DECARBOXYLATIVE C-C BOND CLEAVAGE REACTIONS *VIA* OXAPALLADACYCLES

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Dedicated to Prof. Dr. Albert Eschenmoser's on the occasion of his 85th birthday.

Abstract – In the presence of Pd(0) catalyst and triethylborane, 3-hydroxy-4-pentenoic acids undergo C-C bond cleavage reactions via oxapalladacyclopentanones to provide conjugated dienes with evolution of carbon dioxide.

Metallacycles are attractive key intermediates for constructing important fundamental constituents of complex molecules and fine chemicals.[1]   Oxidative cyclizations of conjugated dienes and carbonyl compounds with transition metals are efficient strategies for highly regio- and stereocontrolled C-C bond formation via oxametallacycles.[2]   Although the C-C bond cleavage reaction involving metallacycles has received less attention in comparison to C-C bond formation, it is equally capable of significant synthetic utility for efficient chemical transformations.[3]

We have previously developed a smooth transformation of vinyl cyclic carbonates into the corresponding ω-dienyl aldehydes by decarboxylative fragmentation through a key oxapalladacyclopentane intermediate, triggered by oxidative addition of a Pd(0) catalyst to the allylic C-O bond (Scheme 1).[4]   Furthermore, 4-pentene-1,3-diols of a wide structural variety, which can be prepared in a straightforward manner from mono- or bicyclic ketones with α,β-unsaturated aldehydes, also underwent the dehydrative β-carbon elimination of oxapalladacycles promoted by Ph$_3$B and Pd(0) catalyst.[5]   This procedure is superior to the cyclic carbonate method, not simply because we can save one step (carbonation), but because we can utilize a wide variety of stereoisomers of diols that cannot form carbonates as single isomers due to steric reasons.
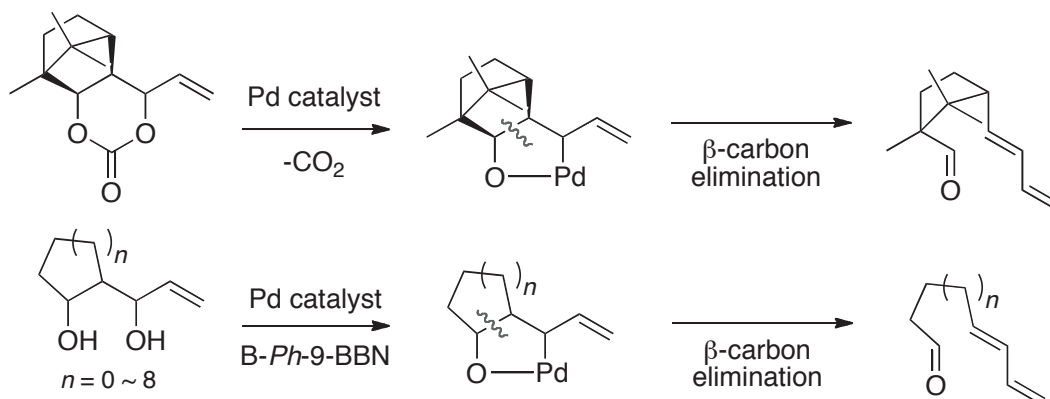
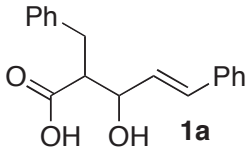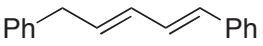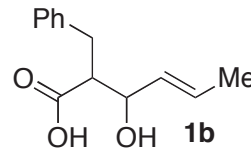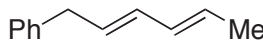**Scheme 1**. Pd-Catalyzed β-Carbon Elimination via Oxapalladacycle
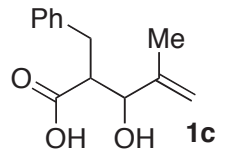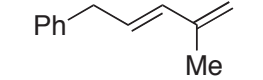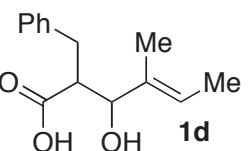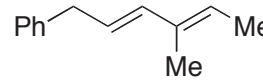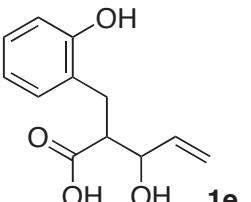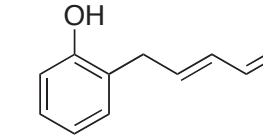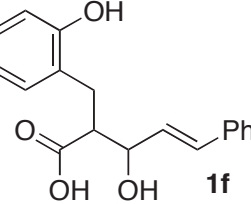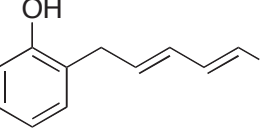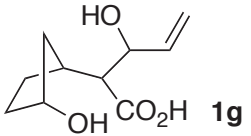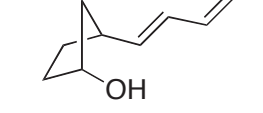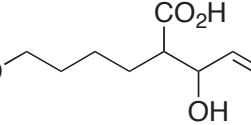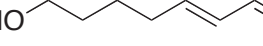
Herein, we report that Et_3B nicely activates 3-hydroxy-4-pentenoic acids which are prepared from esters or lactones with α,β-unsaturated aldehydes to undergo the decarboxylative β-carbon elimination via an oxapalladacyclopentane to afford a conjugated diene (Scheme 2). While it has been reported that 3-acetoxy-4-pentenoic acid underwent a similar decarboxylative C-C bond cleavage reaction promoted by Pd catalyst in the presence of triethylamine,[6] the present study is more convenient for the stereodefined construction of conjugated dienes from readily available starting materials as mixtures of diastereomeric isomers.[7] Furthermore, the Pd-catalyst/Et_3B system is also superior for the direct generation of π-allylpalladium species from allyl alcohols.
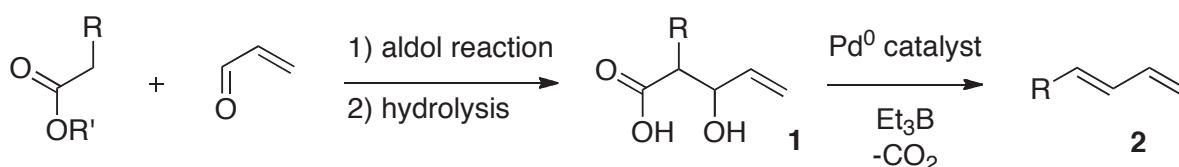
Scheme 2. Efficient Synthesis of Conjugated Diene via Decarboxylative C-C Bond Cleavage Reaction of 3-Hydroxy-4-pentenoic Acid Prepared from Acrolein and Esters

