JOC The Journal of Organic Chemistry



Article

# Systematic investigation into the Matsuda-Heck reaction of alpha-methylene lactones: how conformational constraints direct the beta-H-elimination step

Bernd Schmidt, Felix Wolf, and Christopher Ehlert

*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02207 • Publication Date (Web): 17 Oct 2016



## Just Accepted



ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

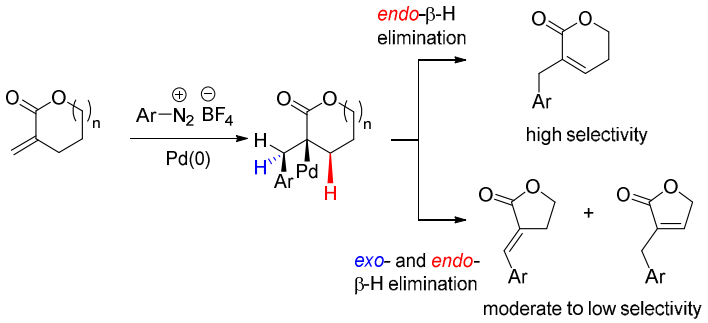
# Systematic investigation into the Matsuda-Heck reaction of α-methylene lactones: how conformational constraints direct the β-H-elimination step

Bernd Schmidt,* Felix Wolf and Christopher Ehlert.

Universitaet Potsdam, Institut fuer Chemie, Karl-Liebknecht-Straße 24-25, D-14476 Potsdam-Golm, Germany.

e-mail: bernd.schmidt@uni-potsdam.de

**Table of contents graphic:**




**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 case of the six-membered lactone an energetically favorable conformer adopts a nearly synperiplanar Pd/*endo*-β-H arrangement, whereas for the

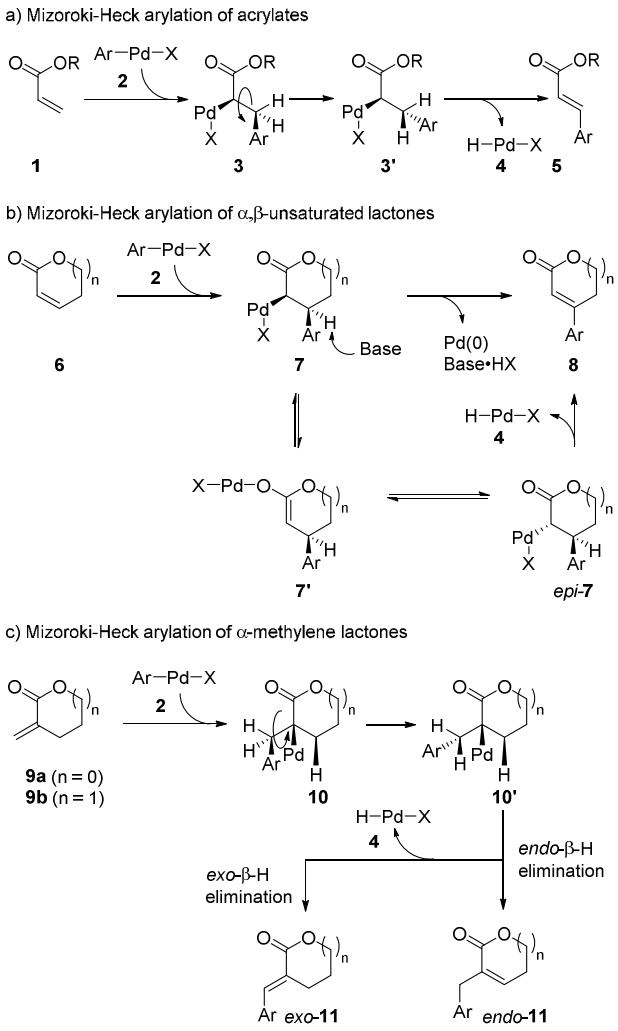
analogous Pd-σ-complex of the five-membered lactone the smallest Pd/*endo*-β-H dihedral angle is observed for a conformer with a comparatively high potential energy. The optimized conditions for Matsuda-Heck arylations of *exo*-methylene lactones were eventually applied to the synthesis of the natural 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 β-position, and a Pd-$C^{\alpha}$-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 $C^{\alpha}$ and one β-hydrogen. To adopt the energetically least unfavorable *syn*-periplanar conformation **3'**, a rotation around the $C^{\beta}$-$C^{\alpha}$-bond must occur. The stereospecificity of the β-H-elimination and the preferred *anti*-orientation of aryl and ester substituent 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 exists, comparatively little is known about the behaviour 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 can not 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**).

