JOC Article

1,2-Oxopalladation versus π-Allyl Palladium Route. A Regioconvergent Approach to a Key Intermediate for Cyclopentanoids Synthesis. New Insights into the Pd(II)-Catalyzed Lactonization Reaction†

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Regioconvergent synthesis of the key lactone **1** from an equimolar mixture of the two olefins **4** and **5** was achieved by unique Pd(II) chemistry. The synthetic versatility of lactone **1** has been demonstrated in the synthesis of iridoids and of the *endo*-Corey lactone **2**, which is a key intermediate for the F_2-isoprostane synthesis. Upon exposure of the sodium salts of **4** and **5** to a catalytic amount of $Pd(OAc)_2$ under oxygen, in the presence of AcOH, an isomeric lactone **12** was obtained in addition to the title compound **1**. The Pd(II) lactonization was optimized by fine-tuning all the factors participating in the catalytic cycle: solvent, oxidant, co-oxidant, and Pd(II) source. The Hosokawa's heterobimetallic couple emerged as the catalyst of choice. With a Cu(II)−Pd(II) couple, the redox process was transferred to copper, and the formal oxidation state of palladium remained constant during the reaction. By virtue of this new methodology, lactone **1** was obtained in a rewarding 60% yield, along with isomeric lactone **12** in 30% yield. A detailed mechanistic study was carried out in order to elucidate the formation of lactones **1** and **12**. Lactone **1** was formed from either olefin **8** or olefin **10**; on the other hand, lactone **12** was formed exclusively from olefin **10**. An intramolecular 1,2-acyloxypalladiation was invoked for the transformation of **8** into **1**, whereas the π-allyl complexes **13** and **11** were involved in the transformation of olefin **10** into **12** and **1**, respectively.

Introduction

Isoprostanes are naturally occurring prostaglandin-like compounds. They are produced on cellular membranes in the human body by a free radical peroxidation of arachidonic acid esterified to phospholipides, along a metabolic process not dependent on the cyclooxygenase isoenzymes COX-1 and COX-2. Roberts II and Morrow demonstrated the in vivo formation of isoprostanes, in mammals as well as in humans,[1] and they found that isolated isoprostanes were isomers of F_2-, D_2-, and E_2-prostaglandins.

The most significant feature of the nonenzymatic process of isoprostane formation is the relative *cis* stereochemistry of the two side chains on the cyclopentanone ring. Although most details of the mechanism of the *endo*-cyclization process of the peroxyradical are still unknown, this stereochemical outcome has been rationalized on the basis of the Beckwith−Houk model proposed for the transition state for 5-*exo*-radical cyclizations of 5-hexenyl radicals.[2]

In 1999, Morrow and Roberts II reported two new members of the isoprostane family, the cyclopentenone A_2- and J_2-isoprostane, which are produced in vivo by dehydration of E_2- and D_2-isoprostane, respectively.[3] Isoprostanes exhibit powerful biological activity as hormonal vasoconstrictors,[4] platelet aggregators, and inducers of cell-proliferation.[5] Moreover, the cyclopentenone prostaglandins exert unique antineoplastic, anti-inflammatory, and antiviral actions.[6] Isoprostanes are probably the most important examples of recently discovered *cis*-1,2-dialkyl-substituted cyclopentanoid derivatives.

As part of our efforts toward the synthesis of these intriguing natural products, we envisioned lactone **1** as a key building block worth the development of a practical synthetic route. The versatility of compound **1** has been

† Dedicated to Prof. Paola Vita Finzi on the happy occasion of her 70th birthday.

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(1) (a) Morrow, J. D.; Hill, T. M. K. E.; Burk, R. F.; Nammour, T. M.; Roberts, J. L., II. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9383. (b) Roberts, J. L., II; Morrow, J. D. *Biochim. Biophys. Acta* **1997**, *1345*, 121.

