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Reinvestigation of a robotically revealed reaction

ARISING FROM: J. M. Granda, L. Donina, V. Dragone, D.-L. Long & L. Cronin *Nature* **559**, 377–381 (2018); <https://doi.org/10.1038/s41586-018-0307-8>

In a recent paper in this journal, Cronin and co-workers created an organic synthesis robot controlled by machine learning.¹ The robot was used to discover four new reactions. One such product, (compound **1**, Fig. 1; compound **22/26** in ¹), was claimed on the basis of spectral data that does not support the proposed structure. We used the original spectroscopic data to identify an alternative connectivity for the product molecule, and then repeated the reported reaction. We found that two diastereomers were produced (rather than the single diastereomer that had originally been described), and confirmed through several lines of enquiry that our revised structures were the correct products.

Fig. 1 | One of four new reactions reported by the Cronin lab, and a structural revision for the isolated product. See Extended Data Figure 1 for complete atom labeling. In the initial assignment,¹ carbons 15 and 30 were assigned to signals >30 ppm upfield of their expected location in the ¹³C NMR, while carbon 14 was assigned to a signal >40 ppm downfield of its expected position.^{2,3,4} See Extended Data Table 1 for additional assignments.

We were intrigued by the Cronin group's report of robot-guided discovery, and particularly attracted to the possibility of using molecules like compound **1** in biological screening experiments. However, on noting inconsistencies in the product characterisation, we calculated the expected NMR shifts for the minimum-energy diastereomer of **1** (i.e. **1a**, Extended Data Fig.

1) using both a parameterized method (MestReNova) and DFT calculation (B3LYP/6-31G*). The results (Extended Data Table 1) did not support the assigned product.

A more plausible interpretation of the NMR data would assign the signal at 169 ppm to an ester carbonyl, and the signal at 124 ppm to the β -position of a vinyl ether or vinyl ester. This agrees almost precisely with the known spectral assignments for comparable enol acetates (Extended Data Fig. 1).⁵ Taking into account mechanistic possibilities as well as 2D-NMR (HMBC) data published by Cronin and co-workers, the most reasonable product is therefore the constitutional isomer **2** (Fig. 1). As illustrated by our proposed mechanism (Extended Data Fig. 2), *C*-acylation of the enolate intermediate **D** would give rise to compound **1**, while *O*-acylation would give **2**. In addition to providing less steric congestion, *O*-acylation would afford a greater degree of electronic conjugation in the product.

Repetition of the reaction in our own laboratory led to a ca. 1:1 mixture of diastereomers (Extended Data Fig. 3). Separation of these two products and full characterization established that they were products **2a** and **2b**. Spectroscopic data for **2a** matched that provided by Cronin and co-workers for their isolated product.

Possessing both an acid-sensitive vinyl ether linkage and a base-sensitive activated ester, **2a** and **2b** would be expected to have poor stability. We found that **2b** was particularly unstable, and a low yield of the product was obtained during chromatographic separation from the diastereomeric mixture. This presumably explains why Cronin and co-workers observed a single compound from their reaction; **2b** likely decomposed prior to isolation.

To further confirm the presence of the ester group in the products, diastereomer **2a** was subjected to saponification. As expected, the hydrolysis product was clearly observed by NMR spectroscopy, and was characterized by accurate mass. This product is even less stable than **2b**, however, and could not be isolated in pure form. We also attempted to isomerize **2a** to produce genuine compound **1**, but this was unsuccessful.

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Author contributions J.S. analyzed the original spectral data and suggested the structure **2** in place of **1**, then carried out all experimental work and constructed the Supplementary Information. J.W. did the calculations and prepared the manuscript with advice from J.S.

Competing interests Declared none.

Additional information

Extended data accompanies this Comment

Supplementary information accompanies this Comment.

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Extended Data Table 1 | Comparison of Spectral Assignments to Calculated ^{13}C NMR Shifts for 1a^a

atom ^b	assigned shift ^c	MNova ^d	$\Delta(\delta)$	DFT ^e	$\Delta(\delta)$
C12	50.8	59.1	+8.3	67.3	+16.5
C13	163.4	172.7	+9.3	158.3	-5.1
C14	124.1	73.4	-50.7	78.2	-46.0
C15	156.2	210.4	+54.2	197.1	+40.9
C30	169.1	206.3	+37.2	199.4	+30.3
C32	40.4	44.1	+3.7	49.3	+8.9

^a Shaded cells indicate poor agreement ($|\Delta(\delta)| > 10$ ppm).

