Organic & Biomolecular Chemistry

c7ob03110f

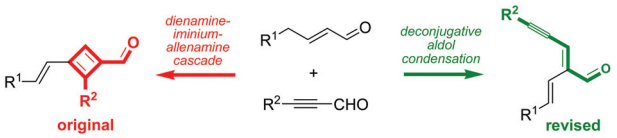
We have presented the Graphical Abstract text and image for your article below. This brief summary of your work will appear in the contents pages of the issue in which your article appears.

1

NMR and experimental reinvestigation of the condensation reaction between γ-methylene-α,β-unsaturated aldehydes and propargyl aldehydes

Martín J. Riveira* and Ariel M. Sarotti*

An experimental and computational study of the reaction between γ-methylene enals and propargyl aldehydes uncovered a deconjugative aldol condensation.



Please check this proof carefully. **Our staff will not read it in detail after you have returned it.**

Proof corrections must be returned as a single set of corrections, approved by all co-authors. No further corrections can be made after you have submitted your proof corrections as we will publish your article online as soon as possible after they are received.

Please ensure that:

- The spelling and format of all author names and affiliations are checked carefully. Names will be indexed and cited as shown on the proof, so these must be correct.
- Any funding bodies have been acknowledged appropriately.
- All of the editor's queries are answered.
- Any necessary attachments, such as updated images or ESI files, are provided.

Translation errors between word-processor files and typesetting systems can occur so the whole proof needs to be read. Please pay particular attention to: tables; equations; numerical data; figures and graphics; and references.

Please send your corrections preferably as a copy of the proof PDF with electronic notes attached or alternatively as a list of corrections – do not change the text within the PDF file or send a revised manuscript. Corrections at this stage should be minor and not involve extensive changes.

Please return your **final** corrections, where possible within **48 hours** of receipt, by e-mail to: obc@rsc.org. If you require more time, please notify us by email.

Funder information

Providing accurate funding information will enable us to help you comply with your funders' reporting mandates. Clear acknowledgement of funder support is an important consideration in funding evaluation and can increase your chances of securing funding in the future. We work closely with Crossref to make your research discoverable through the Funding Data search tool (http://search.crossref.org/funding).

Further information on how to acknowledge your funders can be found on our webpage (http://rsc.li/ funding-info).

What is Funding Data?

Funding Data (http://www.crossref.org/fundingdata/) provides a reliable way to track the impact of the work that funders support. We collect funding information from our authors and match this information to funders listed in the Crossref Funder Registry. Once an article has been matched to its funders, it is discoverable through Crossref's search interface.

PubMed Central

Accurate funder information will also help us identify articles that are mandated to be deposited in PubMed Central (PMC) and deposit these on your behalf.

Providing funder information

We have combined the information you gave us on submission with the information in your acknowledgements. This will help ensure funding information is as complete as possible and matches funders listed in the Crossref Funder Registry. **Please check that the funder names and grant numbers in the table are correct.** This table will not be included in your final PDF but we will share the data with Crossref so that your article can be found *via* the Funding Data search tool.

Funder name	Funder ID (for RSC use only)	Award/grant/contract number
Universidad Nacional de Rosario	100009573	BIO 316 BIO426
Agencia Nacional de Promoción Científica y Tecnológica	501100003074	PICT-2016-0116 BID-PICT-0408
Consejo Nacional de Investigaciones Científicas y Técnicas	501100002923	PIP 11220130100660CO PIP 2012-2014 0448

If a funding organisation you included in your acknowledgements or on submission of your article is not currently listed in the registry it will not appear in the table above. We can only deposit data if funders are already listed in the Crossref Funder Registry, but we will pass all funding information on to Crossref so that additional funders can be included in future.

Researcher information

If any authors have ORCID or ResearcherID details that are not listed below, please provide these with your proof corrections. Please check that the ORCID and ResearcherID details listed below have been assigned to the correct author. Authors should have their own unique ORCID iD and should not use another researcher's, as errors will delay publication.

Please also update your account on our online manuscript submission system to add your ORCID details, which will then be automatically included in all future submissions. See here for step-by-step instructions and more information on author identifiers.

First (given) name(s)	Last (family) name(s)	ResearcherID	ORCID
Martín J.	Riveira		0000-0002-1682-9855
Ariel M.	Sarotti		0000-0002-8151-0306

Queries for the attention of the authors

Journal: **Organic & Biomolecular Chemistry** Paper: **c7ob03110f**

Title: **NMR and experimental reinvestigation of the condensation reaction between γ-methylene-α,β-unsaturated aldehydes and propargyl aldehydes**

For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Org. Biomol. Chem., (year), DOI: 10.1039/c7ob03110f.

Editor's queries are marked like this [Q1, Q2, ...], and for your convenience line numbers are indicated like this [5, 10, 15, ...].

