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MODIFICATION OF D-RING MOIETY OF STEROIDS – A NOVEL PALLADIUM CATALYZED BAEYER–VILLIGER TYPE REARRANGEMENT OF CYCLIC SILYLENOL ETHER DERIVATIVES

Minoru Tamiya,[a]* Futa Takada,[a] Nobuhisa Isaka,[a] Nahoko Iimura,[b] and Masaji Ishiguro[a]*

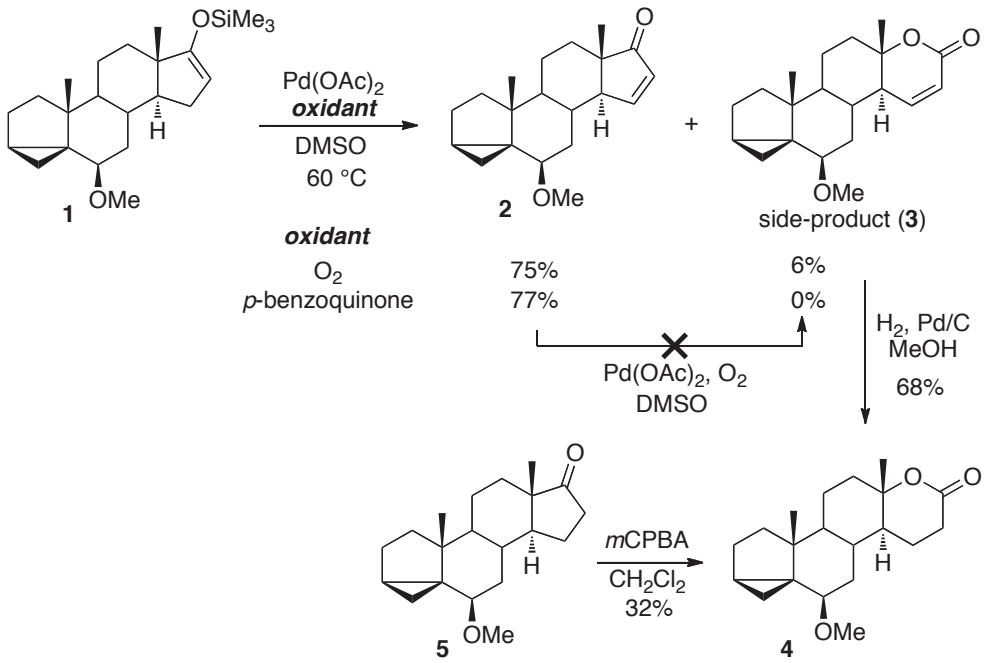
Department of Applied Life Science[a] and Pharmacy[b], Niigata University of Pharmacy and Applied Life Sciences, 265-1 Higashijima Akiha-ku Niigata City, 956-8603, Japan; emails: ishiguro@nupals.ac.jp, tamiya@nupals.ac.jp

This paper is dedicated with respect and admiration to Prof. Albert Eschenmoser on the occasion of his 85th birthday.

Abstract – A novel Baeyer–Villiger type rearrangement reaction of cyclic silylenol ether derived from dehydroepiandrosterone via oxygen and catalytic amount of palladium acetate in the presence of DMSO has been developed. The reaction proceeded at low temperature and high pressure of oxygen to afford corresponding α,β-unsaturated lactones in moderate yields.

Steroids are ubiquitous in many biologically important compounds including natural products, clinical medicines, and hormones.[1] Because of these reasons, many methods and unique reactions for the modification of steroidal skeletons[2] have been developed. Due to the rigidity of the skeleton and the stereochemical property of steroid, the steroidal reactions sometime make themselves very unique. Here we report the unexpected and unique side-reaction, which may demand steroidal backbone of the reactant, found during the course of an oxidative conversion of steroid. Thus, the treatment of cyclic silylenol ether derivative (**1**)[3] under the Larock protocol of Saegusa oxidation,[4] using catalytic amount of $Pd(OAc)_2$ (0.1 equiv.)[5] and O_2 as re-oxidant of palladium(0) in DMSO at 60 °C, gave desired α,β-enone **2** in 75% yield along with a side-product in 6% (Scheme 1; Table 1, entry 1). However, the side-product was not obtained when *p*-benzoquinone was used as a re-oxidant of palladium(0). This result suggested that O_2 probably plays a critical role in the formation of the side-product. According to ^1H and ^{13}C NMR, IR, and Mass spectra, the side-product was anticipated as α,β-unsaturated lactone **3**.[6] To confirm this

