RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 37138

Assigning regioisomeric or diastereoisomeric relations of problematic trisubstituted double-bonds through heteronuclear 2D selective *J*-resolved NMR spectroscopy†

Marie Hoffmann, Solène Miaskiewicz, Jean-Marc Weibel, Patrick Pale* and Aurélien Blanc*

Received 20th February 2015
Accepted 15th April 2015

DOI: 10.1039/c5ra03228h

www.rsc.org/advances

Although one of the first 2D NMR methods, but so far neglected, selective *J*-resolved NMR spectroscopy offers a unique opportunity to help organic chemists in structure elucidation, avoiding natural and non-natural product misassignments. This NMR method indeed allowed us to unambiguously and simply assign (natural) product structures exhibiting trisubstituted unsaturations. For example, as demonstrated here, the isomeric aurone, flavone, coumarin and isocoumarin structures could easily be distinguished; regioisomer assignments in furans could be solved, as well as isomerisms in compounds containing trisubstituted double-bonds (aurones, lactones, divinyl ketones).

Introduction

In natural product research, structural and/or stereochemical assignments are obviously the key step, providing the foundation for a whole set of disciplines, from synthesis to biology, biochemistry or ecology, with often the production of new therapeutic agents as the most practical consequences. Despite the current sophisticated techniques available, assignments often prove delicate and sometimes cumbersome. The number of natural product structural misassignments reported each year is surprisingly high (Fig. 1).[1] These numbers are probably underestimated, since those encountered misassignments are frequent and only revealed through total synthesis enterprises.[2]

Furthermore, the efforts and associated costs required to correct structures and appropriately reassign them could be quite significant and higher than those associated with the initial structure, especially in total synthesis endeavors.[3] Besides the increased enrolments for total syntheses, wrong assignments might have dramatic effects due to the different biological activities the compounds could exhibit.

What was observed for natural products is also true in any synthetic efforts addressing compounds in which stereo- and/or regioisomers could be obtained, especially when only one is formed. In this area, the lack of re-synthesis minimizes the discovery of misassignments. Therefore, it is clear that, since the number of incorrectly determined structures of new products, natural or not, is quite large, reducing errors is clearly an important and useful challenge. Several routes are currently explored, among which are computer-assisted structure elucidation (CASE) method,[4] NMR shift calculations combined with probability analyses[5] or artificial neural network pattern recognition,[6] combination of calculations with various spectroscopies, notably circular dichroism,[7] and even atomic force microscopy imaging at atomic resolution.[8] Despite these recent new developments, structure elucidation of new compounds, including natural products, heavily relies on two-dimensional NMR experiments. Correlation spectroscopy (COSY) and heteronuclear multiple and single bond correlation (HMBC/HSQC) detect interactions (couplings) of protons, respectively, with adjacent protons (from 2 to 4 bonds) or with neighbor carbon atoms (from 2 to 3 bonds). Both techniques provide connectivity between atoms. Stereochemistry and conformation of molecules are usually deduced from two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY). Based on spin relaxation processes *via* dipolar coupling interacting through space, this method is able to detect protons that are in close proximity.

Facing various structural problems either in the total synthesis of natural products[9] or in the development of new methods,[10] we recently applied a neglected but simple NMR method, which successfully helped us to solve connectivity and/or stereochemistry problems. Being very efficient in our hands, we share here our results gained by applying the selective *J*-resolved NMR method during the process of structure elucidation with some typical examples.

Laboratoire de Synthèse, Réactivité Organiques et Catalyse, UMR 7177 associé au CNRS, Institut de Chimie, Université de Strasbourg, 4 rue Blaise Pascal, 67070 Strasbourg, France. E-mail: ablanc@unistra.fr; ppale@unistra.fr

† Electronic supplementary information (ESI) available: Additional schemes, crystallographic structure refinements of compound **10a** and spectral data. CCDC 1047510. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra03228h

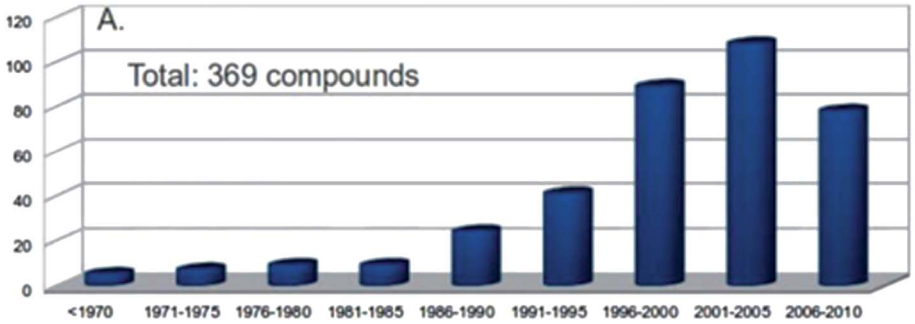


Fig. 1 Numbers of known natural product misassignments per 5 year period. From ref. 1.

Results and discussion

The (selective) *J*-resolved NMR method

Introduced in 1976 by Ernst *et al.*,[11] the 2D *J*-resolved NMR experiments (JRES) are used to separate chemical shifts and *J*-couplings into two independent dimensions.[12,13] The spin coupling may be homocoupling, usually between protons, or heterocoupling, essentially between ^{1}H and ^{13}C, although ^{1}H and ^{31}P have also been reported.[14] The 2D spectra exhibit in one dimension the equivalent of a broad range decoupled proton or carbon spectrum and in the other the coupling, either ^{1}H–^{1}H or ^{13}C–^{1}H. Although one of the first 2D NMR experiments, JRES has been supplanted by the more recent COSY and HMBC methods in chemistry. These NMR techniques could also provide information about such coupling constants, but in a less practical way (see below).

Interestingly, the JRES method is currently re-gaining interest for the study of complex mixtures,[15] mostly in biology and medicine as a tool for metabolic screening[16] and metabolomics[17] as well as for biomarker identification, especially for cancer monitoring.[18]

Stereochemical double-bond assignment is still a problem for the trisubstituted ones,[19] unfortunately quite common in natural products. Classically solved for disubstituted double-bonds with the *E* or *Z* ^{3}J coupling constants (^{1}H NMR), the case of double-bonds carrying a single hydrogen is far from obvious. Coupling between vinylic and allylic hydrogens (^{4}J) can be measured, but the corresponding *E* and *Z* values being low and close to each other do not allow unambiguous assignments.[20] Due to the parallelism between ^{1}H–^{1}H and ^{13}C–^{1}H coupling constants, the *E* or *Z* geometry could also be reflected by the ^{3}J or ^{2}J (^{13}C–^{1}H) coupling constants.[21] The usual way to measure them is to record ^{13}C coupled ^{1}H NMR.[22,23] However, this technique leads to very complex spectra, due to overlapping of signals and to the complexity of multiplets, which may require computational method to solve out. Furthermore, rather long measurement times are needed and typically, signal-to-noise ratio is poor for such spectra.

Some of these aspects could also occur for the classic JRES method, but to a lower extent as all ^{n}J (^{13}C–^{1}H) coupling constants are expressed in 2D. However, the heteronuclear *selective J*-resolved NMR experiment (SELJRES)[12b] elegantly solves this problem by inverting the resonance of *the considered proton* allowing to remove from the 2D map all other coupling constants excepted those of the selectively inverted proton:[24] the required coupling can thus be easily available in one of the two dimensions.

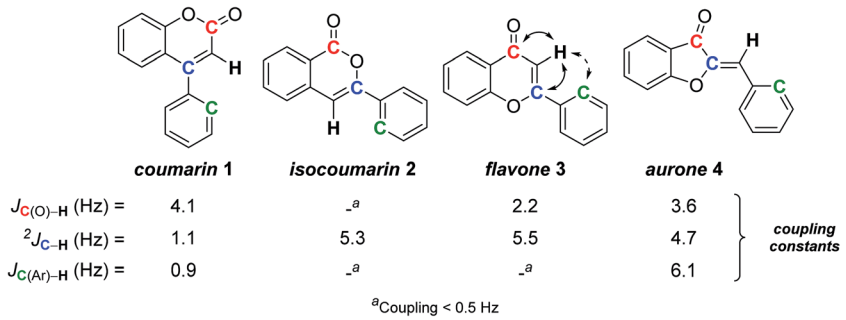
Such stereochemical double-bond problems are often encountered in various families of natural products or in synthesis of unsaturated compounds, but only four typical examples will be detailed here.

Regioisomer assignment of flavonoids

Among flavonoids,[25] coumarins, isocoumarins, aurones, and flavones constitute a sub-family contributing to the pigmentation of flowers and fruits, but also exhibiting interesting pharmaceutical activities.[26] These four subclasses are structurally related, each one being isomeric to the others around a trisubstituted double-bond (Scheme 1). Due to their similarity, the structural elucidation of these natural products remains a challenge, and already led to numerous misassignments, from which only a few were detected and induced structural revision.[9a,27]

Facing such problem, we – as others – relied on total synthesis of each possible isomer,[9a] but this gave us the opportunity to apply heteronuclear SELJRES and to find a useful and quick distinction between these isomers. Indeed, the couplings between the vinylic proton and the carbonyl carbon (red C in Scheme 1), the vinylic carbon (blue C) and the *ortho* carbon on the phenyl substituent (green C) in each series proved typical.[28]

Coumarin **1** showed a weak $^{2}J_{\mathrm{Cvinyl-H}}$ coupling constant of 1.1 Hz compared to the three other isomers **2–4** ($^{2}J_{\mathrm{Cvinyl-H}} = 5.1 \pm 0.4$ Hz), probably reflecting the lack of oxygenated substituent on the double-bond. Isocoumarin **2** could easily be distinguished from the three other possible isomers by the lack of coupling between the vinylic proton and the carbonyl carbon. Flavone **3** and aurone **4** usually cannot be distinguished between themselves by their ^{1}H NMR spectra due to a very similar shift of their vinylic proton (6.8–6.9 ppm) and other chemical shifts. However, they could be unambiguously distinguished by the presence or not of a coupling between the vinylic proton and the *ortho* carbon of the aromatic substituent: aurone **4** exhibits a ^{3}J coupling (6.1 Hz) while flavone **3** can only have a ^{4}J coupling, almost not detectable (Scheme 1).



Scheme 1 Relation structure-SELJRES coupling constants for flavonoid derivatives.

Regioisomer assignment of trisubstituted furans

Furans constitute an important class of aromatic compounds, found in many natural products.[29] Therefore, a large number of synthetic methods have been developed to build such five membered rings.[30] Our group recently contributed to this area, achieving mild and convenient access to trisubstituted furans.[31] During this study, as for furan natural product structural assignments, the regioselectivity has to be determined.

