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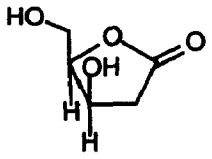
SYNTHESIS OF 2-DEOXYXYLOLACTONE FROM GLYCEROL DERIVATIVES VIA HIGHLY ENANTIOSELECTIVE CARBON-HYDROGEN INSERTION REACTIONS

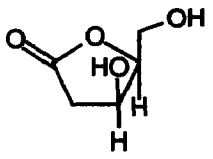
Michael P. Doyle*, Alexey B. Dyatkin, and Jason S. Tedrow
Department of Chemistry, Trinity University, San Antonio, Texas 78212 (U.S.A.)

Summary: *Diazodecomposition of 1,3-dialkoxy-2-propyl diazoacetates catalyzed by chiral dirhodium(II) carboxamides results in highly enantioselective and diastereoselective carbon-hydrogen insertion which forms 3,5-dialkyl 2-deoxyxylolactones in up to 98% enantiomeric excess.*

D- and L-2-Deoxyxylolactones (1) are configurationally well-defined synthetic intermediates[1,2] whose limited availability, often as mixtures with 2-deoxoribonolactone (2),[3-8]



1 D



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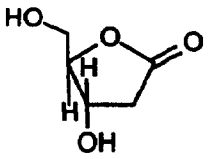
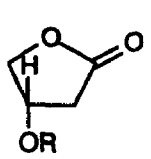


2 D



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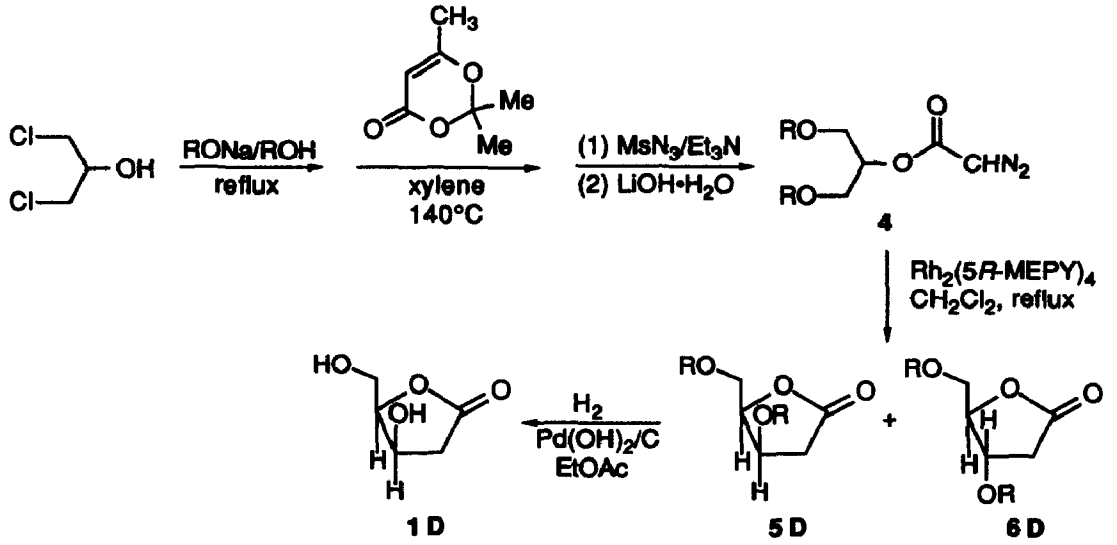
has severely restricted their synthetic use. Formally, 2-deoxyxylolactone is derived from *threo*-3,4,5-trihydroxypentanoic acid and in its reduced form, 2-deoxyxylulose, has been employed for the synthesis of 2-deoxynucleosides.[9-12] We have previously demonstrated that dirhodium(II) catalysts whose carboxamide ligands are chiral 2-pyrrolidone-5-carboxylate or 2-oxazolidinone-4-carboxylate esters are effective for highly enantioselective carbon-hydrogen insertion reactions resulting from diazodecomposition of diazoacetate esters;[13-15] enantiomeric excesses up to 91% have been achieved for the synthesis of β-alkoxy-γ-butyrolactones (3) from 2-alkoxyethyl diazoacetates.[13] We now wish to report a highly enantioselective and diastereoselective synthesis of D- or L-2-deoxyxylolactone and its derivatives from the readily available glycerol derivative, 1,3-dichloro-2-propanol.

1,3-Dialkoxy-2-propyl diazoacetates were prepared by alkoxide displacement from 1,3-dichloro-2-propanol,[16] followed by condensation with the diketene acetone adduct, 2,2,6-

trimethyl-4*H*-1,3-dioxin-4-one,[17] diazo transfer with methanesulfonyl azide,[18] and deacylation with LiOH•H_2O (Scheme I).[19] These prochiral diazoacetates possess four unique sites for C-H