prospect, the side-product was treated with catalytic amount of Pd/C under hydrogen gas. The product of the hydrogenation showed spectroscopic properties identical to lactone **4** derived from ketone **5**. Two possible reaction pathways could be envisioned from these results: 1) Baeyer–Villiger rearrangement proceeded after the formation of the corresponding enone; 2) Baeyer–Villiger type rearrangement occurred before unsaturation of the α,β-position. For the determination of the reaction pathway, enone **2** was subjected to catalytic amount of $Pd(OAc)_2$ and O_2 at atmosphere, which resulted in no reaction (Scheme 1). According to these results mentioned above, lactone **4** was probably produced by Baeyer–Villiger type rearrangement of corresponding ketone followed by the unsaturation of α,β-position of carbonyl via β-hydride elimination of palladium in one pod. Because the conversion of cyclic ketone to the corresponding α,β-unsaturated lactone by using catalytic amount of bivalent palladium and O_2 is completely a novel transformation to our knowledge, we investigated to gain a further insight into this reaction.

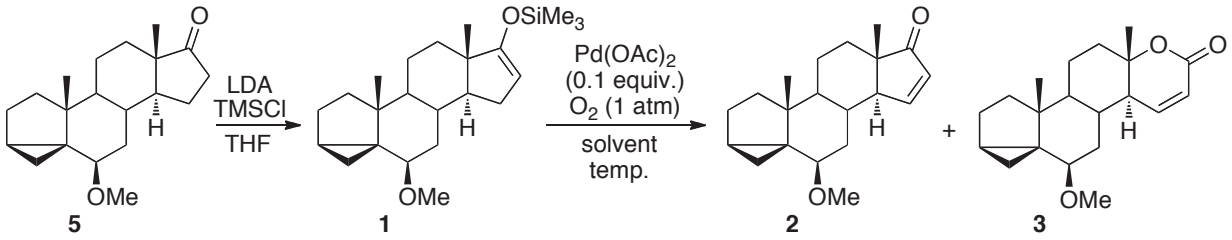


Scheme 1. Characterization of Side-Product in Saegusa Oxidation of Silylenol Ether **1**

We investigated the reaction conditions for producing lactone **3** as a major product. Concerning the reaction temperature, the silylenol ether (**1**) was treated with $Pd(OAc)_2$ (0.1 equiv.) and O_2 (1 atm) in DMSO (0.06 M) at room temperature to afford lactone **3** in 35% yield along with enone **2** in 45% yield (Table 1, entry 2). These results indicated that low temperature would be necessary for the formation of lactone **3**. Because it is impossible to perform the reaction at lower temperature due to high freezing point of DMSO (16~19 °C), other solvent should be applied for the investigation. For the alternative

