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A short synthesis of (±)-laurene: mechanistic reinvestigation in palladium-catalyzed cycloreductions of 1,6-enynes

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Abstract

Two palladium-catalyzed cycloreduction strategies have been applied for the synthesis of laurene. Palladium-catalyzed cyclizations of 1,6-enynes initially form the corresponding alkylpalladium intermediates. While triethylsilane could directly reduce the intermediates to lead to the corresponding cycloreduced products, the intermediates in the presence of even excess formic acid underwent β-elimination to yield the dienes that were further reduced at the less hindered olefins to yield the cycloreduced products. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium; laurene; enyne; cycloreduction; synthesis; formic acid; triethylsilane.

The sesquiterpene laurene, first isolated from *Laurencia glandulifera* and subsequently found in several other *Laurencia* species, has significant steric crowding around a compact cyclopentane ring.[1] Despite a relatively simple substitution pattern on the cyclopentane skeleton, the *cis*-1,2 relationship of the secondary methyl group with the *p*-tolyl group has made both the stereoselective and enantioselective synthesis of this compound difficult.[2] Two different basic approaches are known to this end. One is conducted by group transformations from existing five-membered carbocycles,[3] and the other is the approach of controlling the newly formed five-membered ring. The latter strategy mostly involves radical cyclization,[4] anionic cyclization via enolate or alkyllithium,[5] and intramolecular carbenoid displacement by employing a catalyst.[6] Trost and co-workers found that the H–Pd–X species, generated from a palladium compound and a carboxylic acid, selectively added to an activated triple bond in the presence of internal triple bonds or double bonds.[7] This remarkable observation prompted us to pursue more studies on palladium-catalyzed cyclization of unsaturated substrates such as enediynes,[8] dienyne,[9] triynes,[10] and enynes.[11] Employing triethylsilane or polymethylhydrosiloxane (PMHS) as a hydrogen donor in their Pd-catalyzed enyne cyclizations successfully converted the enyne

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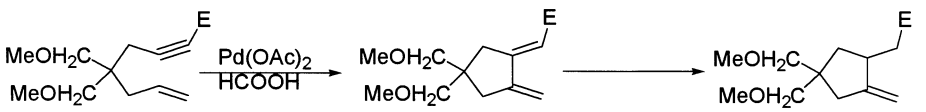
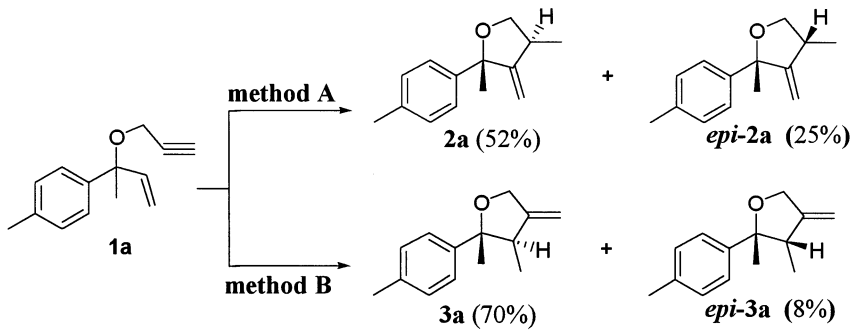
substrates to the corresponding cycloreduced products.[12] Although this is a highly valuable cycloreduction methodology applicable to diverse enyne substrates, one critical disadvantage is the requirement of an excess of silanes, which should cause purification of the products to be problematic. Recently, we reported an alternative method for enyne cycloreduction that could provide easy access to the laurene skeletons via direct reduction of the alkylpalladium species by the formate ligand.[13] During extension of this methodology, we found that enynes conjugated with a carbonyl group proceeded to the γ,δ-unsaturated carbonyl compounds via the diene intermediates (Eq. (1)).[14]



(1)

