Synthesis of ^{13}C Labelled Unsymmetrically Substituted Maleic Anhydrides

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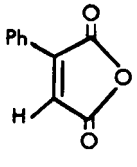
Summary: Methylmaleic (citraconic) and ethoxymaleic anhydrides labelled with ^{13}C at C-4, and phenylmaleic anhydride labelled at C-1 were prepared in excellent yields from inexpensive starting materials. The methodology described here can be applied in a synthesis of a variety of substituted maleic anhydrides.

We wish to report highly efficient syntheses of Carbon-13 labelled maleic anhydrides. Two different routes were developed to introduce ^{13}C into the desired position in the unsymmetrically substituted anhydride rings.



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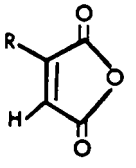

2 R=CH_3

3 R=EtO

2-Phenylmaleic anhydride 1 labelled at C-1 was prepared as shown in scheme 1. 2-Methylmaleic anhydride 2 and 2-ethoxymaleic anhydride 3 marked

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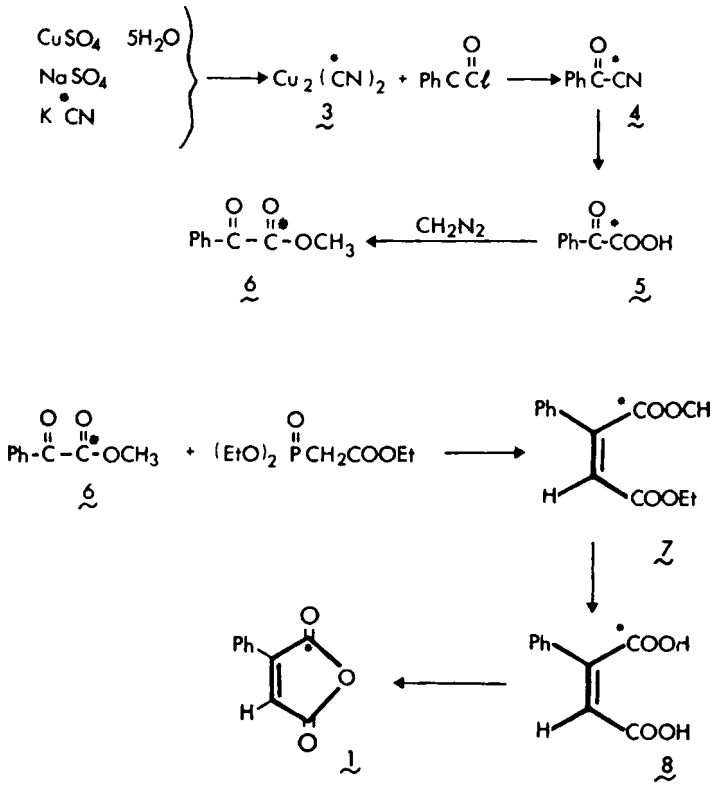
at C-4 were synthesized according to scheme 2.

