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Pd(0)-Catalyzed Lactone Migration: A Facile Route to *cis*-Fused Hydrobenzofurans

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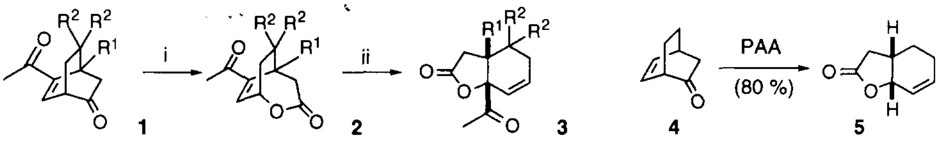
Abstract: Stereospecific conversion of bicyclo[2.2.2]oct-5-en-2-one derivative **1** to fused lactone **3** *via* bicyclic lactone **2** by chemo- and regio-selective Baeyer-Villiger oxidation followed by Pd(0)-catalyzed lactone migration was achieved for the efficient construction of *cis*-fused hydrobenzofuran derivatives. Copyright © 1996 Elsevier Science Ltd

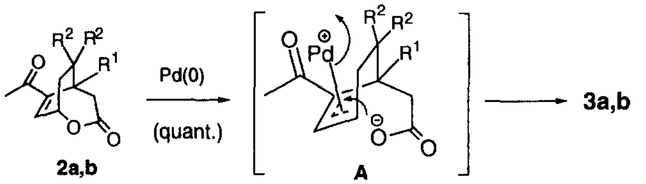
In our synthetic studies on stemodane diterpenes, an efficient conversion of substituted bicyclo[2.2.2]oct-5-en-2-one moiety **1** to *cis*-fused hydrobenzofuran derivative **3** was required. Meinwald *et al.* reported that bicyclo[2.2.2]oct-5-en-2-one (**4**) can be converted in 80% yield to an olefinic fused lactone **5** by treatment with peracetic acid (PAA).[1] This one-pot Baeyer-Villiger oxidation—acid-catalyzed 1,3-rearrangement process seemed attractive for our purpose. Thus, the bicyclic keto-enone **1a** was treated with PAA, but no desired product **3a** was obtained. Consequently, such acidic conditions may not be suitable for a more substituted system, such as **1**. In this paper, we report the stereospecific transformation of bicyclo[2.2.2]octenone **1** into multifunctional hydrobenzofuran **3**, a *cis*-fused 5-membered lactone, *via* bicyclic lactone **2** through an interesting Pd(0)-catalyzed lactone migration reaction.



a : R^1 = Me, R^2 = H
b : R^1 = R^2 = Me

Reagents and Conditions: i) *m*-CPBA, NaH_2PO_4 (anhyd.), CH_2Cl_2, r.t., 8 h; ii) $Pd(Ph_3P)_4$, n-Bu_3P, THF, r.t., 1 h.

The bicyclic keto-enones **1a,b** were prepared from properly substituted cyclohexenones.[2] To realize the transformation **1**→**3**, we selected a two-step conversion: *i.e.*, chemo- and regio-selective Baeyer-Villiger oxidation[3] followed by 1,3-rearrangement. Treatment of **1a,b** with *m*-CPBA in the presence of phosphate buffer selectively gave the bicyclic enone-lactones **2a,b** in 80 and 78 % yields, respectively. Next, rearrangement of the bicyclic 7-membered lactones **2a,b** to fused 5-membered lactones **3a,b** was attempted with *p*-toluenesulfonic acid at room temperature. However, this reaction was rather sluggish and the yield was low. Since acidic conditions are not desirable for compounds bearing acid-labile functionality, we sought milder and more widely applicable conditions. We chose a Pd(0)-catalyzed isomerization reaction. Since the lactone C-O bond in **2** is at an allylic position, π-allylpalladium complex **A** would be formed by treatment with a Pd(0)-catalyst.[4] The energy difference between **2** and **3** is quite large (**3a** and **3b** are more than 10 kcal/mol more stable than **2a** and **2b** respectively, by MM2 calculation[5]). Therefore, we expected a nucleophilic displacement of the palladium moiety by the intramolecularly co-existing carboxylate to form the 5-membered lactones **3a,b** due to absence of any other nucleophiles. Considering that the allylic system of **3** seems too congested to be attacked by Pd-catalyst to reproduce complex **A**, combined with the stability of fused 5-membered lactone, the reverse isomerization **3**→**2** would not be possible. Treatment of **2a,b** with $Pd(Ph_3P)_4$ (0.1 eq.) and Bu_3P (0.4 eq.) in THF under Ar atmosphere afforded **3a,b** quantitatively after 1 h stirring at room temperature.[6] Thus, we achieved an efficient two-step transformation of a bicyclo[2.2.2]octane system (*i.e.*, **1**) to a fused 5-membered lactone system (*i.e.*, **3**) *via* a regio- and chemo-selective Baeyer-Villiger oxidation followed by Pd(0)-catalyzed lactone migration.

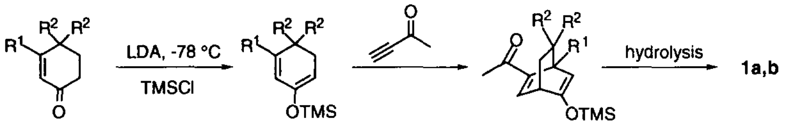


Since asymmetric induction in the Diels-Alder step for the preparation of bicyclo[2.2.2]octenone skeleton is possible and the resulting hydrobenzofurans would possess diverse functionality, this Pd(0)-catalyzed lactone migration reaction driven by the difference in steric ring energy should be a useful tool for the synthesis of natural products. We are currently applying this methodology to the total synthesis of stemodane diterpenes and other natural products.

References and Notes

1 Meinwald, J.; Seidel, M. C.; Cadoff, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 6303–6305; Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235-5239.

2 The substituted bicyclic octenones **1a,b** were obtained from properly substituted cyclohexenones *via* silyl dienol ether formation, Diels-Alder reaction with 2-butyn-3-one, and hydrolysis.



a : R^1 = Me, R^2 = H **b** : R^1 = R^2 = Me

3 A review, see: Krow, G. R. *Organic Reactions*, Vol. 43, ed. by Paquette, L. A., Wiley & Sons: New York, 1993, pp. 251-798.

4 Recent π-allylpalladium reviews, see: Tsuji, J. *Palladium Reagents and Catalysts*, Wiley & Sons: Chichester, 1995, p. 290-527; Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975-1015; Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Asymmetry* **1992**, *3*, 1089-1122; Godleski, S. A. *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991, Vol. 4, pp. 585-661. *Cf.* Bäckvall, J.-E. Ed.; "*Palladium in Organic Synthesis*," Tetrahedron Symposia-in-Print No. 52, *Tetrahedron* **1994**, *50*, 285-607.

5 SONY Tektronix CAChe System was used.

6 Although there have been several reports regarding the substitutive lactone ring-opening reaction catalyzed by Pd(0), this is the first example of a palladium-catalyzed lactone migration reaction. *Cf.* Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756-6758; Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730-4743; Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160-161; Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143-1145; Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749-1752; Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292-3303; Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192-1193.

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