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Intramolecular Nozaki–Hiyama–Kishi reactions and Ln(III)-catalyzed allylic rearrangement as the key steps towards 10-membered ring enediynes

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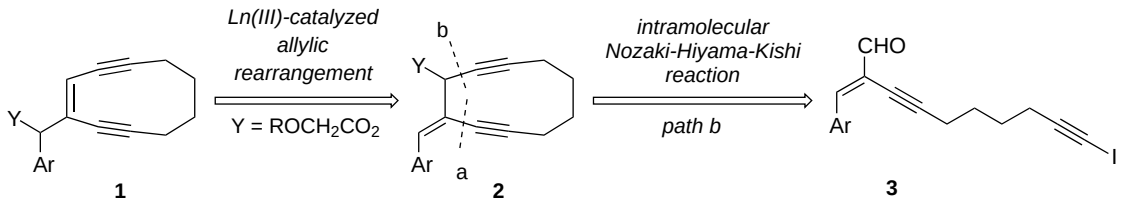
Abstract—A general and facile synthesis of the 3-substituted 10-membered ring enediynes **18**–**22** from the aldehydes **8** and **15** has been established by utilizing the intramolecular Nozaki–Hiyama–Kishi reaction and the lanthanide(III)-catalyzed rearrangement of allylic alkoxyacetates as the key steps. This work provides ready access to the (*E*)-3-acyloxy-4-(arylmethylidene)cyclodeca-1,5-diynes, which can be converted into the bioactive enediynes under physiological conditions.

Substitution at the C3 position of the (*Z*)-hexa-1,5-diyn-3-ene moiety is common to the naturally occurring nine-membered ring enediyne antitumor antibiotics, the kedarcidin chromophore,[1] the C-1027 chromophore[2] and the maduropeptin chromophore.[3a] The C3 substitution forms a part of the macrocyclic ring incorporating the 5/9-fused bicyclic enediyne core. Moreover, the C3 substitution in the maduropeptin chromophore is the key structural feature that allows interconversion between the native enediyne chromophore and its artifacts via allylic rearrangement.[3] We demonstrated a similar allylic rearrangement process in the formation of a 10-membered ring enediyne that exhibits DNA cleavage activity and cytotoxicity against cancer cell lines.[4] These results encouraged us to design and synthesize a novel class of enediyne prodrugs[5] that deliver the enediyne-like biological activity but do not suffer from instability towards cycloaromatization at physiological temperature.[6] We report here a general and facile synthesis of 3-substituted[7] 10-membered ring enediynes **1** from the aldehydes **3** through the intramolecular Nozaki–Hiyama–Kishi (NHK) reaction[8] to form **2** (Y = OH) followed by the lanthanide(III)-catalyzed rearrangement[9] of the allylic alkoxyacetates **2** (Y = $ROCH_2CO_2$) (Scheme 1).

The intramolecular NHK reaction has been successfully applied to the construction of cyclic enediynes possessing a (*Z*)-hexa-1,5-diyn-3-ene moiety.[8] Yields of the cyclization vary from 23 to 95% depending on the substrate structures. Typically, ca. a 30% yield was reported for the monocyclic 10-membered ring enediyne.[10] Suffert and Toussaint described a synthesis of the 4-alkylidenecyclodeca-1,5-diyne skeleton fused with a benzene ring onto the C7 and C8 positions via the intramolecular NHK reaction.[11] However, a general synthesis of compounds **2** possessing an exocyclic double bond via the intramolecular NHK reaction



Scheme 1.

