Tetrahedron Letters, Vol 32, No 29, pp 3473-3476, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

# Rhodium (I)-Catalyzed Cyclizations of 3-C-Alkenyl Pentodialdose Derivatives

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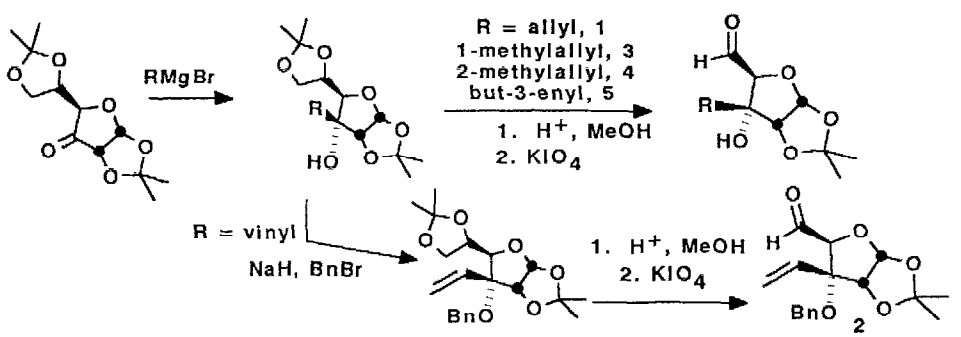
Key Words: Hydroacylation; Carbohydrates, Cyclization; C-branched pentodialdose; Ene reaction.

**Abstract:** Cyclization of 1,2-isopropylidene 3-C-allyl ribo-pentodialdose, and 1-methylallyl and 3-C-vinyl analogs, with $[(Ph_3P)_2RhCl]_2$ under $CH_2CH_2$ leads to intramolecular hydroacylation of the alkene with selective formation of cyclohexanones or cyclopentanones.

Carbohydrates are important synthetic precursors to enantiomerically pure compounds because of their ready availability and well defined stereochemistry. We[1] and others[2] have begun to explore transition metal-mediated reactions of carbohydrates and their derivatives. Our goal has been to combine the unique reactivity of organometallic compounds with the stereochemical consequences of using a chiral sugar-based substrate. We report here that hydroacylation of suitable derivatives can lead to new 5- and 6-membered carbocycles whose stereochemistry is derived from glucose.

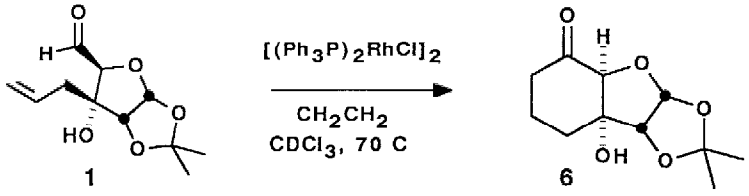
Rhodium catalyzed hydroacylation of 4-pentenals to form cyclopentanones has been known for more than a decade.[3] One group has used the reaction in studies toward prostaglandin synthesis,[3d] and has reported observing enantioselectivity when using a chiral phosphine ligand in the catalyst.[4] Few workers have reported attempts at cyclizing longer chain alkenals.[3b] Our earlier attempt to hydroacylate 3-O-allyl glucose[1] led us to two conclusions: 1) It is desirable to use an aldose which is not in equilibrium with a hemiacetal form, and 2) protection of proximate hydroxyl groups is necessary




Scheme I. Synthesis of isopropylidene 3-C-alkenyl ribo-pentodialdoses.

to suppress transacylation reactions. The straightforward synthesis of derivatives **1-5** from the hexosulose derivative shown in Scheme I[5, 6, 7] suggested these as appropriate substrates.

