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Systematic Investigation into the Matsuda–Heck Reaction of α-Methylene Lactones: How Conformational Constraints Direct the β-H-Elimination Step

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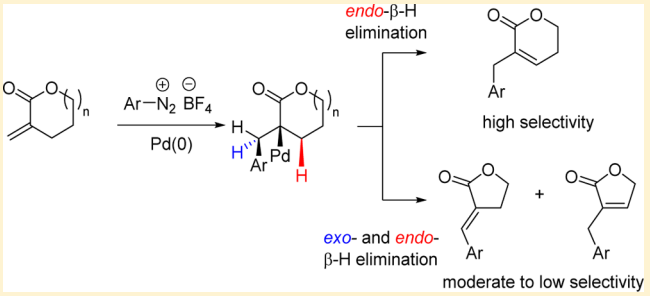
Supporting Information

ABSTRACT: α-Methylene-γ-butyrolactone and α-methylene-δ-valerolactone undergo Pd-catalyzed Matsuda–Heck couplings with arene diazonium salts to α-benzyl butenolides or pentenolides, respectively, or to α-benzylidene lactones. The observed regioselectivity is strongly ring size dependent, with six-membered rings giving exclusively α-benzyl pentenolides, whereas the five-membered α-methylene lactone reacts to mixtures of regioisomers with a high proportion of (*E*)-α-benzylidene-γ-butyrolactones. DFT calculations suggest that the reasons for these differences are not thermodynamic but kinetic in nature. The relative energies of the conformers of the Pd σ-complexes resulting from insertion into the Pd–aryl bond were correlated with the dihedral angles between Pd and *endo*-β-H. This correlation revealed that in the case of the six-membered lactone an energetically favorable conformer adopts a nearly synperiplanar Pd/*endo*-β-H arrangement, whereas for the analogous Pd σ-complex of the five-membered lactone the smallest Pd/*endo*-β-H dihedral angle is observed for a conformer with a comparatively high potential energy. The optimized conditions for Matsuda–Heck arylations of *exo*-methylene lactones were eventually applied to the synthesis of the natural product anemarcoumarin A.



INTRODUCTION

Acrylates **1** are highly reactive benchmark olefins for evaluating novel catalyst systems or reaction conditions for Mizoroki–Heck couplings.[1] The high π-acceptor and poor σ-donor reactivity of acrylates leads to an electronically biased insertion of the olefin into the Pd-σ-aryl bond of **2**, which results in the formation of a Pd σ-complex **3** with the new C–C-bond in the β-position and a Pd–C^{α} σ-bond.[2] The catalytic cycle proceeds with a β-hydride elimination, which requires a *syn*-periplanar or nearly *syn*-periplanar arrangement of the Pd at C^{α} and one β-hydrogen. To adopt the energetically least unfavorable *syn*-periplanar conformation **3′**, a rotation around the C^{β}–C^{α} bond must occur. The stereospecificity of the β-H-elimination and the preferred *anti*-orientation of the aryl and ester substituents explain the very high *E*-selectivity observed for the cinnamates **5** (Scheme 1a).[3] While a plethora of examples for Mizoroki–Heck arylations of simple acrylates exist, comparatively little is known about the behavior of conformationally constrained enoates in this transformation. One type of conformationally restricted enoates are α,β-unsaturated lactones **6**. If the generally accepted mechanism for Heck-type arylations as outlined in Scheme 1a is applied to these substrates, a Pd σ-complex **7** results, which cannot undergo the *syn*-β-H-elimination required to close the catalytic cycle. Nevertheless some examples for successful Mizoroki–Heck reactions of cycloalkenes,[4] including α,β-unsaturated six-membered lactones,[5] lactams,[5,6] and cycloketones,[7,8] have been described in the literature. For lack of a plausible *syn*-β-H elimination pathway, base-induced *trans*-β-H-elimination[4] or epimerization[7] of the Pd σ-complex **7** to *epi*-**7** via a Pd enolate **7′** have been proposed to explain the formation of arylated products **8** (Scheme 1b).

Another, even less investigated type of conformationally restricted enoates are *exo*-methylene lactones **9**. The Pd σ-complex **10** resulting from insertion into the Pd–σ-aryl bond of **2** can in principle undergo β-H-elimination with one *exo*-β-H and the *syn*-*endo*-β-H, leading to α-benzylated-α,β-unsaturated lactones *endo*-**11** or α-benzylidene lactones *exo*-**11** (Scheme 1c). For example, Genêt and co-workers reported that the Pd-catalyzed coupling of an arene diazonium salt with α-methylene-γ-butyrolactone (**9a**) gives exclusively the *exo*-benzylidene lactone (*exo*-**11**) as a mixture of *E*- and *Z*-isomers.[9] Shortly afterward, Arcadi et al. investigated the coupling of **9a** with various aryl iodides and found that mixtures of *endo*- and *exo*-products were formed and that the *exo*-products are exclusively *Z*-configured.[10,11] For more densely substituted α-methylene-γ-butyrolactones, Kim et al. found that both via Mizoroki–Heck arylation or via oxidative C–H-activation mixtures of *endo*- and *E*-*exo*-arylation products were formed.[12] The exclusive formation of *exo*-arylation products as *E*/*Z* mixtures was reported for guaianolide-type sesquiterpene

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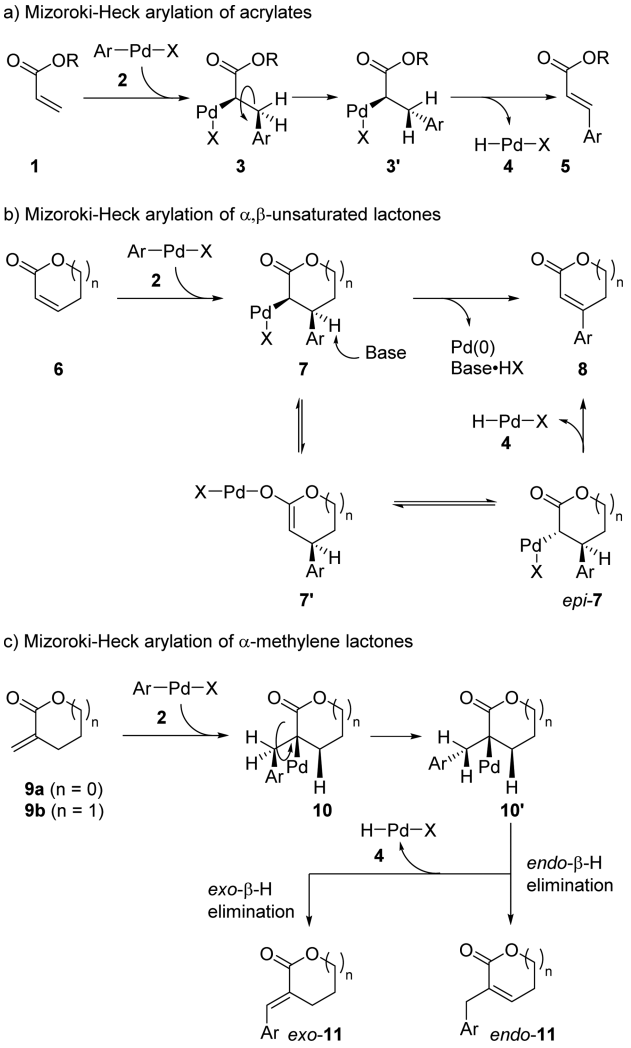
Scheme 1. Heck-Type Arylations of Acrylates, Unsaturated Lactones, and α-Methylene Lactones



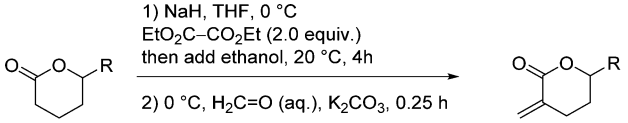
lactones.[13] To date, the above-mentioned studies by Arcadi et al. remain the only systematic investigations into Mizoroki–Heck reactions of α-methylene lactones.[10,11] From their observations, these authors concluded that the electronic effects of *para*-substituents at the aryl iodide and the nature of the base employed in the coupling reaction steer the selectivity. Thus, particularly high *endo*-selectivities were observed for aryl iodides with an electron-withdrawing *para*-substituent and with acetates rather than amines as a base. As a rationale for the beneficial effect of acetate, the authors proposed that Pd-bound acetate participates in the β-H-abstraction through a seven-membered transition state.[10,11]

Over the past few years, we[14−17] and others[18−23] reported a considerable number of examples for Heck-type coupling reactions with arene diazonium salts. This variant of the Mizoroki–Heck coupling, often referred to as the Matsuda–Heck reaction, was originally discovered in the late 1970s by Matsuda and co-workers but lay dormant for many years.[24,25] Over the past 15 years, Matsuda–Heck- and other Pd-catalyzed cross couplings of arene diazonium salts have attracted renewed and still growing interest due to a number of beneficial features.[26−28] For instance, diazonium salts are conveniently synthesized from amines or acetamides[29] (or can be generated in situ,[30] e.g., under flow conditions[31]), are highly reactive, allow for monitoring the kinetics by quantifying the nitrogen evolution over time,[32] and do not require elaborate ligands for catalyst tuning ($Pd(OAc)_2$ and $Pd_2(dba)_3$ are the most commonly used precatalysts). Finally, Matsuda–Heck reactions can be conducted both under basic and base-free conditions,[32,33] which, in light of the assumed vital role of acetate bases in Arcadi's studies, prompted us to revisit Heck-type arylations of *exo*-methylene lactone **9a** using arene diazonium salts. Surprisingly, the homologous six-membered *exo*-methylene lactone **9b** or substituted derivatives of the same ring size have, to the best of our knowledge, never been investigated in Heck-type reactions. As we expected that the ring size affects the Pd–C^{α}–$C^{\beta endo}$–H dihedral angle and hence the regioselectivity of the β-H-elimination step, we included **9b**, its δ-methyl derivative **9c**, and the *N*-benzyl δ-valerolactam **9d** in our study.

RESULTS AND DISCUSSION

Syntheses of *exo*-Methylene Carbonyl Compounds 9 and Diazonium Salt 13m. *exo*-Methylene γ-butyrolactone (**9a**) is widely commercially available from a number of suppliers. It has, like its less conveniently accessible six-membered homologue **9b**, been synthesized from the corresponding lactone by deprotonation, Claisen condensation with ethyl formate, and addition of formaldehyde.[34−36] Several 2-methylene-δ-valerolactones, including **9c**, have been synthesized by conjugate addition of carbonyl compounds to α-phosphono acrylates, subsequent lactonization, and olefination with formaldehyde.[37] For the synthesis of **9b** and **9c**, we used a modification of the former method which was adapted from a synthesis of malyngolide[38] but had not been applied to these particular derivatives (Scheme 2).

Scheme 2. Syntheses of α-Methylene-δ-valerolactones 9b,c



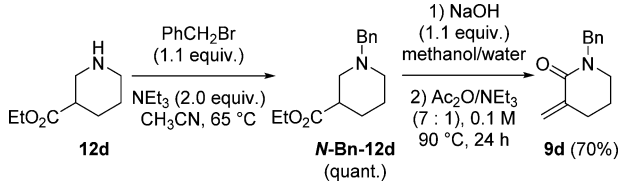
12b (R = H)
12c (R = CH_3)

9b (R = H, 78%)
9c (R = CH_3, 70%)

N-Benzyl-α-methylene-δ-valerolactam (**9d**) was recently synthesized from δ-valerolactam in three steps by aldol condensation with formaldehyde, but we decided to use a two-step synthesis starting from ethyl nipecotate (**12d**). This compound was *N*-benzylated to ***N*-Bn-12d** and then subjected to a base-induced α-methylenelactam rearrangement[39,40] to furnish **9d** (Scheme 3).

These syntheses can be routinely performed on a 20 mmol scale and reliably provide gram quantities of the required *exo*-methylene lactones and lactams **9**.

Scheme 3. Synthesis of α-Methylene-δ-valerolactam (9d)



12d

***N*-Bn-12d** (quant.)

9d (70%)

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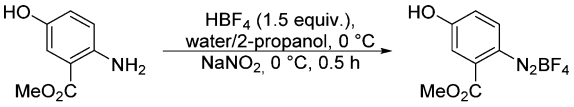
The arene diazonium salts used in this study were obtained either by diazotation of anilines or via deacetylation−diazotation of acetanilides following previously published procedures.[14,29,32,41,42] The hitherto unknown phenol diazonium salt **13l** was synthesized from methyl 4-hydroxyanthranilate (**14l**) through diazotation with $NaNO_2$ in aqueous HBF_4 (Scheme 4).

