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Coupling of Alkynyl Organometallics with 4-Acetoxy-1,3-dioxanes: Synthesis of Propargylic and Allylic *anti*-1,3-Diols

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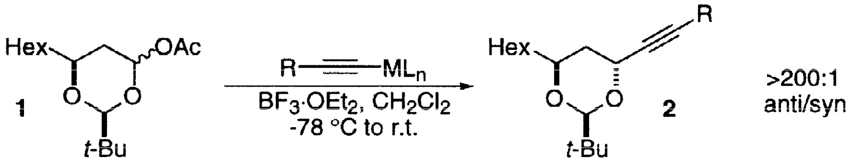
Abstract:
Alkynyl diethylalanes and stannanes couple with 4-acetoxy-1,3-dioxane **1** in the presence of $BF_3 \cdot OEt_2$ to give acetal protected propargylic *anti*-1,3-diols **2** in high yield, with exquisite diastereoselectivity and little acetal epimerization. These propargylic dioxanes **2** are useful intermediates for further diastereoselective reactions.

We have recently described the synthesis of 4-acetoxy-1,3-dioxanes from the corresponding 3-hydroxy carboxylic acids via ketalization and DIBALH reduction/acetylation.[1] These 4-acetoxy-1,3-dioxanes produce oxonium ions on treatment with Lewis acids that couple with a variety of carbon-based nucleophiles such as allyltrimethylsilane,[2] silyl enol ethers,[3] and dialkylzinc reagents[4] to give acetal protected *anti*-1,3-diols with excellent diastereoselectivity. We now wish to report the coupling of 4-acetoxy-1,3-dioxane **1** with alkynyl organometallics to generate acetal-protected propargylic *anti*-1,3-diols **2** which are themselves useful precursors to *E*- and *Z*-allylic *anti*-1,3-diols.



Initial investigations showed that alkynyl diethylalanes[5] readily coupled with 4-acetoxy-1,3-dioxane **1** in the presence of $BF \cdot OEt_2$ to give the propargylic *anti*-dioxanes **2** in excellent yield (Table 1). The anti configuration of the product arises from axial addition to the intermediate oxonium ion. The minor isomers observed were determined to be epimeric at the acetal center, arising from Lewis acid-induced epimerization of the acetal subsequent to the coupling event. GC analysis of the crude reaction mixtures and comparison with authentic standards indicated that the couplings proceeded with > 200:1 selectivity for the *anti*-1,3-diol stereochemistry.

Alkynyl diethylalanes in which the acetylene is substituted with a silyl or sp^2-centered group couple readily with **1** to give a variety of substituted propargylic *anti*-dioxanes **2** (Table 1, entries a-d). Alkyl (sp^3-centered) substituted acetylene diethylalanes failed to give any of the desired dioxanes, resulting in complex mixtures or competitive transfer of the ethyl ligand (entries e & f). A variety of other alkynyl organometallics were examined in an attempt to overcome this problem (entry e). Hexynyl dimethylalane or trimethylalanate also failed to give the coupled product. The use of 1-trimethylsilyl-1-hexyne did result in alkyne transfer to give **2e**, although in very

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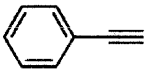
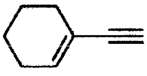
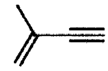
Table 1: Coupling of Alkynyl Organometallics with 4-Acetoxy-1,3-Dioxane **1**