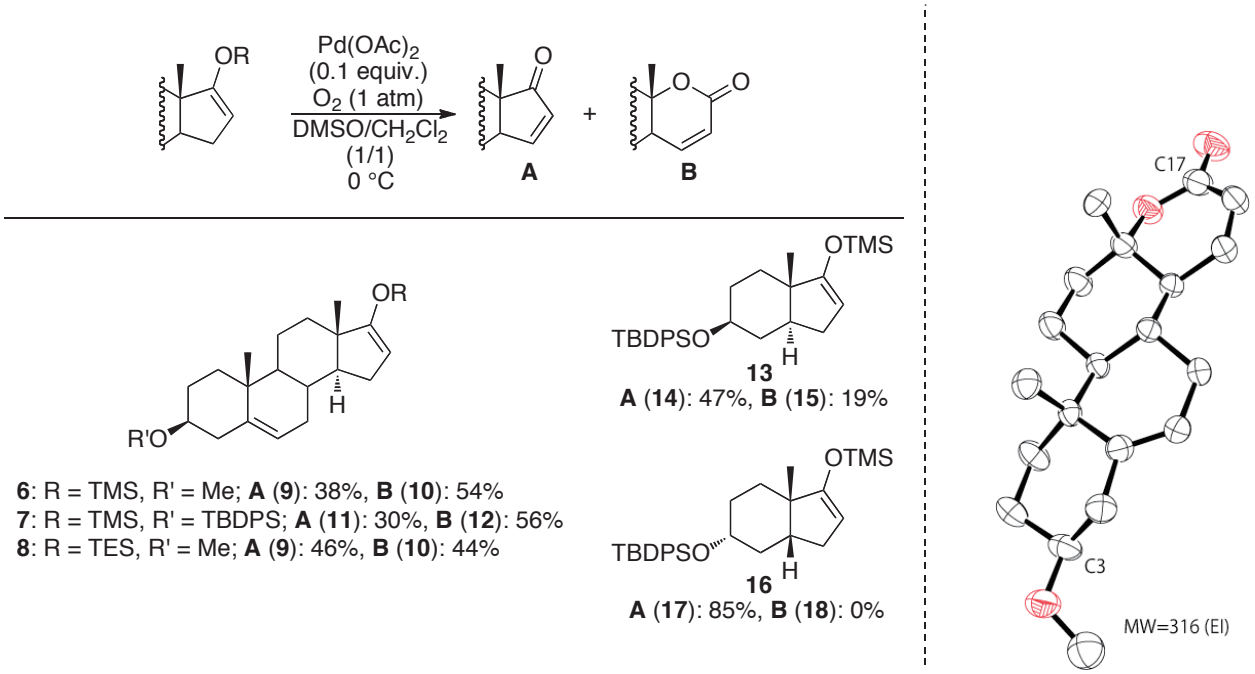
solvent, we examined DMF, DMA, and CH_2Cl_2 that, unfortunately, gave low yields of lactone **3** (entries 3–5). We next examined CH_2Cl_2 as a co-solvent of DMSO, which could stand from freezing at low temperature (DMSO/CH_2Cl_2=1/1, fp. ~–20 °C). To make a comparison between DMSO and DMSO/CH_2Cl_2 co-solvent system, the reaction was performed at room temperature to afford lactone **3** in 37% yield along with enone **2** in 42% yield (entry 6). With the ideal solvents in hand, we next examined the reaction at 0 °C and –15 °C (entries 7, 8). In these conditions, lactone **3** (ca. 43%) was major product to enone **2** (ca. 35%). Further enhancement of the yield of lactone **3** (ca. 50%) was observed in more diluted conditions (0.06 M to 0.03 M) (entries 9, 10).

Table 1. Optimization of Reaction Conditions



entry	solvent	conc./M	temp.	yield/%		
				2	**3**	**5**
1	DMSO	0.06	60 °C	75	6	4
2	DMSO	0.06	rt	45	35	—
3	DMF	0.06	rt	34	7	9
4	DMA	0.06	rt	42	10	8
5	CH_2Cl_2	0.06	rt	3	—	73
6	DMSO/CH_2Cl_2 (3/2)	0.06	rt	42	37	—
7	DMSO/CH_2Cl_2 (3/2)	0.06	0 °C	35	43	—
8	DMSO/CH_2Cl_2 (1/1)	0.06	–15 °C	36	45	—
9	DMSO/CH_2Cl_2 (3/2)	0.03	0 °C	33	50	—
10	DMSO/CH_2Cl_2 (1/1)	0.03	–15 °C	31	51	—