Scheme 4. Synthesis of the Hitherto Unknown Diazonium Salt 13l



14l **13l** (42%)

Matsuda Heck Arylation of α-Methylene-δ-valerolactone (9b). For the purpose of optimization, we investigated the Matsuda−Heck coupling of **9b** and 4-methoxybenzene diazonium salt **13a**. Although other solvents, in particular, water,[43−45] have been tested for Heck-type coupling reactions of arene diazonium salts, methanol[32,41,46] and acetonitrile,[47,48] either under basic or under base-free conditions, are still the most commonly used solvents (Table 1). Base-free conditions in methanol (entries 1 and 2) were chosen for comparison of the catalysts. $Pd(OAc)_2$ was found to perform substantially better than $Pd_2dba_3{\cdot}CHCl_3$ and was, therefore, used in all other experiments. By addition of NaOAc as a base (entry 3), the yield of the Matsuda−Heck coupling product could be further increased to 80%. In marked contrast, the reaction fails completely in acetonitrile in the absence of NaOAc (entry 4). This observation is in line with previous findings by us[14,32] and Correia's mechanistic studies,[47] which suggest that acetonitrile serves as a stabilizing ligand for the Pd hydride species resulting from the β-hydride elimination step. Consequently, added base should facilitate the regeneration of the catalytically active Pd(0) species. Upon addition of NaOAc, we obtained indeed a nearly quantitative yield of the coupling product (entry 5).

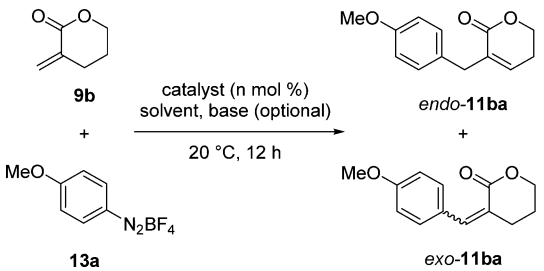
We then investigated a reduced catalyst loading (entry 6), which leads to a dramatically diminished yield. The same was observed when the excess of alkene **9b** was reduced (entry 7). Using the diazonium salt **13a** with an excess of 1 equiv (entry 9) led to an improved yield compared to a 10% excess (entry 8), but application of the *exo*-methylene lactone **9b** in excess appears to be more suitable and more convenient to ensure high yields of the desired coupling product. Careful examination of the crude reaction mixtures revealed that in all cases *endo*-**11ba** was exclusively formed.

Scope and limitations of Matsuda−Heck arylations of **9b** were explored for a number of other arene diazonium salts **13** using 5 mol % of $Pd(OAc)_2$ in all experiments and a ratio of reactants of 2:1 (**9b**/**13**). As solvents, either methanol or acetonitrile (with and without added base) was tested for each diazonium salt. For most diazonium salts, at least one set of conditions was identified to obtain the respective Matsuda−Heck products *endo*-**11b#** in synthetically useful yields and without the formation of any *exo*-isomers (Table 2). These results show that methanol without added base is usually the optimal condition and that acetonitrile with added base is only in exceptional cases superior. This includes the example chosen for the optimization study, which underlines once again that the optimum reaction conditions of Matsuda−Heck reactions are strongly substrate dependent and that generalizations must be made with care.

A perspective application of these Matsuda−Heck products in stereoselective synthesis is their conversion to 2-substituted 2,4-dienoic acids through base-induced elimination. This transformation was originally discovered as early as 1859 for the conversion of the rowan berry oil constituent parasorbic acid to sorbic acid.[49] More recently, the reaction was applied to the total synthesis of complex natural products with conjugated diene moieties,[50−53] and very recently, we demonstrated that a base-mediated eliminative ring opening of β,γ-unsaturated lactones can be incorporated in a tethered ring-closing metathesis sequence.[54−56]

We are not aware of examples for the eliminative ring opening of α-benzylated pentenolides and therefore inves-

Table 1. Optimization of Matsuda−Heck Conditions for 9b



13a

entry	ratio **9b**:**13a**	precatalyst (catalyst loading)	base[a]	solvent	product (yield, %)[b]
1	2.0:1.0	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %)		CH_3OH	*endo*-**11ba** (54)
2	2.0:1.0	$Pd(OAc)_2$ (5.0 mol %)		CH_3OH	*endo*-**11ba** (64)
3	2.0:1.0	$Pd(OAc)_2$ (5.0 mol %)	NaOAc	CH_3OH	*endo*-**11ba** (80)
4	2.0:1.0	$Pd(OAc)_2$ (5.0 mol %)		CH_3CN	*c*
5	2.0:1.0	$Pd(OAc)_2$ (5.0 mol %)	NaOAc	CH_3CN	*endo*-**11ba** (98)
6	2.0:1.0	$Pd(OAc)_2$ (2.5 mol %)	NaOAc	CH_3CN	*endo*-**11ba** (61)
7	1.2:1.0	$Pd(OAc)_2$ (5.0 mol %)	NaOAc	CH_3CN	*endo*-**11ba** (50)
8	1.0:1.1	$Pd(OAc)_2$ (5.0 mol %)	NaOAc	CH_3CN	*endo*-**11ba** (38)
9	1.0:2.0	$Pd(OAc)_2$ (5.0 mol %)	NaOAc	CH_3CN	*endo*-**11ba** (71)

[a]3.0 equiv. [b]Only *endo*-**11ba** was observed in all experiments. [c]No conversion (TLC).

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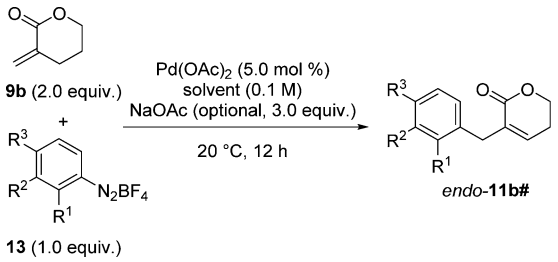
Table 2. Scope and Limitations of Matsuda−Heck Couplings with 9b

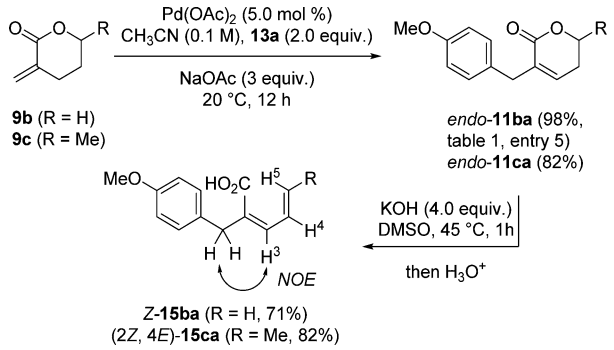


entry	13	R^1	R^2	R^3	solvent	base	product	yield (%)
1	**13a**	H	H	OMe	CH_3CN	NaOAc	*endo*-**11ba**	98
2	**13b**	H	H	OH	CH_3OH		*endo*-**11bb**	74
3	**13c**	H	H	OBn	CH_3CN	NaOAc	*endo*-**11bc**	66
4	**13d**	H	Br	OMe	CH_3OH		*endo*-**11bd**	82
5	**13e**	H	Br	OH	CH_3OH	NaOAc	*endo*-**11be**	68
6	**13f**	H	NO_2	OMe	CH_3OH		*endo*-**11bf**	82
7	**13g**	H	NO_2	OH	CH_3OH		*endo*-**11bg**	99
8	**13h**	NO_2	H	OMe	CH_3OH		*endo*-**11bh**	48
9	**13i**	H	CF_3	H	CH_3OH		*endo*-**11bi**	*a*
10	**13j**	H	H	NO_2	CH_3OH		*endo*-**11bj**	67
11	**13k**	H	CO_2Me	OH	CH_3OH		*endo*-**11bk**	*a*
12	**13l**	CO_2Me	H	OH	CH_3OH		*endo*-**11bl**	49
13	**13m**	H	H	NHAc	CH_3CN	NaOAc	*endo*-**11bm**	31

[a]No conversion in methanol or acetonitrile under either basic or base-free conditions.

tigated the base-induced cleavage of *endo*-**11ba**. Treatment of this lactone with KOH in DMSO at slightly elevated temperature resulted in the clean formation of the 2-benzylated 2,4-dienoic acid *Z*-**15ba** within 1 h. Assignment of the *Z*-configuration as shown in Scheme 5 is based on an NOE

Scheme 5. Base-Induced Eliminative Ring Opening of α-Benzyl Pentenolides



interaction between H^3 and the CH_2 group of the benzyl substituent. To check whether a stereoselective formation of the C^4-C^5 double bond is also possible, we synthesized the pentenolide *endo*-**11ca** from α-methylene lactone **9c** under the same conditions used for *endo*-**11ba** (see Table 1, entry 5) and subjected this compound to the base-induced eliminative ring opening. The conjugated diene (2*Z*,4*E*)-**15ca** was isolated in a comparable yield as a single isomer. Assignment of the 2*Z*-configuration was again achieved by NOE interactions between H^3 and the benzylic CH_2 group, and the 4*E*-configuration was proved by an NOE interaction between the terminal methyl group and H^4 as well as a $^3J(H^4,H^5)$ value of 15.0 Hz (Scheme 5).

Matsuda Heck Arylation of *N*-Benzyl α-Methylene-δ-valerolactam (9d). When we applied the optimized conditions for the Matsuda−Heck coupling of phenoldiazonium salt **13b** and α-methylene lactone **9b** (base-free methanol, 2.0:1.0 ratio of alkene and diazonium salt) to the coupling of this diazonium salt and α-methylene lactam **9d**, we could isolate *endo*-**11db** in 61% yield. As for the analogous lactones, no *exo*-isomers could be detected in the reaction mixture. In contrast to the results observed during the optimization study for Matsuda−Heck couplings with lactone **9b**, we noted an increased yield of 75% when the ratio of **9d** to **13b** was reduced to 1.2:1.0. After testing some other ratios of reactants, we eventually found that the highest yield was obtained for a 2.0:1.0 ratio of diazonium salt **13** and *exo*-methylene lactam **9d**. Scope and limitations of Matsuda−Heck arylations of **9d** with various arene diazonium salts **13** were next evaluated, routinely using a 1.0:2.0 ratio of reactants. Both methanol and acetonitrile were tested with and without added base for each diazonium salt. Apart from base-free acetonitrile, which failed to give a substantial yield of coupling products in all cases, most diazonium salts could be coupled with **9d** in synthetically useful yields under at least one set of conditions (Table 3). Exceptions are the *m*-trifluoromethyl-substituted arene diazonium salt **13i**, which failed to undergo Matsuda−Heck couplings with both lactone **9b** and lactam **9d** (entry 9) and diazonium salts **13h** and **13m**. Both underwent coupling reactions with **9b** in moderate yields, but not with **9d** (entries 8 and 13). On the other hand, methyl carboxylate substituted diazonium salt **13k**, which did not react with lactone **9b**, reacted in a satisfying yield with the lactam (entry 11). In general, the isolated yields of Matsuda−Heck coupling products are lower for the lactam **9d** compared to the analogous lactone **9b**. Although the arene diazonium salts were used in excess, we did not notice the formation of symmetrical biaryls. This transformation has very recently been described when diazonium salts were exposed to catalytic amounts of $Pd(OAc)_2$ in ionic liquids.[57]

Matsuda Heck Arylation of α-Methylene-γ-butyrolactone (9a). In contrast to the Matsuda−Heck couplings

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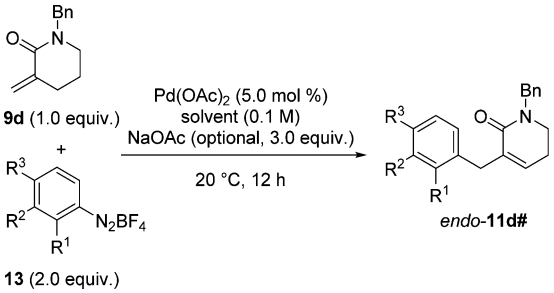
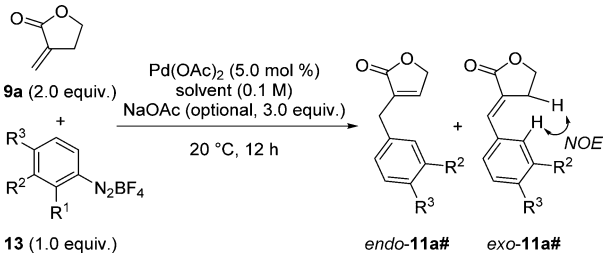
Table 3. Scope and Limitations of Matsuda–Heck Couplings with 9d



entry	13	R^1	R^2	R^3	solvent	base	product	yield (%)
1	**13a**	H	H	OMe	CH_3CN	NaOAc	*endo*-**11da**	72
2	**13b**	H	H	OH	CH_3OH		*endo*-**11db**	86
3	**13c**	H	H	OBn	CH_3CN	NaOAc	*endo*-**11dc**	65
4	**13d**	H	Br	OMe	CH_3OH		*endo*-**11dd**	76
5	**13n**	H	Br	OBn	CH_3OH		*endo*-**11dn**	66
6	**13f**	H	NO_2	OMe	CH_3OH		*endo*-**11df**	80
7	**13g**	H	NO_2	OH	CH_3OH		*endo*-**11dg**	96
8	**13h**	NO_2	H	OMe	CH_3OH		*endo*-**11dh**	*a*
9	**13i**	H	CF_3	H	CH_3OH		*endo*-**11di**	*a*
10	**13j**	H	H	NO_2	CH_3OH		*endo*-**11dj**	34
11	**13k**	H	CO_2Me	OH	CH_3OH		*endo*-**11dk**	66
12	**13l**	CO_2Me	H	OH	CH_3OH		*endo*-**11dl**	65
13	**13m**	H	H	NHAc	CH_3CN	NaOAc	*endo*-**11bm**	*a*

[a]No conversion in methanol or acetonitrile under either basic or base-free conditions.

