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Research Article

Optimized synthesis of four isotopically labeled (^{13}C-enriched) phenolic acids via a malonic acid condensation

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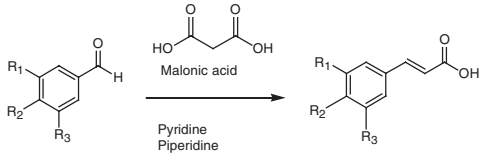
Summary

Four isotopically (^{13}C)-labeled phenolic acids (caffeic [M + 3], sinapic [M + 2], *p*-coumaric [M + 6] and ferulic [M + 6] acids) were synthesized via a simple one-step malonic acid condensation with a series of aldehydes. The aldehydes and the malonic acid were variously labeled and unlabeled to vary the enriched sites. ^{13}C and ^{1}H NMR analyses together confirmed the labeled positions. LC/MS confirmed the masses. These acids are intended for use as internal standards for isotope dilution mass spectrometry (IDMS). Copyright © 2004 John Wiley & Sons, Ltd.



	Caffeic Acid	Sinapic Acid	p-Coumaric Acid	Ferulic Acid
R_1	-H	-OCH_3	-H	-H
R_2	-OH	-OH	-OH	-OH
R_3	-OH	-OCH_3	-H	-OCH_3
IM	M+3	M+2	M+6	M+6

IM= isotopic mass

Key Words: stable isotope; phenolic acids; malonic acid condensation; ^{13}C labeled; hydroxycinnamic acids; IDMS; NMR; LC/MS; biochemical marker

Introduction

Interest in naturally occurring plant phenolics stems from their potential protective role against oxidative damage diseases (coronary heart disease, stroke, and cancers) through ingestion of fruits and vegetables.[1–3] The term 'phenolics' encompasses a large variety of naturally occurring molecules

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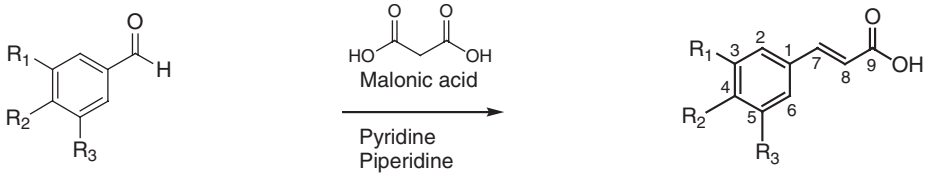
currently classified according to the number of phenol subunits. Polyphenols consist of two or more phenol subunits and encompass compounds such as the flavonoids and tannins.[4] The monomeric subclass consists of the phenolic acids that include two distinguishing constitutive carbon frameworks: the hydroxycinnamic and hydroxybenzoic structures.[5] Beyond the protective antioxidant behavior, other biological activities of phenolic acids have been reported. Caffeic acid, one of the most prominent, naturally occurring cinnamic acids, is known to selectively block the biosynthesis of leukotrienes (components involved in immunoregulation diseases, asthma, and allergic reactions).[6] Recent investigations by Maggi-Capyeron *et al*. have linked a series of phenolic acids (gallic, caffeic, protocatechuic, *p*-coumaric, sinapic, ferulic) with the inhibition of AP-1 transcriptional activity. AP-1 is an activator protein implicated in the processes that control inflammation as well as cell differentiation and proliferation.[7] To better assess the potential health benefits of these phenolic acids, in both their roles in nutrition and as potential pharmaceutical agents, it is necessary to be able to measure these components in plant sources (e.g. food composition data) and in biological fluids (e.g. serum for metabolic investigations). Developing accurate analytical methodologies for their detection and measurement is crucial in this endeavor.

IDMS is an analytical technique of proven accuracy which uses stable (non-radioactive) isotopes.[8] Synthesized isotopically enriched compounds can be used as markers to identify pathways and biochemical transformations such as complex conjugates and metabolites. However, one major factor limiting its use is the lack of commercially available isotopically labeled (^{13}C or D) compounds of the desired chemical structure. Although analytical laboratories can develop these measurement systems, they are often not equipped to carry out lengthy and complicated synthesis reactions. Additionally, the cost of a customized chemical enrichment synthesis from an outside laboratory is often prohibitive. In this communication, we report a simple one-step conversion of a series of aldehydes to hydroxycinnamic acids (Table 1). Starting with commercially available ^{13}C labeled and unlabeled aldehydes and ^{13}C labeled and unlabeled malonic acid, we obtained four site-selective, isotopically enriched, hydroxycinnamic acids.