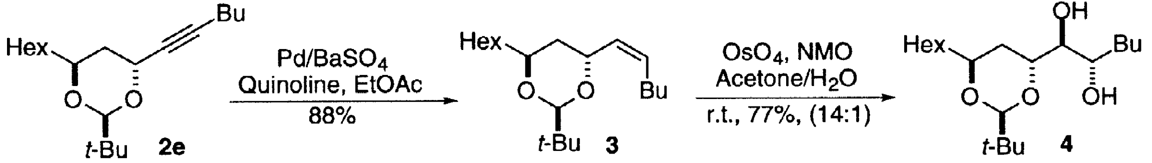
Entry	R—≡	ML_n[a]	% Yield of **2**[b]	Acetal Epimer Ratio
a	TMS—≡	$AlEt_2$	85 %	43:1
		$SnBu_3$	71 %	1:0
b		$AlEt_2$	90 %	1:0
		$SnBu_3$	84 %	1:0
c		$AlEt_2$	75 %	1:0
d		$AlEt_2$	69 %	1:0
e	Bu—≡	$AlEt_2$	Complex Mixture	--
		$AlMe_2$	Degradation of **1**	--
		$AlMe_3(-)$	Complex Mixture	--
		$SiMe_3$	18 %	1:0
		ZnCl	59 %	1:1
		$SnBu_3$	94 %	53:1
f	$TBSOCH_2CH_2$—≡	$AlEt_2$	--[c]	--
		$SnBu_3$	87 %	1:0

a) Alkynyl diethylalane reactions were carried out using a 1:1 mixture of CH_2Cl_2/Et_2O.
b) All compounds were characterized by ^1H and ^{13}C NMR, IR, m. p., HRMS, and EA.
c) The ethyl transfer adduct was the only product isolated (45% as a single diastereomer).

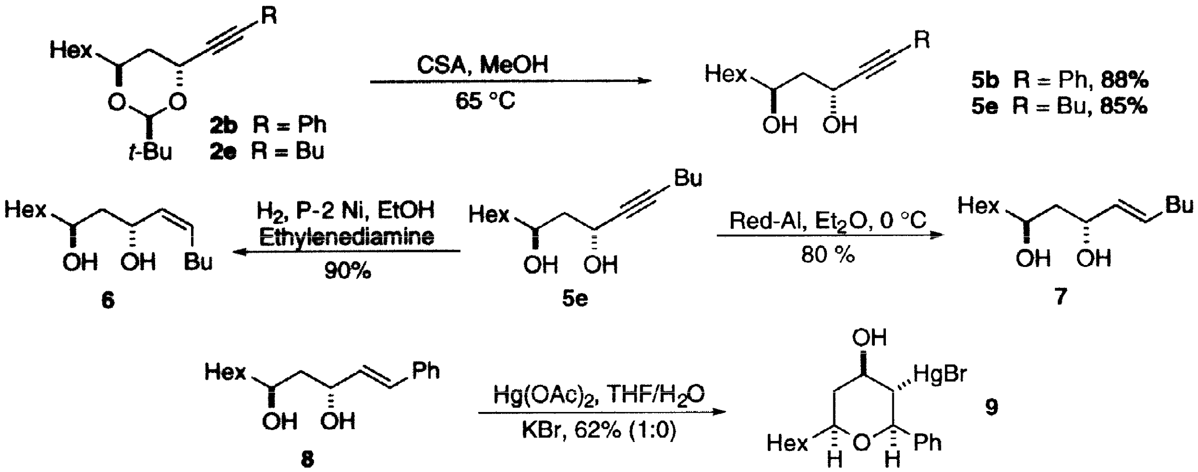
low yield. Hexynylzinc chloride reacted sluggishly to give **2e** in 59% yield. However, the extended reaction times resulted in a 1:1 mixture of acetal epimers upon work-up.

A satisfactory solution to the problem of non-transfer of alkyl alkynes was found with the use of the alkynyl tributylstannanes.[6] These air- and moisture-stable nucleophiles[7] are easily prepared by trapping the lithium acetylide with tributyltin chloride and purified by Kugelrohr distillation. They coupled readily with **1** to give the corresponding dioxanes **2** independent of the alkyne substitution (Table 1). Alkyl, silyl, and aryl-substituted alkynyl stannanes all coupled readily in the presence of $BF_3 \cdot OEt_2$ to give the *anti*-dioxanes **2** in excellent yields and > 200 : 1 diastereoselectivities. Again, the minor isomers observed were epimeric at the acetal center.

