0040-4039/80/1215-4927\$02.00/0

STEREOSELECTIVE SYNTHESIS OF TETRAHYDROFURAN-3-CARBALDEHYDE

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<u>Abstract</u>: Trans-tetrahydrofuran-3-carbaldehydes are prepared by ruthenium-catalyzed isomerization of 4,7-dihydro-1,3-dioxepines and subsequent Lewis acid-catalyzed 1,3-alkyl migration.

Applications of the double bond migration catalyzed by transition metal complexes to organic synthesis have been successively performed by several investigators.¹⁾ We have recently reported selective isomerizations of allyl silyl ethers to silyl enol ethers²⁾ and propargyl silyl ethers to silyl dienol ethers³⁾ by ruthenium hydride complexes. In this communication, we wish to report an extention of the works directed to the synthesis of tetrahydrofuran-3-carbaldehydes via the double bond migration of a series of cyclic allyl ethers.

4,7-Dihydro-1,3-dioxepine (1) is easily derived from cis-2-buten-1,4-diol with aldehydes or ketones at acidic conditions. Isomerization of 1 to 4,5-dihydro-1,3-dioxepine (2) is accomplished by the double bond migration catalyzed by ruthenium hydride complexes giving 2 as a sole product.



In a typical example, 2-methyl-4,7-dihydro-1,3-dioxepine (1b) (3.72 mmol) was heated at 100°C in the presence of $H_2Ru(PPh_3)_4$ (0.025 mmol) in a sealed tube.

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	R ¹	R ²	Cat ^{a)}	[Cat]/[1]	Solvent	Temp(°C)	Time(hr)	Yield ^{b)}
a	н	н	A	1/100	none	100	1	quant (51)
ь	CH 3	н	A	1/150	none	100	1	quant (65)
С	с ₂ н ₅	н	A	1/100	none	100	1	quant
đ	n-C ₃ H ₇	н	A	1/100	none	100	1	quant
е	i-C3H7	Н	A	1/100	none	100	1	quant
f	n-C4H9	н	А	1/100	none	100	1	quant
g	n-C5H11	н	A	1/100	none	100	1	quant
h	i-C5H11	н	A	1/100	none	100	1	quant
i	n-C6 ^H 13	н	A	1/100	none	100	1	quant
j	с ₆ н ₅	Н	A	1/100	none	100	1	quant (58)
k	с ₂ н ₅	^С 2 ^Н 5	в	1/230	с ₆ н ₆	rfx	2	quant
1	- (CH ₂)	4	с	1/550	С ₆ н ₆	rfx	2	quant
m	- (CH ₂)	- 5 ⁻	С	1/550	C6 ^H 6	rfx	2	quant (72)
n	CH ₃ COCH ₂	CH 3	С	1/100	C ₆ H ₆	rfx	2	quant

Table 1. Double bond migration of 1 to 2 catalyzed by ruthenium hydrides.

a) Catalyst: A; $H_2Ru(PPh_3)_4$, B; $H_2Ru(CO)(PPh_3)_3$, C; $HRuCl(CO)(PPh_3)_3$.

b) Yields were determined by means of nmr spectra. Values in parentheses show the results by Scharf et al.⁴⁾

After 1 hr, 2-methyl-4,5-dihydro-1,3-dioxepine (2b) was obtained in a quantitative yield. The reaction is available for not only mono-alkylated dioxepines $(1a^{1}j)$ but also dialkylated ones $(1k^{1}n)$ to afford the corresponding 4,5-dihydro-1,3-dioxepines $(2a^{2}n)$ in excellent yields. The results are summarized in Table 1.

Since 2 has both acetal and enol ether moieties in the molecule, an aldol type C-C bond formation is expected via the acid-catalyzed 1,3-alkyl migration.⁴) When 2 was treated with a catalytic amount of Lewis acid in CH_2Cl_2 , 1,3-0- to C-alkyl migration proceeded quantitatively affording the corresponding tetrahydrofuran-3-carbaldehyde (3). Catalytic activity of various Lewis acids was examined for the 1,3-alkyl migration of 2b to 3b. Isomerization of 2b with Pd(II) gave a poor result (rt, 120 hr, 16%), whereas BF_3 -Et₂O, AlCl₃, SnCl₄, TiCl₄, ZnCl₂ and NiCl₂ promoted the reaction smoothly at -73°Cort to give 3b in a quantitative yield. The results of the 1,3-alkyl migration of 2 catalyzed by BF_3 -Et₂O are summarized in Table 2.