^b Atom numbering adopted from Cronin and shown in Fig. 1.

^c Assignments taken from Cronin et al.¹

^d Calculated using MestReNova's 'mnova best' method.

^e DFT / B3LYP / 6-31G*

Extended Data Fig. 1 | Minimum energy diastereomer of compound 1, and two diastereomers of an alternative product; comparison with a known vinyl acetate. Compound numbering is indicated in red. Chemical shift values (in ppm) are shown in blue.

Supplementary Information

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General Considerations

Reagent grade MeCN was used for the coupling reaction. Fresh phenylacetyl chloride was purchased from Aldrich and used as received. Analytical thin layer chromatography (TLC) was performed on MACHEREY-NAGEL pre-coated ALUGRAM® SILG/UV₂₅₄ TLC plates (0.20 mm silica gel 60 with 254 nm fluorescent indicator). TLC plates were visualized under UV light (254 nm). Flash column chromatography was performed on silica gel (60 Å, 40-63 µm, Silicycle SiliaFlash® F60). All NMR spectra were recorded at ambient temperature (298-300 K). ¹H spectra were either recorded at 500.27 or 300.27 MHz, respectively, on a Bruker AVANCE NEO 500 spectrometer equipped with a BBF probe or a Bruker AVANCE 300 spectrometer equipped with a 5mm PABBO BB-1H/D Z-GRD probe. ¹³C NMR spectra were recorded at 125.81 MHz on a Bruker AVANCE NEO 500 spectrometer equipped with a BBF probe. ¹H chemical shifts (δ) are reported in parts-per-million (ppm) relative to tetramethylsilane and referenced to the solvent peak (CDCl₃, δ 7.26; (CD₃)₂CO, δ 2.05). NMR data is presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, app = apparent), coupling constants (*J*, reported in Hz), integration. All ¹³C NMR spectra are proton-decoupled (¹³C{¹H}). ¹³C chemical shifts (δ) are reported in parts-per-million (ppm) relative to tetramethylsilane and referenced to the solvent peak (CDCl₃, δ 77.16; (CD₃)₂CO, δ 29.84). Infrared spectra were obtained using a Perkin-Elmer ATR spectrometer. Wavenumbers are reported in cm⁻¹. Accurate masses were obtained by electrospray ionization (positive mode) high resolution mass spectrometry (HRMS) using a Thermo Scientific™ Exactive™ Plus Orbitrap Ultimate 3000 LC-MS system. Melting points were measured using a Gallenkamp melting point apparatus, and are uncorrected.

Synthesis of Diastereomers 2a and 2b:

In a 50-mL round-bottom flask, phenylacetyl chloride (0.80 mL, 6.05 mmol) was dissolved in MeCN (10.0 mL). DBU (0.90 mL, 6.02 mmol) was added dropwise at room temperature over 3.5 minutes, resulting in the formation of a clear, bright yellow solution. The reaction was stirred for another ten minutes, then decanted into a solution of saturated aqueous NH₄Cl (75 mL). The aqueous phase was extracted with Et₂O (3 x 50 mL). The combined Et₂O phases were washed with sat. NaHCO₃ (3 x 80 mL) and brine (1 x 80 mL), dried over Na₂SO₄, then concentrated *in vacuo* to afford 0.53 g of a sticky yellow residue. The crude residue was re-dissolved in acetone, adsorbed onto Celite (~2.1 g), loaded onto a silica gel column, and rinsed with hexanes. The residue was purified by column chromatography (5:1 Hexanes/ EtOAc) to afford diastereomers **2a** and **2b** (521 mg, 51 % combined yield).