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

Query Reference	Query	Remarks
Q1	Please confirm that the spelling and format of all author names is correct. Names will be indexed and cited as shown on the proof, so these must be correct. No late corrections can be made.	
Q2	"Wang" is not cited as an author of ref. 14 and 15. Please indicate any changes that are required here.	
Q3	In the sentence beginning "However, in our case" there is a citation to No. 2 in Figure 2, however Figure 3 does not appear to contain a part (b). Please resupply the figure (preferably in TIF format >600 dpi) or amend the text accordingly.	

Organic & Biomolecular Chemistry

COMMUNICATION

NMR and experimental reinvestigation of the condensation reaction between γ-methylene-α,β-unsaturated aldehydes and propargyl aldehydes†

Cite this: DOI: 10.1039/c7ob03110f

Received 15th December 2017,
Accepted 24th January 2018

DOI: 10.1039/c7ob03110f

Q1 rsc.li/obc

Martín J. Riveira * and Ariel M. Sarotti *

The condensation reaction between a γ-methylene-α,β-unsaturated aldehyde and phenylpropargyl aldehyde was revisited and guided by extensive DFT calculations of NMR shifts. It was found to afford a deconjugative aldol condensation product. Accordingly, a simple protocol for the preparation of valuable *cross*-conjugated oxatrienes was uncovered.

Unsaturated aldehydes comprise a priceless class of molecules. For example, polyenal retinal (**1**) constitutes the chemical basis of animal vision (Fig. 1).[1] Several other conjugated aldehydes have also been isolated from marine and terrestrial sources and shown to be bioactive.[2] For example, [3]-1-oxadendralene onchidal (**2**) takes part in the chemical defense of mollusc *Onchidella* acting as an irreversible acetylcholinesterase inhibitor.[3] Taxifolial D (**3**), bearing a conjugated alkyne moiety, is also supposed to be part of the chemical armamentum of the toxic and invasive alga *Caulerpa taxifolia* introduced into the Mediterranean.[4] Furthermore, many aromatic enals have been used as flavour and fragrance molecules. Therefore, much of the interest on the synthesis and study of these molecules has relied on this and the fact that as potential Michael acceptors, many unsaturated aldehydes are prone to exhibit toxicity.[5]

From a different chemical viewpoint, several groups including ours are interested in these materials as versatile building blocks that engage in fascinating domino processes leading to diverse cyclic and polycyclic frameworks, including heterocyclic systems.[6]

There are numerous methods for the preparation of different classes of unsaturated aldehydes, such as enals,[7] conjugated dienals,[8] ynals,[9] enynals[10] and [3]-1-oxadendralenes,[6f] which are increasing. In this context, a new organocatalytic cascade for the preparation of cyclobutadiene-carbaldehydes, an unprecedented class, was recently reported (Scheme 1).[11a] The condensation reaction between γ-methylene-α,β-unsaturated aldehydes (**4**) and propargyl aldehydes (**5**) affords polyunsaturated aldehydes **8** *via* a proposed secondary-amine catalyzed dienamine-iminium-allenamine cascade. Thus, after the formation of the dienamine of **4**, regioselective conjugate addition to iminium-activated **5** provides an intermediate of type **6** which undergoes cycle formation *via* imine addition. Subsequently, final elimination on **7** installs the cyclobutadiene moiety.[11a] Almost four months after their publication, and during the preparation of this manuscript, the authors retracted the article on the basis that *the reported cyclobutadiene structures **8** were not fully supported by their ^{13}C NMR data* and *other plausible structures could not be ruled out*.[11b]

It should be noted that examples of additions of enamines to electrophilic alkynes have been reported in the past.[12] However, none of these cases reported the formation of cyclobutadiene, a well-known highly reactive species.[13] Instead,

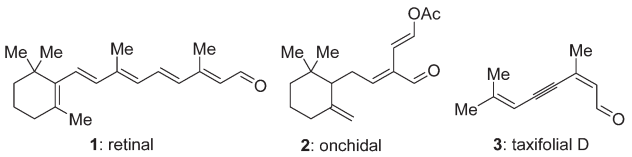
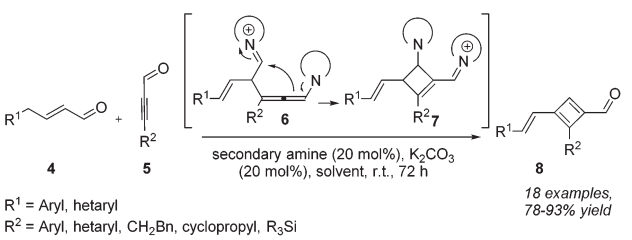


Fig. 1 Examples of bioactive natural polyunsaturated aldehydes.



Scheme 1 Originally reported organocatalytic cascade towards cyclobutadiene-carbaldehydes **8**.