SCHEME 1

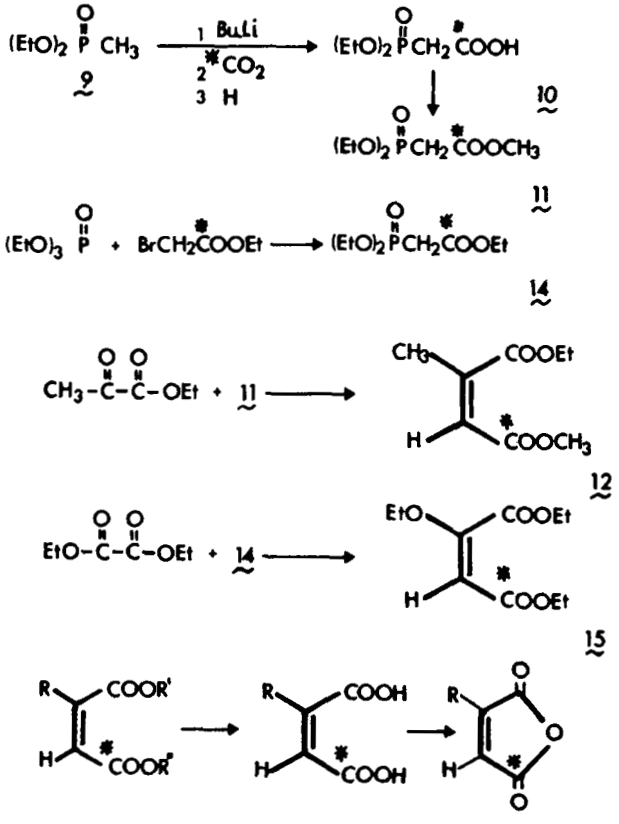


These sequences provide simple routes to regioselectively labelled anhydrides from readily available and inexpensive starting materials.

The simplest and most successful method for the preparation of benzoyl cyanide involves the reaction of benzoyl chloride with cuprous cyanide.

$K^{13}CN$ was converted quantitatively to cuprous cyanide-^{13}C 3 according to the procedure described by Reid and Weaver (1). The reaction of dry cuprous cyanide - ^{13}C with freshly distilled benzoyl chloride for 1.5 hours at 220-230° gave benzoyl cyanide-1-^{13}C 4 which was subsequently hydrolized and methylated with diazomethane to methyl phenylglyoxylate-1-^{13}C 6 without isolation of the intermediate benzoylformic acid 5. after the four steps described above, the yield of 6, based on $K^{13}CN$, was 70%.

SCHEME 2



12 R=CH_3 R'=Et R''=CH_3 13 R=CH_3 2 R=CH_3
15 R=EtO R'=R''=Et 16 R=EtO 3 R=EtO

The condensation of 6 with triethylphosphonoacetate produced only cis 4-ethyl-1-methyl-2-phenylmaleate-1-^{13}C 7, which was converted to 2-phenylmaleic anhydride-1-^{13}C in better than 80% yield.

In order to introduce carbon-13 into the opposite C-4 carbonyl group of the maleic anhydride ring, use was made of ^{13}C labelled Wadworth-Emmons reagent. The labelled reagent was prepared by condensation of triethylphosphite with ethyl bromoacetate-1-^{13}C in 95% isolated yield. In the alternate synthesis of the labelled reagent, $Ba^{13}CO_3$ was a source of ^{13}C.

The reaction of diethyl methyl phosphonate anion with $^{13}CO_2$ generated from $Ba^{13}CO_3$ gave carboxymethanephosphonate 10 which was treated with diazomethane without purification. The yields of isolated diethyl methylphosphonate-1-^{13}C 11 varied from 31% to 47%. Clearly, the latter preparation is considerably less efficient, however in view of the moderate price of $Ba^{13}CO_3$, may be preferred to the former method.

The condensation step between ^{13}C labelled Wadsworth-Emmons reagent and ethyl pyruvate gave a respectable 70% yield of the isolated product 12. The reaction with diethyloxalate was less successful as only 48% yield of the maleic ester 15 could be obtained. Unfortunately, attempts to improve that yield have thus far not been successful. The subsequent steps, the hydrolysis of diesters and dehydration of diacids, gave in both cases excellent results.

Labelled organic compounds are always synthesized for the specific purpose. However, the fundamental approach described in this paper can serve as a general and versatile method for the preparation of substituted maleic anhydrides.

Experimental

Synthesis of phenylmaleic anhydride-1-^{13}C.

