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Palladium-Catalyzed Oxidative Cyclizations: Synthesis of Dihydropyranones and Furanones

Maud Reiter, Hazel Turner, Rebecca Mills-Webb, and Véronique Gouverneur*

Chemistry Research Laboratory, University of Oxford, 12, Mansfield Road, Oxford OX1 3TA, United Kingdom

veronique.gouverneur@chemistry.oxford.ac.uk

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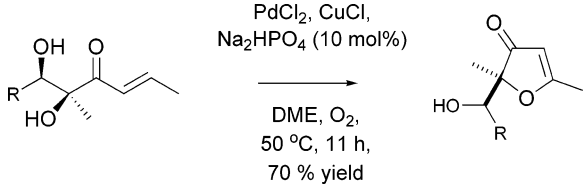
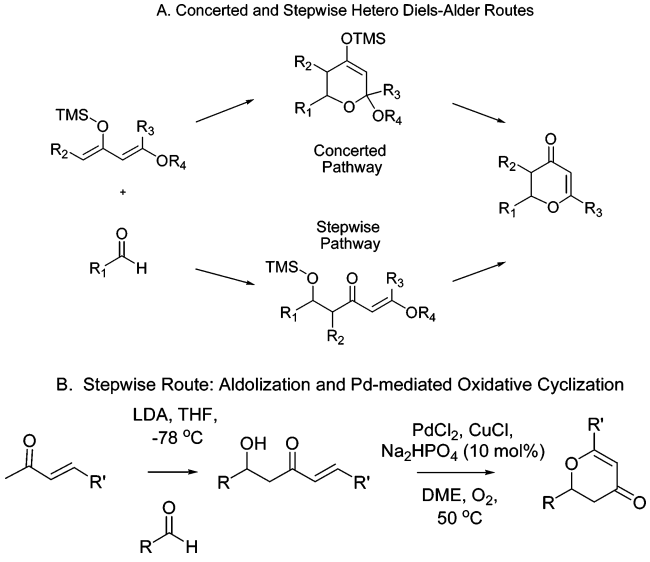


A boron-mediated *syn*- and *anti*-stereoselective aldol reaction giving rise to various β-hydroxyenones was coupled to a $Pd^{(II)}$-mediated oxidative cyclization to give 2,3,6-trisubstituted *syn*- and *anti*-dihydropyranones in good yields. The $Pd^{(II)}$-mediated oxidative cyclization was expanded to α-hydroxyenones leading to furan-3(2*H*)-one derivatives, which include natural product bullatenone and a known precursor of geiparvarin. The sole product of the oxidative cyclization of α,β-dihydroxyenone was a five-membered furan-3(2*H*)-one derivative, suggesting that the ring closure of these diols is both chemo- and regioselective.

Introduction

Palladium(II)-promoted cyclizations of alkenes with pending nucleophiles are widely used in the preparation of heterocycles.[1] When these cyclizations involve β-hydride eliminations, a secondary oxidant must be used to ensure catalysis. Various five- and six-membered heterocycles were prepared by using these palladium(II)-catalyzed oxidative cyclizations with the ring size depending on the substitution pattern of the alkene and its position within the acyclic precursor. We have demonstrated[2] that when β-hydroxylated enones are used as starting materials, an intramolecular oxidative conjugated addition can take place to afford dihydropyranones in good yields. This unprecedented route to hetero-Diels–Alder-type compounds derived from carbonyl dienophiles involves two steps: the preparation of the β-hydroxyenones by using an aldol reaction and the regioselective oxidative ring closure. Hence this strategy could be regarded as a variant of a stepwise hetero-Diels–Alder (HDA) reaction (Scheme 1). A key feature of this novel

SCHEME 1. Concerted and Stepwise Routes to HDA Adducts of Carbonyl Dienophiles



(1) (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Strecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257–259. (b) Tietze, L. T.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. (c) Sigman, M. S.; Schultz, M. *J. Org. Biomol. Chem.* **2004**, *2*, 2551–2554. (d) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004,** *43*, 3400–3420. (e) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002,** *41*, 164–166. (f) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625–655. (g) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (h) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907–2908. (i) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063–5064. (j) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585. (k) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300.

(2) (a) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91–94. (b) Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* **2005,** *127*, 1481–1486.

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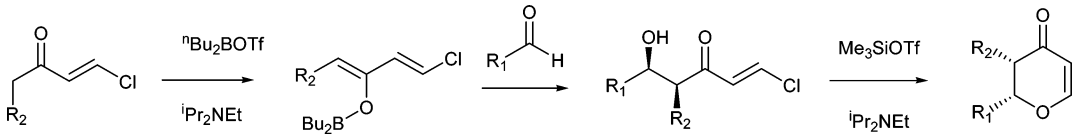
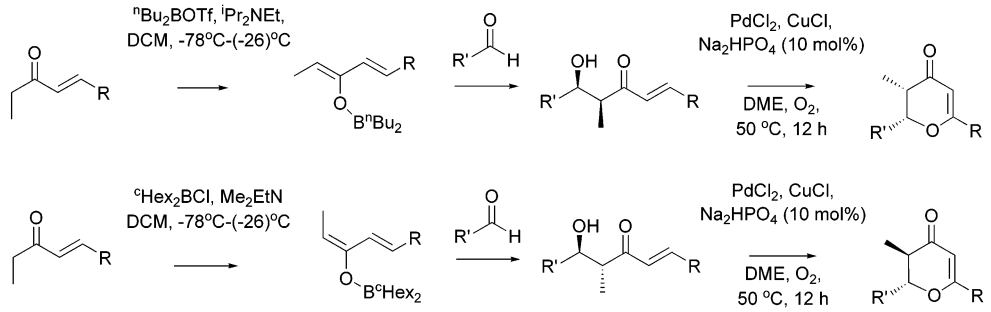
SCHEME 2. Diastereoselective Route to *syn*-Dihydropyranones



SCHEME 3. $Pd^{(II)}$-Mediated Diastereoselective Synthetic Route to *syn*- and *anti*-Dihydropyranones



route to HDA-type adducts is that it works particularly well for the preparation of 2,6-disubstituted dihydropyranones. These compounds are less conveniently synthesized with use of conventional hetero-Diels–Alder routes due to the more lengthy synthesis and the lower reactivity of the dienes necessary for their preparation.[3]

So far, the palladium-mediated oxidative cyclization of β-hydroxyenones has been applied successfully only to the preparation of racemic and enantiopure 2,6-disubstituted dihydropyranones possessing a single stereogenic center. Palladium(II)-mediated diastereoselective synthetic routes toward *syn*- and *anti*-dihydropyranones have yet to be developed. In 1990, Paterson et al.[4] reported a somewhat related stepwise diastereoselective synthesis of *syn*-dihydropyranones from aldehydes and dienol borinates derived from β-chlorovinyl ketones (Scheme 2).