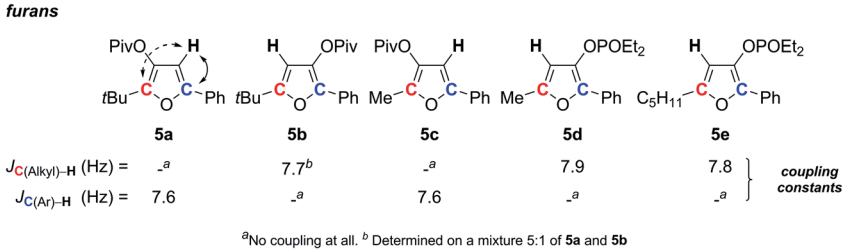
With a single proton, such isomeric furans may be difficult to distinguish. When substituents in positions 2 and 5 do not carry hydrogen, there is no possibility to measure the ^3J (^{1}H–^{1}H) coupling with the furanic proton. Since the situation of the furanic proton can be compared to those described in the previous section, we envisaged to solve this question by applying the SELJRES method. Indeed, the single proton should exhibit ^2J coupling with the furanic carbon (red or blue C in Scheme 2), reflecting the proximity between the two atoms.

To look at this hypothesis, five different trisubstituted furans **5a–e** were submitted to JRES by selecting the frequency of the furanic proton for acquisition. The analysis showed a ^2J coupling constant around 7 to 8 Hz between the furanic proton and its adjacent β-carbon (red or blue C on Scheme 2). Interestingly, no ^3J coupling was expressed with the γ-furanic carbon. This combination thus allowed for the unambiguous determination of the substitution pattern of furans. Furthermore, the analysis can be done on a mixture of two isomers as it was shown with **5a** and **5b**.

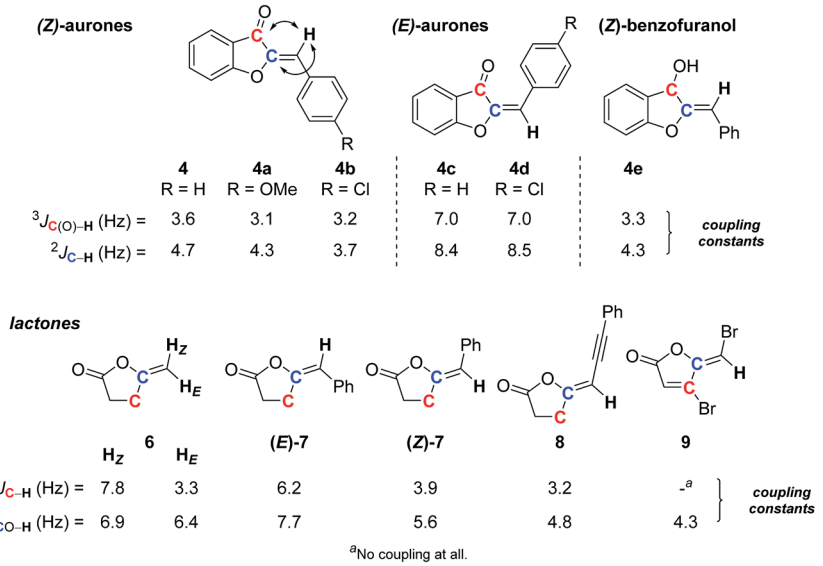
Diastereomer assignment of aurones and alkylidenelactones

As for the previous examples, the *E* or *Z* stereochemical assignment of trisubstituted double-bonds may not be obvious. This could also be true for methylenic systems. Aurones are typical of the former case, and our synthetic endeavor[31] again provided us the opportunity to look at the JRES potential. Naturally occurring aurones usually exhibit a *Z* configuration of the double-bond, but such type of compounds can isomerize under irradiation or on silica gel.[32] Alkylidene lactones also offer useful examples,[9a,10b] with the methylene lactones being typical of the latter case. Both allowed interesting comparisons.

As before, SELJRES allowed us to get ^2J or ^3J (^{13}C–^{1}H) coupling constants, from which those between the vinylic proton and the carbonyl or vinylic carbons simply proved distinctive for each stereoisomer. The data collected for *E* or *Z* aurones **4** and **4a–d** and related compound **4e** clearly showed a correlation between such coupling constants and the stereochemistry of the double-bond (Scheme 3). The *Z* always exhibited ^3J and/or ^2J (^{13}C–^{1}H) values of 3–4 Hz, while the *E* isomer exhibited values of 7–8 Hz. Such clear-cut differences could obviously be fruitful in assigning stereochemistry and would have predictive value. This was confirmed with the alkylidene lactone series, the stereochemistry of which being already assigned by other techniques. Indeed, even in the simple methylene lactone **6**, the same set of values was observed for the *E* and *Z* protons for the ^3J (^{13}C–^{1}H) coupling (3.3 and 7.8 Hz, respectively) (Scheme 3). In other alkylidene lactones **(*Z*)-7** and **8**, similar trends could be observed with ^3J (^{13}C–^{1}H) values of 3.5 ± 0.4 Hz noticed in *Z* isomers and 6.2 Hz for the *E* isomer **(*E*)-7**. In some specific cases, no ^3J value was detected as for the bromomethylene furanone **9**, structurally very close to the fimbrolide natural product family.[33] However, a ^2J coupling constant of 4.3 Hz was expressed in SELJRES, which could be



Scheme 2 Relation structure-SELJRES coupling constants for furan derivatives.



Scheme 3 Simple *E*/*Z* assignment of aurones and lactone derivatives by SELJRES spectral analysis.

attributed to the *Z* isomer by comparison with lactones **(*E*)-7**, **(*Z*)-7** and **8**.

It is worth mentioning that correlations from ^{1}H-coupled ^{13}C spectra with double-bond diastereoisomery have already been observed and compiled from around forty examples in the seventies (Table 1).[21] The listed values are surprisingly large and similar to classical ^{1}H–^{1}H coupling constants, the *E* ^{3}J (^{13}C–^{1}H) coupling constants being always larger than the *Z* ones, but with a strong influence upon hybridization of the selected carbon. Although the general tendency is the same, with larger coupling constants for *E* relative to *Z* proton, the ^{3}J SELJRES values we collected are far different from those already reported: between 3–4 Hz *vs.* 4–10 Hz for *Z* and 7–8 Hz *vs.* 9–17 Hz for *E* (Scheme 3 *vs.* Table 1) and, in our study, no influence of the hybridization has been noticed (see compound **4** *vs.* **4e**). More surprisingly, all our measured SELJRES values should correspond to *cis* proton/*Z* systems according to Table 1 data.

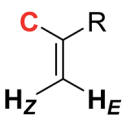
Diastereomer assignment of divinyl ketones

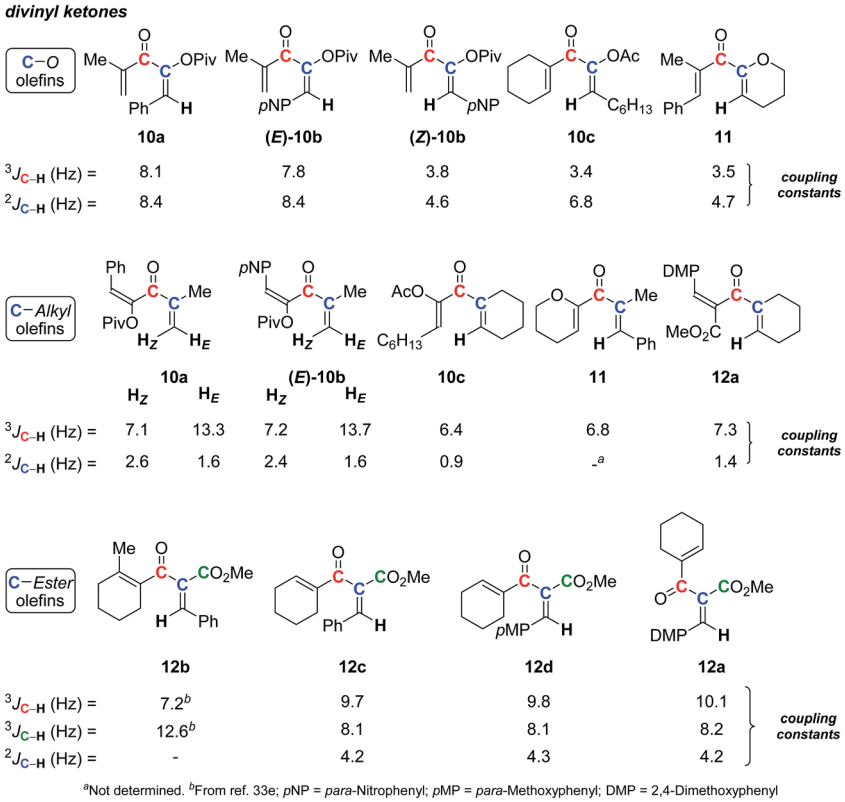
For a program devoted to gold catalysis and to the synthesis of cyclopentenone derivatives *via* the Nazarov reaction,[34] we obtained various divinyl ketones,[35] for which we had to assign the double-bond stereochemistry. Indeed, the reaction we developed led to divinyl ketones in which one double-bond stereochemistry was not defined by the synthetic pathway. In a first attempt, 2D NOESY was used, leading to some conclusions. However, based on the absence of correlation and due to the flexibility of such structures, assignments were suspicious. Fortunately, we were able to obtain crystal structures allowing us to unambiguously determine the stereochemistry. This helped us to look again at the correlations between ^{13}C–^{1}H SELJRES values and double-bond stereochemistry. Among the divinyl ketones we prepared, different examples were selected and submitted to SELJRES NMR experiments.

A series of *O*-substituted divinyl ketones (**10a–c** and **11**) was first evaluated, including one (**10a**) with X-ray crystallography structure (see ESI†) and one (**(*E*)-10b** and **(*Z*)-10b**) with both diastereomers. Their ^{3}J and ^{2}J (^{13}C–^{1}H) coupling constants, respectively, between the vinylic proton and the carbonyl carbon or the adjacent sp^{2} carbon were extracted (Scheme 4). Values similar to those already gained (see preceding section and Scheme 3) were obtained, with ^{3}J and ^{2}J (^{13}C–^{1}H) coupling constants of 8 ± 0.2 Hz for *E* isomers (**10a** and **(*E*)-10b**) and 3.6 ± 0.2 Hz for *Z* compounds (**(*Z*)-10b**, **10c** and **11**). These two sets of constants clearly depend on the geometry of the system and can easily be exploited to unambiguously assign double-bond geometry.

We also looked at the coupling constants of the double-bonds having C-substituents (**10a–c**, **11**, and **12a**). Once again, the geometry of each diastereomer could be easily determined by SELJRES with ^{3}J (^{13}C(O)–^{1}H) values around 13 Hz for *trans* isomers (H_E) and between 6.4 and 7.3 Hz for *cis* isomers (H_Z). However, in the case of C-substituted divinyl ketones, the ^{2}J (^{13}C–^{1}H) coupling constants did not follow the tendency of ^{3}J (^{13}C–^{1}H) values: only weak values were measured (1.8 ± 0.8 Hz) without direct correlation with the *E* and *Z* nature of olefins.