The reactions, conducted to generate about 100 g of product, were adapted from a procedure by Koo *et al*.[9] Conditions were first optimized for maximum yield with unlabeled compounds. Identification of labeled compounds was achieved using LC/UV and LC/MS. Three out of the four phenolic acids synthesized had a mass 3 or more units greater than their naturally occurring, non-labeled analogs. The sites at which ^{13}C enrichment occurred were determined using ^{1}H and ^{13}CNMR techniques. This information enables subsequent identification of LC-MS fragments generated by chemical or biochemical alteration.

Table 1. Condensation of commercially available aldehydes (^{13}C labeled and unlabeled) and malonic acid (^{13}C labeled and unlabeled)



Starting aldehyde	R1	R2	R3	Phenolic acid product
Vanillin (**1**) ($^{13}C_6$ benzene ring)	-H	-OH	$-OCH_3$	Ferulic acid [M + 6][a] (**5**)
p-hydroxybenzaldehyde (**2**) ($^{13}C_6$ benzene ring)	-H	-OH	-H	*p*-Coumaric acid [M + 6][a] (**6**)
Protocatechuic aldehyde (**3**) ($^{13}C_1$-aromatic ring)	-H	-OH	-OH	Caffeic acid [M + 3][b] (**7**)
Syringealdehyde (**4**) (Unlabeled)	$-OCH_3$	OH	$-OCH_3$	Sinapic acid[M + 2][b] (**8**)

[a] Malonic acid was unlabeled.
[b] Malonic acid was $^{13}C_3$ labeled: condensation followed by decarboxylation added 2 ^{13}C labels, thereby increasing mass by 2 units.

Discussion and results

To achieve optimal yields of isotopically labeled product as well as a minimal loss of starting material, a variety of synthetic methods were investigated. Mitra *et al*. reported using the same basic catalysts (piperidine and pyridine) with microwave irradiation as the heating source.[10] In our attempts to reproduce those conditions we obtained lower than expected yields. Although we were able to increase the yield by extracting the supernatant, we were unable to recover any unconverted starting material. Exploring alternate condensation conditions, we examined the use of ammonium acetate under both solvent free (microwave) and conventional heating conditions.[11] Again, recovery yields were low compared to our scaled down process. Stoichiometric concentrations of the reactants improved the recoveries. When equivalents of the malonic acid were increased from 2 to 3 in the synthesis of ferulic acid (**5**) the yield dropped from 76 to 35%. Increasing the amount of piperidine two-fold also reduced the yield. Extracting the entire mixture immediately after acidification also reduced recovery rates. Isolating the first batch of crystals followed by an attempt to obtain a second crop proved unfruitful. Extracting the supernatant with ethyl ether after collecting the first batch of crystals consistently gave the best recoveries.

A high-performance liquid chromatography (HPLC) method, using photodiode array detection, which separates 16 phenolic acids, was used to validate identities both by retention times[12] and UV-Vis spectra. Masses of the isotopic analogs were obtained using HPLC with mass spectrometric detection

Table 2. Percent yields, masses, and λ_{max} for synthesized ^{13}C-labeled hydroxycinnamic acids

Acid	% Yield[a]	Mass (M-1)[b]	UV-Vis λ Max[c]
(**5**)	76	199	240, 324
(**6**)	78	169	229, 310
(**7**)	50	182	241, 325
(**8**)	66	225	238, 326

[a] Percent yields calculated after recrystallization from water.
[b] LC/MS–ESI: full scan in negative ion mode detected the molecular ion minus 1hydrogen.
[c] Observed values are nearly identical to those reported in the literature.

(LC/MS) (Table 2). The retention times of the ^{13}C-enriched compounds were indistinguishable from those of the un-enriched compounds.