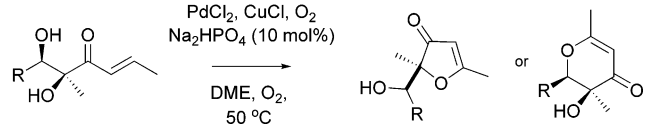
Paterson's route consists of a boron-mediated aldolization followed by an acid-mediated non-oxidative ring closure. In contrast to our methodology, this approach establishes the oxidation state of the cyclic adduct within the precursors, in analogy with the Diels–Alder reaction. Although attractive, this stepwise route presents some limitations. 2,3,6-Trisubstituted dihydropyranones were not prepared, possibly due to the difficulty of producing the required β-substituted β-chlorovinyl ketones, which upon cyclization would deliver adducts possessing a substituent on the sp^2-hydridized carbon adjacent to the endocyclic oxygen. The diastereoselective production of *anti*-adducts was not reported and for the preparation of *syn*-adducts, partial epimerization of the enolizable carbon occurred upon cyclization. Finally, adducts derived from conjugated aldehydes were not accessible as a competitive dehydration process of the intermediate aldol product occurred in the ring closure step.

In this article, we would like to expand on our recently published palladium(II)-catalyzed oxidative cyclization methodology leading to disubstituted dihydropyranones and thereby address some of the limitations of Paterson's stepwise route to HDA products. We report that this novel route to HDA adducts can deliver structurally diverse *syn*- and *anti*-trisubstituted dihydropyranones (eq 1). In addition, we demonstrate that furanones, including a representative natural product, can be prepared from the corresponding α-hydroxyenones using this palladium-catalyzed oxidative intramolecular conjugate addition as the key step (eq 2). Finally, we have investigated the product outcome of the oxidative ring closure of α,β-dihydroxyenones that could potentially lead to either dihydropyranones or furanones (eq 3).

Equation 1: Synthesis of trisubstituted 2,3-dihydropyran-4-ones

Equation 2: Synthesis of trisubstituted dihydrofuran-3(2*H*)-ones

Equation 3: Cyclization of α,β- dihydroxyenones



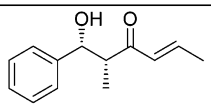
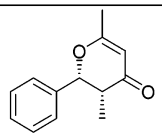
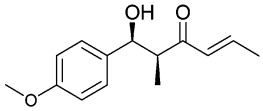
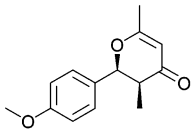
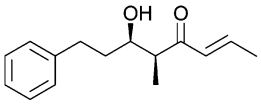
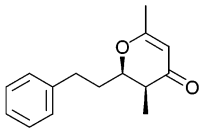
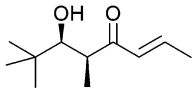
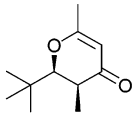
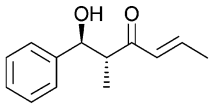
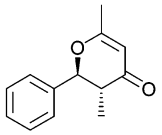
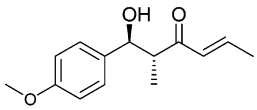
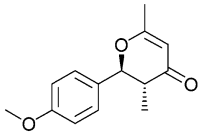
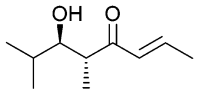
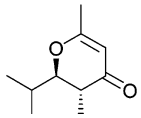
Results and Discussion

Diastereoselective Synthesis of 2,3,6-Trisubstituted Dihydropyranones. Our investigation began with an effort to prepare *syn*- and *anti*-aldol products derived from structurally diverse enones and aldehydes. Upon oxidative cyclization, these aldol products would be converted into the corresponding *syn*- and *anti*-trisubstituted dihydropyranones (Scheme 3, Table 1).

Despite the abundant literature available for the preparation of aldol products,[5] synthetic routes to *syn*- or *anti*-α′,β-dialkyl-β′-hydroxyenones are rare. Only recently, Trost et al.[6] reported the first asymmetric Zn-aldol reaction of methyl vinyl ketone and its synthetic applications. Inspired by the diastereoselective boron-mediated

(3) Gouverneur, V.; Reiter, M. *Chem. Eur. J.* **2005**, published ASAP.
(4) (a) Paterson, I.; Osborne, S. *Tetrahedron Lett.* **1990**, *31*, 2213–2216. (b) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652.

TABLE 1. Pd(II)-Mediated Formation of Trisubstituted Dihydropyranones

Entry	1	Starting Material	Yield, *de* (%), *ee* (%)	2	Cyclic	Yield, *de* (%), *ee* (%)
1	**1a**		62, >99 (*de*), 91 (*ee*)	**2a**		74, >99 (*de*), 89 (*ee*)[a]
2	**1b**		72, >99	**2b**		in DME: 42, 68 (*de*) in PBS : 63, 98 (*de*)
3	**1c**		71, >99	**2c**		68, >99
4	**1d**		64, >99	**2d**		55, >99
5	**1e**		72, 65 (99)	**2e**		50[b], >99
6	**1f**		61, 50	**2f**		82[c], 58 (99)
7	**1g**		78 (*de*)	**2g**		30[c,d] 70 (99)

[a] Enantioenriched β-hydroxyenone **1a** was obtained by reaction with chiral boron reagent (+)-Ipc_2BCl; absolute configuration assigned by analogy.[4] [b] Cyclization carried out on diastereomerically pure **1e**. [c] Cyclization carried out on a mixture of diastereomers. [d] Yield over two steps.

aldol reaction developed by Paterson et al.[4] for the preparation of structurally related *syn*-α′-alkyl-β′-hydroxy-β-chloroenones, we adopted this boron-aldol strategy for the preparation of various aldol products derived from α,β-unsaturated ketones (Scheme 3, Table 1). We were pleased to find that (*E*)-4-hexen-3-one was an excellent substrate for the stereoselective boron-mediated aldol reaction of various aldehydes, involving a presumed (*E*,*Z*) boron dienolate to give the desired diastereomerically pure *syn*-α′,β-dimethyl-β′-hydroxyenone products. A range of *syn*-α′-methyl-β′-hydroxy-β-methylenones were formed by using a $^nBu_2BOTf$ and $^iPr_2EtN$ mediated aldol reaction between commercially available (*E*)-4-hexen-3-one and four representative aldehydes in good yields (43−72%) and in excellent diastereoselectivities (>99% de) (Table 1, entries 1−4). However, we found that this boron-mediated aldol reaction is limited in scope, as it did not work for longer chains in the α′-position. Propyl vinyl ketone, for example, did not give the desired diastereomerically pure aldol products, forming decomposition products instead.