The reaction was undertaken with great ease just by exposing the 3-hydroxy-4-pentenoic acids to a mixture of $Pd(PPh_3)_4$ catalyst and Et_3B in THF under nitrogen atmosphere. Among these investigations with excess amount of Et_3B, the reaction required 3.6 equivalents of Et_3B at 67 ˚C to consume the substrate completely.[8] Table 1 summarizes the results obtained for a wide structural variety of 3-hydroxy-4-pentenoic acids under optimized conditions.[9]

$$\text{(1)}$$
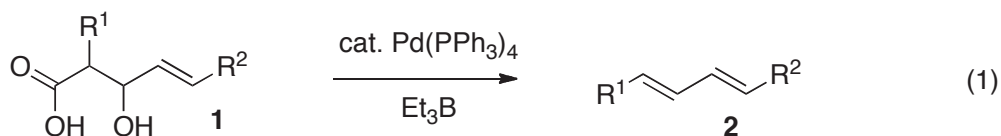
Table 1. Pd-Et$_3$B Promoted Decarboxylative C-C Bond Cleavage Reaction[a]

run	substrate [ratio]	time (h)	product % isolated yield [E:Z]
1	**1a** [3:1]	1	**2a**: 95% [18:1]
2	**1b** [1:1]	1	**2b**: 78% [5:1:1] [b]
3	**1c** [2:1]	18	**2c**: 86% [E]
4	**1d** [1:1]	72	**2d**: 65% [26:7:1] [c]
5	**1e** [2:1]	3	**2e**: 64% [3:1]
6	**1f** [2:1]	3	**2f**: 48% [3:1]
7	**1g** [single]	3	**2g**: 84% [11:1]
8	**1h** [2:1]	1	**2h**: 99% [4:1]

[a] Reaction conditions: substrate (0.5 mmol), Pd(PPh$_3$)$_4$ (5 mol %), Et$_3$B (3.6 eq) in THF (2.5 mL) at 67 °C under N$_2$. [b] Ratio of 1-phenyl-2,4-hexadiene. (2E,4E):(2E,4Z):(2Z,4E) = 5:1:1. [c] Ratio of 4-methyl-1-phenyl-2,4-hexadiene. (2E,4E):(2E,4Z):(2Z,4E) = 26:7:1.

