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Eu(fod)$_3$–Catalyzed Rearrangement of Allylic Esters Possessing a Chelating Site. Application to Enediyne Synthesis

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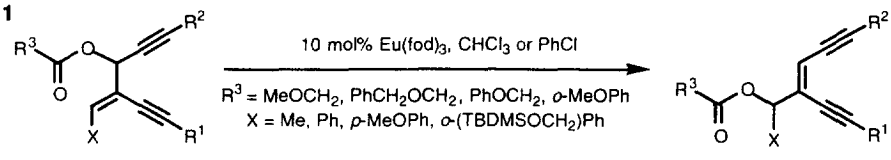
Abstract: A number of 1,2-dialkynyl-3-alkyl or 3-aryl allylic esters underwent a facile Eu(fod)$_3$-catalyzed rearrangement at 20-132 °C to give exclusively *cis*-enediynes. The esters capable of forming a chelate with Eu(III) exhibited a remarkably enhanced reactivity; the C_3 aryl group facilitated the rearrangement as well.

Enediynes are a novel class of antitumor antibiotics which cause DNA strand cleavage through the carbon-centered radical species formed by the Bergman cyclization of the enediyne core.[1] The maduropeptin chromophore is one of the naturally occurring 9-membered ring enediynes. It produces 1,2-dialkynyl-substituted allyl alcohol or allylic ethers during separation from the associated apoprotein.[2] These artifacts show the maduropeptin chromophore-like activity on DNA damage, though with reduced potency. It was proposed that the artifact (for example, the allylic methyl ether) is converted into the enediyne via an intramolecular allylic rearrangement and delivers the biological activity.[2] In our previous work, we have demonstrated that rearrangement of an allylic double bond in the 1,2-dialkynyl-substituted allyl alcohols can be achieved either under acidic conditions[3a-c] or by quenching the corresponding allylic mesylates with H_2O[3d] with good regio- and *cis/trans* diastereocontrol. However, a C_3 aryl group is required for the acid-catalyzed rearrangement.[3a-c] In this communication, we report on a novel synthesis of enediynes via rearrangement of allylic esters under the catalysis of Eu(fod)$_3$ (Scheme 1). An additional chelating site other than the ester carbonyl group is found to be essential for the facile rearrangement.

Recently, Shull, Sakai, and Koreeda first reported the rearrangement of allylic methoxyacetates catalyzed by Eu(fod)$_3$ [europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)].[4] In one example, these authors demonstrated that the propargylic moiety did not undergo the rearrangement using Eu(fod)$_3$. It gives a

Scheme 1



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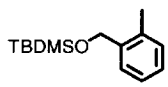
selective transformation of the allylic system.[4] This unique selectivity of $Eu(fod)_3$, being different from the well-established palladium(II)-catalyzed rearrangement,[5] encouraged us to examine the rearrangement of allylic esters **1** for synthesis of enediynes **2**. We are particularly interested in exploring rearrangement of esters other than the methoxyacetate. Table 1 and Scheme 1 summarize the results.[6] Condensation of the allyl alcohols[7] with the carboxylic acids under DCC-DMAP conditions (CH_2Cl_2, 20 °C, 1-7 h) gave the allylic esters **1a-g,i-k** in 53-91% yield. The benzyloxyacetate **1h** and the benzoate **1l** were obtained from reaction of the allyl alcohol with the acyl chloride (CH_2Cl_2, Et_3N, 20 °C, 5-9 h) in 65-84% yield.

Table 1. Enediynes Synthesized through $Eu(fod)_3$-Catalyzed Allylic Rearrangement.[a]

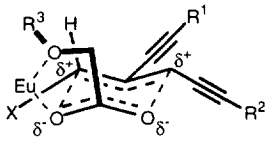
Substrate	X	R^1	R^2	R^3	T (°C), t (h)	Product (%)
1a	Me	$-(CH_2)_4OMe$	CH_2SPh	$MeOCH_2$	60, 96	**2a** (62)
1b	Ph	$-(CH_2)_4OMe$	CH_2SPh	$MeOCH_2$	20, 48	**2b** (73)
1c	Ph	$-(CH_2)_4OMe$	Ph	$MeOCH_2$	20, 48	**2c** (85)
1d	Ph	$-(CH_2)_4OTBDMS$	$SiMe_3$	$MeOCH_2$	20, 48	**2d** (85)
1e	*p*-MeOPh	$-(CH_2)_4OMe$	CH_2SPh	$MeOCH_2$	20, 3.5	**2e** (79)
1f		$-(CH_2)_4OMe$	CH_2SPh	$MeOCH_2$	60, 48	**2f** (75)
1g		$-(CH_2)_4OMe$	Ph	$MeOCH_2$	60, 48	**2g** (69)
1h	Ph	$-(CH_2)_4OMe$	Ph	$PhCH_2OCH_2$	20, 7	**2h** (75)
1i	Ph	$-(CH_2)_4OMe$	CH_2SPh	$PhOCH_2$	60, 24	**2i** (80)
1j	Me	$-(CH_2)_4OMe$	CH_2SPh	$PhOCH_2$	150, 24[b]	no reaction
1k	Ph	$-(CH_2)_4OMe$	CH_2SPh	*o*-MeOPh	132, 3[c]	**2k** (67)
1l	Ph	$-(CH_2)_4OMe$	CH_2SPh	Ph	132, 4[c]	**2l** (79)
1m	Ph	$-(CH_2)_4OMe$	CH_2SPh	Me	132, 4[c]	**2m** (74)

