titrated mixtures with water and extraction with pentane, etc. In order to recover 2-pentanol and 2-hexanol, the organic extract was carefully boiled down under a Vigreaux column. Reaction products from long chain fatty acids were freed of the ester products prior to GLC analysis by passage through small columns of silica gel in hexane. The alcohol was obtained by elution with moist ether. Derivatization of the recovered alcohols with the isocyanate (using excess isocyanate to avoid fractionating enantiomers) was as previously described.[1] Analytical GLC data for the carbamates follows (T (°C), k' for R,S, k' for S,S): 3-methyl-2-butanol (185, 3.08, 3.15), 2-pentanol (175, 4.50, 4.65), 2-hexanol (185, 4.85, 5.10), 2-octanol (220, 3.58, 3.77), 2-decanol (240, 3.40, 3.20), 2-dodecanol (260, 3.23, 3.42), cyclohexylmethylcarbinol (220, 4.40, 4.60), phenylmethylcarbinol (220, 4.30, 4.50), 3-dodecyn-2-ol (260, 3.18, 3.32), 3-octanol (220, 2.42, 2.50), 4-methyl-2-pentanol (185, 3.48, 3.65), and 3-methyl-2-hexanol (185, 5.78, 5.91, 6.09, 6.22). Primary alcohols were oxidized to acids by using Jones Reagent;[14a] the acids were then converted to acid halides with $SOCl_2$/DMF in ether[14b] and then to amides with excess (S)-α-methylbenzylamine. Control experiments with chiral 1,2-isopropylideneglycerol indicated that no racemization occurred when using this sequence. Similarly α-branched primary carbinols suffer no loss of configurational integrity during Jones oxidation.[15] Analytical GLC data for the amides follows (T (°C), k' for R,R, k' for R,S): 2-methyl-1-decanoic acid (240, 3.36, 3.59), 2-methyl-1-dodecanoic acid (260, 3.32, 3.55), 2-phenylpropanoic acid (220, 3.14, 3.45), isopropylideneglyceric acid (210, 2.23, 2.04), and citronellic acid (225, [4.04, 4.12]). Order of elution for diastereomers for citronellic acid was not determined.

Examples of Resolutions of Several Methylcarbinols. The procedure employed was similar to that previously described for obtaining the enantiomers of 2-octanol.[1] The racemic alcohol (2.5 mmol), octanoic acid (8.0 mL, 50 mmol), and 3.0 g of Lipozyme were swirled in 20 mL of either pentane or hexane at 30 °C for a period of 3–5 weeks. The progress of the resolution was monitored by derivatizing samples of the mixture directly with (S)-α-methylbenzyl isocyanate followed by GLC analysis. The mixture was worked up by suction filtration; the resin was washed thoroughly with solvent and stored at 0–5 °C for future use. The combined organic phase was washed with 1.25 N NaOH and then with H_2O. After drying ($MgSO_4$), the solvent was removed by careful distillation, and the concentrate was fractionally distilled to obtain the S alcohol and (R)-octanoate ester. The ester was saponified by heating with 25 mL of 6 N KOH and 20 mL of methanol under reflux for 16 h. The resulting R alcohol was recovered from the saponification step in the usual manner and then distilled. In this way we obtained (S)-2-hexanol [0.90 g (34.6%), bp 55–60 °C (30 mm), 87.2% ee, $[\alpha]^{25}_D$ +8.69° (5.35, EtOH) [lit.[16] $[\alpha]^{20}_D$ +11.6°]], (R)-2-hexanol [1.11 g (47.7%), 83.2% ee, $[\alpha]^{25}_D$ −7.74° (c 5.55, EtOH)], (S)-2-decanol [2.10 g (52.5%), bp 112–115 °C (30 mm), 83.0% ee, $[\alpha]^{25}_D$ +4.22° (c 6.28, EtOH)], (R)-2-decanol [1.49 g (40.3%), 87.0% ee, $[\alpha]^{25}_D$ −5.37° (c 5.31, EtOH)]; (S)-4-methyl-2-pentanol [1.03 g (39.6%), bp 54–57 °C (30 mm), 47.2% ee, $[\alpha]^{25}_D$ +7.93° (c 5.49, EtOH) [lit.[16] $[\alpha]^{20}_D$ +20.54°]], (R)-4-methyl-2-pentanol [0.63 g (29.5%), 87.4% ee, $[\alpha]^{25}_D$ −16.47° (c 5.24, EtOH)], (S)-cyclohexylmethylcarbinol [1.35 g (42%), bp 100 °C (30 mm), 67% ee, $[\alpha]^{25}_D$ +3.59° (5.10, EtOH)], (R)-cyclohexylmethylcarbinol [1.18 g (37%), 86% ee, $[\alpha]^{25}_D$ −2.39° (c 5.53, EtOH)], (S)-phenylmethylcarbinol [0.31 g (10%), bp 99–100 °C (30 mm), 71% ee, $[\alpha]^{25}_D$ −16.6° (c 4.72, EtOH) [lit.[17] for R $[\alpha]^{20}_D$ +42.86°]], and (R)-phenylmethylcarbinol [0.34 g (11%), 87% ee, $[\alpha]^{25}_D$ +33.2° (c 4.67, EtOH)].[18]