A mixture of *syn*-**1a** and *anti*-**1a** in a 3:1 ratio, which was prepared from cinnamaldehyde and methyl 3-phenylpropionate, clearly undergoes β-decarboxylative C-C bond cleavage to provide (*E*,*E*)-pentadiene **2a** with high stereoselectivity in excellent yield (run 1). A methyl group substituted allylic alcohol **1b** afforded (2*E*,4*E*), (2*E*,4*Z*), and (2*Z*,4*E*)-1-phenyl-2,4-hexadiene **2b** in a 5:1:1 ratio (run 2). β-Methallyl alcohol shows exclusive *E*-stereoselectivity to give (*E*)-**2c** as the sole product owing to the bulky steric repulsion between the benzyl group and the methyl substituent on the allylic moiety (run 3). β,γ-Dimethyl substituted allylic alcohol **1d** displays moderate yield with three isomers of (2*E*,4*E*), (2*E*,4*Z*), and (2*Z*,4*E*)-**2d** in a 26:7:1 ratio (run 4). 3-Hydroxy-4-pentenoic acids possessing *o*-hydroxyphenyl groups participate in similar C-C bond cleavage reactions in 48-64% yields (runs 5 and 6). The lower yields stem from competing partial lactonization, which leads to the original dihydrocoumarin skeletons.[10] β-Hydroxycarboxylic acids **1g** and **1h**, which were prepared from 7-membered ring lactones with acrolein, provided the desired dienyl alcohols **2g** and **2h** in excellent to quantitative yields (runs 7 and 8).

The stereochemical outcome of the dienyl moiety may be rationalized according to the proposed reaction mechanism shown in Scheme 3. We postulate that *syn*-oxapalladacyclopentanone-**I** is generated by oxidative addition of the Pd(0) metal to the allylic position of *anti*-**1** activated by Et₃B with inversion of configuration. The intermediate *syn*-**I** then isomerizes to the sterically more stable *anti*-**I** form by σ−π−σ interconversion via the seven-membered ring palladacycle **II**. Thus, the π-allylpalladium intermediates *syn*-**I** and *anti*-**I** could both undergo the C3-C4 bond fission with evolution of carbon dioxde to provide (*Z*)-**2** and (*E*)-**2**, respectively.
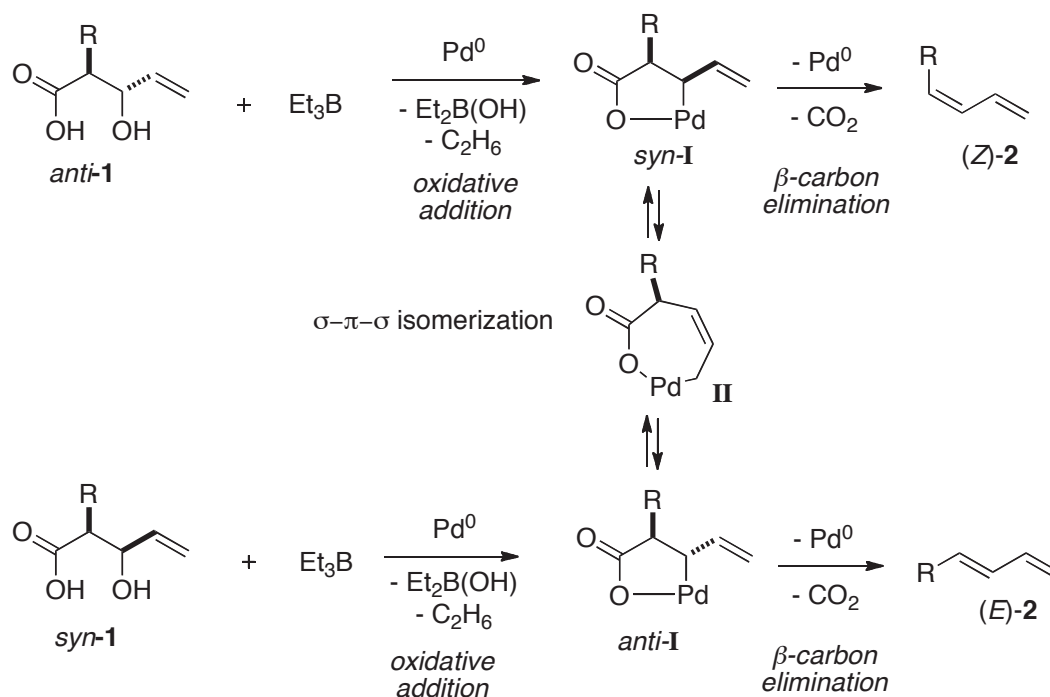
Scheme 3. Reaction Mechanism for Pd-Catalyzed Decarboxylative C-C Bond Cleavage

