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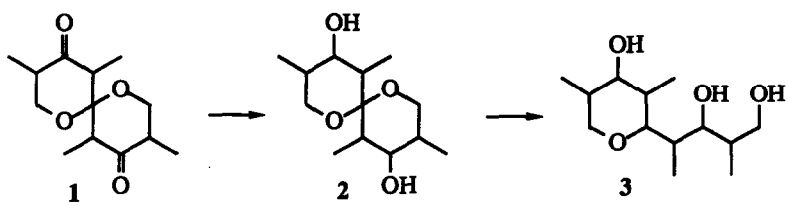
STEREOCONTROLLED SYNTHESIS OF TETRAHYDROPYRANS VIA REDUCTIVE MANIPULATION OF 4,10-DIOXO-3,5,9,11-TETRAMETHYL-1,7-DIOXASPIRO[5.5]UNDECANES

Yun-bo Zhao and Kim F. Albizati*
Department of Chemistry, Wayne State University, Detroit, MI 48202

Summary: Stereocontrol in the carbonyl reductions of the titled compounds leads to a variety of hydroxylated spiroketals. Reductive cleavage leads to tetrahydropyrans with complete stereocontrol over 7 stereogenic centers.

1,7-Dioxaspiro[5.5]undecanes have been recognized as key substructures of several biologically important metabolites for some time.[1] More recently, these spiroketals have been utilized as templates for stereospecific synthesis of compounds which do not contain oxygen heterocycles. A key strategy has emerged from several laboratories, most notably those of Ireland,[2] in which a spiroketal is produced, manipulated and then fully hydrolyzed to give open chain compounds containing a protected carbonyl and two hydroxyls. Our own approaches in this area utilize a multiple equilibration strategy to produce highly functionalized and stereodifferentiated spiroketals in three-step processes.[3] We wish to report the reductive manipulation of such

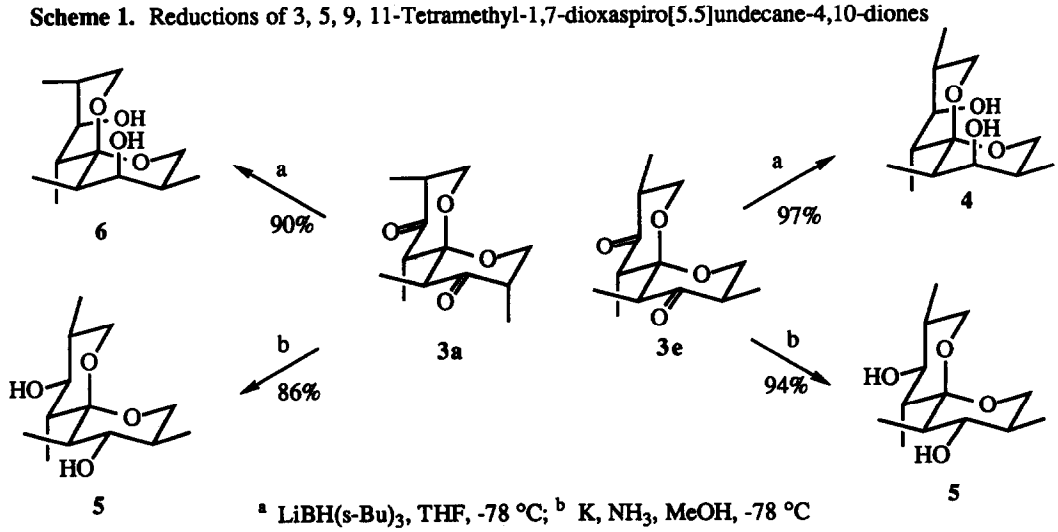


compounds to give 4,10-dihydroxy-3,5,9,11-tetramethyl-1,7-dioxaspiro[5.5]undecanes (**2**) and the stereospecific reductive cleavage of these to give highly substituted tetrahydropyrans (**3**).

We have reported the synthesis of spiroketals **3a** and **3e** in three steps from 3-pentanone and 3-alkoxy-2-methylpropanal using a tandem aldol process[4] and a multiple equilibration as key transformations to establish 5 stereocenters in a single process. Reduction of the all-equatorial methyl isomer **3e** with $LiBH(s\text{-}Bu)_3$ in THF at low temperature produces the diol **4** as the sole product in 97% yield (Scheme 1). No isomeric diols were observed spectroscopically in the crude reaction product. The stereospecificity of the transformation is not surprising, given the high selectivities for producing axial alcohols that is characteristic of this reagent. Reduction to the diequatorial diol was anticipated to be more problematic because few reagents provide this type of selectivity with complete stereocontrol. Clearly, we must have a completely stereospecific method because any stereochemical leakage to the axial alcohol could be expected to be multiplied in a symmetrical difunctional substrate. Evans has reported a very promising result in the reduction of a functionalized 4-oxo-1,7-dioxaspiro[5.5]undecane[5] using SmI_2 in isopropanol, a variant of the classical Meerwein-Verley-Pondorff reagent. However, this reagent failed to reduce

