Pergamon

Tetrahedron Letters, Vol. 35, No. 12, pp. 1905-1908, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0205-C

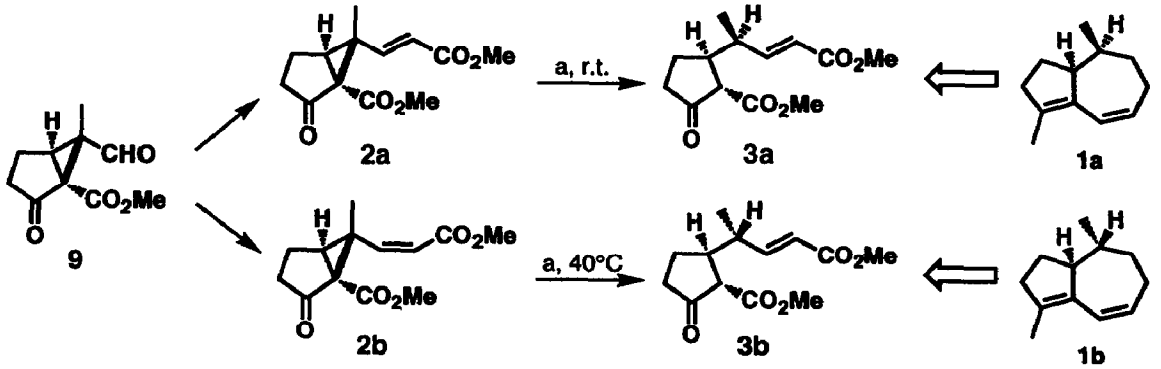
Stereoselective Synthesis of (±)-Clavukerin A and (±)-Isoclavukerin A Based on Palladium-Catalyzed Reductive Cleavage of Alkenylcyclopropanes with Formic Acid

Isao Shimizu* and Tomoko Ishikawa

Department of Applied Chemistry, School of Science and Engineering, Waseda University, Ookubo 3-4-1, Shinjuku-ku, Tokyo 169, Japan.

Abstract: (±)-Clavukerin A and (±)-isoclavukerin A were synthesized stereoselectively utilizing stereospecific palladium-catalyzed reductive cleavage of alkenylcyclopropanes with formic acid.

