APPLICATION OF ALLYLPALLADIUM INTERMEDIATE TO A SIMPLE STEREOSELECTIVE

SYNTHESIS OF (±)-11-HYDROXY-*trans*-8-DODECENOIC ACID, A PRECURSOR

OF NATURALLY OCCURRING MACROLIDE FROM *CEPHALOSPORIUM RECIFEI*

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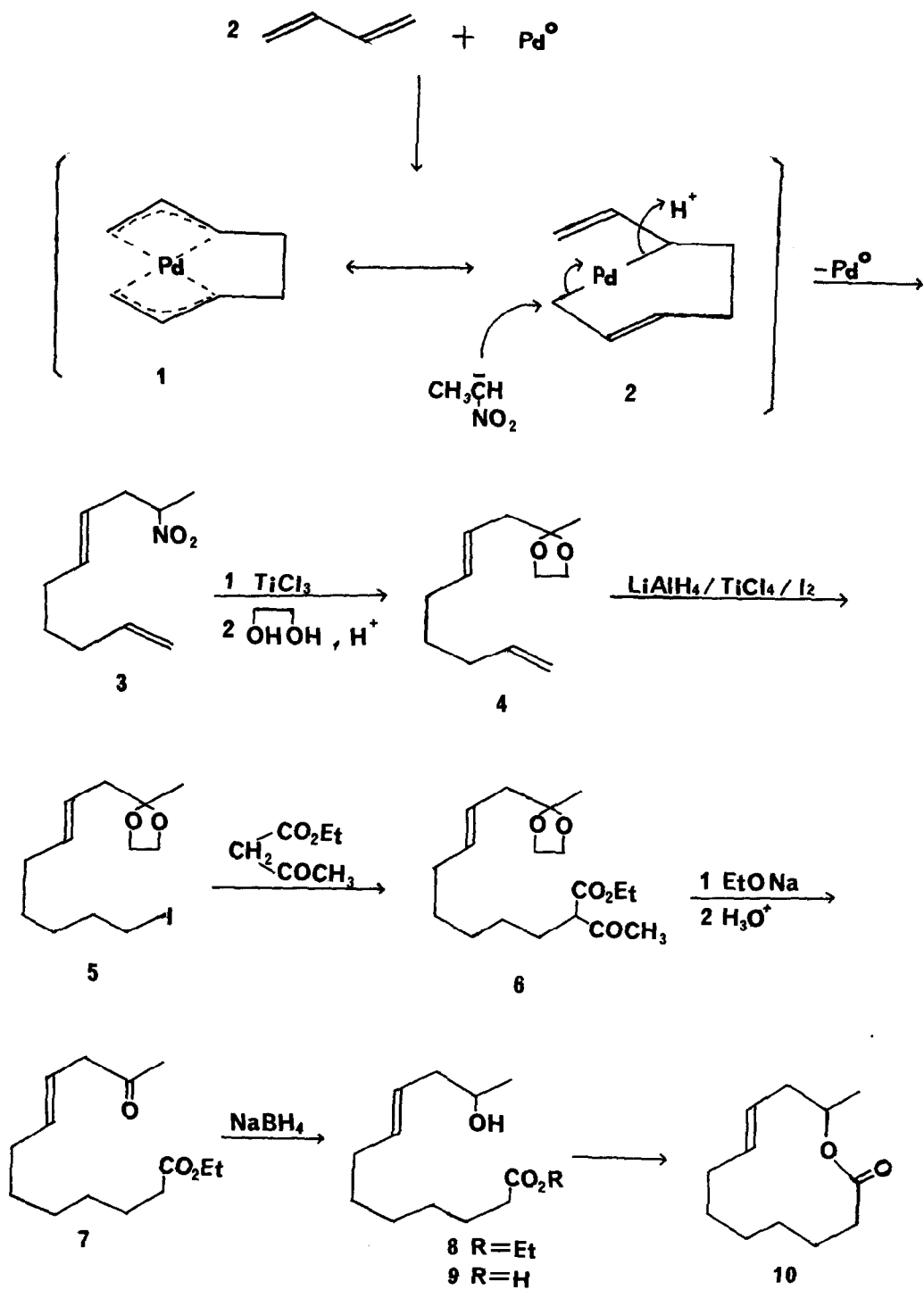Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Palladium-catalyzed telomerization of butadiene with various nucleophiles offers a number of useful compounds.[1] In our continuous effort to utilize these compounds for natural product syntheses, we have already synthesized Matsutake alcohol,[2,3] 2,15-hexadecanedione,[4] royal jelly acids,[5,6] queen substance,[7] pellitorine,[8] and civetone.[9] Another elegant application is the synthesis of brevicomin by Byron.[10] We now wish to report the application of the palladium catalyzed telomerization of butadiene with nitroethane to a very simple stereoselective synthesis of (±)-11-hydroxy-*trans*-dodecenoic acid (9). The lactone of this acid is a naturally occurring macrolide, called recifeiolide (10).[11]

One crucial problem in the synthesis of the acid 9 is the stereoselective introduction of a *trans* double bond at carbon 8. Mechanistic consideration that the telomer 3 is formed by the nucleophilic attack of nitroethane to the σ-allylic palladium complex 2 gives an important clue to the solution of this problem. As shown in the following scheme, the *trans* double bond in the intermediate complex 2 retains its *trans* configuration to become the *trans* double bond at carbon 6 of 9-nitro-1,6-decadiene (3), thus produced. This is exactly the desired configuration and position for the synthesis of 9. Also terminal double bond and nitro group are very suitable functionalities for the construction of 9. Thus the telomer 3 is a very good synthon of 9.