Cuprous cyanide-1-^{13}C 3 was prepared according to the method of Reid and Weaver (2). A 250 ml flask was fitted with a two-hole rubber stopper, an addition funnel and a gas outlet tube connected to a trap filled with an alkaline permanganate solution to trap any cyanogen formed. The solution of cupric sulfate pentahydrate (5.0 g), in water (50 ml) containing 0.50 ml of 12 N sulfuric acid was placed in reaction flask. In a separate flask, sodium sulfite heptahydrate (5.20 g) in water (80 ml), containing a few drops of phenolphthalein, was treated with 0.5 N sodium hydroxide solution until pink colour developed. At this point potassium cyanide-^{13}C (1.00 g) was added followed by a few drops of 12 N sulfuric acid until the disappearence of the colour. The colourless solution was added immediately dropwise through an addition funnel to the well stirred solution of cupric

sulfate. A white flaky product precipitated instantaneously. After 15 min., a current of air was drawn through the apparatus to sweep any gaseous products into the absorbent solution. The product was filtered on a sinter glass funnel, washed with water (2 x 10 ml), ethanol 95 % (2 x 10 ml), absolute ethanol (2 x 10 ml) and ether 2 x 10 ml). During the washing, a thin film of solvent was left over the product in order to avoid any contact between the wet crystals and air. The white product was dried under vacuum til constant weight, to yield cuprous cyanide-^{13}C (1.50 g, 100 %).

Benzoyl cyanide-1-^{13}C 4 was prepared by the method of Oakwood and Weisgerber (3). Cuprous cyanide (1.50 g), dried under reduced pressure at 110^{o}C for 3 hrs, and freshly distilled benzoyl chloride (2.33 g) were placed in a 25 ml flask fitted with a condenser. The flask was shaken to moisten almost all the cuprous cyanide and was placed in an oil bath which was preheated to 145 - 150^{o}C. The reaction mixture was stirred and the temperature of the bath was raised to 220 - 230^{o}C and maintained between these limits for 1.5 hrs. Then the flask was cooled and the reaction mixture was extracted with ether (6 x 15 ml). The ether was evaporated to leave crude benzoyl cyanide-1-^{13}C (2.30 g, 100 %).

IR (thin film): ν max = 3080, 2140, and 1680 cm^{-1}.

Methyl phenylglyoxylate-1-^{13}C 6 was prepared as described by Oakwood and Weisgerber (4). In a 50 ml flask were placed crude benzoyl cyanide-1-^{13}C (2.00 g, 15.1 mmole) and concentrated hydrochloric acid (sp. gr. 1.19, 23 ml). The mixture was slowly stirred at room temperature for 5 days. The resulting clear yellow solution was poured into 90 ml of ice cold water and extracted exhaustively with ether (1 x 50 ml and 5 x 20 ml). The ether extracts were combined, cooled in an ice bath, and an excess of etheral solution of diazomethane was added. After an additional hour at 0^{o}C, the ether was evaporated to leave a pale yellow oil. Chromatography with petroleum ether (30 - 60^{o}) / ether (100 : 0 to 90 : 10) gave methyl phenylglyoxalate-1-^{13}C, 6 (1.74 g, 70 %), eluted first, as a pale yellow oil.

IR (thin film): ν max = 3070, 2960, 1740, and 1690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.92 (d, J_{H*C} = 4 Hz, 3H, $^*COOCH_3$), 7.22 - 7.65 (m, 3H), 7.87 - 8.13 (m, 2H).

4-Ethyl-1-methyl-2-phenylmaleate-1-^{13}C 7 was synthesized by the modified procedure of Moppett and Sutherland (5). Triethyl-phosphonoacetate (0.54 g, 2.4 mmole) was dissolved in THF (7.0 ml) and cooled to 0^oC under nitrogen. A slurry of sodium hydride (58 mg, 3.0 mmole, made from 97 mg of NaH 60 % in mineral oil, (washed with 3 x 1.0 ml of dry THF) in dry THF (5 ml), was added dropwise with stirring. After the addition of NaH, the reaction mixture was stirred at room temperature until gas evolution had ceased (about 30 min). To the yellow, precipitate-free solution, was added dropwise a solution of methyl phenyl-glyoxylate-1-^{13}C (0.40 g, 2.4 mmole) in dry THF (5 ml). A yellow-orange gelantinous precipitate was formed instantaneously, and the reaction was heated at 50^oC for 1 hour. After cooling, the reaction mixture was diluted with water (5 ml) and extracted with ether (1 x 50 ml and 5 x 15 ml). The ether extracts were combined, dried over anhydrous $MgSO_4$ and evaporated to leave a pale yellow oil. Chromatography with petroleum ether (30 - 60^o / ether (100 : 0 to 75 : 25), gave the pure 4-ethyl-1-methyl-2-phenylmaleate-1-^{13}C (0.50 g, 88 %), eluted third, as a colourless oil.