N.B. Although diastereomers **2a** and **2b** could be separated with the reported column conditions, approximately 20 % of the combined yield accounts for co-eluted **2a** and **2b** (205.3 mg). In our hands, column chromatography was ineffective for the complete removal of residual phenylacetic acid even when the eluent was spiked with NEt₃ (~1 % v/v). This problem was solved by washing column-purified **2a** and **2b** with saturated aqueous NaHCO₃.

Yield: 22 %

Physical state: colourless, sticky semi-solid

R_f (3:1 Hexanes/ EtOAc): 0.29

IR: 3029, 2927, 2859, 1750, 1731, 1676, 1633, 1600, 1116, 697 cm⁻¹

¹H NMR (500.27 MHz, CDCl₃) δ 7.34-6.91 (m, 13H), 6.92 (app d, *J* = 7.2 Hz, 2H), 4.58 (ddd, *J* = 13.6, 6.8 1.3 Hz, 1H), 4.10 (s, 1H), 3.42 (d, *J* = 15.3 Hz, 1H), 3.38 (d, *J* = 15.3 Hz, 1H), 2.96-2.86 (m, 2H), 2.71 (app ddd, *J* = 15.1, 5.1, 2.9 Hz, 1H), 2.55 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.48-2.40 (m, 2H), 1.98 (app dt, *J* = 12.3, 6.1 Hz, 1H), 1.82-1.77 (m, 2H), 1.70-1.63 (m, 3H), 1.55-1.41 (m, 3H).

¹³C NMR (125.81 MHz, CDCl₃) δ 169.71, 164.02, 156.81, 136.36, 132.71, 132.14, 130.06, 129.82, 129.24, 128.74, 128.21, 127.91, 127.80, 127.77, 127.35, 124.73, 80.21, 51.34, 49.61, 45.68, 40.99, 38.23, 36.23, 28.68, 28.60, 23.62, 22.36.

HRMS (ESI+) *m/z* [M + H] calcd for C₃₃H₃₅N₂O₃+ 507.26424, found: 507.26413.

Yield: 9 %

Physical state: white solid

m.p.: decomposes to a red solid at 73-75 °C.

R_f (3:1 Hexanes/ EtOAc): 0.21

IR: 3055, 3032, 2962, 2937, 2919, 2901, 2866, 2856, 2838, 1755, 1740, 1669, 1629, 1598, 1117, 698 cm⁻¹

¹H NMR (500.27 MHz, CDCl₃) δ 7.30-7.12 (m, 13H), 6.66 (d, *J* = 7.2 Hz, 2H), 5.05 (s, 1H), 4.68 (ddd, *J* = 13.0, 6.9, 1.5 Hz, 1H), 3.76 (ddd, *J* = 14.0, 8.6, 6.1 Hz, 1H), 3.34 (td, *J* = 12.5, 12.4, 5.4 Hz, 1H), 3.19 (d, *J* = 16.1 Hz, 1H), 3.11 (d, *J* = 16.1 Hz, 1H), 2.99 (ddd, *J* = 13.1, 10.7, 4.8 Hz, 1H), 2.76 (m, 1H), 2.34 (dt, *J* = 16.0, 3.3 Hz, 1H), 2.05-2.01 (m, 1H), 1.91-1.85 (m, 3H), 1.69-1.61 (m, 3H), 1.34-1.30 (m, 2H), 0.94-0.89 (m, 1H).

¹³C NMR (125.81 MHz, CDCl₃) δ 168.22, 164.00, 156.19, 134.75, 132.71, 132.50, 129.78, 129.52 (impurity), 129.27, 128.68, 128.52, 127.95, 127.68, 127.52, 127.23, 127.14, 124.70, 80.82, 52.43, 51.30, 45.01, 40.34, 37.75, 34.11, 31.26, 29.50, 24.41, 22.83.