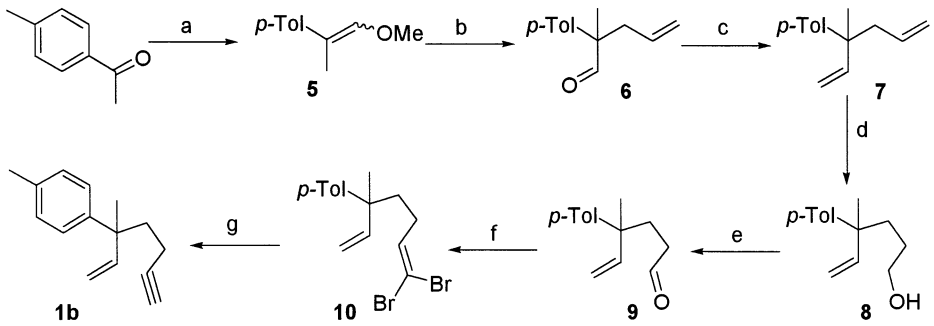
The latter result has led us to reexamine our proposed mechanism of palladium-catalyzed enyne cycloreductions, where we found structural uncertainty based upon NMR analyses of our previously reported products. Here we wish to revise the mechanisms in palladium-catalyzed enyne cycloreductions under different conditions and to apply the laurene synthesis. Thus, we retested the enyne **1a**, which is a good model substrate for the natural product laurene and is very easy to prepare.

Cycloreductions of the enyne **1a** were conducted under two conditions (**A** and **B**), and the resultant products were separated by using preparative HPLC to give the products **2a**, ***epi*-2a**, **3a**, and ***epi*-3a** as shown in Scheme 1. ^{1}H, ^{13}C NMR, DEPT, COSY, TOCSY, HETCOR experiments enabled us to accomplish complete ^{1}H and ^{13}C NMR signal assignments of compounds **2a**, ***epi*-2a**, and **3a** and to confirm the relative configurations of each compound. Coupling constants given by the DQF-COSY experiment were analyzed to identify the orientation of *J*-coupled proton networks and to see possible 5-membered ring puckering. In addition, the temperature-dependency ($-20 \sim 25°C$) and variable mixing times ($\tau_m = 50$, 100, 250, 500 ms) of NOESY experiments were carried out to observe the direct NOE connectivities exhibiting the orientation of side chains.[15]



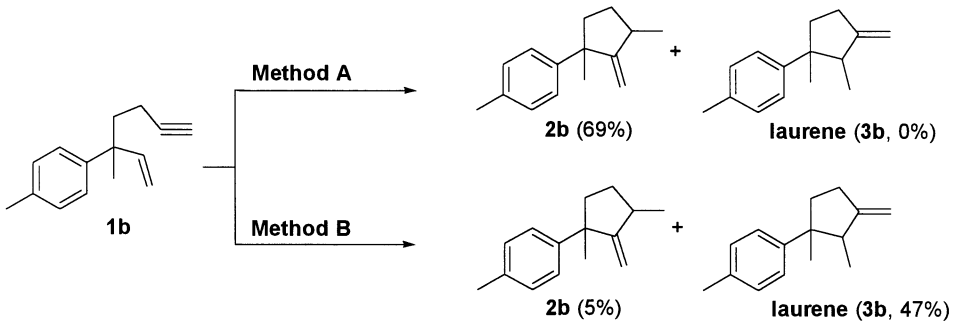
Scheme 1. **Method A**: 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.2 equiv. HCOOH, toluene, 60°C, 1.0 h. **Method B**: 5 mol% $Pd_2(dba)_3$, 10 mol% PPh_3, 2 equiv. AcOH, 10 equiv. Et_3SiH, toluene, 50°C, 2.0 h

Next, we prepared the enyne **1b** as a laurene precursor as shown in Scheme 2. 4-Methylacetophenone was transformed to the diene **7** in two consecutive olefinations. Hydroboration of the diene, followed by H_2O_2 oxidation, gave the alcohol **8**. The alcohol **8** was oxidized to the aldehyde **9** that was further transformed to the dibromoolefin **10**. Elimination of dibromoolefin **10** with *n*-butyllithium at −78°C provided the enyne **1b** in gram quantity (Scheme 2).