**Scheme 1**. Heck-type arylations of acrylates, unsaturated lactones and α-methylene lactones.




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 coworkers 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 afterwards, 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 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 sevenmembered transition state.[10,11]

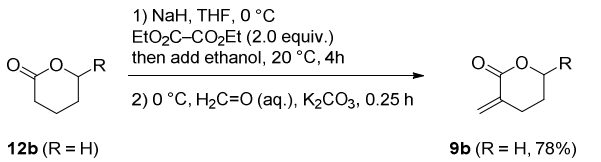
Over the past few years we[14-17] and others[18-23] reported a considerable number of examples for Heck-type coupling reactions with arene diazonium salts. This variant of the Mizoroki-Heck coupling, often referred to as Matsuda-Heck-reaction, was originally discovered in the late 1970's by Matsuda and 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 ($Pd(OAc)_2$ or $Pd_2(dba)_3$ are the most commonly used precatalysts). Finally, Matsuda-Heck reactions can be conducted both under basic and under 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-$C^{\alpha}$-$C^{\beta endo}$-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**).

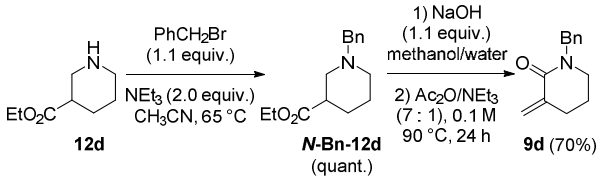
**Scheme 2**. Syntheses of α-methylene-δ-valerolactones **9b**,**c**.




*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**).

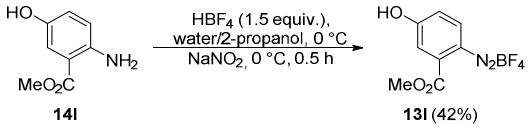
**Scheme 3**. Synthesis of α-methylene-δ-valerolactam (**9d**).




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

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-hydroxy anthranilate (**14l**) through diazotation with $NaNO_2$ in aqueous $HBF_4$ (**Scheme 4**).

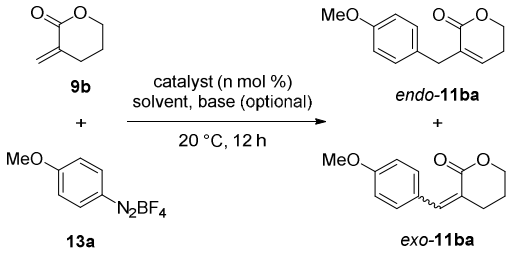
**Scheme 4**. Synthesis of the hitherto unknown diazonium salt **13l**.




**Matsuda Heck arylation of α-methylene-δ-valerolacton (9b)**. For optimization purpose 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 $Pd_2dba_3$•$CHCl_3$, 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).

**Table 1**. Optimization of Matsuda-Heck conditions for **9b**.




| entry | Ratio **9b**:**13a** | Precatalyst (catalyst loading) | Base[a)] | solvent | Product (yield, %)[b)] |
|---|---|---|---|---|---|
| 1 | 2.0:1.0 | $Pd_2(dba)_3$•$CHCl_3$ (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) |

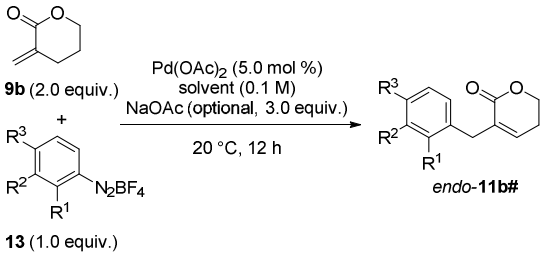
[a] 3.0 equiv. [b] only *endo*-**11ba** was observed in all experiments. [c] no conversion (TLC).

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 one equivalent (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) were 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 are usually the optimal conditions, 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]

**Table 2**. Scope and limitations of Matsuda-Heck couplings with **9b**.



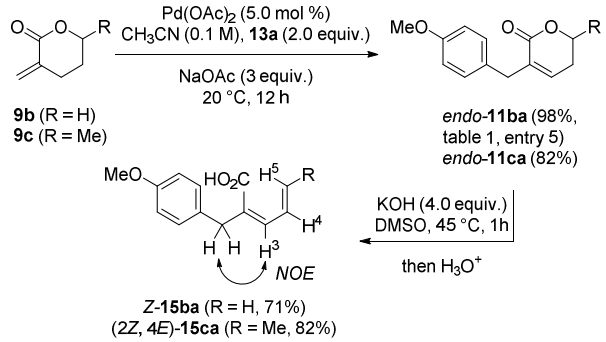

| entry | **13** | $R^1$ | $R^2$ | $R^3$ | solvent | base | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **13a** | H | H | OMe | $CH_3CN$ | NaOAc | *endo*-**11ba** | 98 |
| 2 | **13b** | H | H | OH | $CH_3OH$ | -- | *endo*-**11bb** | 74 |
| 3 | **13c** | H | H | OBn | $CH_3CN$ | 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.

We are not aware of examples for the eliminative ring opening of α-benzylated pentenolides and investigated therefore 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 one hour. Assignment of the *Z*-configuration as shown in scheme 5 is based on an NOE-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**).

