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Stereoselective Synthesis of D-Desosamine and Related Glycals via Tungsten-Catalyzed Alkynol Cycloisomerization

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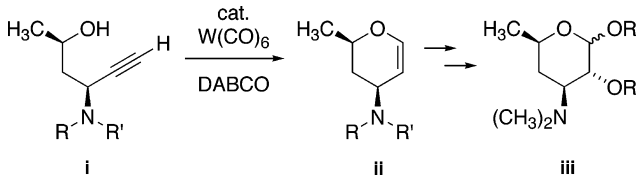
ABSTRACT



Stereoselective synthesis of D-desosamine diacetate ester (iii, R = Ac) was achieved from the glycal (ii) generated by tungsten carbonyl-catalyzed cycloisomerization of the corresponding amino-alkynol (i). A wide variety of N-substituents (R, R′) are compatible with the cycloisomerization, provided that at least one R or R′ is an acyl derivative.

Deoxy amino sugars occur widely in nature, exhibiting varied biological activities.[1] In particular, amino sugars have been identified as critical recognition and selectivity elements of many classes of carbohydrate antibiotics.[2] A strong potential for pharmaceutical use, coupled with their intrinsic stereocomplexity, makes these molecules worthy synthetic targets.[3] Since its structural elucidation by chemical degradation and NMR studies,[4] D-desosamine, the 3,4,6-trideoxy-3-dimethylaminohexose component of several important macrolide antibiotics (erythromycin, narbomycin, picromycin, oleandomycin),[5] has elicited considerable synthetic interest.[6] Herein, we report preparation of D-desosamine from the glycal generated by our simple and versatile tungsten-catalyzed alkynol *endo*-cycloisomerization reaction.[7]

Previous work from our laboratory has applied the tungsten-catalyzed isomerization protocol to the preparation of 1,2-pyranose glycals from non-carbohydrate alkynol substrates, with subsequent elaboration to 2,3,6-trideoxyhexose oligosaccharides.[8] Iterative application of the methodology provided stereoselective preparation of 2,6-dideoxy disaccharides,[9] whereas synthesis of vancosamine and saccharosamine glycals extended the methodology to 3-amino-2,3,6-trideoxyhexose structures.[10] In this paper a series of differentially acylated 3-amino-3,4,6-trideoxyhexose glycal

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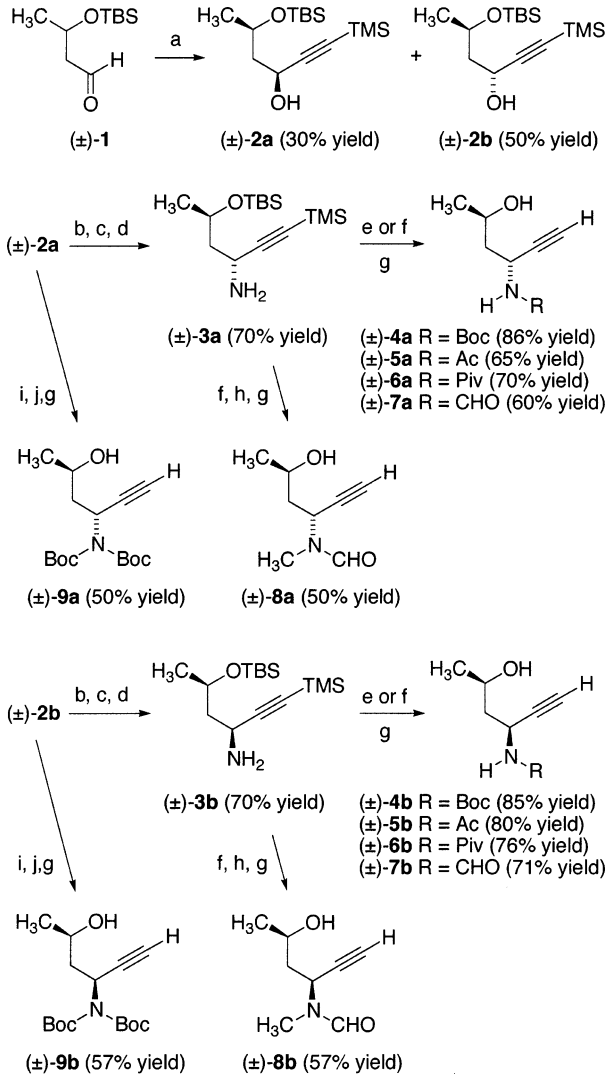
Scheme 1. Preparation of Aminoalkyne Substrates **4**−**9**[a]



