Tetrahedron Letters, Vol.31, No.33, pp 4747-4750, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PALLADIUM CATALYZED STEREOSPECIFIC CYCLIZATION OF HYDROXY EPOXIDES. STEREOCONTROLLED SYNTHESIS OF CIS- AND TRANS-2-ALKENYL-3-HYDROXYTETRAHYDROPYRANS

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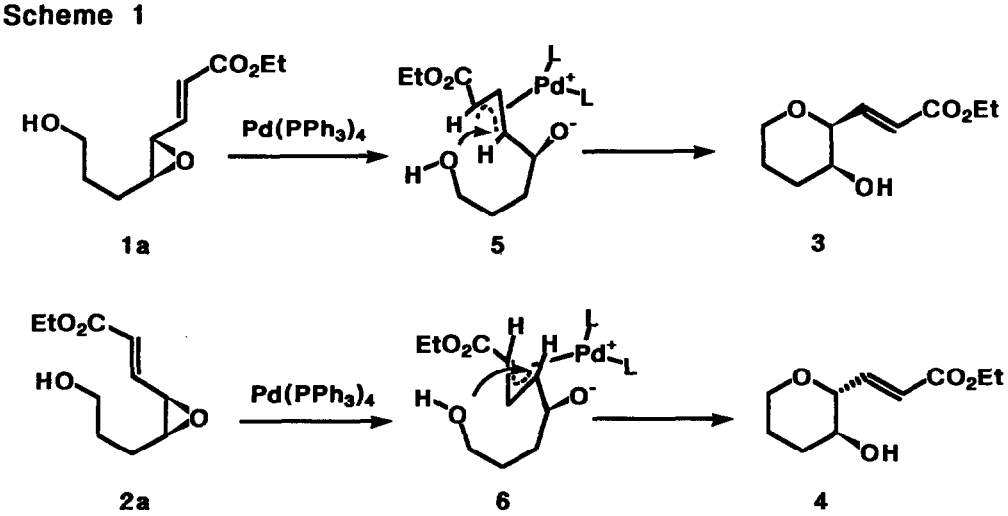
Summary: Stereospecific constructions of the cis- and trans-2-alkenyl-3-hydroxytetrahydropyrans have been achieved by the one-pot procedure of desilylation-palladium catalyzed cyclization of the silyl ethers of ω-hydroxy trans- and cis-γ,δ-epoxy-α,β-unsaturated esters, respectively.

The unusual cis-fused pyranopyran systems are becoming frequently encountered in the marine natural products such as dactomelyne,[1] norhalichondrin,[2] and elatenyne.[3] General method useful for them, however, is still very few[4] while the trans-fused pyranopyran or its equivalents, trans-2,3-disubstituted tetrahydropyran systems, are now readily obtainable.[4,5] Regio- and stereo-selective intramolecular opening of the hydroxy epoxides would be the most straightforward access to those systems. Nicolaou's strategy to control the acid-catalyzed cyclization of hydroxy epoxides in the 6-endo mode over the usually favored 5-exo mode[6] by the activation through the vinyl substituent succeeded in the regio- and stereo-control for the trans-epoxides, but for the cis-epoxides it suffered from 5-exo cyclization to give a mixture of the tetrahydropyran and the tetrahydrofuran rings.[5a] Another rational approach using palladium-catalyzed cyclization of hydroxy vinyl

Scheme 1



epoxides via π-allylpalladium intermedates has been tested by Trost very recently, but the stereochemical outcome has not been described definitely.[7] In connection with the synthetic studies toward the above marine natural products we examined this approach in more detail and realized the complete regio- and stereo-control for the construction of both cis- and trans-2,3-disubstituted tetrahydropyrans starting from the silyl ethers instead of the free alcohols.

As summarized in Scheme I, the trans-epoxide **1a** theoretically should afford the cis-2-alkenyl-3-hydroxytetrahydropyran **3** via the π-allylpalladium intermediate **5** if each process proceeds with complete stereochemical inversion,[8] while the cis-epoxide **2a** should produce the trans-isomer **4** via **6**. In this expectation, the stereochemically homogeneous trans-epoxide **1a** and cis-epoxide **2a** were treated with $Pd(PPh_3)_4$ (3.3-9.1 mol %) in THF at room temperature. As shown in Table 1, they gave the cis **3**[5a,9] and the trans product **4**[5a,9] as major product, respectively, in about 45% yields (entries 1 and 6). Thus, the stereoselectivity as well as the chemical yield turned out to be only moderate while neither regioisomers, such as tetrahydrofuran and oxocene, nor ketone via palladium catalyzed hydrogen shift[10] were detected.[7]