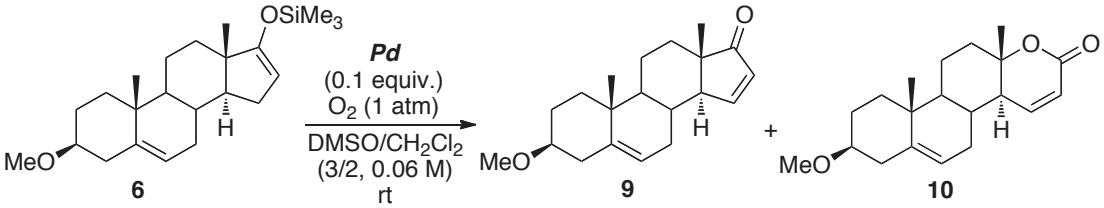
The other trimethylsilylenol ethers **6** and **7** possessing tri-substituted double bond at C5–C6 position (Δ5) were also converted to lactone (**B**) in 54% and 56% yield, respectively, along with enone (**A**) in 38% and 30% yield without any touch of Δ5 (Scheme 2). Since compound **10** formed single crystals suitable for X-ray analysis, the structure of **10** was unambiguously established by the single-crystal X-ray analysis.[7] The triethylsilylenol ether **8** and the *trans*-fused bicyclic compound **13**[8] were also converted to enone (**9**: 46% and **14**: 47%) and lactone (**10**: 44% and **15**: 19%) at 0 °C, while the *cis*-fused compound **16** was quickly converted solely to enone **17** in 85% yield without any trace of lactone **18**. This suggests that the *trans* junction of CD ring moiety of steroid is suitable for the rearrangement.



Scheme 2. Other Substrates and X-Ray Analysis of **10**

In an attempt to increase the yield of lactone, we then examined a variety of Pd catalysts (Table 2), comparing with $Pd(OAc)_2$ (entry 1). The Pd(II) catalysts such as $PdCl_2$ and $Pd(COCF_3)_2$ were not effective to afford the lactone (entries 2 and 3), whereas Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$ were able to give the lactone (entries 4–7). These results indicate that Pd(II) species resulted from the oxidation of Pd(0) by O_2 are possibly important intermediates for the formation of the lactone. Among the catalysts examined, $Pd(OAc)_2$ was the most suitable reagent for this reaction.

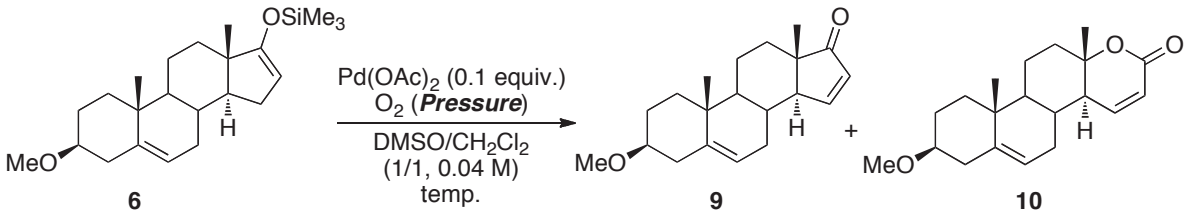
Table 2. Effect of the Pd catalysts



entry	*Pd*	yield/%		
		9	**10**	17-keto
1	$Pd(OAc)_2$	46	39	—
2	$PdCl_2$	—	—	88
3	$Pd(OCOCF_3)_2$	trace	trace	93
4	$Pd(PPh_3)_4$	44	22	18
5	$Pd(dba)_2$	33	36	7
6	$Pd_2(dba)_3CHCl_3$	52	22	3
7	$Pd_2(dba)_3$	52	33	3

All the results described above indicate that O_2 is important in this rearrangement reaction. Thus, we next examined the effects of O_2 pressure (Table 3). Although 8 atm O_2 atmosphere showed no significant difference in a yield of lactone **10** at room temperature and/or 0 °C (entry 1), the treatment of silylenol ether **6** at lower temperature (0 °C and –15 °C) gave lactone **10** in a yield of 53% and 61% respectively exceeding the yield of enone **9** (entries 2 and 3). Furthermore, the reaction at 28 atm gave the best result, affording lactone **10** in 70% yield (entry 5) although the reaction at 20 atm gave only a little improvement of a yield of lactone **10** (63%, entry 4). It is noted that this reaction also proceeded with 5 mol% of $Pd(OAc)_2$ (entry 6).