Instituto de Química Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario-CONICET, Suipacha 531, S2002LRK, Rosario, Argentina. E-mail: riveira@iquir-conicet.gov.ar, sarotti@iquir-conicet.gov.ar

†Electronic supplementary information (ESI) available: Experimental procedures, copies of NMR data, computational procedures, experimental and calculated NMR data, and Cartesian coordinates of all compounds. See DOI: 10.1039/c7ob03110f

cyclobutenes (derived from intermediates such as 7) or products arising from their electrocyclic ring-opening are generally isolated.[12]

Cyclobutadienes have fascinated and intrigued several generations of experimental and theoretical chemists.[14] Due to its intrinsic reactivity, cyclobutadiene derivatives tend to dimerize following an orbital symmetry allowed [4 + 2] cycloaddition.[14] The findings of Wang and co-workers represent a significant opportunity to shed light on the NMR spectroscopy of cyclobutadienes, an elusive area of research due to the difficulty in preventing the dimerization of the sample.[14,15] In this regard, the observation of significantly shielded sp^2-hybridized carbons at δ 74.2–90.6 ppm in all the isolated compounds **8** caught our attention, which is possibly the same observation that led the original authors to retract their publication (Scheme 1).[11] Although the NMR data was not assigned by the authors (no definition of which resonance signal belongs to which nuclei was provided), we hypothesized that provided the structures **8** were the actual products, the upfield signal should be attributed to one of the carbons of the cyclobutadiene moiety since no other fragment in these products could account for the resonances in that region.

Intrigued by whether the antiaromatic character of the cyclobutadiene moiety could be responsible for this observation, we decided to compute the NMR shifts of **8a** (R^1 = R^2 = Ph) at a quantum level to test the theoretical reproducibility of such unusual experimental finding. Recent years have witnessed an increase in the popularity of theoretical methods to accurately reproduce NMR shifts and coupling constants; information that in turn can be extremely helpful in solving structural and stereochemical issues in complex organic molecules.[16–18]

Following standard procedures, exhaustive conformational searches of **8a** were carried out using both the MMFF and MM+ force fields. All conformations located were further optimized at B3LYP/6-31G* for final GIAO NMR calculations at the PCM/mPW1PW91/6-31+G** level of theory. This level has been shown to provide good results at affordable computational cost.[18a,b] It is known that cyclobutadienes in their ground state geometries exist in the form of two valence isomers with a rectangular geometry, which are involved in a dynamical equilibrium with typically small automerization barriers.[14,15] Thus, both types of rectangular geometries were taken into consideration in this study. Fig. 2 shows the global minima geometry located at the B3LYP/6-31G* level with the C-2/C-3 bonds and C-4/C-5 bonds shorter (1.35 Å and 1.38 Å, respectively) than the corresponding C-2/C-5 and C-3/C-4 bonds (1.57 Å and 1.52 Å, respectively).

Given that unassigned NMR data was originally reported, the experimental and calculated NMR shifts were arranged in descending order of size for comparison. As depicted in Fig. 2, the match between the experimental and calculated ^{13}C NMR values was poor, showing an R^2 value of only 0.7077. The MAE (mean average error, defined as $\Sigma_n|\delta_{calc} - \delta_{exp}|/n$) and CMAE (corrected mean average error, defined as $\Sigma_n|\delta_{scaled} - \delta_{exp}|/n$) values were 12.1 and 10.1 ppm, respectively, which are much

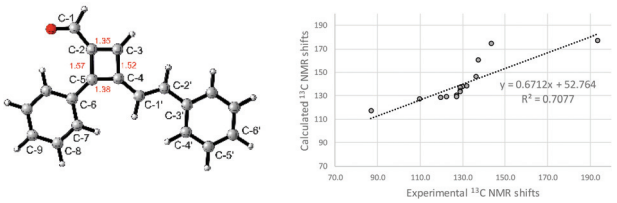


Fig. 2 (Left) B3LYP/6-31G* global minima geometry of **8a** with selected distances (in Å). (Right) Correlation of the experimental and calculated ^{13}C NMR shifts of **8a** at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory.

higher than expected for this level of theory.[18a,b] The maximum errors were also prohibitively high with MaxErr (maximum error, defined as $\max|\delta_{calc} - \delta_{exp}|$) and CMaxErr (corrected maximum error, defined as $\max|\delta_{scaled} - \delta_{exp}|$) values of 31.2 ppm and 38.2 ppm, respectively. In the low field region, the carbonyl group was predicted to be much more shielded than experimentally reported (177.3 ppm *vs* 193.3 ppm, $\Delta\delta$ = 16.0 ppm). Moreover, the shifts of C-3 and C-5 were located at 174.6 ppm and 160.6 ppm, respectively, far from the second and third more deshielded signals in the experimental ^{13}C NMR spectrum of **8a** (143.3 and 137.2 ppm, respectively). Regarding the key signal at δ 86.9 ppm, none of the computed shifts were predicted nearby. In fact, according to our calculations, the most shielded carbon of the four-membered ring should be C-3 (138.3 ppm), whereas the most shielded carbon of the molecule should be C-6 (117.3 ppm). Noticeably, in both cases significant deviations from the experimental signal at 86.9 ppm were observed ($\Delta\delta$ = 51.4 and 30.4 ppm, respectively). Furthermore, while correlating the experimental and computational data using our artificial neural network pattern recognition analysis, the originally proposed structure **8a** (R^1 = R^2 = Ph) was identified as incorrect.[18c]