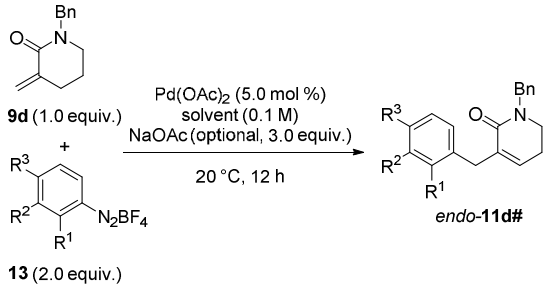
**Scheme 5**. Base-induced eliminative ring opening of α-benzyl pentenolides.




**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, 13). On the other hand, methylcarboxylate 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]

**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 |

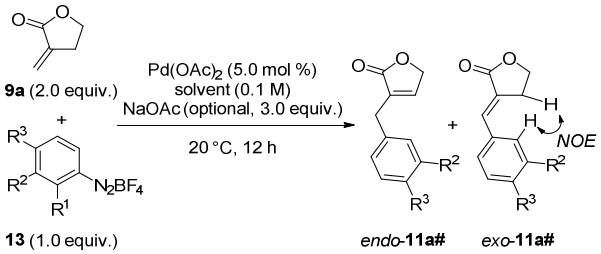
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | **13c** | H | H | OBn | $CH_3CN$ | NaOAc | *endo*-**11dc** | 65 |
| 4 | **13d** | H | Br | OMe | $CH_3OH$ | -- | *endo*-**11dd** | 76 |
| 5 | **13n** | H | Br | OBn | $CH_3OH$ | -- | *endo*-**11dn** | 66 |
| 6 | **13f** | H | $NO_2$ | OMe | $CH_3OH$ | -- | *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.

**Matsuda Heck arylation of α-methylene-γ-butyrolacton (9a)**. In contrast to the Matsuda-Heck couplings 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. A 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-spectroscopical data obtained by us for the *para*-

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 towards 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 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.

**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 |

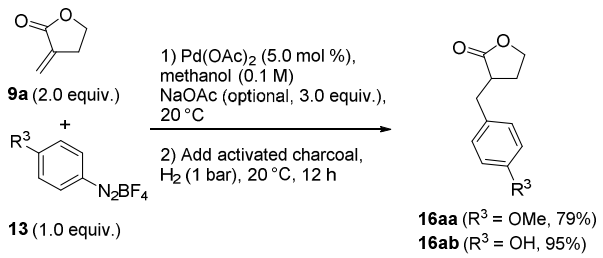
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9 | **13g** | $NO_2$ | OH | $CH_3OH$ | -- | 2.0 : 1.0 | **11ag** | 99 |

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

We found a comparable selectivity towards 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 favouring *endo*-β-H-elimination.[11] This might explain why even in the absence of acetate no pronounced selectivity towards 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 seeked 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 running Matsuda-Heck couplings of **13a** and **13b** 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**).

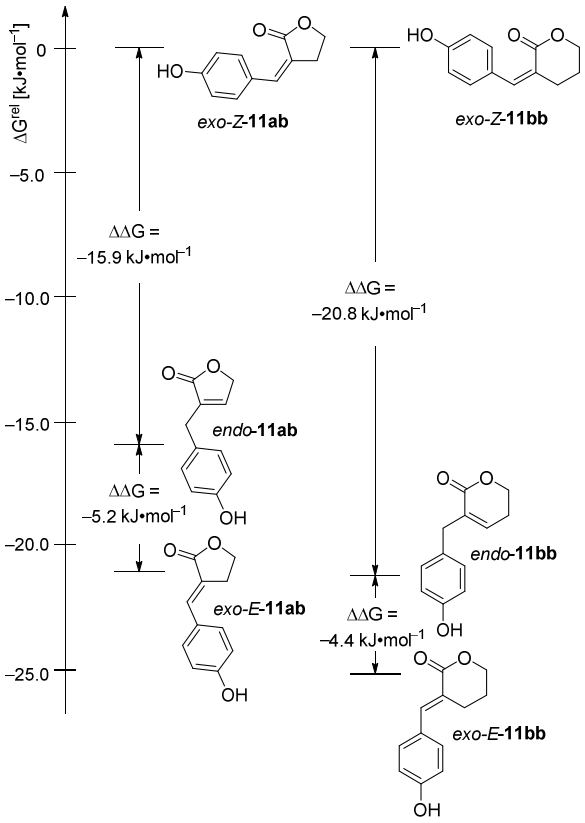



**Figure 1**. Calculated relative Gibbs free energies of isomers of **11ab** and **11bb**.

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 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. 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-$C^{\alpha}$-$C^{\beta}$-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**).