Table 1 Range of ^{13}C–^{1}H ^{3}J coupling constants values depending on carbon hybridization from ref. 21

		^{3}J (*C–H*) coupling constant	
C Hybridization		H_Z (Hz)	H_E (Hz)
	sp (*C*N, *CC*)	8.2–9.0	13.8–15.0
	sp^{2} (*C*O)	4.3–10.0	9.5–16.9
	sp^{3} (*C*H$_2$X)	5.7–8.0	7.7–11.0



[a]Not determined. [b]From ref. 33e; *p*NP = *para*-Nitrophenyl; *p*MP = *para*-Methoxyphenyl; DMP = 2,4-Dimethoxyphenyl

Scheme 4 ^3J and ^2J ($^{13}C-^1H$) SELJRES values of variously substituted divinyl ketones **10–12**.

Being well represented in the literature due to their good reactivity in the Nazarov reaction,[36] divinyl ketones carrying an ester group (**12a–d**) were also investigated. In our case, only *E* isomers were available. SELJRES spectra showed that their ^3J ($^{13}C(O)-^1H$) (*trans* values) and ^3J ($^{13}CO_2Me-^1H$) (*cis* values) coupling constants lay, respectively, between 9 to 10 Hz and around 8 Hz for compounds **12a** and **12c–d**. Working on the Nazarov reaction, Frontier *et al.* have also been interested in assigning the stereochemistry of divinyl ketones, and they have reported the ^3J ($^{13}C-^1H$) extracted from ^{13}C non-decoupled ^1H NMR spectra, for *Z* and *E* isomers analogs.[36e] In this report, the coupling constants for *E* isomers correlated perfectly with the range of values obtained for **12a** and **12c–d** (9–10 Hz). However, the ^3J ($^{13}CO-^1H$) (*cis* values, 4.6–7.2 Hz) and ^3J ($^{13}CO_2Me-^1H$) (*trans* values, 10.7–12.8 Hz) for *Z* isomers are far different, such as in **12b**, which confirmed the *Z* nature of the considered olefin.

Conclusion

In this work, we have demonstrated that SELJRES NMR spectra gave direct and unambiguous access to the regioisomerism of various types of molecules, such as flavonoids and furans. SELJRES NMR thus offers a simple and easy method to rapidly determine the *E* and *Z* diastereochemistry of trisubstituted double-bonds in aurone, alkylidene lactone or divinyl ketone derivatives. Indeed, the ^3J ($^{13}C-^1H$) coupling constants extracted from SELJRES are always larger for the *E* isomers, between 7–13 Hz, than for the *Z* isomers (3–8 Hz) depending on the substrate nature.

Experimental section

General informations

Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a 500- or 600 MHz Bruker Avance II spectrometer equipped with a 5 mm DCH dual cryoprobe, with a *z*-gradient and operating at 500.130 MHz for ^1H and 125.758 MHz for ^{13}C. The solvent peak was used as reference value, for ^1H NMR: $CHCl_3$ = 7.26 ppm or benzene-d = 7.16 ppm and for ^{13}C NMR: $CHCl_3$ = 77.16 ppm or benzene-d = 128.06 ppm. For ^1H NMR, data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants (*J*/Hz), integration, and attribution. For ^{13}C NMR, data are presented as follows: chemical shift (ppm) and attribution. For $^{13}C-\{^1H\}$ selective *J*-resolved NMR, data are presented as follows: (chosen proton), ^{13}C chemical shift (ppm) and coupling constant (*J*/Hz) or folded ^1J ($^{13}C-^1H$), actually the acquisition method prevented the direct detection of the ^1J ($^{13}C-^1H$) constant that is folded. Remark: despite all discussions about trisubstituted double-bonds, during the characterization it was observed that, for a chosen proton, sometimes the ^2J ($^{13}C-^1H$) is smaller than its ^3J ($^{13}C-^1H$).[37] Assignments were determined either on the basis of unambiguous chemical shifts or coupling patterns, COSY, HSQC, HMBC, and NOESY experiments, to fully interprete spectra for related compounds. The pulse sequence used for measuring ^nJ ($^{13}C-^1H$) coupling constants is similar to the *seljresqfsp* sequence of the Bruker

library. Experiments were acquired at 293 K with a relaxation delay of 3 s. Acquisition parameters were adjusted when necessary, but typically spectral windows were set to 25 kHz (200 ppm) for ^{13}C and 50 Hz for ^{n}J (^{13}C–^{1}H). Data size was at least 16k points in the direct dimension and 32 points in the indirect dimension. Broadband decoupling during acquisition was achieved by a composite pulse sequence Waltz16. Refocusing of ^{13}C magnetization during evolution period was performed with an adiabatic shape pulse Crp60comp.4 of 2 ms. Simultaneously, a selective 180° pulse focused on the chosen proton frequency was achieved with a refocusing band-selective pulse (REBURP) of 80 ms. Melting points were recorded on a Melting Point Apparatus SMP3 and are uncorrected. Infrared spectra were recorded neat with Hewlett-Packard spectrometer. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm^{-1}). High resolution mass spectra (HR-MS) data were recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions $[M + Na]^+$ $[M + H]^+$ is quoted. Analytical thin-layer chromatography (TLC) was carried out over silica gel 60 F254 plates or basic alumina (63–200 μm) with visualization by ultraviolet light, cerium ammonium molybdate (CAM) or potassium permanganate dip ($KMnO_4$). Flash-column chromatography was carried out using silica gel 60 (40–63 μm) and the procedure included the subsequent evaporation of solvents *in vacuo*. Solvents were purified using standard means. 1,2-Dichloroethane (DCE), benzene and triethylamine (NEt_3) were distilled from CaH_2; pyridine (py) was distilled from potassium carbonate; diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled from KOH; all under an argon atmosphere. Tetrahydrofuran (THF), acetonitrile (CH_3CN) and dichloromethane (DCM) were dried using Glasstechnology GT S100 device. AuCl (Premion grade, 99.99%) and $NaAuCl_4 \cdot 2H_2O$ (Premion grade, 99.99%) were purchased from Alfa Aesar. $AgSbF_6$ (98%) and $PdCl_2$(dppf)·DCM were purchased from STREM Chemicals. IPrAuCl, $PdCl_2(PPh_3)_2$ (98%), $HNTf_2$ and CuI (98%) were purchased from Aldrich. $AgNTf_2$ was prepared from $HNTf_2$ (Aldrich) and Ag_2CO_3.[38] All phosphinegold(I) chloride precatalysts were prepared by reduction of $NaAuCl_4 \cdot 2H_2O$ with thiodiethanol and subsequent addition of the appropriate phosphine.[39] PPh_3AuNTf_2 catalyst was prepared from the corresponding triphenylphosphinegold(I) chloride and $AgNTf_2$.[40] All other chemicals were used as received.

4-Phenyl-2*H*-chromen-2-one (1)

4-Phenyl-2*H*-chromen-2-one (**1**) was obtained in 91% yield over 2 steps from chromane-2,4-dione, using reported procedures (see ESI†).[41] White solid; TLC R_f 0.23 (cyclohexane/EtOAc 20%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H, H_3), 7.23 (dd, J = 7.9, 7.1 Hz, 1H, H_6), 7.41 (d, J = 8.1 Hz, 1H, H_8), 7.44–7.47 (m, 2H, $H_{2'}$), 7.50 (d, J = 7.9 Hz, 1H, H_5), 7.52–7.55 (m, 3H, $H_{3'/4'}$), 7.55 (dd, J = 8.1, 7.1 Hz, 1H, H_7); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 115.3 (C_3), 117.5 (C_8), 119.1 (C_{4a}), 124.3 (C_6), 127.1 (C_5), 128.6 ($C_{2'}$), 129.0 ($C_{3'}$), 129.8 ($C_{4'}$), 132.1 (C_7), 135.3 ($C_{1'}$), 154.3 (C_{8a}), 155.8 (C_4), 160.9 (C_2); ^{13}C–{^1H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 6.38 ppm) δ 115.3 (folded $^1J_{CH}$), 119.1 ($^3J_{CH}$ = 7.2 Hz), 128.6 ($^4J_{CH}$ = 0.9 Hz), 135.3 ($^3J_{CH}$ = 5.0 Hz), 155.8 ($^2J_{CH}$ = 1.1 Hz), 160.9 ($^2J_{CH}$ = 4.1 Hz).

3-Phenyl-1*H*-isochromen-1-one (2) (commercially available)

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H, H_4), 7.41–7.53 (m, 5H, $H_{3'/4'}$, H_8 and H_6), 7.72 (dd, J = 8.0, 6.9 Hz, 1H, H_7), 7.89 (d, J = 8.1 Hz, 2H, $H_{2'}$), 8.31 (d, J = 8.2 Hz, 1H, H_5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 102.0 (C_4), 120.7 (C_{4a}), 125.4 ($C_{2'}$), 126.1 (C_6), 128.3 (C_8), 129.0 ($C_{3'}$), 129.8 (C_5), 130.1 ($C_{4'}$), 132.1 ($C_{1'}$), 135.0 (C_7), 137.6 (C_{8a}), 153.7 (C_3), 162.5 (C_1); ^{13}C–{^1H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4 6.96 ppm) δ 102.0 (folded $^1J_{CH}$), 120.7 ($^2J_{CH}$ = 5.4 Hz), 153.7 ($^2J_{CH}$ = 5.3 Hz).

2-Phenyl-4*H*-chromen-4-one (3)[42]

2-Phenyl-4*H*-chromen-4-one (**3**)[42] was obtained in 41% yield over 3 steps from salicylaldehyde, using reported procedures (see ESI†).[9a,43] White solid; TLC R_f 0.30 (cyclohexane/EtOAc 30%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H, H_3), 7.42 (dd, J = 8.1, 7.4 Hz, 1H, H_6), 7.49–7.55 (m, 3H, $H_{3'/4'}$), 7.57 (d, J = 8.1 Hz, 1H, H_8), 7.70 (dd, J = 8.1, 7.4 Hz, 1H, H_7), 7.93 (d, J = 7.7 Hz, 2H, $H_{2'}$), 8.23 (d, J = 8.1 Hz, 1H, H_5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 107.7 (C_3), 118.2 (C_8), 124.1 (C_{4a}), 125.4 (C_6), 125.8 (C_5), 126.4 ($C_{2'}$), 129.2 ($C_{3'}$), 131.7 ($C_{4'}$), 131.9 ($C_{1'}$), 133.9 (C_7), 156.4 (C_{8a}), 163.5 (C_2), 178.6 (C_4); ^{13}C–{^1H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 6.83 ppm) δ 107.7 (folded $^1J_{CH}$), 124.1 ($^3J_{CH}$ = 3.8 Hz), 163.5 ($^2J_{CH}$ = 5.5 Hz), 178.6 ($^2J_{CH}$ = 2.2 Hz).