Table 4. Scope and Limitations of Matsuda–Heck Couplings with 9a



entry	13	R^2	R^3	solvent	base	ratio[a] *endo*: *exo*	product	yield[b] (%)
1	**13a**	H	OMe	CH_3CN	NaOAc	2.7:1.0	**11aa**	85
2	**13a**	H	OMe	toluene	NaOAc	2.0:1.0	**11aa**	84
3	**13a**	H	OMe	CH_3OH		1.0:6.6	**11aa**	73
4	**13b**	H	OH	CH_3OH		1.0:6.0	**11ab**	76
5	**13d**	Br	OMe	CH_3CN	NaOAc	1.0:1.4	**11ad**	96
6	**13e**	Br	OH	CH_3OH	NaOAc	10.0:1.0	**11ae**	44
7	**13e**	Br	OH	CH_3OH		10.0:1.0	**11ae**	32
8	**13f**	NO_2	OMe	CH_3OH		2.0:1.0	**11af**	94
9	**13g**	NO_2	OH	CH_3OH		2.0:1.0	**11ag**	99

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Combined isolated yield of *endo*- and *exo*-products.

investigated so far, all arylations of the five-membered *exo*-methylene lactone **9a** proceed with formation of both *endo*- and *exo*-isomers in varying ratios (Table 4). For each experiment, the *endo*/*exo* ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture prior to chromatographic purification. *Endo*- and *exo*-isomers are conveniently distinguished by the chemical shift values for the olefinic proton and by the presence of a triplet integrating for two protons at ca. 3 ppm for the H^3 protons of the *exo*-isomers. An NOE interaction between this methylene group and the *ortho*-protons of the aromatic substituent is indicative for the assigned *E*-configuration. Our configurational assignment differs from that made by Arcadi et al. in their pioneering study,[10,11] who stated that the double bonds of their *exo*-products are exclusively *Z*-configured. However, a comparison of the NMR-spectroscopic data obtained by us for the *p*-methoxybenzylidene lactone *E*-*exo*-**11aa** and those reported by Arcadi et al. for *Z*-*exo*-**11aa** revealed that both data sets are identical, which suggests that the original assignment of a *Z*-configuration might be erroneous. As mentioned in the Introduction, Arcadi et al. proposed that acetate bases steer the *β*-hydride elimination toward the *endo*-*β*-H leading to a preferred formation of *endo*-butenolides. We found that the Matsuda–Heck coupling of **9a** and **13a** in acetonitrile in the presence of

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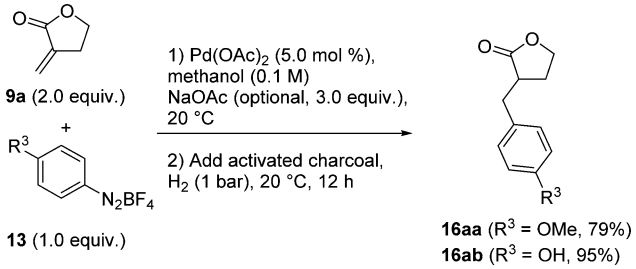
acetate resulted in the formation of **11aa** in a 2.7:1.0 ratio of *endo*- and *exo*-products (entry 1). In base-free methanol, the ratio is inverted to 1.0:6.6 (*endo*-**11aa**/*exo*-**11aa**), which seems to corroborate Arcadi's hypothesis that the base plays a crucial role for the regioselectivity (entry 3). Replacing acetonitrile by toluene under basic conditions (entry 2) gives **11aa** in a comparable yield and very similar *endo*/*exo* ratio, which suggests that the base, rather than the solvent, is the dominant selectivity-controlling factor.

We found a comparable selectivity toward the *exo*-isomer for the phenoldiazonium salt **13b** in methanol under base free conditions (entry 4). However, as pointed out by Arcadi et al., the electronic effects of substituents at the arene moiety have a strong influence on the regioselectivity, with electron-withdrawing groups favoring *endo*-β-H-elimination.[11] This might explain why even in the absence of acetate no pronounced selectivity toward the *exo*-isomer was observed for the diazonium salts **13d–g** (bearing an additional bromo or nitro substituent), although one should not overestimate the electronic effects of these substituents as they are located in a *meta*-position relative to the oxidative addition site.

Arcadi et al. showed that a homogeneous product can be obtained by hydrogenation of the crude *endo*/*exo*-mixtures with Pd/C.[11] While Arcadi's two-step sequence of Heck reaction and hydrogenation requires orthogonal solvents for each step (DMF and ethyl acetate, respectively), we sought to develop a one-pot, single-catalyst sequence[14,19] by exploiting the advantages of arene diazonium salts as coupling partners. In particular, Matsuda–Heck reactions can be run in the absence of bases or ligands that might have detrimental effects on a subsequent hydrogenation step, they proceed normally at ambient temperature, which should be beneficial for catalyst longevity, and methanol is a suitable solvent for both coupling and hydrogenation step. After Matsuda–Heck couplings of **13a** and **13b** were run with α-methylene-γ-butyrolactone **9a** in methanol under either basic or base-free conditions, activated charcoal was added once the evolution of nitrogen had ceased, and the reaction mixture was flushed with hydrogen and stirred under hydrogen at atmospheric pressure for 12 h. The expected α-benzylated γ-butyrolactones **16aa** and **16ab** were isolated in high yields (Scheme 6).

Scheme 6. One-Pot, Single-Catalyst Matsuda–Heck Coupling/Hydrogenation Sequence



Analysis of the Regioselectivity of the β-H-Elimination Step Based on DFT Calculations. The strikingly different selectivities observed for Matsuda–Heck arylations of five- and six-membered *exo*-methylene lactones might be of thermodynamic or kinetic origin. Thermodynamic control would require a feasible "post-Mizoroki–Heck" double-bond isomerization mechanism,[58] e.g., via a sufficiently stable Pd hydride species [H–Pd–X] (**4**, Scheme 1) originating from the β-H-elimination step. This Pd hydride might be capable of isomerizing the kinetic product into the thermodynamic one by hydropalladation–β-H-elimination steps. Destabilization of Pd hydrides, e.g., by trapping stabilizing iodide ligands with silver[59] or thallium salts,[60] is hence a measure to suppress unwanted post-Mizoroki–Heck double-bond migration reactions. With arene diazonium tetrafluoroborates as arylating agents, strongly coordinating halide ligands are absent from the outset and the catalytically relevant intermediates are supposedly cationic,[47,61] which means that rather unstable Pd hydride species have to be expected. It is, for instance, in line with this assumption that no subsequent isomerization of the double bond has been observed in Matsuda–Heck reactions with cyclic enol ethers, while the analogous reactions with aryl iodides were found to be prone to post-Mizoroki–Heck reactions.[62] In light of these considerations, it appears unlikely that the different regioselectivities observed for five- and six-membered *exo*-methylene lactones result from a Pd hydride catalyzed double-bond migration following the Matsuda–Heck reaction. To corroborate this supposition, the relative stabilities of all possible Matsuda–Heck products resulting from the reaction of phenol diazonium salt **13b** with **9a** and **9b**, respectively, were determined by calculating their Gibbs free energy values using DFT methods (Figure 1).

Both *exo*-*Z*-isomers were found to be clearly the least stable products. In Figure 1 their Gibbs free energy is set to 0, and the free energies of the isomeric *endo*- and *exo*-*E*-products are denoted relative to *exo*-*Z*-**11ab** and *exo*-*Z*-**11bb**, respectively. For both ring sizes, the order of stability is identical: *exo*-*E* > *endo* ≫ *exo*-*Z*. This underlines that the strikingly different

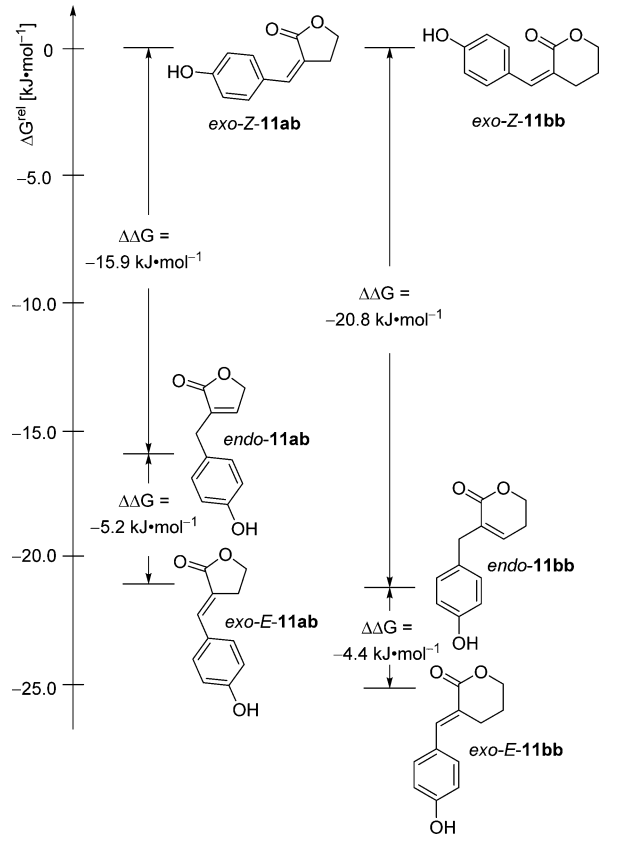


Figure 1. Calculated relative Gibbs free energies of isomers of **11ab** and **11bb**.

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product distributions observed for Matsuda–Heck reactions of five- and six-membered α-methylene lactones most likely do not originate from thermodynamic but from kinetic control. It should be noted in this context that a single report exists which describes selective Rh-catalyzed *exo*-to-*endo* double-bond migrations, including conversions of *exo*-*E*-**11aa** and *exo*-*E*-**11ba** to *endo*-**11aa** and *endo*-**11ba**, respectively, which apparently contradicts our assumption.[84] Although alternative β-H-elimination scenarios such as *trans*-β-H-elimination have been proposed in cases of conformationally constrained Pd σ-complexes, we assumed that a β-H-elimination will preferably proceed via the *syn*-mechanism, provided that a *syn*-β-H is available. To gain a deeper understanding of the different β-H-elimination pathways, the cationic Pd σ-complexes **10** (Scheme 1) resulting from the migratory insertion into the *exo*-double bonds of **9a** and **9b**, respectively, were analyzed using DFT methods. For the Pd an oxidation state of +II and the coordination of two molecules of methanol was assumed. The Pd–C^{α}–C^{β}–Ar dihedral angles were then locked to 0°, and geometry optimizations were performed. The structures shown in Figure 2 mirror the situation immediately after the migratory insertion step (Figure 2).