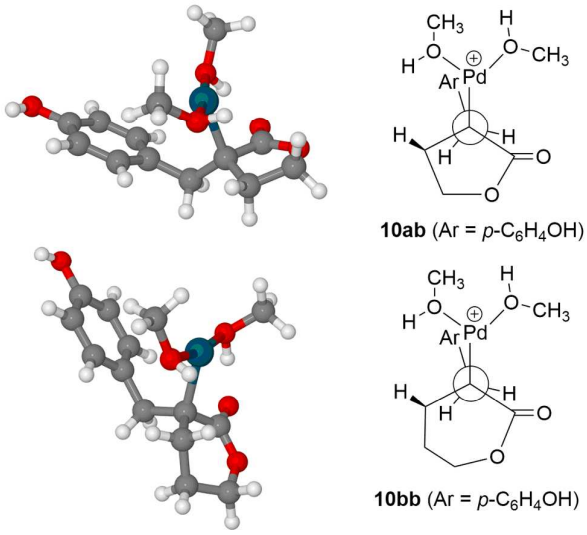



**Figure 2**. Geometry optimized structures of Pd-σ-complexes **10ab** and **10bb** with a dihedral angle [Pd-$C^{\alpha}$-$C^{\beta exo}$-Ar] = 0 °.

Starting from these eclipsed-conformations, which are highest in energy, the aryl moiety was rotated stepwise around the $C^{\alpha}$-$C^{\beta exo}$-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-$C^{\alpha}$-$C^{\beta endo}$-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 $C^{\alpha}$-$C^{\beta exo}$-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 disfavoured. Rotating the aryl substituent by a further 120 ° (dihedral angle [Pd-$C^{\alpha}$-$C^{\beta exo}$-Ar] = 240 °) leads to another *syn*-β-$H^{exo}$-arrangement, which is energetically much more favourable 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 measure for the probability of a *syn*-β-$H^{endo}$-elimination we considered the *endo*-dihedral angle [Pd-$C^{\alpha}$-$C^{\beta endo}$-H], which varies from 37 ° to 44 °, depending on the *exo*-dihedral angle [Pd-$C^{\alpha}$-$C^{\beta exo}$-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 favourable. 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 favourable conformers at *exo*-dihedral angles of 180 ° and 300 ° have larger *endo*-dihedral angles of ca. 39 ° (**Figure 3**).

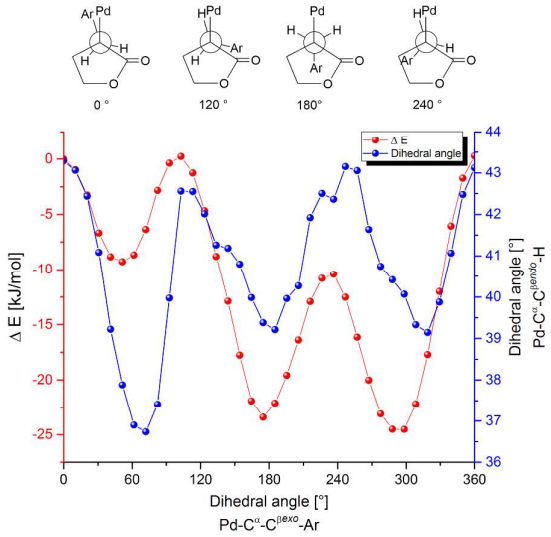



**Figure 3**. [Pd-C$^{\alpha}$-C$^{\beta endo}$-H] dihedral angle (blue curve) and relative energy (red curve) as a function of the [Pd-C$^{\alpha}$-C$^{\beta exo}$-Ar] dihedral angle for Pd-σ-complex **10ab**.

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 favourable 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.

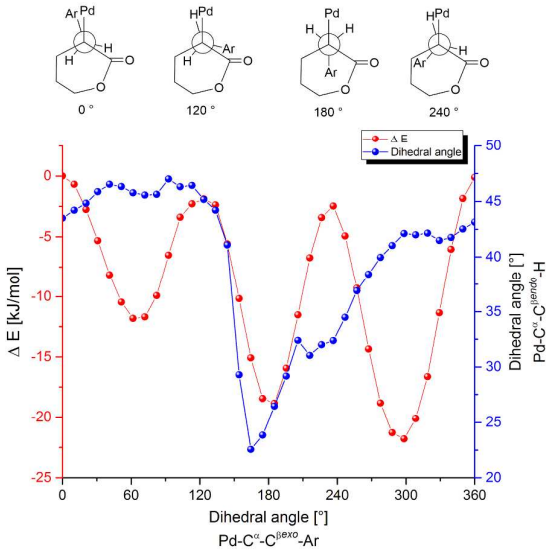



**Figure 4**. [Pd-C$^{\alpha}$-C$^{\beta endo}$-H] dihedral angle (blue curve) and relative energy (red curve) as a function of the [Pd-C$^{\alpha}$-C$^{\beta exo}$-Ar] dihedral angle for Pd-σ-complex **10bb**.