Both ^{1}H and ^{13}C NMR techniques were required to assign frequencies to the enriched sites of the chemical structures (Table 3). In a standard ^{13}C spectrum after proper data processing, all peaks have a positive intensity and are above the zero baseline. In the same number of scans, however, using the attached proton test (APT) pulse sequence, ^{13}C peaks having an odd number of protons attached (one or three) will have the same intensity as in the regular ^{13}C spectrum, but they will be below the zero baseline; peaks with an even number of protons attached (zero or two) will be unaffected by the pulse sequence, appearing above the baseline.[13] Thus, the APT immediately enables identification of the ^{13}C sites in these structures that only have single protons attached. From the APT experiment, the signals for the ferulic acid carbons (see numbering system in Table 1, Figure 1) C1, C4 and C5 were thus easily differentiated from the C2, C3, and C6 sites which have single protons bound to them. In *p*-coumaric acid only four ^{13}C-enriched signals were observed. C1 and C4 were above the baseline, and, because of molecular symmetry, only two additional sets of peaks were also observed below for C2/C6 and C3/C5. As expected from the chemical shift data, the relative intensity of each peak was similar to that of C6 in ferulic acid. Sinapic acid had two enriched sites: at C8 below the baseline and at C9 above the baseline. Because ^{13}C enrichment is more than 50 times greater than the natural abundance, naturally occurring ^{13}C frequencies are not included in these results (nor are they required to assign sites of enrichment). Caffeic acid had three ^{13}C-enriched sites, with the two sites at C8 and C9 the same as in sinapic acid. If not ^{13}C-enriched, all APT spectra are singlets. The reason the peaks are doublets instead of singlets is that there is a second *J* coupling that is occurring. C9 was a doublet because of ^{2}J coupling to enriched site C8 (74 Hz). The C8 proton is a doublet due to ^{2}J coupling to enriched site C7 (75 Hz). The aromatic chemical shifts at averaging at 148 ppm were very different from the C1 sites of other structural analogs (127 ppm); however, it was similar to the shift for both C4 and C5 in ferulic acid (150 ppm).

Table 3. ^{1}H and ^{13}C chemical shift assignments

	Ferulic acid (**5**)		*p*-coumaric acid (**6**)		Caffeic acid (**7**)		Sinapic acid (**8**)	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
R_1	6.80m	R = H	6.79m	R = H	6.76.ddd	R = H	3.87s	R = OCH3
R_2	—	R = OH	—	R = OH	—	R = OH	—	R = OH
R_3	3.88d	R = OCH3	6.79m	R = H	—	R = OH	3.87s	R = OCH3
1	—	127.9m	—	127.2m	—	—	—	—
2	7.05m	124.0m	7.41m	131.1dt	6.92m	—	6.89s	—
3	—	116.5m	—	116.8m	—	—	—	—
4	—	150.0m	—	161.2dt	—	146.9	—	—
5	—	150.0m	—	116.8m	—	149.5	—	—
6	7.17m	111.7m	7.41m	131.1dt	7.02dt	—	6.89s	—
7	7.59m	—	7.59m	—	7.51ddd	—	7.58ddd	—
8	6.30dd	—	6.27dd	—	6.21ddd	115.7d	6.33ddd	116.5d
9	—	—	—	—	—	171.1d	—	170.9d