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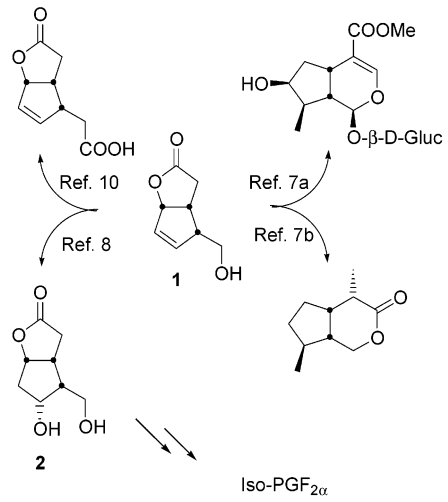
SCHEME 1



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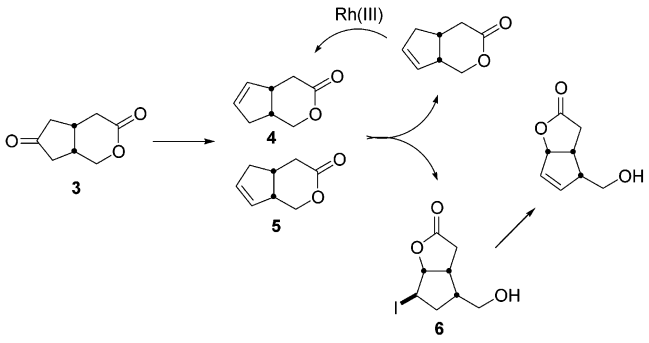
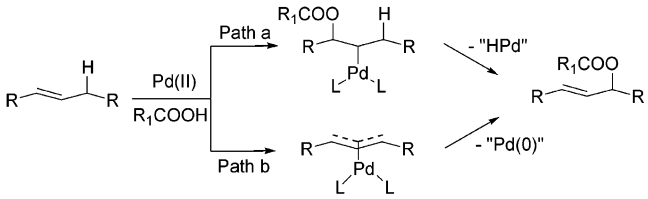


demonstrated in the synthesis of iridoids,[7] of compounds in the 12-oxophytodienoic cascade path, and of the *endo*-Corey lactone **2**,[8] which in turn paved the way for the total synthesis of biologically active F_2-isoprostanes (Scheme 1).[9]

In a previous report of ours,[10] we described a short and stereoselective synthesis of racemic lactone **1** starting from ketolactone **3**, in which the key step was the resolution of the ~1:1 inseparable mixture of olefins **4** and **5**, carried out by a regioselective iodolactonization reaction. Accordingly, only olefin **4** smoothly underwent iodolactonization (Scheme 2),[10] whereas unreacted olefin **5** was recovered and recycled to a mixture of **4** and **5** upon exposure to a Rh(III) salt. Lactone **1** was thus obtained in 30% overall yield.

In the pursuit of atom economy[11] and improvement of the overall efficiency of our approach, we explored a different synthetic sequence capable of maximizing the conversion of the two olefins **4** and **5** into the same lactone **1.** To this purpose, we focused our attention on a

SCHEME 3



Pd(II)-promoted lactonization reaction that could be considered as an intramolecular Pd(II)-catalyzed allylic oxidation.[12] For the intermolecular version of this reaction two mechanisms have been proposed: (1) a 1,2-acyloxypalladiation, immediately followed by β-hydride elimination (Scheme 3, path a),[13] and (2) an allylic C−H bond activation, with the formation of a π-allyl complex.[14] Intermolecular nucleophilic trapping of the π-allyl complex followed by fast β-hydride elimination led to the corresponding oxidation product (Scheme 3, path b).

By contrast, the mechanism of the Pd(II)-catalyzed lactonization reaction is still a subject of debate.[15] In strict analogy to the allylic oxidation, two different pathways have been proposed: either an intramolecular acyloxypalladiation or a π-allyl intermediate formation through the allylic C−H bond activation.[16] On the basis of this assumption, we anticipated that the C−H allylic activation would have converted both olefins **4** and **5** to the same π-allyl intermediate, which in turn accomplished the target compound after intramolecular carboxylate attack in an atom economical fashion (Scheme 4).

Results and Discussion

In accordance with our synthetic plan (Scheme 4), the sodium salts **8** and **10**[10] were treated with a catalytic amount of $Pd(OAc)_2$ in DMSO under an atmosphere of O_2.[17] The expected lactone **1** was obtained in a fair 43% yield, still accompanied by unreacted starting olefins (Table 1, entry 1).

We speculated that the basic conditions might have been detrimental to the catalytic activity of Pd(II) through the formation of insoluble $Pd(OH)_2$. Indeed, a free carboxylic acid and a weak base (NaOAc) were used in Larock's original procedure for the Pd lactonization.[16c] The main problem lies with the nature of the proton donor required to generate the two carboxylic acids **7** and **9**. This donor must be strong enough to protonate the

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(11) Trost, B. M. *Science* **1991**, *254*, 1471.