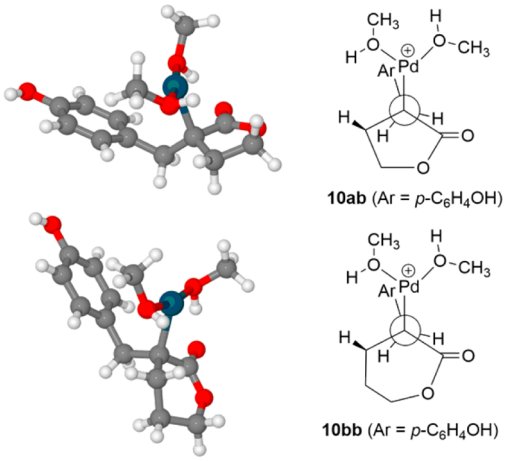

Figure 2. Geometry-optimized structures of Pd σ-complexes **10ab** and **10bb** with a dihedral angle [Pd–C^{α}–$C^{\beta exo}$–Ar] = 0°.

Starting from these eclipsed-conformations, which are highest in energy, the aryl moiety was rotated stepwise around the C^{α}–$C^{\beta exo}$ bond between 0° and 360°. Geometry optimizations were performed for 36 conformers, and the differences in energy relative to the starting conformation and the dihedral angles [Pd–C^{α}–$C^{\beta endo}$–H] were calculated for these 36 conformers for each Pd σ-complex **10ab** and **10bb**. The results for the five-membered lactone structure **10ab** are shown in Figure 3. The first relevant conformation arises after rotation of 120° around the C^{α}–$C^{\beta exo}$ bond. A β-H^{exo} elimination from this conformer would lead to *exo*-*Z*-**11ab**, but this conformer is as high in energy as the starting conformer. *exo*-*Z*-**11ab** is obviously not only thermodynamically (see Figure 1) but also kinetically strongly disfavored. Rotating the aryl substituent by a further 120° (dihedral angle [Pd–C^{α}–$C^{\beta exo}$–Ar] = 240°) leads to another *syn*-β-H^{exo} arrangement, which is energetically much more favorable than the structure at 120°. *syn*-β-H-elimination from this conformer would lead to *exo*-*E*-**11ab**, which is indeed the main product observed in this Matsuda–Heck reaction (see Table 4). As a

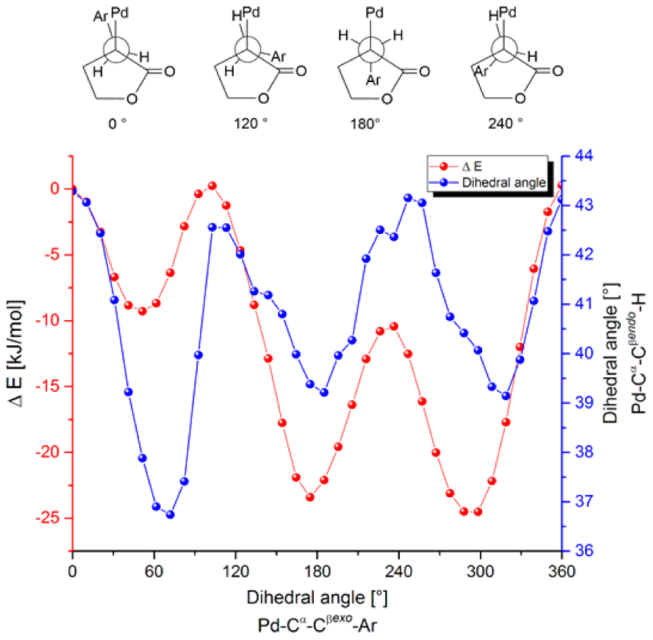

Figure 3. [Pd–C^{α}–$C^{\beta endo}$–H] dihedral angle (blue curve) and relative energy (red curve) as a function of the [Pd–C^{α}–$C^{\beta exo}$–Ar] dihedral angle for Pd σ-complex **10ab**.

measure for the probability of a *syn*-β-H^{endo} elimination, we considered the *endo*-dihedral angle [Pd–C^{α}–$C^{\beta endo}$–H], which varies from 37° to 44°, depending on the *exo*-dihedral angle [Pd–C^{α}–$C^{\beta exo}$–Ar] (blue curve in Figure 3). We reasoned that for a *syn*-β-H^{endo} elimination to proceed efficiently two conditions have to be met: the *endo*-dihedral angle needs to be sufficiently small and the respective conformer should be energetically favorable. The smallest *endo*-dihedral angle (36.5°) coincides with the *gauche* conformation at 60° (*exo*-dihedral angle), but this conformer is, although at a local minimum, still rather high in energy. On the other hand, the two energetically most favorable conformers at *exo*-dihedral angles of 180° and 300° have larger *endo*-dihedral angles of ca. 39° (Figure 3).

In the case of the six-membered lactone structure **10bb**, the analogous analysis revealed some striking differences (Figure 4). Both conformers of Pd σ-complex **10bb** with a *syn*-β-H^{exo} arrangement (at 120° and at 240°, which would hypothetically give *exo*-*Z*- and *exo*-*E*-**11bb**, respectively, upon β-H-elimination) are equally high in energy and only marginally more stable than the starting conformer. In contrast, the conformer at 240° of the five-membered lactone structure **10ab**, which is the precursor for the *exo*-*E*-product, is ca. 10 kJ·mol^{-1} lower in energy than the respective starting conformer. This might explain why no *exo*-*E*-products were observed for Matsuda–Heck reactions with six-membered α-methylene lactones. The pronounced preference for the formation of *endo*-products can be explained by considering the *endo*-dihedral angle (blue curve in Figure 4). Compared to the five-membered lactone structures, this crucial dihedral angle is generally smaller, and an energetically favorable conformer exists at 180°, which nearly coincides with the smallest calculated *endo*-dihedral angle of ca. 22°. For the two other local energy minima *endo*-dihedral angles larger than 40° were calculated. It appears unlikely that a *syn*-β-H^{endo}-elimination will occur from these conformers.

Total Synthesis of Anemarcumarin A. Several natural products with a 3-benzylated coumarin pattern have been

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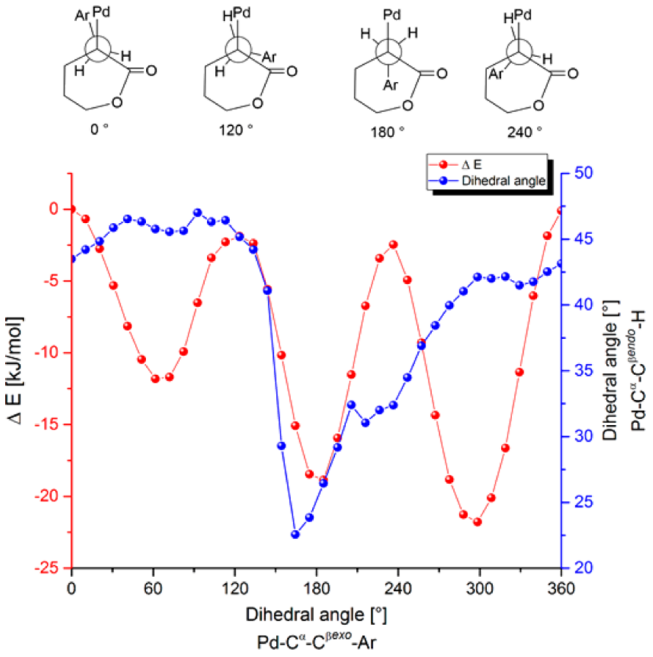


Figure 4. [Pd−C^{α}−$C^{\beta endo}$−H] dihedral angle (blue curve) and relative energy (red curve) as a function of the [Pd−C^{α}−$C^{\beta exo}$−Ar] dihedral angle for Pd σ-complex **10bb**.

isolated from plants.[63,64] Examples are sarcandracoumarin, a weakly active cytotoxic compound isolated from the plant *Sarcandra glabra*,[65] or anemarcoumarin A, which has been isolated from the rhizomes of *Anemarrhena asphodeloides*, a medicinal plant native to Korea, China, and Japan.[66] Synthetic 3-benzylated coumarins have recently been evaluated for various medicinal chemistry purposes, e.g., as selective CB_2 agonists,[67−69] as inhibitors of TNF-α,[70] or as inhibitors of estrogen receptors (Figure 5).[71] A previously described synthetic route to these 3-benzylcoumarins proceeds through umpolung−domino reactions of salicylic aldehydes and enals.[72]

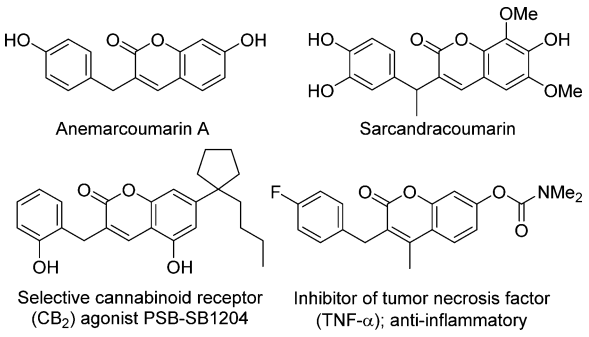
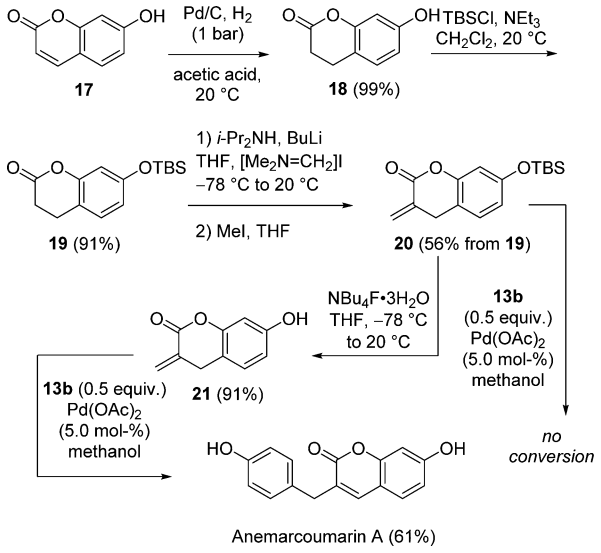


Figure 5. Examples for 3-benzylated coumarins as potential target structures.

We applied the Matsuda−Heck conditions developed herein the synthesis of anemarcoumarin A from umbelliferone (**17**). Umbelliferone was first hydrogenated and then protected as TBS ether **19**. Application of the conditions used for *exo*-methylenation of lactones **12** as described in Scheme 2 failed in this particular case and resulted in a complex mixture of products. However, deprotonation of **19** with in situ generated LDA, followed by addition of Eschenmoser's salt[73] and methyl iodide, furnished the required *exo*-methylene coumarine **20**.[74]

Matsuda−Heck arylation of **20** with phenol diazonium salt **13b** led to an inseparable mixture of products, which contained only minor amounts of the desired coupling product. Interestingly, the Matsuda−Heck coupling worked satisfactorily with **21**, obtained after desilylation of **20**, under otherwise identical conditions and furnished anemarcoumarin A in six steps from umbelliferone in an overall yield of 28% (Scheme 7).

Scheme 7. Total Synthesis of Anemarcoumarin A from Umbelliferone



CONCLUSIONS

In summary, we report conditions for the base- and ligand-free Heck-type arylation of α-methylene lactones with arene diazonium salts. While mostly poor levels of regioselectivity were observed for α-methylene-γ-butyrolactone, the homologous six-membered α-methylene lactone and the analogous lactam react to the Matsuda−Heck products with perfect *endo*-selectivity. Based on DFT calculations, we suggest that the high levels of *endo*-selectivity observed for six-membered substrates result from kinetic rather than thermodynamic control. We found that for the Pd σ-complex an energetically favorable conformation coincides with a comparatively small [Pd−C^{α}−$C^{\beta endo}$−H] dihedral angle, which is not the case for the five-membered lactone. On the other hand, a conformer with a Pd−$H^{\beta exo}$ *syn* arrangement which is lower in energy and leads to an *exo*-*E*-product was observed for the five-membered lactone. An *endo*-selective Matsuda−Heck arylation of an α-methylene coumarin was finally applied to the synthesis of the plant natural product anemarcoumarin A.