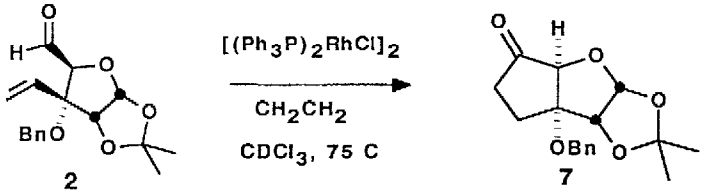
Allyl derivative **1** reacted with a catalytic amount of $[(Ph_3P)_2RhCl]_2$ (Rh/substrate = 0.3) under 1 atm ethylene in $CH_2Cl_2$ solvent to give compound **6** after 60 hr at 25°C The reaction also proceeds at 70°C in $CDCl_3$ with the same result in 6 hr (Eq. 1). The cyclization was also performed with $[(C_2H_4)_2RhCl]_2$ and 2 eq/Rh of $PPh_3$. Ketone **6** was isolated in 60% yield by column chromatography (silica, 1:1 hexane-ether) and structurally characterized by IR and $^1H$ and $^{13}C$ NMR.[8] The IR spectrum showed an absorbance at 1720 $cm^{-1}$, indicating the presence of a cyclohexanone. COSY and heteronuclear correlation 2-D NMR experiments demonstrated the presence of 3 contiguous methylene groups, confirming that the product was a cyclohexanone as shown rather than a methylcyclopentanone.




**1** **6** (Eq 1)

Examination of the $^1H$ and $^{31}P$ NMR revealed no observable intermediates during the conversion of **1** to **6**. The $^{31}P$ spectrum in particular showed only a doublet at -35.3 ppm[9] ($J_{P\text{-}Rh}$ = 128 Hz) due to the bis-phosphine (ethylene) rhodium chloride.[10] Monitoring the reaction at 30°C by NMR led to an estimate of reaction half-life of 16 hr.

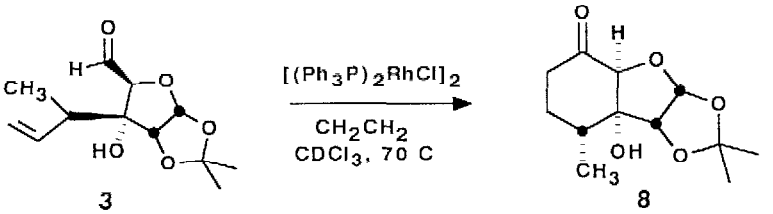
Given the previous observation that 5-hexenal hydroacylates to form methylcyclopentanone[3b], we were surprised with our result. This is, to our knowledge, the first hydroacylation of a hexenal to form a cyclohexanone. One possible explanation is that formation of a fused 5, 5, 5 tricyclic product may be inhibited by ring strain. The vinyl derivative **2**[11] did not react in 15 hr at 30°C, but heating to 75°C for 15 hr led to quantitative (by NMR) conversion to **7** (Eq. 2). This new compound was isolated by chromatography in 60% yield and identified by $^1H$ and $^{13}C$ NMR and IR ($\nu_{CO}$ = 1755 $cm^{-1}$).




**2** **7** (Eq 2)

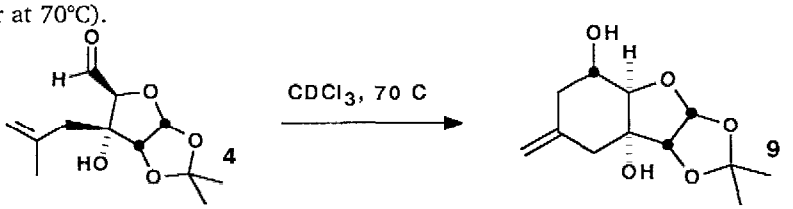
Cyclization of 1-methylallyl derivative **3** (15 hr, 70°C) also leads to a cyclohexanone, **8** (Eq 3); $\nu_{CO}$ = 1726 $cm^{-1}$. For compounds with an unsubstituted vinyl group, hydroacylation therefore appears to be general for these systems We wished to turn to compounds where cyclization would lead to

formation of a new stereocenter; we find, however, that substitution of the vinyl group leads to reactions other than hydroacylation.



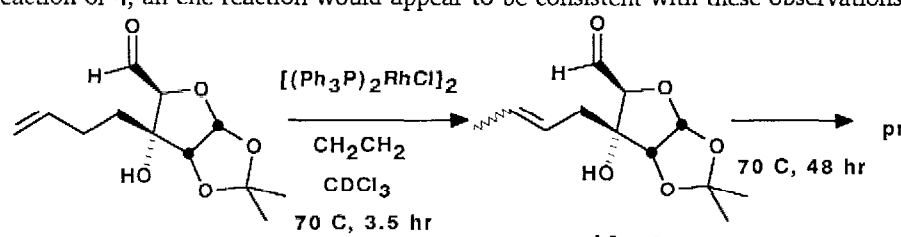

3 8 (Eq 3)

The 2-methylallyl derivative **4** undergoes an ene reaction to give alcohol **9** (Eq 4). It is much more rapid, being complete after 4 hr at 35°C. This reaction may not be catalyzed by rhodium;[12] the same product forms on heating a $CDCl_3$ solution of the alkenal, although this conversion is somewhat slower (15 hr at 70°C).