The propargylic *anti*-1,3-dioxanes **2** formed in this reaction are useful synthetic intermediates for further diastereoselective reactions. Hydrogenation of **2e** over $Pd/BaSO_4$ gave the Z-allylic *anti*-1,3-dioxane **3**, which underwent dihydroxylation with excellent diastereoselectivity to give the protected tetraol **4** as the major product.



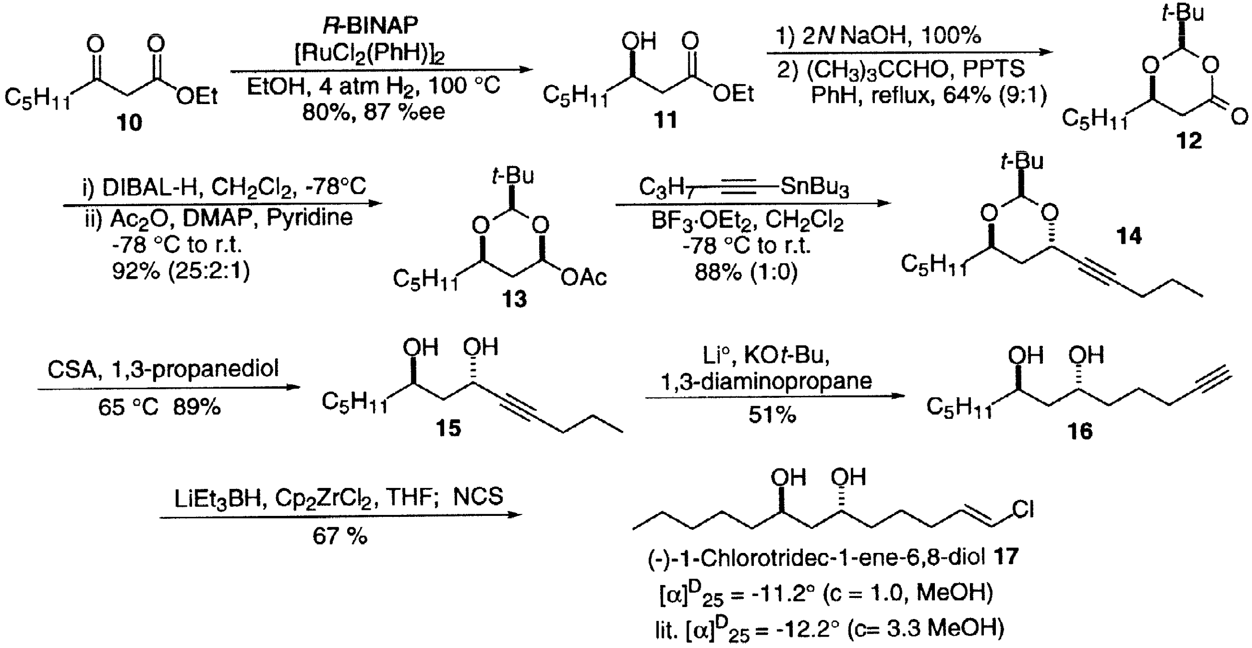
All attempts to form the *E*-allylic *anti*-1,3-dioxane by Li/NH_3 or $LiAlH_4$ reduction of the alkyne have been unsuccessful. The acetal protected diols **2** can be deprotected under acidic conditions to give the corresponding propargylic *anti*-1,3-diols **5** in excellent yields. Periodic removal of the methanol and dimethyl acetal side products helped drive the reactions to completion and improved the yield. Treatment of the propargylic diol **5e** with H_2/P-2 Ni or Red-Al® resulted in reduction of the alkyne to the *Z*- and *E*-allylic diols **6** and **7**, respectively.



The *E*-allylic diol **8**, formed from **5b** by Red-Al® reduction, underwent a diastereoselective intramolecular oxymercuration to form the mercurated pyran **9** as a single diastereomer in good yield.