¹H NMR (500.27 MHz, (CD₃)₂CO) δ 7.36 (bs, 5H), 7.33-7.26 (m, 3H), 7.25-7.20 (m, 2H), 7.19-7.10 (m, 3H), 6.70 (app d, *J* = 7.6 Hz, 2H), 5.04 (s, 1H), 4.61 (ddd, *J* = 12.9, 6.9, 1.6 Hz, 1H), 3.81 (ddd, *J* = 13.9, 8.6, 5.9 Hz, 1H), 3.33 (dt, *J* = 12.6, 6.3 Hz, 1H), 3.28 (d, *J* = 16.2 Hz, 1H), 3.16 (d, *J* = 16.2 Hz, 1H), 3.09 (ddd, *J* = 13.2, 10.5, 5.0 Hz, 1H), 2.84-2.79 (m, 1H), 2.42 (dt, *J* = 16.2, 2.8 Hz, 1H), 2.01-1.95 (m, 3H), 1.88-1.75 (m, 1H), 1.71-1.64 (m, 3H), 1.44-1.41 (m, 1H), 1.32-1.29 (m, 1H), 1.02-0.90 (m, 1H).

¹³C NMR (125.81 MHz, (CD₃)₂CO) δ 168.71, 163.81, 156.75, 135.87, 134.07, 133.84, 130.76, 130.08, 129.07, 129.06, 128.51, 128.30, 128.26, 128.08, 127.66, 127.48, 125.11, 81.31, 52.85, 52.11, 45.52, 40.51, 37.99, 34.76, 31.75, 25.11, 23.36.

HRMS (ESI+) *m/z* [M + H] calcd for C₃₃H₃₅N₂O₃+ 507.26424, found: 507.26444.

Hydrolysis of Diastereomer 2a:

Compound 4. Ester **2a** (23.1 mg, 0.0456 mmol) was dissolved in MeOH (2 mL) at room temperature. Aqueous 1 M NaOH (1.0 mL, 21.9 equiv.) was added dropwise over 1.5 minutes, and the reaction was stirred for an additional 7 minutes. The MeOH was removed *in vacuo*, and the resulting aqueous solution was transferred to a 50-mL Falcon tube. The solution was diluted with water (10 mL) and saturated NH₄Cl solution (3 mL) was carefully added (until pH $\approx$ 8). The solution was extracted with EtOAc (4 x 5 mL). The combined EtOAc phases were dried over Na₂SO₄ and concentrated *in vacuo* to afford crude **4** (11.5 mg) as an off-white, acid-sensitive solid.

N.B. Upon sitting at room temperature in acetone-*d*₆, **4** started decomposing within an hour (as determined by ¹H NMR analysis). Consequently, we did not attempt to fully characterize **4** by NMR.

Yield (crude): 65 %

Physical state: beige, off-white solid

R_f (1:1 Hexanes/ EtOAc): 0.36

HRMS (ESI+) *m/z* [M + H] calcd for C₂₅H₂₉N₂O₂+ 389.22238, found: 389.22209.

Figure S1. TLC plate (1:1 hexanes/EtOAc) visualized under 254 nm light showing complete hydrolysis of ester **2a**. Lane 1 = ester **2a**; lane 2 = co-spot; lane 3 = crude reaction mixture (t = 3.5 min).

Figure S2. Mass spectrum of compound **4** showing the [M+H] peak with m/z = 389.22209.

Table S1. Comparison of Spectral Assignments to Calculated ^{13}C NMR Shifts for **1a**