The Pd(II)-mediated oxidative cyclizations of the *syn*-β-hydroxyenones **1a**−**d** were performed using $PdCl_2$, CuCl, Na_2HPO_4 (10 mol %) and O_2 in DME or in a biphasic toluene/PBS solvent system, leading to the formation of the desired trisubstituted *syn*-dihydropyranones **2a**−**d** in good yields without affecting the integrity of the two existing stereocenters (entries 1−4). With aldol **1a** derived from benzaldehyde, the cyclization gave *syn*-**2a** in 74% isolated yield and with de > 99%. The crude mixture of this reaction revealed the presence of a single diastereomer allowing us to conclude that no detectable epimerization occurred under these conditions. Also the product outcome for this Pd(II)-mediated oxidative Michael

(5) For selected examples of early papers in this field: (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566−1568. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. (c) Inoue, T.; Mukaiyama T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174−178. (d) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *20*, 2225−2228. (e) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *20*, 2229−2232. (f) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120−6123. (g) Mukaiyama, T.; Inomata, K.; Muraki, M. *J. Am. Chem. Soc.* **1973**, *95*, 967−968. (h) Mahrwald, R., Ed. *Modern Aldol Reactions*; Wiley-VCH Verlag: Weinheim, Germany, 2004; Vols. 1 and 2.

(6) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602−8603.

addition was clean with no side products arising from a competitive dehydration process being formed. When the *syn*-α′,*β*-hydroxyenone **1b** was treated with a catalytic amount of $PdCl_2$ under our standard conditions, the dihydropyranone **2b** resulting from the oxidative cyclization process was the only product formed, albeit in a lower yield of 42%, and with de = 68%. The choice of solvent is critical for this transformation as we found that, when the cyclization was performed in a biphasic PBS/toluene system[2] instead of DME, we were able to improve the chemical yield of this reaction and fully prevent epimerization of the stereogenic center positioned α to the carbonyl group. In this biphasic solvent system, the dihydropyranone **2b** was isolated in 63% yield with 98% de (entry 2). The cyclizations of aldols **1a** and **1b** derived from benzaldehyde and *p*-methoxybenzaldehyde respectively are of particular interest as previous work carried out by Paterson et al.[4] revealed that the structurally related chlorinated aldol products derived from these aldehydes and *β*-chloroenone could not be cyclized under acidic conditions due to a competitive elimination process. The cyclization in DME of the *syn*-aldol products derived from hydrocinnamaldehyde and pivaldehyde was successful, affording the corresponding dihydropyranones **2c** and **2d** with chemical yields of 68% and 55% respectively and de higher than 99%. An enantioenriched sample of *syn*-1-hydroxy-2-methyl-1-phenylhex-4-en-3-one **1a** (99% de, 91% ee) prepared from the chiral boron enolate derived from (+)-Ipc_2BCl was cyclized to give the corresponding dihydropyranone **2a** with no significant loss of diastereo- or enantioselectivity (99% de, 89% ee, entry 1). The stereochemical integrity observed upon ring closure allowed us to conclude that no equilibration of the *syn*-adducts into the more stable *trans*-adducts occurred under these conditions.

For the preparation of the a*nti*-α′,*β*-dimethyl-*β*′-hydroxyenones, we reacted the corresponding aldehydes with the presumably formed (*E*,*E*)-boron dienolate produced from (*E*)-4-hexen-3-one in the presence of $^cHex_2BCl$ and $EtMe_2N$.[4] Analysis of the crude reaction mixtures revealed that these aldol products were produced with diastereomeric excesses ranging from 50% to 78% (entries 5−7). The *anti*-aldol **1e** was obtained as a single diastereomer after purification but compounds **1f** and **1g** were used in the next step as a mixture of diastereomers. The cyclization of aldol **1e** proceeded smoothly under our standard conditions to give the desired trisubstituted *trans*-dihydropyranone **2e** in 50% yield as a single diastereomer (entry 5). This result suggested that the intramolecular oxidative Michael addition occurred with no epimerization. The trisubstituted HDA-type adduct **2f** was obtained from aldol **1f** with an isolated yield of 82% and a diastereomeric excess of 58% (entry 6). The *trans*-dihydropyranone **2g** bearing three alkyl groups could also be prepared with an overall yield of 30% over two steps and a diastereomeric excess of 70% (entry 7). For the cyclizations of **1f** and **1g**, the diastereomeric excess measured on the crude mixtures mirrored the de of the starting *anti*-aldol products suggesting that, for these two substrates, the stereochemical integrity of the two stereogenic centers is also preserved upon ring closure. For compounds **2f** and **2g**, the two diastereomers can be separated by column chromatography allowing for the preparation of diastereomerically pure *anti*-dihydropyranones.

In comparison with the acid-mediated non-oxidative ring closures of aldol products derived from *β*-chlorovinyl ketones, the two-step strategy reported herein based on a palladium(II)-catalyzed intramolecular oxidative conjugated addition presents three advantages: (i) it allows for the formation of trisubstituted dihydropyranones, (ii) it can be extended to aldol products derived from conjugated aldehydes as no competitive dehydration takes place upon ring closure, and (iii) *syn*-dihydropyranones are now accessible with no loss of diastereomeric excess upon cyclization.