**Total synthesis of anemarcumarin A**. Several natural products with a 3-benzylated coumarin pattern have been 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 in 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-benzyl coumarins proceeds through umpolungs-domino reactions of salicylic aldehydes and enals.[72]

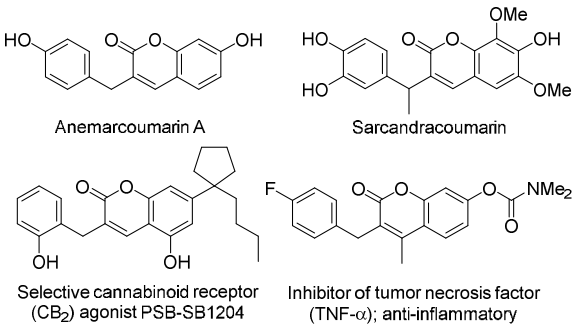
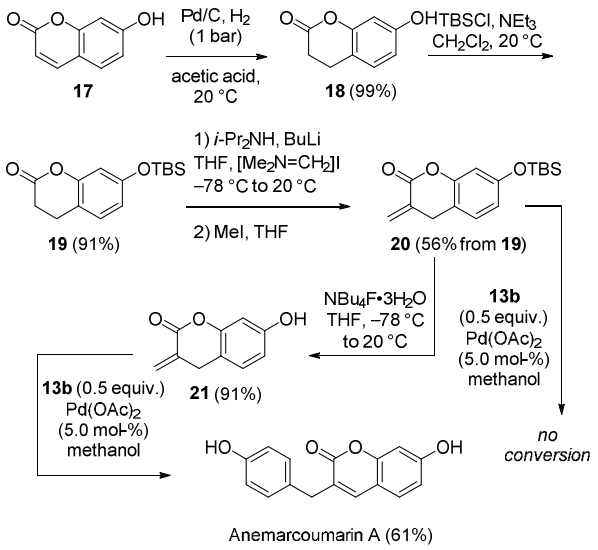



**Figure 5**. Examples for 3-benzylated coumarins as potential target structures.

We applied the Matsuda-Heck conditions developed herein to 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 favourable conformation coincides with a comparatively small [Pd-$C^{\alpha}$-$C^{\beta endo}$-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 $CHCl_3$ ($\delta$ = 7.26 ppm) as an internal standard. Coupling constants are given in Hz. $^{13}$C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ ($\delta$ = 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, $\delta$ = 2.50 ppm, DMSO-$d_6$ as internal standard for $^{13}$C NMR spectroscopy, $\delta$ = 39.5 ppm); $C_6D_6$ ($C_6D_5$ as internal standard for $^{1}$H NMR spectroscopy, $\delta$ = 7.16 ppm, $C_6D_6$ as internal standard for $^{13}$C NMR spectroscopy, $\delta$ = 128.1 ppm); acetone-$d_6$ (acetone-$d_5$ as internal standard for $^{1}$H NMR spectroscopy, $\delta$ = 2.05 ppm, $C$D$_3$COCD$_3$ as internal standard for $^{13}$C NMR spectroscopy, $\delta$ = 29.8 ppm); methanol-$d_4$ (CD$_2$*H*OD as internal standard for $^{1}$H NMR spectroscopy, $\delta$ = 3.31 ppm, *C*D$_3$OD as internal standard for $^{13}$C NMR spectroscopy, $\delta$ = 49.0 ppm). IR spectra were recorded as ATR-FTIR spectra. Wavenumbers ($\nu$) 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 it is 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-2*H*-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 completed addition, ethanol (4.5 mL) was added, the reaction was warmed to ambient temperature and stirred for 4 h. After cooling 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 165.6, 134.2, 128.3, 69.8, 28.2, 23.3; IR (ATR) $\nu$ 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-2*H*-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, $C_6D_6$) $\delta$ 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, $C_6D_6$) $\delta$ 164.4, 134.5, 126.4, 76.0, 29.8, 27.0, 21.2; IR (ATR) $\nu$ 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 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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, the residue was suspended in toluene and evaporated again. To the dry residue was 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 164.4, 137.9, 137.4, 128.7, 128.2, 127.4, 122.0, 50.8, 47.9, 30.3, 23.2; IR (ATR) $\nu$ 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)benzenediazoniumtetrafluoroborate (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 washed with cold water (15 mL), ethanol and then diethylether and dried in vacuum to give **13l** (0.71 g, 2.7 mmol, 42%). Greyish solid; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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-$d_6$) $\delta$ 174.6, 162.4, 136.7, 132.9, 123.9, 123.6, 87.4, 53.6; IR (KBr-disc) $\nu$ 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 the 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 the 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, 0.29 mmol, 73%). *NMR-data of endo-**11aa***: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 the 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-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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-methoxybenzylidene)dihydrofuran-2(3H)-one 3-(3-bromo-4-methoxybenzyl)furan-2(5H)-one (exo-**11ad**)*. Following the 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 the 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 the 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-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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 the 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 173.5, 152.0, 146.0, 134.8, 125.8, 113.9, 70.3, 56.6, 30.6, other signals can not be unambigously assigned due to signal overlap.

