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Neighboring nucleophilic group assisted rearrangement of allylic esters under $Eu(fod)_3$ catalysis

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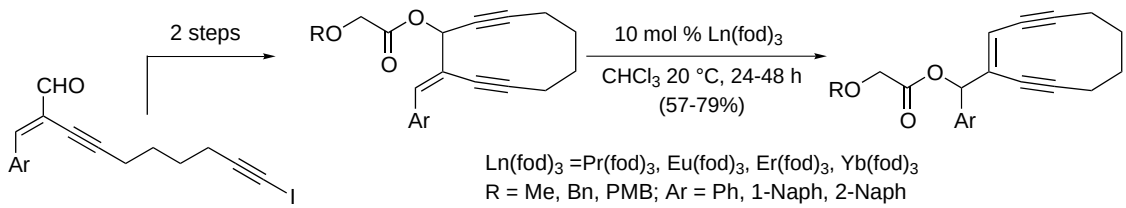
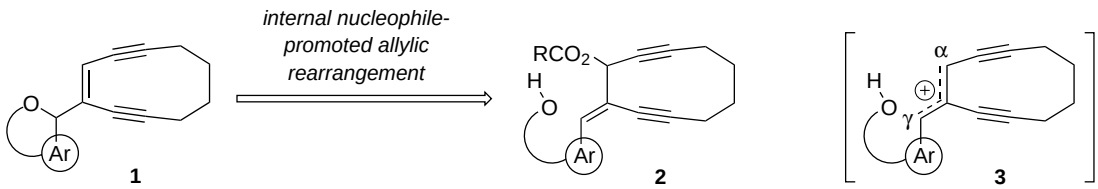
Abstract—The acetate **13a** and methoxyacetate **13b** of (*E*)-3-hydroxy-4-(arylmethylidene)cyclodeca-1,5-diyne possessing a free hydroxy group underwent an allylic rearrangement at 20°C in the presence of catalytic $Eu(fod)_3$ to give the enediyne **14** in excellent yields. In contrast, the acetate **10a** with a silyloxy group failed to rearrange under the same conditions. These results demonstrated that an internal nucleophilic group promotes the $Eu(fod)_3$-catalyzed rearrangement of allylic esters under mild conditions.

Recently, we reported a general synthesis of 3-substituted 10-membered ring enediynes as illustrated in Scheme 1.[1] It took advantage of the $Ln(fod)_3$-catalyzed rearrangement of allylic alkoxyacetates to migrate the exocyclic double-bond into the cyclic skeleton.[2] The mild reaction conditions used were crucial to minimize decomposition of the 10-membered ring enediynes which are known to readily undergo cycloaromatization at physiological temperature.[3] It was reported that allylic esters lacking the α oxygen functionality in the acyloxy units failed to rearrange at room temperature.[2a,b] Therefore, we planned to equip an internal nucleophilic group in the esters **2** to facilitate the rearrangement through combined 'pushing and pulling' interactions (Scheme 2). When the acyloxy group (RCO_2) is activated by complexation with a lanthanide(III) catalyst, the hydroxyl group would attack at the exocyclic double bond in an S_N2' fashion to form the enediynes **1**. Alternatively, in the case where an allylic cation **3** would be generated from **2** by heterolytic cleavage of the acyloxy group, the internal hydroxy group is also ideal for attack at the γ position



Scheme 1.



Scheme 2.

Keywords: benzofurans; diynes; lanthanides; rearrangement.

