Synthesis of Nonracemic β-Hydroxy Ketones and Carbonate Derivatives from Homopropargylic Alcohols through Iodolactonization

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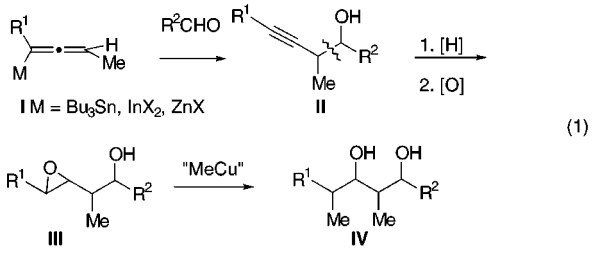
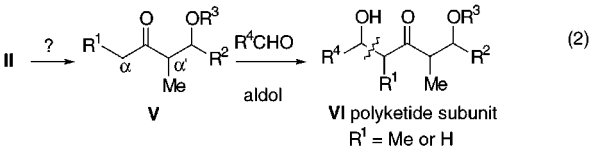
Additions of nonracemic allenylmetal reagents **I** to aldehydes yield syn or anti adducts **II** with high diastereoselectivity, particularly when α-branched aldehydes are employed.[1] These homopropargylic alcohol adducts can be efficiently elaborated to stereotriad, tetrad, and pentad subunits (e.g. **IV**) of polyketide natural products by a sequence involving partial reduction of the alkyne, epoxidation, and addition of methylcuprate or hydride reagents to the intermediate epoxide **III** (eq 1).[2] Such subunits have



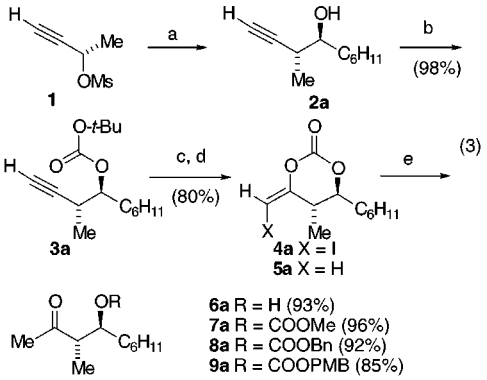
(1)

traditionally been accessed by means of aldol reactions employing chiral auxiliaries.[3] In the aldol approach, high levels of substrate-induced stereocontrol can be realized in cases where the enolate partner possesses stereogenic centers at the α′ position (**V** → **VI**).[4] With the aim of merging the allenylmetal and aldol approaches to polyketide subunits, we initiated an investigation directed toward the regioselective hydration of the alkyne moiety of the homopropargylic alcohols adducts **II** to afford enantioenriched α′-methylated ketones **V** (eq 2).



(2)

For our initial studies we employed the racemic homopropargylic alcohol **2a**, readily prepared through addition of an allenylzinc reagent formed in situ from propargylic mesylate **1**, to cyclohexanecarboxaldehyde. Attempts to prepare the β-hydroxy ketone **6a** directly through oxymercuration[5] of alkyne **2a** resulted in complex mixtures of inseparable products. In an effort to trap the intermediate mercurium species, we attempted an oxymercuration of the *tert*-butyl carbonate **3a**. Once again a complex mixture of products was formed. We then considered subjecting carbonate **3a** to iodolactonization conditions, a transformation well precedented for homoallylic carbonates[6] but not the homopropargylic analogues. Thus, we were pleased to find that upon treatment with IBr in methylene chloride,[6] carbonate **3a** was cleanly converted to the cyclic iodo carbonate **4a** (eq 3). This



(3)

intermediate was readily isolable but proved rather labile and was therefore reduced without purification. Reduction was achieved with Bu_3SnH to afford the novel cyclic carbonate **5a** in 80% overall yield. Initiation of the hydrogenolysis reaction was best achieved with Et_3B.[7] Use of AIBN as the initiator required higher temperatures which caused partial destruction of the iodo lactone.

Cleavage of enol carbonate **5a** to the β-hydroxy ketone **6a** was not successful under typical saponification conditions. For example, treatment with methanolic K_2CO_3 led to products of elimination and epimerization. However, the desired conversion was readily effected with LiOOH at room temperature.[8] Methanolic *i*-Pr_2NEt effected methanolysis of cyclic carbonate **5a** leading to the methyl carbonate **7a** at room temperature. Methanolysis could also be achieved with DMAP as the base catalyst, but only at reflux. The use of Et_3N gave the carbonate **7a** along with 5−10% of elimination product. Amine-catalyzed alcoholysis with BnOH or *p*-$MeOC_6H_4CH_2OH$ (PMBOH) could not be achieved. However, prolonged heating with these alcohols at 115−130 °C yielded the carbonates **8a** and **9a** in high yield. Presumably other alcohols could be used as well to afford a variety of carbonate derivatives.