our substrates, returning starting material in high yield. It was found that treatment of **3e** with potassium in liquid NH_3 using methanol as a proton source resulted in stereospecific reduction to the diequatorial diol **5** in 94% yield. Again, no other isomers were observed. Reductions of the isomeric spiroketal **3a** provided somewhat surprising results. Reduction with K/NH_3 gave rise to the all-equatorially-substituted spiroketal **5**. We have found that **3a** can be quantitatively converted to **3e** by treatment with NaOMe/MeOH. Presumably, equilibration of **3a** to **3e** is occurring prior to reduction. This is not unexpected, considering the strongly basic conditions of

Scheme 1. Reductions of 3, 5, 9, 11-Tetramethyl-1,7-dioxaspiro[5.5]undecane-4,10-diones



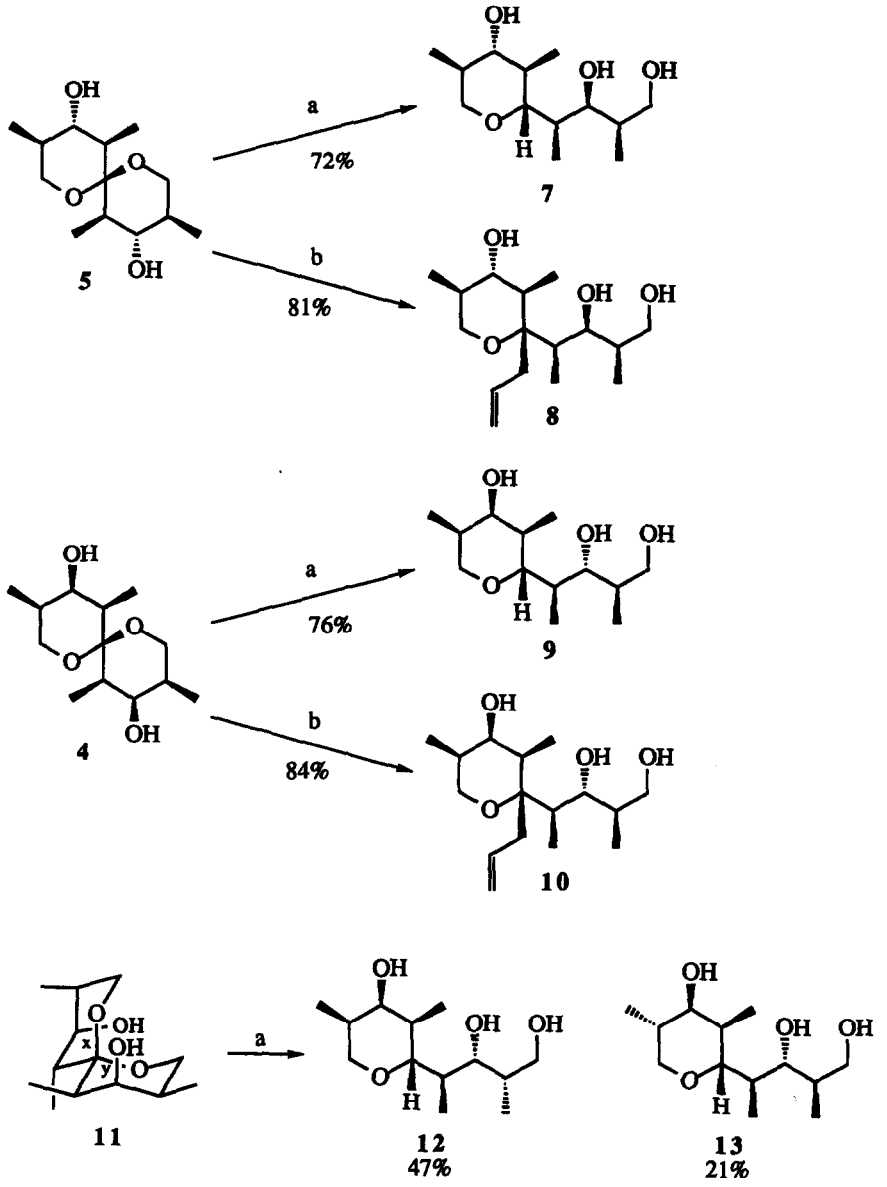
[a] $LiBH(s\text{-}Bu)_3$, THF, -78 °C; [b] K, NH_3, MeOH, -78 °C

