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Neighboring Group Effect in Pd-Catalyzed Carbonylation Terminated by Lactonization: A Need for a Protective Group and/or DMF†

Radan Schiller,‡ Milan Pour,‡,* Helena Fáková,‡ Jiří Kuneš,‡ and Ivana Císařová§

Laboratory of Structure and Interactions of Biologically Active Molecules, Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic, and Department of Inorganic Chemistry, Faculty of Sciences, Charles University, Albertov 6, CZ-118 23 Prague, Czech Republic

pour@faf.cuni.cz

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Synthesis of analogues of antifungal podolactones via Pd-catalyzed processes revealed that tandem 6-*exo*-alkyne carbopalladation/carbonylative lactonization sequence is strongly solvent-dependent. Contrary to earlier reports, premature esterification was the predominant pathway when the starting enynes derived from (*Z*)-2-iodohex-2-en-1,4-diol were subjected to Pd-catalyzed carbonylation in MeOH. Apparently, irreversible complexation of Pd by the OH group prevented decarbonylation and hence 6-*exo*-alkyne carbopalladation. Similarly, the influence of the chelation was also evident when the reaction was applied to the analogous preparation of 3-hydroxymethylbutenolides. The neighboring group effect can be efficiently overcome through using DMF as the solvent in combination with protection of the OH function.

Introduction

In the course of exploring antifungal properties of analogues of natural butenolides, we found that the presence of an unsaturated γ-lactone moiety in combination with a halogen-substituted phenyl ring (structure **1**) attached to the α-position is essential for a compound to display significant antifungal activity.[1] Following on from these results, we became interested in elucidating the properties of δ-lactones bearing a similar substitution, since literature reports indicated that structurally related pyranones would highly likely exhibit the same biological effect. Most notably, Barrero et al. concluded[2] that the presence of the 7,9(11)-dien-12,17-olide moiety in podolactones and related compounds, exemplified by **2**, is the structural feature responsible for their antifungal activity, and the structure of another potent natural antifungal,[3] CR 377 (**3**), is based on 5-methylene-5,6-dihydro-2*H*-pyran-2-one. Thus, we assumed that biological evaluation of simple analogues of type **4** and **5** will provide further insight into the origin of antifungal activity of podolactone-related compounds.

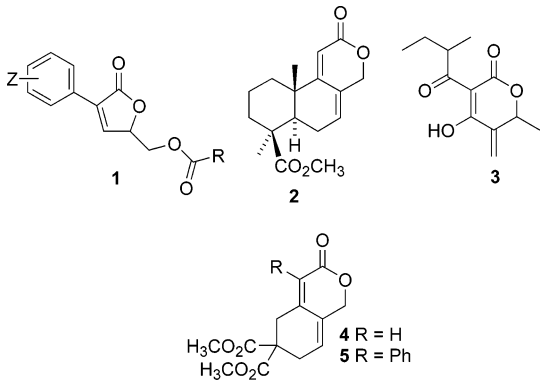

FIGURE 1. Selected butenolides and pentenolides with antifungal activity.

In choosing compounds **4** and **5** for a large-scale synthesis and biological screening, we were guided by two requirements. First, consistent with the natural products, the analogues must incorporate the above structural features, and, second, they should be preparable in quantities, sufficient for extensive pharmacological evaluation, as economically as possible. While both compounds possess the dienolide function, lactone **5** has also a phenyl ring attached to the α-position of the functional group, as in butenolides of type **1**. As regards the latter requirement, these compounds would be easily accessible via intramolecular carbopalladation/carbonylative lactonization of easy-to-make enyne precursors, a sequence, the

* Corresponding author.

† Dedicated to Professor Lew Mander on the occasion of his 65th birthday.

‡ Department of Inorganic and Organic Chemistry.

§ Department of Inorganic Chemistry

(1) (a) Pour, M.; Špulák, M.; Balšánek, V.; Kuneš, J.; Buchta, V.; Waisser, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1893. (b) Pour, M.; Špulák, M.; Buchta, V.; Kubanová, P.; Vopršalová, M.; Wsól, V.; Fáková, H.; Koudelka, P.; Pourová, H.; Schiller, R. *J. Med. Chem.* **2001**, *44*, 2701. (c) Pour, M.; Špulák, M.; Balšánek, V.; Kuneš, J.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843. (d) Buchta, V.; Pour, M.; Kubanová, P.; Silva, L.; Votruba, I.; Vopršalová, M.; Schiller, R.; Fáková, H.; Špulák, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 873.