Synthesis of Furan-3(2*H*)-ones from α-Hydroxyenones. Furan-3(2*H*)-ones are found in many natural products such as bullatenone,[7] furaneol,[8] jatrophone,[8] eremantholides,[8] chinolone,[8] and geiparvarin.[9] Furaneol is often utilized as a strawberry flavoring agent.[10] Geiparvarin isolated from *Geijera parviflora* displays antiproliferative activity and has been targeted for the treatment of different types of cancer. In pursuit of more potent analogues of geiparvarin, it is essential that these compounds can be synthesized by a general route. Traditionally furan-3(2*H*)-ones are synthesized by an acid-catalyzed intramolecular cyclocondensation of substituted α-hydroxy-1,3-diketones. Smith et al.[11] have shown that a convenient approach to substituted 1,3-diketone precursors is through aldol condensation of aldehydes with the enolate derived from 3-methyl-3-(trimethylsiloxy)-2-butanone followed by Collins oxidation. Recently, Chimichi et al.[12] employed *β*-aminoenones as synthetic equivalents of α-hydroxy-1,3-diketones to form geiparvarin analogues in a multistep sequence. Takeda et al. synthesized furan-3(2*H*)-ones derivatives as geiparvarin precursors via an acylation step of 3-methyl-2,3-bis(trimethylsilyloxy)-1-butene with (*E*)-2-methyl-2-butenoyl in the presence of phenyllithium.[13] Another method has been reported by Colins et al.,[14] where the cyclization of *E*-α′-trialkylsilyloxy-α,*β*-unsaturated ketones is carried out in the presence of zinc bromide or dry silica to produce phenylsulfanyl-substituted 4,5-dihydrofuran-3(2*H*)-ones which undergo oxidative elimination to form furan-3(2*H*)-ones. Simple thermolysis produced bullatenone in 73% yield. Takeda et al.[15] also prepared bullatenone via a decarboxylative hydrolysis of ethyl 2,3-dihydro-2,2-dimethyl-3-oxo-5-phenylfuran-4-

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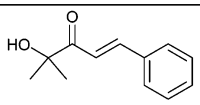
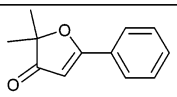
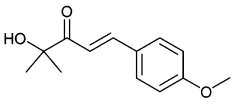
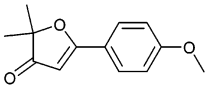
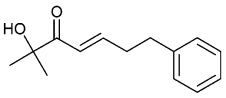
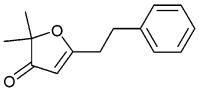
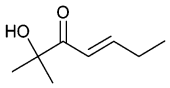
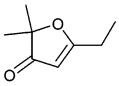
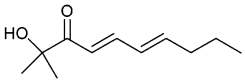
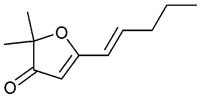
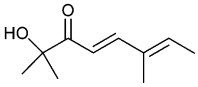
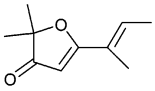
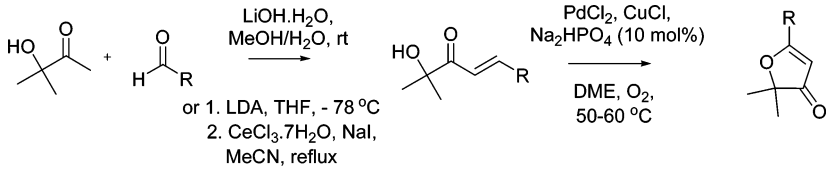
TABLE 2. Pd(II)-Mediated Formation of Trisubstituted Furanones

Entry	3	Enone	Yield (%)	4	Furanone	Yield (%)
1	**3a**		66	**4a**		93
2	**3b**		46	**4b**		74
3	**3c**		77	**4c**		67
4	**3d**		60	**4d**		41
5	**3e**		63	**4e**		0
6	**3f**		15	**4f**		64

SCHEME 4. Pd(II)-Mediated Synthetic Route toward Furan-3(2*H*)-ones



carboxylate, readily prepared from α-bromoisobutyryl bromide and ethyl sodiobenzoyl acetate, in 58% total yield. Baldwin et al.[16] have shown that it is possible to form bullatenone via a 5-endo-dig cyclization step of the corresponding α-hydroxyynones in 93% yield. The precursor was obtained over a sequence of five steps. Work by Jackson et al.[17] has shown that α-bromoynones can also be used as starting materials in the synthesis of geiparvarin and bullatenone. The overall yields for this approach are superior in comparison with those reported by Baldwin et al.[16] due to the more effective synthesis of the starting material.

Herein, we present an additional route toward furan-3(2*H*)-ones by subjecting readily obtained α′-hydroxyenones to the Pd(II)-mediated oxidative Wacker-type reaction conditions ($PdCl_2$, CuCl, Na_2HPO_4, O_2, DME, 50−60 °C) (Scheme 4, Table 2).

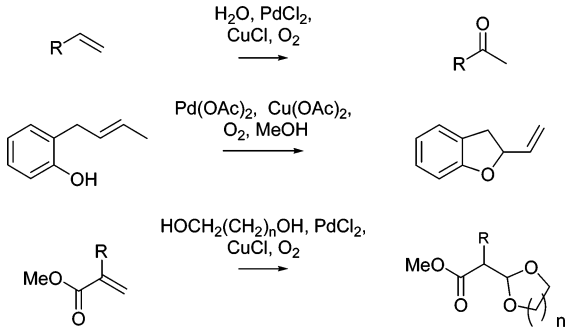
The starting materials (*E*)-**3a**,**b**, which contain aromatic substituents conjugated with the enone, were easily prepared in 46−66% yield, via a direct route, involving a LiOH·H_2O-mediated aldol reaction between the commercially available 3-methyl-3-hydroxybutan-2-one and the corresponding aromatic aldehydes, followed by a stereoselective in situ dehydration reaction (Table 2, entries 1 and 2).[18] Starting materials (*E*)-**3c**−**f** were obtained from a LDA-mediated aldol reaction, followed by a diastereoselective dehydration promoted by $CeCl_3 \cdot 7H_2O$ and NaI (entries 3−6).[19] All the expected furanones **4a**−**d**, featuring both alkyl and aryl substituents, were formed and isolated in good yields (Table 2, entries 1−4, 41−93%). No side product could be identified from the crude mixture or isolated after purification. Compound **4a** is bullatenone, a natural compound, now accessible in just two steps from commercially available precursors in 62% overall yield (entry 1). We also studied the reactivity of two precursors **3e** and **3f** featuring a dienone conjugated system (entries 5 and 6). We found that compound **3e** did not cyclize to give the desired product **4e** but yielded a complex mixture of numerous unidentified products along with some unreacted starting material (entry 5). This result suggests that the catalyst is not able to discriminate between the two double bonds leading therefore to the formation of a complex reaction mixture. In our preliminary study,[2] we have found that

(16) Baldwin, J.; Thomas, R.; Kruse, L.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846−3852.
(17) Jackson, R.; Raphael, R. *Tetrahedron Lett.* **1983**, *24*, 2117−2120.
(18) Palomo, C.; Oiarbide, M.; Garcia, J.; Gonzalez, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942−13943.
(19) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gomez-Bengoa, E.; Garcia, J. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189.

these oxidative ring closures are sensitive to steric effects and that this chemistry could not be applied to β-hydroxyenones possessing a substituent on the sp^2 carbon positioned α to the carbonyl. Taking advantage of the sensitivity of these heterocyclizations to steric effects, we subsequently studied the reactivity of α-hydroxydienone **3f** featuring two double bonds with different degree of substitutions hoping to direct the catalyst onto the less substituted olefin. When the hydroxyenone **3f** was subjected to our standard Wacker conditions, we were pleased to find that this reaction allowed for the formation of the desired furanone **4f** as the sole product. This compound, a direct precursor of geiparvarin, was isolated in 64% yield (entry 6).