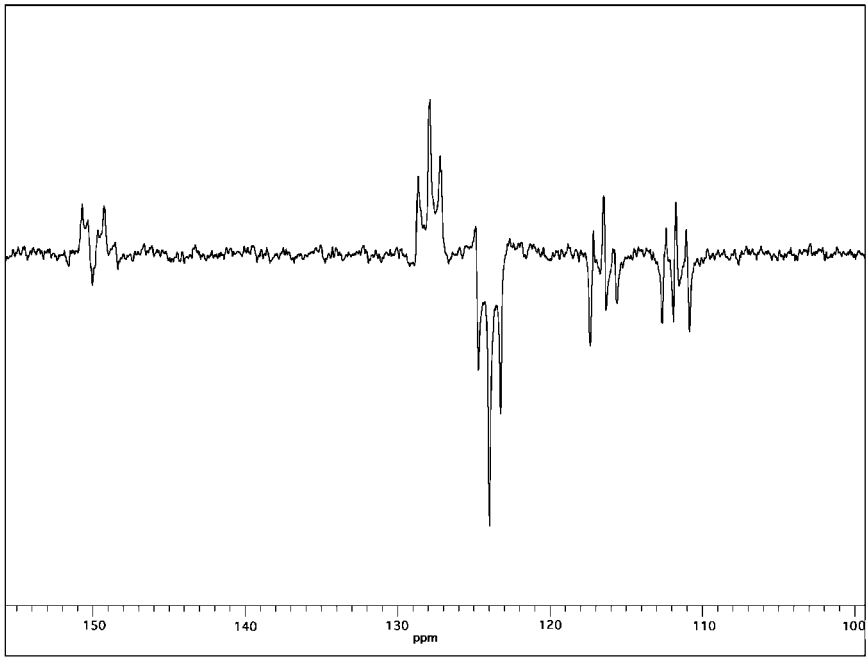


Figure 1. APT ^{13}C labeled (6) spectrum of ferulic acid (aromatic region). Peaks are multiplets because of ^{13}C–^{13}C-enriched $^{1}J_{CC}$, $^{2}J_{CC}$, $^{3}J_{CC}$ and $^{4}J_{CC}$ coupling. Peaks below the baseline have $^{1}J_{HC}$ coupling

Assigning the third enriched site was initially misleading. Normally a peak below the baseline is unambiguous evidence of the presence of $^{1}J_{CH}$ coupling. The apparent doublet for the C4 or C5 site was 199 Hz apart, too large for typical *J* coupling constants.[14,15] Additional NMR experiments were required

to resolve the uncertainty. Inverse gated ^{13}C spectra (i.e. decoupler turned off only during acquisition) found the additional J coupling values confirming the assignments. C8 was a doublet of doublets: $^{2}J_{C8H8} = 160$ Hz and $^{1}J_{C8C9} = 74$ Hz. C9 was a doublet of a doublet of doublets: $^{1}J_{C9C8} = 74$ Hz, $^{2}J_{C9H8} = 7$ Hz and $^{3}J_{C9H7} = 3$ Hz. The peak at 148 ppm was not the sharp doublet present in $^{1}J_{CH}$ coupling. The (199.9 Hz) separation between the two peaks was also larger than $^{1}J_{HC}$ and $^{1}J_{CC}$ literature values. The lower intensity peak was more consistent with a site having no proton attached. The absence of two doublets in the inverse gated experiment proves that $^{1}J_{C4C5}$ is not taking place.

When ^{13}C sites are enriched however, multiplicity in both the ^{1}H and ^{13}C spectra is observed.[14] Multiplicity in coupling patterns in the ^{13}C spectra does not alone provide definitive answers on assignments of site enrichment, and, as such, the results are not definitive unless one knows which sites are coupling to each other. The adjacent enriched sites in C8 and C9 in sinapic acid and in caffeic acid resulted in a doublet, confirming they are adjacent, but sinapic acid produced a doublet of quartets. The corresponding ^{1}H spectra found the coupling in both caffeic acid and in sinapic acid at the H7 and H8 sites were doublets of quartets. H7 was split by H8 into two peaks; C8 then split it into four and C9 split it further into a second set of four. Likewise C8 was split by C9 into two peaks; H8 then split it into four and H7 split it into a second set of four. Long range coupling to proton frequencies was also seen in ferulic acid at the R3 methoxy site: although no enrichment was observed at R3 in the ^{13}C domain, a doublet was displayed at that site in the ^{1}H spectrum. Thus the ^{1}H spectrum can be used to determine which sites on the aromatic ring are enriched. Additional information ($^{2}J_{CCH}$, $^{3}J_{CCCH}$ and $^{4}J_{CCCCH}$ couplings), however, would be required to identify which specific site(s) on the ring are enriched. Selective ^{13}C enrichment at various sites in the ring would verify which specific J coupling is responsible for the doubling of the R3 ^{1}H frequency.

As expected from the chemical syntheses starting materials, NMR experiments confirmed in ferulic acid and *p*-coumaric acid, carbons C1–C6 were enriched, and C7, C8, and C9 were not; in sinapic acid, only C8 and C9 were enriched. With caffeic acid, however, the site(s) of enrichment of the starting material were uncertain.

The protocatechuic aldehyde (**3**), used to produce caffeic acid (Table 1), was purchased with enrichment at position(s) C4 and/or C5. From the APT experiment for caffeic acid, the two aromatic carbon frequencies separated by 199.9 Hz could be occurring because the starting material is a binary mixture of C4 and C5 enriched isotopes which averages out to one site ^{13}C enriched (at C4 or C5) on the aromatic ring. A limited amount of C4-enriched compound in C5-enriched compound can explain the APT inversion of the

C5 peak: an odd number of J couplings is occurring. Similarly, a limited amount of C5-enriched compound in C4-enriched compound can explain the APT inversion of the C4 peak. The C5 signal is about 34% more intense than the C4 signal so J coupling to the C5 site should be more predominant in corresponding proton spectra.