metal-ammonia reductions. More surprising was that reduction of **3a** with $LiBH(s\text{-}Bu)_3$ in THF resulted in the diaxial diol **6** in which one methyl group had epimerized.[6] We have observed this phenomenon with $LiBH(s\text{-}Bu)_3$ previously in a 3-substituted camphor system, perhaps indicating the result of a kinetic epimerization.[7] However, we cannot account for the high specificity with this substrate. In any case, the spiroketals **3a** and **3e** can be cleanly doubly-reduced to stereochemically complementary diols in high yield.

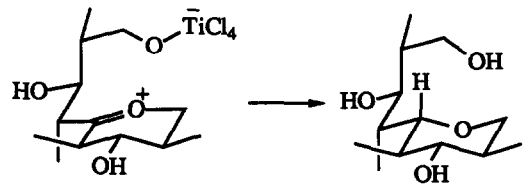
The reductive cleavage of these diols to tetrahydropyrans can be accomplished without protection of the hydroxyl groups (Scheme 2). Treatment of **5** with Et_3SiH / $TiCl_4$ in CH_2Cl_2 at low temperature followed by stirring with TsOH to desilylate any derivatized hydroxyls provided the tetrahydropyran **7** as the sole product in 72% yield. The isomeric substrate **4** provided an analogous result, giving rise to the isomeric system **9** in 76% yield. Presumably, the Lewis acid promotes opening of the system to an oxenium cation (**14**) which is axially reduced to give the observed products. Both **4** and **5** may also be reductively cleaved, forming a new carbon-carbon bond in the process. Treatment of **4** or **5** with allyltrimethylsilane and $TiCl_4$ at low temperature provides the axially allylated tetrahydropyrans **10** and **8** respectively in good yields.

In the cases of **4** and **5**, cleavage of either spiro C-O bond leads to the same product. Reductive cleavage of the unsymmetrical spiroketal **11** can lead to two different spiroketals, depending on which C-O bond is broken. One might expect that the C-O bond in the ring with an axial methyl group (bond *x* in **11**) would be cleaved to an oxenium ion faster than bond *y* due to relief of steric strain as the transition state is approached. When **11** is treated with Et_3SiH / $TiCl_4$ the two spiroketals **12** and **13** were produced in a 2.2 : 1 ratio confirming this

Scheme 2. Reductive Cleavage of Substituted 1,7-Dioxaspiro[5.5]undecanes



[a] Et_3SiH, $TiCl_4$, CH_2Cl_2, -78 - -20 °C; [b] allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 - -20 °C; all reactions followed by stirring with pTsOH in aq THF to desilylate partially silylated alcohols.



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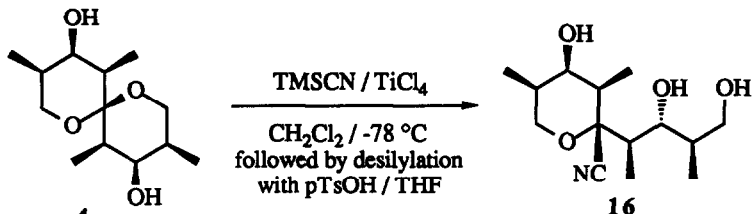
prediction. This result indicates that there will be predictable control in the cleavage of unsymmetrical substrates.

Finally, we have found that the related silicon reagent trimethylsilyl cyanide (TMSCN) can also reductively cleave a spiroketal with incorporation of a one carbon fragment at the erstwhile spiro carbon. Treatment of **4** with



4 16

$TMSCN / TiCl_4$ in CH_2Cl_2 at low temperature provides a single tetrahydropyran, assigned the axial cyano structure **16** by analogy with previous results.

To summarize, 4,10-dioxo-3,5,9,11-tetramethyl-1,7-dioxaspiro[5.5]undecanes (**1**) exhibit high and diverse stereospecificity in their carbonyl reduction reactions. The resulting diols may be reductively cleaved with a variety of reagents to give highly functionalized and stereocomplementary tetrahydropyrans in good yield. Further results in this area will be forthcoming.

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6 The product of this reaction is actually a mixture of two deceptively diastereomeric compounds, corresponding to epimerization in one or the other ring. The presence of the asymmetric spiro carbon consigns the reactivity in each ring to diastereomeric, but essentially equivalent transition states. Only the isomer **6** is drawn for clarity.

7 Valerie Vaillancourt, unpublished results.

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