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Evaluation of alkene isomerization as a trigger for enediyne activation

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Abstract—The concept of non-conjugated-to-conjugated double bond isomerization as a triggering mechanism for a calicheamicin model was tested. A bicyclo[7.3.1] enediyne framework was prepared with a bridgehead double bond and an acetonyl side chain. Base-promoted exchange failed to produce the conjugated isomer. Computational analysis suggested that additional conjugating groups would favor the isomerization, but experiment proved that not to be correct. © 2002 Published by Elsevier Science Ltd.

1. Introduction

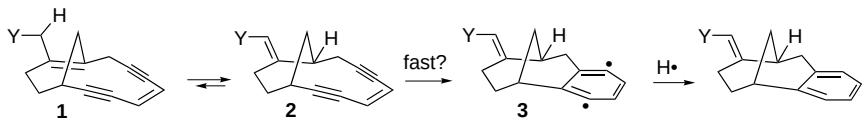
The removal of a bridgehead double bond in the calicheamicin/esperamicin family of enediyne toxins is a primary step in the activation toward arene-1,4-diyl formation, H-atom abstraction, and DNA cleavage.[1] With the natural toxins very high toxicity is observed but low selectivity.[2] It has been challenging to design functional analogs of the enediynes which preserve the toxicity, but take advantage of alternative triggering mechanisms which might be tailored for useful selectivity. In a simple analog of the calicheamicin structural type, one might consider the *endo*-to-*exo* isomerization of the alkene unit in a bicyclo[7.3.1] framework (i.e. **1**→**2**) as the basis of a new triggering mechanism. It is proposed that the thermodynamic (relative stability of **1** versus **2**) and kinetic features (i.e. rate of rearrangement under physiological conditions) can be tuned with the substituent **Y** to provide chemical control for activation at the target site (Scheme 1).

2. Results and discussion

Our initial target was compound **4**, which bears the propargylic hydroxyl group appropriate for the standard methods of ring closure to form the cyclic enediyne, and important as a point of attachment for side chains to optimize DNA binding. It also bears a ketal group or equivalent, which could be unmasked to initiate the *endo–exo* alkene isomerization via enolization–ketonization. The ketone **5** would then equilibrate with enone **6** (Scheme 2).

Even with an unfavorable equilibrium, the further steps through **7** are expected to be essentially irreversible. The other structural features of **4** result from our synthesis strategy in a related system.[3] Based on the earlier work, enone **6** is predicted to have a half-lifetime for cycloaromatization of 30–60 min at 37°C.

The synthesis is shown in Scheme 3. A Diels–Alder reaction of Danishefsky's diene with methacrolein fol-



Scheme 1. *endo–exo* Isomerization as a trigger.

Keywords: enediynes; alkene isomerization; enol–keto isomerization.

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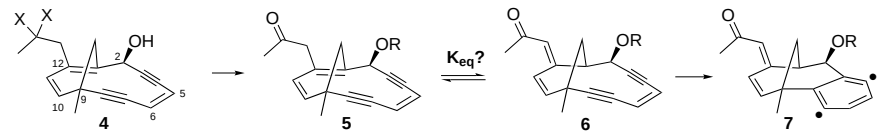
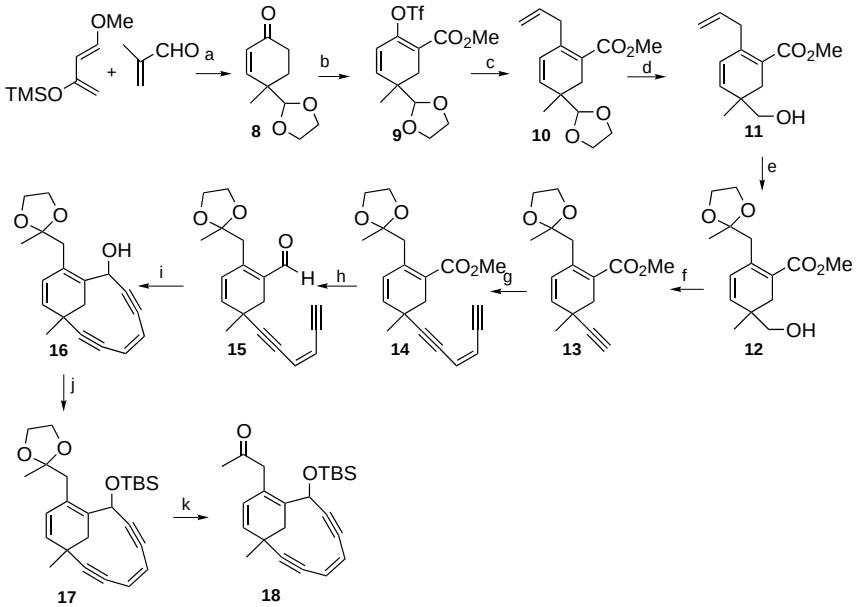


Scheme 2. The ketal/ketone target.

