Pergamon

Tetrahedron Letters 41 (2000) 7493–7497

TETRAHEDRON LETTERS

Pd-catalyzed hydrogenolysis of 4,5-epoxy-2-alkenoates: model study of the acyl side-chain of polyoxypeptin

Yasuo Noguchi,† Tatsuhiro Yamada, Hiromi Uchiro and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya-Funagawara-machi, Shinjuku-ku, Tokyo 162-0826, Japan

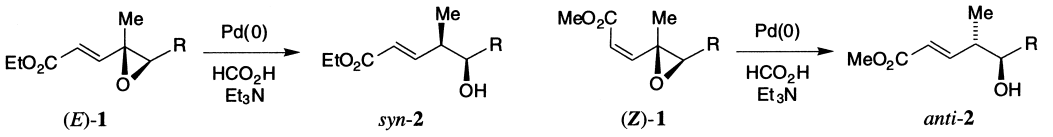
Received 21 June 2000; revised 17 July 2000; accepted 24 July 2000

Abstract

Palladium-catalyzed hydrogenolysis of 4,5-epoxy-2-alkenoates to 5-hydroxy-2-alkenoates was examined, and it was shown that the (*Z*)-alkenoate with a bulky substituent at C-4 underwent hydrogenolysis with a decrease in the stereospecificity. Mechanistic considerations and steps for improvement of the stereospecificity are also presented.

Keywords: Pd-catalyzed hydrogenolysis; 4,5-epoxy-2-alkenoate; π–σ–π interconversion; polyoxypeptin.

Pd-catalyzed hydrogenolysis of 4,5-epoxy-2-alkenoate developed by Shimizu and Tsuji is an interesting methodology for acyclic stereocontrol.[1] For example, (*E*)-**1** and (*Z*)-**1** are transformed into *syn*-**2** and *anti*-**2**, respectively, with high stereospecificity by treatment with a catalytic amount of Pd(0) and HCO_2H–Et_3N. One characteristic feature of this method is that the hydrogenolysis proceeds with inversion or retention of the configuration depending on the stereochemistry of alkenoates (Scheme 1).

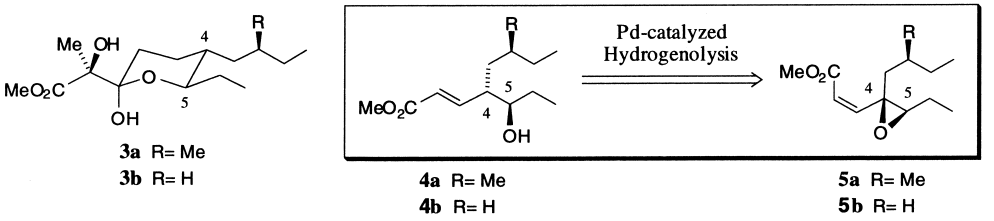


Scheme 1.

* Corresponding author. Tel: +81-3-3260-8848; fax: +81-3-3260-8848; e-mail: kobayashi@ps.kagu.sut.ac.jp
† Visiting scientist from Sankyo Co., Ltd.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01281-8

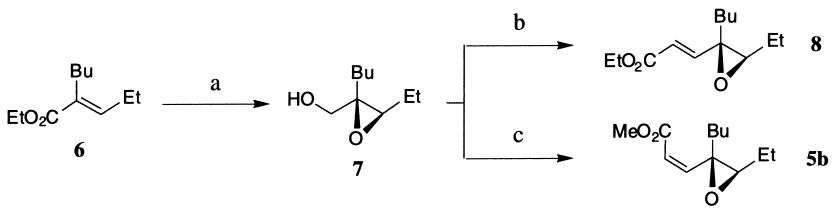
During the course of our synthetic investigation of polyoxypeptin,[2] we became interested in the Shimizu–Tsuji reaction for stereocontrol in the tetrahydropyran moiety of the acyl side-chain **3a**. The requisite 4,5-*anti*-isomer **4** could be derived from (*Z*)-alkenoate **5**. Since the substituent at C-4 was limited to a methyl group in the original report by Shimizu and Tsuji,[1] we were also interested in the reactivity and stereoselectivity in the case of other examples with sterically bulky substituents at C-4 (Scheme 2).