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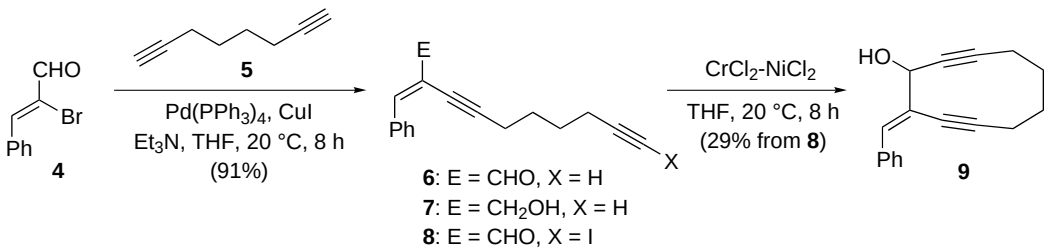
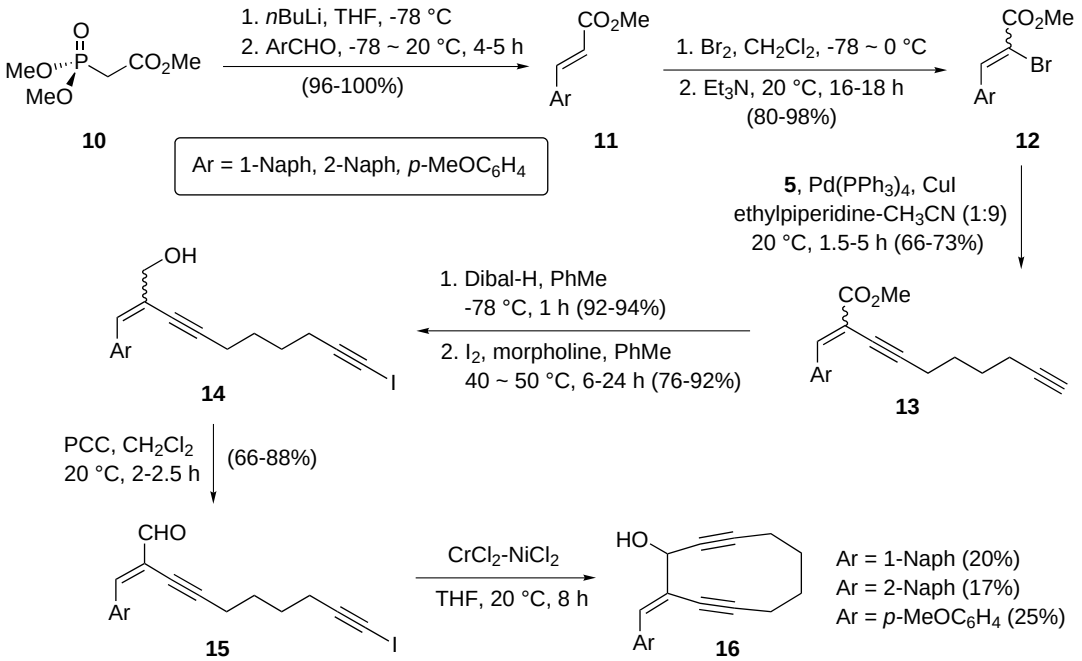
(*path b*, Scheme 1) has not appeared in the literature. Very recently, an intramolecular Sonogashira cross-coupling approach to compounds **2** (Ar = Ph, 1-Naph and Y = OH, *path a*) was reported from our laboratory.[12]

We first examined the intramolecular NHK reaction of the aldehyde **8** (Scheme 2).[13] The Pd(0)–Cu(I)-catalyzed cross-coupling of the commercially available α-bromocinnamaldehyde **4** with 1,7-octadiyne **5** gave the enyne **6** in 91% yield. Because compound **6** failed to give the iodoalkyne **8** directly, it was reduced to the alcohol **7** by using $NaBH_4$ in MeOH (20°C, 30 min, 91%). Iodination of **7** was carried out by using 3 equiv. of I_2 and 8 equiv. of morpholine[10,14] (PhMe, 40–50°C, 6 h, 89%) to give the corresponding iodoalkyne, which was oxidized to the aldehyde **8** by using PCC (CH_2Cl_2, 20°C, 2 h, 75%). Treatment of **8** with 3 equiv. of $CrCl_2$ and 1 equiv. of $NiCl_2$ under high dilution conditions (0.005 M in THF, 20°C, 8 h) furnished the 10-membered ring alcohol **9** in 29% yield as the only isolated product.

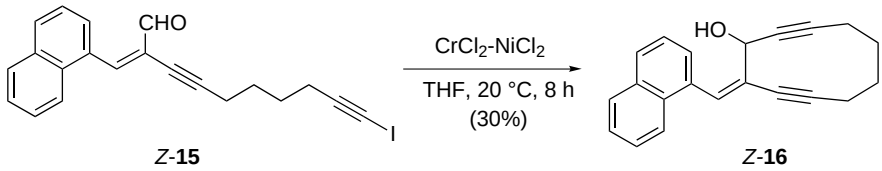
With the successful synthesis of **9**, we developed a general synthesis of (*E*)-3-hydroxy-4-(arylmethylidene)cyclodeca-1,5-diynes **16** as shown in Scheme 3.[13] The Horner–Wadsworth–Emmons reactions of aryl aldehydes with **10** gave the α,β-unsaturated esters **11** in excellent yields. Treatment of **11** with Br_2 followed by exposure to triethylamine furnished the α-bromoesters **12** as a mixture of *E* and *Z* isomers.[4e,15] Because both isomers can be converted into the desired aldehydes **15**, the mixtures were used for further elaborations. The cross-coupling of **12** with 1,7-octadiyne **5** under Sonogashira conditions provided **13** in good yields. The esters **13** were then subjected to Dibal-H reduction followed by iodination to yield the alcohols **14**. The *E* and *Z* isomers of **14**, upon PCC oxidation in CH_2Cl_2 at 20°C, gave the same *E* aldehydes **15** in 66–88% yield. In a separate set of experiments, we confirmed that isomerization of the *Z* aldehydes occurred under the slightly acidic PCC oxidation conditions.[16] For instance, the *E* aldehyde **15** with Ar = *p*-$MeOC_6H_4$ was obtained from the pure *Z*-**14** in 66% yield. Finally, the intramolecular NHK reaction within **15** gave the cyclic alcohols **16** in 17–25% yields. The effect of the aryl group on the cyclization of **15** was observed and the yields for the naphthalene derivatives **16** (Ar = 1- and 2-Naph) were slightly lower compared to the phenyl analogs **9** and **16** (Ar = *p*-$MeOC_6H_4$). Similarly, the