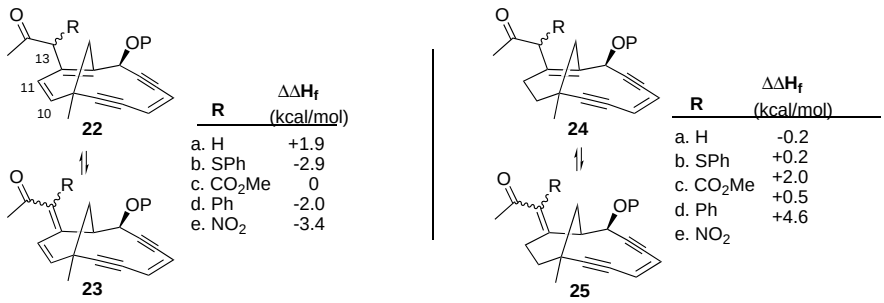


Scheme 3. Synthesis of the ketal/ketone pair. (a) i. Δ, benzene, ii. $HOCH_2CH_2OH$, 0.10 mol equiv. $CuCl_2$, 60% (two steps); (b) i. LiHMDS, HMPA, MeOCOCN, 84%, ii. NaH, $PhN(Tf)_2$, 91%; (c) $Allyl_2Cu(CN)Li_2$, 71%; (d) i. 30% HOAc, ii. 0.37 mol equiv. $NaBH_4$ in EtOH, 76%; (e) i. 0.3 mol equiv. $PdCl_2$, 0.04 mol equiv. CuCl, DMF, H_2O, O_2, ii. $HOCH_2CH_2OH$, 0.10 mol equiv. PPTS, 70% (two steps); (f) i. Dess–Martin, ii. $(MeO)_2POCHN_2$, ^tBuOK, 57% (two steps); (g) i. 0.20 mol equiv. CuI, 0.05 mol equiv. $Pd(PPh_3)_4$, (*Z*)-ClCHCHCCTMS, ii. K_2CO_3 in MeOH, 84% (two steps); (h) i. DIBALH, ii. $RuCl_2(PPh_3)_3$, *N*-methylmorpholine *N*-oxide, 74% (two steps); (i) 2.5 mol equiv. $CeCl_3$, 25 mol equiv. LiHMDS, 79%; (j) 2,6-lutidine, TBStriflate, 77%; (k) 2 mol equiv. $CuCl_2{\cdot}2H_2O$ in CH_3CN, 85%.

lowed by acid treatment and selective protection of the aldehyde group furnishes the enone–ketal **8** in 60% overall yield.[4] Generation of the enolate of **8** followed by trapping with methyl cyanoformate[5] gave an enol ester which was treated with *N*-phenyl trifluoromethanesulfonimide[6] to give the triflate **9** in 76% yield overall. Selective allyl coupling with a higher order cuprate[7] converted **9** to **10** in 71% yield. The acetal unit was hydrolyzed and the resulting aldehyde group was reduced to the alcohol (in **11**) as a protecting group strategy (76% yield overall). Then selective Wacker oxidation of the terminal alkene followed by protection of the resulting ketone as the ethylene ketal gave **12** in 70% yield. The alcohol was re-oxidized with Dess–Martin periodinane[8] and the aldehyde unit was converted to the alkyne with dimethyl diazomethylphosphonate[9] (57%, two steps). Sonogashira coupling[10] of the alkyne with 1-chloro-4-trimethylsilyl-(*Z*)-but-1-en-3-yne followed by desilylation gave the acyclic enediyne **14** in 84% yield. A reduction/re-oxidation protocol was optimal for preparation of the precursor (**15**, 74%) for ring closure. Ring closure to give **16** was accomplished in 79% yield using high dilution conditions in THF with Ce(III) and a large excess of lithium hexamethyldisilazide.[11] The overall yield to this point in Scheme 3 is about 5%, and the procedures can be carried out on multi-gram scale. The structure of **16** was confirmed by X-ray diffraction analysis.[12] Protection of the alcohol as the *tert*-butyldimethylsilyl derivative (**17**) was useful for further manipulations. Deprotection of the ketal unit to expose the ketone functionality proved delicate, but treatment with $CuCl_2{\cdot}2H_2O$ (20 min, 23°C) produced **18** in 85% yield.

The isolation of the non-conjugated isomer **18** was surprising in light of the acidic conditions employed in the deprotection, and suggested a thermodynamic preference for the non-conjugated ketone. This preference was established by treatment of **18** with $NaOCD_3$ in CD_3OD until deuterium introduction was complete (giving **20** without a trace of a conjugated analog, e.g. **21**). It is also supported by computational analysis, using a comparison of the ΔH_f values obtained by AM1 calculations (Table 1, compare structures **22a** and **23a**, R = H).[13] The non-conjugated isomer **22a** is favored by 1.9 kcal/mol. A more elaborate calculation using density functional theory reversed the preference, and suggested **23a** is the more stable by 1.7 kcal/mol.[14] The

Table 1. AM1 estimates of relative stability of conjugated and non-conjugated isomers (**P** = H)



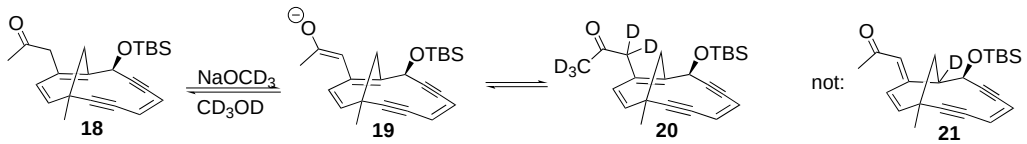
computations suggest at best a small difference (Scheme 4).