(12) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, U.K., 1995; p 37.

(13) L refers to a general Pd ligand such as a solvent or acetate anion.

(14) Grennberg, H.; Simon, V.; Bäckwall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 265.

(15) The palladium-lactonization reaction of conjugated dienes is known to proceed through the intermediacy of a π-allyl complex. See: (a) Bäckwall, J. E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, *30*, 137. (b) Bäckwall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.* **1993**, *58*, 5445.

(16) (a) Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1673. (b) Korte, D. E.; Hegedus, L.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329. (c) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (d) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (e) Annby, U.; Stenkula, M.; Andersson, C. M. *Tetrahedron Lett.* **1993**, *34*, 8545.

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SCHEME 4

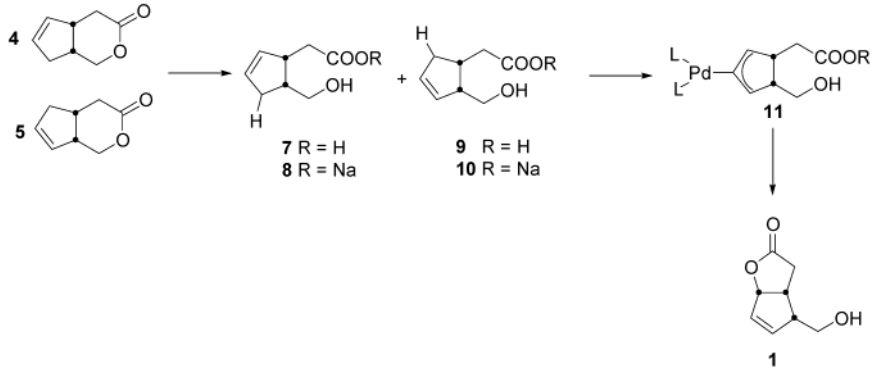


TABLE 1. Optimization of the Conditions for the Pd(II) Lactonization of Olefins 8 and 10

entry[a]	solvent	Pd source (10 mol %)	oxidant/ co-oxidant	yield of **1** (%)	yield of **12** (%)
1[b]	DMSO	$Pd(OAc)_2$	O_2	43[c]	
2	DMSO	$Pd(OAc)_2$	O_2	50	15
3[d]	MeOH/MeCN	$Pd(OAc)_2$	$NOBF_4$	30	
4	MeOH/MeCN	$Pd(OAc)_2$	DDQ	*e*	
5	MeOH/MeCN	$Pd(OAc)_2$	$Cu(OAc)_2$[f]	30[g]	
6	MeOH/MeCN	$Pd(OAc)_2$	$O_2/Cu(OAc)_2$[h]	60	30
7	MeOH/MeCN	$PdCl_2$	$CuCl_2$[h]	20	
8	MeOH/MeCN	$PdCl_2$	$O_2/CuCl_2$[i]	55	25
9[b]	MeOH/MeCN	$Pd(OAc)_2$	$O_2/Cu(OAc)_2$	45	

[a] Unless otherwise noted, AcOH (1.1 equiv) was used as a proton source. Run time was 12 h. [b] Without AcOH. [c] Unreacted olefins **4** and **5** were recovered (10% yield). [d] Ketolactone **3** was obtained in 15% yield. [e] Decomposition of starting olefins. [f] 1.1 equiv of $Cu(OAc)_2$. [g] Extensive relactonization to olefins **4** and **5** was observed. [h] 1.1 equiv. [i] 0.1 equiv.