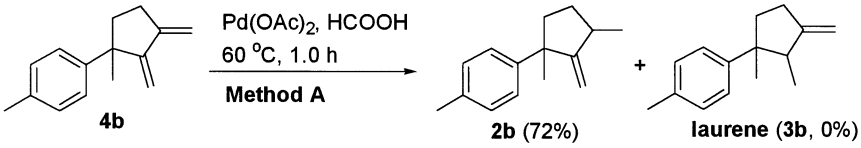
Scheme 2. (a) $MeOCH{=}PPh_3$, THF, −78°C to rt, 73%; (b) $CH_2{=}CHCH_2OH$, *p*-TsOH (cat), xylene, heat, 78%; (c) CH_3PPh_3Br, *n*-BuLi, THF, 70%; (d) (i) 9-BBN, THF, then (ii) H_2O_2, NaOH, 86%; (e) PCC, CH_2Cl_2, 68%; (f) CBr_4, PPh_3, 84%; (g) *n*-BuLi, THF, 91%

As mentioned, a completion of the laurene synthesis required a stereoselective introduction of the methyl substituent, which can be generated from cycloreduction of the enyne **1b** (Scheme 3).



Scheme 3.

Under the best conditions we have tested, the enyne **1b** did not furnish the desired laurene but gave the cycloreduced product **2b** in 69% yield (**Method A**). This result revealed that the present alkyl-palladium intermediates were labile to form the diene **4b** via β-elimination. A control experiment was conducted by employing only a catalytic amount of formic acid or acetic acid to give the diene **4b**. The diene **4b** was then further subjected to **Method A** in order to confirm the real intermediate of this reaction as shown in Eq. (2). As expected, the palladium acetate–HCOOH conditions reduced the diene to the product **2b** exclusively. We could conclude that formation of the laurene isomer resulted from reduction of the β-eliminated diene **4b** of the alkylpalladium intermediate.

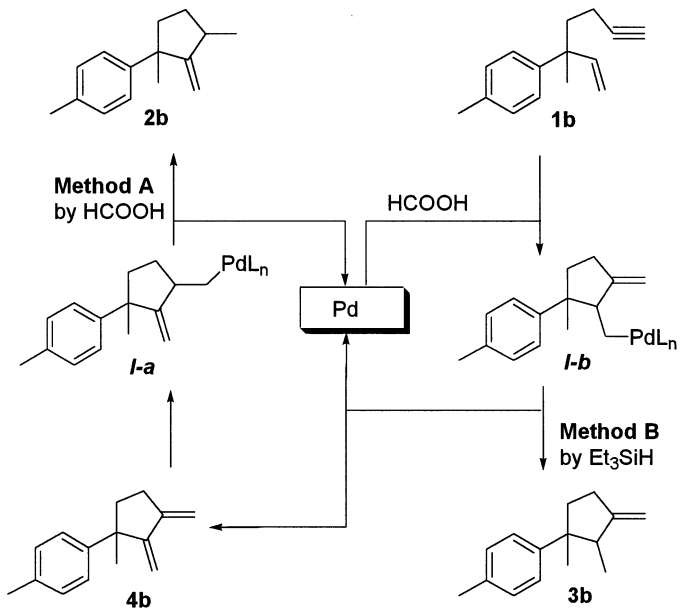


(2)

To prevent such β-elimination, we have employed the Trost method in our system. When the enyne **1b** was treated with a catalytic amount of $Pd_2(dba)_3$, acetic acid and 10 equivalents of triethylsilane, the enyne was cycloreduced to the natural product laurene along with its

stereoisomer in combined 52% yield (**Method B**). To maximize the formation of our desired laurene, we replaced triethylsilane in the Trost conditions by tributyltin hydride, catecholborane, sodium hydride or sodium borohydride, but no successful results were obtained.