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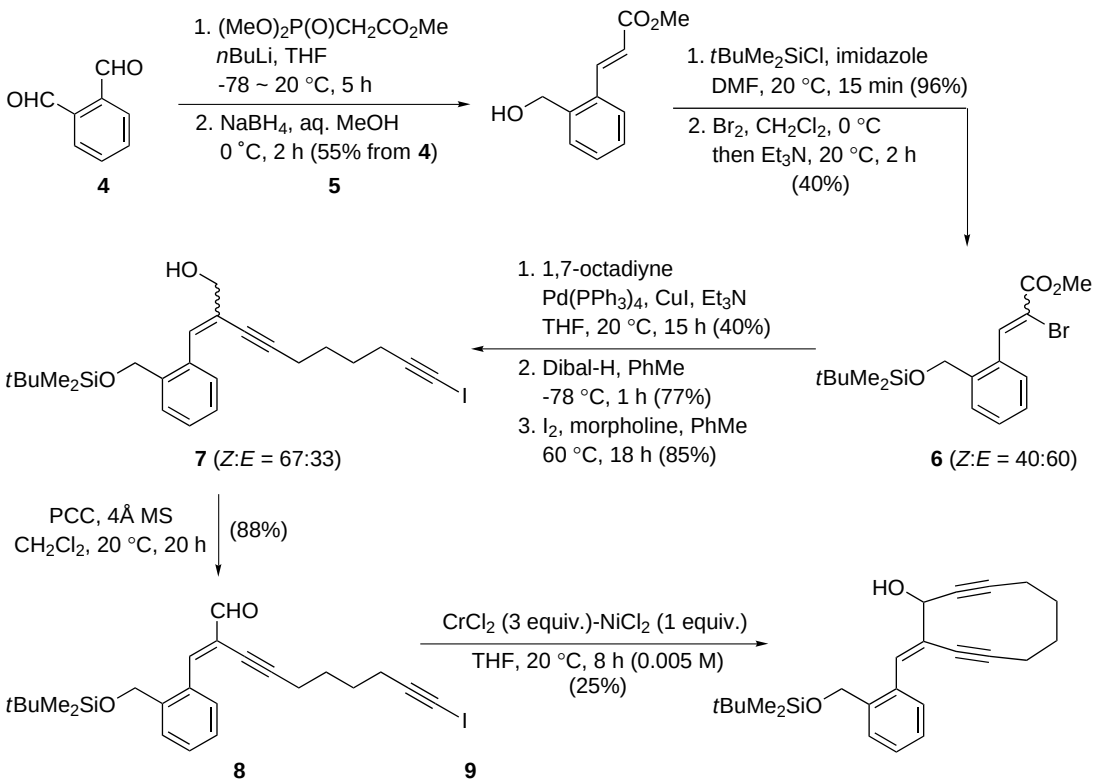
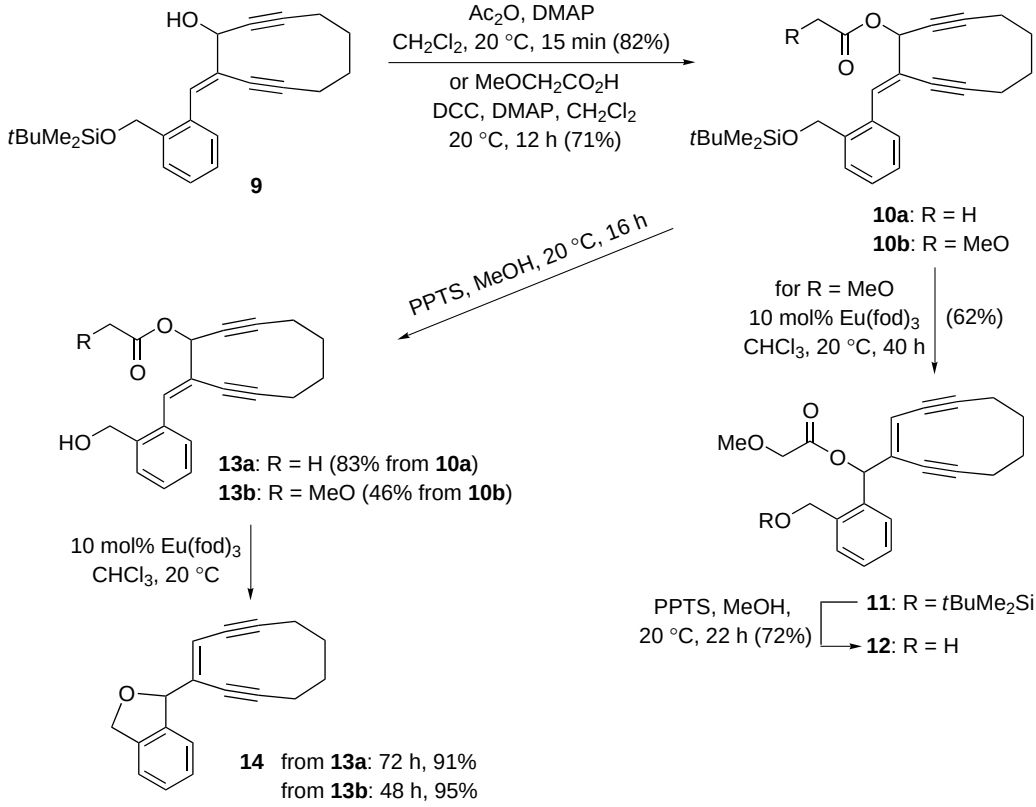
of **3** in a regiospecific manner to give the enediynes.[4] We report here on the synthesis of the cyclic alcohol **9** possessing an *ortho* substituted phenyl group and the rearrangement reactions of its esters **10b** and **13a**,**b** under $Eu(fod)_3$ catalysis.