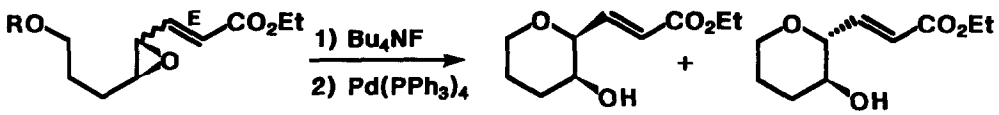
Then, we turned our attention to ammonium alkoxides which could be generated from the silyl ethers **1b** and **2b** by Bu_4NF, since the ammonium alkoxides might be good nucleophiles in palladium catalyzed allylic etherifications.[11] t-Butyldiphenylsilyl (TBPS) ethers **1b** and **2b** were treated with 1.3 equivalent of Bu_4NF in THF and then with a catalytic amount of $Pd(PPh_3)_4$ in one pot. Remarkably the yields and the stereoselectivity were improved as shown in Table 1 (entries 2 and 7). More surprisingly, these palladium catalyzed cyclizations undergo a dramatic solvent effect: In acetonitrile very high stereoselections for either isomers, particularly excellent for **1b**, were obtained though the reaction took time (entries 3 and 8). In halogenated solvents such as chloroform (entries 4 and 9) and dichloromethane (entries 5 and 10), the reactions turned out to proceed rapidly, and gave in the excellent yields (≥90%) as well as the complete stereoselectivities (≥98%).

The typical procedures are as follows: To a stirred solution of **1b** (47.7 mg, 0.109 mmol) in dry THF (1.1 ml) was dropwise added a 1.0 M THF solution of Bu_4NF (0.140 ml, 1.3 equiv) at room temperature under argon atmosphere and the mixture was stirred for 20 min. After the solvent was removed in vacuo, dry $CHCl_3$ (distilled over CaH_2) was transfered into the flask. To this solution were added $Pd(PPh_3)_4$ (3.9 mg, 3.1 mol%) and PPh_3 (5.8 mg, 20.3 mol%) at room temperature. After the mixture was stirred for 10 min under argon atmosphere, the volatiles were removed in vacuo and the residue was purified by silica gel chromatography (eluant: AcOEt-hexane=1:1) to give pure **3** (19.5 mg) in 90% yield.

Since the optically active epoxides **1b** and **2b** are readily available by using Sharpless asymmetric epoxidation,[12] we are now able to prepare all stereoisomers of 3-hydroxy-2-alkenyltetrahydropyran in a stereospecific manner. Applications of the present methodology to synthesize the cis-fused pyranopyran family of marine natural products[1-3] are currently under way in our laboratory.

Acknowledgement: We thank professor Tamio Hayashi, Hokkaido University, for his valuable discussions.

Table 1



1, trans-epoxide
2, cis-epoxide

3 4

Entry	Substrate	Solvent	Reaction Time [c]	Yield(%) [d]	3 : 4[e]
1	1a (R=H)[a]	THF	4 h	45	74 : 26
2	1b (R=TBPS)	THF	11.5 h	82	92 : 8
3	1b (")	CH_3CN[b]	14.5 h	85	>99 : 1[f]
4	1b (")	$CHCl_3$[b]	10 min	90	>99 : 1[f]
5	1b (")	CH_2Cl_2[b]	5 min	90	>99 : 1[f]
6	2a (R=H)[a]	THF	45 min	42	36 : 64
7	2b (R=TBPS)	THF	23 h	71	12 : 88
8	2b (")	CH_3CN[b]	17.5 h	80	3 : 97
9	2b (")	$CHCl_3$[b]	5 min	89	2 : 98
10	2b (")	CH_2Cl_2[b]	6 min	86	2 : 98

[a] Directly treated with $Pd(PPh_3)_4$. [b] Desilylation was carried out in THF. After the solvent was removed in vacuo, the residue was dissolved in a relevant solvent and then treated with $Pd(PPh_3)_4$. [c] Reaction time of palladium catalyzed reaction. [d] Combined yield of 3 and 4. [e] Determined by 200 or 270 MHz-^{1}H NMR. [f] The isomer 4 not detected.

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9) **3**: ^{1}H-NMR (400MHz, $CDCl_3$) 1.28 (3H, t, J=7.1Hz), 1.41-1.48 (1H, m), 1.74 (1H, dddd, J=13.0, 13.0, 4.6, 2.9Hz), 1.89 (OH, d, J=7.1Hz), 1.91-2.05 (3H, m), 3.54 (1H, ddd, J=12.1, 11.4, 2.4Hz), 3.84 (1H, dddd, J=7.1, 2.9, 2.9, 1.9Hz), 4.07 (1H, dddd, J=11.4, 4.0, 2.0, 2.0Hz), 4.09 (1H, ddd, J=3.8, 1.9, 1,9Hz), 4.20 (2H, q, J=7.1Hz), 6.12 (1H, dd, J=15.8, 1.9Hz), 6.89 (1H, dd, J=15.8, 3.8Hz). **4**:^{1}H-NMR (400MHz, $CDCl_3$) 1.29 (3H, t, J=7.1Hz), 1.49 (1H, dddd, J=12.3, 10.5, 10.5, 6.9Hz), 1.69 (OH, d, J=5.0Hz), 1.69-1.76 (2H, m), 2.13-2.20 (1H, m), 3.37 (1H, dddd, J=10.5, 9.0, 6.2, 5.0Hz), 3.40 (1H, ddd, J=11.4, 8.9, 6.0Hz), 3.68 (1H, ddd, J=9.0, 5.0, 1.7Hz), 3.97 (1H, dddd, J=11.4, 3.0, 3.0, 1.8Hz), 4.20 (2H, q, J=7.1Hz), 6.17 (1H, dd, J=15.8, 1.7Hz), 7.08 (1H, dd, J=15.8, 5.0Hz).

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(Received in Japan 30 May 1990)