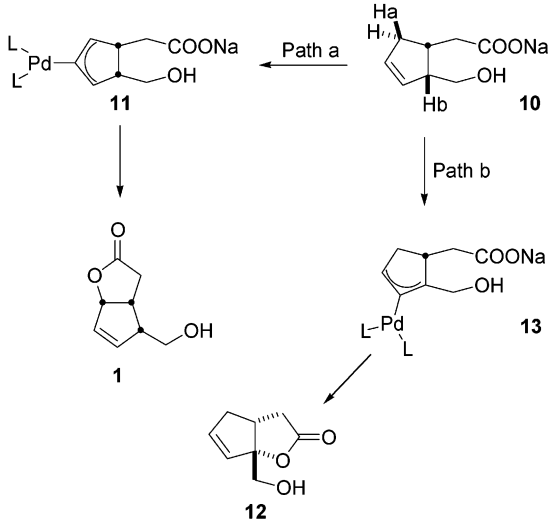
two carboxylates but not so strong as to promote the relactonization of **7**, **9** to **4**, **5**. After some experimentation, acetic acid emerged as the proton source of choice for this reaction. Under these conditions, the desired lactone **1** was thus obtained in 50% isolated yield (entry 2). Not surprisingly, besides lactone **1,** an isomeric lactone **12** was also obtained, albeit in a lower 15% yield. The structure of this new lactone was unequivocally established by single crystal X-ray diffraction analysis.

At first glance, formation of lactone **12** could be explained through the intermediacy of a π-allyl complex **13**, derived from olefin **10** with a different regiochemistry from that of the expected π-allyl complex **11**. In other words, the allylic C−H activation could occur at the ring junction carbon (Scheme 5, path b) instead of involving the ring methylenic carbon (Scheme 5, path a).

Elicited by these promising preliminary results, we addressed two major issues in order to optimize the conversion of both olefins **4** and **5** into lactone **1**. First, the Pd(II) catalyst species was to be kept active and in solution throughout the entire catalytic cycle. Second, the regiochemistry of the allylic C−H activation (therefore, the π-allyl complex formation) had to be controlled. The former issue required a fine-tuning of all factors participating in the cycle, namely the solvent, the oxidant, the co-oxidant, and the Pd(II) source. Optimization efforts in this context are herein reported.

Solvent. In the Pd(II)-promoted lactonization protocol described by Larock,[16c] DMSO plays a crucial role for the success of the reaction as stabilizing ligand for the giant

SCHEME 5



palladium cluster, the actual allyl-active Pd species present in solution, as already described by Speckcamp.[17] In the presence of DMSO, dissolved O_2 is able to reoxidize Pd(0) to Pd(II) so that Pd-black does not precipitate out. However, DMSO suffers from some disadvantages, such as a high boiling point and a fairly high solubility in almost all the organic solvents except Et_2O and hexane, in which lactone **1** was almost insoluble, thus making a routine aqueous workup rather troublesome. We found out that a better alternative to DMSO was a 3:2 mixture of MeOH and MeCN, able to both dissolve the sodium salts **8** and **10** and retain the Pd(II) salt in solution throughout the entire catalytic process (entries 3−8), possibly because of the weak coordinating property of the cyano group toward Pd(II).[18] With MeOH alone, a gradual precipitation of metallic palladium was observed.

Oxidant and Co-oxidant.[19] The use of MeOH/MeCN instead of DMSO as solvent requires a reoxidant to keep the process catalytic in palladium. The employment of classical stoichiometric oxidants such as MnO_2, BQ, *t*-BuOOH, $LiNO_3$, and $K_3[Fe(CN)_6]$ gave disappointing results.[20] In the presence of the powerful oxidizing agent $NOBF_4$, the ketolactone **3** was obtained only in very low

(18) Hartley, F. R. *The Chemistry of Platinum and Palladium*; Applied Science Publishers LTD: London, 1973.

(19) In all of the experiments, $Pd(OAc)_2$ was used as a Pd(II) source.

(20) (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, U.K., 1995; p 19. (b) McMurry, J. E.; Koèovso, P. *Tetrahedron Lett.* **1984**, *25*, 4187.

yield (entry 3), whereas extensive decomposition was observed with DDQ (entry 4). On the other hand, both $CuCl_2$ and $Cu(OAc)_2$ in stoichiometric amounts gave the products of relactonization **4** and **5**, along with lactone **1** in low yield (entries 5 and 7). Then, we turned our attention to copper(II) used as a co-oxidant in catalytic amount. In this context, in 1981, Hosokawa et al. reported a Pd(II)-catalyzed asymmetric oxidative cyclization of 2-allylphenols using a catalytic combination of $Cu(OAc)_2$ and $Pd(OAc)_2$ in MeOH under O_2.[21] The authors demonstrated that the active catalytic species is a heterobimetallic Cu(II)−Pd(II) couple, linked via μ-acetate and -peroxo ligands. This bimetallic complex prevents the decomposition of the Pd−H intermediate (see Scheme 3) and accelerates the oxygenation of the Pd−H bond by O_2.[22] In other words, the oxidation process is transferred from palladium to copper, and the formal oxidation state of Pd(II) remains constant during the reaction. The heterobimetallic couple is formed in situ by adding equimolar amounts of $Cu(OAc)_2$ and $Pd(OAc)_2$, with Cu(II) acting as the co-oxidant and O_2 as the stoichiometric oxidant. When the sodium salts **8** and **10** were exposed to the heterobimetallic couple in the MeOH/MeCN solvent mixture under a stream of O_2, the desired lactone **1** was obtained in a gratifying 60% isolated yield, in addition to a 30% yield of the isomeric lactone **12** (entry 6).