We next turned our attention to the other derivatives synthesized in the original report, such as **8i** (R^1 = cyclopropyl, R^2 = Ph) and **8l** (R^1 = $PhMe_2Si$, R^2 = Ph), but yet again, the NMR calculations exhibited bad correlation with the experimental values.[11a]‡ For instance, in the case of **8i**, the MAE and CMAE values were 15.1 and 12.7 ppm with MaxErr and CMaxErr values of 41.3 ppm and 30.1 ppm, respectively. In the case of **8l**, the disagreement was lower than that observed for **8a** and **8i** (MAE = 10.1 ppm, CMAE = 7.4 ppm, MaxErr = 23.0 ppm, CMaxErr = 21.3 ppm), but still considerably high (see ESI†).

As stated above, the discrepancies between the experimental and calculated NMR data were much higher than expected for the level of theory used for the NMR calculations. However, our previous experience with the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level was mainly limited to natural product-like organic molecules containing few (or none) strained sp^2 systems in their structures.[18a,b] In an additional effort to rule out the possible (but not least unexpected) modest performance of this level of theory in this particular case, we undertook NMR calculations of four related strained sp^2-carbon-containing three- or four-membered cycles.

However, as discussed in the ESI,† good agreement with the experimental shifts was observed in all cases (MAE in the range of 1.4–2.9 ppm and CMAE in the range of 1.3–2.2 ppm).

On the other hand, the NMR shifts of **8a** were recomputed at 104 different levels of theory by combining different functionals (mPW1PW91, B3LYP, PBE0 and LC-TPSSTPSS), basis sets (6-31+G**, cc-PVTZ and 6-311++G(3df,2pd)) and methods to solve the gauge origin problem (GIAO, CSGT and IGAIM),[16b] both in the gas phase and solution with a variety of geometry optimization levels (including B3LYP, M06-2X and MP2 with the 6-31G* and 6-311+G** basis sets both in the gas phase and solution). In a recent study by Mark Iron to understand the factors impacting the accuracy of ^{13}C NMR calculations, the combination of CSGT with LC-TPSSTPSS was among the optimal levels of theory.[19] However, in our case, the NMR shifts of **8a** calculated at 104 different levels of theory reflected minor differences with that initially observed for the PCM/mPW1PW91/6-31+G** level (No. 2 in Fig. 3). This suggests that the poor reproduction of the experimental shifts of **8a** was not caused by the choice of the level of theory employed during the NMR calculation procedure, but instead, a probably incorrect structural proposal.

At this point, we proposed a set of 14 different plausible structures, some of which were products of logical alternative reaction mechanisms whose NMR data would be in accordance with that of **8a** (compounds **9a–22a**, see ESI†). Consequently, NMR calculations at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory were undertaken. As depicted in Fig. 4, diastereoisomeric compounds **9a** and **10a** (featuring a conjugated *E*- or *Z*-enyne moiety, respectively) displayed the best agreement between the experimental and calculated ^{13}C NMR shifts (see ESI†). The MAE (2.1 ppm and 1.4 ppm, respectively) and CMAE (1.6 and 0.6 ppm, respectively) values were much lower than that estimated for the other candidates (MAE in the range of 3.3–10.6 ppm and CMAE in the range of 2.9–9.5 ppm). In the case of **9a**, the C-5 signal of the alkyne was predicted to be considerably more deshielded than experimentally observed (119.1 ppm vs 109.6 ppm, respectively), accounting to a large extent for the higher MAE and related parameters in relation to that simulated for **10a**. Hence, according to the ^{13}C NMR data, we concluded that **10a** should be the real structure of **8a**. However, when analyzing the ^{1}H NMR data, significant errors were noticed for both compounds. For instance, in **10a** the H-1 and H-3 signals were predicted to be 0.85 and 0.47 ppm shifted downfield than experimentally observed ($\delta_{calc(H\text{-}1)}$ = 10.50 ppm, $\delta_{exp(H\text{-}1)}$ = 9.65 ppm and $\delta_{calc(H\text{-}3)}$ = 6.99 ppm, $\delta_{exp(H\text{-}3)}$ = 6.52 ppm, respectively). A significantly better reproduction of these signals was noticed for **9a** ($\Delta\delta$ = 0.26 ppm (H-1) and 0.25 ppm (H-3)), whereas the resonance assigned to H-2′ represented the main outlier ($\Delta\delta$ = 0.46 ppm). Notwithstanding, the agreement of **10a** improved upon scaling (CMAE = 0.16 ppm *vs* 0.19 ppm), where the size of the unscaled errors obscured the assignment of the correct structure of **8a**. As discussed in the ESI,† this trend was unaffected upon re-computing the NMR shifts of **9a** and **10a** at 24 different levels of theory arising from the use of three functionals (mPW1PW91, PBE0 and LC-TPSSTPSS), four basis sets (6-31+G*, 6-311+G**, cc-PVTZ and 6-311++G(3df,2pd)) and two methods for conducting the NMR calculations (GIAO and CSGT). Importantly, we concluded that the key C-4, C-5, H-1, H-3 and H-1′ signals were among the most affected by the changes in the level of theory, albeit with remarkable different trends.