Scheme 2.

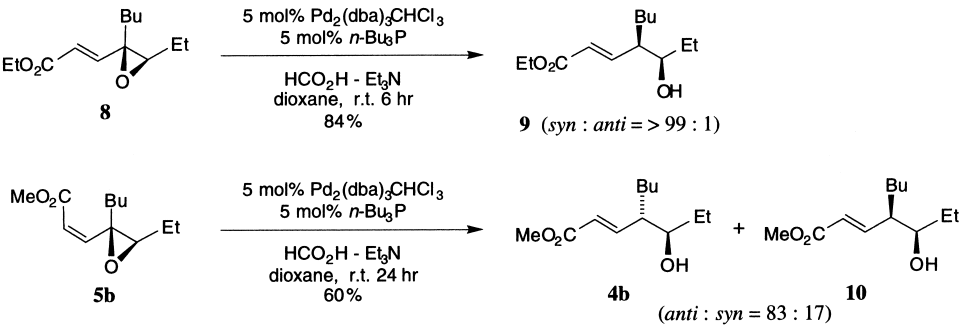
Here we would like to report our results obtained with a model substrate **5b** and its isomers together with new findings and some improvement of the methodology.[3] Mechanistic considerations are also presented. Application to the synthesis of the acyl side-chain moiety **3a** is described in the following paper.

(*E*)-Epoxyalkenoate **8** and (*Z*)-epoxyalkenoate **5b** were prepared stereoselectively from unsaturated ester **6**. Thus, **6** was reduced with DIBAL to an allylic alcohol, and the latter was subjected to Sharpless asymmetric epoxidation using D-(−)-DET to give the epoxy alcohol **7** in 80% yield with high enantioselectivity (>98% e.e.). Alcohol **7** was oxidized by Swern oxidation, and the resulting aldehyde was reacted with (*E*)-selective phosphonate and (*Z*)-selective phosphonate[4] to obtain **8** and **5b**, respectively. The purity of these epoxyalkenoates is over 99% in all respects (Scheme 3).



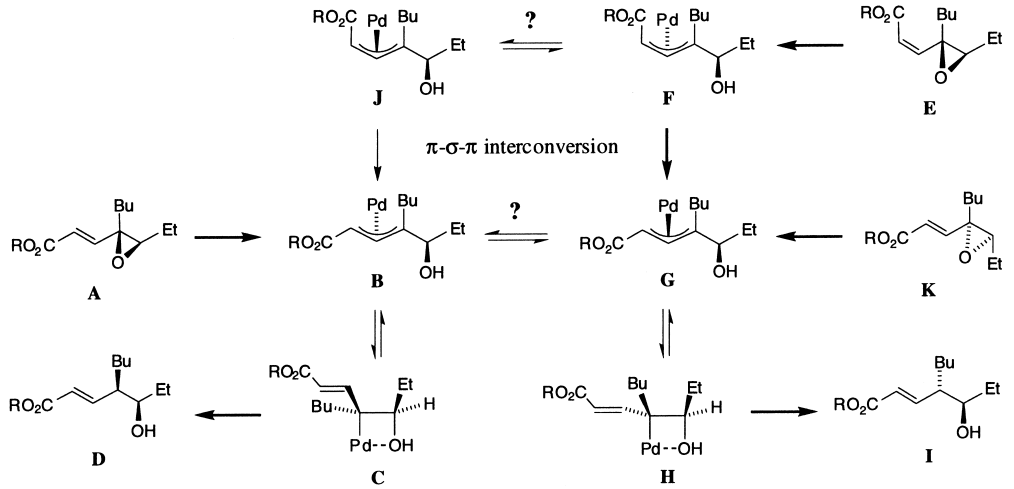
Scheme 3. *Reagents and conditions*: **a**: (i) DIBAL/Et_2O, 0°C, 1 h, 69%. (ii) TBHP, Ti(O-*i*-Pr)$_4$, D-(−)-DET, MS4A/CH_2Cl_2, −23°C, 80%. **b**: (i) $(COCl)_2$, DMSO, −78°C, then Et_3N/CH_2Cl_2, rt, 1 h. (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH/THF, 0°C, 1 h, 61% (two steps). **c**: (i) $(COCl)_2$, DMSO, −78°C, then Et_3N/CH_2Cl_2, rt, 1 h. (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6/THF −78°C, 1 h, 64% (two steps)