(2) Barrero, A. F.; Arseniyadis, S.; Quílez del Moral, J. F.; Mar Herrador, M.; Valdivia, M.; Jiménez, D. *J. Org. Chem.* **2002**, *67*, 2501.

(3) Brady, S. F.; Clardy, J. *J. Nat. Prod.* **2000**, *63*, 1447.

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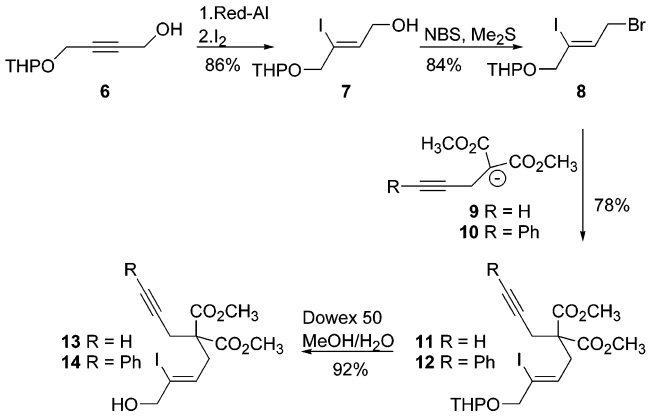
development of which is connected with the contributions of E. Negishi and his group as well as some others.[4]

Results and Discussion

The preparation of enynes **13** and **14** is outlined in Scheme 1. Hydroalumination of THP-protected but-2-yn-

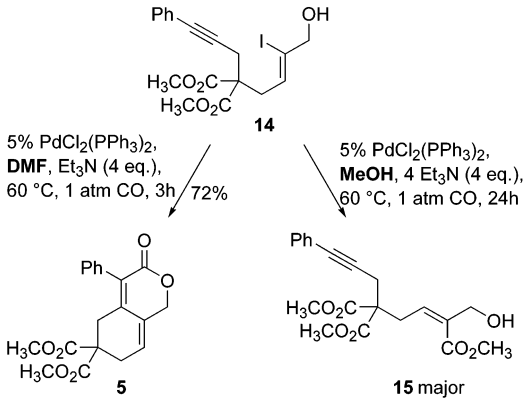
SCHEME 1. Preparation of Carbopalladation/ Carbonylative Lactonization Precursors



1,4-diol **6** with Red-Al terminated by iodination[5] afforded alkenyl iodide **7**. The hydroxy group in compound **7** was converted, instead of the somewhat unstable mesylate,[6] into the bromo substituent with NBS/Me_2S.[7] The resultant derivative **8** was again formed in high yield[8] and was stable enough to be purified by conventional column chromatography. Finally, compound **8** readily furnished enynes **11** and **12** on treatment with carbanions **9** and **10**, respectively (anion **10** was generated from dimethyl-(3-phenylprop-2-yn-1-yl)malonate, prepared via standard Sonogashira coupling from dimethyl-propargylmalonate, see Supporting Information), and the hydroxy group was liberated by hydrolysis.

Following the finding[4b] that in similar reactions, methanol proved to be a highly satisfactory solvent, superior to, e.g., DMF, THF, and others, enynes **13** and **14** were subjected to standard carbonylation at 1 atm CO in MeOH (Scheme 2). In our hands, however, several

SCHEME 2. Tandem Carbopalladation/ Carbonylative Lactonization of 14 in MeOH and DMF



attempts to reproduce the cyclization[4b] of the known enyne **13** with a terminal triple bond resulted only in obtaining polymeric material. Surprisingly, cyclization of enyne **14** turned out to be an extremely sluggish reaction (ca. 50% conversion after 24 h), affording one major product. Contrary to previous reports,[4b] the material was identified as a 4:1 mixture of the product of premature esterification **15** and the desired lactone **5**, extremely difficult to separate by column chromatography. The structure of the major triester **15** was evident from one-dimensional NMR spectra: the carbons of the triple bond at 84.1 and 83.9 ppm were clearly apparent in the ^{13}C spectrum, while a new singlet of a methyl ester group appeared at 3.72 ppm in the ^{1}H spectrum. Since our experience hinted at a possible negative role of the hydroxy function in the vicinity of the reaction center, the reaction was run in DMF[9] as the solvent. In this case, the desired bicyclic compound was obtained in 72% yield in a mere 3 h.