Compounds **4**, **4a**, **4b** and **4e** were prepared from salicylaldehyde, using reported procedures (see ESI†).[9a]

(*Z*)-2-Benzylidenebenzofuran-3-one (4)[9a]

(*Z*)-2-Benzylidenebenzofuran-3-one (**4**)[9a] was obtained in 68% yield over 3 steps. Yellow solid; TLC R_f 0.16 (pentane/Et_2O 10%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H, $H_{1'}$), 7.21 (dd, J = 7.8, 7.4 Hz, 1H, H_5), 7.32 (d, J = 8.3 Hz, 1H, H_7), 7.39 (t, J = 7.3 Hz, 1H, $H_{5'}$), 7.45 (dd, J = 8.1, 7.3 Hz, 2H, $H_{4'}$), 7.64 (dd, J = 8.3, 7.4 Hz, 1H, H_6), 7.80 (d, J = 7.8 Hz, 1H, H_4), 7.92 (d, J = 8.1 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 113.0 (C_7), 113.1 ($C_{1'}$), 121.7 (C_{3a}), 123.6 (C_5), 124.8 (C_4), 129.0 ($C_{4'}$), 129.995 ($C_{5'}$), 131.6 ($C_{3'}$), 132.4 ($C_{2'}$), 137.0 (C_6), 147.0 (C_2), 166.2 (C_{7a}), 184.9 (C_3); ^{13}C–{^1H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.89 ppm) δ 113.1 (folded $^1J_{CH}$), 131.6 ($^3J_{CH}$ = 6.1 Hz), 147.0 ($^2J_{CH}$ = 4.7 Hz), 184.9 ($^3J_{CH}$ = 3.6 Hz).

(*Z*)-2-(4-Methoxybenzylidene)benzofuran-3-one (4a)[9a]

(*Z*)-2-(4-Methoxybenzylidene)benzofuran-3-one (**4a**)[9a] was obtained in 17% yield over 3 steps. Yellow solid; TLC R_f 0.38 (cyclohexane/EtOAc 30%); ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H, $H_{p\text{-OMe}}$), 6.89 (s, 1H, $H_{1'}$), 6.98 (d, J = 8.9 Hz, 2H, $H_{4'}$), 7.21 (dd, J = 7.9, 7.2 Hz, 1H, H_5), 7.32 (d, J = 8.3 Hz, 1H, H_7), 7.64 (dd, J = 8.3, 7.2 Hz, 1H, H_6), 7.80 (d, J = 7.9 Hz, 1H, H_4), 7.92 (d, J = 8.9 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 55.5 ($C_{p\text{-OMe}}$), 113.0 (C_7), 113.6 ($C_{1'}$), 114.6 ($C_{4'}$), 122.0 (C_{3a}), 123.4 (C_5), 124.7 (C_4), 125.1 ($C_{2'}$), 133.6 ($C_{3'}$), 136.7 (C_6), 146.0 (C_2), 161.2 ($C_{4'}$), 165.9 (C_{7a}), 184.7 (C_3); ^{13}C–{^1H} selective *J*-resolved NMR (125.8

MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.89 ppm) δ 113.6 (folded $^1J_{CH}$), 133.6 (^3J = 6.2 Hz), 146.0 ($^2J_{CH}$ = 4.3 Hz), 184.7 ($^3J_{CH}$ = 3.1 Hz).

(*Z*)-2-(4-Chlorobenzylidene)benzofuran-3-one (4b)[9a]

(*Z*)-2-(4-Chlorobenzylidene)benzofuran-3-one (**4b**)[9a] was obtained in 39% yield over 3 steps. Yellow solid; TLC R_f 0.38 (cyclohexane/EtOAc 30%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H, $H_{1'}$), 7.23 (dd, J = 7.7, 7.0 Hz, 1H, H_5), 7.33 (d, J = 8.4 Hz, 1H, H_7), 7.42 (d, J = 8.9 Hz, 2H, $H_{4'}$), 7.67 (dd, J = 8.4, 7.0 Hz, 1H, H_6), 7.80 (d, J = 7.7 Hz, 1H, H_4), 7.84 (d, J = 8.9 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 111.7 ($C_{1'}$), 113.1 (C_7), 121.6 (C_{3a}), 123.8 (C_5), 124.9 (C_4), 129.3 ($C_{4'}$), 130.9 ($C_{5'}$), 132.7 ($C_{3'}$), 136.0 ($C_{2'}$), 137.2 (C_6), 147.1 (C_2), 166.193 (C_{7a}), 184.8 (C_3); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.82 ppm) δ 111.7 (folded $^1J_{CH}$), 132.7 (^3J = 6.1 Hz), 147.1 ($^2J_{CH}$ = 3.7 Hz), 184.8 ($^3J_{CH}$ = 3.2 Hz).

(*Z*)-2-Benzylidene-2,3-dihydrobenzofuran-3-ol (4e)[9a]

(*Z*)-2-Benzylidene-2,3-dihydrobenzofuran-3-ol (**4e**)[9a] was obtained in 61% yield over 2 steps. White solid; TLC R_f 0.22 (cyclohexane/EtOAc 20%); ^{1}H NMR (500 MHz, C_6D_6) δ 1.52 (br, 1H, *H*O), 5.32 (dd, J = 5.4, 1.6 Hz, 1H, H_3), 5.83 (d, J = 1.6 Hz, 1H, $H_{1'}$), 6.76 (dd, J = 7.6, 7.3 Hz, 1H, H_5), 6.82 (d, J = 7.9 Hz, 1H, H_7), 6.96 (dd, J = 7.9, 7.6 Hz, 1H, H_6), 7.09 (t, J = 7.4 Hz, 1H, $H_{5'}$), 7.18 (d, J = 7.3 Hz, 1H, H_4), 7.28 (dd, J = 7.9, 7.4 Hz, 2H, $H_{4'}$), 7.82 (d, J = 7.9 Hz, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 72.5 (C_3), 106.1 ($C_{1'}$), 110.6 (C_7), 122.9 (C_5), 125.9 (C_4), 127.0 ($C_{5'}$), 127.8 (C_{3a}), 128.8 ($C_{4'}$), 129.2 ($C_{3'}$), 130.4 (C_6), 135.4 ($C_{2'}$), 157.6 (C_2), 158.1 (C_{7a}); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 5.83 ppm) δ 72.5 ($^3J_{CH}$ = 3.3 Hz), 106.1 (folded $^1J_{CH}$), 129.2 ($^3J_{CH}$ = 5.8 Hz), 157.6 ($^2J_{CH}$ = 4.3 Hz).

(*E*)-2-Benzylidenebenzofuran-3-one (4c)

A solution of (*Z*)-2-benzylidenebenzofuran-3-one (**4**) (93 mg, 0.42 mmol) in $CDCl_3$ (20 mL) was irradiated by the sunlight during 6 days. Solvent was then evaporated and the residue was purified by flash chromatography over silica gel (pentane/Et_2O 5 to 10%) to yield the desired (*E*)-2-benzylidenebenzofuran-3-one in 42% yield (39 mg, 0.18 mmol). Starting material was also partially recovered (29%, 27 mg, 0.12 mmol). Yellow solid; mp 178 °C; TLC R_f 0.28 (pentane/Et_2O 10%); IR (neat) ν_{max} 481, 552, 598, 666, 696, 752, 857, 884, 1023, 1037, 1085, 1144, 1186, 1239, 1297, 1323, 1459, 1475, 1495, 1596, 1656, 1712, 1727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H, $H_{1'}$), 7.18 (dd, J = 8.2, 6.8 Hz, 1H, H_5), 7.21 (d, J = 8.2 Hz, 1H, H_7), 7.39–7.48 (m, 3H, $H_{4'/5'}$), 7.63 (dd, J = 7.5, 6.8 Hz, 1H, H_6), 7.79 (d, J = 7.5 Hz, 1H, H_4), 8.17 (d, J = 7.9 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 112.7 (C_7), 122.8 ($C_{1'}$), 122.9 (C_5), 123.5 (C_{3a}), 124.8 (C_4), 128.6 ($C_{4'}$), 130.5 ($C_{5'}$), 131.0 ($C_{3'}$), 131.9 ($C_{2'}$), 136.9 (C_6), 148.2 (C_2), 165.4 (C_{7a}), 182.9 (C_3); HR-MS 245.0606 ($C_{15}H_{10}O_2$ + Na calcd 245.0573); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.97 ppm) δ 122.8 (folded $^1J_{CH}$), 131.0 ($^3J_{CH}$ = 6.3 Hz), 131.9 ($^2J_{CH}$ = 1.7 Hz), 148.2 ($^2J_{CH}$ = 8.4 Hz), 182.9 ($^3J_{CH}$ = 7.0 Hz).

(*E*)-2-(4-Chlorobenzylidene)benzofuran-3-one (4d)

(*E*)-2-(4-Chlorobenzylidene)benzofuran-3-one (**4d**) was obtained as a 1 : 6 mixture of **4b** : **4d** over 1 step from the corresponding (*Z*) isomer (**4b**), after irradiation at 350 nm in methanol for 30 h.[27a] SELJRES NMR Analysis was directly performed on the crude mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H, $H_{1'}$), 7.53 (dd, J = 7.7, 7.6 Hz, 1H, H_5), 7.55 (d, J = 8.2 Hz, 1H, H_7), 7.74 (d, J = 8.6 Hz, 1H, $H_{4'}$), 7.98 (dd, J = 8.2, 7.6 Hz, 1H, H_6), 8.13 (d, J = 7.7 Hz, 1H, H_4), 8.47 (d, J = 8.6 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 112.7 (C_7), 121.4 ($C_{1'}$), 123.0 (C_5), 123.3 (C_{3a}), 124.8 (C_4), 128.8 ($C_{4'}$), 130.4 ($C_{2'}$), 132.3 ($C_{3'}$), 136.3 ($C_{5'}$), 137.1 (C_6), 148.4 (C_2), 165.4 (C_{7a}), 183.0 (C_3); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 7.25 ppm) δ 121.4 (folded $^1J_{CH}$), 130.4 ($^2J_{CH}$ = 1.6 Hz), 132.3 ($^3J_{CH}$ = 6.4 Hz), 148.4 ($^2J_{CH}$ = 8.5 Hz), 183.0 ($^3J_{CH}$ = 7.0 Hz).

Compounds **5a**, **5b** and **5c** were prepared using reported procedures (see ESI†).[31]

2-(*tert*-Butyl)-5-phenylfuran-3-yl pivalate (5a)[31]

2-(*tert*-Butyl)-5-phenylfuran-3-yl pivalate (**5a**)[31] was obtained in 43% yield over 2 steps, from 4,4-dimethylpent-1-yn-3-yl pivalate. Colorless oil; TLC R_f 0.64 (pentane/Et_2O 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H, $H_{3''}$), 1.37 (s, 9H, $H_{2'}$), 6.59 (s, 1H, H_4), 7.23 (t, J = 7.3 Hz, 1H, $H_{4'''}$), 7.35 (dd, J = 8.0, 7.3 Hz, 2H, $H_{3'''}$), 7.59 (d, J = 8.0 Hz, 2H, $H_{2'''}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 27.3 ($C_{3''}$), 29.0 ($C_{2'}$), 33.2 ($C_{1'}$), 39.1 ($C_{2''}$), 102.7 (C_4), 123.4 ($C_{3'''}$), 127.3 ($C_{4'''}$), 128.7 ($C_{2'''}$), 131.0 ($C_{1'''}$), 134.0 (C_2), 148.9 (C_5), 149.1 (C_3), 176.4 ($C_{1''}$); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4 6.59 ppm) δ 102.7 (folded $^1J_{CH}$), 131.0 ($^3J_{CH}$ = 1.0 Hz), 148.9 ($^2J_{CH}$ = 7.6 Hz), 149.1 ($^2J_{CH}$ = 4.9 Hz).