[a] Conditions: (a) TMS−acetylene, *n*-BuLi, THF, −78 °C; then chromatographic separation. (b) $ClSO_2Me$, Et_3N, CH_2Cl_2. (c) NaN_3, 15-C-5, DMF. (d) $LiAlH_4$, THF, 0 °C. (e) $(RCO)_2O$, Et_3N, CH_2Cl_2. (f) HCO_2H, DCC, CH_2Cl_2. (g) TBAF, THF, 0 °C. (h) NaH, CH_3I, DMF. (i) PPh_3, Boc_2NH, Et_3N, DEAD, THF. (j) HF-py, THF, 0 °C.

analogues has been prepared in conjunction with the target amino sugar, expanding our repertoire and the scope of tungsten-mediated deoxyhexose precursors to include C4 methylene structures.

Preparation of amido-alkynol cycloisomerization substrates (**4**−**9**) began with addition of TMS-acetylene to the known TBS-protected aldehyde **1**,[11] and incorporation of amine functionality by addition of sodium azide to the mesylate followed by $LiAlH_4$ reduction (Scheme 1). Although this reaction was not stereoselective, the alcohol diastereomers **2a**,**b** could be separated by careful silica gel chromatography and permitted our exploration of each diastereomeric pattern.

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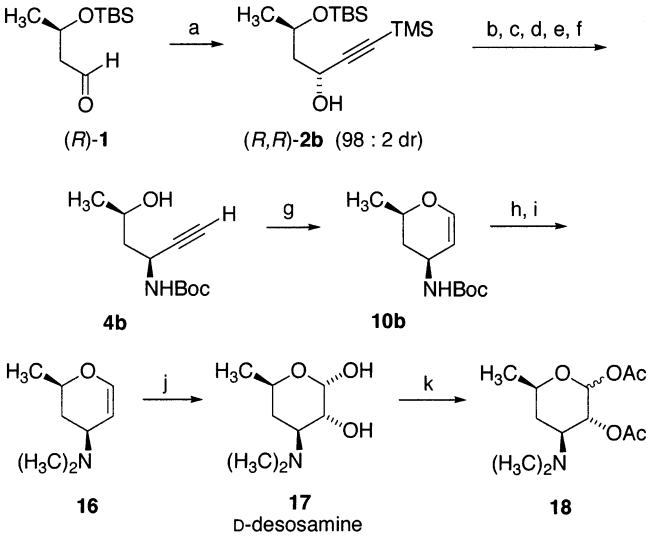
Acylation of amines **3a**,**b** followed by removal of silyl ether and silyl alkyne protective groups provided amido alkynol cycloisomerization substrates **4**−**8**, while application of a Mitsunobu protocol[12] to protected **2a**,**b** provided the bis-BOC carbamate-substituted substrates **9a**,**b** after sequential removal of silyl ether and silyl alkyne protective groups.

The tungsten-catalyzed cyclizations were conducted with both diastereomers of the alkynol substrates **4**−**9** and in all cases required only relatively low (5−15 mol %) catalytic loading, proceeding with nearly universal *endo* selectivity and resulting in good to excellent yields of the glycal cycloisomerization product (Table 1).