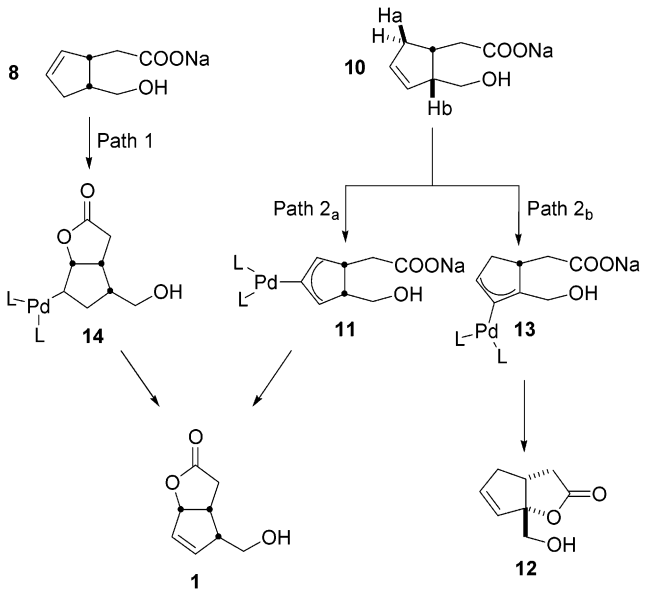
Pd(II) Source. With this efficient catalytic system in hand, other Pd(II) sources were then explored, including $Pd(CF_3COO)_2$, $PdCl_2$, Li_2PdCl_4, and allylpalladium(II)-chloride dimer. The first tried $Pd(OAc)_2$ proved to be superior, giving a complete consumption of the two olefins within 12 h.

Regiochemical Control of the C−H Allylic Activation. As from relevant literature precedents, the regiochemistry in the formation of π-allyl complexes can be dictated either by kinetics or by thermodynamics.[23] In the former case, the presence of $CuCl_2$ or of acetate buffer (as in our standard conditions) could affect the regioselectivity of hydrogen abstraction.[24] However, in our hands, the couple $PdCl_2$−$CuCl_2$, either in equimolar (entry 7) or in catalytic amount (entry 8), did not improve the ratio between **1** and **12**. Moreover, yields with the $PdCl_2$ system alone were not reproducible.

In summary, the optimized reaction was carried out under a stream of O_2 in a 3: 2 MeOH/MeCN mixture, in the presence of $Pd(OAc)_2$ (0.01 equiv), $Cu(OAc)_2$ (0.01 equiv), and AcOH (1.1 equiv). The reaction proceeded smoothly at room temperature and provided lactones **1** and **12** in 60% and 30% isolated yields, respectively.

Mechanistic Considerations. Pd(II)-mediated lactonization reactions of unsaturated carboxylic acids are generally assumed to proceed through two different mechanisms, either via an intramolecular 1,2-acyloxypalladiation or via π-allyl complex formation by allylic C−H activation. Conclusive evidence has not been yet

SCHEME 6



brought forth in favor of either mechanism. In this report, we provide some evidence for the coexistence of both mechanisms. The intramolecular 1,2-acyloxypalladiation is operative in the transformation of olefin **8** into lactone **1** (Scheme 6, path 1), whereas the π-allyl complex is responsible for the formation of **1** from olefin **10** (Scheme 6, path 2_a). Moreover, the formation of isomeric lactone **12** can be rationalized by assuming the intermediacy of π-allyl complex **13** (Scheme 6, path 2_b). Some experimental findings support the mechanism depicted in Scheme 6.

