Studies on the Synthesis of 2,6-Disubstituted Dihydropyrans: Intervention of Oxonia-Cope Rearrangements in the Lewis Acid Mediated Cyclodehydrative Reactions of Aldehydes and β-Hydroxyallylsilanes

William R. Roush,* Garrett J. Dilley
Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055, USA
Fax +1 734 6479279; E-mail: roush@umich.edu
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Dedicated to Professor Ryoji Noyori in admiration of his seminal contributions to organic chemistry.

Abstract: The dehydrative coupling reactions of anti-β-hydroxyallylsilanes 5 and aldehydes provide 2,6-cis-dihydropyrans 27 by pathways involving oxonium ions that cyclize via boat-like transition state 21, with the intervention of oxonia-Cope rearrangements (21 → 29).

Key words: addition reactions, intramolecular allylations, sigmatropic rearrangement, allylsilanes, dihydropyrans

During the course of our work on the total synthesis of scytophycin C,2 we became interested in developing a new strategy for synthesis of the 2,6-trans disubstituted dihydropyran nucleus of 4 by the late stage coupling of two advanced aldehyde fragments (1 and 2) with the bifunctional allylating agent, 3 (X2 = DIPT or IpCl).3,4 While numerous strategies for synthesis of substituted pyrans are available,5 none have the potential modularity of the method that we sought to develop.

The plan was that β-hydroxyallylsilanes 5, which are available with high diastereo- and enantioselectivity via the asymmetric γ-silylallylboration of aldehydes with allylborane reagents,3,4,6 would combine with a second aldehyde in the presence of a Lewis acid to give oxonium ion 6, which would then undergo an intramolecular allylation to produce the 2,6-trans-disubstituted dihydropyran 7.7,8 This process is related to the well established Prins cyclization reactions of homoallylic alcohols and aldehydes, which provide cis-2,6-disubstituted dihydropyrans preferentially.9,14 However, owing to the strong stereoelectronic preference for the silyl substituent to adopt an axial position in reactions that develop carbocationic character at the γ-position,15,16 we expected that the conversion of 5 to 7 would provide the 2,6-trans-dihydropyran selectively. Implicit in this prediction was the assumption that the intramolecular allylation would proceed by way of a chair-like transition state (as in 6). The stereochemistry of the trans-dihydropyran product then follows from the 3,4-anti stereochemistry of the allylsilane 5, which dictates that both the R group (deriving from the aldehyde used in the synthesis of 5) and the silyl substituent will adopt axial positions in 6, and the equatorial placement of the R’ substituent (deriving from the second aldehyde, R’CHO).

No examples of intramolecular allylation of the type 5 to 7 had been reported at the time that our studies were initiated.7,8 However, Speckamp had suggested that ions like 6 (with R’ = CO2Me) are intermediates in the vinylsilane-terminated cyclizations of ester-substituted oxocarbonium ions.17,18 Consequently, we anticipated that our method would intercept a known class of reactive intermediates by starting from 5, rather than from a vinylsilane precursor.8,19 While our studies were in progress, Panek reported an analogous method for the synthesis of substituted dihydropyrans via the reactions of β-hydroxycrotylsilanes and aldehydes.5
Initial studies were performed using allylsilane $8a^1$ and the corresponding TMS ether $8b$ as substrates. After screening a number of Lewis acid and solvent combinations, we settled on use of TMS-OTf in CH$_2$Cl$_2$ at -78 °C in the presence of 4 Å molecular sieves for these reactions.$^{20,21}$ The optimal conditions for the reaction of $8a$ with dihydrocinnamaldehyde involved use of 3 equiv. of the aldehyde and 0.5 equiv. of TMS-OTf at a final concentration of 0.15 M (for $8a$). Under these conditions, an 82% yield of dihydropyran 9 was obtained with excellent stereoselectivity (94: 6 d.s.). Comparative experiments using $8a$ and the TMS ether $8b$ indicated that there was no significant advantage to use of $8b$ as the substrate. However, use of smaller amounts of aldehyde led to substantially decreased yields owing to competitive Lewis acid catalyzed Peterson elimination of $8a/8b$, as well as the TMS-OTf promoted cyclotrimerization of the aldehyde. The Peterson elimination process was completely suppressed using the optimal conditions (3 equiv. RCHO, 0.5 equiv. TMS-OTf, 0.15 M concentration of $8a$).