insertion by metal carbene intermediates generated through diazodecomposition using chiral dirhodium(II) carboxamide catalysts. However, treatment of 1,3-dibenzyloxy-2-propyl diazoacetate with dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*R*)-carboxylate], $Rh_2(5R\text{-MEPY})_4$, in refluxing dichloromethane resulted in the production of 3,5-dibenzyl (3*R*,4*R*)-2-deoxyxylolactone (**5D**, R = $PhCH_2$) in 94% ee and in a 93:7 diastereomeric excess over 3,5-dibenzyl (3*S*,4*R*)-2-deoxyribonolactone (**6D**, R = $PhCH_2$) which was formed in 65% ee. As little as 0.1 mol % of catalyst was required to effect complete reaction (1000 turnovers), and isolated product yields following chromatography on silica (hexane: ethyl acetate = 7.3) were 65-70%. Catalytic hydrogenolysis over 20% $Pd(OH)_2$ on carbon followed by chromatography on silica (ethyl acetate:methanol = 9:1) provided pure 2-deoxyxylolactone (**1D**) in 83% yield.[20] Diazodecomposition of **4** (R = $PhCH_2$) in the presence of catalytic quantities of $Rh_2(5S\text{-MEPY})_4$ afforded 3,5-dibenzyl (3*S*,4*S*)-2-deoxyxylolactone (**5L**, R = $PhCH_2$) in 94% ee and in a 93:7 diastereomeric excess over 3,5-dibenzyl (3*R*,4*S*)-2-deoxyribonolactone (**6L**, R = $PhCH_2$).

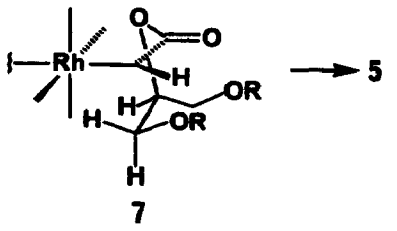
Treatment of a series of 1,3-dialkoxy-2-propyl diazoacetates with $Rh_2(5R\text{-MEPY})_4$, $Rh_2(5S\text{-MEPY})_4$, and dirhodium(II) tetrakis[methyl 2-oxazolidinone-4(*S*)-carboxylate], $Rh_2(4S\text{-MEOX})_4$, provided comparable results (Table 1) to those achieved with the dibenzyl ethers. The ether alkyl group had very little influence on diastereoselectivity but, as was found from reactions of 2-alkoxyethyl diazoacetates,[13] the smaller methyl group is conducive to a higher degree of enantiocontrol.

Table 1. Enantioselective carbon-hydrogen insertion reactions from diazodecomposition of 1,3-dialkoxy-2-propyl diazoacetates catalyzed by chiral dirhodium(II) carboxamides[a]

catalyst	4, R =	5:6	config. 5	% ee 5[b]	config. 6	% ee 6[b]
Rh_2(5*R*-MEPY)$_4$	Me	93:7	(3*R*,4*R*)	97	(3*S*,4*R*)	50
	Et	93:7	(3*R*,4*R*)	89	(3*S*,4*R*)	50
	$PhCH_2$	93:7	(3*R*,4*R*)	94	(3*S*,4*R*)	45
Rh_2(5*S*-MEPY)$_4$	Me	94:6	(3*S*,4*S*)	(97)	(3*R*,4*S*)	45
	Et	94:6	(3*S*,4*S*)	90	(3*R*,4*S*)	45
	$PhCH_2$	93:7	(3*S*,4*S*)	94	(3*R*,4*S*)	*c*
Rh_2(4*S*-MEOX)$_4$	Me	91:9	(3*S*,4*S*)	(98)	(3*R*,4*S*)	76
	Et	90:10	(3*S*,4*S*)	96	(3*R*,4*S*)	85
	$PhCH_2$	90:10	(3*S*,4*S*)	94	(3*R*,4*S*)	*c*

[a]Reactions were performed by the addition of 4 (1.0 mmol) in 10 mL of anhydrous CH_2Cl_2 over 10 h to a refluxing solution of the catalyst (0.1-0.5 mol %) in 50 mL of refluxing CH_2Cl_2. Isolated yields following chromatography were 65-81%. [b]Enantiomeric excesses of 5 and 6 (R = Et) were determined by GC with baseline resolution on a Chiraldex G-TA column. Those where R = Me were cleanly separated for 6, but with 5 the leading (3*S*,4*S*)-isomer trailed over the (3*R*,4*R*)-isomer giving a less accurate estimate of % ee for reactions catalyzed by Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*S*-MEOX)$_4$. [c]Not determined.

The high preference for 2-deoxyxylolactone derivatives in these catalytic reactions is consistent with a transition state configuration (**7**) in which the alkoxy group on carbon that is undergoing C-H insertion is syn to the carboxylate group rather than anti (**8**) which would be sterically less congested. The influence of the polar face of the dirhodium(II) catalyst in repelling the polar ether group, thus favoring **7** over **8**, is implicated, but a gauche effect in **7** cannot be disregarded, and both effects may be operative. Conformational arrangement **7** also explains the enantiomeric



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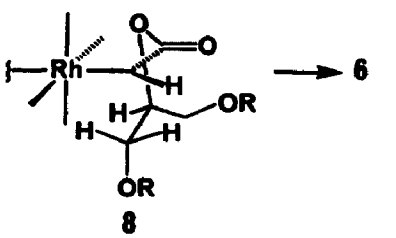

→ 6

8

preference found for C-H insertion reactions of 2-alkoxyethyl diazoacetates where Rh_2(5*S*-MEPY)$_4$ → **3S** and Rh_2(5*R*-MEPY)$_4$ → **3R**.[13]

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(20) **ID**: $[\alpha]_D^{26}$ = +56.2° (*c* 0.49, MeOH) for 91% ee; lit.[7] $[\alpha]_D^{25}$ = +49.3° (*c* 0.56, MeOH) for pure **ID**. Enantiomeric excesses of **4D** (R = $PhCH_2$) could be determined by HPLC analyses using a Chiralpak AD column. 2-Deoxyxylolactone **1D** was converted to its acetone ketal using 2-methoxypropene, and enantiomeric excesses were determined on the ketal by GC using a Chiraldex G-TA column.

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