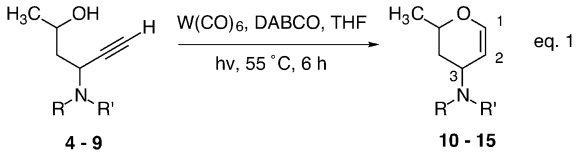
Stereoselective synthesis of D-desosamine could be accomplished beginning with application of the Carreira protocol[13] for zinc-mediated addition of TMS-acetylene to (*R*)-3-*tert*-butyldimethylsiloxybutanal (**1**).[11] Although the overall yield for our substrate was somewhat lower than the yields reported by Carreira for simpler substrates, the stereoselectivity was nearly 100%. None of the undesired diastereomer was recovered during purification by column chromatography. Methylation and LAH reduction of the Boc-protected nitrogen of glycal (**10b**) quickly established the dimethylamine functionality required for desosamine. An acidic protocol for dihydroxylation of problematic olefins substituted with trialkylamines recently described by the Sharpless laboratory[14] proved to be effective when applied to dimethylamino glycal (**16**) and generated the C2 hydroxyl group anti to the tertiary amine group at C3 as well as the α anomeric hydroxyl group at C1. Finally, D-desosamine (**17**) was treated with acetic anhydride to facilitate characterization

Scheme 2. Stereoselective Synthesis of D-Desosamine[a]



[a] Conditions: (a) $Zn(OTf)_2$, Et_3N, (+)-*N*-methylephedrine, TMS−acetylene, toluene, 23 °C, 18 h (60% yield). (b) $ClSO_2CH_3$, Et_3N, CH_2Cl_2. (c) NaN_3, 15-C-5, DMF. (d) LAH, THF, 0 °C. (e) Boc_2O, Et_3N, CH_2Cl_2. (f) TBAF, THF, 0 °C (60% yield, five steps). (g) 5% $W(CO)_6$, THF, DABCO, hν, 55 °C (90% yield). (h) NaH, MeI, DMF, 23 °C. (i) LAH, THF, 0 °C (90% yield, two steps). (j) 10% OsO_4, citric acid, Me_3NO/H_2O, BuOH/H_2O. (k) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (46% yield, two steps).

Table 1. 3-Nitrogen-Substituted Glycals from $W(CO)_6$-Catalyzed Alkynol Cycloisomerization



entry	(series a)	$W(CO)_6$	yield	entry	(series b)	$W(CO)_6$	yield
1	R_1 = H, R_2 = Boc (**4a**)	5%	88% (**10a**)	7	R_1 = H, R_2 = Boc (**4b**)	5%	90% (**10b**)
2	R_1 = H, R_2 = Ac (**5a**)	10%	75% (**11a**)	8	R_1 = H, R_2 = Ac (**5b**)	10%	75% (**11b**)
3	R_1 = H, R_2 = Piv (**6a**)	10%	40%[a] (**12a**)	9	R_1 = H, R_2 = Piv (**6b**)	10%	60% (**12b**)
4	R_1 = H, R_2 = CHO (**7a**)	5%	85% (**13a**)	10	R_1 = H, R_2 = CHO (**7b**)	5%	90% (**13b**)
5	R_1 = CH_3, R_2 = CHO (**8a**)	10%	80% (**14a**)	11	R_1 = CH_3, R_2 = CHO (**8b**)	10%	84% (**14b**)
6	R_1 = Boc, R_2 = Boc (**9a**)	15%	85% (**15a**)	12	R_1 = Boc, R_2 = Boc (**9b**)	15%	85% (**15b**)

[a] Also 8% *exo* isomer found.

as the diacetate (**18**, Scheme 2). The ^{1}H NMR data for the diacetate **18** is identical with that reported for the natural product-derived D-desosamine diacetate.[4b]

In conclusion, we have demonstrated the generality of our tungsten-catalyzed alkynol *endo*-cycloisomerization reaction for a broad spectrum of N-protective groups. The nearly exclusive *endo*-cycloisomerization observed herein for alkynol substrates with propargylic nitrogen substituents regardless of relative stereochemistry is notable, especially when compared to the lower regioselectivity recently reported by Wipf and Graham for certain diastereomers of alkynol substrates with propargylic oxygen substituents.[15] This suggests possible stabilization of the vinylidene-$W(CO)_5$ intermediate by propargylic nitrogen substituents.

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Supporting Information Available: Experimental details and procedures for compounds **2**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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