Surprisingly, the major product of the reaction of $8a$ and dihydrocinnamaldehyde was the 2,6-cis-dihydropyran 9, and not the originally targeted trans diastereomer. The stereochemistry of 9 was easily assigned by hydrogenation (H$_2$, Pd/C) to the meso tetrahydrofuran ([α]$_D$ = 0), as well as by the observation of an NOE between the two axial hydrogens at C(2) and C(6) of 9. The reaction of $10$ and dihydrocinnamaldehyde similarly provided dihydropyran 11 (85: 15 d.s., 57% yield), again with the cis-isomer predominating (as confirmed by an NOE between H-2 and H-6).

Attempts to extend these results to additional hydroxyallylsilane-aldehyde combinations led to complex product mixtures. For example, the reaction of allylsilane $8a$ with isobutyaldehyde (1.0 equiv., using non-optimized conditions) gave three products after HPLC separation: the desired product 12 (12%), dihydropyran 13 (17%) that differs from 12 in terms of the placement of the double bond in the ring, and dihydropyran 9 (7%) with two phenylethyl substituents! The same three products were obtained (70% combined yield) from the reaction of allylsilane 14 with dihydrocinnamaldehyde (4 equiv.). In this case, the bis-phenylethyl substituted cis-dihydropyran 9 was obtained in 50% yield, with the desired product 13 being isolated in 17% yield along with the olefin regioisomer 12 in 3% yield (after HPLC separation). The cis-stereochemistry of dihydropyran 12 and 13 was assigned by $^1$H NOE studies.

The side chain exchange process that complicates the reactions of allylsilanes $8a$ and 14 leading to unsymmetrically substituted dihydropyran 12 and 13 can be suppressed by using α-acetoxy acetal such as 16 and 19 as the cyclization substrates. The α-acetoxy acetal were synthesized by using Rychnovsky’s procedure for in situ acylation of the tetrahedral intermediates generated by DIBAL reduction of esters.$^{23,24}$ The optimal conditions for cyclization of 16 involved use of SnCl$_4$ (1.5 equiv.) in toluene at -78 °C to -15 °C. Under these conditions, the 2,6-cis-dihydropyran 17 was obtained in 66% yield with 94: 6 d.s., and the symmetrically substituted dihydropyran 9 (resulting from side chain exchange) was obtained in only 4% yield. As another illustration of this method, cis-dihydropyran 9 was obtained in 50% overall yield (94: 6 d.s.) for the three step sequence from 18.

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The preferential formation of the 2,6-cis-dihydropyran and the unanticipated exchange of allylsilane side chains can be explained by invoking competitive and extremely facile oxonia-Cope rearrangements\textsuperscript{17,18,25} in the intramolecular allylation process.\textsuperscript{26} We assumed at the outset that oxonium ion 22 (c.f., 6) would cyclize via a chair-like transition state to give the 2,6-trans-dihydropyran 23 (c.f., 7). However, the experimental record clearly establishes that this pathway (22 → 23) is slow. We initially speculated that ion 22 undergoes a [3,3]-sigmatropic rearrangement, or an oxonia-Cope rearrangement, to give 24 in which the phenylethyl substituent adopts a thermodynamically unfavorable axial position. Oxonium ion 24 could isomerize to 25 with an equatorial phenylethyl substituent, by reversible addition of a nucleophile (e.g., TMS-OH in the TMS-OTf catalyzed reactions of 8a; chloride or acetate ions in the SnCl\textsubscript{4} promoted reactions of the α-acetoxy acetals, 20). Ion 25 is structurally equivalent to the intermediates generated by Speckamp and Markó from homoallylsilans like 28.\textsuperscript{8,17-19} It could be expected that 25 would cyclize directly to the 2,6-cis-dihydropyran ent-27 or undergo a facile reverse oxonia-Cope rearrangement to 26 which can then undergo intramolecular allylation to the 2,6-cis-disubstituted dihydropyran ent-27. The intermediacy of ions 24 and 25 also accounts for the side chain scrambling that occurs in the reaction of 8a with isobutyraldehyde and of 16 with dihydrocinnamaldehyde, as addition of TMS-OH to 24 or 25 creates the opportunity for release of dihydrocinnamaldehyde into solution and give 28, which can then recombine with the second aldehyde, R‘CHO, which is used in excess.\textsuperscript{28}
A striking conclusion of this analysis is that if this process proceeds via the intermediacy of chair-like transition states, the 2,6-cis-dihydropyran ent-27 will be produced with inversion of the original C-O stereochemistry of 8a. This stereochemical inversion occurs at the stage of the oxonium ion isomerization, 24 → 21. However, if the oxonia-Cope rearrangements and the intramolecular allylation proceed by way of boat-like transition structures 21 and 29, then the overall conversion of 8a or 20 to the 2,6-cis-dihydropyran 27 will proceed with retention of stereochemistry.