Chemo- and Regioselectivity of the Pd(II)-Mediated Wacker-Type Oxidative Cyclization of α,β-Dihydroxyenones. Different factors influence the chemo- and regioselectivity of $Pd^{(II)}$-mediated oxidative addition reactions such as the size of the newly formed cycle, the substitution pattern of the substrate, as well as the electronic properties of the substituents attached to the reacting alkene. When these factors reinforce each other, the product selectivity makes these reactions synthetically useful. The Wacker oxidation of terminal alkenes leads to the exclusive formation of methyl ketones as the palladiohydroxylation of alkenes occurs in a Markovnikov fashion to afford an intermediate that subsequently undergoes dehydropalladation. For internal olefins, Hosokawa et al.[20] and Stoltz et al.[1] observed that the formation of five-membered rings was preferred when given the choice between five- and six-membered-ring formation. The introduction of an electron-withdrawing group adjacent to terminal olefins, as shown by Hosowaka et al.,[20] slows down the reaction but leads to good product selectivity resulting from an addition of the nucleophile onto the β-carbon of α,β-unsaturated carbonyl derivatives (Scheme 5).

SCHEME 5. Regioselectivity of $Pd^{(II)}$-Mediated Additions on Unsymmetrical Alkenes



We have shown that β-hydroxyenones cyclize in a regioselective manner to give exclusively the six-membered dihydropyranones.[2] In this case, electronic effects predominate and the entropically favored five-membered ring is not formed. For the formation of the five-membered furanones from the corresponding α-hydroxyenones, electronic and entropic effects reinforce each other, resulting in easy ring closure. We have also explored the reactivity of α,β-dihydroxyenone **10** to study the product outcome of the palladium(II)-mediated oxidative cyclization. This substrate could potentially lead to the formation of a dihydropyranone, a furanone derivative, or to a mixture of these two products (Scheme 6).

The starting α,β-dihydroxyenone **10** was prepared in a high-yielding six-step sequence. The Horner−Wadsworth−Emmons-type reaction between hydrocinnamaldehyde and triethyl-2-phosphonopropionate (TEPP) gave **5** in 89% yield and an *E*/*Z* ratio of 88/12.[21] OsO_4-catalyzed dihydroxylation,[22] followed by the acid-catalyzed 2,2-dimethoxypropane protection step,[23] occurred in 94% yield over the two steps to give the dihydroxylated ester **7** as a mixture of diastereomers (de = 76%). Reaction with *N*,*O*-dimethylhydroxylamine gave the two diastereomeric Weinreb amides **8** that were separated by column chromatography in a quantitative overall yield.[24] Addition of 1-propenylmagnesium bromide to the major diastereomer gave the desired protected dihydroxylated enone **9** in a 91% yield. Protection group removal was successfully carried out in a TFA/H_2O mixture at room temperature in 92% yield to afford the target α,β-dihydroxyenone **10** as a single diastereomer. The oxidative intramolecular conjugate addition was subsequently carried out with $PdCl_2$, CuCl, and O_2 in DME. This reaction gave the five-membered furan-3(*2H*)-one derivative **11** as the sole product in 70% yield for the final step and in 44% yield over the total six steps. The product was unambiguously identified as the five-membered ring by its characteristic ^{13}C NMR peaks at 207 ppm for the C=O, and at 190 ppm for the double bond carbon adjacent to the endocyclic oxygen and by X-ray crystallography. This X-ray analysis also confirmed the relative stereochemistry of the product. No trace of the six-membered ring was detected. A similar result was obtained for the $Pd^{(II)}$-mediated cyclization of the unsubstituted α,β-dihydroxyenone *syn*-4,5-dihydroxy-4-methyl-7-phenylhept-1-en-3-one **13**, obtained from the addition of vinylmagnesium bromide to the diastereomerically pure Weinreb amide **8** followed by deprotection.[24] This led to the exclusive formation of the five-membered furan-3*(2H)*-one derivative **14** in 55% yield. These experiments conclusively demonstrate that under the given reaction conditions, the catalytic 5-endo oxidative heterocyclization is the only reaction pathway taking place.

Conclusion

In conclusion, a number of trisubstituted dihydropyranones have been prepared according to a two-step process involving an aldolization yielding various *syn*- and *anti*-β-hydroxyenones, followed by an intramolecular palladium-mediated oxidative Michael-type addition. These oxidative heterocyclizations take place without affecting the stereochemical integrity of the starting aldol products. When the acyclic precursors are α-hydroxyenones, the corresponding furanones are obtained in good

(20) Hosokawa, T.; Miyagi, S.; Murahashi S.-I.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752−2757. Hosokawa, T.; Uno, T.; Inui, S.; Murahashi S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318−2323. Hosokawa, T.; Ohta, T.; Murahashi S.-I. *J. Chem. Soc., Chem. Commun*. **1983**, 848−849.

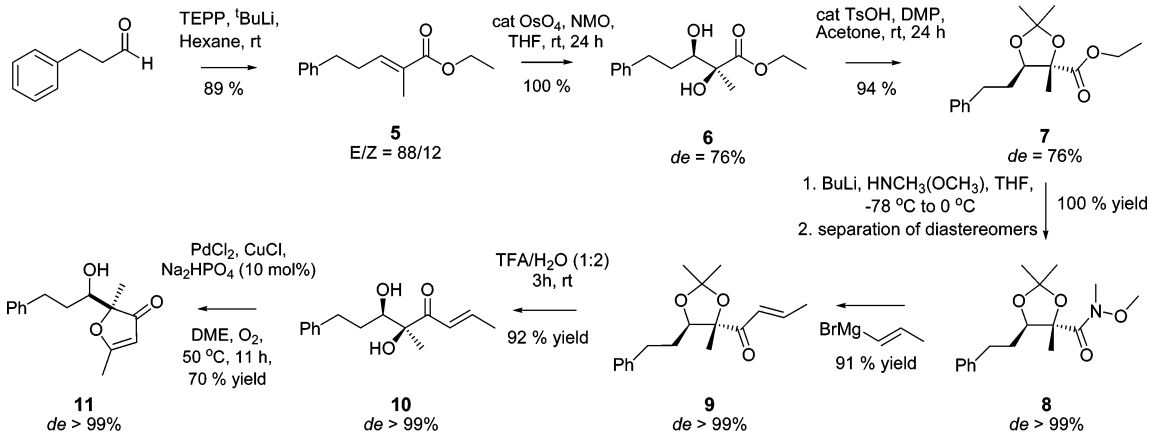
(21) Petroski, R. J.; Weisleder, D. *Synth. Commun*. **2001**, *31*, 89−95.