Assigning the coupling pattern in the ^{1}H spectrum of caffeic acid to chemical structure confirms the ^{13}C sites at which enrichment occurred. Figure 2 is an overlay of the ^{1}H NMR of both the ^{13}C labeled (**7**) and unlabeled caffeic acid. A comparison of the aromatic resonance patterns clearly demonstrates that the presence of ^{13}C coupling does not alter the chemical shift from that of the unlabeled compound. The ^{13}C-enriched malonic acid condensate differs from un-enriched caffeic acid only by the addition of J coupling at the relevant molecular sites. The ^{13}C enrichment at C8 is obvious from the large $^{1}J_{H8C8}$ coupling constant (160.0 Hz); the central frequency is 6.21 ppm. The same $^{1}J_{HC}$ coupling value was found in the APT and the inverse gated ^{13}C experiments. The absence of a corresponding $^{1}J_{HC}$ coupling constant at 7.51 ppm for H7 proves this site is not enriched. In un-enriched caffeic acid H8 is a doublet and H7 is a doublet $^{3}J_{HH}$ (16 Hz), the expected coupling constant for the trans configuration of protons on the double bond.[16] The multiplicity of H7 and H8 as doublets of quartets indicates two additional coupling constant are present: $^{2}J_{H7C8}$ (7 Hz) and $^{3}J_{H7C9}$ (3 Hz). The identical $^{3}J_{H7C9}$ (3 Hz) coupling values were observed in the inverse gated ^{13}C experiments.

The changes in multiplicity of the coupling patterns in the un-enriched caffeic acid identified the sites of enrichment in the chemical structure. In the

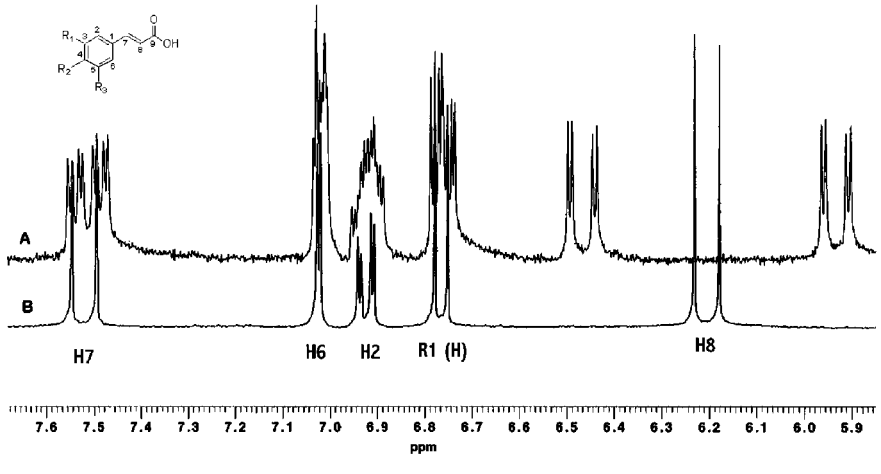


Figure 2. Overlay of the ^{1}H NMR of ^{13}C labeled (7) (spectrum A) and unlabeled (spectrum B) caffeic acid

un-enriched sample, R1 is coupled to H2 $^{3}J_{H2H3}$ (16 Hz) and is a doublet; H6 is coupled to H2 $^{4}J_{H6H2}$ (3 Hz) and is a narrower doublet; H2 is coupled to R1 (16 Hz) and to H6 (3 Hz) and is a doublet of doublets. The absence of any $^{1}J_{HC}$ coupling (160 Hz) precludes enrichment at C2, C3 or C6. The normal coupling magnitudes in an aromatic ring are: $^{2}J_{HCC}$ (0.4–2 Hz); $^{3}J_{HCCC}$ (5–8 Hz); and $^{4}J_{HCCCC}$ (0.6–2 Hz).[14,15]