As a result of the formation of (2*E*,4*E*)-**2b** as a major product along with (2*E*,4*Z*) and (2*Z*,4*E*)-**2b** from a mixture of *syn*-(*E*)-**1b** and *anti*-(*E*)-**1b** (runs 2, Table 1), a plausible mechanism for the C-C bond cleavage reaction of 2,5-disubstituted-3-hydroxy-4-pentenoic acids **1** might be illustrated in Scheme 4.
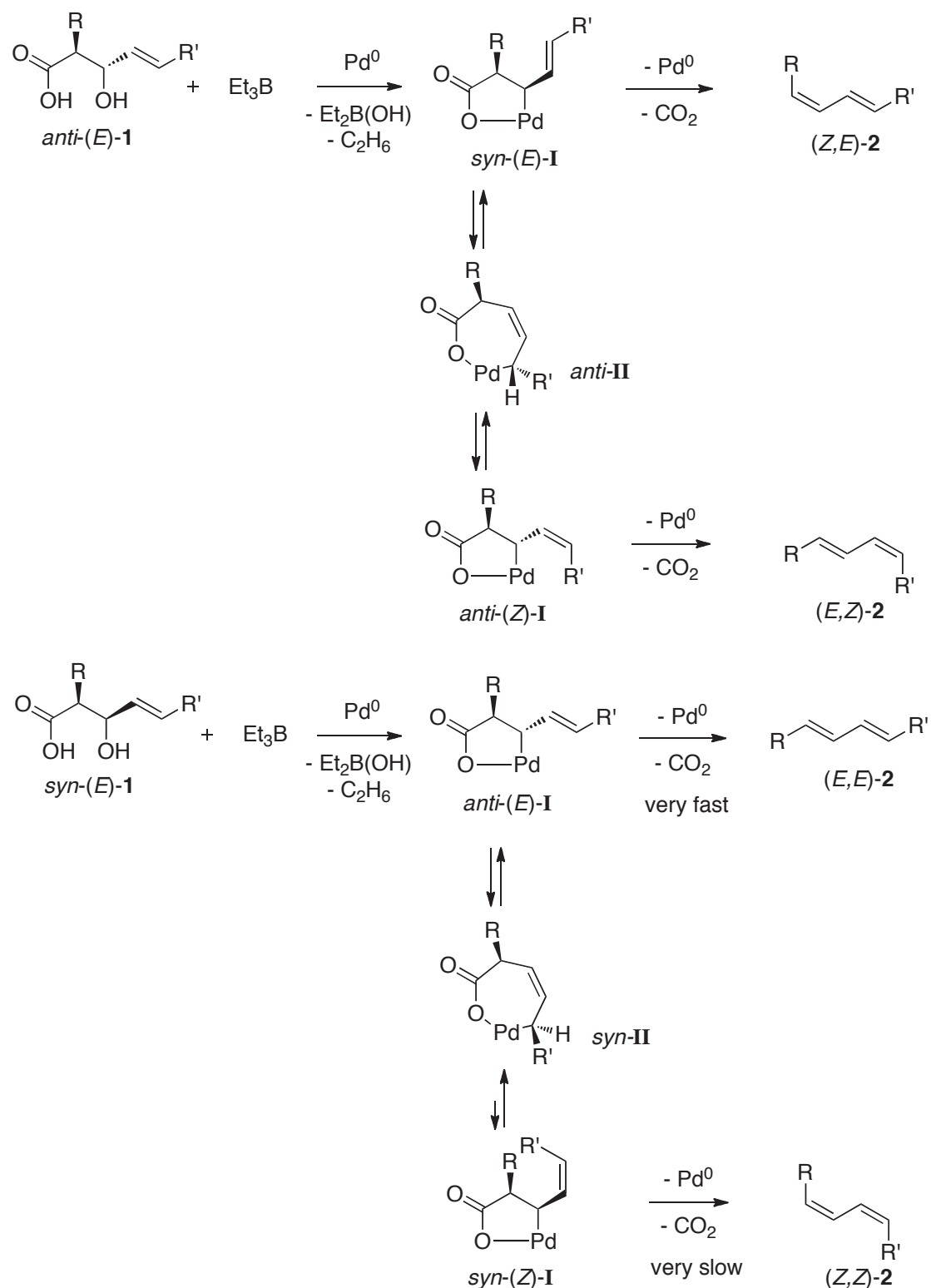
Scheme 4. C-C Bond Cleavage of 2,5-Disubstituted-3-hydroxy-4-pentenoic Acids