(22) Muñiz, K. *Eur. J. Org. Chem.* **2004**, 2243−2252.

(23) Schneider, C.; Kazmaier, U. *Synthesis* **1998**, *9*, 1314−1320.

(24) Stark, L. M.; Pekari, K.; Sørensen, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101,* 12064−12066.

SCHEME 6. Preparation and Cyclization of *syn*-5,6-Dihydroxy-5,6-dialkylhex-2-en-4-one 10



yields. These reactions are therefore suitable for the preparation of both five- and six-membered heterocycles. When both reaction pathways are possible, the five-membered ring is formed exclusively. This chemistry further establishes the synthetic utility of these palladium oxidative reactions for the preparation of structurally diverse oxygenated heterocycles.

Experimental Section

Preparation of Substrates. Compounds **1a**−**g** were synthesized according to an adapted version of a procedure reported in the literature.[4] Compounds **3a**−**c** were prepared according to a procedure reported in the literature.[18,19]

Typical Procedure for the Preparation of *syn*-α′-Methyl-*β*-hydroxyenones.[4] To a stirred solution of diisopropylethylamine (1.3 equiv) and di-*n*-butylborontriflate (1 M solution in CH_2Cl_2, 1.2 equiv) in anhydrous CH_2Cl_2 (10 mL) at −78 °C was added the ketone (1 equiv) in dry DCM (2 mL). The reaction mixture was warmed to 0 °C and stirred for 2 h, before it was cooled to −78 °C again and the aldehyde (2.5 equiv) was added. The reaction was then maintained at −78 °C for 2 h and at −26 °C for 16 h. The resulting reaction mixture was quenched by the addition of methanol (2 mL/mmol), a pH 7 (PBS) buffer solution (2 mL/mmol), and a H_2O_2 peroxide solution (30% sol, 2 mL/mmol) at 0 °C. Stirring was continued for 1 h. Then the mixture was partitioned between H_2O (30 mL), and DCM (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give a residue further purified by column chromatography on silica.

Typical Procedure for the Preparation of *anti*-α′-Methyl-*β*-hydroxyenones.[4] To a cooled (−78 °C) solution of $^cHex_2BCl$ (1.5 equiv) in Et_2O (10 mL) was added dimethylethylamine (1.8 equiv), followed by the ketone (1 equiv) in Et_2O (2 mL). The reaction mixture was warmed to 0 °C and stirred for 2 h, before being cooled down to −78 °C. The required aldehyde (2.5 equiv) was added and stirring continued for 2 h at −78 °C followed by 16 h at −26 °C. Workup and purification were as described above.

Typical Procedure for the $Pd^{(II)}$-Mediated Oxidative Cyclizations.[2] A 25 mL Schlenk tube was charged with $PdCl_2$, CuCl, and Na_2HPO_4 (all 10 mol %) and evacuated and backfilled with oxygen (3 times, balloon). The substrate in anhydrous DME (2−3 mL) was added via cannula. The resulting reaction mixture was heated to 50 or 60 °C and allowed to stir at this temperature until completion. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O, filtered through a pad of silica, and concentrated in vacuo to give a crude residue that was further purified by flash column chromatography on silica.

Characterization of Products. All products were fully characterized by IR, ^1H NMR, and ^{13}C spectroscopies, MS spectrometry, and in the case of **11** X-ray crystallography (see the Supporting Information). ^1H NMR and ^{13}C NMR spectra were prepared as $CDCl_3$ solutions and recorded at 400 and 100 MHz, respectively, with Me_4Si as internal reference. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. All reactions were carried out under an argon or oxygen atmosphere respectively in dried glassware with magnetic stirring. Tetrahydrofuran (THF) was distilled from sodium and benzophenone and both 1,2-dimethoxyethane (DME) and diisopropylamine were distilled from calcium hydride. All other commercially obtained reagents were used as received.

***syn*-1-Hydroxy-2-methyl-1-phenylhex-4-en-3-one (1a).** From 1.1 mL of diisopropylethylamine (7.34 mmol), 5 mL of di-*n*-butylborontriflate (6 mmol), 0.46 mL of 4-hexen-3-one (4 mmol), and 1.02 mL of benzaldehyde (10 mmol) was obtained **1a** in 62% yield, >99% d*e*, as a colorless oil; υ_{max} (film/cm^{-1}) 3455, 1626; δ_H (400 MHz, $CDCl_3$) 1.07 (d, J = 7.3 Hz, 3H), 1.91 (3H, dd, J = 6.8 and 1.5 Hz, 3H), 3.05 (1H, qd, J = 7.1 and 3.3 Hz), 3.54 (1H, s), 5.13 (1H, s), 6.16 (1H, dq, J = 15.7 and 1.8 Hz), 6.93 (1H, dq, J = 15.7 and 7.1 Hz), 7.24−7.37 (5H, m); δ_C (100 MHz, $CDCl_3$) 10.4, 18.4, 49.4, 72.8, 125.9, 127.2, 128.2, 130.5, 141.8, 144.4, 205.0; HRMS *m/z* 204.1150 ($C_{13}H_{16}O_2$ requires 204.1147). Asymmetric synthesis employing DIP-Cl gave **1a** with an enantiomeric excess of 91% ee.

***anti*-1-Hydroxy-2-methyl-1-phenylhex-4-en-3-one (1e).** From 0.8 mL of dimethylethylamine (7.34 mmol), 6.1 mL of dicyclohexylboron chloride (6 mmol), 0.46 mL of 4-hexen-3-one (4 mmol), and 1.02 mL of benzaldehyde (10 mmol) was obtained **1e** in 72% overall yield as a colorless oil (0.6 g, 3 mmol), with de = 65% (de = 99% upon purification); υ_{max} (film/cm^{-1}) 3444, 1627; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, J = 7.1 Hz), 1.92 (3H, dd, J = 6.8 and 1.8 Hz), 3.16 (1H, q, J = 7.8 Hz), 3.04 (1H, s), 5.13 (1H, s), 6.20 (1H, dq, J = 15.7 and 1.8 Hz), 6.94 (1H, dq, J = 15.4 and 6.8 Hz), 7.27−7.39 (5H, m); δ_C (100 MHz, $CDCl_3$) 15.0, 18.4, 50.3, 76.5, 126.6, 127.8, 128.4, 131.3, 142.1, 144.1, 204.2; HRMS *m/z* 204.1150 ($C_{13}H_{16}O_2$ requires 204.1147).