IR (thin film): ν max = 1717, 1696 and 1622 cm^{-1}

^1H NMR ($CDCl_3$): δ = 1.25 (t, J = 7 Hz, 3H, OCH_2CH_3), 3.90 (d, J_{H*C} = 4 Hz, 3H, $COOCH_3$), 4.20 (q, J = 7 Hz, 2H, OCH_2CH_3), 6.31 (d, J_{H*C} = 12 Hz, 1H, :CH), 7.20 - 7.65 (m, 5H, Ar H).

Phenylmaleic acid-1-^{13}C 8. A solution of 4-ethyl-1-methyl-2-phenylmaleate -1-^{13}C, 7 (300 mg, 1.28 mmole), 4.0 M sodium hydroxide (2.0 ml, 8.0 mmole) and absolute ethanol (4.0 ml) was stirred for 24 hrs at room temperature, in a tightly stoppered 25 ml flask. The reaction mixture was evaporated to dryness under reduced pressure at room temperature. The residue was acidified with 6.0 N HCl until pH of 0 - 0.60 was obtained, (approximately 5 ml). The pale yellow precipitate formed was extracted with ether (2 x 15 ml). The aqueous layer was evaporated to dryness and extracted with ether

(2 x 15 ml). The combined ether extracts were dried and the ether was evaporated to give 2-phenylmaleic acid-1-^{13}C, 8 (0.23 g, 92%) as pale yellow needles.

^{1}H NMR (acetone-d): δ = 6.33 (d, J_{H*C}= 12 Hz, 1H, :CH), 7.28 - 7.72 (m, 5H, Ar H), 10.00 (br.s, 2H, COOH).

2-Phenylmaleic anhydride-1-^{13}C 1. A solution of 2-phenylmaleic acid-1-^{13}C, 8 (210 mg, 1.09 mmole) in acetic anhydride (2.00 g, 18.8 mmole) was refluxed for 1 hour. The reaction mixture was cooled and evaporated to dryness. The brown residue was sublimed to give the pure phenylmaleic anhydride-1-^{13}C, 1 (190 mg, 100 %) as pale yellow needles, m.p. 113 - 115^{o}C.

IR ($CHCl_3$): ν max = 1830, 1770, 1740 and 1615 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.97 (d, J_{H*C} = 13 Hz, 1H, :CH), 7.35 - 7.65 (m, 3H, m,p-Ar H), 7.85 - 8.11 (m, 2H, o-Ar H).

Synthesis of 2-methylmaleic anhydride-4-^{13}C 2

Diethyl methyl phosphonate 9 was synthesized according to the literature procedure (6). A solution of triethyl phosphite (25.0 g, 0.150 mole) and iodomethane (25.0 g, 0.176 mole) was refluxed for 4 hrs. Fractional distillation gave the pure diethyl methyl phosphonate (21.2 g, 93 %) as a colourless oil b.p. 190 - 194^{o}C / 760 torr, (lit.(7), 194^{o}C).