It seems that *anti*-(*E*)-**1b** provides a mixture of (*Z*,*E*)- and (*E*,*Z*)-**2b** in modest yields being in equilibrium with *syn*-(*E*)-**I** and *anti*-(*Z*)-**I** via seven-membered palladacycle *anti*-**II**. On the contrary, formation of *anti*-(*E*)-**I** from *syn*-(*E*)-**1b** by oxidative addition of Pd(0) catalyst with Et₃B predominates over the formation of *syn*-(*Z*)-**I** by σ–π–σ interconversion through *syn*-**II**, and causes the C-C bond cleavage reaction smoothly providing (*E*,*E*)-**2b** in excellent yield. Selective formation of (*Z*,*Z*)-**2b** through the unstable intermediate *syn*-(*Z*)-**I** is extremely improbable owing to the most unfavorable stereochemistry.

In summary, we have shown that a combination of Pd(0) catalyst and Et₃B effectively activates 3-hydroxy-4-pentenoic acid to undergo β-decarboxylative C-C bond cleavage reaction via β-vinyloxapalladacyclopentanone to form a conjugated diene with high stereoselectivity. The present methodology would be utilized for the convenient and stereodefined construction of conjugated dienes from readily available esters and α,β-unsaturated aldehydes with great operational ease.

ACKNOWLEDGEMENTS

REFERENCES AND NOTES

1. E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson, and T. Takahashi, *J. Am. Chem. Soc.*, 1989, **111**, 3336; N. M. Kablaoui, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1995, **117**, 6785; W. E. Crowe, and M. J. Rachita, *J. Am. Chem. Soc.*, 1995, **117**, 6787; M. Caellani, *Synlett*, 2003, 298; M. Kimura and Y. Tamaru, *Topics in Current Chemistry*, 2007, **279**, 173; M. Jeganmohan and C.-H. Cheng, *Chem. Eur. J.*, 2008, **14**, 10876; M. Catellani, E. Motti, and N. D. Cá, *Acc. Chem. Res.*, 2008, **41**, 1512.

2. Y. Sato, M. Takimoto, K. Hayashi, T. Katsuhara, K. Takagi, and M. Mori, *J. Am. Chem. Soc.*, 1994, **116**, 9771; Y. Sato, N. Saito, and M. Mori, *Tetrahedron*, 1998, **54**, 1153; M. Kimura, A. Ezoe, K. Shibata, and Y. Tamaru, *J. Am. Chem. Soc.*, 1998, **120**, 4033; M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto, and Y. Tamaru, *Angew. Chem. Int. Ed.*, 1999, **38**, 397; M. Kimura, S. Matsuo, K. Shibata, and Y. Tamaru, *Angew. Chem. Int. Ed.*, 1999, **38**, 3386; Y. Sato, M. Takimoto, and M. Mori, *J. Am. Chem. Soc.*, 2000, **122**, 1624; Y. Sato, R. Sawaki, and M. Mori, *Organometallics*, 2001, **20**, 5510; Y. Sato, N. Saito, and M. Mori, *J. Org. Chem.*, 2002, **67**, 9310; R. Sawaki, Y. Sato, and M. Mori, *Org. Lett.*, 2004, **6**, 1131; M. Kimura, A. Ezoe, M. Mori, K. Iwata, and Y. Tamaru, *J. Am. Chem. Soc.*, 2006, **128**, 8559; S. Ogoshi, K. Tonomori, M. Oka, and H.