*NMR-data of exo-**11af***: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 65.4, 56.8, 27.2, other signals can not 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 the 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 173.5, 154.0, 146.2, 138.4, 124.7, 120.4, 70.4, 30.6, other signals can not be unambigously assigned. *NMR-data of exo-**11ag***: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 165.3, 158.6, 140.2, 133.6, 130.7, 130.7, 114.4, 66.8, 55.7, 36.3, 24.8; IR (ATR) $\nu$ 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 the 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%): colourless solid, mp 106 - 108 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 165.7, 154.8, 140.5, 133.2, 130.4, 129.9, 115.6, 66.6, 36.0, 24.5; IR (ATR) $\nu$ 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 the 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%): colourless liquid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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 the 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%): colourless liquid; $^{1}$H NMR (300 MHz, $C_6D_6$) $\delta$ 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, $C_6D_6$) $\delta$ 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) $\nu$ 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.

*3-(3-Bromo-4-hydroxybenzyl)-5,6-dihydro-2H-pyran-2-one (endo-**11be**)*. Following the 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%): colourless liquid; $^{1}$H NMR (300 MHz, acetone-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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) $\nu$ 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 the 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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 the 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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 the 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%): colourless liquid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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 the 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, $C_6D_6$) $\delta$ 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, $C_6D_6$) $\delta$ 163.6, 147.1, 146.5, 140.5, 131.6, 129.9, 123.7, 65.9, 37.0, 24.3; IR (ATR) $\nu$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 the 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%): colourless liquid; $^1$H NMR

(300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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(3*H*)-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%): colourless liquid; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 179.3, 158.8, 130.7, 130.3, 114.5, 67.0, 55.7, 41.6, 35.7, 28.3; IR (ATR) $\nu$ 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(3*H*)-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%): colourless liquid; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$

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, $CDCl_3$) $\delta$ 180.7, 155.4, 130.5, 130.0, 116.1, 65.7, 41.8, 35.5, 28.1; IR (ATR) $\nu$ 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 cooling 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%): colourless liquid; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 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-$d_6$) $\delta$ 167.8, 158.7, 139.9, 134.5, 132.7, 131.7, 130.1, 122.7, 114.1, 54.9, 39.6; IR (ATR) $\nu$ 2941 (bw), 1676 (s), 1511 (s), 1242 (s); HRMS (EI) calcd for $C_{13}H_{14}O_3$ $[M^+]$ 218.0943, found 218.0934.

**(2*Z*,4*E*)-2-(4-Methoxybenzyl)hexa-2,4-dienoic acid ((2*Z*,4*E*)-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%): colourless liquid; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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 silicia 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $v$ 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 the 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%): colourless solid, mp 123 - 124 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $v$ 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 the 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%): colourless solid, mp 189 - 190 °C; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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) $v$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $v$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $v$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $v$ 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) *v* 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) *v* 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 the 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) *v* 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.

*1-Benzyl-3-(4-hydroxy-2-(methylbenzoate)benzyl)-5,6-dihydropyridin-2-(1H)-one (endo-**11dl**)*. Following the 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%): colourless

liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 3207 (bw), 1716 (m), 1597 (s), 1293 (m).

**7-Hydroxy-chroman-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%): colourless solid, mp 134 - 136 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 169.3, 156.0, 152.7, 128.8, 114.5, 111.9, 104.5, 29.6, 23.1; IR (ATR) $\nu$ 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 completed addition, 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%): colourless liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ 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%): colourless solid, mp 46 – 47 °C; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 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, $C_6D_6$) $\delta$ 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) $\nu$ 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 hydrolysed

with a satured 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%): colourless solid, decomposition at 230 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 163.8, 155.9, 151.3, 131.9, 128.9, 128.5, 112.9, 112.1, 104.4, 31.2; IR (ATR) $\nu$ 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%): colourless solid, mp 206 – 209 °C; $^1$H NMR (600 MHz, methanol-$d_4$) $\delta$ 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-$d_4$) $\delta$ 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) $\nu$ 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]

**Acknowledgments**

We thank Evonik Oxeno for generous donations of solvents and Umicore (Hanau, Germany) for generous donations of catalysts.

**Supporting Information Available statement**

Copies of $^{1}H$ and $^{13}C$ NMR spectra for all compounds; documentation of the DFT calculations (tables of atom coordinates and absolute energies). This material is available free of charge via the Internet at http://pubs.acs.org.

**References and Footnotes**

(1) *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009.

(2) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7.

(3) Jutand, A. In *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009, p 1-50.

(4) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679-3682.

(5) Kamisaki, H.; Nanjo, T.; Tsukano, C.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 626-633.

(6) Canterbury, D. P.; Hesp, K. D.; Polivkova, J. *Org. Biomol. Chem.* **2016**, *14*, 7731-7734.