5-(*tert*-Butyl)-2-phenylfuran-3-yl pivalate (5b)[31]

5-(*tert*-Butyl)-2-phenylfuran-3-yl pivalate (**5b**)[31] was obtained in 5% yield over 2 steps, from 4,4-dimethylpent-1-yn-3-yl pivalate, and analyzed as a **5a** : **5b** 5.1 : 1 mixture of regiosisomers. TLC R_f 0.71 (pentane/Et_2O 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H, $H_{2'''}$), 1.39 (s, 9H, $H_{3''}$), 6.24 (s, 1H, H_4), 7.21 (t, J = 7.3 Hz, 1H, $H_{4'}$), 7.38 (dd, J = 8.0, 7.3 Hz, 2H, $H_{3'}$), 7.68 (d, J = 8.0 Hz, 2H, $H_{2'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 27.4 ($C_{3''}$), 29.0 ($C_{2'''}$), 33.1 ($C_{1'''}$), 39.3 ($C_{2''}$), 101.2 (C_4), 123.9 ($C_{3'}$), 126.7 ($C_{4'}$), 128.6 ($C_{2'}$), 130.3 ($C_{1'}$), 135.7 (C_2), 138.4 (C_3), 161.6 (C_5), 176.0 ($C_{1''}$); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4 6.24 ppm) δ 101.2 (folded $^1J_{CH}$), 138.4 ($^2J_{CH}$ = 5.0 Hz), 161.6 ($^2J_{CH}$ = 7.7 Hz).

2-Methyl-5-phenylfuran-3-yl pivalate (5c)[44]

2-Methyl-5-phenylfuran-3-yl pivalate (**5c**)[44] was obtained in 22% yield over 2 steps, from but-3-yn-2-yl pivalate. White solid; TLC R_f 0.60 (pentane/Et_2O 5%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H, $H_{3''}$), 2.26 (s, 3H, $H_{1'}$), 6.64 (s, 1H, H_4), 7.23 (t, J = 7.3 Hz, 1H, $H_{4'''}$), 7.36 (dd, J = 7.8, 7.3 Hz, 2H, $H_{3'''}$), 7.59 (d, J = 7.8 Hz, 2H, $H_{2'''}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 10.8 ($C_{1'}$), 27.3 ($C_{3''}$), 39.2 ($C_{2''}$), 102.1 (C_4), 123.4 ($C_{2'''}$), 127.3 ($C_{4'''}$), 128.7 ($C_{3'''}$), 131.0 ($C_{1'''}$), 135.9 (C_2), 139.8 (C_3), 150.1 (C_5), 176.2 ($C_{1''}$); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4

6.64 ppm) δ 102.1 (folded $^{1}J_{CH}$), 131.0 ($^{3}J_{CH}$ = 1.1 Hz), 139.8 ($^{2}J_{CH}$ = 5.4 Hz), 150.1 ($^{2}J_{CH}$ = 7.6 Hz).

Compounds **5d** and **5e** were prepared using reported procedures (see ESI†).[31,45]

Diethyl (5-methyl-2-phenylfuran-3-yl) phosphate (5d)[45]

Diethyl (5-methyl-2-phenylfuran-3-yl) phosphate (**5d**)[45] was obtained in 10% yield over 5 steps, from but-1-yn-3-ol. Colorless oil; TLC R_f 0.30 (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 490, 578, 659, 693, 761, 800, 905, 1011, 1147, 1277, 1445, 1630, 2913, 2985 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (td, J = 7.1 Hz, J_{HP} = 0.9 Hz, 6H, $H_{2''}$), 2.32 (s, 3H, $H_{2'''}$), 4.15–4.27 (m, 4H, $H_{1''}$), 6.28 (s, 1H, H_4), 7.21 (t, J = 7.5 Hz, 1H, $H_{4'}$), 7.37 (dd, J = 8.6, 7.5 Hz, 2H, $H_{3'}$), 7.73 (d, J = 8.6 Hz, 2H, $H_{2'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3 ($C_{2'''}$), 16.2 (d, J_{CP} = 6.9 Hz, $C_{2''}$), 64.9 (d, J_{CP} = 6.4 Hz, $C_{1''}$), 103.5 (C_4), 123.6 ($C_{2'}$), 126.6 ($C_{4'}$), 128.6 ($C_{3'}$), 129.9 ($C_{1'}$), 135.6 (d, J_{CP} = 6.9 Hz, C_2), 138.1 (d, J_{CP} = 6.9 Hz, C_3), 150.0 (C_5); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ −5.32; HR-MS 333.084 ($C_{15}H_{19}O_5P$ + Na calcd 333.086); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4 6.28 ppm) δ 14.3 ($^{3}J_{CH}$ = 1.2 Hz), 103.5 (folded $^{1}J_{CH}$), 150.0 ($^{2}J_{CH}$ = 7.9 Hz).

Diethyl (5-pentyl-2-phenylfuran-3-yl) phosphate (5e)[45]

Diethyl (5-pentyl-2-phenylfuran-3-yl) phosphate (**5e**)[45] was obtained in 24% yield over 5 steps, from oct-1-yn-2-ol (see ESI†). Colorless oil; TLC R_f 0.24 (cyclohexane/EtOAc 40%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 3H, $H_{5'''}$), 1.33 (td, J = 7.2 Hz, J_{HP} = 1.1 Hz, 6H, $H_{2''}$), 1.33–1.37 (m, 4H, $H_{4'''/3'''}$), 1.64–1.70 (m, 2H, $H_{2'''}$), 2.61 (t, J = 7.7 Hz, 2H, $H_{1'''}$), 4.16–4.26 (m, 4H, $H_{1''}$), 6.29 (s, 1H, H_4), 7.20 (t, J = 7.4 Hz, 1H, $H_{4'}$), 7.37 (dd, J = 8.6, 7.4 Hz, 2H, $H_{3'}$), 7.73 (d, J = 8.6 Hz, 2H, $H_{2'}$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 14.1 ($C_{5'''}$), 16.2 (d, J_{CP} = 6.8 Hz, $C_{2''}$), 22.5 ($C_{4'''}$), 27.5 ($C_{2'''}$), 28.6 ($C_{1'''}$), 31.4 ($C_{3'''}$), 64.9 (d, J_{CP} = 6.1 Hz, $C_{1''}$), 102.7 (C_4), 123.7 ($C_{2'}$), 126.6 ($C_{4'}$), 128.6 ($C_{3'}$), 130.0 ($C_{1'}$), 135.6 (d, J_{CP} = 6.2 Hz, C_2), 137.9 (d, J_{CP} = 10.5 Hz, C_3), 154.4 (C_5); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −5.18; ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_4 6.29 ppm) δ 28.6 ($^{3}J_{CH}$ = 1.0 Hz), 102.7 (folded $^{1}J_{CH}$), 154.4 ($^{2}J_{CH}$ = 7.8 Hz).

Compounds **6**, **(*Z*)-7** and **8** were prepared using reported procedures (see ESI†).[9b]

5-Methylenedihydrofuran-2-one (6)[9b]

5-Methylenedihydrofuran-2-one (**6**)[9b] was obtained in 96% yield over 1 step, from pent-4-ynoic acid. Colorless oil; TLC R_f 0.18 (pentane/Et_2O 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64–2.70 (m, 2H, H_3), 2.85–2.91 (m, 2H, H_4), 4.31 (dt, J = 2.2, 2.0 Hz, 1H, H_E), 4.72 (td, J = 2.3, 2.2 Hz, 1H, H_Z); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.2 (C_4), 28.1 (C_3), 88.9 ($C_{1'}$), 155.7 (C_5), 175.0 (C_1); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_Z 4.72 ppm) δ 25.2 ($^{3}J_{CH}$ = 7.8 Hz), 28.1 ($^{4}J_{CH}$ = 1.0 Hz), 88.9 (folded $^{1}J_{CH}$), 155.7 ($^{2}J_{CH}$ = 6.9 Hz); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_E 4.31 ppm) δ 25.2 ($^{3}J_{CH}$ = 3.3 Hz), 88.9 (folded $^{1}J_{CH}$), 155.7 ($^{2}J_{CH}$ = 6.4 Hz).

(*Z*)-5-Benzylidenedihydrofuran-2-one ((*Z*)-7)[9b]

(*Z*)-5-Benzylidenedihydrofuran-2-one (**(*Z*)-7**)[9b] was obtained in 49% yield over 1 step, from 5-phenylpent-4-ynoic acid. Beige solid; TLC R_f 0.17 (cyclohexane/EtOAc 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68–2.74 (m, 2H, H_3), 3.03 (td, J = 8.6, 1.8 Hz, 2H, H_4), 5.55 (t, J = 1.8 Hz, 1H, $H_{1'}$), 7.21 (t, J = 7.4 Hz, 1H, $H_{5'}$), 7.33 (dd, J = 7.8, 7.4 Hz, 2H, $H_{4'}$), 7.55 (d, J = 7.8 Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 26.5 (C_4), 27.1 (C_3), 105.0 ($C_{1'}$), 126.9 ($C_{5'}$), 128.4 ($C_{3'}$), 128.6 ($C_{4'}$), 134.0 ($C_{2'}$), 148.2 (C_5), 175.1 (C_1); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 5.55 ppm) δ 26.5 ($^{3}J_{CH}$ = 3.9 Hz), 105.0 (folded $^{1}J_{CH}$), 128.4 ($^{3}J_{CH}$ = 5.6 Hz), 148.2 ($^{2}J_{CH}$ = 5.6 Hz).

(*Z*)-5-(3-Phenylprop-2-yn-1-ylidene)dihydrofuran-2-one (8)[9b]

(*Z*)-5-(3-Phenylprop-2-yn-1-ylidene)dihydrofuran-2-one (**8**)[9b] was obtained in 75% yield over 1 step, from 7-phenylheptan-4,6-diynoic acid. Yellow solid; TLC R_f 0.47 (cyclohexane/EtOAc 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72–2.77 (m, 2H, H_3), 2.99 (td, J = 8.5, 1.9 Hz, 2H, H_4), 5.04 (t, J = 1.9 Hz, 1H, $H_{1'}$), 7.27–7.24 (m, 3H, $H_{6'/7'}$), 7.42–7.48 (m, 2H, $H_{5'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.6 (C_4), 27.5 (C_3), 82.3 ($C_{2'}$ or $C_{3'}$), 85.6 ($C_{1'}$), 93.8 ($C_{2'}$ or $C_{3'}$), 123.4 ($C_{4'}$), 128.3 ($C_{7'}$), 128.4 ($C_{6'}$), 131.6 ($C_{5'}$), 158.3 (C_5), 173.9 (C_1); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 5.04 ppm) δ 25.6 ($^{3}J_{CH}$ = 3.2 Hz), 82.3 ($^{2/3}J_{CH}$ = 2.3 Hz), 85.6 (folded $^{1}J_{CH}$), 93.8 ($^{2/3}J_{CH}$ = 4.6 Hz), 123.4 ($^{4}J_{CH}$ = 1.7 Hz), 131.6 ($^{5}J_{CH}$ = 1.7 Hz), 158.3 ($^{2}J_{CH}$ = 4.8 Hz).