4 9 (Eq 4)

The but-3-enyl derivative **5** undergoes a more complex set of reactions. After 3.5 hr at 73°C, the substrate has completely reacted to give a mixture of but-2-enyl derivatives **10c, t**. The mixture of these can be isolated by chromatography of the reaction mixture. They are identified primarily through 2D COSY and HETCOR experiments revealing two distinct but-2-enyl fragments; the $^{13}C$ NMR is particularly revealing.[13] No such isomerization is observed in the allyl derivatives, and indicates that competition between rearrangement and hydroacylation is finely balanced. Further reaction with $(PPh_3)_2(C_2H_4)RhCl$ at 75°C over 48 hr leads to disappearance of the aldehyde and formation of an unidentified mixture of products; no new carbonyl stretch is seen in the IR spectrum. In light of the reaction of **4**, an ene reaction would appear to be consistent with these observations.




5 10c, t (Eq 5)

In conclusion, it is evident that hydroacylation is a useful cyclization of carbohydrate derivatives, and that it may be used to form cyclohexanones as well as cyclopentanones. It is, however, sensitive to substitution of the alkene moiety because of alternative reactivity of these substrates. We are currently exploring the cyclization of derivatives made from carbohydrates other than glucose.

**Acknowledgements:** Financial support from Oregon State University and the National Institutes of Health (Biomedical Research Support Grant RR07079) is gratefully acknowledged. We would like to thank Prof. Andrea Vasela for useful discussions, and Mr. Rodger Kohnert for assistance with structure determinations.

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7 New compounds **1-5** are oils. They have been characterized by $^{1}H$, $^{13}C$ NMR and IR, and give satisfactory HRMS parent ions

8 $^{1}H$ NMR ($CDCl_3$): 1.33 s, 3H; 1 55 s, 3H; 1.66 ddd, J = 14, 13, 2.0 Hz, 1H; 1.87 dddd, J = 14, 5.0, 3.3, 1 5 Hz, 1H; 2.0 m, 2H; 2.35 m, 1H; 2.61 ddd, J = 14, 13, 6.6 Hz, 1H, 2.76 br s, 1H; 3.83 br s, 1H; 4.21 d, J = 3.5 Hz, 1H, 5.89 d, J = 3.5 Hz, 1H. $^{13}C$ NMR ($CDCl_3$): 206.3, 113.4, 105.1, 82.7, 82.6, 82.3, 37 5, 30.0, 26.5, 26.4, 22.0. IR: 1720 $cm^{-1}$.

9. Shift measured vs. 85% aq. $H_3PO_4$; negative shift = low field

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11. The 3-hydroxyl group is benzylated to protect the tertiary, allylic alcohol from acid-catalyzed epimerization during synthesis

12. Although rhodium catalysis of an ene reaction has been claimed for citronellal (Sakai, K.; Oda, O. Tetrahedron Lett., **1972**, 4375-4376), the same cyclization has been demonstrated to be Lewis acid-catalyzed: Nakatani, Y.; Kawashima, K. Synthesis, **1978**, 147-148, Sakane, S ; Maruoka, K.; Yamamoto, H. Tetrahedron, **1986**, 42 2203-2207. See also Oppolzer, W.; Snieckus, V. Angew. Chem., Int. Ed. Engl., **1978**, 17, 476-486.

13. For **5**. 198.7, 137.2, 115.4, 113.1, 103.9, 86.5, 81.5, 80.7, 31.2, 27.0, 26.6, 26 5. For **10c, t**, assigned to **10c**: 198.2, 128.5, 122.6, 103.9, 81.5, 19.8, 13.1. Assigned to **10t**: 198.6, 130.9, 123.5, 103.8, 81.3, 35.9, 18.0. Not assigned: 113.1, 113.0, 86.3, 86 2, 82.5, 81.5, 26.7, 26.7, 26.6, 26.5.

(Received in USA 3 April 1991)