Table 3. Effect of the O_2 Pressure



6 **9** **10**

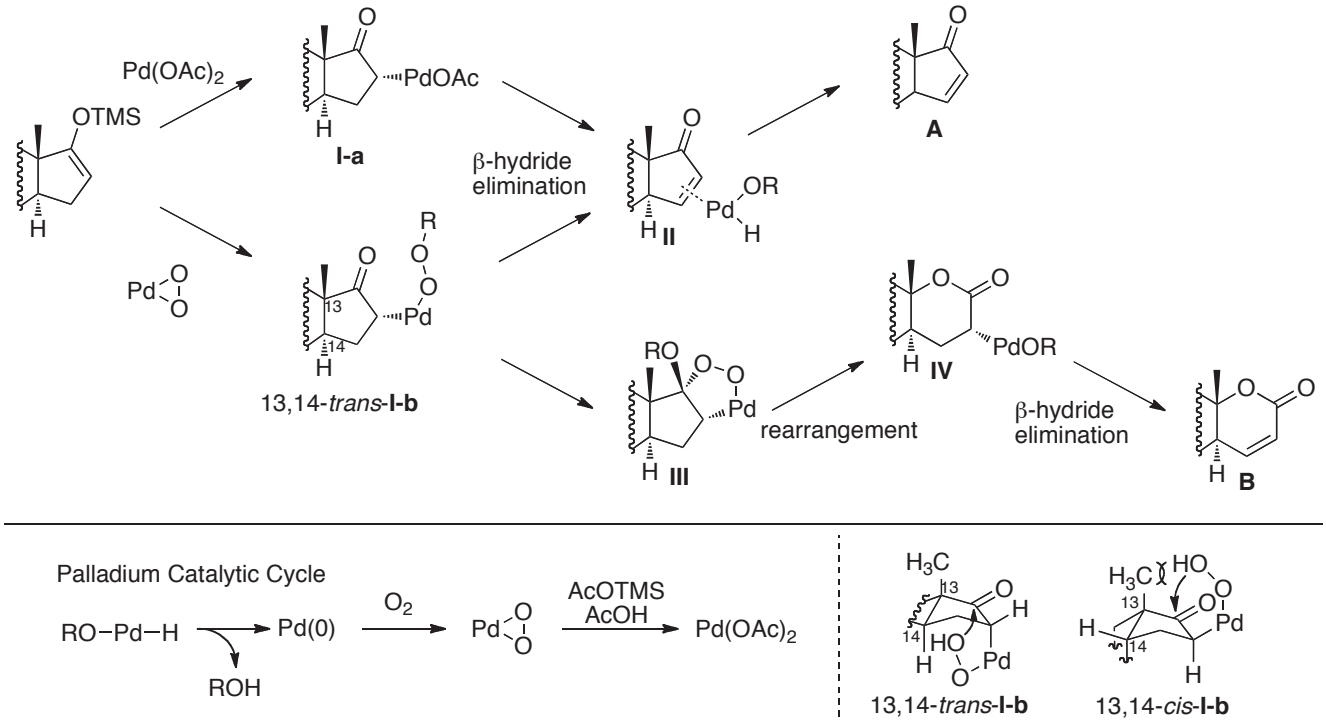
entry	*Pressure*/atm	temp.	yield/%	
			9	**10**
1	8	rt	48	42
2	8	0	39	53
3	8	–15 °C	32	61
4	20	–15 °C	29	63
5	28	–15 °C	25	70
6*	28	–15 °C	25	73

* 0.05 equiv. of $Pd(OAc)_2$ was employed.