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Synthesis and Reactions of *p*-Nitrophenyl 2,2-Diethoxypropionate and *p*-Nitrophenyl 2-Ethoxypropenoate[1]

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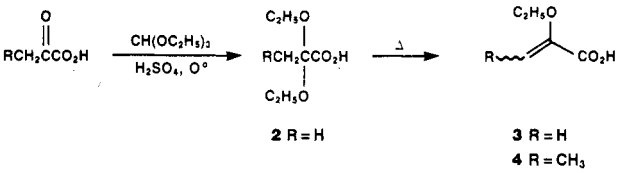
Previous reports from these laboratories have documented the versatility of *p*-nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP), a reagent useful for the synthesis of both heterocycles and highly functionalized small molecules.[2,3] As an extension of this work, it was decided to exploit the utility of *p*-nitrophenyl ester derivatives of pyruvic acid by investigating the reactivity of the nonhalogenated equivalent of NPBDP, *p*-nitrophenyl 2,2-diethoxypropionate (**1**). Surprisingly, 2,2-diethoxypropionic acid (**2**), the key intermediate for the preparation of **1**, has only been referred to once in the literature.[4] This previous synthesis involves hydrolysis of ethyl 2,2-diethoxypropionate with aqueous KOH followed by acidic workup. In our hands, this method proved to be somewhat capricious and gave variable yields. An alternate route to **2** involving ketalization of pyruvic acid with triethyl orthoformate was found to be superior.

Regardless of the method of synthesis, subsequent purification of **2** by distillation surprisingly resulted in the conversion of this material to 2-ethoxypropenoic acid (**3**) in moderate yield. Furthermore, this sequence appears to be somewhat general since application to 2-ketobutyric acid gave 2-ethoxy-2-butenoic acid (**4**) as a mixture of E and Z isomers in 55% overall yield. It should be noted



2 R = H
3 R = H
4 R = CH_3

that the diethyl ketals undergo elimination more readily than the dimethyl ketals (presumably due to higher boiling points), and thus the former are the preferred substrates. This synthesis of 2-ethoxypropenoic acids is exceedingly simple to execute and should prove to be the method of choice for preparing these intermediates.

Although **2** cannot be readily purified by distillation, it can be used successfully in crude form. Thus, reaction of **2** with *p*-nitrophenyl trifluoroacetate using previously described conditions[3] afforded *p*-nitrophenyl 2,2-diethoxypropionate (**1**) without difficulty. As expected, reactions of **1** with nucleophiles such as ammonia, the sodium salt of ethyl acetoacetate, and lithioacetonitrile proceeded smoothly to afford the corresponding adducts **5–7**. It should be noted that the previous synthesis of **5** from the reaction of ethyl 2,2-diethoxypropionate with ammonia employed high temperature in a sealed vessel.[3] The present method is clearly easier.

While it was gratifying that **1** behaved as expected, we were intrigued by the potential utility of the *p*-nitrophenyl ester derivative of 2-ethoxypropenoic acid (**3**). Such a reagent offers two potential modes of nucleophilic addition, i.e., 1,4 vs. 1,2. Thus, **3** was converted into *p*-nitrophenyl 2-ethoxypropenoate (**8**), a crystalline solid, in 82% yield.