***syn*-3,6-Dimethyl-2-benzyl-2,3-dihydropyran-4-one (2a).**[25] **2a** was obtained from 10 mg of $PdCl_2$ (0.05 mmol), 5.3 mg of CuCl (0.05 mmol), 7.6 mg of Na_2HPO_4 (0.05 mmol), and 0.11 g of **1a** (0.5 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by silica gel chromatography (1:4; EtOAc: hexane) gave **2a** as a colorless oil in 74% yield (0.08 g, 0.40 mmol), de > 99%; υ_{max} (film/cm^{-1}) 1668, 1615; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, J = 7.6 Hz), 2.13 (3H, s), 2.52 (1H, qd, J = 7.3 and 3.3 Hz), 5.38 (1H, s), 5.51 (1H, d, J = 3.0 Hz), 7.33−7.44 (5H, m), δ_C (100 MHz, $CDCl_3$) 10.0, 20.9, 44.9, 82.9, 103.6 125.5, 128.0,128.5, 136.7, 173.6, 197.6; *m/z* calcd 202.1070 ($C_{13}H_{15}O_2$ requires 202.1072). $Pd^{(II)}$-mediated cyclization of the enantioenriched **1a** gave **2a** with an ee = 89%.

(25) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392−393.

***syn*-3,6-Dimethyl-2-(4-methoxyphenyl)-2,3-dihydropyran-4-one (2b).** A solution of **1b** (0.24 g, 1.03 mmol) in toluene (0.5 mmol/ml) was added to $PdCl_2$ (18.9 mg, 0.1 mmol) and CuCl (10.5, 0.1 mmol), followed by PBS (pH 7.4, 0.5 mmol/mL). The resulting mixture was stirred at 50 °C for 3.5 days. Upon cooling, the reaction mixture was diluted with Et_2O and filtered through a pad of silica gel. Purification by silica gel chromatography on silica (1:3, EtOAc:hexane) gave **2b** as a colorless oil in 63% yield, de = 98%; υ_{max} (film/cm^{-1}) 1667, 1615; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, J = 7.5 Hz), 2.11 (3H, s), 2.48 (1H, qd, J = 7.5 and 3.4 Hz), 3.84 (3H, s), 5.37 (1H, s), 5.45 (1H, d, J = 3.4 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz); δ_C (100 MHz, $CDCl_3$) 10.0, 20.9, 45.0, 55.3, 82.7, 103.6, 113.9, 127.9, 128.8, 159.3, 173.7, 197.7; *m/z* 233.1180 ($C_{14}H_{17}O_3$ requires 233.1178).

(*E*)-4-Hydroxy-1-phenyl-4-methylpent-1-en-3-one (3a).[18] A mixture of 3-hydroxy-3-methyl-2-butanone (0.8 mL, 7.58 mmol), $LiOH{\cdot}H_2O$ (63 mg, 1.516 mmol), and benzaldehyde (1.54 mL, 15.17 mmol) in MeOH (20 mL) and H_2O (75 mL) was stirred overnight at room temperature. The MeOH was removed in vacuo and water was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo and the crude product was purified by silica gel chromatography (1:6, EtOAc:hexane) to give **3a** in 66% yield as a pale yellow oil; υ_{max} (film/cm^{-1}) 3444, 1680; δ_H (400 MHz, $CDCl_3$) 1.44 (6H, s), 4.00 (1H, s), 7.02 (1H, d, J = 15.4 Hz), 7.40 (3H, m), 7.58 (2H, m), 7.82 (1H, d, J = 15.4 Hz); δ_C (100 MHz, $CDCl_3$) 26.4, 75.4, 118.4, 125.8, 128.8, 130.8, 134.1, 145.4, 202.3; *m/z* 191.1075 ($C_{12}H_{15}O_2$ requires 191.1072).

(*E*)-2-Hydroxy-2-methyl-7-phenylhept-4-en-3-one (3c).[19] As adopted from literature, the aldol reaction employed 3-hydroxy-3-methyl-2-butanone (1 mL, 10 mmol), 3-phenylpropionaldehyde (0.87 mL, 6.6 mmol), ^{n}BuLi (2.3 M solution in hexanes, 10.63 mL, 25 mmol), and diisopropylamine (3.5 mL, 25 mmol) in THF (40 mL) to give the intermediate 2,5-dihydroxy-2-methyl-7-phenylheptan-3-one (0.72 g, 3 mmol) in 46% yield. The dehydration employed $CeCl_3{\cdot}7H_2O$ (1.37 g, 3.7 mmol), NaI (0.55 g, 3.7 mmol), and 2,5-dihydroxy-2-methyl-7-phenylheptan-3-one (0.58 g, 2.45 mmol) in anhydrous MeCN (35 mL). Purification by silica gel chromatography (1:4 EtOAc:hexane) gave **3c** (0.41 g) in 77% yield, as a pale orange oil; υ_{max} (film/cm^{-1}) 3446, 2973, 1617, 1630; δ_H (400 MHz, $CDCl_3$) 1.35 (6H, s), 2.60 (2H, q, J = 7.0 Hz), 2.82 (2H, t, J = 7.3 Hz), 3.95 (1H, bs), 6.38 (1H, dt, J = 15.4 and 1.5 Hz), 7.18 (1H, dt, J = 15.0 and 7.0 Hz), 7.18−7.32 (5H, m); δ_C (100 MHz, $CDCl_3$) 26.2, 34.2, 34.4, 75.1, 122.9, 126.2, 128.3, 128.5, 140.5, 149.4, 202.3; *m/z* 219.1371 ($C_{14}H_{19}O_2$ requires 219.1385).

2,2-Dimethyl-5-phenylfuran-3(2*H*)-one (Bullatenone) (4a).[7] **4a** was obtained from 300 mg of **3a** (1.57 mmol), 27.96 mg (0.16 mmol) of $PdCl_2$, 15.60 mg (0.16 mmol) of CuCl, and 22.37 mg (0.16 mmol) of Na_2HPO_4 in DME (3 mL). The reaction mixture was left to stir at 48 °C for 4 days, followed by 2 days at 80 °C. Purification by silica gel chromatography (1:6, EtOAc:hexane) gave **4a** as a crystalline white solid in 93% yield; υ_{max} (film/cm^{-1}) 1681, 1607; δ_H (400 MHz, $CDCl_3$) 1.48 (6H, s), 5.96 (1H, s), 7.44−7.56 (3H, m), 7.80−7.84 (2H, m); δ_C (100 MHz, $CDCl_3$) 23.1, 88.9, 98.5, 127.1, 128.8, 129.1, 132.6, 183.5, 207.0; *m/z* 189.0914 ($C_{12}H_{13}O_2$ requires 189.0916).

