$Eu(fod)_3$-Catalyzed Rearrangement of Allylic Methoxyacetates

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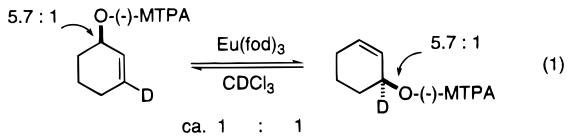
Received August 5, 1996

Stereo- and regiocontrolled allylic rearrangement reactions have played a central role in synthetic organic chemistry.[1] A number of the stereoselective rearrangement reactions of allylic esters to their more stable regioisomers have been reported in the literature[2] including those that utilize various transition metals as catalysts.[3] However, these reactions are usually carried out under harsh conditions and are often plagued with low selectivity and/or low yield with the notable exception of the highly versatile stereospecific palladium(II)-catalyzed rearrangement of allylic acetates.[4] In the following, we describe the stereospecific, facile rearrangement reactions of allylic methoxyacetates under exceptionally mild conditions.

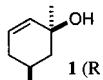
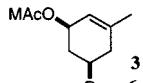
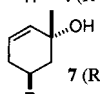
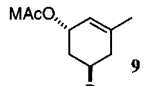
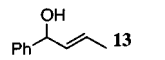
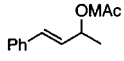
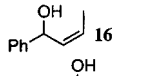
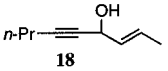
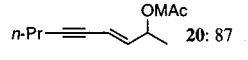
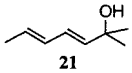
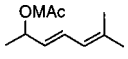
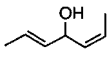
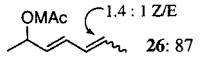
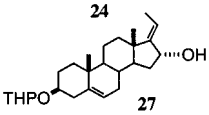
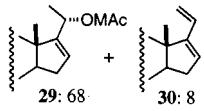
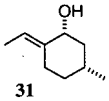
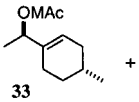
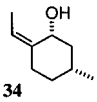
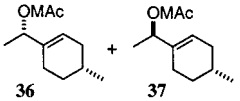
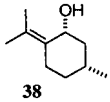
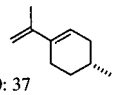
During the course of our investigation on the Mitsunobu reaction[5] of cyclic allylic alcohols, it was found that the (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl [(−)-MTPA] ester of optically active 3-deuterio-2-cyclohexen-1-ol[6] undergoes regiochemical scrambling within the same face of the cyclohexyl ring when kept in $CDCl_3$ at room temperature in the presence of the shift reagent $Eu(fod)_3$ (see eq 1). It should be noted that



(1)

neither the acetate nor the benzoate derivative of this alcohol showed any scrambling after extended periods of time under the same conditions. It was further observed that the (−)-MTPA ester scrambled the regiochemistry fastest (reaction half-life, $t_{1/2}$ = 18 h) in the presence of 0.70 equiv of $Eu(fod)_3$, followed closely by the methoxyacetate ($t_{1/2}$ = 35 h) and then by the α-methoxyphenylacetate ($t_{1/2}$ > 20 days). These results seem to suggest that the phenyl group is a detriment to the rate of the rearrangement, whereas the CF_3 group greatly enhances the rate. Since this rearrangement does not proceed with the acetate or the benzoate, it is conceivable that the methoxy group provides an additional coordination site for the Eu atom of the catalyst (*vide infra*). In view of the ready availability of methoxyacetic acid and the facility of the rearrangement reaction, the methoxyacetate derivatives of various allylic alcohols were prepared and their $Eu(fod)_3$-catalyzed rearrangements examined (see Table 1).

Table 1. The Preparation and $Eu(fod)_3$-Catalyzed Rearrangement of Allylic Methoxyacetates[a]

entry	allylic alcohol	methoxyacetate: yield (%)[b]	rearranged methoxyacetates[b] and other products: yield (%)[c]
a	 **1** (R = Me)	**2**: 94	 **3** (R = Me): 80
b	R **4** (R = *t*-Bu)	**5**: 85	R **6** (R = *t*-Bu): 73
c	 **7** (R = Me)	**8**: 99	 **9** (R = Me): 81
d	R **10** (R = *t*-Bu)	**11**: 76	R **12** (R = *t*-Bu): 68
e	 **13**	**14**: 92	 **15**: 98
f	 **16**	**17**: 98	**15**: 91
g	 **18**	**19**: 97	 **20**: 87
h	 **21**	**22**: 82	 **23**: 88
i	 **24**	**25**: 98	 **26**: 87
j	 **27**	**28**: 98	 **29**: 68 **30**: 8
k	 **31**	**32**: 93	 **33** + **32** 84 (**33**/**32** = 4.6 : 1)
l	 **34**	**35**: 84	 **36** + **37** 82 (**36**/**37** = 6.6 : 1)
m	 **38**	**39**: 98	 **40**: 37