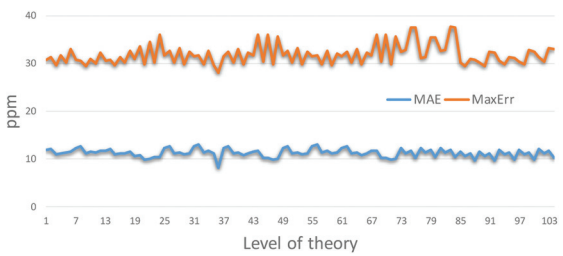


Fig. 3 Mean average error (MAE) and maximum error (MaxErr) values computed after correlating the experimental NMR shifts of **8a** with the corresponding calculated values at 104 different levels of theory.

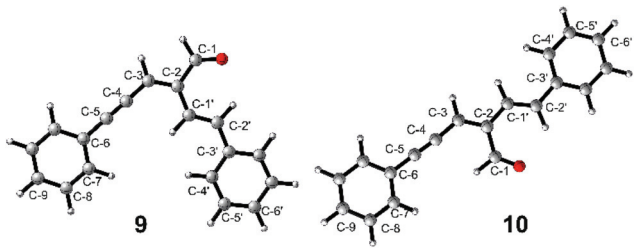


Fig. 4 B3LYP/6-31G* global minima geometry of **9a** and **10a**, the most likely structures of **8a** according to our calculations.

To understand the origins of the modest reproduction of the experimental shifts of these types of hydrogen atoms, we next evaluated the performance of the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory on a selected set of 10 known related conjugated carbonyl systems. Detailed analysis of the collected data (see ESI†) allowed us to draw interesting conclusions. On one hand, we observed that the shift of most carbons was nicely reproduced by our calculations with the exception of the alkyne carbons located at the end of a polyenic chain (equivalent to C-5 in **9a** and **10a**). In these cases, a systematic overestimation of the chemical shifts by 7.1–10.1 ppm was found, which curiously was the same trend discussed above for compound **9a**. On the other hand, we observed that the accuracy in the ^{1}H NMR shift prediction strongly depended upon subtle structural issues. This effect was particularly important in the case of the vinylic protons, which yielded the highest unscaled errors in most cases (ranging from 0.14 ppm to 0.92 ppm). Comparatively, for the compounds bearing conjugated aldehyde moieties (**23–29** and **32**, see ESI†), the formyl hydrogens were estimated considerably better with unscaled errors of up to 0.27 ppm, which are much lower than that observed for **10a** (0.85 ppm).

The origins of this unstable NMR shift reproduction can be found in the choice of the reference standards for computing

the unscaled chemical shifts from the isotropic magnetic shielding constants. From a historical perspective, TMS is perhaps the most popular and common standard of reference,[16b] but we demonstrated that the combination of benzene and methanol as references for sp–sp^2 and sp^3 hybridized carbons (or protons attached to), respectively, significantly improved the accuracy of the calculations.[20] This so-called multi-standard approach (MSTD) performs typically well for common organic molecules, and thus was the method of choice in this study. However, in some specific molecular architectures, the use of only one (or two) standards (TMS or MSTD) does not allow a good performance for all nuclei. To overcome this limitation, Spivey and co-workers developed the fragment referencing method, which could be seen as the natural extension of MSTD. Hence, any nuclei in any known molecule can be used as the standard with the sole prerequisite that its experimental NMR shift must be known. This guarantees the flexibility needed to model small molecules with challenging magnetic environments by selecting different nuclei of fragment analogues to reference different nuclei in the molecule of interest.[21]

Hence, using the different ^{13}C NMR signals of (*E*)- and (*Z*)-5-phenylpent-2-en-4-ynal as internal carbon references for **9a** and **10a**, respectively, and the ^{1}H NMR signals of (*E*)-2-benzylidenebut-3-enal as internal proton standards, the NMR shifts of **9a** and **10a** were recomputed. As shown in Table 1, the key resonances were nicely reproduced in the case of **9a**, whereas large errors were observed for **10a**. As a result, alkyne **9a** should be the most likely structure of **8a** (among the set of 14 candidates).