Synthesis of the cyclic alcohol **9** started with phthalic dicarboxaldehyde **4** (Scheme 3).[5] Selective mono Horner–Wadsworth–Emmons olefination of **4** followed by reduction ($NaBH_4$, aq. MeOH) gave the hydroxy ester **5** in 55% overall yield from **4**.[4a] Protection of the hydroxy group in **5** as the silyl ether and addition of Br_2 to the double bond followed by the triethylamine-mediated elimination of HBr furnished the α-bromoester **6** as a mixture of the *Z* and *E* isomers. This mixture was used in the selective mono cross-coupling reaction with 1,7-octadiyne under Sonogashira conditions[6] to form the eneyne ester in 40% yield. This ester was reduced to the alcohol (Dibal-H, PhMe, −78°C, 77%), which was subjected to the iodination conditions (3 equiv. of I_2, 8 equiv. of morpholine, PhMe, 60°C) to provide the hydroxy iodoalkyne **7** in 85% yield.[1,7,8] Oxidation of the mixture of **7** using PCC gave a single *E* aldehyde **8** in 88% yield. Isomerization of the initially formed aldehyde *Z*-**8** from the alcohol *Z*-**7** occurred under the PCC oxidation conditions, presumably due to the presence of a trace of acidic residue.[1] Finally, the intramolecular Nozaki–Hiyama–Kishi reaction[1,9,10] of **8** under high dilution conditions formed the cyclic alcohol **9** in 25% isolated yield. Compared to the *para*-methoxyphenyl analog,[1] the bulky *ortho* substituent in **8** has no influence on the efficiency of the ring-closure reaction.

Treatment of the alcohol **9** with acetic anhydride in the presence of DMAP (CH_2Cl_2, 20°C) gave the acetate **10a** in 82% yield (Scheme 4).[5] Condensation of **9** with methoxyacetic acid under the DCC–DMAP conditions (CH_2Cl_2, 20°C) formed the methoxyacetate **10b** in 71% yield. The latter ester underwent an allylic rearrangement catalyzed by 10 mol% $Eu(fod)_3$ ($CHCl_3$, 20°C, 40 h) to furnish the enediyne **11** in 62% yield. The result is comparable with that of the phenyl analog[1] and indicated that the bulky *ortho* substituent in **10b** does not interfere with the rearrangement. Removal of the silyl group in **11** under weakly acidic conditions (PPTS, MeOH, 20°C, 72%) afforded the hydroxy ester **12** which did not convert into the 2,5-dihydro-2-benzofuryl enediyne **14** under the reaction conditions. Upon exposure of the hydroxy methoxyacetate **13b**, prepared by deprotection of **10b**, to 10 mol% $Eu(fod)_3$ ($CHCl_3$, 20°C, 48 h), an intramolecular nucleophilic group assisted allylic rearrangement took place to form the enediyne **14** in 95% yield. We carefully monitored the course of the reaction by TLC and did not observe the formation of compound **12** during the conversion of **13b** into **14**. The result clearly indicated that the neighboring hydroxyl group in **13b** participated in the double bond migration presumably in an S_N2' fashion.[11] Moreover, activation of the methoxyacetate group by Eu(III) is essential for the rearrangement because **13b** survived the weak acidic conditions used for removal of the silyl group in **10b**. In our earlier work on synthesis of acyclic enediynes, we found that allylic acetates rearranged at high temperature (132°C in PhCl).[2b] To our surprise, the hydroxy acetate **13a** converted into the enediyne **14** in 91% yield at 20°C ($CHCl_3$, 72 h). The pushing force



Scheme 3.



Scheme 4.

provided by the free hydroxyl group in **13a** accounts for the enhanced reactivity of the allylic acetate toward the $Eu(fod)_3$-catalyzed rearrangement. This example demonstrated that a combined 'pushing and pulling' effect resulted in an efficient and high yielding chemical transformation. The longer reaction time observed for the acetate **13a** may be explained by the non-chelation interation with Eu(III) or the relatively lower stability of the acetate anion compared to the methoxyacetate anion.[12]

In summary, we have accomplished a nine-step synthesis of the (*E*)-3-hydroxy-4-(arylmethylidene)cyclodeca-1,5-diyne **9** possessing an *ortho* substituted phenyl group and investigated the rearrangement of the corresponding esters under the lanthanide(III) catalysis. For the substrates with a protected hydroxy group, only the allylic methoxyacetate **10b** underwent the double bond migration to form the enediyne **11**. On the other hand, for the allylic acetate **13a** and methoxyacetate **13b** with a free hydroxy group, an intramolecular nucleophile assisted allylic rearrangement proceeded at 20°C in the presence of catalytic Eu(III) to afford the 2,5-dihydro-2-benzofuryl enediyne **14** in excellent yields. This transformation might not involve the allylic cation **3**[11] and should take place through an S_N2' mechanism. Therefore, compounds **13a**,**b** represent a synthetic model system that resembles the intramolecular allylic rearrangement for the activation of the maduropeptin chromophore artifacts.[13]

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