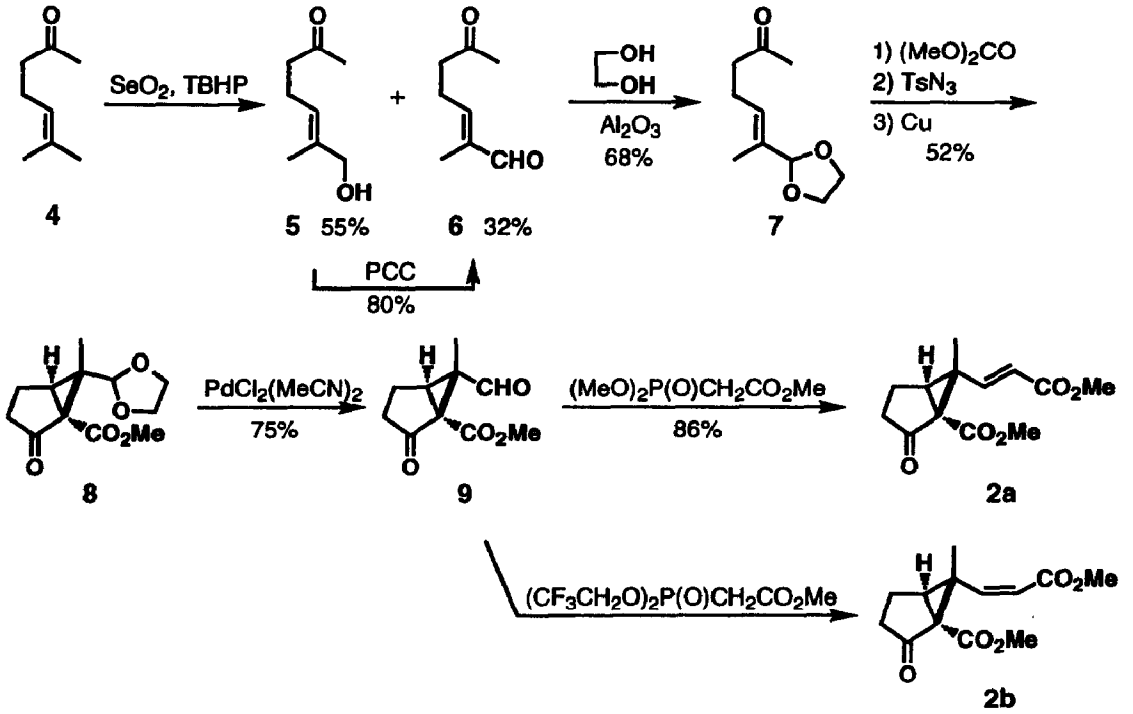
Cyclopentanoids which have vicinal asymmetric carbon centers on both their cyclopentane rings and their side chains are ubiquitous in natural terpenoids and steroids, and stereocontrolled synthesis of these compounds has been of importance in organic synthesis. (-)-Clavukerin A (**1a**) and (-)-isoclavukerin A (**1b**) were isolated from the Okinawan soft coral and their structures were determined as **1a** and **1b**.[1,2] A few synthetic methods for these compounds were reported.[3] Several years ago we reported that reductive cleavage of the alkenylcyclopropane **2a** having two electron withdrawing groups was carried out with formic acid in the presence of palladium catalyst.[4] The reaction proceeded stereoselectively, thus the cyclopentanoid **3a** was obtained by inversion of hydride attack. In our synthetic efforts for cyclopentanoids utilizing the palladium catalysis, we have succeeded to prepare both diastereomers **3a** and **3b**, which have relative asymmetric carbon centers corresponding to **1a** and **1b**, with high selectivity as shown in Scheme 1. In this paper we describe the synthesis of (±)-**1** by controlling the relative vicinal asymmetric centers as an application of the palladium-catalyzed reductive cleavage of alkenylcyclopropanes with formic acid.