(*E*)-5-Benzylidenedihydrofuran-2-one ((*E*)-7)

(*E*)-5-Benzylidenedihydrofuran-2-one (**(*E*)-7**) was obtained in 68% yield over 1 step from pent-4-ynoic acid, using reported procedure (see ESI†).[46] Beige solid; TLC R_f 0.20 (pentane/Et_2O 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73–2.79 (m, 2H, H_3), 3.17 (td, J = 8.6, 2.2 Hz, 2H, H_4), 6.33 (t, J = 2.2 Hz, 1H, $H_{1'}$), 7.20–7.25 (m, 3H, $H_{3'/5'}$), 7.35 (dd, J = 7.8, 7.8 Hz, 2H, $H_{4'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.3 (C_4), 27.9 (C_3), 107.2 ($C_{1'}$), 126.8 ($C_{5'}$), 127.9 ($C_{3'}$), 128.8 ($C_{4'}$), 134.5 ($C_{2'}$), 151.3 (C_5), 174.3 (C_1); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.33 ppm) δ 25.3 ($^{3}J_{CH}$ = 6.2 Hz), 107.2 (folded $^{1}J_{CH}$), 127.9 ($^{3}J_{CH}$ = 5.3 Hz), 151.3 ($^{2}J_{CH}$ = 7.7 Hz).

(*Z*)-4-Bromo-5-(bromomethylene)-2-furanone (9) (commercially available)

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (s, 1H, $H_{1'}$), 6.50 (s, 1H, H_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 93.9 ($C_{1'}$), 121.2 (C_3), 135.4 (C_5), 151.2 (C_4), 165.6 (C_1); ^{13}C–{^{1}H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{1'}$ 6.42 ppm) δ 93.9 (folded $^{1}J_{CH}$), 135.4 ($^{2}J_{CH}$ = 4.3 Hz), 151.2 ($^{3}J_{CH}$ = 10.6 Hz).

Compounds **10a** and **(*E*)-10b** were prepared using reported procedures (see ESI†).[35a]

(*E*)-4-Methyl-1-phenyl-2-pivaloxypenta-1,4-dien-3-one (10a)[35a]

(*E*)-4-Methyl-1-phenyl-2-pivaloxypenta-1,4-dien-3-one (**10a**)[35a] was obtained in 59% yield over 3 steps, from 2-methylbut-1-en-3-yne. Yellow solid; mp 35 °C; TLC R_f 0.51 (cyclohexane/EtOAc 20%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H, $H_{3''}$), 1.82 (dd,

$J = 1.4$, 1.2 Hz, 3H, $H_{1'''}$), 5.53 (dq, $J = 1.6$, 1.4 Hz, 1H, H_{5E}), 5.94 (dq, $J = 1.6$, 1.2 Hz, 1H, H_{5Z}), 6.84 (s, 1H, H_1), 7.10–7.14 (m, 2H, $H_{2'}$), 7.25–7.29 (m, 3H, $H_{3'/4'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.3 ($C_{1'''}$), 27.0 ($C_{3''}$), 38.7 ($C_{2''}$), 124.2 (C_1), 127.8 (C_5), 128.5 ($C_{3'}$), 128.5 ($C_{4'}$), 129.2 ($C_{2'}$), 133.3 ($C_{1'}$), 142.7 (C_4), 144.0 (C_2), 177.0 ($C_{1''}$), 193.3 (C_3); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_1 6.84 ppm) δ 124.2 (folded $^1J_{CH}$), 129.2 ($^3J_{CH} = 6.4$ Hz), 144.0 ($^2J_{CH} = 8.4$ Hz), 193.3 ($^3J_{CH} = 8.1$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_{5Z} 5.94 ppm) δ 17.3 ($^3J_{CH} = 10.3$ Hz), 127.8 (folded $^1J_{CH}$), 142.7 ($^2J_{CH} = 2.6$ Hz), 193.3 ($^3J_{CH} = 7.1$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_{5E} 5.53 ppm) δ 17.3 ($^3J_{CH} = 6.1$ Hz), 127.8 (folded $^1J_{CH}$), 142.7 ($^2J_{CH} = 1.6$ Hz), 193.3 ($^3J_{CH} = 13.3$ Hz).

(*E*)-4-Methyl-1-(4-nitrophenyl)-2-pivaloxypenta-1,4-dien-3-one ((*E*)-10b)

(*E*)-4-Methyl-1-(4-nitrophenyl)-2-pivaloxypenta-1,4-dien-3-one (**(*E*)-10b**) was obtained in 18% yield over 3 steps, from 2-methylbut-1-en-3-yne (see ESI†). Yellowish solid; mp 78 °C; TLC R_f 0.42 (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 695, 738, 821, 858, 1037, 1103, 1152, 1202, 1273, 1342, 1513, 1592, 1667, 1720, 1745, 2874, 2935, 2976, 3079 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H, $H_{3''}$), 1.84 (dd, $J = 1.7$, 1.0 Hz, 3H, $H_{1'''}$), 5.67 (dq, $J = 1.7$, 1.2 Hz, 1H, H_{5E}), 5.94 (dq, $J = 1.2$, 1.0 Hz, 1H, H_{5Z}), 6.80 (s, 1H, H_1), 7.30 (d, $J = 8.9$ Hz, 2H, $H_{2'}$), 8.14 (d, $J = 8.9$ Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.2 ($C_{1'''}$), 26.9 ($C_{3''}$), 38.7 ($C_{2''}$), 121.2 (C_1), 123.8 ($C_{3'}$), 128.3 (C_5), 129.8 ($C_{2'}$), 139.8 ($C_{4'}$), 142.9 (C_4), 146.5 (C_2), 147.4 ($C_{1'}$), 176.5 ($C_{1''}$), 192.1 (C_3); HR-MS 340.1175 ($C_{17}H_{19}NO_5$ + Na calcd 340.1155); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_1 6.80 ppm) δ 121.2 (folded $^1J_{CH}$), 129.8 ($^3J_{CH} = 4.7$ Hz), 146.5 ($^2J_{CH} = 8.4$ Hz), 147.4 ($^2J_{CH} = 1.0$ Hz), 192.1 ($^3J_{CH} = 7.8$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_{5Z} 5.94 ppm) δ 17.2 ($^3J_{CH} = 10.2$ Hz), 128.3 (folded $^1J_{CH}$), 142.9 ($^2J_{CH} = 2.4$ Hz), 192.1 ($^3J_{CH} = 7.2$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_{5E} 5.67 ppm) δ 17.2 ($^3J_{CH} = 6.0$ Hz), 128.3 (folded $^1J_{CH}$), 142.9 ($^2J_{CH} = 1.6$ Hz), 192.1 ($^3J_{CH} = 13.7$ Hz).

Compounds **(*Z*)-10b** and **10c** were prepared using reported procedures (see ESI†).[35a,47]

(*Z*)-4-Methyl-1-(4-nitrophenyl)-2-pivaloxypenta-1,4-dien-3-one ((*Z*)-10b)

(*Z*)-4-Methyl-1-(4-nitrophenyl)-2-pivaloxypenta-1,4-dien-3-one (**(*Z*)-10b**) was obtained in 45% yield over 2 steps, from 2-methylbut-1-en-3-yne. Yellowish solid; mp 68 °C; TLC R_f 0.46 (pentane/Et_2O 10%); IR (neat) ν_{max} 691, 748, 778, 850, 892, 1031, 1092, 1164, 1270, 1340, 1514, 1596, 1656, 1716, 1751, 2874, 2934, 2977 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H, $H_{3''}$), 2.01 (dd, $J = 1.4$, 1.0 Hz, 3H, $H_{1'''}$), 5.86 (dq, $J = 1.4$, 1.2 Hz, 1H, H_5), 5.90 (dq, $J = 1.2$, 1.0 Hz, 1H, H_5), 6.88 (s, 1H, H_1), 7.75 (d, $J = 8.9$ Hz, 2H, $H_{2'}$), 8.23 (d, $J = 8.9$ Hz, 2H, $H_{3'}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 18.4 ($C_{1'''}$), 27.0 ($C_{3''}$), 39.0 ($C_{2''}$), 123.7 (C_1), 123.9 ($C_{3'}$), 125.9 (C_5), 130.7 ($C_{2'}$), 138.9 ($C_{4'}$), 142.6 (C_4), 147.0 (C_2), 147.7 ($C_{1'}$), 176.0 ($C_{1''}$), 191.5 (C_3); HR-MS 340.1175 ($C_{17}H_{19}NO_5$ + Na calcd 340.1155); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_1 6.88 ppm) δ 123.7 (folded $^1J_{CH}$), 130.7 ($^3J_{CH} = 5.4$ Hz), 147.0 ($^2J_{CH} = 4.6$ Hz), 191.5 ($^3J_{CH} = 3.8$ Hz).

(*Z*)-2-Acetoxy-1-(cyclohex-1-enyl)non-2-en-1-one (10c)

(*Z*)-2-Acetoxy-1-(cyclohex-1-enyl)non-2-en-1-one (**10c**) was obtained in 90% yield over 2 steps, from ethynylcyclohex-1-ene. Colorless oil; TLC R_f 0.22 (pentane/Et_2O 20%); IR (neat) ν_{max} 590, 701, 745, 835, 883, 975, 1014, 1092, 1136, 1204, 1250, 1276, 1307, 1435, 1647, 1759, 2857, 2927 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H, H_9), 1.23–1.25 (m, 6H, $H_{8/7/6}$), 1.43 (tt, $J = 7.4$, 7.1 Hz, 2H, H_5), 1.59–1.69 (m, 4H, $H_{4''/5''}$), 2.02 (dt, $J = 7.6$, 7.4 Hz, 2H, H_4), 2.21 (s, 3H, $H_{2'}$), 2.20–2.30 (m, 4H, $H_{3''/6''}$), 6.05 (t, $J = 7.6$ Hz, 1H, H_3), 6.69–6.73 (m, 1H, $H_{2''}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2 (C_9), 20.5 ($C_{2'}$), 21.7 ($C_{4''}$), 22.0 ($C_{5''}$), 22.6 (C_8), 24.0 ($C_{6''}$), 25.9 ($C_{3''}$), 26.1 (C_4), 28.5 (C_5), 29.1 (C_6), 31.6 (C_7), 131.9 (C_3), 137.7 ($C_{1''}$), 140.8 ($C_{2''}$), 145.3 (C_2), 169.0 ($C_{1'}$), 191.1 (C_1); HR-MS 301.175 ($C_{17}H_{26}O_3$ + Na calcd 301.177); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 6.05 ppm) δ 26.1 ($^2J_{CH} = 1.8$ Hz), 28.5 ($^3J_{CH} = 3.2$ Hz), 131.9 (folded $^1J_{CH}$), 145.3 ($^2J_{CH} = 6.8$ Hz), 191.1 ($^3J_{CH} = 3.4$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{2''}$ 6.69–6.73 ppm) δ 21.7 ($^3J_{CH} = 5.5$ Hz), 24.0 ($^3J_{CH} = 7.2$ Hz), 25.9 ($^2J_{CH} = 3.7$ Hz), 137.7 ($^2J_{CH} = 0.9$ Hz), 140.8 (folded $^1J_{CH}$), 191.1 ($^3J_{CH} = 6.4$ Hz).