Palladium-catalyzed hydrogenolysis of **8** and **5b** was then carried out according to Shimizu and Tsuji protocol. In the case of (*E*)-alkenoate **8**, *syn*-isomer **9**[5] was produced almost exclusively in 84% yield. On the other hand, although the expected *anti*-isomer **4b**[5] was produced as a major isomer, a considerable amount of *syn*-isomer **10** was also formed by the hydrogenolysis of (*Z*)-alkenoate **5b**. This result was quite unexpected since high stereospecificity was always observed in both (*E*)- and (*Z*)-alkenoates. It is apparent that the decrease in the stereospecificity might be due to the presence of a sterically bulky substituent (*n*-butyl group) at C-4 (Scheme 4).



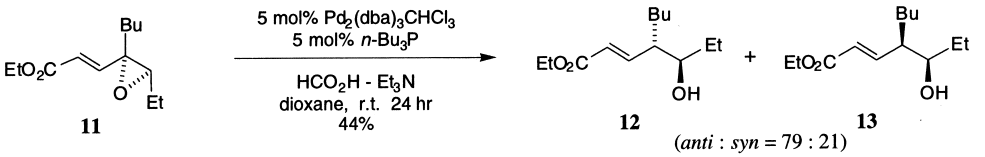
Scheme 4.

Low stereospecificity was sometimes observed in a Pd-catalyzed intramolecular alkylation of allylic acetate or carbonate,[6] and the mechanism of the epimerization or racemization has been extensively discussed.[6,7] Together with the proposed mechanism for epimerization in allylic alkylation,[6] the present Pd-catalyzed hydrogenolysis might proceed by the mechanism shown in Scheme 5. (*E*)-Alkenoate **A** was converted to *syn*-isomer **D** via π-allylpalladium **B** and **C**. In the case of (*Z*)-alkenoate **E**, the initially formed π-allylpalladium **F** was isomerized into the more stable π-allylpalladium **G** by π–σ–π interconversion, and the latter was transformed into *anti*-isomer **I**. The formation of *syn*-isomer **D** from **E** could be explained by the nucleophilic attack of Pd(0) either to the π-allylpalladium **F** (**F**→**J**→**B**→**D**) or **G** (**G**→**B**→**D**). In this context, we were interested in (*E*)-alkenoate **K** having *syn*-epoxide. Since hydrogenolysis of **K** proceeds without the π–σ–π interconversion process, its stereochemical behavior might provide some information regarding the epimerization.



Scheme 5.

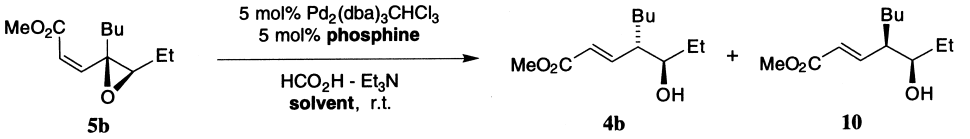
When *syn*-epoxide **11** (racemic), prepared from (*Z*)-2-butyl-2-penten-1-ol, was treated with Pd(0)–HCO_2H–Et_3N, *anti*-isomer **12** and *syn*-isomer **13** were formed in 44% yield in a ratio of 79:21. A similar degree of stereospecificity (83/17 and 79/21) strongly indicates that the epimerization might be explained by the nucleophilic attack of Pd(0) on π-allylpalladium **G** rather than **F**. We think that the repulsion between Bu and Et in **H** retards a smooth conversion of **G** to **I** via **H** (Scheme 6).



Scheme 6.