EXPERIMENTAL SECTION

General Methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Coupling constants are given in hertz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal standard. Whenever the solubility of the sample or signal separation were insufficient in $CDCl_3$, it was replaced by one of the following solvents: DMSO-d_6 (DMSO-d_5 as internal standard for ^{1}H NMR spectroscopy, δ = 2.50 ppm, DMSO-d_6 as internal standard for ^{13}C NMR spectroscopy, δ = 39.5 ppm); C_6D_6 (C_6D_5 as internal standard for

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^{1}H NMR spectroscopy, δ = 7.16 ppm, C_6D_6 as internal standard for ^{13}C NMR spectroscopy, δ = 128.1 ppm); acetone-d_6 (acetone-d_5 as internal standard for ^{1}H NMR spectroscopy, δ = 2.05 ppm, CD_3COCD_3 as internal standard for ^{13}C NMR spectroscopy, δ = 29.8 ppm); methanol-d_4 (CD_2HOD as internal standard for ^{1}H NMR spectroscopy, δ = 3.31 ppm, CD_3OD as internal standard for ^{13}C NMR spectroscopy, δ = 49.0 ppm). IR spectra were recorded as ATR-FTIR spectra. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high-resolution mass spectra were obtained by EI-TOF or ESI-TOF. The following arene diazonium salts were synthesized from anilines by diazotation or from acetanilides through the deacetylation−diazotation sequence, according to previously published procedures: **13a**,[29] **13b**,[14] **13c**,[29] **13d**,[29] **13e**,[14] **13f**,[29] **13g**,[14] **13h**,[29] **13i**,[32] **13j**,[42] **13k**,[14] **13m**,[46] **13n**.[29]

Computational Methods. All DFT calculations were performed with the B3LYP density functional[75−77] as implemented in the ORCA[78] program package. We used the def2-TZVP basis set[79] for all atoms and a Stuttgart−Dresden effective core potential (SD(28, MWB))[80] for palladium. To further account for the methanol solvent effects, the conductor-like screening model (COSMO)[81] was used. A frequency calculation was performed for the stationary points to calculate the thermochemical properties.

*3-Methylenetetrahydro-2H-pyran-2one (**9b**).*[36] A suspension of NaH (60 wt % dispersion in mineral oil, 1.12 g, 28.2 mmol) in THF (100 mL) was cooled to 0 °C, and a solution of **12b** (1.70 g, 17.1 mmol) and diethyl oxalate (5.10 g, 35.1 mmol) in THF (100 mL) was added dropwise. After addition was complete, ethanol (4.5 mL) was added, and the reaction mixture was warmed to ambient temperature and stirred for 4 h. After the mixture was cooled to 0 °C, a solution of K_2CO_3 (9.60 g, 70.0 mmol) in water (14.1 mL) and formaldehyde (37 wt % aq solution, 18.9 g) were added, and the reaction mixture was stirred for 0.25 h at this temperature. After this time, the mixture was diluted with brine (50 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (50 mL each). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **9b** (1.50 g, 13.4 mmol, 78%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41−6.37 (m, 1H), 5.55−5.51 (m, 1H), 4.35 (t, J = 5.4 Hz, 2H), 2.68−2.58 (m, 2H), 1.99−1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 134.2, 128.3, 69.8, 28.2, 23.3; IR (ATR) ν 1714 (s), 1624 (w), 1399 (m), 1294 (s), 1143 (s); HRMS (EI) calcd for $C_6H_8O_2$ [M$^+$] 112.0524, found 112.0528.

*6-Methyl-3-methylenetetrahydro-2H-pyran-2one (**9c**).*[37] Following the procedure for **9b**, **12c** (2.00 g, 17.1 mmol) was converted to **9c** (1.50 g, 12.0 mmol, 70%): colorless liquid; ^{1}H NMR (300 MHz, C_6D_6) δ 6.41−6.37 (m, 1H), 5.10−5.07 (m, 1H), 3.91−3.78 (m, 1H), 2.10 (dm, J = 16.3 Hz, 1H), 1.96 (ddm, J = 16.4, 12.2 Hz, 1H), 1.20 (dm, J = 13.9 Hz, 1H), 1.10−0.95 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 164.4, 134.5, 126.4, 76.0, 29.8, 27.0, 21.2; IR (ATR) ν 1714 (s), 1387 (m), 1295 (s), 1170 (m), 1129 (s).

*Ethyl 1-Benzylpiperdine-3-carboxylate (**N-Bn-12d**).* A solution of ethyl nipecotate (**12d**, 7.90 g, 50.0 mmol), NEt_3 (14.10 mL, 100.0 mmol), and benzyl bromide (6.60 mL, 55.0 mmol) in acetonitrile (30 mL) was heated to 80 °C until full conversion of the starting material. The solvent was evaporated, and aq NaOH (1 M) was added (pH = 12). The residue was extracted three times with CH_2Cl_2 (50 mL each). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **N-Bn12d** (12.30 g, 50.0 mmol, quant): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.12 (m, 5H), 4.13 (q, J = 7.1 Hz, 2H), 3.58 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 2.97 (dm, J = 11.0 Hz, 1H), 2.74 (dm, J = 11.3 Hz, 1H), 2.66−2.54 (m, 1H), 2.26 (dd, J = 10.5, 10.5 Hz, 1H), 2.07 (ddd, J = 10.8, 10.8, 2.8 Hz, 1H), 2.00−1.88 (m, 1H), 1.82−1.70 (m, 1H), 1.70−1.40 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 138.4, 129.0, 128.2, 127.0, 63.3, 60.2, 55.4, 53.6, 41.9, 27.0, 24.6, 14.2; IR (ATR) ν 2941 (w), 1729 (s), 1189 (m), 1154 (m); HRMS (EI) calcd for $C_{15}H_{21}NO_2$ [M$^+$] 247.1572, found 247.1576.

*1-Benzyl-3-methylenepiperidin-2-one (**9d**).*[82] A solution of ***N*-Bn-12d** (9.50 g, 38.4 mmol) and NaOH (1.70 g, 42.5 mmol) in water (18 mL) and methanol (350 mL) was stirred at ambient temperature for 12 h. After this time, the solvent was evaporated, and the residue was suspended in toluene and evaporated again. To the dry residue were added acetanhydride (370 mL) and NEt_3 (54 mL), and the reaction mixture was heated to 90 °C for 12 h. All volatiles were evaporated, and water (100 mL) and CH_2Cl_2 (100 mL) were added. The aqueous layer was extracted three times with CH_2Cl_2 (100 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **9d** (5.40 g, 26.8 mmol, 70%): yellowish liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 5H), 6.28 (ddd, J = 1.8, 1.8, 1.8 Hz, 1H), 5.31 (dd, J = 1.8, 1.8, 1.8 Hz, 1H), 4.66 (s, 2H), 3.32−3.24 (m, 2H), 2.67−2.49 (m, 2H), 1.99−1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 137.9, 137.4, 128.7, 128.2, 127.4, 122.0, 50.8, 47.9, 30.3, 23.2; IR (ATR) ν 2932 (w), 1656 (s), 1610 (s), 1486 (m), 1451 (m), 1222 (m); HRMS (EI) calcd for $C_{13}H_{15}NO$ [M$^+$] 201.1154, found 201.1158.

*4-Hydroxy-2-(methoxycarbonyl)benzenediazonium Tetrafluoroborate (**13l**).* A suspension of **14l** (1.00 g, 6.0 mmol), tetrafluoroboric acid (50 wt % in water, 1.20 mL, 9.6 mmol), water (0.74 mL) and 2-propanol (1.00 mL) was stirred for 0.5 h at ambient temperature. The resulting solution was then cooled to 0 °C, and $NaNO_2$ (0.82 g, 12.0 mmol) was added in small portions. The suspension was stirred for 0.5 h at 0 °C and filtered through a Büchner funnel. The solid was washed with cold water (15 mL), ethanol, and then diethyl ether and dried in vacuum to give **13l** (0.71 g, 2.7 mmol, 42%): grayish solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, J = 9.4 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 9.4, 2.3 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.6, 162.4, 136.7, 132.9, 123.9, 123.6, 87.4, 53.6; IR (KBr-disc) ν 3320 (w), 2181 (s), 1735 (s), 1709 (s), 1437 (m), 1292 (s); HRMS (ESI) calcd for $C_8H_7N_2O_3$ [M$^+$] 179.0457, found 179.0454.

General Procedure 1: Matsuda−Heck Couplings of 9a,b under Base-Free Conditions. The appropriate arene diazonium salt **13** (0.40 mmol) and $Pd(OAc)_2$ (4.5 mg, 5.0 mol %) were suspended in the corresponding solvent as indicated in Table 2 (4.0 mL). α-Methylene-γ-butyrolactone **9a** (78 mg, 0.80 mmol) or α-methylene-δ-valerolactone **9b** (90 mg, 0.80 mmol) was added, and the reaction mixture was stirred at ambient temperature for 12 h. The solvent was evaporated, and the residue was purified by column chromatography on silicia using hexane−MTBE mixtures of increasing polarity as eluent.

General Procedure 2: Matsuda−Heck Couplings of 9a,b under Basic Conditions. The appropriate arene diazonium salt **13** (0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 5.0 mol %), and NaOAc (98 mg, 1.20 mmol) were suspended in the corresponding solvent as indicated in Table 2 (4.0 mL). α-Methylene-γ-butyrolactone **9a** (78 mg, 0.80 mmol) or α-methylene-δ-valerolactone **9b** (90 mg, 0.80 mmol) was added, and the reaction mixture was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was partitioned between water (10 mL) and MTBE (10 mL). The aqueous layer was separated and extracted with MTBE (3 times, 10 mL for each extraction). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica using hexane−MTBE mixtures of increasing polarity as eluent.

*3-(4-Methoxybenzyl)furan-2(5H)-one (endo-**11aa**)*[11] *and (E)-3-(4-Methoxybenzylidene)dihydrofuran-2(3H)-one (exo-**11aa**).*[83] Following general procedure 2 (solvent: acetonitrile), **9a** (78 mg, 0.80 mmol) and **13a** (89 mg, 0.40 mmol) were converted to a 2.7:1.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11aa** (70 mg, 0.34 mmol, 85%). Following general procedure 1 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13a** (89 mg, 0.40 mmol) were converted to a 1.0:6.6 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11aa** (60 mg,

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0.29 mmol, 73%). NMR data of *endo*-**11aa**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.5 Hz, 2H), 6.92 (pent, J = 1.8 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 4.72 (q, J = 1.9 Hz, 2H), 3.76 (s, 3H), 3.50 (q, J = 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 158.5, 145.5, 134.5, 129.9, 129.4, 114.1, 70.3, 55.3, 31.0. NMR data of *exo*-**11aa**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 2.9 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.41 (t, J = 7.3 Hz, 2H), 3.82 (s, 3H), 3.17 (td, J = 7.3, 2.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 160.9, 136.3, 131.8, 127.4, 120.7, 114.4, 65.4, 55.4, 27.4; HRMS (ESI) calcd for $C_{12}H_{13}O_3$ $[M + H]^+$ 205.0865, found 205.0865.

*3-(4-Hydroxybenzyl)furan-2(5H)-one (endo-**11ab**) and (E)-3-(4-Hydroxybenzylidene)dihydrofuran-2(3H)-one (exo-**11ab**).*[83] Following general procedure 1 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13b** (83 mg, 0.40 mmol) were converted to a 1.0:6.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11ab** (58 mg, 0.30 mmol, 76%). NMR data of *endo*-**11ab**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.32 (s (br.), 1H), 7.28 (pent, J = 1.6 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 4.80 (q, J = 1.8 Hz, 2H), 3.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.0, 156.0, 148.0, 132.3, 129.8, 128.1, 115.4, 70.7, 30.2. NMR data of *exo*-**11ab**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s (br.), 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.31 (t, J = 2.6 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 4.37 (t, J = 7.3 Hz, 2H), 3.15 (td, J = 7.2, 2.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 159.3, 135.2, 132.3, 125.8, 120.9, 116.1, 65.5, 27.0; HRMS (ESI) calcd for $C_{11}H_{11}O_3$ $[M + H]^+$ 191.0708, found 191.0709.