(*E*)-1-(4,5-Dihydro-6*H*-pyran-2-yl)-2-methyl-3-phenylprop-2-en-1-one (11)[48]

(*E*)-1-(4,5-Dihydro-6*H*-pyran-2-yl)-2-methyl-3-phenylprop-2-en-1-one (**11**)[48] was obtained in 26% yield over 2 steps from dihydropyrane, using reported procedure (see ESI†).[35a] Colorless oil; TLC R_f 0.40 (cyclohexane/EtOAc 30%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (tdd, $J = 6.4$, 6.0, 4.3 Hz, 2H, $H_{5'}$), 2.13 (d, $J = 1.4$ Hz, 3H, $H_{1''}$), 2.26 (td, $J = 6.4$, 4.2 Hz, 2H, $H_{4'}$), 4.17 (dd, $J = 6.0$, 4.3 Hz, 2H, $H_{6'}$), 5.82 (t, $J = 4.2$ Hz, 1H, $H_{3'}$), 7.24 (q, $J = 1.4$ Hz, 1H, H_3), 7.29–7.36 (m, 1H, $H_{4'''}$), 7.35–7.42 (m, 4H, $H_{2'''/3'''}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.9 ($C_{1''}$), 21.0 ($C_{4'}$), 21.7 ($C_{5'}$), 66.5 ($C_{6'}$), 113.4 ($C_{3'}$), 128.4 ($C_{4'''}$), 128.5 ($C_{3'''}$), 129.7 ($C_{2'''}$), 135.9 ($C_{1'''}$ or C_2), 136.0 ($C_{1'''}$ or C_2), 138.9 (C_3), 151.4 ($C_{2'}$), 193.9 (C_1); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{3'}$ 5.82 ppm) δ 14.9 ($^3J_{CH} = 8.3$ Hz), 21.0 ($^2J_{CH} = 2.6$ Hz), 21.7 ($^3J_{CH} = 5.5$ Hz), 113.4 (folded $^1J_{CH}$), 151.4 ($^2J_{CH} = 4.7$ Hz), 193.9 ($^3J_{CH} = 3.5$ Hz); ^{13}C–{^{1}H} selective *J*-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 7.24 ppm) δ 138.9 (folded $^1J_{CH}$), 193.9 ($^3J_{CH} = 6.8$ Hz).

Compounds **12a**, **12c** and **12d** were prepared using reported procedures (see ESI†).[36e,49]

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-(2,4-dimethoxyphenyl)prop-2-enoate (12a)

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-(2,4-dimethoxyphenyl) prop-2-enoate (**12a**) was obtained in 64% yield over 2 steps, from cyclohex-1-en-1-carboxylic acid. Yellowish solid; mp 99 °C; TLC R_f 0.09 (pentane/Et_2O 30%); IR (neat) ν_{max} 401, 461, 530, 768, 802, 826, 927, 995, 1030, 1044, 1072, 1124, 1162, 1192, 1207, 1237, 1301, 1313, 1422, 1434, 1459, 1501, 1593, 1632,

1646, 1706, 2836, 2929, 2945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50–1.57 (m, 2H, $H_{4''}$), 1.58–1.64 (m, 2H, $H_{5''}$), 2.07–2.14 (m, 2H, $H_{3''}$), 2.29–2.35 (m, 2H, $H_{6''}$), 3.77 (s, 3H, H_{OMe}), 3.79 (s, 3H, $H_{o\text{-}}$ or $_{p\text{-}OMe}$), 3.82 (s, 3H, $H_{o\text{-}}$ or $_{p\text{-}OMe}$), 6.35 (dd, J = 8.8, 2.5 Hz, 1H, $H_{3'}$ or $_{5'}$), 6.39 (d, J = 2.5 Hz, 1H, $H_{3'}$ or $_{5'}$), 6.80–6.84 (m, 1H, $H_{2''}$), 7.12 (d, J = 8.8 Hz, 1H, $H_{6'}$), 8.14 (s, 1H, H_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.6 ($C_{4''}$), 21.9 ($C_{5''}$), 22.8 ($C_{6''}$), 26.3 ($C_{3''}$), 52.4 (C_{OMe}), 55.6 ($C_{o\text{-}}$ or $_{p\text{-}OMe}$), 55.6 ($C_{o\text{-}}$ or $_{p\text{-}OMe}$), 98.3 ($C_{3'}$ or $_{5'}$), 105.0 ($C_{3'}$ or $_{5'}$), 115.6 ($C_{1'}$), 128.1 (C_2), 131.2 ($C_{6'}$), 136.9 (C_3), 139.2 ($C_{1''}$), 144.8 ($C_{2''}$), 159.8 ($C_{2'}$), 162.9 ($C_{4'}$), 166.5 (C_1), 197.8 ($C_{1''}$); HR-MS 353.1389 ($C_{19}H_{22}O_5$ + Na calcd 353.1359); ^{13}C–{^1H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 8.14 ppm) δ 128.1 ($^2J_{CH}$ = 4.2 Hz), 131.2 ($^3J_{CH}$ = 6.3 Hz), 136.9 (folded $^1J_{CH}$), 159.8 ($^3J_{CH}$ = 3.5 Hz), 166.5 ($^3J_{CH}$ = 8.2 Hz), 197.8 ($^3J_{CH}$ = 10.1 Hz); ^{13}C–{^1H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: $H_{2''}$ 6.80–6.84 ppm) δ 21.6 ($^3J_{CH}$ = 5.3 Hz), 22.8 ($^3J_{CH}$ = 6.8 Hz), 26.3 ($^2J_{CH}$ = 3.7 Hz), 139.2 ($^2J_{CH}$ = 1.4 Hz), 144.8 (folded $^1J_{CH}$), 197.8 ($^3J_{CH}$ = 7.3 Hz).

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-phenylprop-2-enoate (12c)

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-phenylprop-2-enoate (**12c**) was obtained in 54% yield over 2 steps, from cyclohex-1-en-1-carboxylic acid. Yellowish solid; mp 43 °C; TLC R_f 0.19 (cyclohexane/EtOAc 10%); IR (neat) ν_{max} 401, 492, 551, 580, 680, 770, 830, 929, 992, 1068, 1102, 1185, 1212, 1391, 1421, 1497, 1619, 1647, 1713, 2861, 2929 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.58 (m, 2H, $H_{4''}$), 1.60–1.66 (m, 2H, $H_{5''}$), 2.09–2.14 (m, 2H, $H_{3''}$), 2.32–2.38 (m, 2H, $H_{6''}$), 3.79 (s, 3H, H_{OMe}), 6.83 (t, J = 7.6 Hz, 1H, $H_{2''}$), 7.29–7.35 (m, 5H, $H_{2'/3'/4'}$), 7.81 (s, 1H, H_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.5 ($C_{4''}$ or $C_{5''}$), 21.8 ($C_{4''}$ or $C_{5''}$), 22.8 ($C_{6''}$), 26.4 ($C_{3''}$), 52.7 (C_{OMe}), 128.8 ($C_{3'}$), 130.1 ($C_{2'}$), 130.3 ($C_{4'}$), 131.4 (C_2), 133.4 ($C_{1'}$), 139.3 ($C_{1''}$), 142.1 (C_3), 145.6 ($C_{2''}$), 165.9 (C_1), 196.9 ($C_{1''}$); HR-MS 293.114 ($C_{17}H_{18}O_3$ + Na calcd 293.115); ^{13}C–{^1H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 7.81 ppm) δ 130.1 ($^3J_{CH}$ = 5.6 Hz), 131.4 ($^2J_{CH}$ = 4.2 Hz), 133.4 ($^2J_{CH}$ = 1.2 Hz), 142.1 (folded $^1J_{CH}$), 165.9 ($^3J_{CH}$ = 8.1 Hz), 196.9 ($^3J_{CH}$ = 9.7 Hz).

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-(4-methoxyphenyl) prop-2-enoate (12d)

Methyl (*E*)-2-(cyclohex-1-enylcarbonyl)-3-(4-methoxyphenyl) prop-2-enoate (**12d**) was obtained in 56% yield over 2 steps, from cyclohex-1-en-1-carboxylic acid. Colorless oil; TLC R_f 0.16 (pentane/Et_2O 30%); IR (neat) ν_{max} 520, 540, 830, 924, 989, 1027, 1070, 1119, 1171, 1200, 1250, 1305, 1433, 1511, 1599, 1632, 1651, 1704, 2839, 2859, 2933 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54–1.61 (m, 2H, $H_{4''}$), 1.63–1.69 (m, 2H, $H_{5''}$), 2.11–2.16 (m, 2H, $H_{3''}$), 2.35–2.40 (m, 2H, $H_{6''}$), 3.78 (s, 3H, H_{OMe}), 3.81 (s, 3H, $H_{p\text{-}OMe}$), 6.83 (d, J = 8.9 Hz, 2H, $H_{3'}$), 6.85–6.88 (m, 1H, $H_{2''}$), 7.27 (d, J = 8.9 Hz, 2H, $H_{2'}$), 7.75 (s, 1H, H_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.6 ($C_{4''}$ or $C_{5''}$), 21.8 ($C_{4''}$ or $C_{5''}$), 22.8 ($C_{6''}$), 26.4 ($C_{3''}$), 52.5 (C_{OMe}), 55.5 ($C_{p\text{-}OMe}$), 114.3 ($C_{3'}$), 125.9 ($C_{1'}$), 128.7 (C_2), 132.2 ($C_{2'}$), 139.3 ($C_{1''}$), 141.8 (C_3), 145.4 ($C_{2''}$), 161.3 ($C_{4'}$), 166.2 (C_1), 197.5 ($C_{1''}$); HR-MS 323.125 ($C_{18}H_{20}O_4$ + Na calcd 323.125); ^{13}C–{^1H} selective J-resolved NMR (125.8 MHz, $CDCl_3$, chosen proton: H_3 7.75 ppm) δ 125.9 ($^2J_{CH}$ = 1.1 Hz), 128.7 ($^2J_{CH}$ = 4.3 Hz), 132.2 ($^3J_{CH}$ = 5.9 Hz), 141.8 (folded $^1J_{CH}$), 166.2 ($^3J_{CH}$ = 8.1 Hz), 197.5 ($^3J_{CH}$ = 9.8 Hz).