(1) Presented in part at the 16th Northeast Regional Meeting of the American Chemical Society, SUNY Binghamton, Binghamton, June 1986.
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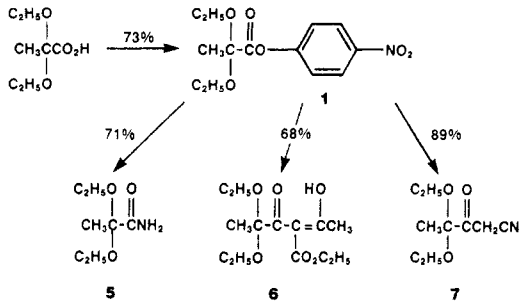
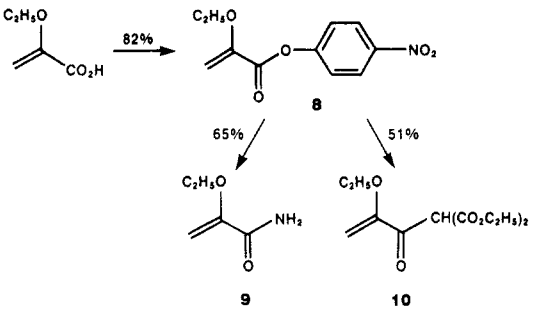
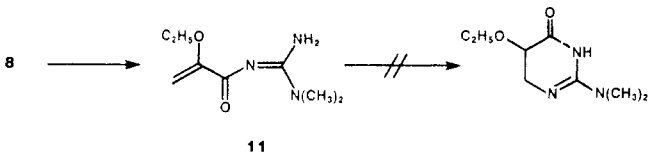


Initial reactions of 8 with ammonia (to yield 9) and the sodium salt of diethyl malonate (to yield 10) indicated that 1,2-addition of nucleophiles occurs exclusively in this system.



While 8 behaves like NPBDP in that intermolecular reactions occur exclusively in a 1,2-fashion, it was quite surprising to find that reaction of 8 with bifunctional nucleophiles such as *N,N*-dimethylguanidine gave the 1,2-adduct 11 *without* concomitant intramolecular cyclization. (In contrast, the reaction of NPBDP with guanidines does yield the 4-pyrimidones via intramolecular cyclization of the initial adduct.[5])



In summary, *p*-nitrophenyl esters of pyruvic acid derivatives are stable compounds which react well with nucleophiles to afford highly functionalized small molecules. Further work is underway exploring the potential of these compounds, particularly 8, in other reactions such as Diels–Alder cycloadditions. In addition, a novel synthesis of 2-ethoxypropenoic acids has been described which should facilitate the availability of these compounds.

Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 spectrometer unless otherwise noted. Chemical shifts from tetramethylsilane are reported on the δ scale. High-resolution mass spectra were recorded on an AEI MS30 spectrometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvents and reagents were commercially available and, unless otherwise noted, were used directly.

2,2-Diethoxypropionic Acid (2). A mixture of 14 mL (0.20 mol) of pyruvic acid and 80 mL of triethylorthoformate was stirred at 10 °C (ice bath), and 1 mL of concentrated sulfuric acid was added. The mixture was stirred at 5–10 °C for 0.5 h and then diluted with 200 mL of methylene chloride. The organic solution was washed successively with water (2 × 100 mL) and saturated sodium chloride solution (1 × 100 mL) and then dried over anhydrous sodium sulfate. The mixture was filtered and then concentrated leaving a quantitative yield of 2,2-diethoxypropionic acid (2) as an oil. This material could be used without further purification: NMR ($CDCl_3$) 9.83(s, 1 H), 3.57 (q, 4 H), 1.61 (s, 3 H), 1.30 (t, 3 H).

2-Ethoxypropenoic Acid (3). 2,2-Diethoxypropionic acid (2) (32 g, 0.2 mol) was distilled under reduced pressure. The material that distilled below 100 °C (1.5 mmHg) was set aside. The material that distilled above 100 °C (1.5 mmHg) was collected, and this solidified on standing. The crystalline solid was triturated with pentane, filtered, and dried in vacuo to afford 7 g of 2-ethoxypropenoic acid (3). The pentane filtrate was concentrated, then combined with the <100 °C distillate and redistilled at 1.5 mmHg. Following the procedure described above, another 2.4 g of product was obtained, thereby bringing the total yield to 9.4 g (40%) of 3 as a white crystalline solid, mp 54–57 °C (lit.[6] mp 57–58 °C).