Kurosawa, *J. Am. Chem. Soc.,* 2006, **128**, 7077; Y. Yang, S. F. Zhu, H. F. Duan, C. Y. Zhou, L. X. Wang, and Q. L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 2248; H. Y. Cho, and J. P. Morken, *J. Am. Chem. Soc.*, 2008, **130**, 16140; N. Saito, T. Yamazaki, and Y. Sato, *Tetrahedron Lett.,* 2008, **49**, 5073; N. Saito, T. Yamazaki, and Y. Sato, *Chem. Lett.*, 2009, 594.

3. M. Mori, M. Kimura, Y. Takahashi, and Y. Tamaru, *Chem. Commun.*, 2006, 4303.

4. H. Harayama, K. Kuroki, S. Tanaka, M. Kimura, and Y. Tamaru, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2352; H. Harayama, M. Kimura, S. Tanaka, and Y. Tamaru, *Tetrahedron Lett.*, 1998, **39**, 8475.

5. M. Kimura, M. Mori, and Y. Tamaru, *Chem. Commun.*, 2007, 4504.

6. B. M. Trost and J. M. Fortunak, *J. Am. Chem. Soc.*, 1980, **102**, 2841.

7. 3-Hydroxy-4-pentenoic acids **1** were easily prepared from lactones or esters with α,β-unsaturated aldehydes by crossed-aldol reaction followed by hydrolysis in aqueous alkaline conditions.

8. Under similar conditions, no reaction proceeds in the presence of Ph_3B, instead of Et_3B.

9. Typical reaction procedure (run 1, Table 1): Into a N_2 purged flask containing 3-hydroxy-4-pentenoic acid **1a** (141 mg, 0.5 mmol), $Pd(PPh_3)_4$ (27.8 mg, 0.025 mmol) purged with nitrogen were successively THF (2.5 mL) and triethylborane (1.8 mL, 1 M hexane; Aldrich) were introduced successively *via* a syringe. The reaction mixture was stirred at 67 °C for 1 h, during which the reaction was monitored by means of TLC. After dilution with EtOAc (30 mL), the mixture was washed with sat. aq. NaCl (30 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was subjected to the column chromatography over silica gel (Wakogel C-300; eluent: hexane) and (1*E*,3*E*)-1,5-diphenylpenta-1,3-diene **2a** (209 mg, 95%) was obtained in 18:1 ratio. **(1*E*,3*E*)-1,5-Diphenylpenta-1,3-diene (2a)**: IR (neat) 3024 (m), 1596 (w), 1495 (m), 1452 (m), 988 (s), 741 (m), 694 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, major isomer): δ 3.48 (d, J = 7.0 Hz, 2 H), 5.96 (dt, J = 14.9, 7.0 Hz, 1 H), 6.25 (dd, J = 14.9, 10.5 Hz, 1 H), 6.47 (d, J = 15.7 Hz, 1 H), 6.77 (dd, J = 15.7, 10.5 Hz, 1 H), 7.19 - 7.41 (m, 10 H); ^{13}C NMR (400 MHz, CDCl$_3$, major isomer): δ 39.2, 126.0, 126.1, 127.1, 128.3, 128.4, 128.5, 128.8, 130.8, 131.6, 133.5, 137.4, 140.0; ^{1}H NMR (400 MHz, CDCl$_3$, minor isomer): δ 3.65 (d, J = 7.6 Hz, 2 H), 5.69 (dt, J = 10.5, 7.6 Hz, 1 H), 6.25 (t, J = 10.5 Hz, 1 H), 6.61 (d, J = 15.6 Hz, 1 H), 6.77 (dd, J = 15.7, 10.5 Hz, 1 H), 7.19 - 7.41 (m, 10 H); ^{13}C NMR (400 MHz, CDCl$_3$, minor isomer): δ 34.2, 126.0, 126.3, 127.4, 128.3, 128.4, 128.5, 129.5, 130.6, 131.6, 133.0, 137.4, 140.3; High-resolution MS, calcd for $C_{17}H_{16}$: 220.3089. Found *m/z* (relative intensity): 221.1271 (18), 220.1252 (M$^+$, 100), 219.1181 (3).

10. The original dihydrocoumarins by competing lactonization of **1e** and **1f** were produced in 12% and 20% yields, respectively (runs 5 and 6, Table 1).