(A) Mechanism for the Formation of Lactone 12. Lactone **12** is formed exclusively from olefin **10**, since the regioisomerically pure olefin **8**[8] gave lactone **1** as the only isolated product in almost quantitative yield upon exposure to the Pd(II)−Cu(II) heterobimetallic couple.

The observed regioselectivity for the formation of π-allyl complexes **11** and **13** seems to be in contrast with the rules proposed by Trost for π-allyl complex formation.[24] According to these rules, π-allyl complex **11** was predicted to be preferred to **13**. Conversely, by reacting pure olefin **10**[10] under our standard Pd(II)-lactonization protocol, lactones **1** and **12** were obtained in a 3:7 ratio. Electronic and conformational factors can alter the selectivity predicted by the Trost rules. This is the case for olefin **10**, in which a coordination of Pd(II) with the hydroxyl group could direct the formation of the π-allyl complex (Figure 1).[25]

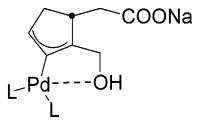
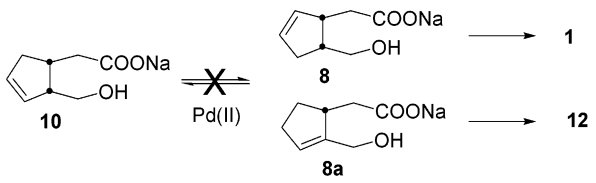


FIGURE 1. Hydroxyl-directed π-allyl formation.

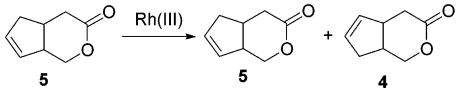
(B) Mechanism for the Formation of Lactone 1. Olefin **10** is believed to give rise to lactone **1** through the intervention of the π-allyl complex **11**. Pd(II) salts are

(21) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.
(22) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49.
(23) In our case, it was not possible to set thermodynamic conditions, which required an AcOH solution of $PdCl_2$ at 90 °C. See: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.
(24) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.
(25) Tamaru, Y.; Higashimura, H.; Naka, K.; Hojo, M.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1045.

SCHEME 7



SCHEME 8



known to induce double bond isomerization,[26] and an in situ isomerization of olefin **10** to **8** could be an alternative pathway (Scheme 7). Such isomerization has been observed upon exposing olefin **5** to Rh(III) in boiling EtOH (Scheme 8).[10] The formed olefin **8** could then undergo the intramolecular 1,2-acyloxypalladiation to give lactone **1** (Scheme 6, path 1). In a similar way, isomerization of **10** to **8a**, followed by 1,2-acyloxypalladiation, could lead to **12**.

However, these paths can be ruled out since regioisomerically pure olefin **5**[10] could be recovered unchanged when added to the reaction medium set for the Pd(II) lactonization of olefins **8** and **10**.

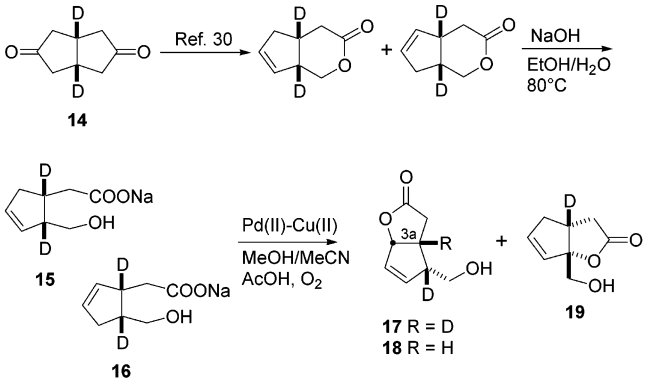
In contrast with the behavior of olefin **10**, the regioisomeric olefin **8** afforded lactone **1** solely via a 1,2-acyloxypalladiation mechanism, and the intermediacy of a π-allyl complex is excluded for the following reasons.

(1) When an equimolar mixture of **8** and **10** was reacted with the Pd(II)−Cu(II) couple in the absence of AcOH in MeOH/MeCN (entry 9), an incomplete conversion was observed. Unreacted starting material was isolated in 45% yield as a 3:1 mixture of **5** and **4**, thus indicating a faster comsumption of olefin **8**. The difference in reactivities of **8** and **10** toward Pd(II) seems unlikely if both olefins are assumed to react by the same mechanism through intermediate **11**; therefore, two different mechanisms are responsible for the transformations of **8** in **1** and **10** in **1**. The former reaction is obviously faster than the latter, which entails the rupture of a C−H bond as the determining step.