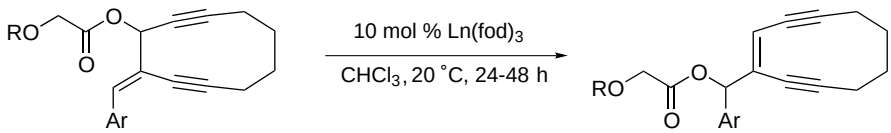
Scheme 2.



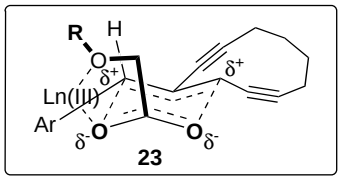
Scheme 3.



Scheme 4.



$Ln(fod)_3$ = $Pr(fod)_3$ **18**: R = Me, Ar = Ph (59%)
$Eu(fod)_3$ **18**: R = Me, Ar = Ph (79%)
$Er(fod)_3$ **18**: R = Me, Ar = Ph (57%)
$Yb(fod)_3$ **18**: R = Me, Ar = Ph (58%)
$Eu(fod)_3$ **19**: R = Me, Ar = 1-Naph (59%)
$Eu(fod)_3$ **20**: R = Bn, Ar = 1-Naph (60%)
$Eu(fod)_3$ **21**: R = PMB, Ar = 1-Naph (58%)
$Eu(fod)_3$ **22**: R = Me, Ar = 2-Naph (79%)



Scheme 5.

intramolecular NHK reaction of the aldehyde *Z*-**15**, which was obtained as a mixture with **15** (Ar = 1-naphthyl) from the PDC oxidation of **14**,[16] provided the alcohol *Z*-**16** in 30% yield (Scheme 4).

Rearrangement of (*E*)-3-alkoxyacetyloxy-4-(arylmethylidene)cyclodeca-1,5-diynes **17** prepared from **9** and **16** (Ar = 1- and 2-Naph) was carried out in the presence of 10 mol% $Ln(fod)_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) as the catalyst at 20°C in $CHCl_3$ (Scheme 5).[9,13] We found that the methoxyacetate of **16** (Ar = *p*-$MeOC_6H_4$) decomposed over silica gel during flash column chromatography to give the rearranged enediyne alcohol **1** (Ar = *p*-$MeOC_6H_4$, Y = OH, Scheme 1) in 43% isolated yield. An allylic cation stabilized by the *p*-$MeOC_6H_4$ group is the likely intermediate of the transformation.[4e] We examined four $Ln(fod)_3$ (Ln = Pr, Eu, Er, Yb) catalysts[9c] for the rearrangement of the phenyl-substituted methoxyacetate **17** and found that the reactions were completed within 48 h in all cases to provide the enediyne **18** (Scheme 5). The rearrangement was clean as confirmed by TLC analysis of the reaction mixture. Due to complexation of the product with the catalyst, the isolated yield of **18** varied from 57 to 79% depending on the scale of the reaction. We investigated the rearrangement of three alkoxyacetates **17** possessing the 1-naphthalene moiety in the presence of 10 mol% $Eu(fod)_3$. All reactions were completed within 24 h at 20°C to form the enediynes **19**–**21** (Bn = benzyl and PMB = *p*-$MeOC_6H_4CH_2$) in ca. 60% isolated yields. The 2-naphthalene-substituted methoxyacetate **17** rearranged to the enediyne **22** after 40 h in 79% yield. In accordance with our previous results on 1,3-chirality transfer in the $Eu(fod)_3$-catalyzed rearrangement of a chiral substrate,[9b] we assume that the Ln(III)-catalyzed allylic rearrangement of **17** may involve a 'concerted' transition state **23**.

In summary, we have established a general and facile synthesis of (*E*)-3-hydroxy-4-(arylmethylidene)cyclodeca-1,5-diynes **9** and **16** via the intramolecular Nozaki–Hiyama–Kishi reaction. The subsequent rearrangement of the corresponding alkoxyacetates **17** under lanthanide(III) catalysis gave the 3-substituted enediynes **18**–**22** under very mild reaction conditions. Our preliminary biological screening results showed that (*E*)-3-acyloxy-4-(arylmethylidene)cyclodeca-1,5-diynes, such as **17**, can deliver the same or even higher DNA cleavage activity and cytotoxicity against cancer cell lines compared to the enediynes **18**–**22**.[17] Therefore, (*E*)-3-acyloxy-4-(arylmethylidene)cyclodeca-1,5-diynes can be used as lead compounds for the development of a novel class of enediyne prodrugs.

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