Propargylic *anti*-1,3-dioxane **14** was a useful intermediate in the synthesis of the antibiotic (–)-1-chlorotridec-1-ene-6,8-diol **17**, a natural product isolated from mixture of cyanophytes off the Enewetak Atoll.[8] Noyori hydrogenation[9] of the known β–ketoester **10**[10] set the C-3 stereochemistry to give **11**. Basic hydrolysis of the ester followed by acidic ketalization with trimethylacetaldehyde gave 1,3-dioxan-4-one **12** as a mixture of diastereomers. A one-pot DIBAL-H reduction/acetylation procedure[1] gave 4-acetoxy-1,3-dioxane **13** in which the *syn* stereochemistry predominated. Coupling of **13** with 1-pentynyltributylstannane in the presence of $BF_3{\cdot}OEt_2$ under the standard conditions gave **14** in excellent yield as a single diastereomer, suggesting that the mixture of acetal diastereomers underwent isomerization to a single oxonium ion prior to coupling. CSA-catalyzed acetal deprotection gave the propargylic *anti*-1,3-diol **15** in good yield. Alkyne isomerization with KAPA[11] gave the terminal alkyne **16** in reasonable yield. Hydrozirconation of **16** with Schwartz reagent formed *in situ*,[12] and chlorination with *N*-chlorosuccinimide gave the final product **17** in just 8 steps overall. Synthetic **17** showed

Scheme 1



identical spectral data with those reported for the natural product, and the optical rotations confirmed the proposed absolute stereochemistry of the natural product.[8]

In summary, we have presented a novel method for the synthesis of acetal protected propargylic *anti*-1,3-diols which proceeds in high yields and extremely high diastereoselectivities. These acetal protected diols are useful synthetic intermediates for further diastereoselective reactions and for the formation of *E*- and *Z*-allylic alcohols. We expect that this methodology will be useful in total synthesis.[13]

Experimental: General procedure for the coupling of alkynyl diethylalanes with 4-acetoxy-1,3-dioxane 2: A flame-dried, 15-mL round-bottomed flask was charged with 0.130 mL (1.15 mmol) phenylacetylene and 5 mL Et_2O under a N_2 atmosphere and cooled in an ice bath. Then *n*-BuLi (2.33 M in hexanes, 0.45 mL, 1.05 mmol) was added dropwise to form a yellow solution which was stirred at 0 °C for 15 min., followed by addition of Et_2AlCl (1.8 M in $PhCH_3$, 0.58 mL, 1.05 mmol). The resulting white suspension was stirred at 0 °C for 30 min, and then cooled to -78 °C in a dry ice/acetone bath. $BF_3 \cdot OEt_2$ (100 μL, 0.786 mmol) was added and the mixture stirred for 10 min. A solution of 150 mg (0.587 mmol) of **2** in 5 mL CH_2Cl_2 was added via cannula. The mixture was allowed to warm to r.t. overnight and then quenched with sat'd $NaHCO_3$. The solution was washed with sat'd $NaHCO_3$, dried over $MgSO_4$, and concentrated by rotary evaporation. The residue was purified by flash chromatography (SiO_2, 10% and then 20% CH_2Cl_2/hexanes) to yield 0.161 g (90%) of a yellow oil as a single diastereomer: FT-IR (neat) 3080, 3059, 3028, 2956, 2929, 2860, 2227, 1599, 1487, 1462, 1363, 1336, 1118, 1047, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.34 (m, 3 H), 5.09 (d, J = 4.2 Hz, 1 H), 4.73 (s, 1 H), 3.98 (m, 1 H), 1.88 (ddd, J = 12.1, 12.1, 5.6 Hz, 1 H), 1.63 (d, J = 11.9 Hz, 1 H), 1.56 (m, 1 H), 1.44 (m, 2 H), 1.32 (m, 7 H), 0.95 (s, 9 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 122.7, 87.5, 87.0, 34.7; *C*H 131.7 (2), 128.4, 128.3 (2), 101.9, 72.7, 64.5; *C*H_2 36.1, 35.8, 31.8, 29.2, 24.9, 22.6; *C*H_3 24.7 (3), 14.8; HRMS (CI/isobutane) calcd for $[C_{22}H_{32}O_2]^+$ 328.2402, found 328.2400. Anal. calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.37; H, 9.80.

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