[a] All $Eu(fod)_3$-catalyzed rearrangement reactions of allylic methoxyacetates were carried out in $CHCl_3$ (**8** and **22**) or $CDCl_3$ (all others) in the presence of $Eu(fod)_3$ (0.10 equiv) at room temperature, except for **28** and **32** (60 °C). Reaction times are as follows: **2** (1.5 h), **5** (1 h), **8** (5 h), **11** (16 h), **14** (2.5 h), **17** (48 h), **19** (36 h), **22** (2 h), **25** (8 h), **28** (6 d), **32** (40 h), **35** (43 h), **39** (3 d). [b] MAc = CH_3OCH_2CO-. [c] Yields of isolated chromatographically pure samples.

Preparation of the requisite allylic methoxyacetates was best achieved by the treatment of allylic alcohols with methoxyacetic acid in the presence of DCC/catalytic DMAP (*N*,*N*-dicyclohexylcarbodiimide/4-(dimethylamino)pyridine) in CH_2Cl_2 at room temperature, producing the methoxyacetate derivatives of labile allylic alcohols in excellent yield. Exposure of these esters

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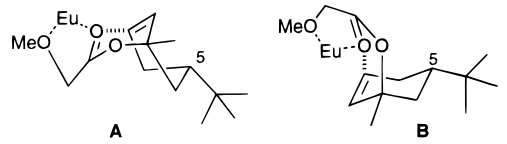

Figure 1. Postulated conformations **A** and **B** of the Eu(III)-chelated *cis*- (**5**) and *trans*-5-*tert*-butyl-1-methyl-2-cyclohexen-1-yl methoxyacetates (**11**), respectively, that lead to their respective favorable transition states for their Eu(fod)$_3$-catalyzed rearrangements.

to 0.10 equiv of Eu(fod)$_3$, at room temperature with the exception of esters **28** and **32** where the reaction temperature was raised to 60 °C, resulted in the rearrangement into the more stable alkene isomers. The results of the rearrangement of the methoxyacetates **2**, **5**, **8**, and **11**[7] (entries a−d) indicate that these rearrangements proceed in a stereospecific manner. Surprisingly, the rates of rearrangement of *tert*-butyl group-containing allylic methoxyacetates **5** and **11** were found to be quite similar with ester **5** having the equatorially fixed methoxyacetate group rearranging slightly faster ($t_{1/2}$ = 9 min) than ester **11** with the axially fixed methoxyacetate group ($t_{1/2}$ = 29 min). This observation on similar rates of rearrangement may be rationalized in terms of the two Eu(III)-chelated conformers **A** and **B** (see Figure 1) that may closely resemble the conformations of their corresponding, most favorable transition states for the Eu(fod)$_3$-catalyzed rearrangement of methoxyacetates **5** and **11**, respectively. Thus, cis ester **5** might be able to adopt conformer **A** where the atoms involved with the allylic rearrangement adopt a chair conformation if the cyclohexene ring system assumes a quasi-boat conformation. In contrast, the rearranging atoms in conformer **B** is likely to adopt a boat conformation in order to avoid the unfavorable interaction between the axial H at C-5 and the ester functionality. Therefore, the bicyclic transition state structure of both *cis*- and *trans*-5-*tert*-butyl-1-methyl-2-cyclohexen-1-yl methoxyacetate should be close to those having one chair and one boat conformation for the rearranging allylic ester system and the *tert*-butyl group-bearing cyclohexene skeleton, and thus, the observed rates of rearrangement might be expected to be similar.

For *cis*- (**17**) and *trans*-1-phenyl-2-buten-1-yl methoxyacetate (**14**) (entries f and e, respectively), the rearrangement was found to proceed 18 times faster for the trans ($t_{1/2}$ = 18 min) than the cis isomer ($t_{1/2}$ = 330 min). This large difference in rates may be regarded as a manifestation of the relative energies of the two chairlike transition states which should resemble the conformation **C** given in Figure 2 (i.e., R = Me, R′ = H and R = H, R′ = Me for the cis and trans isomers, respectively). Thus, the difference in the steric energies between the quasi-axial and quasi-equatorial methyl groups in the chairlike transition states of the stereospecific concerted process might account for the observed difference in the rates of the rearrangements. However, a distinct possibility exists that this doubly activated allylic and benzylic ester system involves dissociative pathway, and the rate difference reflects the rate-limiting dissociative process (see structure **D** in Figure 2). It is quite conceivable that the cis isomer (R = Me, R′ = H in **D**) requires a higher activation energy for the dissociation of the Eu-chelated methoxyacetate group than the trans isomer (R = H, R′ = Me) does due to the

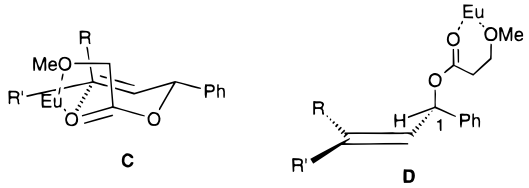

Figure 2. Postulated Eu(III)-chelated conformations that lead to the favorable transitions states for the concerted (**C**) and dissociative (**D**) pathways for the Eu(fod)$_3$-catalyzed rearrangements of *cis*- (**17**; R = Me, R′ = H) and *trans*-1-phenyl-2-buten-1-yl methoxyacetates (**14**; R = H, R′ = Me).

severe A^{1,3} strain between the methyl group and the proton at C-1 in the transition state.