(*E*)- and (*Z*)-2-Ethoxy-2-butenoic Acids (4). A mixture of 10.2 g (0.10 mol) of 2-ketobutyric acid and 50 mL of triethyl orthoformate was stirred at 5 °C, and 1 mL of concentrated sulfuric acid was added. The mixture was stirred at 5 °C for 0.5 h and then diluted with 100 mL of ether. The organic portion was separated and then washed successively with water (2 × 50 mL) and saturated sodium chloride solution (1 × 50 mL). The organic solution was dried over anhydrous sodium sulfate and evaporated, leaving an oil. This was distilled under reduced pressure. The material that distilled below 80 °C (1 mmHg) was set aside. The material that distilled above 80 °C amounted to 6.1 g of a clear liquid. Redistillation of the first fraction afforded another 1.1 g of this liquid, bringing the total of 7.2 g (55%) of 2-ethoxy-2-butenoic acid as a 2:1 mixture of *E*/*Z* isomers as determined by 300-MHz NMR[7] ($CDCl_3$): 6.43 (q, 1 H, CH, *E* isomer), 5.42 (q, 1 H, CH, *Z* isomer), 3.80 (q, 2 H, CH_2O, *E* isomer), 3.67 (q, 2 H, CH_2O, *Z* isomer), 1.93 (d, 3 H, CH_3, *Z* isomer), 1.73 (d, 3 H, CH_3, *E* isomer), 1.26 (t, 3 H, CH_3, *Z* isomer), 1.22 (t, 3 H, CH_3, *E* isomer); HRMS, obsd M^+ *m*/*z* 130.0630, $C_6H_{10}O_3$ calcd 130.0630.

***p*-Nitrophenyl 2,2-Diethoxypropionate (1).** A mixture of 4.9 g (30 mmol) of 2,2-diethoxypropanoic acid (2), 7.0 g (30 mmol) of *p*-nitrophenyl trifluoroacetate, and 20 mL of pyridine was stirred at room temperature for 16 h. The mixture was diluted with 100 mL of water and then extracted with ether (4 × 50 mL). The combined ether extracts were washed with 5% aqueous sodium hydroxide (4 × 15 mL), then dried over anhydrous sodium sulfate, filtered, and thoroughly evaporated leaving an oil. This was taken up into hot low-boiling petroleum ether and then cooled in a dry ice/acetone bath to afford 6.2 g (73%) of a white solid, mp 34–35 °C: NMR ($CDCl_3$) 8.20 (d, 2 H), 7.23 (d, 2 H), 3.8–3.3 (m, 4 H), 1.68 (s, 3 H), 1.24 (t, 6 H).

Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found: C, 54.90; H, 5.88; N, 4.92.

2,2-Diethoxypropionamide (5). A solution of 4.25 g (15 mmol) of 1 in 80 mL of dry tetrahydrofuran was stirred at room temperature, and gaseous ammonia was bubbled into the mixture for 1 h. The yellow mixture was concentrated, and the residue was taken up into 80 mL of ethyl acetate. This solution was washed with 5% aqueous sodium hydroxide (4 × 30 mL), then dried over anhydrous sodium sulfate, filtered, and evaporated leaving a white solid. Recrystallization from low-boiling petroleum ether afforded 1.72 g (71%) of 5 as a white crystalline solid, mp 70–71 °C (lit.[3] mp 65–66 °C).

Anal. Calcd for $C_7H_{15}NO_3$: C, 52.15; H, 9.38; N, 8.69. Found: C, 51.93; H, 9.50; N, 8.58.

3-Carbethoxy-5,5-diethoxyhexane-2,4-dione (6). A slurry of 0.80 g (33 mmol) of sodium hydride in 60 mL of dry tetrahydrofuran was stirred at room temperature under nitrogen, and 4.36 g (33 mmol) of ethyl acetoacetate in 10 mL of dry tetrahydrofuran was added dropwise over 10 min. After addition was complete, the solution was stirred at room temperature for 15 min, and then a solution of 4.25 g (15 mmol) of 1 in 30 mL of dry tetrahydrofuran was added dropwise over 15 min. After addition was complete, the mixture was stirred at room temperature for 4 h, then poured carefully into 200 mL of ice–water, and brought to pH 7 with 2 N hydrochloric acid. The aqueous mixture was

(5) Manuscript in preparation.