*3-(3-Bromo-4-methoxybenzyl)furan-2(5H)-one (endo-**11ad**) and (E)-3-(3-Bromo-4-methoxy-benzylidene)dihydrofuran-2(3H)-one 3-(3-Bromo-4-methoxybenzyl)furan-2(5H)-one (exo-**11ad**).* Following general procedure 2 (solvent: acetonitrile), **9a** (78 mg, 0.80 mmol) and **13d** (120 mg, 0.40 mmol) were converted to a 1.0:1.4 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11ad** (108 mg, 0.38 mmol, 96%). NMR data of *endo*-**11ad**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.34 (m, 1H, signal overlap with endo isomer), 7.14 (dd, J = 8.3, 1.8 Hz, 1H), 7.00 (pent, J = 1.7 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.75 (q, J = 1.8 Hz, 2H), 3.84 (s, 3H), 3.51−3.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 154.7, 145.9, 133.7, 133.5, 130.9, 129.0, 112.1, 111.6, 70.3, 56.3, 30.5. NMR data of *exo*-**11ad**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 1.8 Hz, 1H), 7.43−7.34 (m, 2H, signal overlap with endo isomer), 6.94 (d, J = 8.3 Hz, 1H), 4.43 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.18 (td, J = 7.3, 2.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.9, 134.6, 134.3, 131.1, 128.6, 122.3, 112.2, 112.0, 65.4, 56.4, 27.2; HRMS (ESI) calcd for $C_{12}H_{12}{}^{79}BrO_3$ $[M + H]^+$ 282.9970, found 282.9957.

*3-(3-Bromo-4-hydroxybenzyl)furan-2(5H)-one (endo-**11ae**) and (E)-3-(3-Bromo-4-hydroxybenzylidene)dihydrofuran-2(3H)-one (exo-**11ae**).* Following general procedure 2 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13e** (115 mg, 0.40 mmol) were converted to a 10.0:1.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11ae** (47 mg, 0.18 mmol, 44%). Following general procedure 1 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13e** (115 mg, 0.40 mmol) were converted to a 10.0:1.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11ae** (34 mg, 0.13 mmol, 32%). Selected ^{1}H NMR data of *exo*-**11ae**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s (br.), 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.48 (dd, J = 8.6, 2.0 Hz, 1H), 7.31 (t, J = 2.7 Hz, 1H), 4.40 (t, J = 7.2 Hz, 2H), 3.20 (td, J = 7.2, 2.7 Hz, 2H). NMR data of *endo*-**11ae**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.38−7.34 (m, 2H), 7.05 (dd, J = 8.3, 2.0 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 4.83 (q, J = 1.7 Hz, 2H), 3.43 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 152.6, 148.3, 132.8, 131.6, 130.0, 129.0, 116.3, 109.1, 70.6, 29.6; HRMS (EI) calcd for $C_{11}H_9{}^{79}BrO_3$ $[M^+]$ 267.9735, found 267.9728.

*3-(4-Methoxy-3-nitrobenzyl)furan-2(5H)-one (endo-**11af**) and (E)-3-(4-Methoxy-3-nitrobenzylidene)dihydrofuran-2(3H)-one (exo-**11af**).* Following general procedure 1 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13f** (108 mg, 0.40 mmol) were converted to a 2.0:1.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11af** (93 mg, 0.38 mmol, 94%). NMR data of *endo*-**11af**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 8.9, 2.0 Hz, 1H), 7.09−7.05 (m, 2H), 4.82 (q, J = 1.7 Hz, 2H), 3.97 (s, 3H), 3.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 152.0, 146.0, 134.8, 125.8, 113.9, 70.3, 56.6, 30.6, other signals cannot be unambigously assigned due to signal overlap. NMR data of *exo*-**11af**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 1.8 Hz, 1H), 7.69 (dd, J = 8.8, 1.9 Hz, 1H), 7.51−7.48 (m, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.52 (t, J = 7.2 Hz, 2H), 4.04 (s, 3H), 3.28 (td, J = 7.2, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.4, 56.8, 27.2, other signals cannot be unambigously assigned due to signal overlap; HRMS (ESI) calcd for $C_{12}H_{12}NO_5$ $[M + H]^+$ 250.0715, found 250.0702.

*3-(4-Hydroxy-3-nitrobenzyl)furan-2(5H)-one (endo-**11ag**) and (E)-3-(4-Hydroxy-3-nitrobenzylidene)dihydrofuran-2(3H)-one (exo-**11ag**).* Following general procedure 1 (solvent: methanol), **9a** (78 mg, 0.80 mmol) and **13g** (101 mg, 0.40 mmol) were converted to a 2.0:1.0 mixture (determined by ^{1}H NMR analysis of the crude mixture) of *endo*- and *exo*-**11ag** (93 mg, 0.40 mmol, 99%). NMR data of *endo*-**11ag**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.52 (dd, J = 8.6, 1.9 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.13−7.10 (m, 1H), 4.82 (q, J = 1.7 Hz, 2H), 3.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 154.0, 146.2, 138.4, 124.7, 120.4, 70.4, 30.6, other signals cannot be unambigously assigned. NMR data of *exo*-**11ag**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.26 (d, J = 1.6 Hz, 1H), 7.74 (dd, J = 8.7, 1.9 Hz, 1H), 7.48 (t, J = 2.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 4.52 (t, J = 7.2 Hz, 2H), 3.28 (td, J = 7.2, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.6, 133.6, 127.4, 124.6, 120.9, 65.4, 27.2, other signals can not be unambigously assigned; HRMS (ESI) calcd for $C_{11}H_{10}NO_5$ $[M + H]^+$ 236.0559, found 236.0560.

*3-(4-Methoxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11ba**).*[84] Following general procedure 2 (solvent: acetonitrile), **9b** (112 mg, 1.00 mmol) and **13a** (111 mg, 0.50 mmol) were converted to *endo*-**11ba** (106 mg, 0.49 mmol, 98%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.5 Hz, 2H), 6.85 (d, J = 7.4 Hz, 2H), 6.55−6.33 (m, 1H), 4.33 (t, J = 5.9 Hz, 2H), 3.81 (s, 3H), 3.56 (s, 2H), 2.44−2.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 158.6, 140.2, 133.6, 130.7, 130.7, 114.4, 66.8, 55.7, 36.3, 24.8; IR (ATR) ν 1710 (s), 1510 (s), 1398 (m), 1243 (s); HRMS (ESI) calcd for $C_{13}H_{14}O_3$ $[M + H]^+$ 219.1016, found 219.1016.

*3-(4-Hydroxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bb**).* Following general procedure 1 (solvent: methanol), **9b** (112 mg, 1.00 mmol) and **13b** (105 mg, 0.50 mmol) were converted to *endo*-**11bb** (76 mg, 0.37 mmol, 74%): colorless solid; mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 6.36 (t, J = 4.3 Hz, 1H), 6.28 (s, 1H), 4.23 (t, J = 6.3 Hz, 2H), 3.43 (d, J = 1.1 Hz, 1H), 2.35−2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 154.8, 140.5, 133.2, 130.4, 129.9, 115.6, 66.6, 36.0, 24.5; IR (ATR) ν 3341 (bw), 1668 (s), 1513 (s), 1273 (m), 1117 (s); HRMS (EI) calcd for $C_{12}H_{12}O_3$ $[M^+]$ 204.0786, found 204.0776.

*3-(4-(Benzyloxy)benzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bc**).* Following general procedure 2 (solvent: acetonitrile), **9b** (90 mg, 0.80 mmol) and **13a** (119 mg, 0.40 mmol) were converted to *endo*-**11bc** (78 mg, 0.26 mmol, 66%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.31 (m, 5H), 7.15 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 6.44 (t, J = 4.2 Hz, 1H), 5.02 (s, 2H), 4.36 (t, J = 6.2 Hz, 2H), 3.59 (s, 2H), 2.47−2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 157.9, 140.2, 137.5, 133.6, 131.0, 130.7, 129.0, 128.3, 127.9, 115.3, 70.5, 66.8, 36.3, 24.8; IR (ATR) ν 1711 (s), 1609 (m), 1509 (s), 1237 (s); HRMS (EI) calcd for $C_{19}H_{18}O_3$ $[M^+]$ 294.1256, found 294.1245.

*3-(3-Bromo-4-methoxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bd**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13d** (120 mg, 0.40 mmol) were converted to *endo*-**11bd** (98 mg, 0.33 mmol, 82%): colorless liquid; ^{1}H NMR (300 MHz, C_6D_6) δ 7.36 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 8.4, 2.1 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 5.69 (t, J = 4.2 Hz, 1H), 3.55 (t, J = 6.2 Hz, 2H), 3.39 (s, 2H), 3.25 (s, 3H), 1.50−1.29 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 164.0, 155.1, 139.5, 134.1, 132.9, 132.9, 129.7, 112.3, 112.2, 65.8, 55.7, 36.2, 24.3; IR (ATR) ν 1712 (s), 1495 (s), 1400 (m), 1276 (s), 1255 (s), 1114 (s); HRMS (EI) calcd for $C_{13}H_{13}{}^{79}BrO_3$ $[M^+]$ 296.0048, found 296.0047.

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*3-(3-Bromo-4-hydroxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11be**).* Following general procedure 2 (solvent: methanol), **9b** (112 mg, 1.00 mmol) and **13e** (143 mg, 0.50 mmol) were converted to *endo*-**11be** (95 mg, 0.34 mmol, 68%): colorless liquid; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.75 (s, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 4.3 Hz, 1H), 4.32 (t, J = 6.2 Hz, 2H), 3.48 (d, J = 1.1 Hz, 2H), 2.57−2.36 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.0, 153.3, 141.9, 134.1, 133.0, 132.9, 130.2, 117.1, 110.1, 67.1, 36.3, 25.1; IR (ATR) ν 3258 (m), 1648 (s), 1494 (m), 1416 (m), 1274 (s), 1115 (s); HRMS (ESI) calcd for $C_{12}H_{12}{}^{79}BrO_3$ $[M + H]^+$ 282.9964, found 282.9970.

*3-(4-Methoxy-3-nitrobenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bf**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13f** (107 mg, 0.40 mmol) were converted to *endo*-**11bf** (86 mg, 0.33 mmol, 82%): yellowish liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 2.2 Hz, 1H), 7.43 (dd, J = 8.6, 2.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.58 (t, J = 4.3 Hz, 1H), 4.34 (t, J = 6.3 Hz, 2H), 3.91 (s, 3H), 3.58 (s, 2H), 2.50−2.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 151.8, 141.0, 139.5, 135.2, 132.0, 131.1, 125.9, 113.9, 66.5, 56.7, 35.9, 24.5; IR (ATR) ν 1711 (s), 1624 (m), 1527 (s), 1351 (m), 1281 (w), 1261 (s), 1116 (s); HRMS (EI) calcd for $C_{13}H_{13}NO_5$ $[M^+]$ 263.0794, found 263.0803.

*3-(4-Hydroxy-3-nitrobenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bg**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13g** (101 mg, 0.40 mmol) were converted to *endo*-**11bg** (98 mg, 0.39 mmol, 99%): yellow solid; mp 90−92 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.49 (dd, J = 8.5, 2.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.60 (t, J = 4.3 Hz, 1H), 4.37 (t, J = 6.1 Hz, 2H), 3.60 (d, J = 1.2 Hz, 2H), 2.57−2.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 154.0, 141.0, 138.8, 133.5, 132.1, 131.1, 124.8, 120.2, 66.6, 36.1, 24.6; IR (ATR) ν 3281 (bw), 1715 (s), 1629 (m), 1536 (s), 1329 (m), 1116 (s); HRMS (EI) calcd for $C_{12}H_{11}NO_5$ $[M^+]$ 249.0637, found 249.0647.

*3-(4-Methoxy-2-nitrobenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bh**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13g** (107 mg, 0.40 mmol) were converted to *endo*-**11bh** (51 mg, 0.19 mmol, 48%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.6, 2.7 Hz, 1H), 6.43 (t, J = 4.2 Hz, 1H), 4.32 (t, J = 6.2 Hz, 2H), 3.86 (d, J = 1.4 Hz, 2H), 3.84 (s, 3H), 2.55−2.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 158.9, 149.8, 140.7, 134.1, 130.9, 124.9, 119.8, 109.7, 66.4, 55.9, 33.5, 24.5; IR (ATR) ν 1711 (s), 1524 (s), 1505 (m), 1251 (s), 1114 (s); HRMS (EI) calcd for $C_{13}H_{13}NO_5$ $[M^+]$ 263.0794, found 263.0792.

*3-(4-Nitrobenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bj**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13j** (95 mg, 0.40 mmol) were converted to *endo*-**11bj** (62 mg, 0.27 mmol, 67%): yellowish liquid; ^{1}H NMR (300 MHz, C_6D_6) δ 7.84 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.62 (t, J = 4.0 Hz, 1H), 3.60 (t, J = 6.2 Hz, 2H), 3.29 (s, 2H), 1.49−1.39 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 163.6, 147.1, 146.5, 140.5, 131.6, 129.9, 123.7, 65.9, 37.0, 24.3; IR (ATR) ν 1709 (s), 1512 (s), 1341 (s), 1110 (s); HRMS (ESI) calcd for $C_{12}H_{12}NO_4$ $[M + H]^+$ 234.0761, found 234.0762.