(*E*)-Ethyl-2-methyl-5-phenylpent-2-enoate (5).[26] Lithium *tert*-butoxide (18.6 mL, 1 M in hexanes) was added to a solution of triethyl-2-phosphonopropionate (4 mL, 18.6 mmol) and the resulting torpid solution was stirred at room temperature for 15 min, upon which 3-phenylpropionaldehyde (1.63 mL, 12.3 mmol) was added over a 10 min interval. The resulting clear reaction solution was stirred for a further hour, then washed with water (4 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give a residue further purified by silica gel chromatography (1:7, EtOAc:hexane) to give **5** as a colorless oil in 89% yield, with E/Z = 88/12 (2.38 g, 10.9 mmol); υ_{max} (film/cm^{-1}) 1711, 1650; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, J = 7.1 Hz), 1.80 (3H, s), 2.50 (2H, q, J = 7.6 Hz), 2.77 (2H, t, J = 7.6 Hz), 4.20 (2H, q, J = 7.1 Hz), 6.82 (1H, tq, J = 7.6 and 1.5 Hz), 7.19−7.33 (5H, m); δ_C (100 MHz, $CDCl_3$) 12.3, 14.3, 30.6, 34.7, 60.4, 126.1, 128.3, 128.4, 128.5, 140.8, 141.3, 168.1; *m/z* 219.1368 ($C_{14}H_{19}O_2$ requires 219.1385).

***syn*-*N*,2,2,4-Tetramethyl-5-phenylethyl-1,3-dioxolane-4-carboxamide (8). 8** was obtained from ^{n}BuLi (7 equiv) and *N*,*O*-dimethylhydroxyamine (5 equiv) and **7** in THF. Purification by silica gel chromatography (1:3, EtOAc:hexane) gave *syn*-**8** in 82% and *anti*-**8** in 18% yield (100% yield overall), both as colorless oils. For *syn*-**8**: υ_{max} (film/cm^{-1}) 1645; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s), 1.35 (3H, s), 1.50 (3H, s), 1.85 (1H, m), 2.05 (1H, m), 2.75 (1H, ddd, J = 14.0 10.8, and 6.3 Hz), 2.92 (1H, ddd, J = 14.3, 12.1, and 4.2 Hz), 3.26 (3H, bs), 3.71 (3H, s), 4.45 (1H, ddd, J = 10.1, 2.2, and 1.5 Hz), 7.17−7.31 (5H, m); δ_C (100 MHz, $CDCl_3$) 25.6, 28.6, 32.5, 33.4, 61.0, 80.0, 82.9, 107.9, 125.8, 128.3, 128.5, 142.0, 172.8; *m/z* 308.1822 ($C_{17}H_{26}NO_4$ requires 308.1862).

***syn*-1-(2,2,4-Trimethyl-5-phenylethyl-1,3-dioxolane-4-yl)-prop-2-en-1-one (9). 9** was obtained from freshly prepared 1-propenylmagnesium bromide (2.5 equiv) and *syn*-**8** in THF. Purification by silica gel chromatography (1:5, EtOAc:hexane) gave *syn*-**9** as a pale yellow oil in 91% yield. υ_{max} (film/cm^{-1}) 1643; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s), 1.38 (3H, s), 1.52 (3H, s), 1.86 (2H, m), 1.91 (3H, dd, J = 6.8 and 1.7 Hz), 2.68 (1H, ddd, J = 13.6, 9.9, and 6.8 Hz), 2.86 (1H, ddd, J = 13.6, 9.9, and 6.0 Hz), 4.07 (1H, dd, J = 8.5 and 4.4 Hz), 6.80 (1H, dq, J = 15.3 and 1.7 Hz), 7.02 (1H, dq, J = 15.3 and 6.8 Hz), 7.17−7.31 (5H, m); δ_C (100 MHz, $CDCl_3$) 18.5, 19.3, 26.0, 28.5, 31.7, 33.0, 78.4, 86.6, 108.5, 125.2, 125.9, 128.3, 128.4, 141.9, 145.2, 200.9; *m/z* 289.1789 ($C_{18}H_{25}O_3$ requires 289.1804).

2-(1-Hydroxy-3-phenylpropyl)-2,5-dimethylfuran-3(2*H*)-one (11). 11 was obtained from 5.7 mg of $PdCl_2$ (0.032 mmol), 3.2 mg of CuCl (0.032 mmol), 4.5 mg of Na_2HPO_4 (0.032 mmol), and 0.072 g of *syn*-5,6-dihydroxy-5-methyl-8-phenyloct-2-en-4-one **10** (0.32 mmol) in anhydrous DME (2 mL). The reaction mixture was stirred at 50 °C overnight. Purification by silica gel chromatography (1:1; EtOAc:hexane) gave **11** as white solid in 70% yield. Recrystallization from ethyl acetate. υ_{max} (film/cm^{-1}) 3455, 1683, 1593; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s), 1.65 (1H, dddd, J = 14.0, 10.8, 9.6, and 4.8 Hz), 1.92 (1H, dddd, J = 13.9, 9.6, 7.1, and 2.2 Hz), 2.25 (3H, s), 2.40 (1H, bs), 2.64 (1H, ddd, J = 13.6, 9.3, and 7.1 Hz), 2.94 (1H, ddd, J = 13.9, 9.8, and 4.8 Hz), 3.76 (1H, d, J = 10.8 Hz), 5.41 (1H, s), 7.18−7.31 (5H, m); δ_C (100 MHz, $CDCl_3$) 17.0, 18.8, 32.0, 32.4, 73.6, 91.5, 104.0, 126.0, 128.4, 128.5, 141.6, 190.0, 207.0; *m/z* 246.1259 ($C_{15}H_{20}O_3$ requires 246.1256).

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Supporting Information Available: Experimental details of compounds **1b**−**d**, **1f**−**g**, **2c**−**g**, **3b**, **3d**−**f**, **4b**−**f**, **6**, **7**, **10**, **12**−**14**; ^{1}H NMR and ^{13}C NMR of selected compounds; X-ray crytallographic data for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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