In a final attempt to clarify the scenario portrayed by our calculations and taking into consideration the lack of detailed 2D NMR data for compounds **8** in the original report, we decided to gather experimental evidence to support our conclusion. Hence, compound **8a** was synthesized by condensation between (2*E*)-4-phenyl-2-butenal (**4a**) and phenylpropargyl aldehyde (**5a**) (Scheme 1, R^1 = Ph, R^2 = Ph) using pyrrolidine and potassium carbonate as catalysts (20 mol% each) and dichloromethane as the solvent, as reported in the seminal reference (58% yield of desired product, see ESI†).[11a,22] Although the physical data of the only isolable compound was exactly the same as that originally reported (**8a**), upon analysis of the spectral data we arrived at a different interpretation of the original result.

Even though the composition of **9a** was verified by 2D NMR data (COSY, HSQC and HMBC), the configuration of the C-2/C-3 double bond was cleanly assigned as *E* by the NOE correlation observed between H-1 and H-3 (Fig. 5 and ESI†), which is in perfect agreement with our computational findings. Another key observation in favor of our revision is the small *J* coupling between H-1 and H-1′ ($J_{1,1'}$ = 1.8 Hz), which was missed by the original authors probably due to the resolution problems. In the case of **9a**, this coupling could be assigned to a typical ^4J W-type coupling, but in the case of the originally proposed structure (**8a**, Fig. 2), it should correspond to a long-range ^6J coupling, which to the best of our knowledge is much less common. To unravel this issue, we undertook *J* calculations at the B3LYP/6-311+G** and B3LYP/6-31G** levels of theory, using the global minima geometries located at the B3LYP/6-31G* level of **8a** and **9a**. As expected, the $J_{1,1'}$ coupling computed for **9a** (2.4 Hz) was in the experimental range (1.8 Hz), whereas an almost null (0.5 Hz) coupling was estimated for **8a**.

To reinforce our analysis, we computed the NMR shifts of compounds **9i** and **9l** (which should be the revised structures of **8i** and **8l**, respectively) at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory. To our delight, very good agreement between the experimental and calculated data was observed (CMAE values of 1.6 and 1.0 ppm for the carbon data and 0.11 and 0.10 for the proton data, respectively). The less accurate results obtained for the simulation of the ^{1}H NMR shifts of **9a** (CMAE = 0.19 ppm) underscores that the conjugative effect exerted by the phenyl ring at C-5 was not correctly described by our calculations.

Based on the structure of the isolated product **9a**, a reasonable mechanism for its formation was proposed (Scheme 2). Initial dienamine assembly followed by regioselective 1,2-addition to **5a** and final elimination could account for the formation of product **9a**.[23] Naturally, the same mechanism should apply for the remaining 17 examples provided in the seminal reference.[11a] Remarkably, although examples of deconjugative α-alkylation and α-alkylidenation of esters are

Table 1 Experimental NMR shifts of **8a** and calculated NMR shifts of **9a** and **10a** of selected nuclei using the fragment referencing approach at the PCM/mPWPW91/6-31+G**//B3LYP/6-31G* level of theory

		δ_{calc}		Abs. error ($\delta_{exp} - \delta_{calc}$)	
Nuclei	δ_{exp}	**9a**	**10a**	**9a**	**10a**
C-1	193.3	195.2	192.8	1.9	0.5
C-2	143.2	142.4	143.2	0.9	0.1
C-3	127.1	128.7	127.8	1.5	0.6
C-4	86.9	88.6	85.6	1.7	1.3
C-5	109.6	110.1	105.1	0.5	4.5
C-1′	119.4	118.0	120.8	1.4	1.4
C-2′	136.6	137.1	133.8	0.5	2.8
			Average	**1.2**	**1.6**
H-1	9.65	9.60	10.72	0.05	1.07
H-3	6.54	6.36	7.07	0.16	0.55
H-1′	7.25	6.90	6.24	0.35	1.01
H-2′	7.99	8.14	7.67	0.15	0.32
			Average	**0.18**	**0.74**

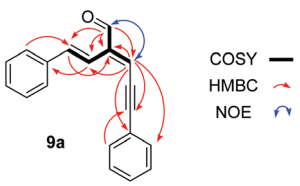
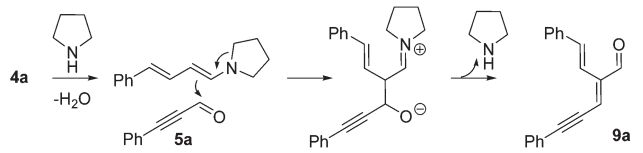


Fig. 5 Key COSY, HMBC and NOE correlations of synthetic **9a**.



Scheme 2 Generation of **9a** through a deconjugative aldol reaction.

found throughout the literature,[24] this deconjugative aldol condensation reaction seems to be largely unknown.[25]

Conclusions

In summary, we concluded that the condensation reaction between γ-methylene-α,β-unsaturated aldehydes (**4**) and propargyl aldehydes (**5**) does not afford trisubstituted cyclobutadienes as originally proposed. Instead, the corresponding acetylenic [3]-1-oxadendralenes are formed through a deconjugative aldol reaction. This conclusion was reached after exhaustive calculations of NMR shifts and coupling constants, and re-examination of the spectroscopic data of a synthesized compound. As a result, a straightforward entry to valuable unsaturated aldehydes was uncovered.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by UNR (BIO 316, BIO426), ANPCyT (PICT-2016-0116, BID-PICT-0408), and CONICET (PIP 11220130100660CO, PIP 2012-2014 0448).

