only one isomer corresponding to




**Scheme 3.**




**Scheme 4.**




**Scheme 5.**

**E** was formed). The substrate with the smallest R group, the ethynyl substrate **7e**, afforded the expected product **3e*Z***, namely the *Z*-alkene corresponding to **F**, since the methyl substituent is now the larger one and prefers the equatorial position, for example **D**. The only somewhat surprising case is the olefin **7d** where both vinylic units prefer the equatorial position vs. the sterically slightly larger methyl group (A values: methyl, 1.74; vinyl, 1.49–1.68).[3] The small difference in A values does not correspond well with the 3:1 ratio of *E* to *Z* products observed, which is in the opposite direction for a purely steric influence. Therefore we believe that an electronic effect must be responsible and suggest the following. If the bond breaking is fairly advanced in the transition state (which may be reasonable for a trimethyl-substituted pentadienyl acetoacetate), then the relative stability of the conformations of the nascent pentadienyl cations would play a role. Thus for the transition states leading to the products **3d**, **G** and **H**, breaking the C–O bond to generate the enolate and the pentadienyl cation would be more favorable for **G** generating **I** since that forms the pentadienyl cation in its more stable W conformation whereas breaking the same bond in **H** to generate **J** would be less favorable since now the pentadienyl cation is formed in its less stable S conformation (Scheme 5). Streitweiser has calculated that the difference in energy favors the W conformation over the S conformation by about 3.7 kcal/mol with the U conformation being quite high in energy.[4] Thus we suggest that the energy difference of the two conformations of the pentadienyl cations being partially formed in the transition state outweighs the very small difference in the steric size of the two groups and determines the stereochemistry of the product.

In summary, we have shown that the substrates **7a**–**e** can be tuned to provide varying olefin geometries according to the steric demand of the substituents.[5] By changing the size of the group at the olefinic carbon, one can change the selectivity from modestly *Z*-selective (1.8:1) to completely *E*-selective (100:1).

## Acknowledgements

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## References and Notes

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5. The methyl ester derivative of **7** ($R = CO_2Me$) was also prepared, but when the β-keto ester derived from it was subjected to treatment with LDA the corresponding tetronic acid was formed instead of the desired α,β-unsaturated ester. For a similar result, see Takaiwa et al.[6] Similarly, the dithiane derivative of **7** [$R = CH(SCH_2)_2CH_2$] did not provide the desired β-keto acid, **8** [$R = CH(SCH_2)_2CH_2$], perhaps due to complications due to the presence of the relatively acidic dithiane proton.
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