Following is a summary for the present studies. The enyne **1b** was hydro- and subsequently carbopalladated to the corresponding alkylpalladium intermediates ***I-b***. In **Method A**, the alkylpalladium intermediates readily underwent β-elimination to the diene **4b**, which was rebounded with HPdOOCH species to form presumably via the intermediate ***I-a*** and reduced to give the product **2b** as shown in Scheme 4. In **Method B**, the initially formed vinylpalladium intermediate was carbopalladated to give the alkylpalladium intermediates ***I*-b**, which was directly reduced by triethylsilane to yield the product **3b**.



Scheme 4.

In conclusion, the synthesis of laurene was attempted by two palladium-catalyzed cycloreduction strategies. While triethylsilane directly reduced the intermediates ***I-b*** to lead to the corresponding cycloreduced product **3b**, formic acid did not. The intermediates in the presence of 1.5 equivalents of formic acid underwent β-elimination to yield the diene **4b** that was further reduced at the less hindered olefin to yield the cycloreduced product **2b**. Although the β-elimination was facile in alkylpalladium intermediates, trapping such a C–Pd sigma bond with a hydrogen donor like triethylsilane has been accomplished. We believe that the present study will provide more insight into regioselective syntheses of exomethylenecyclopentane derivatives.

Acknowledgements

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References

1. (a) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343–3349. (b) Irie, T.; Yasunari, Y.; Suzuki, T.; Imai, N.; Kurosawa, E.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 3619–3624. (c) Irie, T.; Suzuki, T.; Yasunari, Y.; Kurosawa, E.; Masamune, T. *Tetrahedron* **1969**, *25*, 459–468. (d) Hall, J. G.; Reiss, J. A. *Aust. J. Chem.* **1986**, *39*, 1401–1409.
2. (a) Kulkarni, M. G.; Pendharkar, D. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3127–3128. (b) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2329–2332.
3. Taber, D. F.; Anthony, J. M. *Tetrahedron Lett.* **1980**, *21*, 2779–2782. (b) Posner, G. H.; Lentz, C. M. *Tetrahedron Lett.* **1977**, *37*, 3215–3218. (c) McMurry, J. E.; von Beroldingen, L. A. *Tetrahedron* **1974**, *30*, 2027–2032.
4. (a) Srikrishna, A.; Sundarababu, G. *Tetrahedron* **1991**, *47*, 481–496. (b) Srikrishna, A.; Sundarababu, G. *Tetrahedron Lett.* **1989**, *30*, 3561–3562.
5. Bailey, W. F.; Jiang, X.-L.; McLeod, C. E. *J. Org. Chem.* **1995**, *60*, 7791–7795.
6. Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 193–199.
7. For reviews, see (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42. (c) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053–6054. (d) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636–644.
8. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491–12509.
9. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701–703.
10. Oh, C. H.; Park, B. S. *Bull. Kor. Chem. Soc.* **1996**, *17* (12), 1174–1176.
11. (a) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625–6633. (b) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781–1783. (c) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651–654. (d) Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687–8691. (e) Oh, C. H.; Rhim, C. Y.; Hwang, S. K. *Chem. Lett.* **1997**, 777–778.
12. (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163. (b) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520–522.
13. (a) Oh, C. H.; Rhim, C. Y.; Kang, J. H.; Kim, A.; Park, B. S.; Seo, Y. *Tetrahedron Lett.* **1996**, *37*, 8875–8878. (b) Oh, C. H.; Jung, H. H. *Tetrahedron Lett.* **1999**, *40*, 1535–1538.
14. Oh, C. H.; Jung, H. H.; Kim, J. S.; Cho, S. W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 752–755.
15. In a previous paper, the major product **2a** obtained from **Method A** has been assigned to be the oxa-laurene **3a**, based upon the coupling pattern of the product at 200 MHz NMR spectrometer. The products **2a**, ***epi*-2a**, **2b**, **3a**, and ***epi*-3a** were characterized by ^{1}H NMR, ^{13}C NMR, IR and high-resolution mass spectroscopy. Furthermore, relative stereochemistry of **2a** and **3a** has been unambiguously assigned based upon NOESY spectral data obtained from a 400 MHz NMR spectrometer. The structure of natural product laurene **2a** and its isomer ***epi*-2a** has been confirmed by comparing with the known spectral data.