[a]All reactions were carried out in $CHCl_3$ in the presence of 10 mol% of $Eu(fod)_3$ (3-14 mM). [b]Reaction was carried out in DMSO. [c]Reaction was carried out in PhCl. TBDMS = *t*-$BuMe_2Si$.

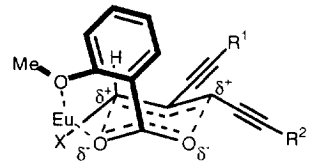
Treatment of C_3 methyl-substituted allylic methoxyacetate **1a** with 10 mol% $Eu(fod)_3$ in $CHCl_3$ at 20 °C failed to initiate the rearrangement; but the reaction took place on heating at 60 °C for 96 h to give *cis*-enediyne **2a** in 62% yield. The *trans*-enediyne was not detected. Compared to the rearrangement of (*E*)-2-nonen-5-yn-4-yl methoxyacetate (rt, 36 h, 87%),[4] **1a** is greatly deactivated by the C_2 alkynyl unit. The methoxyacetates **1b-d** bearing a C_3 phenyl group underwent the rearrangement at 20 °C within 48 h to furnish *cis*-enediynes **2b-d** in 73-85% yield. We found that both steric and electronic effects influence reactivity of the allylic methoxyacetates. A *para* methoxy group in the C_3 phenyl moiety remarkably reduced the reaction time of **1e** to 3.5 h compared to the 48 h required for **1b**. On the other hand, esters **1f,g** having a bulky *ortho* $TBDMSOCH_2$ in the C_3 phenyl moiety needed higher temperature (60 °C) than **1b,c** to promote the rearrangement. In general, the $Eu(fod)_3$-catalyzed rearrangement of allylic methoxyacetates **1a-g** gives a clean and diastereospecific reaction to form the *cis*-enediynes **2a-g**. The alkynyl groups remain intact during the rearrangement.

We found that the benzyloxyacetate **1h** exhibited a greatly accelerated reactivity toward rearrangement

when compared to **1c** (7 h *versus* 48 h at 20 °C). In contrast, the phenoxyacetate **1i** underwent the allylic migration only upon heating (60 °C, 24 h). The diminished reactivity of the phenoxyacetate was confirmed again by the observation that ester **1j** failed to give enediyne after heating at 150 °C for 24 h. The result might be explained by the reduced coordination ability of the benzene ring-stabilized oxygen in the phenoxyacetate. As reported in the literature,[4] allylic acetates and benzoates do not undergo the rearrangement under $Eu(fod)_3$ catalysis. However, we found that both the benzoate **1l** and the acetate **1m** gave *cis*-enediynes **2l** and **2m** (74-79%) in refluxing PhCl with catalytic $Eu(fod)_3$, though the reaction did not take place at 60 °C. We considered that if an additional chelating site is available within the benzoate moiety, for example, in the *o*-methoxybenzoate **1k**, the $Eu(fod)_3$-catalyzed rearrangement should occur much more readily. In fact, **1k** was transformed into **2k** in refluxing PhCl for 3 h in 67% yield. *Thus, the following order of migrating ability is established: benzyloxyacetate > methoxyacetate > phenoxyacetate > o-methoxybenzoate ≈ benzoate ≈ acetate.*



3a: R^3 = Me
3b: R^3 = $PhCH_2$
3c: R^3 = Ph



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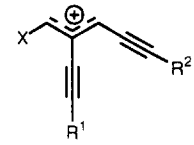