Notes and references

‡In this manuscript we kept the numbering used for compounds **8** in the original report (Ref. 11*a*).

1 P. J. M. Johnson, M. H. Farag, A. Halpin, T. Morizumi, V. I. Prokhorenko, J. Knoester, T. L. C. Jansen, O. P. Ernst and R. J. D. Miller, *J. Phys. Chem. B*, 2017, **121**, 4040.
2 M. Morita, K. Nakajima, Y. Ikeya and H. Mitsuhashi, *Phytochemistry*, 1991, **30**, 1543.
3 S. N. Abramson, Z. Radic, D. Manker, D. J. Faulkner and P. Taylor, *Mol. Pharmacol.*, 1989, **36**, 349.
4 P. Amade and R. Lemée, *Aquat. Toxicol.*, 1998, **43**, 287.
5 E. Hansen, Y. Even and A.-M. Genevière, *Toxicol. Sci.*, 2004, **81**, 190.
6 (*a*) M. Meazza, F. Tur, N. Hammer and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2017, **56**, 1634; (*b*) M. J. Riveira, A. La-Venia and M. P. Mischne, *J. Org. Chem.*, 2016, **81**, 7977; (*c*) A.-S. Marques, V. Coeffard, I. Chataigner, G. Vincent and X. Moreau, *Org. Lett.*, 2016, **18**, 5296; (*d*) M. J. Riveira, G. N. Quiroga, E. G. Mata, V. Gandon and M. P. Mischne, *J. Org. Chem.*, 2015, **80**, 6515; (*e*) P. H. Poulsen, K. Santos Feu, B. Matos Paz, F. Jensen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 8203; (*f*) S. Kobayashi, K. Kudo, A. Ito, S. Hirama, T. Otani and T. Saito, *Org. Biomol. Chem.*, 2014, **12**, 4061; (*g*) M. J. Riveira and M. P. Mischne, *Chem. – Eur. J.*, 2012, **18**, 2382.
7 For example, see: M. G. Mura, L. De Luca, M. Taddei, J. M. J. Williams and A. Porcheddu, *Org. Lett.*, 2014, **16**, 2586.
8 For example, see: T. D. Michels, J. U. Rhee and C. D. Vanderwal, *Org. Lett.*, 2008, **10**, 4787.
9 For example, see: H. Kuroda, E. Hanaki, H. Izawa, M. Kano and H. Itahashi, *Tetrahedron*, 2004, **60**, 1913.
10 For example, see: C. Thongsornkleeb and R. L. Danheiser, *J. Org. Chem.*, 2005, **70**, 2364.
11 (*a*) W. Li, M. Lang and J. Wang, *Org. Lett.*, 2017, **19**, 4564; (*b*) W. Li, M. Lang and J. Wang, *Org. Lett.*, 2018, **20**, 316.
12 (*a*) N. N. B. Kumar, O. A. Mukhina and A. G. Kutateladze, *J. Am. Chem. Soc.*, 2013, **135**, 9608; (*b*) N. Tunoglu and N. Uludag, *Org. Prep. Proced. Int.*, 1997, **29**, 541; (*c*) B. Tinant, J. Feneau-Dupont, J.-P. Declercq, B. De Boeck and H. G. Viehe, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1821; (*d*) T. Tokumitsu, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3871; (*e*) D. N. Reinhoudt, W. Verboom, G. W. Visser, W. P. Trompenaars, S. Harkema and G. J. Van Hummel, *J. Am. Chem. Soc.*, 1984, **106**, 1341; (*f*) P. D. Davis and D. C. Neckers, *J. Org. Chem.*, 1980, **45**, 456; (*g*) A. J. Birch and E. G. Hutchinson, *J. Chem. Soc. C*, 1971, 3671; (*h*) K. C. Brannock, R. D. Burpitt, V. W. Goodlett and J. G. Thweatt, *J. Org. Chem.*, 1964, **29**, 818; (*i*) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson and P. Strachan, *J. Org. Chem.*, 1963, **28**, 3134; (*j*) K. C. Brannock, R. D. Burpitt, V. W. Goodlett and J. G. Thweatt, *J. Org. Chem.*, 1963, **28**, 1464; (*k*) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, 1963, **28**, 1459.
13 J. Limanto, J. A. Tallarico, J. R. Porter, K. S. Khuong, K. N. Houk and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 14748.
14 For example, see: (*a*) A. Kostenko, B. Tumanskii, Y. Kobayashi, M. Nakamoto, A. Sekiguchi and Y. Apeloig, *Angew. Chem., Int. Ed.*, 2017, **56**, 10183; (*b*) B. J. Esselman and R. J. McMahon, *J. Phys. Chem. A*, 2012, **116**, 483; (*c*) T. Bally, *Angew. Chem., Int. Ed.*, 2006, **45**, 6616; (*d*) A. Fattahi, L. Lis, Z. Tian and S. R. Kass, *Angew. Chem., Int. Ed.*, 2006, **45**, 4984.
15 D. W. Whitman and B. K. Carpenter, *J. Am. Chem. Soc.*, 1982, **104**, 6473.
16 For leading reviews, see: (*a*) N. Grimblat and A. M. Sarotti, *Chem. – Eur. J.*, 2016, **22**, 12246; (*b*) M. W. Lodewyk, M. R. Siebert and D. J. Tantillo, *Chem. Rev.*, 2012, **112**, 1839; (*c*) A. Bagno and G. Saielli, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2015, **5**, 228; (*d*) D. J. Tantillo, *Nat. Prod. Rep.*, 2013, **30**, 1079; (*e*) G. Bifulco, P. Dambruoso,