	Assigned ^{13}C (Cronin et al)	Attached ^1H		DFT predictions (B3LYP/6-31G*)		MestReNova predictions	
				^{13}C	$\Delta(\delta)$	^{13}C	$\Delta(\delta)$
C1	21.76	1.62	1.42	26.1	+4.3	25.9	+4.1
C2	35.63	4.56	2.93	38.5	+2.8	43.1	+7.5
C4	79.59	/	/	76.8	-2.8	75.5	-4.1
C6	45.08	2.43	1.97	51.8	+6.7	48.2	+3.1
C7	37.65	2.53	2.41	47.1	+9.5	39.0	+1.4
C8	28.08	1.69	1.49	26.2	-1.9	23.3	-4.8
C9	23.02	1.76	1.65	23.8	+0.7	26.1	+3.1
C10	27.99	1.80	1.49	28.0	+0.1	27.0	-1.0
C11	49.01	2.87	2.68	51.5	+2.5	50.6	+1.6
C12	50.76	4.06	/	67.3	+16.5	59.1	+8.3
C13	163.41	/	/	158.3	-5.1	172.7	+9.3
C14	124.13	/	/	78.2	-46.0	73.4	-50.7
C15	156.19	/	/	197.1	+40.9	210.4	+54.2
C16	135.76	/	/	127.9	-7.9	131.8	-4.0
C17/21	(a)	(a)	/	123.2	n/a	128.0	n/a
C18/20	(a)	(a)	/	120.7	n/a	129.0	n/a
C19	(a)	(a)	/	120.1	n/a	127.5	n/a
C23	131.55 or 132.11	/	/	129.9	n/a	135.0	n/a
C25/29	(a)	(a)	/	122.4	n/a	127.0	n/a
C26/28	(a)	(a)	/	121.1	n/a	128.5	n/a
C27	(a)	(a)	/	120.4	n/a	128.4	n/a
C30	169.08	/	/	199.4	+30.3	206.3	+37.2
C32	40.39	3.32-3.45	3.32-3.45	49.3	+8.9	44.1	+3.7
C33	131.55 or 132.11	/	/	129.8	n/a	134.2	n/a
C34/38	(a)	6.90	/	123.3	n/a	129.1	n/a
C35/37	(a)	(a)	/	120.7	n/a	128.9	n/a
C36	(a)	(a)	/	119.3	n/a	127.2	n/a

^(a) overlapping aromatic signals

Table S2. Comparison of Spectral Assignments to Calculated ^{13}C NMR Shifts for **2a**

	Assigned ^{13}C (this work)	Attached ^1H		DFT predictions (B3LYP/6-31G*)		MestReNova predictions	
				^{13}C	$\Delta(\delta)$	^{13}C	$\Delta(\delta)$
C1	22.36	1.65	1.44	25.5	+3.2	25.9	+3.6
C2	36.23	4.58	2.93	39.0	+2.8	44.1	+7.9
C4	80.21	/	/	78.2	-2.0	75.2	-5.0
C6	45.68	2.44	1.98	52.5	+6.8	48.6	+2.9
C7	38.23	2.55	2.46	46.7	+8.5	38.4	+0.1
C8	28.60	1.82 ^(a) , 1.71 ^(a) , 1.53 ^(a)		24.8	-3.8	23.5	-5.1
C9	28.68			23.3	-5.4	26.1	-2.6
C10	23.62	1.82	1.68	28.0	+4.3	27.3	+3.7
C11	49.61	2.90	2.71	50.7	+1.1	50.6	+1.0
C12	51.34	4.10	/	59.6	+8.3	50.6	-0.7
C13	164.02	/	/	155.6	-8.4	168.5	+4.5
C14	124.73	/	/	121.2	-3.6	113.3	-11.4
C15	156.81	/	/	151.6	-5.2	150.2	-6.6
C16	136.36	/	/	130.8	-5.6	133.3	-3.0
C17/21	129.82 ^(b)	(c)	/	123.3	-6.5	127.8	-2.0
C18/20	130.06 ^(b)	(c)	/	120.8	-9.3	128.3	-1.8
C19	(c)	(c)	/	120.2	n/a	127.2	n/a
C23	(c)	/	/	127.4	n/a	131.4	n/a
C25/29	(c)	(c)	/	124.7	n/a	129.2	n/a
C26/28	(c)	(c)	/	120.0	n/a	129.3	n/a
C27	(c)	(c)	/	120.3	n/a	128.6	n/a
C30	169.71	/	/	155.2	-14.6	170.2	+0.5
C32	40.99	3.42	3.38	42.9	+1.9	40.5	-0.5
C33	132.71	/	/	128.2	-4.5	133.4	+0.7
C34/38	129.24	6.92	/	123.5	-5.8	128.9	-0.4
C35/37	127.35	7.23	/	121.3	-6.0	128.8	+1.5
C36	(c)	(c)	/	120.0	n/a	127.1	n/a

^(a) overlapping signals in HSQC^(b) both assigned by HMBC correlation with H12; assignments could be reversed^(c) overlapping aromatic signals

Table S3. Comparison of Spectral Assignments to Calculated ^{13}C NMR Shifts for **2b**