Table 2. 1,3-Alkyl migration of 2 to 3.^{a)}

	R ¹	r ²	[BF ₃ -Et ₂ 0]/[2]	Time(hr)	Isolated yield(%)	3 ^{tr} :3 ^{cis}
b	CH3	н	1/10	0.5	67	100:0
с	C ₂ H ₅	н	1/5	0.6	93	100:0
đ	n-C ₃ H ₇	н	1/5	0.5	90	100:0
е	i-C ₃ H ₇	н	1/5	0.5	90	100:0
f	n-C ₄ H _Q	н	1/5	0.5	90	100:0
g	n-C ₅ H ₁₁	н	1/5	0.5	90	100:0
i	$n - C_6 H_{13}$	н	1/5	0.2	95	100:0
j	C6H5	н	1/5	0.3	90	100:0
k	С ₂ Н ₅	C ₂ H ₅	1/5	0.5	33	
1	$-(CH_2)_A -$		1/5	0.5	92	
m	$-(CH_2)_5 -$		1/5	0.5	91	
n	CH3COCH2	сн ₃	1/3	0.5	90	50:50

a) The usual scale is 4 mmol of 2 in 10ml of dry CH_2Cl_2 .

Notable advantages of the present method for the preparation of tetrahydrofuran-3-carbaldehydes compared with the previous one⁴⁾ are (i) excellent overall yields without formation of any byproduct, (ii) simplicity of the procedure requiring no purification of intermediates, (2), and (iii) profound stereoselectivity $(3^{cis}/3^{tr}, 0)$ of the final products. The observed stereochemistry is well accounted for in terms of the acyclic zwitter ion in the transition state. Steric repulsion may be minimized at a transition state 4^{tr} to form 3^{tr} , whereas another transition state 4^{cis} leading to 3^{cis} is sterically unfavorable as can be seen in

the following figure. The proximity of the anionic moiety to the cationic one by the electrostatic attraction may increase the effect



Further transformations of $\frac{3}{2}$ to $\frac{5}{2}$ and $\frac{6}{2}$ were achieved via acid-catalyzed recyclizations of $\frac{3}{2}$. Treatment of $\frac{3}{2}$ with a catalytic amount of BF_3 -Et₂0 in CCl₄ for 2 hr gave 2,7-dioxabicyclo[3,2,0]heptane ($\frac{5}{2}$)⁵⁾ quantitatively.



Similarly, $\frac{6}{2}$ was prepared in excellent yields by the reaction of $\frac{3}{2}$ with methanolic HCl at ambient temperature.



References and Notes

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- 5) 5b; nmr (CCl₄) δ l.10(3H,d,J=6Hz), l.7 \circ 2.05(2H,m), 2.35(1H,tt,J=7.5Hz), 3.36 \circ 4.10(3H,m), 4.80(1H,d,J=7.5Hz). ir(CCl₄) v_{max} 1105 cm⁻¹. 5c; nmr (CCl₄) δ 0.93(3H,t,J=6Hz), 1.15 \circ 1.65(2H,m), 1.70 \circ 2.50(2H,m), 2.33(1H, tt,J=6Hz,J=6Hz), 3.35 \circ 3.85(3H,m), 4.73(1H,d,J=6Hz). ir(CCl₄) v_{max} 1110 cm⁻¹.
- 6) 6b; nmr (CCl₄) δ 1.05(3H,d,J=6Hz), 1.70 \vee 2.00(2H,m), 2.43(1H,tt, J=8Hz,J=6Hz), 3.20(3H,s), 3.23(3H,s), 3.50 \vee 4.06(3H,m), 4.20(1H,d,J=6Hz). ir(CCl₄) \vee_{max} 1056 cm⁻¹. 6c; nmr (CCl₄) δ 0.92(3H,t,J=6Hz), 1.10 \vee 1.65(2H,m), 1.70 \vee 1.95(2H,m), 2.40(1H, tt, J=7.5Hz,J=7.5Hz), 3.15(3H,s), 3.22(3H,s), 3.40 \vee 3.80(3H,m), 4.15(1H,d,J= 7.5Hz). ir(CCl₄) \vee_{max} 1065 cm⁻¹.

(Received in Japan 11 September 1980)