*3-(2-Methylcarboxylate-4-hydroxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bl**).* Following general procedure 1 (solvent: methanol), **9b** (90 mg, 0.80 mmol) and **13l** (107 mg, 0.40 mmol) were converted to *endo*-**11bl** (51 mg, 0.20 mmol, 49%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 2.6 Hz, 1H), 7.27 (s (br.), 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.96 (dd, J = 8.3, 2.7 Hz, 1H), 6.32−6.25 (m, 1H), 4.31 (t, J = 6.2 Hz, 2H), 3.87 (s, 2H), 3.79 (s, 3H), 2.48−2.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 166.0, 155.1, 140.3, 133.3, 132.8, 130.8, 130.8, 119.7, 117.8, 66.6, 52.2, 34.0, 24.4; IR (ATR) n 1714 (s), 1688 (s), 1435 (m), 1274 (s), 1216 (s); HRMS (EI) calcd for $C_{14}H_{14}O_5$ $[M^+]$ 262.0841, found 262.0853.

*3-(4-Acetamidobenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11bm**).* Following general procedure 2 (solvent: acetonitrile), **9b** (90 mg, 0.80 mmol) and **13m** (100 mg, 0.40 mmol) were converted to *endo*-**11bm** (30 mg, 0.12 mmol, 31%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.47 (t, J = 4.0 Hz, 1H), 4.32 (t, J = 6.3 Hz, 2H), 3.53 (s, 2H), 2.51−2.34 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 165.1, 140.6, 136.8, 134.0, 132.7, 129.6, 120.3, 66.5, 36.4, 24.5, 24.4; HRMS (EI) calcd for $C_{14}H_{15}NO_3$ $[M^+]$ 245.1052, found 245.1048.

*3-(4-Methoxybenzyl)-6-methyl-5,6-dihydro-2H-pyran-2-one (endo-**11ca**).* Following general procedure 2 (solvent: methanol), **9c** (126 mg, 1.00 mmol) and **13a** (111 mg, 0.50 mmol) were converted to *endo*-**11ca** (95 mg, 0.41 mmol, 82%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.35 (t, J = 4.3 Hz, 1H), 4.58−4.44 (m, 1H), 3.79 (s, 3H), 3.57 (s, 2H), 2.33−2.25 (m, 2H), 1.41 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 158.2, 139.2, 132.8, 130.4, 130.2, 114.0, 74.2, 55.2, 35.7, 31.4, 20.7; IR (ATR) ν 1711 (s), 1511 (s), 1242 (s), 1119 (m); HRMS (ESI) calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178, found 233.1164.

*3-(4-Methoxybenzyl)dihydrofuran-2(3H)-one (**16aa**).*[85] Arene diazonium salt **13a** (89 mg, 0.40 mmol) and $Pd(OAc)_2$ (4.5 mg, 5.0 mol %) were suspended in methanol (4.0 mL). Lactone **9a** (78 mg, 0.80 mmol) was added, and the reaction mixture was stirred at ambient temperature until the evolution of nitrogen gas had ceased. Activated charcoal (45 mg) was added, the solution was flushed with hydrogen, and the reaction mixture was kept under an atmosphere of hydrogen for 12 h. The solvent was evaporated, and the residue was partitioned between water (10 mL) and MTBE (10 mL). The aqueous layer was separated and extracted three times with MTBE (10 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **16aa** (65 mg, 0.32 mmol, 79%): colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.21 (td, J = 8.8, 3.2 Hz, 1H), 4.14 (td, J = 9.2, 6.8 Hz, 1H), 3.80 (s, 3H), 3.16 (dd, J = 13.8, 4.2 Hz, 1H), 2.82 (dddd, J = 18.5, 9.5, 8.8, 4.2 Hz, 1H), 2.73 (dd, J = 13.8, 9.1 Hz, 1H), 2.25 (dddd, J = 12.6, 8.7, 6.8, 3.2 Hz, 1H), 2.04−1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 158.8, 130.7, 130.3, 114.5, 67.0, 55.7, 41.6, 35.7, 28.3; IR (ATR) ν 1762 (s), 1512 (s), 1246 (s), 1022 (s); HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1021, found 207.1037.

*3-(4-Hydroxybenzyl)dihydrofuren-2(3H)-one (**16ab**).* Following the procedure given above for **16aa**, lactone **9a** (78 mg, 0.80 mmol) and diazonium salt **13b** (83 mg, 0.40 mmol) were converted to **16ab** (74 mg, 0.38 mmol, 95%): colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (s (br.), 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.22−4.10 (m, 2H), 3.10 (dd, J = 13.9, 4.4 Hz, 1H), 2.83 (dddd, J = 18.4, 9.5, 8.9, 4.4 Hz, 1H), 2.72 (dd, J = 13.9, 8.8 Hz, 1H), 2.23 (dddd, J = 12.5, 8.8, 6.8, 3.6 Hz, 1H), 2.03−1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 155.4, 130.5, 130.0, 116.1, 65.7, 41.8, 35.5, 28.1; IR (ATR) ν 3357 (bm), 1742 (s), 1515 (s), 1205 (m); HRMS (ESI) calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0865, found 193.0866.

*(Z)-2-(4-Methoxybenzyl)penta-2,4-dienoic Acid (**Z-15ba**).* To a solution of *endo*-**11ba** (21.8 mg, 0.10 mmol) in DMSO (1.0 mL) was added KOH (22.4 mg, 0.40 mmol), and the reaction mixture was stirred at 45 °C until the starting material was fully consumed as indicated by TLC (ca. 1 h). After the mixture was cooled to ambient temperature, aq HCl (1 M, 10 mL) was added followed by ethyl acetate (10 mL). The aqueous layer was separated and extracted three times with ethyl acetate (10 mL for each extraction). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish *Z*-**15ba** (15.4 mg, 0.07 mmol, 71%): colorless liquid; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.37 (ddd, J = 17.0, 11.0, 10.2 Hz, 1H), 7.16 (d, J = 8.7, 2H), 6.86 (d, J = 8.7, 2H), 6.51 (d, J = 11.1 Hz, 1H), 5.44 (dd, J = 17.0, 1.7 Hz, 1H), 5.34 (dd, J = 10.0, 1.8 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.8, 158.7, 139.9, 134.5, 132.7, 131.7, 130.1, 122.7, 114.1, 54.9, 39.6; IR (ATR) ν 2941 (bw), 1676 (s), 1511 (s), 1242 (s); HRMS (EI) calcd for $C_{13}H_{14}O_3$ $[M^+]$ 218.0943, found 218.0934.

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*(2Z,4E)-2-(4-Methoxybenzyl)hexa-2,4-dienoic Acid ((2Z,4E)-**15ca**).* Following the procedure given above for *Z*-**15ba**, *endo*-**11ca** (23.7 mg, 0.10 mmol) was converted to (2*Z*,4*E*)-**15ca** (16.4 mg, 0.07 mmol, 69%): colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (ddq, J = 15.0, 11.3, 1.6 Hz, 1H), 7.15 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 11.3 Hz, 1H), 6.04 (dq, J = 15.0, 6.8 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 2H), 1.89 (dd, J = 6.9, 1.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 158.5, 144.4, 139.6, 132.0, 130.2, 129.5, 127.0, 114.2, 55.6, 39.3, 19.1; IR (ATR) ν 2929 (bw), 1677 (s), 1511 (s), 1247 (s); HRMS (EI) calcd for $C_{14}H_{17}O_3$ [M^+] 233.1178, found 233.1181.

General Procedure 3: Matsuda−Heck Couplings of 9d under Base-Free Conditions. The appropriate arene diazonium salt **13** (0.80 mmol) and $Pd(OAc)_2$ (4.5 mg, 5.0 mol %) were suspended in the corresponding solvent as indicated in Table 3 (4.0 mL). *N*-Benzyl-α-methylene-δ-valerolactam **9d** (81 mg, 0.40 mmol) was added, and the reaction mixture was stirred at ambient temperature for 12 h. The solvent was evaporated, and the residue was purified by column chromatography on silica using hexane−MTBE mixtures of increasing polarity as eluent.

General Procedure 4: Matsuda−Heck Couplings of 9d under Basic Conditions. The appropriate arene diazonium salt **13** (0.80 mmol), $Pd(OAc)_2$ (4.5 mg, 5.0 mol %), and NaOAc (98 mg, 1.20 mmol) were suspended in the corresponding solvent as indicated in Table 3 (4.0 mL). *N*-Benzyl-α-methylene-δ-valerolactam **9d** (81 mg, 0.40 mmol) was added, and the reaction mixture was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was partitioned between water (10 mL) and MTBE (10 mL). The aqueous layer was separated and extracted with MTBE (3 times, 10 mL for each extraction). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica using hexane−MTBE mixtures of increasing polarity as eluent.

*1-Benzyl-3-(4-methoxybenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11da**).* Following the general procedure 4 (solvent: acetonitrile), **9d** (81 mg, 0.40 mmol) and **13a** (177 mg, 0.80 mmol) were converted to *endo*-**11da** (90 mg, 0.29 mmol, 72%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.08−6.01 (m, 1H), 4.62 (s, 2H), 3.77 (s, 3H), 3.60 (s, 2H), 3.26 (t, J = 7.1 Hz, 2H), 2.35−2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 158.0, 137.7, 135.9, 132.3, 131.7, 130.3, 128.6, 127.9, 127.3, 113.8, 55.3, 50.1, 44.8, 35.9, 23.9; IR (ATR) ν 1663 (m), 1621 (s), 1508 (s), 1242 (s), 1031 (m); HRMS (EI) calcd for $C_{20}H_{21}NO_2$ [M^+] 307.1572, found 307.1585.

*1-Benzyl-3-(4-hydroxybenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11db**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13b** (166 mg, 0.80 mmol) were converted to *endo*-**11db** (101 mg, 0.34 mmol, 86%): colorless solid, mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 7.04 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.11 (t, J = 4.3 Hz, 1H), 4.64 (s, 2H), 3.58 (s, 2H), 3.30 (t, J = 7.1 Hz, 2H), 2.33−2.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.6, 137.6, 135.9, 134.7, 131.2, 130.4, 128.7, 128.1, 127.5, 155.5, 50.4, 45.0, 36.2, 24.4; IR (ATR) ν 3256 (bm), 1661 (m), 1607 (s), 1592 (s), 1514 (s); HRMS (EI) calcd for $C_{19}H_{19}NO_2$ [M^+] 293.1416, found 293.1410.

*1-Benzyl-3-(4-(benzyloxy)benzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dc**).* Following general procedure 4 (solvent: acetonitrile), **9d** (81 mg, 0.40 mmol) and **13c** (238 mg, 0.80 mmol) were converted to *endo*-**11dc** (100 mg, 0.26 mmol, 65%): colorless solid, mp 189−190 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.48 (d, J = 8.4 Hz, 2H), 7.43−7.22 (m, 8H), 7.18 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.23 (t, J = 4.1 Hz, 1H), 5.09 (s, 2H), 4.60 (s, 2H), 3.55 (s, 2H), 2.06 (t, J = 7.1 Hz, 2H), 2.28−2.25 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.7, 162.5, 143.6, 142.9, 140.8, 139.7, 137.7, 135.2, 133.6, 133.6, 133.0, 132.9, 132.7, 132.2, 119.7, 74.7, 54.7, 50.0, 40.9, 29.0; IR (ATR) ν 1664 (m), 1622 (s), 1507 (s); HRMS (EI) calcd for $C_{26}H_{25}NO_2$ [M^+] 383.1885, found 383.1882.

*1-Benzyl-3-(3-bromo-4-methoxybenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dd**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13d** (240 mg, 0.80 mmol) were converted to *endo*-**11dd** (117 mg, 0.30 mmol, 76%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.33−7.24 (m, 5H), 7.16 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.12 (t, J = 3.8 Hz, 1H), 4.62 (s, 2H), 3.86 (s, 3H), 3.59 (s, 2H), 3.28 (t, J = 7.1 Hz, 2H), 2.35−2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 154.2, 137.6, 135.3, 134.7, 133.7, 133.5, 129.4, 128.6, 127.9, 127.3, 111.9, 111.4, 56.3, 50.1, 44.8, 35.7, 23.9; IR (ATR) ν 1663 (m), 1621 (s), 1495 (s), 1252 (m), 1055 (m); HRMS (EI) calcd for $C_{20}H_{20}N^{79}BrO_2$ [M^+] 385.0677, found 385.0667.