(2) After exposing the bis-deuterated olefins **15** and **16** to the Pd(II)-lactonization reaction conditions, neither loss nor scrambling of deuterium atoms was observed in the corresponding lactones **17** and **19** (Scheme 9). Olefins **15** and **16** were readily prepared from known bis-deuterated diketone **14**[27] (87% of deuterium content), following our standard procedure.[28] The lactone **17** obtained from the Pd(II)−Cu(II) couple showed the same 87% deuterium content as that of diketone **14**.

In the event of a π-allyl Pd complex intermediacy in the transformation of **8** to **1**, a complex scenario of equilibrating π-allylic complexes would be expected (Scheme 10), with a consequent loss and/or scrambling of D atoms.[29] The key point for the deuterium loss is the Cu(II)-assisted decomposition of the palladium deuteride

SCHEME 9



intermediate **20** with subsequent formation of the unproductive π-allyl complex **21**.[24] Acetic acid protonation of **21** would give the hydride complex **22**, which in turn would afford the mono-deuterated lactone **18**; the net result would be the loss of D at C-3a in lactone **17** to give the never observed compound **18** (Scheme 9). Conversely**,** scrambling of deuterium atoms was reported to occur in the π-allyl-mediated alkene isomerization.[30]

Conclusions

In summary, we have developed an atom-economical synthesis of the versatile lactone **1** from easily achievable olefins **4** and **5**, using a catalytic combination of $Pd(OAc)_2$ and $Cu(OAc)_2$. A clear mechanistic picture of the Pd(II)-lactonization reaction has been described for the first time. Two different mechanisms cooperate to transform the inseparable mixture of olefins **4** and **5** into the desired compound in a 60% satisfactory yield. According to our experimental findings, intramolecular 1,2-acyloxypalladiation was the energetically preferred pathway for the Pd(II)-promoted lactonization reaction (e.g., starting from olefin **8)**. However, allylic C−H bond activation and consequent π-allyl formation were operative in an alternative pathway on substrates where 1,2-acyloxypalladiation is prevented, as in olefin **10**.

Though more complicated mechanistic rationales (see Schemes 7 and 10) cannot be excluded, there is no evidence so far supporting such possibilities. The Ockham's Razon otherwise inspired the simplified scenario represented by Scheme 6: "*That which is explained with the assumption of fewer things is explained in vain by the assumption of more things*".[31]

Experimental Section

Crystallographic data for the lactone **12** have been deposited with the Cambridge Crystallograpic Data Centre and allocated the deposition number CCDC 178234. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB1EZ, U.K. (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

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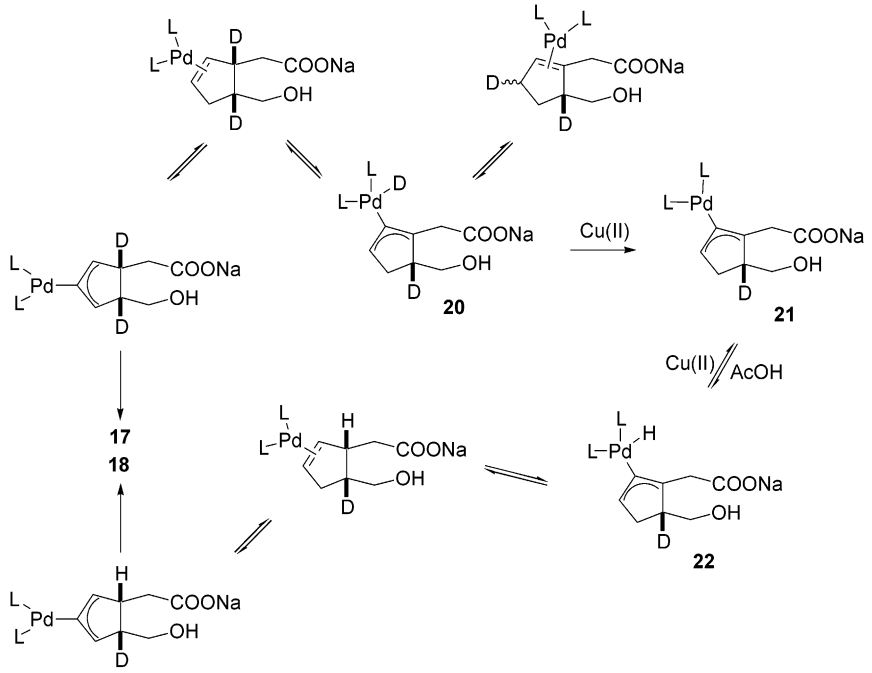
SCHEME 10