In order to attain higher stereospecificity in the case of **5b**, the effects of phosphine ligands and solvents were next investigated. The cone angle in Table 1 reflects the bulkiness of the phosphine ligand. Among several phosphine ligands examined, Ph_3P showed the highest stereospecificity (entry 2; 88:12). It seems that the hydrogenolysis proceeds slowly when a bulky ligand is used, and that the longer the time for completion, the lower the stereospecificity. A bulky phosphine ligand might cause the severe steric repulsion between Bu and Et in **H** in Scheme 5. The solvent effects on using Ph_3P are also shown in Table 1, and DMF (entry 7; 95:5) was found to be the solvent of choice in the present reaction. We assume that the reductive elimination of **H** to **I** proceeds smoothly in aprotic polar solvents such as DMF. Typical procedure is as follows: to a suspension of $Pd_2(dba)_3CHCl_3$ (5 mol%) and Ph_3P (5 mol%) in DMF was added a solution of HCO_2H (5 equiv.) and Et_3N (2 equiv.) in DMF. After 30 min, DMF solution of an epoxyalkenoate was added, and the reaction mixture (total 30 ml DMF/mmol **5b**) was stirred for 1 h. The product was isolated by the usual work-up, followed by chromatography on silica gel.

Table 1



Entry	Phosphine (cone angle)	Solvent	Time (h)	Yield (%)	**4b**:**10**
1	Bu_3P (130°)	Dioxane	24	60	83:17
2	Ph_3P (145°)	Dioxane	5	83	88:12
3	Cy_3P (170°)	Dioxane	48	70	51:49
4	*o*-Tol_3P (194°)	Dioxane	48	40[a]	45:55
5	dppe (–)	Dioxane	24	76	82:18
6	Ph_3P	THF	24	95	84:16
7	**Ph_3P**	**DMF**	**1**	**84**	**95:5**
8	Ph_3P	DMAc	6	60	94:6
9	Ph_3P	DMPU	3	58	93:7

[a] **5b** was recovered in 28% yield.

In conclusion, we have described in this paper that, (1) complete stereospecificity is not always observed in the Pd-catalyzed hydrogenolysis of 4,5-epoxy-2-alkenoate, particularly in the case of (*Z*)-alkenoate with a bulky substituent at C-4; (2) the stereospecificity is markedly dependent upon the bulkiness of the phosphine ligand; (3) relatively high stereospecificity was attained

using Ph_3P as a phosphine ligand in DMF; and (4) from a mechanistic point of view, we propose that the epimerization occurs after π–σ–π interconversion.

The following paper describes the application of the present methodology to the synthesis of the side-chain moiety of polyoxypeptin.

References

1. (a) Shimizu, I.; Oshima, M.; Nisar, M.; Tsuji, J. *Chem. Lett*. **1986**, 1775–1776. (b) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc*. **1989**, *111*, 6280–6287.
2. (a) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett*. **1998**, *39*, 1389–1392. (b) Umezawa, K.; Nakazawa, K.; Ikeda, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem*. **1999**, *64*, 3034–3038.
3. Pd catalyst and $Me_2NH{\cdot}BH_3$ complex method was recently reported: David, H.; Dupuis, L.; Guillerez, M.-G.; Guibe, F. *Tetrahedron Lett*. **2000**, *41*, 3335–3338.
4. Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405–4408.
5. ^{1}H NMR ($CDCl_3$, 400 MHz) spectra are as follows: Compound **9**: δ 0.88 (t, $J=7.1$ Hz, 3H), 0.96 (t, $J=7.6$ Hz, 3H), 1.31 (t, $J=7.1$ Hz, 3H), 1.08–1.70 (m, 9H), 2.23–2.26 (m, 1H), 3.43–3.52 (m, 1H), 4.19 (q, $J=7.1$ Hz, 2H), 5.85 (d, $J=15.4$ Hz, 1H), 6.78 (dd, $J=15.4$, 9.8 Hz, 1H). Compound **4b**: δ 0.88 (t, $J=7.1$ Hz, 3H), 0.95 (t, $J=7.6$ Hz, 3H), 1.12–1.71 (m, 9H), 2.17–2.25 (m, 1H), 3.50–3.57 (m, 1H), 3.74 (s, 3H), 5.86 (d, $J=15.9$ Hz, 1H), 6.87 (dd, $J=15.9$, 9.8 Hz, 1H).
6. Tsuji, J. *Tetrahedron* **1986**, *42*, 4361–4401.
7. (a) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **1992**, *114*, 6858–6863. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc*. **1980**, *102*, 4730–4743.