The structure of unsaturated lactone **5** was unequivocally corroborated by X-ray (Figure 2). The cyclization of

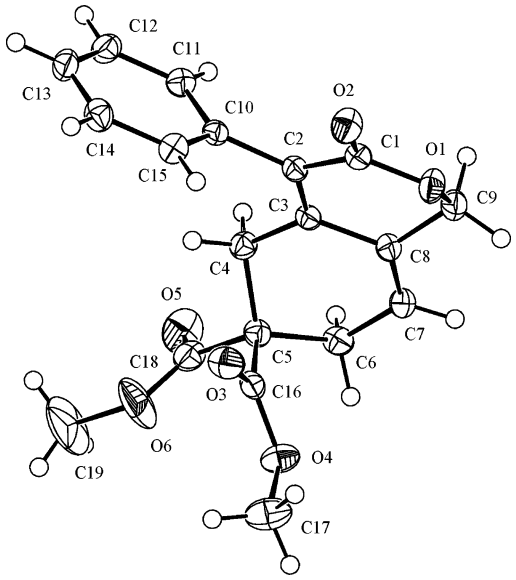


FIGURE 2. X-ray structure of dienolide **5**.

14 was also attempted in *i*-PrOH as a solvent and under the conditions described by Stille[10] (THF, K_2CO_3, NH_2NH_2). The use of *i*-PrOH[11] led to a complex mixture of products, while no reaction was observed in the latter case.

(4) (a) For a review, see: Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E.-i. *J. Am. Chem. Soc.* **1994**, *116*, 7923. (c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

(5) (a) Denis, R. C.; Gravel, D. *Tetrahedron Lett.* **1994**, *35*, 4531. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(6) Treatment of (*Z*)-3-iodo-4-triphenylmethoxybut-2-en-1-ol with MsCl afforded the corresponding mesylate in 40% isolated yield; see: Copéret, C.; Ma, S.; Sugihara, T.; Negishi, E.-i. *Tetrahedron* **1996**, *52*, 11529.

(7) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

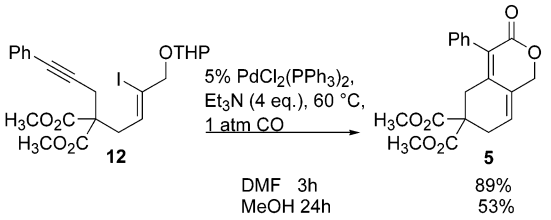
(8) Piers et al. obtained nearly the same results on treatment of (*Z*)-3-iodo-4-benzyloxybut-2-en-1-ol, prepared via a different route, with $Ph_3P{\cdot}Br_2$/imidazole; see: Piers, E.; Harrison, C. L.; Zetina-Rocha, C. *Org. Lett.* **2001**, *3*, 3245.

(9) DMF has been shown to be one of the most desirable solvents for Pd-catalyzed cross-coupling reactions (Negishi, E.-i.; Owczarczyk, Z.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4456) and has been frequently used in carbonylation reactions as well.

(10) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

Encouraged by these results, we subjected the THP-protected enyne **12** to the same cyclization conditions. This time, lactone **5 was the sole product regardless of the solvent used**; time and yield was the only difference[12] (Scheme 3). When DMF was employed as the

SCHEME 3. Tandem Carbopalladation/ Carbonylative Lactonization of Protected Compound 12 in MeOH and DMF

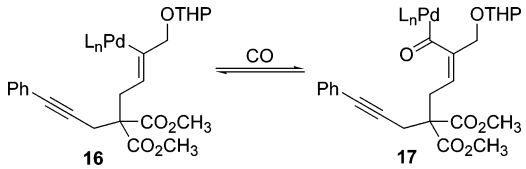


solvent, the yield was significantly higher (by 17%) as compared to the cyclization of enyne **14** with the OH function free.

Thus, the preparation of **5** was cut by one step, and the smooth cyclization of the protected compound brought further evidence of the unfavorable influence of the OH group.

The results obtained with DMF as the solvent and/or with the OH group protected can be interpreted in terms of the well-documented reversibility of CO insertion. With an equilibrium between **16** and **17** being established, the major reaction pathway is dictated by the relative rates of the subsequent conversions of the vinyl- and acylpalladium species[4b,13] (Scheme 4). Consequently, the fast

SCHEME 4. Equilibrium between Alkenylpalladium Species 16 and Acylpalladium Intermediate 17



6-*exo*-alkyne carbopalladation opens up the channel leading to **5**, while trapping acylpalladium species **17** with a solvent nucleophile proceeds at a negligible rate. Importantly, the reversibility of the CO insertion step also indicates that a possible stabilization of **17** arising from O to Pd coordination (vide infra), if any occurs at all, is very weak.