(7) Kirschbaum, S.; Waldmann, H. *Tetrahedron Lett.* **1997**, *38*, 2829-2832.

(8) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433-436.

(9) Brunner, H.; de Courcy, N. L. C.; Genet, J. P. *Tetrahedron Lett.* **1999**, *40*, 4815-4818.

(10) Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollàr, L. *Org. Lett.* **2000**, *2*, 69-72.

(11) Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollár, L. *Eur. J. Org. Chem.* **2001**, 3165-3173.

(12) Kim, S. H.; Kim, K. H.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2013**, *54*, 329-334.

(13) Ding, Y.-H.; Fan, H.-X.; Long, J.; Zhang, Q.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6087-6092.

(14) Schmidt, B.; Hölter, F.; Berger, R.; Jessel, S. *Adv. Synth. Catal.* **2010**, *352*, 2463-2473.

(15) Schmidt, B.; Hölter, F.; Kelling, A.; Schilde, U. *J. Org. Chem.* **2011**, *76*, 3357-3365.

(16) Schmidt, B.; Elizarov, N. *Chem. Commun.* **2012**, *48*, 4350-4352.

(17) Schmidt, B.; Elizarov, N.; Berger, R.; Holter, F. *Org. Biomol. Chem.* **2013**, *11*, 3674-3691.

(18) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983-1992.

(19) Felpin, F.-X.; Coste, J.; Zakri, C.; Fouquet, E. *Chem. Eur. J.* **2009**, *15*, 7238-7245.

(20) Barancelli, D. A.; Salles, A. G.; Taylor, J. G.; Correia, C. R. D. *Org. Lett.* **2012**, *14*, 6036-6039.

(21) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2002**, *8*, 3901-3906.

(22) Raduán, M.; Padrosa, J.; Pla-Quintana, A.; Parella, T.; Roglans, A. *Adv. Synth. Catal.* **2011**, *353*, 2003-2012.

(23) Li, Z.; Ip, F. C. F.; Ip, N. Y.; Tong, R. *Chem. Eur. J.* **2015**, *21*, 11152-11157.

(24) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159-162.

(25) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, K. *Tetrahedron* **1981**, *37*, 31-36.

(26) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815-2831.

(27) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622-4643.

(28) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403-1428.

(29) Schmidt, B.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2010**, *8*, 1406-1414.

(30) Susperregui, N.; Miqueu, K.; Sotiropoulos, J.-M.; Le Callonnec, F.; Fouquet, E.; Felpin, F.-X. *Chem. Eur. J.* **2012**, *18*, 7210-7218.

(31) Oger, N.; Le Grognec, E.; Felpin, F.-X. *J. Org. Chem.* **2014**, *79*, 8255-8262.

(32) Schmidt, B.; Wolf, F.; Brunner, H. *Eur. J. Org. Chem.* **2016**, 2972-2982.

(33) Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191-5204.

(34) Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1978**, *42*, 1585-1588.

(35) Murray, A. W.; Reid, R. G. *Synthesis* **1985**, 35-38.

(36) Song, L.; Yao, H.; Zhu, L.; Tong, R. *Org. Lett.* **2013**, *15*, 6-9.

(37) Krawczyk, H.; Śliwiński, M. *Tetrahedron* **2003**, *59*, 9199-9211.

(38) Ichimoto, I.; Machiya, K.; Kirihata, M.; Ueda, H. *Agric. Biol. Chem.* **1990**, *54*, 657-662.

(39) Jacobs, W. A.; Craig, L. C. *J. Am. Chem. Soc.* **1938**, *60*, 1701-1702.

(40) Lee, D. L.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 893-902.

(41) Schmidt, B.; Elizarov, N.; Schilde, U.; Kelling, A. *J. Org. Chem.* **2015**, *80*, 4223-4234.

(42) Erb, W.; Hellal, A.; Albini, M.; Rouden, J.; Blanchet, J. *Chem. Eur. J.* **2014**, *20*, 6608-6612.

(43) Salabert, J.; Sebastián, R. M.; Vallribera, A.; Cívicos, J. F.; Nájera, C. *Tetrahedron* **2013**, *69*, 2655-2659.

(44) Gaikwad, D. S.; Pore, D. M. *Synlett* **2012**, *23*, 2631-2634.

(45) Kutonova, K. V.; Trusova, M. E.; Stankevich, A. V.; Postnikov, P. S.; Filimonov, V. D. *Beilstein J. Org. Chem.* **2015**, *11*, 358-362.

(46) Schmidt, B.; Elizarov, N.; Riemer, N.; Hölter, F. *Eur. J. Org. Chem.* **2015**, 5826-5841.

(47) Machado, A. H. L.; Milagre, H. M. S.; Eberlin, L. S.; Sabino, A. A.; Correia, C. R. D.; Eberlin, M. N. *Org. Biomol. Chem.* **2013**, *11*, 3277-3281.

(48) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305-308.