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(7) Recorded on a Varian XL300 spectrometer.

extracted with chloroform (4 × 50 mL). The combined extracts were dried over sodium sulfate, filtered and then evaporated leaving an oil. The oil was chromatographed over 200 g of silica gel by using 9:1 hexane/ethyl acetate as eluent to give 2.78 g (68%) of **6** as a colorless oil; the NMR spectrum of this material shows it to be a mixture of its keto–enol forms: IR (neat) 1750 (CO_2-C_2H_5), 1720 and 1705 cm−1 (C=O).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; O, 35.00. Found: C, 56.55; H, 8.12.

4,4-Diethoxy-3-oxovaleronitrile (7). Dry tetrahydrofuran (20 mL) was placed in a three-necked 250-mL round-bottomed flask fitted with an addition funnel, thermometer, and septum. The flask was cooled to −70 °C under nitrogen, and 18.8 mL (30 mmol) of 1.6 M *n*-butyllithium was added over 5 min. To this mixture was added dropwise over 15 min a solution of 1.23 g (30 mmol) of acetonitrile in 20 mL of dry tetrahydrofuran. After addition was complete, the mixture was stirred at −70 °C for 1 h, and then a solution of 4.25 g (15 mmol) of **1** in 20 mL of dry tetrahydrofuran was added dropwise over 15 min. After addition was complete, the mixture was stirred at −70 °C for 0.5 h and then allowed to warm to room temperature. The mixture was treated with 40 mL of 1 N hydrochloric acid, and then the organic layer was separated. The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated, leaving an oil. This was chromatographed over 150 g of silica gel by using 1.6:0.3:0.1 of chloroform/cyclohexane/ethyl acetate to afford 2.48 g (89%) of **7** as an oil: NMR ($CDCl_3$) 3.80 (s, 2 H), 3.51 (q, 4 H), 1.47 (s, 3 H), 1.23 (t, 6 H); IR (neat) 2260 (CN), 1745 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 57.90; H, 8.01; N, 7.21.

***p*-Nitrophenyl 2-Ethoxypropenoate (8).** A mixture of 7.0 g (60 mmol) of 2-ethoxypropenoic acid (**3**), 14.1 g (60 mmol) of *p*-nitrophenyl trifluoroacetate, and 40 mL of pyridine was stirred at room temperature for 24 h. The mixture was poured into 200 mL of water and extracted with ether (5 × 50 mL). The combined extracts were washed with 5% aqueous sodium hydroxide (5 × 25 mL), then dried (Na_2SO_4), filtered, and thoroughly evaporated, leaving a solid. Recrystallization from cyclohexane afforded 11.6 g (82%) of **8** as a white crystalline solid, mp 91–92 °C; NMR ($CDCl_3$) 8.30 (d, 2 H), 7.34 (d, 2 H), 5.52 (d, 1 H), 4.81 (d, 1 H), 3.91 (q, 2 H), 1.42 (t, 3 H).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: 55.57, H, 4.71; N, 6.04.

2-Ethoxy-2-propenamide (9). A solution of 3.56 g (15 mmol) of **8** in 80 mL of tetrahydrofuran was stirred at room temperature, and gaseous ammonia was bubbled into the mixture for 0.5 h. The mixture was concentrated, and the residue was taken up into 80 mL of ethyl acetate. The organic solution was washed with 5% aqueous sodium hydroxide (4 × 30 mL), then dried (Na_2SO_4), filtered, and evaporated, leaving a white solid. Recrystallization from isopropyl ether afforded 1.12 g (65%) of **9** as a white crystalline solid, mp 68–69 °C; NMR ($CDCl_3$) 6.60 (br, 2 H), 5.33 (d, 1 H), 4.46 (d, 1 H), 3.84 (q, 2 H), 1.34 (t, 3 H).

Anal. Calcd for $C_5H_9NO_2$: C, 52.15; H, 7.88; N, 12.16. Found: C, 52.61; H, 7.42; N, 12.01.