	Assigned ^{13}C (this work)	Attached ^1H		DFT predictions (B3LYP/6-31G*)		MestReNova predictions	
				^{13}C	$\Delta(\delta)$	^{13}C	$\Delta(\delta)$
C1	24.41	2.01	1.87	27.0	+2.6	25.9	+1.5
C2	37.75	4.68	3.34	36.3	-1.4	44.1	+6.4
C4	80.82	/	/	81.3	+5	75.2	-5.6
C6	45.01	3.76	2.99	47.4	+2.4	48.6	+3.6
C7	34.11	2.76	1.88	30.3	-3.8	38.4	+4.3
C8	22.83	1.62 ^(a)	1.62 ^(a)	24.0	+1.2	23.5	+0.7
C9	29.50	1.67	0.92 ^(b)	23.9	-5.6	26.1	-3.4
C10	31.26	1.32 ^(c)	1.32 ^(c)	27.2	-4.1	27.3	-4.0
C11	52.43	2.34	1.89	49.7	-2.7	50.6	-1.8
C12	51.30	5.05	/	50.2	-1.1	50.6	-0.7
C13	164.00	/	/	153.8	-10.2	168.5	+4.5
C14	124.70	/	/	122.6	-2.1	113.3	-11.4
C15	156.19	/	/	152.3	-3.9	150.2	-6.0
C16	134.75	/	/	131.4	-3.4	133.3	-1.4
C17/21	129.78	(d)	/	126.9	-2.9	127.8	-2.0
C18/20	(d)	(d)	/	120.9	n/a	128.3	n/a
C19	(d)	(d)	/	120.2	n/a	127.2	n/a
C23	(d)	/	/	128.0	n/a	131.4	n/a
C25/29	(d)	(d)	/	123.3	n/a	129.2	n/a
C26/28	(d)	(d)	/	120.5	n/a	129.3	n/a
C27	(d)	(d)	/	119.6	n/a	128.6	n/a
C30	168.22	/	/	161.0	-7.2	170.2	+2.0
C32	40.34	3.19	3.11	42.1	+1.7	40.5	+0.2
C33	132.50	/	/	126.8	-5.7	133.4	+0.9
C34/38	129.27	6.66	/	122.9	-6.3	128.9	-0.4
C35/37	127.14	(d)	/	121.8	-5.4	128.8	+1.7
C36	(d)	(d)	/	120.1	n/a	127.1	n/a

^(a) overlapping geminal protons; difficult to assign exact shifts for the two signals^(b) upfield proton shift (relative to the equivalent proton in **2a**), possibly due to shielding from the C16–C20 pi system^(c) overlapping geminal protons; difficult to assign exact shifts for the two signals^(d) overlapping aromatic signals

Table S4. Comparison of Energies for the Four Possible Diastereomers of Compound **1**^(a)

ΔH_f : -62.634 kJ/mol	-64.974 kJ/mol	-66.312 kJ/mol	-66.013 kJ/mol
$\Delta[\Delta H_f]$: +3.68 kJ/mol	+1.34 kJ/mol	+0.00 kJ/mol	+0.30 kJ/mol

^(a) Semiempirical calculations.

Figure S3. **A)** ^1H NMR of compound **2a** (500.27 MHz, acetone- d_6). **B)** ^1H NMR of crude **4** (500.27 MHz, acetone- d_6).

Figure S4. IR spectrum of compound **2a**.

Figure S5. IR spectrum of compound **2b**.

Figure S7. ^1H NMR of compound **2a** (500.27 MHz, CDCl_3).

Figure S8. Upfield region (5.0-1.0 ppm) of the ^1H NMR for compound **2a** (500.27 MHz, CDCl_3).

Figure S9. ¹³C NMR of compound **2a** (125.81 MHz, CDCl₃).

Figure S10. Gradient COSY spectrum of compound **2a** (500.27 MHz, CDCl_3); PAA = phenylacetic acid.

Figure S11. Gradient COSY spectrum of compound **2a** (500.27 MHz, CDCl_3).

Figure S12. Gradient HSQC-DEPT spectrum of compound **2a** (500.27, 125.80 MHz, CDCl_3).

Figure S13. Gradient HSQC-DEPT spectrum of compound **2a** (500.27, 125.80 MHz, CDCl_3).