L. Gomez-Paloma and R. Riccio, *Chem. Rev.*, 2007, **107**, 3744; (*f*) A. Navarro-Vázquez, *Magn. Reson. Chem.*, 2017, **55**, 29.

17 For leading references, see: (*a*) F. Cen-Pacheco, J. Rodríguez, M. Norte, J. J. Fernández and A. Hernández Daranas, *Chem. – Eur. J.*, 2013, **19**, 8525; (*b*) G. Saielli, K. C. Nicolaou, A. Ortiz, H. Zhang and A. Bagno, *J. Am. Chem. Soc.*, 2011, **133**, 6072; (*c*) A. G. Kutateladze and O. A. Mukhina, *J. Org. Chem.*, 2014, **79**, 8397; (*d*) A. G. Kutateladze and O. A. Mukhina, *J. Org. Chem.*, 2015, **80**, 5218; (*e*) A. G. Kutateladze and O. A. Mukhina, *J. Org. Chem.*, 2015, **80**, 10838; (*f*) S. G. Smith and J. M. Goodman, *J. Am. Chem. Soc.*, 2010, **132**, 12946; (*g*) T. Bally and P. R. Rablen, *J. Org. Chem.*, 2011, **76**, 4818; (*h*) E. Troche-Pesqueira, C. Anklin, R. R. Gil and A. Navarro-Vázquez, *Angew. Chem., Int. Ed.*, 2017, **56**, 3660; (*i*) M. W. Lodewyk, C. Soldi, P. B. Jones, M. M. Olmstead, J. Rita, J. T. Shaw and D. J. Tantillo, *J. Am. Chem. Soc.*, 2012, **134**, 18550.

18 For recent references from our group, see: (*a*) N. Grimblat;, M. M. Zanardi and A. M. Sarotti, *J. Org. Chem.*, 2015, **80**, 12526; (*b*) M. M. Zanardi, A. G. Suárez and A. M. Sarotti, *J. Org. Chem.*, 2017, **82**, 1873; (*c*) M. M. Zanardi and A. M. Sarotti, *J. Org. Chem.*, 2015, **80**, 9371; (*d*) N. Grimblat, T. S. Kaufman and A. M. Sarotti, *Org. Lett.*, 2016, **18**, 6420.

19 M. A. Iron, *J. Chem. Theory Comput.*, 2017, **13**, 5798.

20 (*a*) A. M. Sarotti and S. C. Pellegrinet, *J. Org. Chem.*, 2012, **77**, 6059; (*b*) A. M. Sarotti and S. C. Pellegrinet, *J. Org. Chem.*, 2009, **74**, 7254.

21 K. G. Andrews and A. C. Spivey, *J. Org. Chem.*, 2013, **78**, 11302.

22 According to the original authors, using α,α-diphenylprolinol trimethylsilyl ether as organocatalyst in toluene, an 87% yield of product can be achieved. See ref. 11*a*.

23 For a recent review on dienamine activation of α,β-unsaturated aldehydes, see: V. Marcos and J. Alemán, *Chem. Soc. Rev.*, 2016, **45**, 6812.

24 (*a*) R. Sun, W. Song, C. Ma, H. Zhang and X. Yu, *Adv. Synth. Catal.*, 2016, **358**, 3977; (*b*) C. Harcken and R. Brückner, *Tetrahedron Lett.*, 2001, **42**, 3967; (*c*) P. Galatsis, S. D. Millan and G. Ferguson, *J. Org. Chem.*, 1997, **62**, 5048; (*d*) A. S. Kende and B. H. Toder, *J. Org. Chem.*, 1982, **47**, 163.

25 We could only find one example in which a product of a deconjugative aldol condensation is incorrectly described as a Baylis–Hillman side-product: (*a*) B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su and J.-H. Liao, *J. Org. Chem.*, 2007, **72**, 8459; (*b*) In addition, patent US 7632973 B2 describes the self-condensation of prenyl aldehyde via deconjugative aldol condensation.