So far four synthetic methods for 10 have been reported. Corey[12] and Mukaiyama[13] used 4-pentyn-2-ol as a building block and the *trans* double bond was derived from the triple bond. Utimoto also used a triple bond as a source of the *trans* double bond.[14] In the Gerlach synthesis, the *trans* double bond was introduced by a Wittig reaction.[15] Our method offers a completely different approach. Since the lactonization of the acid 9 has been carried out by these four groups, the synthesis of the acid 9 constitutes the total synthesis of recifeiolide (10).

We found the telomerization reaction of butadiene with nitroalkanes catalyzed by a palladium-phosphine complex.[16] 2,7-Octadienyl group is introduced to an α-position of nitroalkanes. The telomer 3 can be prepared by the reaction of butadiene with nitroethane. The reaction of nitroethane (30.0 g, 0.4 mol) and

2 [butadiene] + Pd^o

1 ⟷ 2

CH$_3$CH NO$_2$

H$^+$

$-$Pd^o →

3 NO$_2$

$\xrightarrow{\begin{array}{c}1\ TiCl_3\\2\ \overline{OHOH},\ H^+\end{array}}$

4

$\xrightarrow{LiAlH_4/TiCl_4/I_2}$

5 I

$\xrightarrow{\begin{array}{c}CH_2\ {CO_2Et \atop COCH_3}\end{array}}$

6 CO$_2$Et COCH$_3$

$\xrightarrow{\begin{array}{c}1\ EtONa\\2\ H_3O^+\end{array}}$

7 CO$_2$Et

$\xrightarrow{NaBH_4}$

8 R=Et CO$_2$R OH
9 R=H

10

butadiene (21.6 g, 0.4 mol) in the presence of $Pd(OAc)_2$ (100 mg) and PPh_3 (300 mg) was carried out at room temperature for 12 hr. 9-Nitro-1,6-decadiene (3) was isolated by distillation (20 g, 56% yield) as a colorless oil at 88°/1.5 Torr; ^1H NMR (CCl_4) δ 1.50 (m, 5H), 2.05 (m, 4H), 2.55 (m, 2H), 4.50 (m, 1H), 4.90–6.10 (m, 5H); IR (film), 2930, 1640, 1550, 975 (*trans* double bond), 919 cm^{-1}.

The nitro group of 3 (3.00 g, 16.3 mmol) was treated with $TiCl_3$[17] in aqueous ammonium acetate at room temperature and 9-oxo-1,6-decadiene was obtained. The ketone was protected by acetal formation to give 4 (2.23 g, 70% yield). In order to increase a two-carbon unit, the terminal double bond was modified selectively to iodide without attacking the internal double bond. For this purpose, recently discovered hydroalumination catalyzed by a titanium compound was adopted.[18,19] Treatment of the acetal 4 (1.96 g, 10 mmol) with $LiAlH_4$ (125 mg, 3.3 mmol) in THF in the presence of $TiCl_4$ (0.5 mmol) gave an aluminate, which was treated *in situ* with iodine (3.8 g, 15 mmol) to give the terminal iodo compound 5 (1.95 g, 60% yield). IR (film) 2930, 975 cm^{-1}. ^1H NMR (CCl_4) δ 1.20 (s, 3H), 1.30 (m, 6H), 1.90 (m, 2H), 2.20 (m, 2H), 3.05 (t, 2H), 3.75 (s, 4H), 5.30 (m, 2H). The iodo compound 5 (1.30 g, 4.01 mmol) was treated with anion of ethyl acetoacetate (770 mg, 4.81 mmol) in THF/HMPA (5 : 1) to give 6 (1.04 g, 80% yield); IR (film), 1740, 1720, 975 cm^{-1}. ^1H NMR (CCl_4) δ 1.10–1.40 (m, 14H), 1.60–2.10 (m, 4H), 2.10 (s, 2H), 3.20 (t, 1H), 3.80 (s, 4H), 4.05 (q, 2H), 5.30 (m, 2H).

Deacetylation and deacetalization of 6 gave ethyl 11-oxo-*trans*-8-dodecenoate (7) in 88% yield. The ketone was reduced with $NaBH_4$ to give ethyl 11-hydroxy-*trans*-8-dodecenoate (8) (98% yield, bp 175°C/4 Torr by Kugel rohr). The structure was fully confirmed by mass spectrum (m/e 242, mol. wt. 242), elemental analysis, NMR and IR spectra. Anal. Found: C, 69.29; H, 10.73. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. IR (film), 3440, 2935, 1738, 975 (*trans* double bond) cm^{-1}; ^1H NMR (CCl_4) δ 1.05–1.75 (m, 14H), 1.85–2.40 (m, 6H), 2.50 (s, 1H), 3.65 (m, 1H), 4.05 (q, 2H), 5.40 (m, 2H).

Finally hydrolysis of the ester produced 11-hydroxy-*trans*-8-dodecenoic acid (9). The overall yield from 3 to 9 was 29%. IR (film), 3400, 1710, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3H), 1.35 (m, 8H), 2.25 (m, 6H), 3.80 (m, 1H), 5.45 (m, 2H), 6.40 (s, 1H).

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