Based on the above results, we anticipate that formation of palladium(II) complex **I-b** by the reaction of silylenol ether and three-membered palladium peroxide,[9] resulting from palladium catalytic cycle, followed by cyclization of **I-b**, rearrangement of **III**, and β-hydride elimination of alkylpalladium complex **IV** gave lactone **B** as outlined in Scheme 3. The high pressure of O_2 probably accelerated the formation of palladium peroxide and low temperature may avoid the β-hydride elimination pathway from **I-b** to **II**. The conformation of the *trans*-fused CD-ring may allow the formation of the intermediate **III** (see, 13,14-*trans*-**I-b**) whereas *cis*-fused CD-ring system (see, 13,14-*cis*-**I-b**) would disturb the formation of the intermediate **III** due to the steric hindrance at the β-face of the 5-membered ring. However, the other possible reaction mechanism cannot be ruled out.

In summary, we have developed Baeyer–Villiger type rearrangement reaction of silylenol ether derivatives promoted by 5 mol% of Pd $(OAc)_2$ at high pressure of O_2 and low temperature. At this point,

the substrates of this rearrangement reaction were limited to the 17-oxosteroid derivatives; however, more scopes of this reaction are now under investigation.



Scheme 3. Proposed Mechanism

ACKNOWLEDGEMENTS

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3. Compound **1**, **2**, and **3** are all contaminated with 3-OMe derivatives **6**, **9**, and **10** respectively in the ratio of 9:1. For the synthesis of compound **5**, see: H. Suginome, Y. Nakayama, and H. Senboku, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1837.
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5. Contaminated by-products were removed by filtration. Thus, after dissolution of $Pd(OAc)_2$ in hot benzene and its filtration, the filtrate was concentrated in vacuo to give pure $Pd(OAc)_2$.
6. Chemical data of **3**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.86 (dd, *J* = 2.1, 9.9 Hz, 1H), 6.04 (dd, *J* = 2.9, 9.9 Hz, 1H), 3.37 (s, 3H), 2.89 (t, *J* = 2.9 Hz, 1H), 2.38–2.30 (m, 1H), 2.23 (td, *J* = 2.9, 13.2 Hz, 1H), 2.01 (td, *J* = 3.4, 12.0 Hz, 1H), 1.90–1.70 (m, 4H), 1.63–1.51 (m, 2H), 1.44–1.32 (m, 1H), 1.38 (s, 3H), 1.25–1.18 (m, 1H), 1.12–1.05 (m, 1H), 1.02 (s, 3H), 0.98–0.89 (m, 2H), 0.74–0.71 (m, 1H), 0.54 (dd, *J* = 5.1, 8.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=164.0, 145.5, 121.5, 83.6, 81.4, 56.7, 48.1, 47.6, 43.5, 38.2, 34.6, 34.0, 33.2, 30.6, 24.7, 23.2, 21.1, 19.1, 18.5, 13.2 ppm; IR (NaCl): $\tilde{\nu}$ = 2946, 2869, 1722, 1457, 1381, 1097, 816 cm^{-1}; MS (EI): *m/z* (%): 316 (14)[M^+], 301 (45), 284 (37), 261 (100), 243 (11), 226 (5), 211 (8), 159 (20), 123 (15), 105 (22), 91 (31), 79 (25), 55 (16).
7. The structure of lactone **10** was determined by X-ray crystallographic analysis. CCDC-788111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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10. General Procedure: The reactions were carried out in an HPG-10-1 (Taiatsu Techno®) autoclave. To a solution of silylenol ether **6** (99.2 mg, 0.265 mmol) in CH_2Cl_2/DMSO (1/1, 12 mL) was added $Pd(OAc)_2$ (2.8 mg, 0.012 mmol) at –15 °C. After O_2 was pumped into the autoclave to reach 28 atm, the reaction mixture was stirred for 141 h at –15 °C. After venting O_2, the reaction was stopped by adding brine and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 8/2) to afford **9** (19.9 mg, 25%) as a white solid and **10** (59.5 mg, 73%) as a white solid.