We established that the cyclization reactions of the α-acetoxy acetal proceed with retention of stereochemistry by the synthesis of 33, a known precursor of a civet cat pheromone. Thus, treatment of α-acetoxy acetal 31, prepared in 75% yield from ester 30 by using the Rychnovsky procedure, with TMS-OTf in CH₂Cl₂ at -78 °C provided 32 in 41% yield (volatile!) with 94:6 selectivity. The 2,6-cis stereochemistry was confirmed by the observation of a NOE between H-2 and H-6. Hydrogenation of 32 over Pd/C provided (-)-33, the stereochemistry of which was confirmed by comparison with two independent literature assignments.

![Chemical structure of 33 with stereochemistry confirmation](image)

Based on these results, we conclude that all of the intramolecular alkylation reactions leading to 2,6-cis-disubstituted dihydropyrans described in this paper, as well as the oxonia-Cope rearrangement reactions implicated in the side chain exchange process, proceed with high stereochemical fidelity via boat-like transition states (e.g., 8a/20 → 21/27 for the alkylation, and 8a → 21 → 29 → 28 → 29 → 21 → 27 for the alkylation process with exchange of the allylsilane side chain; see Scheme). Our results also explain the preferential formation of 2,6-cis-disubstituted dihydrodipyrans from the InCl₃-mediated reactions of aldehydes and 3-trimethylsilylallyl tributylstannane recently described by Li and coworkers.

We conclude by commenting briefly on the related dihydropyran synthesis recently reported by Panek. The dehydrative cyclizations of crotylsilanes 34 and 36 proceed with excellent selectivity to the substituted dihydropyrans.
35 and 37, respectively. While Panek has suggested that these reactions proceed by way of boat-like transition states, it is more likely that they proceed by way of the chair-like transition structures 38 (for 34) and 40 (for 36) because the boat-like transition states 39 and 41 (in which the oxonium ions adopt the more stable ($E$)-geometry) suffer from eclipsing interactions involving the aldehyde R group and the Me group deriving from the crotylsilane reagent; transition structure 39 also suffers from an eclipsing interaction between the axial carboxemthoxyl and the pseudoaxial -SiMe$_2$Ph.

Based on these results, it appears that the boat-like transition state 21 in the reactions of the allylsilanes reported herein is favored owing to the absence of the eclipsing interactions highlighted in 39 and 41. Finally, we note that products deriving from oxonia-Cope rearrangements were not observed in the Panek study, a result that is consistent with the dehydrative cyclization reactions of carboxalkoxy-substituted allylsilane 10. It may be inferred that the oxonia-Cope process is disfavored with intermediates 21 (R = CO$_2$Bu) since the electron withdrawing carboxalkoxy group destabilizes the oxonia-Cope product 29 in which the -CO$_2$Bu group is directly attached to the oxonium ion carbon. If this analysis is correct, then the dehydrative cyclization reactions of aldehydes and crotylsilanes analogous to 8a and 14, etc., will also experience competitive oxonia-Cope processes.

Additional studies on the stereoselective synthesis of 2,6-trans-disubstituted dihydropyran, required for our synthesis of scytophycin C and other natural products, are ongoing and will be reported in due course.

Acknowledgement

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References and Notes

(1) Taken in part from the 2000 Ph. D. Thesis of G. J. Dilley, University of Michigan.
(6) Allyltrimethylsilanes of general structure 5 were synthesized by alkylation of aldehydes with the chiral allylborane reagent generated by metallation of allyltrimethylsilane with $n$-BuLi and KO$\text{Bu}$ in THF at -25 $^\circ$C followed by addition of MeOH(1pc), at -78 $^\circ$C. BF$_3$Et$_2$O and then an aldehyde (see ref. 4 for a related procedure), or by using the DIPT modified (E)-$\gamma$-trimethylsilylallylboronate (Marron, T. G.; Roush, W. R. Tetrahedron Lett. 1995, 36, 1581).

(24) Esters 15 and 18 were prepared by acylation of 8a with the appropriate acid chlorides (DMAP, pyridine, CH$_2$Cl$_2$) in 82-84% yield.
(26) Analogous aza-Cope rearrangements of iminium ions have been documented previously: Daub, G. W.; Heering, D. A.; Overman, L. E. Tetrahedron 1988, 44, 3919.
(31) Chiral allylsilane 30 was synthesized from the corresponding homoallylic silanol that was prepared as described in ref. 4. The absolute stereochemistry of the alcohol was assigned by using the modified Mosher ester method.
(32) Panek’s analysis indicates that the favored boat-like transition states have the thermodynamically less favorable (Z)-oxonium ion geometry.

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