Only R1 has an additional *J* coupling of 7 Hz. Only C1 and C5 enrichment in the aromatic ring would explain the additional ^{3}J couplings. The multiplicity in the enriched sample is actually a doublet of doublets with the middle two doublets having nearly the same chemical shift, i.e. an apparent doublet of triplets. Strong ^{3}J coupling (7 Hz) at both H2 and H6 would be required for the C4 site to be enriched, but is not observed. A $^{3}J_{H6C5}$ (2 Hz) coupling is also consistent with C4 or C5 enrichment. The multiplicity in the enriched caffeic acid of H6 ppm contains an abundance of sharp peaks separated by small *J* coupling values (ca. 1 Hz). The APT evidence that C1 is not enriched is corroborated by the ^{1}H spectrum. If C1 were enriched, similar couplings would be expected from C1 to three adjacent sites: H7, H2 and H6 $^{3}J_{HCC}$ (1 Hz). H7 and H8 would both have an additional set of couplings. Results were consistent with the LC-MS data that showed enriched caffeic acid had an M + 3 ion and, therefore, on average only three sites of enrichment. In summary, in caffeic acid (**7**), C1, C2, C3, C6 and C7 are not, but sites C4, C5, C8, and C9 are sites of ^{13}C enrichment; and C4 and C5 together equal only one site of enrichment.

In conclusion, we demonstrated that several commercially unavailable ^{13}C-labeled hydroxycinnamic acids can be prepared with a modified, one-step malonic acid condensation procedure. Starting with commercially available aldehydes (**1-4**) and malonic acid, hydroxycinnamic acids (**5-8**) were synthesized in yields ranging from 50 to 78%. Identities were confirmed using LC/UV and LC/MS, and sites of ^{13}C labeling were verified using NMR data.

Experimental

Reagents

Piperidine, pyridine, syringealdehyde (**4**), malonic acid, as well as phenolic acids (ferulic, caffeic, sinapic, *p*-coumaric) employed as standards were obtained from Aldrich (Milwaukee, WI). Malonic acid ($^{13}C_3$, 99.2%), 4-hydroxybenzaldehyde (**2**) ($^{13}C_6$, 99%), vanillin (**1**) ($^{13}C_6$, 99%), and 3,4 dihydroxybenzaldehyde (**3**) (purchased as random 3,4 $^{13}C_1$, 99%) were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA). De-ionized water (18 Ω) was produced using a Millipore Milli-Q purification system (Millipore Corp., New Bedford, MA).

Condensation reaction

The condensation reaction for ferulic acid (**5**), as well as for all the other acids reported (with their respective starting materials), was carried out as follows: 94.0 mg of vanillin (**1**) and 137 mg of malonic acid were placed in a 1 ml conical vial (American Scientific Products) and dissolved in 330 µl of pyridine. Piperidine (6.5 µl) was added, and the reaction was heated to 68°C for a period of 24 h. Then, the mixture was transferred to a 25 ml beaker, and 5 ml of water was added. Concentrated HCl (0.4 ml) was added drop-wise until a white precipitate appeared. The precipitate was collected using a Hirsch funnel. The supernatant was extracted with 3 portions of diethyl–ether (5 ml each) which was dried with $MgSO_4$ and evaporated on a rotary evaporator. The solids were combined and recrystallized from water. Yields are reported in Table 2.

LC/UV/MS

LC/MS analyses were performed on an Agilent LC/MSD SL (Agilent Technologies, Palo Alto, CA). The HPLC (1100), equipped with a quaternary pump (G1311A), an autosampler (G1313A), photodiode array detector (G1315B), degasser (G1379A), and column heater (G1316A), was controlled by Agilent software, HPCore Chemstation. The HPLC/UV method developed for the measurement of phenolic acids in foods has been described elsewhere.[12] Mobile phase consisted of solvent A = 0.1% formic acid in deionized water and solvent B = methanol. Linear gradient was 5–30% B in 50 min, and then hold at 30% for 15 min. The Luna C18-high purity silica column (150 × 4.6 mm, 5 µ) (Phenomenex, Torrance, CA) was set to a flowrate of 0.7 ml/min at 25°C. UV spectra were recorded at 270 and 325 nm.

NMR Spectroscopy

The ^{1}H and ^{13}C-NMR relaxation experiments were conducted on a Bruker QE Plus spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Proton spectra were typically acquired with a spectral width of 3100 Hz and 8192 data points. The ^{13}C NMR spectra were acquired using spectral widths of 7000 and 20 000 Hz with 16 384 data points. Chemical shift values were referenced to TMS and measured from the chemical shift of the residual solvent peak.

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