The allylic acetate systems in which Pd(II)-catalyzed rearrangements are reported not to proceed effectively include those containing alkynyl group(s) and those whose proximal alkenyl carbons are fully substituted.[11] In a marked contrast to the Pd(II)-catalyzed reaction, both of these types of allylic systems with methoxyacetates undergo facile rearrangements under the Eu(fod)$_3$-catalysis (see entries g and j[12] −l). Interestingly, the rearrangement of methoxyacetate **35** afforded the byproduct **37** which is likely to have been generated as the result of the two consecutive rearrangements from **35** via **36**. It should be noted that the Lewis acidity of Eu(fod)$_3$, albeit its weak potency, could prove potentially problematic, as exemplified by the attempted rearrangement of the methoxyacetate of the extremely acid-labile pulegol (**38**) (entry m). Interestingly, although only the volatile diene **40** was isolated from the reaction of pulegyl methoxyacetate (**39**), the presence of an intermediate corresponding to the rearranged product structure in the reaction medium could be verified when the reaction was monitored by ^{1}H NMR spectroscopy.

The Eu(fod)$_3$-catalyzed rearrangement of allylic methoxyacetates described above is extremely efficient and has a number of distinct advantages over the existing methods. It does not seem to be subject to steric hindrance, since the metal associates with the methoxyacetate "tether" and not with the potentially congested olefin. This notion was further corroborated by the observation of the characteristic large downfield shifts and significant line-broadening of both the methyl and the methylene peaks of the OC(=O)CH$_2$OCH$_3$ group in the ^{1}H NMR spectra of all of the methoxyacetates examined. Therefore, it appears quite reasonable to assume that the Eu(fod)$_3$ reagent exerts its catalytic activity for the rearrangement through the chelate formation with the oxygen atoms of the methoxy and ester carbonyl groups.[13] Unlike Pd(II) catalysts, the present method with Eu(fod)$_3$ is compatible with the presence of alkynyl group(s). Additionally, it may be inferred on the basis of the experiments with various type of esters of 2-cyclohexen-1-ol that the present method seems selective to α-alkoxyacetates, and thus, other allylic esters should remain unaffected by exposure to the reagent. All of these advantages should prove the Eu(fod)$_3$-catalyzed rearrangement to be an excellent complement to the existing methods for the rearrangement of allylic esters.

Acknowledgment. The authors thank the National Institutes of Health (DK 30025 awarded to M.K.) for the support of this research.

Supporting Information Available: Full experimental details with spectral and combustion analytical data of all methoxyacetates and products from rearrangement as well as **7**, **10**, and **21** (13 pages). See any current masthead page for ordering and Internet access instructions. JA962718D

(7) Synthesis of allylic alcohol precursors **1**, **4**, **7**, and **10**: *cis*-1,5-Dimethyl-2-cyclohexen-1-ol (**1**; R = Me) was prepared by the treatment of 5-methyl-2-cyclohexen-1-one[8] with MeLi at −78 °C in diethyl ether (87%). The trans isomer **7** (R = Me) was obtained by Jones oxidation of the cis isomer to obtain 3,5-dimethyl-2-cyclohexen-1-one (70%), followed by application of the protocol of Wharton[9] involving (i) the H_2O_2 epoxidation of the enone (65%) and (ii) the hydrazine reduction of the epoxy ketone (73%) to give a 15:1 mixture of stereoisomers favoring *trans*-1,5-dimethyl-2-cyclohexen-1-ol (**7**: R = Me). The two *tert*-butyl containing cyclohexenols **4** and **10** were prepared in a similar manner starting from 5-*tert*-butyl-2-cyclohex-1-one.[10]

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(12) Stereochemistry in the steroid case was confirmed by de-esterification followed by removal of the THP group and comparison of the spectra to those reported (Benn, W. R. *J. Org. Chem.* **1963**, *28*, 3557).

(13) The propensity of the Eu for this methoxyacetoxy system is to the extent that silica gel chromatography does not rid the substrate of all of the Eu (the fod ligand is lost). Interestingly, even Kugelrohr distillation of the methoxyacetates presents the same problem. The Eu reagent is best removed by washing the ether solution of the product with a 2.5% ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA) slurry.