It was interesting but not totally surprising that the acetal protective group constituted no obstacle to lactonization and was deprotected under the reaction conditions that were essentially basic, with the yield of lactone **5** having been higher than in the cyclization of **14**. While it is tempting to speculate that the cleavage of the THP group in the acylpalladium species **18** is assisted by Pd^{II}, the above conclusion that the chelation ability of THP-protected oxygen is very low even if a relatively stable 5-membered complex (see Scheme 6) could be formed

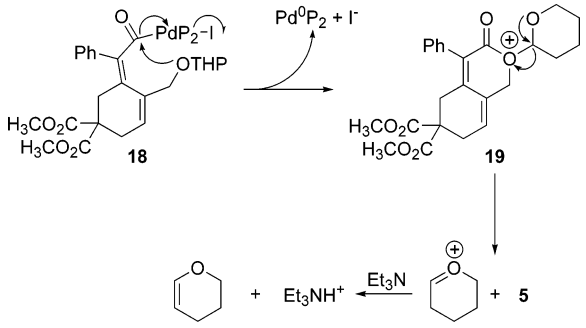
(11) See the literature in ref 6.

(12) In MeOH as the solvent (53% yield), the rest was recovered starting material.

(13) For the most recent results supporting this view, see also: Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423.

renders this assumption very unlikely. A plausible mechanism (Scheme 5) probably involves a direct nucleophilic

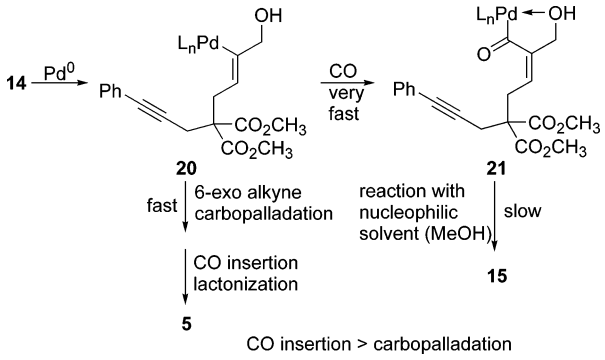
SCHEME 5. Possible Mechanism of THP Deprotection



displacement of Pd, enabled by the lability of the C(O)−Pd bond, which results in the regeneration of Pd^0. The protective group is then cleaved, with this process being boosted by the assistance of the oxygen in the tetrahydropyranyl ring, and, finally, the resultant cation is quenched by the reaction with Et_3N. Similarly, Larock has shown[13] by converting 2-iodoanisole into 3,4-dipropylcoumarin in the presence of oct-4-yne that even a methoxy group can be deprotected under carbonylative lactonization conditions. In that case, the need of a direct nucleophilic attack for the methyl group to be sequestered was probably the only difference from the cleavage of the THP moiety described herein. Thus, it is more than likely that a similar mechanism would also operate for all those protective groups, which do not substantially reduce the nucleophilicity of the protected oxygen atom (acetals, silyl groups, etc.). For this reason, the cleavage of acyl groups (see Scheme 8) in these reactions is improbable.

On the other hand, when the OH function is free and a less coordinating solvent is employed in the carbonylative lactonization process, it is highly likely that there is no equilibrium between alkenylpalladium **20** and acylpalladium species **21** due to the formation of a relatively stable five-membered cyclic complex, arising from the coordination of the OH group to Pd (Scheme 6).

SCHEME 6. Prevention of Decarbonylation by the Formation of Chelate 21

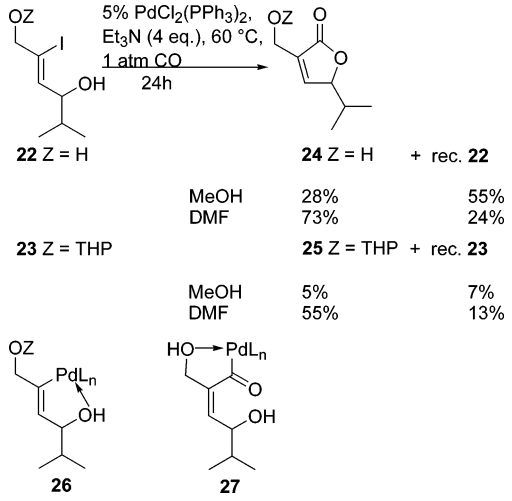


Given the fact that 6-*exo* intramolecular carbopalladation is a fast process, the isolation of **15** as the major product of the reaction of **14** in MeOH indicates that (1) the complexation is an irreversible process and (2) CO insertion must be faster than intramolecular carbopalladation, even at 1 atm CO. With CO being "locked" as a