In an effort to develop derivatives more likely to favor the isomer with the exocyclic double bond, similar calculations were carried out with groups at C_{13} (R in **22**, Table 1) expected to have a stabilizing interaction with the double bond. In addition, the effect of the double bond at C_{10}–C_{11} was considered. Table 1 displays the derivatives evaluated and gives the $\Delta\Delta H_f$ between the non-conjugated isomer (e.g. **22**, **24**) and the most stable conformer of the conjugated isomer (**23**, **25**). For the cases **22b**–**e**, the calculations suggest that the substituent is predicted to favor (or not disfavor, as for **22c**) the exocyclic isomer.

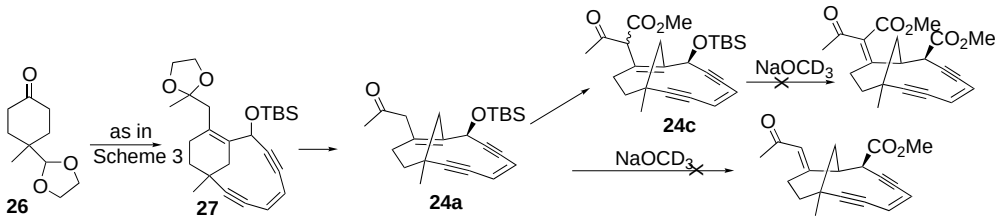
To test this analysis, **22b** and **22c** were prepared as the TBS ethers by direct functionalization of **18**. Treatment of **18** with lithium hexamethyldisilylazide (LiHMDS) generated the enolate at C_{13}, and reaction with *S*-phenylbenzenethiosulfonate[15] gave **22b** (TBS ether) in 59% yield, while reaction with methyl cyanoformate[5] gave **22d** (TBS ether) in 93% yield. Efforts to induce rearrangement to the conjugated isomers (**23**) using $NaOCD_3$ in CD_3OD failed, as the acidic protons adjacent to the ketone group simply exchanged without structural rearrangement; this is clearly inconsistent with the results of the calculations, The products were isolated and shown by ^1H NMR, IR and TLC to have no change in structure other than introduction of four D atoms.

While the AM1 calculations (Table 1) did not favor rearrangement for the dihydro versions, **24**, the test cases were readily synthesized and were evaluated. A modified synthesis starting by reduction[16] of **8** to give **26** ran parallel with that in Scheme 3. The ketone **24a** was obtained by ketal hydrolysis, and the addition of a carbomethoxy group proceeded as before, to give ketoester **24c**. Again, the nonconjugated isomers **24a** and **24c** showed no tendency toward alkene isomerization while undergoing proton exchange in basic CD_3OD (Scheme 5).

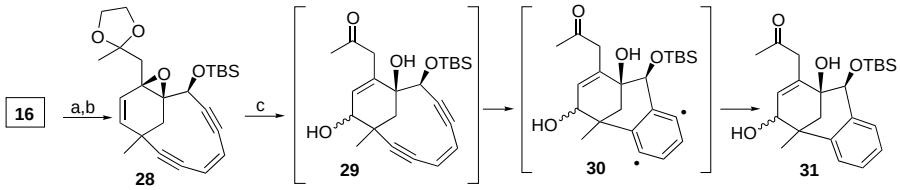
In a preliminary set of experiments, we evaluated an alternative mechanism for dislodging the double bond from the bridgehead position. The epoxide was obtained in essentially quantitative yield by reaction of **16** with *m*-chloroperbenzoic acid,[17] and protection gave **28**. We anticipated that ketal hydrolysis (to **29**) would lead to ring opening of the epoxide to give a structure activated toward cycloaromatization. However, under all conditions tested, the solvolysis of the epoxide was faster than ketal hydrolysis and the proposed product (**30**) underwent diradical formation (to **31**) rapidly (25°C). For example, $CuCl_2/H_2O$ for 20 min at 25°C (in the presence of excess 1,4-cyclohexadiene) gave the cycloaromatized diol **31** in 62% yield, based on 33%



Scheme 4. Attempted ketone–enone rearrangement.



Scheme 5. Preparation and evaluation of the dihydro series.



Scheme 6. Activation via epoxidation. (a) mCPBA, 0°C; (b) TBSOTf, lutidine; (c) $CuCl_2$, H_2O, 25°C.

recovery of the starting epoxide **28**. This result confirms the high reactivity of this framework toward *cyclo*-aromatization, and suggests the basis for a chemically triggerable derivative (Scheme 6).

Acknowledgements

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