a: $Pd_2(dba)_3CHCl_3$ (2.5mol%), n-Bu_3P (5mol%), HCO_2H - Et_3N, dioxane

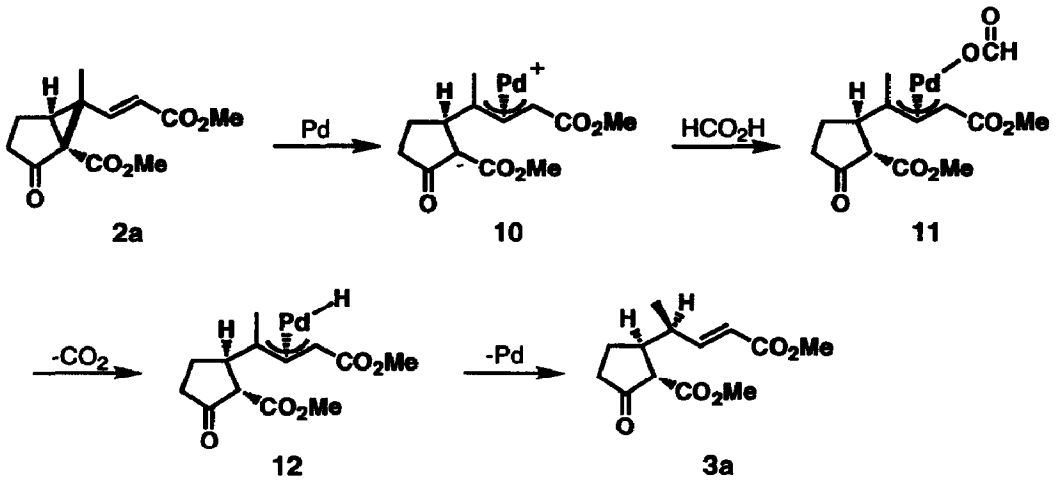
Scheme 1

Preparation of the alkenylcyclopropanes **2a** and **2b** is shown in Scheme 2. Oxidation of **4** with TBHP using SeO_2 catalyst gave the alcohol **5** (55%) and the aldehyde **6** (32%). The alcohol **5** was oxidized to **6** with PCC in 80% yield. Selective protection of aldehyde moiety of **6** to **7** was carried out by Hojo's method.[5] Methoxycarbonylation, reaction with TsN_3, and cyclopropanation gave the bicyclic compound **8** in 52% yield from **7**. The deprotection of **8** to the aldehyde **9** was carried out with $PdCl_2(MeCN)_2$ in 75% yield.[6] Emmons-Horner reaction of **9** gave the (*E*)-unsaturated ester **2a** in 86% yield. On the other hand the reaction of **9** with $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ gave the *Z* isomer **2b**.[7,8]



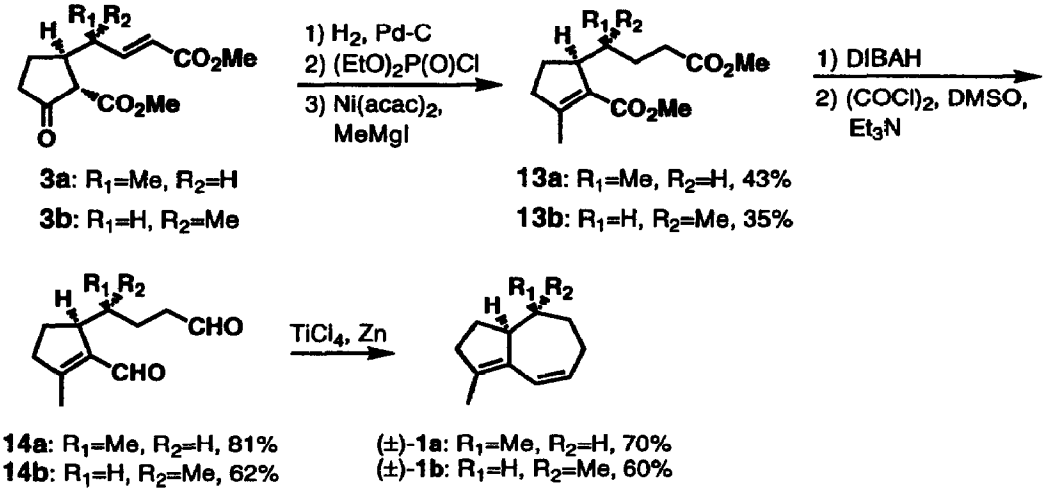
Scheme 2

Reaction of the ester **2a** with formic acid in the presence of palladium catalyst at room temperature gave **3** in 95% yield and the ratio of the isomer **3a** and **3b** was found to be 95:5 by NMR after converting to **1a**. The reaction proceeded with inversion of the stereochemistry, which is explained as shown in Scheme 3. π-Allylpalladium complexes **10** are formed by nucleophilic attack of Pd(0) species to **2a** with inversion. Addition of formic acid to **10** gives the π-allylpalladium formate complexes **11** which decompose to hydride complexes **12**. The intramolecular hydride attack of **12** proceeds from the palladium side to give the product **3a**. Similarly, the reaction of **2b** gave **3** (2 steps 54%) in a ratio of **3a**:**3b**=11:89. Thus the reaction of **2b** proceeded with retention of hydride attack and olefin isomerization from (*Z*) to (*E*) took place simultaneously. This result of hydride attack is similar to the hydrogenolysis of (*Z*)-alkenyloxiranes and the stereochemical outcome is explained by the well known π-σ-π interconversion process.[9,10] In both reactions small amounts of isomers (5% and 11%) were obtained, which is considered to be caused by epimerization of π-allylpalladium complexes during the reaction.[11,12]