consequence of complex formation, **21** has no choice but to undergo a slow decomposition by an external nucleophile (carbonylation of **14** in MeOH, vide supra) or remain unchanged in the reaction mixture (carbonylation of **14** in THF, vide supra). The picture outlined in Scheme 6 complements the conclusions (Scheme 4), valid in those cases[4b,13] where the equilibrium between vinyl- or aryl- and acylpalladium intermediates exists. In this instance, decarbonylation is prevented and the rate of CO insertion versus that of intramolecular carbopalladation governs the composition of the reaction mixture.

With a view to obtaining further experimental support for chelate formation, we turned our attention to more simple vinyl iodides **22**, **23**, and **28**, because they possess the same structural features giving rise to chelate formation as **11**−**14**, and subjected them to carbonylation in both DMF and MeOH under otherwise identical conditions. Apart from having different protective group patterns that offer interesting possibilities of complex formation, the carbonylation of compounds **22** and **23** would furnish 3-hydroxymethylbutenolides, potentially useful as synthetic intermediates. Compound **23** was prepared via hydroalumination/iodination of 2-methyl-6-(tetrahydropyran-2-yloxy)hex-4-yn-3-ol[14] (see Scheme 1) and converted into its derivatives **22** and **28** by standard deprotection and acetylation, respectively. As expected, carbonylation of iodo alcohols **22** and **23** (Scheme 7) brought further evidence of O to Pd chelation

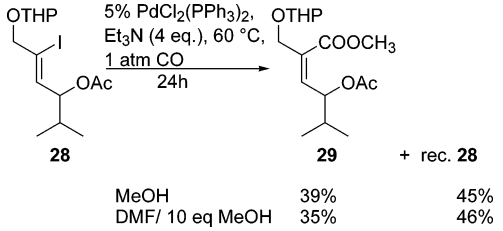
SCHEME 7. Carbonylation of Butenolide Precursors 22 and 23



in Pd-catalyzed reactions: while the formation of complex **26** may occur in both cases, CO insertion is apparently facilitated through another complex formation (**27**) only when the second OH group remains free. Consequently, carbonylations of diol **22** gave significantly higher yields of the butenolide product[15] than those of **23**, and the reaction of monoprotected compound **23** in MeOH was synthetically useless, since most of the starting material underwent decomposition.

On the other hand, the bis-protected compound **28** offered very low, if any, chance of O to Pd chelation as well as participation by the ether oxygen as an internal

SCHEME 8. Carbonylation of Bis-Protected Compound 26



nucleophile. Accordingly, a slow external trapping of the acylpalladium intermediate[16] with MeOH in a sterically demanding environment leading to ester **29** was the predominant pathway both in MeOH and DMF with 10 equiv of MeOH, as shown in Scheme 8.

Some literature results provide further support for the assumption on the formation of five-membered *σ*-acylpalladium complexes as intermediates in the Pd-catalyzed carbonylative lactonizations (Figure 3). Thus, Hegedus

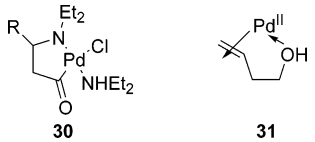


FIGURE 3. Examples of the formation of five-membered Pd chelates.

and others[17] explored aminocarbonylation of olefins and showed that Pd forms analogous *β*-aminoacylpalladium-(II) chelates (**30**) through the coordination of N to Pd. Having been much more stable than the oxygen analogues described herein, the complexes could be isolated and characterized by X-ray. Closely related *σ*-alkylpalladium complexes were also isolated and characterized, if they were part of a five-membered chelate ring.[18] In a similar case, Kočovský and co-workers[19] reported a convincing example of steering the attack on a double bond by the precoordination of the metal to a neighboring OH group (**31**).