Optimized Procedure for the Pd(II)-Lactonization Reaction. In a three-neck round-bottom flask, equipped with a gas-inlet system, a double surface condenser, and a silicon septum, the sodium salts **8** and **10** (14.48 g, 25 mmol) were dissolved in MeOH (43 mL). MeCN (28 mL) and AcOH (1.1 equiv) were then added with stirring, while O_2 was bubbled in the reaction mixture (3 mL min^{-1}). The heterobimetallic couple was then prepared, dissolving $Pd(OAc)_2$ (0.032 g, 0.145 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.030 g, 0.145 mmol) in MeCN (5 mL). The emerald solution thus obtained was stirred under oxygen for 15 min and then was added via cannula to the substrate solution. The resulting mixture was stirred under a stream of O_2 for 18 h. Solvents were evaporated under vacuum, and the brown residue was dissolved in AcOEt and filtered. The organic phase was washed with brine and dried over $MgSO_4$. Rotary evaporation of the volatiles left a crude residue as a yellow oil, which was purified by flash chromatography on silica gel (100 g). Elution with hexanes/EtOAc (1:1) gave lactone **1** as a colorless oil (1.3 g, 60%) and lactone **12** (0.67 g, 30%).

Spectroscopic data for 4-hydroxymethyl-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one, **1**, have been already reported.[10]

Spectroscopic Data for 6a-Hydroxymethyl-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one, 12: mp 28−29 °C; IR (liquid film) ν 3424, 2936, 1758, 1222, 1049, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (dd, J = 17.5 and 2.5 Hz, 1H), 2.39 (m, 1H), 2.83 (ddt, J = 17.5, 8.0, and 2.3 Hz, 1H), 2.98−3.10 (m, 2H), 3.39 (d, J = 12.5 Hz, 1H), 3.58 (d, J = 12.5 Hz, 1H), 5.75 (dt, J = 6.0 and 2.3 Hz, 1H), 6.10 (dt, J = 6.0 and 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9 (C), 137.9 (CH), 129.0 (CH), 101.4 (C), 65.1 (CH_2), 39.6 (CH_2), 37.5 (CH_2), 26.9 (CH). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54; O, 31.13. Found: C, 62.41; H, 6.55. HRMS calcd for $C_8H_{10}O_3$ 154.0630. Found 154.060 27. The deuterium contents were calculated according to ref 27 using the formula % $d = 100(d_1 + 2d_2)/2(d_0 + d_1 + d_2)$.

Lactonization reactions on bis-deuterated compounds **15** (87% D) and **16** (87% D) were carried out following the above experimental procedure.

Spectroscopic Data for 4-Hydroxymethyl-3a,4-dideutero-3,6a-dihydrocyclopenta[*b*]furan-2-one 17: IR (liquid film) ν 3426, 2932, 1766, 1268, 1100, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (d, J = 2.5 Hz, 2H), 3.15 (bs, 1H), 3.62 (d, J = 12.5 Hz, 1H), 3.73 (d, J = 12.5 Hz, 1H), 5.46 (bd, J = 2.5 Hz, 1H), 5.97 (dd, J = 2.5 and 6 Hz, 1H), 6.02 (dd, J = 1 and 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1 (C), 138.4 (CH), 129.5 (CH), 88.9 (CH), 61.2 (CH_2), 48.9 (CH), 38.8 (CH), 29.5 (CH_2). HRMS calcd for $C_8H_8D_2O_3$ 156.0753. Found 156.0749. % of deuterium contents: 87%.

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Supporting Information Available: Unit cell parameters and intensity X-ray data; ^1H NMR, ^{13}C NMR, and DEPT data for compound **12**; and ^1H NMR and ^{13}C NMR data for compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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