Figure S14. Gradient HMBC spectrum of compound **2a** (500.27, 125.81 MHz, CDCl_3).

Figure S15. Gradient HMBC spectrum of compound **2a** (500.27, 125.81 MHz, CDCl_3).

Figure S16. Gradient HMBC spectrum of compound **2a** (500.27, 125.81 MHz, CDCl₃).

Figure S17. Gradient HMBC spectrum of compound **2a** (500.27, 125.81 MHz, CDCl_3).

Figure S18. Gradient HMBC spectrum of compound **2a** (500.27, 125.81 MHz, CDCl₃).

Figure S19. Top to bottom: ^1H NMR of compound **2a** stacked with 1D NOE sub-spectra (500.27 MHz, CDCl_3); PAA = phenylacetic acid.

Figure S20. Summary of the diagnostic NOE interactions observed for compound **2a**.

Figure S21. Top: ^1H NMR of compound **2a**. Bottom: 1D gradient TOCSY spectrum of compound **2a** (500.27 MHz, 40 ms mixing time, CDCl_3). The irradiated peak (H34/ H38) is denoted with a blue star. PAA = phenylacetic acid.

Figure S22. A) ^1H NMR of compound **2a** (500.27 MHz, CDCl_3). **B)** 1D gradient TOCSY spectrum of compound **2a** (500.27 MHz, CDCl_3) from irradiation of H2 (denoted with blue star). **C)** 1D gradient TOCSY spectrum of compound **2a** (500.27 MHz, CDCl_3) from irradiation of H11' (denoted with blue star). PAA = phenylacetic acid.

Figure S23. ^1H NMR of compound **2b** (500.27 MHz, acetone- d_6).

Figure S24. Upfield region (5.5-0.5 ppm) of the ^1H NMR (500.27 MHz, acetone- d_6) for compound **2b**.

Figure S25. ^{13}C NMR of compound **2b** (125.81 MHz, acetone- d_6).

Figure S26. DEPT-135 spectrum of compound **2b** (125.81 MHz, acetone-*d*₆).

Figure S27. ^1H NMR of compound **2b** (500.27 MHz, CDCl_3).

Figure S29. ^{13}C NMR of compound **2b** (125.81 MHz, CDCl_3).

Figure S30. Gradient COSY spectrum of compound **2b** (500.27 MHz, CDCl_3).

Figure S31. Gradient HSQC-DEPT spectrum of compound **2b** (500.27, 125.80 MHz, CDCl_3).

Figure S32. Gradient HSQC-DEPT spectrum of compound **2b** (500.27, 125.80 MHz, CDCl_3).

Figure S33. Gradient HMBC spectrum of compound **2b** (500.27, 125.81 MHz, CDCl_3).

Figure S34. Gradient HMBC spectrum of compound **2b** (500.27, 125.81 MHz, CDCl_3).

Figure S35. Gradient HMBC spectrum of compound **2b** (500.27, 125.81 MHz, CDCl_3).

Figure S36. Gradient HMBC spectrum of compound **2b** (500.27, 125.81 MHz, CDCl_3).

Figure S37. **A)** ^1H NMR of compound **2b**. **B)** 1D gradient TOCSY spectra of compound **2b** (500.27 MHz, 40 ms mix time, CDCl_3) from irradiation of H2. **C)** 1D gradient TOCSY spectra of compound **2b** (500.27 MHz, 40 ms mix time, CDCl_3) from irradiation of H11. PAA = phenylacetic acid.

Figure S38. A) ^1H NMR of compound **2b**. **B-D** 1D gradient NOE spectra for compound **2b** (500.27 MHz, acetone- d_6). **B)** Irradiation of H12. **C)** Irradiation of H2. **D)** Irradiation of H6.

Figure S39. Top: ^1H NMR of compound **2b**. Bottom: 1D gradient NOE spectra of compound **2b** (500.27 MHz, CDCl_3) arising from selective irradiation of H12. PAA = phenylacetic acid.

Figure S40. Summary of the diagnostic NOE interactions observed for compound **2b**.

Figure 41. Summary of the key HMBC Correlations for compounds **2a** and **2b**.