Conclusion

In summary, we have described the influence of the free hydroxy function, arising from the complexation of

(14) Kimura, M.; Tanaka, S.; Tamaru, I. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689.

(15) Similar *β*-hydroxyalkylbutenolides were prepared by Hoye et al. under the Stille carbonylation conditions, see: Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

(16) In this case, the initially formed alkenylpalladium intermediate could have been stabilized by the chelation of the carbonyl oxygen to Pd, even though it should be noted that a seven-membered chelate ring would thus be formed. This kind of stabilizing effect has been proposed by Maleczka et al. to explain the regioselectivity of Pd-mediated hydrostannations of terminal alkynes; see: Rice, B. M.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E., Jr. *Synthesis* **2001**, 1495.

(17) (a) Hemmer, H.; Rambaud, J.; Tkatchenko, I. *J. Organomet. Chem.* **1975**, *97*, C57. (b) Hegedus, L. S.; Anderson, O. P.; Zetterberg, K.; Allen, G.; Siirala-Hansen, K.; Olsen, D. J.; Packard, A. B. *Inorg. Chem.* **1977**, *16*, 1887.

(18) (a) See ref 17a. (b) Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 485. (c) Cope, A. C.; Kliegman, M.; Friedrich, E. C. *J. Am. Chem. Soc.* **1967**, *89*, 287. (d) Holton, R. A.; Kjonaas, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 4177. (e) Holton, R. A.; Kjonaas, R. A. *J. Organomet. Chem.* **1977**, *142*, C15.

(19) Kočovský, P.; Dunn, V.; Gogoll, A.; Langer, V. *J. Org. Chem.* **1999**, *64*, 101.

the OH group to Pd, in Pd-mediated carbonylations. Even though the resultant chelates are mere intermediates in these reactions, they are stable enough to influence the rate and even prevent the reversibility of the CO insertion step. Hence, this phenomenon can play an important role in the synthesis of biologically interesting butenolide and pentenolide analogues via catalytic reactions involving Pd. The effect can be overcome by a judicious choice of the protective group and/or solvent; interestingly, the lactonization step does not require a free hydroxy function and proceeds with a THP-protected internal OH group as well. On the basis of this observation, we have established access to the desired bicyclic lactones via a high-yielding, short, and reproducible path. Further utilization of these results both in synthesis of natural products and their analogues as well as biological evaluation is in progress, and the results will be reported in due course.

Experimental Section

Dimethyl-4-phenyl-3-oxo-3,5,6,7-tetrahydro-1*H*-isochromene-6,6-dicarboxylate (5). A solution of iodide **14** (150 mg, 0.28 mmol), Et_3N (0.16 mL, 1.12 mmol), and $Cl_2Pd(PPh_3)_2$ (10 mg, 5 mol %) in dry DMF (3 mL) was stirred at 60 °C under 1 atm CO for 3 h. The mixture was poured into H_2O and extracted with Et_2O. Organic layers were dried over anhydrous Na_2SO_4 and the solvent removed. The residue was chromatographed on silica gel (hexanes/Et_2O 7:3) to afford 87 mg (89%) of white crystals of lactone **5**. Mp 126−128 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.46−7.33 (3H, m, Ar), 7.29−7.25 (2H, m, Ar), 6.08−6.03 (1H, m, H8), 4.96−4.93 (2H, m, H1), 3.68 (6H, s, $COOCH_3$), 2.90 (2H, s, H5), 2.88−2.84 (2H, m, H7). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.3, 163.9, 143.2, 133.6, 129.9, 128.2, 127.9, 127.3, 126.95, 126.90, 68.6, 53.7, 53.1, 32.4, 31.0. IR: ($CHCl_3$) ν_{max} 3027 (s), 2956 (s), 2845 (w), 2359 (w), 1732 (s), 1712 (s), 1647 (m), 1437 (s), 1264 (s) cm^{-1}. MS: 343 (M^+, 1), 329 (2), 325 (50), 311 (5), 297 (8), 283 (32), 281 (10), 279 (1), 265 (100), 255 (10), 251 (8), 237 (14), 233 (1), 223 (42), 221 (4), 205 (4), 193 (6), 189 (4), 167 (1), 149 (2), 121 (1), 115 (1), 104 (2). Identity and purity of the crystals was confirmed by X-ray analysis (see Supporting Information for details).

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Supporting Information Available: Experimental procedures and spectral data for new compounds, copies of ^{13}C NMR spectra, and crystallographic information on dienolide **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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