*1-Benzyl-3-(4-(benzyloxy)-3-bromobenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dn**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13n** (301 mg, 0.80 mmol) were converted to *endo*-**11dn** (122 mg, 0.26 mmol, 66%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.44 (m, 3H), 7.44−7.20 (m, 8H), 7.14 (dd, J = 8.3, 1.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.13 (t, J = 4.1 Hz, 1H), 5.14 (s, 2H), 4.64 (s, 2H), 3.60 (s, 2H), 3.29 (t, J = 7.1 Hz, 2H), 2.35−2.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 153.4, 137.6, 136.7, 135.2, 134.8, 133.9, 133.8, 129.2, 128.6, 128.6, 127.9, 127.9, 127.3, 127.0, 113.9, 112.3, 70.9, 50.1, 44.8, 35.7, 23.9; IR (ATR) ν 1664 (m), 1619 (s), 1490 (s); HRMS (EI) calcd for $C_{26}H_{25}N^{79}BrO_2$ [$M + H$]$^+$ 462.1063, found 462.1088.

*1-Benzyl-3-(4-methoxy-3-nitrobenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11df**).* Following general procedure 3 (solvent: methanol), **9d** (56 mg, 0.28 mmol) and **13f** (150 mg, 0.56 mmol) were converted to *endo*-**11df** (79 mg, 0.22 mmol, 80%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 2.0 Hz, 1H), 7.49 (dd, J = 8.6, 2.0 Hz, 1H), 7.38−7.12 (m, 5H), 7.03 (d, J = 8.6 Hz, 1H), 6.24 (t, J = 4.1 Hz, 1H), 4.62 (s, 2H), 3.93 (s, 3H), 3.67 (s, 2H), 3.31 (t, J = 7.1 Hz, 2H), 2.34−2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 151.4, 139.4, 137.4, 135.4, 135.2, 134.6, 132.5, 128.6, 127.9, 127.4, 125.7, 113.6, 56.6, 50.1, 44.8, 35.9, 24.0; IR (ATR) ν 1665 (m), 1620 (s), 1528 (s); HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4$ [$M + H$]$^+$ 353.1496, found 353.1514.

*1-Benzyl-3-(4-hydroxy-3-nitrobenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dg**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13g** (202 mg, 0.80 mmol) were converted to *endo*-**11dg** (129 mg, 0.38 mmol, 96%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.6, 1.8 Hz, 1H), 7.39−7.19 (m, 5H), 7.09 (d, J = 8.6 Hz, 1H), 6.27 (t, J = 3.9 Hz, 1H), 4.62 (s, 2H), 3.65 (s, 2H), 3.32 (t, J = 7.1 Hz, 2H), 2.43−2.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 153.6, 138.9, 137.4, 135.5, 134.5, 133.4, 132.5, 128.6, 127.9, 127.4, 124.5, 119.8, 50.1, 44.8, 36.0, 23.0; IR (ATR) ν 3246 (bw), 1662 (m), 1620 (s), 1536 (s), 1342 (s); HRMS (EI) calcd for $C_{19}H_{18}N_2O_4$ [M^+] 338.1267, found 338.1282.

*1-Benzyl-3-(4-nitrobenzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dj**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13j** (189 mg, 0.80 mmol) were converted to *endo*-**11dj** (44 mg, 0.14 mmol, 34%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.38−7.19 (m, 5H), 6.27 (t, J = 4.0 Hz, 1H), 4.62 (s, 2H), 3.76 (s, 2H), 3.33 (t, J = 7.1 Hz, 2H), 2.36−2.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 148.1, 146.6, 137.5, 135.9, 134.4, 129.9, 128.7, 128.0, 127.6, 123.7, 50.2, 44.9, 37.2, 24.1; IR (ATR) ν 1664 (m), 1621 (s), 1512 (s), 1342 (s); HRMS (EI) calcd for $C_{19}H_{18}N_2O_3$ [M^+] 322.1317, found 322.1313.

*1-Benzyl-3-(4-hydroxy-3-(methylbenzoate)benzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dk**).* Following general procedure 3 (solvent: methanol), **9d** (81 mg, 0.40 mmol) and **13k** (212 mg, 0.80 mmol) were converted to *endo*-**11dk** (93 mg, 0.26 mmol, 66%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.66 (s, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.36 (dd, J = 8.6, 2.0 Hz, 1H), 7.49−7.16 (m, 5H), 6.93 (d, J = 8.5 Hz, 1H), 6.12 (t, J = 4.0 Hz, 1H), 4.63 (s, 2H), 3.93 (s, 3H), 3.63 (s, 2H), 3.30 (t, J = 7.1 Hz, 2H), 2.31−2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.1, 160.1, 137.6, 136.9, 135.5, 134.6, 130.4, 130.2, 128.6, 128.0, 127.5, 117.4, 112.1, 52.3, 50.1, 44.8, 36.0, 24.0; IR (ATR) ν 3190 (bw), 1664 (s). 1620 (s), 1439 (m), 1209 (s), 1090 (m); HRMS (ESI) calcd. for $C_{21}H_{22}NO_4$ [$M + H$]$^+$ 352.1543, found 352.1563.

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*1-Benzyl-3-(4-hydroxy-2-(methylbenzoate)benzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dl**).* Following general procedure 3 (solvent: methanol), **9d** (66 mg, 0.34 mmol) and **13l** (181 mg, 0.68 mmol) were converted to *endo*-**11dl** (77 mg, 0.22 mmol, 65%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.37−7.14 (m, 5H), 7.08 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.3, 2.5 Hz, 1H), 5.94 (t, J = 4.3 Hz, 1H), 4.68 (s, 2H), 3.95 (s, 2H), 3.75 (s, 3H), 3.30 (t, J = 7.1 Hz, 2H), 2.24−2.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 165.9, 155.1, 137.3, 135.5, 134.7, 132.9, 131.7, 130.8, 128.7, 128.0, 127.5, 119.6, 117.7, 52.0, 50.4, 44.9, 34.1, 23.9; IR (ATR) ν 3207 (bw), 1716 (m), 1597 (s), 1293 (m).

*7-Hydroxychroman-2one (**18**).*[86] A suspension of **17** (3.24 g, 20.0 mmol) and Pd/C (200 mg, 10 wt %) in glacial acetic acid (60 mL) was stirred under an atmosphere of hydrogen for 12 h. The solvent was evaporated, and the residue purified by column chromatography on silica using hexane/MTBE mixtures of increasing polarity as eluent to furnish **18** (3.24 g, 19.7 mmol, 99%): colorless solid, mp 134−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 1H), 6.66−6.58 (m, 2H), 5.74 (bs, 1H), 2.96−2.89 (m, 2H), 2.82−2.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 156.0, 152.7, 128.8, 114.5, 111.9, 104.5, 29.6, 23.1; IR (ATR) ν 3340 (bw), 1764 (m), 1627 (m), 1141 (s), 1106 (s); HRMS (EI) calcd for $C_9H_8O_3$ [M^+] 164.0473, found 164.0475.

*7-((tert-Butyldimethylsilyl)oxy)chroman-2-one (**19**).*[87] A solution of **18** (3.00 g, 18.3 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and NEt_3 (2.80 mL, 27.5 mmol) was added, followed by dropwise addition of a solution of TBSCl (4.10 g, 27.5 mmol) in CH_2Cl_2 (20 mL). After addition was completed, the reaction mixture was warmed to ambient temperature and stirred until complete conversion of the starting material. The reaction was quenched by addition of water (50 mL), the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (25 mL for each extraction). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **19** (4.63 g, 19.7 mmol, 91%): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.1 Hz, 1H), 6.57 (dd, J = 8.1, 2.4 Hz, 1H), 6.54 (m, 2H), 2.96−2.88 (m, 2H), 2.81−2.68 (m, 2H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 155.8, 152.6, 128.4, 116.3, 115.3, 108.8, 29.6, 25.7, 23.2, 18.3, −4.4; IR (ATR) ν 2930 (w), 1767 (s), 1620 (m), 1504 (s), 1134 (s), 1105 (s); HRMS (EI) calcd for $C_{15}H_{22}O_3Si$ [M^+] 278.1338, found 278.1339.

*7-((tert-Butyldimethylsilyl)oxy)-3-methylenchroman-2-one (**20**).* To a solution of diisopropylamine (2.53 mL, 18.0 mmol) in THF (50 mL) was added BuLi (2.5 M solution in hexane, 7.20 mL, 18.0 mmol) dropwise at −78 °C. After 0.25 h, a solution of **19** (1.67 g, 6.0 mmol) in THF (10 mL) was added dropwise, and stirring was continued for 1 h at −78 °C, followed by addition of Eschenmoser's salt (3.88 g, 21.0 mmol) in one portion. The reaction mixture was then warmed to ambient temperature and stirred for 12 h. A satured aqueous solution of NH_4Cl (25 mL) was added, and the layers were separated. The aqueous layer was extracted three times with diethyl ether (25 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was dissolved in THF (20 mL), and methyl iodide (1.87 mL, 30.0 mmol) was added. The reaction mixutere was stirred for 12 h at ambient temperature. The suspension was filtered through a pad of Celite and washed with diethyl ether (25 mL). All volatiles were evaporated, and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **20** (0.97 g, 3.4 mmol, 56%): colorless solid; mp 46−47 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 6.63 (d, J = 2.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.52 (dd, J = 8.2, 2.3 Hz, 1H), 6.17−6.14 (m, 1H), 5.04−5.00 (m, 1H), 2.98 (s, 2H), 0.94 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 162.3, 156.0, 152.1, 132.5, 128.4, 127.4, 116.5, 114.6, 109.0, 31.3, 25.8, 18.4, − 4.5; IR (ATR) ν 2930 (w), 2858 (w), 1751 (m), 1622 (m), 1504 (s), 1151 (s), 1099 (s); HRMS (EI) calcd for $C_{16}H_{22}O_3Si$ [M^+] 290.1338, found 290.1346.

*7-Hydroxy-3-methylenchroman-2-one (**21**).* To a solution of **20** (100 mg, 0.34 mmol) in THF (10 mL) was added a solution of TBAF·$3H_2O$ (108 mg, 0.34 mmol) in THF (3 mL) at −78 °C. After full conversion of the starting material, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (3 mL) and warmed to ambient temperature. Diethyl ether (15 mL) was added, and the layers were separated. The aqueous layer was extracted three times with diethyl ether (15 mL for each extraction). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish **21** (55 mg, 0.31 mmol, 91%): colorless solid, decomposition at 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.63 (dd, J = 8.2, 2.3 Hz, 1H), 6.42 (s, 1H), 5.81 (bs, 1H), 5.78 (s, 1H), 3.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 155.9, 151.3, 131.9, 128.9, 128.5, 112.9, 112.1, 104.4, 31.2; IR (ATR) ν 3363 (bm), 1723 (s), 1628 (s), 1298 (s), 1153 (s); HRMS (EI) calcd for $C_{10}H_8O_3$ [M^+] 176.0473, found 176.0478.

Anemarcoumarin A. To a suspension of phenoldiazonium salt **13b** (31 mg, 0.15 mmol) and $Pd(OAc)_2$ (1.7 mg, 5.0 mol %) in methanol (3.0 mL) was added **21** (53 mg, 0.30 mmol), and the reaction mixture was stirred at ambient temperature until the gas evolution had ceased. The solvent was evaporated, and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, to furnish anemarcoumarin A (24.5 mg, 0.09 mmol, 61%): colorless solid; mp 206−209 °C; ^{1}H NMR (600 MHz, methanol-d_4) δ 7.33 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 6.68 (dd, J = 8.5, 2.3 Hz, 1H) 6.61 (d, J = 2.3 Hz, 1H), 3.61 (s, 2H); ^{13}C NMR (150 MHz, methanol-d_4) δ 164.2, 162.0, 157.1, 156.0, 141.5, 131.2, 130.4, 130.0, 126.0, 116.3, 114.3, 113.6, 103.0, 36.4; IR (ATR) ν 3324 (bm), 1688 (m), 1612 (s), 1513 (m), 1233 (m); HRMS (EI) calcd for $C_{16}H_{13}O_4$ [M + H]$^+$ 269.0808, found 269.0822. All analytical data match those reported for the natural product.[66]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02207.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Documentation of the DFT calculations (tables of atom coordinates and absolute energies) (PDF)

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Notes

The authors declare no competing financial interest.

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