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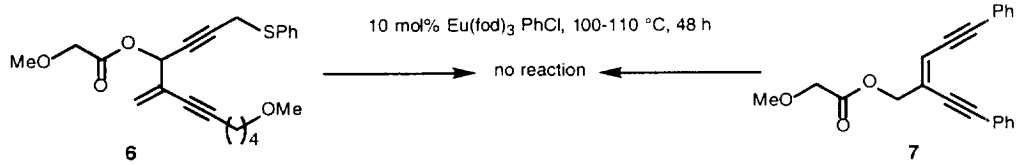
We propose the transition state (TS) **3a-c** for a *concerted* rearrangement of the allylic alkoxyacetates **1a-h** and allylic phenoxyacetate **1i**. This TS features a chair-like 6-membered ring fused with the 5-membered ring Eu(III) chelate.[4] The three substituents at C_1-C_3 are aligned in the equatorial positions. From TS **3a-c**, only *cis*-enediynes are formed. The *concerted* pathway is supported by rearrangement of the chiral ester **1h**. Optically active **2h** was obtained in 84% ee from the chiral ester **1h** of 92% ee.[8] This result rules out the involvement of the allylic cation **5** in the $Eu(fod)_3$-catalyzed allylic rearrangement. According to TS **3a-c**, the C_1-C_3 sub-unit has allylic cation character while the ester moiety carries partial negative charge at the oxygen atoms. The effect of the C_3 substituent X on the reactivity can then be interpreted according to the stabilization of X toward the partial positive charge at C_3. *The following stabilization order of p-MeOPh > Ph > Me is consistent with the observed reactivity.* A similar TS **4** can be used for rearrangement of *o*-methoxybenzoate **1k**. Due to the less favored 6-membered ring Eu(III) chelate, rearrangement of **1k** requires higher temperature. Reaction of the benzoate **1l** and the acetate **1m** in refluxing PhCl is unique for our allylic system having a C_3 aryl group. Deviation from the co-planarity of the aryl group in respect to the double bond might be the possible reason for this finding.

Both C_1- and C_3-unsubstituted allylic substrates were not tackled in the reported work.[4] We noted that the C_3-unsubstituted allylic methoxyacetate **6** did not undergo the rearrangement in the presence of $Eu(fod)_3$ at elevated temperature (100 °C, 48 h; Scheme 2). Also, *cis*-enediyne ester **7**, prepared from (Z)-methyl 2,3-dibromopropenoate in 3 steps, remained intact after heating at 110 °C for 2 days. These results demonstrate the

Scheme 2



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low reactivity of the C_1- and C_3-unsubstituted allylic esters toward $Eu(fod)_3$-catalyzed rearrangement.

In summary, we have explored and expanded the $Eu(fod)_3$-catalyzed rearrangement of allylic esters and demonstrated the first application of this methodology to the synthesis of *cis*-enediynes. A number of allylic esters possessing a chelating site undergo facile rearrangement at room temperature or on heating below 132 °C. 1,3-Chirality transfer is observed in the allylic rearrangement which supports a concerted mechanism. A remarkable substituent effect at the C_3 position is noted. It can be rationalized in terms of stabilization toward the developing positive charge in the TS. Moreover, the inexpensive and readily available reagents coupled with the mild reaction conditions make the $Eu(fod)_3$-catalyzed rearrangement of allylic esters very attractive in organic synthesis. The different reactivity of allylic esters provides an idea tool for selective chemical transformation. Application of this novel reaction in multi-step organic synthesis is expected.

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References and Notes:

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6. All new compounds are characterized by ^1H and ^{13}C NMR, IR, and MS.
7. The allyl alcohols possessing X = Me, Ph were synthesized from α-bromocrotonaldehyde and α-bromocinnamaldehyde, respectively, according to the reported methods (see ref. 3a,d). The allyl alcohol having X = *p*-MeOPh was synthesized from *p*-anisaldehyde in 6 steps. The allyl alcohols bearing X = *o*-$TBDMSOCH_2Ph$ were synthesized from phthalic dicarboxaldehyde in 8 steps (see ref. 3b).
8. Chiral ester **1h** (92% ee; t = 21.5' over Chiralcel OD column, hexane-*i*-PrOH = 97:3, 1 mL/min, UV 254 nm; for the other enantiomer, t = 20.2') was prepared from the (-)-allyl alcohol. The latter was synthesized through asymmetric reduction of the ketone using (+)-DIP-Chloride. HPLC profile of chiral enediyne **2h**: 84% ee; t = 31.5' over Chiralcel OD column, hexane-*i*-PrOH = 97:3, 1 mL/min, UV 254 nm; for the other enantiomer, t = 33.3'. The absolute stereochemistry of chiral **1h** and **2h** is not determined.