(49) Hofmann, A. W. *Annalen* **1859**, *110*, 129-140.

(50) Cardillo, G.; Orena, M.; Sandri, S. *Tetrahedron* **1976**, *32*, 107-108.

(51) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 2317-2320.

(52) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1982**, *23*, 3773-3776.

(53) Constantino, M. G.; Losco, P.; Castellano, E. E. *J. Org. Chem.* **1989**, *54*, 681-683.

(54) Schmidt, B.; Kunz, O. *Eur. J. Org. Chem.* **2012**, 1008-1018.

(55) Schmidt, B.; Kunz, O. *Org. Lett.* **2013**, *15*, 4470–4473.

(56) Schmidt, B.; Audörsch, S. *Org. Lett.* **2016**, *18*, 1162–1165.

(57) Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett.* **2016**, *57*, 663-667.

(58) Machotta, A. B.; Oestreich, M. In *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009, p 179-213.

(59) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603-2606.

(60) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687-690.

(61) Sabino, A. S.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 2514-2518.

(62) Schmidt, B. *Chem. Commun.* **2003**, 1656-1657.

(63) Awale, S.; Miyamoto, T.; Linn, T. Z.; Li, F.; Win, N. N.; Tezuka, Y.; Esumi, H.; Kadota, S. *J. Nat. Prod.* **2009**, *72*, 1631-1636.

(64) Li, M.-C.; Yao, Z.; Takaishi, Y.; Tang, S.-A.; Duan, H.-Q. *Chem. Biodivers.* **2011**, *8*, 1112-1120.

(65) Feng, S.; Xu, L.; Wu, M.; Hao, J.; Qiu, S. X.; Wei, X. *Fitoterapia* **2010**, *81*, 472-474.

(66) Youn, U. J.; Lee, Y. S.; Jeong, H.; Lee, J.; Nam, J.-W.; Lee, Y. J.; Hwang, E. S.; Lee, J.-H.; Lee, D.; Kang, S. S.; Seo, E.-K. *J. Nat. Prod.* **2009**, *72*, 1895-1898.

(67) Rempel, V.; Volz, N.; Hinz, S.; Karcz, T.; Meliciani, I.; Nieger, M.; Wenzel, W.; Bräse, S.; Müller, C. E. *J. Med. Chem.* **2012**, *55*, 7967-7977.

(68) Rempel, V.; Volz, N.; Gläser, F.; Nieger, M.; Bräse, S.; Müller, C. E. *J. Med. Chem.* **2013**, *56*, 4798-4810.

(69) Behrenswerth, A.; Volz, N.; Toräng, J.; Hinz, S.; Bräse, S.; Müller, C. E. *Bioorg. Med. Chem.* **2009**, *17*, 2842-2851.

(70) Cheng, J.-F.; Chen, M.; Wallace, D.; Tith, S.; Arrhenius, T.; Kashiwagi, H.; Ono, Y.; Ishikawa, A.; Sato, H.; Kozono, T.; Sato, H.; Nadzan, A. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2411-2415.

(71) Dube, P. N.; Waghmare, M. N.; Mokale, S. N. *Chem. Biol. Drug Design* **2016**, *87*, 608-617.

(72) Toräng, J.; Vanderheiden, S.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 943-952.

(73) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1971**, *10*, 330-331.

(74) Paquette, L. A.; Backhaus, D.; Braun, R. *J. Am. Chem. Soc.* **1996**, *118*, 11990-11991.

(75) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789.

(76) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

(77) Hertwig, R. H.; Koch, W. *Chem. Phys. Lett.* **1997**, *268*, 345-351.

(78) Neese, F. *WIREs Comput. Mol. Sci.* **2012**, *2*, 73-78.

(79) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.

(80) Andrae, D.; Häußermann, U.; Dolg, M.; Stoll, H.; Preuß, H. *Theor. Chim. Acta* **1990**, *77*, 123-141.

(81) Sinnecker, S.; Rajendran, A.; Klamt, A.; Diedenhofen, M.; Neese, F. *J. Phys. Chem. A* **2006**, *110*, 2235-2245.

(82) Fu, M.; Chen, L.; Jiang, Y.; Jiang, Z.-X.; Yang, Z. *Org. Lett.* **2016**, *18*, 348-351.

(83) Li, S.; Ma, S. *Chem. Asian J.* **2012**, *7*, 2411-2418.

(84) Tanaka, M.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Chem. Lett.* **1994**, *23*, 1455-1458.

(85) Ito, M.; Ootsuka, T.; Watari, R.; Shiibashi, A.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 4240-4242.

(86) Hernández-Galán, R.; Salvá, J.; Massanet, G. M.; Collado, I. G. *Tetrahedron* **1993**, *49*, 1701-1710.

(87) Kamat, V. S.; Graden, D. W.; Lynn, D. G.; Steffens, J. C.; Riopel, J. L. *Tetrahedron Lett.* **1982**, *23*, 1541-1544.