Additional studies were conducted with the racemic homopropargylic alcohols **2b**−**f** to probe the scope of the new reaction sequence (Table 1). The methyl-substituted adducts **3b**, **3d**, and **3f** were prepared by alkylation of the terminal alkynes **3a**, **3c**, and **3e** with iodomethane. The intermediate iodo lactones **5a**−**f** were quite sensitive to heat and light.

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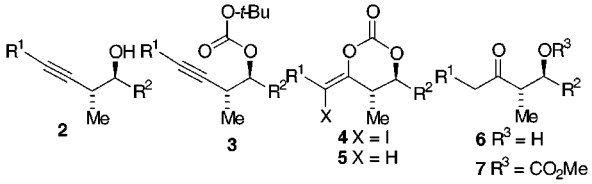
Table 1. Conversion of the Racemic Homopropargylic Alcohols 2a–f to Keto Derivatives

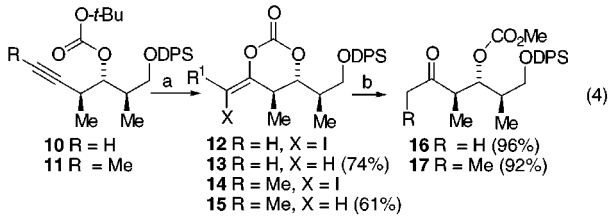


R^1	R^2		3, %	5, %	6, %	7, %
H	c-C_6H_{11}	**2a**	**3a**, 98	**5a**, 80	**6a**, 93	**7a**, 94
Me	c-C_6H_{11}		**3b**, 92	**5b**, 68	**6b**, 96	**7b**, 92
H	*i*-Pr	**2c**	**3c**, 88	**5c**, 65	---	**7c**, 92
Me	*i*-Pr		**3d**, 90	**5d**, 60	**6d**, 85	**7d**, 93
H	C_8H_{17}	**2e**	**3e**, 93	**5e**, 70	**6e**, 93	**7e**, 94
Me	C_8H_{17}		**3f**, 95	**5f**, 72	**6f**, 94	**7f**, 98

Consequently, these intermediates were subjected to the hydrogenolysis reaction without purification. The methyl-substituted hydrogenolysis products **5b**, **5d**, and **5f** were obtained as nearly 1:1 mixtures of (*E*) and (*Z*) isomers.

Additional studies were conducted on the nonracemic anti, anti and syn, anti stereotriads **10**, **11** and **18**, **19**.[2] For these studies the methyl-substituted triads **11** and **19** were prepared by methylation of the alkynyl carbonates **10** and **18**. The ability to alkylate the terminal alkyne of these homopropargylic carbonates adds considerable flexibility to the reaction sequence as both enantiomers of the 3-butyn-2-ol precursor of mesylate **1** are commercially available.[9] Thus, intermediates **10** and **18**, and diastereomers thereof, could serve as precursors to ketones such as **17** and **25** with various R substituents.

(9) The (*S*), (*R*), and racemic forms are available from the Aldrich Chemical Co., Inc., Milwaukee, WI.



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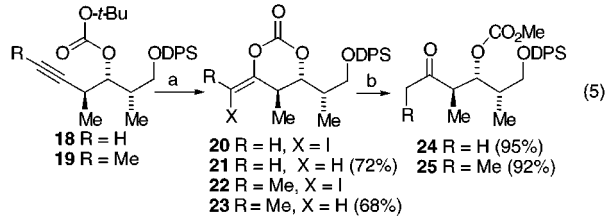

(5)

a) IBr, CH_2Cl_2; Bu_3SnH, Et_3B; b) $(i\text{-}Pr)_2NEt$, MeOH, rt

The methyl carbonate products **16**, **17**, **24**, and **25** of the foregoing sequence were obtained as single isomers. Hence, as expected, methanolysis proceeds without detectable epimerization. These findings extend the utility of enantioenriched homopropargylic alcohols as intermediates for the synthesis of polyketide natural products.

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Supporting Information Available: Experimental procedures for all compounds and ^1H NMR spectra for all new compounds lacking C and H analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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