Acknowledgements

We gratefully acknowledge the Agence Nationale de la Recherche for a grant (ANR-11-JS07-001-01 Synt-Het-Au) and the CNRS. M. H. and S. M. thank the French Ministry of Research for a PhD fellowships. M. H. also thanks Dr L. Allouche and M. Coppe (Service de RMN, Faculté de Chimie, 1 rue Blaise Pascal, University of Strasbourg, Strasbourg, France) for their fruitful help in acquisition of SELJRES spectra.

Notes and references

1 T. L. Suyama, W. H. Gerwick and K. L. McPhail, *Bioorg. Med. Chem.*, 2011, **19**, 6675–6701.
2 K. C. Nicolaou and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2005, **44**, 1012–1044.
3 For selected examples of natural product structure revisions, see: (*a*) K. Ogawa, Y. Koyama, I. Ohashi, I. Sato and M. Hirama, *Angew. Chem., Int. Ed.*, 2009, **48**, 1110–1113; (*b*) S. Kobayashi, S. Ashizawa, Y. Takahashi, Y. Sugiura, M. Nagaoka, M. J. Lear and M. Hirama, *J. Am. Chem. Soc.*, 2001, **123**, 11294–11295.
4 M. Elyashberg, A. J. Williams and K. Blinov, *Nat. Prod. Rep.*, 2010, **27**, 1296–1328.
5 S. G. Smith and J. M. Goodman, *J. Am. Chem. Soc.*, 2010, **132**, 12946–12959.
6 A. M. Sarotti, *Org. Biomol. Chem.*, 2013, **11**, 4847–4859.
7 A. Bihlmeier, E. Bourcet, S. Arzt, T. Muller, S. Bräse and W. Klopper, *J. Am. Chem. Soc.*, 2011, **134**, 2154–2160.
8 L. Gross, F. Mohn, N. Moll, G. Meyer, R. Ebel, W. M. Abdel-Mageed and M. Jaspars, *Nat. Chem.*, 2010, **2**, 821–825.
9 (*a*) H. Harkat, A. Blanc, J.-M. Weibel and P. Pale, *J. Org. Chem.*, 2008, **73**, 1620–1623; (*b*) H. Harkat, A. Y. Dembelé, J.-M. Weibel, A. Blanc and P. Pale, *Tetrahedron*, 2009, **65**, 1871–1879.
10 (*a*) H. Harkat, J.-M. Weibel and P. Pale, *Tetrahedron Lett.*, 2006, **47**, 6273–6276; (*b*) H. Harkat, J.-M. Weibel and P. Pale, *Tetrahedron Lett.*, 2007, **48**, 1439–1442; (*c*) A. Blanc, K. Tenbrink, J.-M. Weibel and P. Pale, *J. Org. Chem.*, 2009, **74**, 4360–4363; (*d*) N. Kern, M. Hoffmann, A. Blanc, J.-M. Weibel and P. Pale, *Org. Lett.*, 2013, **15**, 836–839.
11 (*a*) W. P. Aue, E. Bartholdi and R. R. Ernst, *J. Chem. Phys.*, 1976, **64**, 2229–2246; (*b*) G. Bodenhausen, R. Freeman and D. L. Turner, *J. Magn. Reson.*, 1977, **27**, 511–514.
12 (*a*) M. Bruch, *NMR Spectroscopy Techniques*, CRC Press, 2nd edn, 1996; (*b*) T. D. W. Claridge, Separating shifts and couplings: *J*-resolved spectroscopy, in *High-resolution NMR Techniques in Organic Chemistry*, Elsevier, Oxford, 2nd edn, 2009, 27, ch. 7, Tetrahedron Organic Chemistry Series, pp. 233–246.
13 For recent improvement in JRES NMR spectroscopy, see: A. Martinez, F. Bourdreux, E. Riguet and J.-M. Nuzillard, *Magn. Reson. Chem.*, 2012, **50**, 28–32.

14 E. Cesarotti, M. Grassi and L. Prati, *J. Chem. Soc., Dalton Trans.*, 1989, 161–168.
15 R. Novoa-Carballal, E. Fernandez-Megia, C. Jimenez and R. Riguera, *Nat. Prod. Rep.*, 2010, **28**, 78–98.
16 J. M. Fonville, A. D. Maher, M. Coen, E. Holmes, J. C. Lindon and J. K. Nicholson, *Anal. Chem.*, 2010, **82**, 1811–1821.
17 C. Ludwig and M. R. Viant, *Phytochem. Anal.*, 2010, **21**, 22–32.
18 T. Lange, R. F. Schulte and P. Boesiger, *Magn. Reson. Med.*, 2008, **59**, 966–972.
19 For a recent example, see: K. D. Klika, S. Cheriyamundath, R. Raghavan, K. B. Megha, A. Banerji, R. W. Owen and J. Madassery, *Tetrahedron Lett.*, 2014, **55**, 6550–6553.
20 R. M. Silverstein, F. X. Webster and D. Kiemle, *Spectrometric Identification of Organic Compounds*, Wiley Global Education, 7th edn, 2005.
21 (*a*) C. A. Kingsbury, D. Draney, A. Sopchik, W. Rissler and D. Durham, *J. Org. Chem.*, 1976, **41**, 3863–3868; (*b*) F. H. A. Rummens and J. W. de Haan, *Org. Magn. Reson.*, 1970, **2**, 351–355.
22 For others methods to measure long range CH spin coupling constants, see: T. Parella and J. F. Espinosa, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2013, **73**, 17–55.
23 For examples of trisubstituted olefins assignment by ^{13}C non-decoupled ^{1}H NMR spectroscopy, see: (*a*) M. Tadesse, M. B. Strom, J. Svenson, M. Jaspars, B. F. Milne, V. Torfoss, J. H. Andersen, E. Hansen, K. Stensvag and T. Haug, *Org. Lett.*, 2010, **12**, 4752–4755; (*b*) P. García, M. Martín-Pastor, A. R. de Lera and R. Alvarez, *Magn. Reson. Chem.*, 2010, **48**, 543–549; (*c*) R. H. Contreras, P. F. Provasi, F. P. dos Santos and C. F. Tormena, *Magn. Reson. Chem.*, 2009, **47**, 113–120.
24 A. Bax and R. Freeman, *J. Am. Chem. Soc.*, 1982, **104**, 1099–1100.
25 J. B. Harborne, *The Flavonoids*, Chapman and Hall, 1988.
26 (*a*) G. Blaskó, L. Xun and G. A. Cordell, *J. Nat. Prod.*, 1988, **51**, 60–65; (*b*) J. Budzianowski, M. Morozowska and M. Wesołowska, *Phytochemistry*, 2005, **66**, 1033–1039; (*c*) G. P. Romanelli, E. G. Virla, P. R. Duchowicz, A. L. Gaddi, D. M. Ruiz, D. O. Bennardi, E. del Valle Ortiz and J. C. Autino, *J. Agric. Food Chem.*, 2010, **58**, 6290–6295.
27 (*a*) S. Venkateswarlu, G. K. Panchagnula, A. L. Gottumukkala and G. V. Subbaraju, *Tetrahedron*, 2007, **63**, 6909–6914; (*b*) Y. Usami, *Mar. Drugs*, 2009, **7**, 314–330.
28 J. L. Marshall, *Carbon–Carbon and Carbon–Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis*, Verlag Chemie International, Deerfield Beach, FL, 1983, pp. 40–41.
29 B. A. Keay, J. M. Hopkins and P. W. Dibble, *Furans and their Benzo Derivatives: Applications. Comprehensive Heterocyclic Chemistry III*, Elsevier, The Netherlands, 2008.
30 (*a*) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084–3213; (*b*) W. J. Moran and A. Rodríguez, *Org. Prep. Proced. Int.*, 2012, **44**, 103–130.
31 M. Hoffmann, S. Miaskiewicz, J.-M. Weibel, P. Pale and A. Blanc, *Beilstein J. Org. Chem.*, 2013, **9**, 1774–1780.
32 N. Shanker, O. Dilek, K. Mukherjee, D. W. McGee and S. L. Bane, *J. Fluoresc.*, 2011, **21**, 2173–2184.
33 R. Kazlauskas, P. T. Murphy, R. J. Quinn and R. J. Wells, *Tetrahedron Lett.*, 1977, **18**, 37–40.
34 A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577–7606.
35 (*a*) M. Hoffmann, J.-M. Weibel, P. de Frémont, P. Pale and A. Blanc, *Org. Lett.*, 2014, **16**, 908–911; (*b*) M.-C. Cordonnier, A. Blanc and P. Pale, *Org. Lett.*, 2008, **10**, 1569–1572.
36 (*a*) W. He, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278–14279; (*b*) M. Janka, W. He, A. J. Frontier, C. Flaschenriem and R. Eisenberg, *Tetrahedron*, 2005, **61**, 6193–6206; (*c*) M. Janka, W. He, I. E. Haedicke, F. R. Fronczek, A. J. Frontier and R. Eisenberg, *J. Am. Chem. Soc.*, 2006, **128**, 5312–5313; (*d*) J. Huang and A. J. Frontier, *J. Am. Chem. Soc.*, 2007, **129**, 8060–8061; (*e*) W. He, I. R. Herrick, T. A. Atesin, P. A. Caruana, C. A. Kellenberger and A. J. Frontier, *J. Am. Chem. Soc.*, 2007, **130**, 1003–1011.
37 The factors causing this effect are not clear but were already observed and discussed: see: G. J. Karabatsos, *J. Am. Chem. Soc.*, 1961, **83**, 1230–1232.
38 A. Vij, Y. Y. Zheng, R. L. Kirchmeier and J. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 3281–3288.
39 A. K. Al-Sa'Ady, C. A. Mcauliffe, R. V. Parish, J. A. Sandbank, R. A. Potts and W. F. Schneider, in *Inorganic Syntheses*, ed. S. Kirschner, John Wiley & Sons, Inc., 1985, pp. 191–194.
40 N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133–4136.
41 N. P. Cheval, A. Dikova, A. Blanc, J.-M. Weibel and P. Pale, *Chem.–Eur. J.*, 2013, **19**, 8765–8768.
42 M. Yoshida, Y. Fujino and T. Doi, *Org. Lett.*, 2011, **13**, 4526–4529.
43 M. Yoshida, Y. Fujino, K. Saito and T. Doi, *Tetrahedron*, 2011, **67**, 9993–9997.
44 A. W. Sromek, A. V. Kel'in and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2004, **43**, 2280–2282.
45 T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 9868–9878.
46 A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli and B. R. Pietroni, *J. Org. Chem.*, 1992, **57**, 976–982.
47 K. Ji, J. Nelson and L. Zhang, *Beilstein J. Org. Chem.*, 2013, **9**, 1925–1930.
48 (*a*) G. Liang, S. N. Gradl and D. Trauner, *Org. Lett.*, 2003, **5**, 4931–4934; (*b*) M. Rueping, W. Ieawsuwan, A. P. Antonchick and B. J. Nachtsheim, *Angew. Chem., Int. Ed.*, 2007, **46**, 2097–2100.
49 C. Bee, E. Leclerc and M. A. Tius, *Org. Lett.*, 2003, **5**, 4927–4930.