Scheme 3

The cyclopentanones **3a** and **3b** are useful intermediates for the synthesis of (±)-clavukerin A and (±)-isoclavukerin A because they are easily transformed to dialdehydes **14a** and **14b** which are subjected to McMurry coupling to 1. Thus, hydrogenation of olefins on Pd/C followed by transformation to the enol phosphates and subsequent methylation with MeMgI using $Ni(acac)_2$ catalyst[13] gave the unsaturated esters **13a** in 43% yield and **13b** in 35% yield respectively. Reduction of the esters to diols followed by Swern oxidation gave the dialdehydes **14a** in 81% yield and **14b** in 62% yield. Finally, intramolecular reductive coupling of **14a** with $TiCl_4$-Zn[14] gave (±)-clavukerin A (**1a**) in 70% yield.[15] Similar transformation of **14b** gave (±)-isoclavukerin A (**1b**) in 60% yield.[15]



3a: R_1=Me, R_2=H
3b: R_1=H, R_2=Me

13a: R_1=Me, R_2=H, 43%
13b: R_1=H, R_2=Me, 35%

14a: R_1=Me, R_2=H, 81%
14b: R_1=H, R_2=Me, 62%

(±)-**1a**: R_1=Me, R_2=H, 70%
(±)-**1b**: R_1=H, R_2=Me, 60%

Scheme 4

As conclusion, we have demonstrated the stereoselective cleavage of alkenylcyclopropanes with formic acid using palladium catalyst which is useful for the synthesis of natural products. This research was financially supported by the Grant-in-Aid (No. 05234228) from the Ministry of Education, Culture and Science, Japan.

REFERENCES AND NOTES

1. Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 2160-2163.
2. Kusumi, T.; Hamada, T.; Hara, M.; Ishitsuka, M. O.; Ginda, H.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2019-2022.
3. a) Asaoka, M.; Kosaka, T.; Itahana, H.; Takei, H. *Chem. Lett.* **1991**, 1295-1298. b) Kim, S. K.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829-6832.
4. Shimizu, I.; Aida, F. *Chem. Lett.* **1988**, 601-604.
5. Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T. *Tetrahedron Lett.* **1985**, *26*, 4767-4770.
6. Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705-708.
7. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.
8. This compound **2b** was obtained with a small amount of the Still's reagent, which was not separated by chromatography on SiO_2 using ethyl acetate-hexane as an eluent, and was used in the next step without further purification.
9. Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280-6287.
10. Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642-2653.
11. Granberg, K. L.; Backvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858-6863.
12. When the reaction of **2a** or **2b** was carried out at 80°C, the stereospecificity decreased. (**3a**:**3b**=92:8 in 90% yield from **2a**, and **3a**:**3b**=20:80 in 64% yield from **2b**)
13. Hayashi, T.; Katsuro, Y.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4449-4452.
14. for a review; McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524.
15. NMR data of **1a** and **1b** were identical with those reported.[2, 3b] (±)-**1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J=12.1 Hz, 1H), 5.55 (dt, J=12.1, 5.1 Hz, 1H), 2.89 (m, 1H), 2.30-2.27 (m, 4H), 1.93-1.90 (m, 2H), 1.73 (s, 3H), 1.75-1.25 (m, 3H), 0.75 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.80, 134.92, 128.76, 123.74, 54.51, 37.78, 34.41, 34.18, 27.19, 26.71, 14.49, 11.42. (±)-**1b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (d, J=11.4 Hz, 1H), 5.65 (dt, J=11.4, 4.8 Hz, 1H), 2.41-2.21 (m, 4H), 2.17-2.01 (m, 2H), 1.74 (s, 3H), 1.59-1.54 (m, 1H), 1.43-1.19 (m, 3H), 0.96 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.60, 136.60, 129.23, 124.22, 55.65, 39.88, 36.72, 36.68, 30.30, 29.26, 21.96, 14.66.

(*Received in Japan* 2 *November* 1993; *accepted* 13 *January* 1994)