Ethyl 2-Carbethoxy-4-ethoxy-3-oxo-4-pentenoate (10). A slurry of 0.80 g (33 mmol) of sodium hydride in 60 mL of dry tetrahydrofuran was stirred at room temperature under nitrogen and 5.30 g (33 mmol) of diethyl malonate in 20 mL of dry tetrahydrofuran was added dropwise over 10 min. After addition was complete, the mixture was stirred at room temperature for 15 min, and then a solution of 3.56 g (15 mmol) of **8** in 30 mL of dry tetrahydrofuran was added dropwise over 15 min. After addition was complete, the mixture was stirred at room temperature for 4 h, then poured carefully into 200 mL of ice–water, and brought to pH 7 with 2 N hydrochloric acid. The aqueous mixture was extracted with chloroform (4 × 50 mL), and the combined extracts were dried over anhydrous sodium sulfate, filtered, and then evaporated, leaving an oil. This was chromatographed over 250 g of silica gel by using 19:1 hexane/ethyl acetate as eluent to give 1.98 g (51%) of **10** as an oil: NMR ($CDCl_3$) 5.28 (d, 1 H), 4.87 (s, 1 H), 4.40 (d, 1 H), 4.3–3.8 (m, 6 H), 1.26 (overlapping 9 H).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03; O, 37.17. Found: C, 55.39; H.7.16

***N*,*N*-Dimethyl-*N*'-(2-ethoxypropenoyl)guanidine (11).** Sodium methoxide (1.12 g, 20.7 mmol) was added to 40 mL of *N*,*N*-dimethylformamide, and to this was added 3.84 g (20.7 mmol) of *N*,*N*-dimethylguanidinium sulfate. This mixture was warmed to 60 °C until a consistent slurry resulted, at which point 4.00 g (16.9 mmol) of **8** was added. The new yellow slurry was stirred at 80 °C for 1.5 h, then cooled, and filtered. Concentration of the filtrate afforded an oil, which was chromatographed over silica gel using 20:1 chloroform/methanol as eluent to give 1.70 g (54%) of **11** as a pale yellow solid, mp 148–150 °C: NMR ($CDCl_3$) 7.60 (br, 2 H), 5.48 (d, 1 H), 4.41 (d, 1 H), 3.82 (q, 2 H), 3.07 (s, 6 H), 1.37 (t, 3 H). HRMS, obsd M$^+$ *m*/*z* 185.1174, $C_8H_{15}N_3O_2$ calcd 185.1164.

Registry No. **1**, 108818-40-2; **2**, 25741-02-0; **3**, 32821-76-4; (*E*)-**4**, 108818-41-3; (*Z*)-**4**, 108818-47-9; **5**, 92845-55-1; **6**, 108818-42-4; **7**, 108818-43-5; **8**, 108818-44-6; **9**, 34068-59-2; **10**, 108818-45-7; **11**, 108818-46-8; pyruvic acid, 127-17-3; 2-oxobutanoic acid, 600-18-0.

Use of Tritium and Deuterium in Assigning Proton NMR Spectra: Reinvestigation of the Configuration of 5-Phenylpenta-2,4-dienoic Acid (mp 165 °C)

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Contradictory reports[1-3] concerning the configuration of the 5-phenylpenta-2,4-dienoic acid stereoisomer (Figure 1A) melting at 164–165 °C led us to make a thorough investigation of the NMR characteristics of this compound. Although this isomer has long been thought to have the 2*E*,4*E* configuration,[3] a recent NMR study has suggested that it is the 2*E*,4*Z* form.[1]

As it is known that the configuration of dienoic acids significantly affects their physiological properties, it is important to be certain of the stereochemistry of a particular isomer. There are four stereoisomers of 5-phenylpenta-2,4-dienoic acid, and since 1877 several methods[3-8] have been used to produce the isomer with melting point 164–165 °C. The physiological activity of several of the stereoisomers of the dienoic acid and their esters have been studied,[2,9] and a number of the esters were found to have bactericidal and fungicidal properties.

We have employed a combination of synthetic and analytical methods to extract the NMR data for the isomer of 5-phenylpenta-2,4-dienoic acid with melting point 164–165 °C. This multifaceted approach is an illustration of some generally applicable techniques, which we think may be useful in the elucidation of spectral assignments of peptides and other biomolecules.

The 300-MHz ^{1}H NMR spectrum of 5-phenylpenta-2,4-dienoic acid (mp 164–165 °C) is shown in Figure 1B.

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