Diethyl carboxymethanephosphonate-1-^{13}C 10 was prepared by the modified method of Coutrot et al. (8). In a 500 ml cyclindrical tube (30 cm x 5 cm in dimensions), a solution of diethyl methyl-phosphonate (5.00 g, 32.9 mmole) in dry THF (20 ml), under nitrogen was cooled to - 65^{o}C, and treated dropwise with a solution of n-butyllithium 1.6 M in hexane (20.5 ml, 32.8 mmole). A white translucent solution was formed immediately. After 10 min of stirring, carbon dioxide-^{13}C generated at - 30^{o}C from barium carbonate-^{13}C (5,00 g, 25.2 mmole)[1] was carried with a slow stream of N_2 through a sinter glass tube under the surface of the solution maintained at - 65^{o}C. A white thick gelatinous product was formed slowly. The reaction mixture was stirred for additional 2 hrs at - 65^{o}C and then allowed to warm to room temperature. Water (10 ml) and conc HCl (3.35 g, 33 mmole) were added.

Extraction, with CH_3Cl (5 x 25 ml) gave 4.50 g of a thick oil. Unreacted

1. Carbon dioxide-^{13}C was generated at -30°C from $Ba^{13}CO_3$ by the dropwise addition of conc. H_2SO_4 through an addition funnel with pressure equalizing side arm.

diethyl methylphosphate was removed by distillation under reduced pressure at 80°C / 1 torr, leaving a residue of essentially pure diethyl carboxymethane-phosphonate-1-^{13}C (2.20 g, 31 %).

^1H NMR ($CDCl_3$): δ = 1.35 (t, J = 7 Hz, 6H, 2 x OCH_2CH_3), 3.00 (dd, J_{HP} = 22 Hz and $J_{GEM\cdot H*C}$ = 7 Hz, 2H, P-CH_2-*CO-), 3.90 - 4.45 (dq, J = 7 Hz, 4H, 2 x OCH_2CH_3), 11.22 (br.s, 1H, *COOH).

Diethyl methyl phosphonoacetate-1-^{13}C 11. An excess of etheral solution of diazomethane was added to a solution of diethyl carboxymethanephosphonate (2.02 g, 10.2 mmole) in ether (10 ml). After an additional hour at 0°C, the ether was evaporated to give an oily residue of diethyl methyl-phosphonoacetate (2.10 g, 97 %).

IR (thin film): ν max - 2985, 2935, 2915, 1690 and 1260 cm^{-1}

^1H NMR ($CDCl_3$): δ = 1.35 (t, J = 7 Hz, 6H, 2 x OCH_2CH_3), 2.96 (dd, J_{HP} = 22 Hz and J_{GEM*C} = 8 Hz, 2H, P-CH_2-*CO-), 3.72 (d, J_{H*C} = 4 Hz, 3H, *$COOCH_3$), 3.85 - 4.45 (d q, J = 7 Hz, 4H, 2 x OCH_2CH_3).

1-Ethyl-4-methyl-2-methylmaleate-4-^{13}C 12 was prepared according to the modified procedure of Moppett and Sutherland (5). Diethyl methyl phosphonoacetate-1-^{13}C (1.00 g, 4.74 mmole) was dissolved in THF (10 ml) and cooled to 0°C under nitrogen. A slurry of NaH (0.11 g, 4.7 mmole) in THF (5 ml) was added dropwise with stirring. The resulting solution was stirred at room temperature until gas evolution had ceased, approximately 30 min. A solution of ethyl pyruvate (0.55 g, 4.7 mmole) in THF (5 ml) was added dropwise to the reaction mixture. A gummy precipitate formed instantaneously. The reaction was heated to 50°C for 1 hr, cooled, and then diluted with water (10 ml). Extraction with ether (1 x 50 ml and 4 x 25 ml portions) and evaporation of the solvent left a pale yellow oil.

Chromatography with petroleum ether (30 - 60°) / ether (100 : 0 to 25 : 75) gave the pure 1-ethyl-4-methyl-2-methylmaleate-4-^{13}C, 12 (0.57 g, 70 %), eluted second, as a colourless oil.

IR (thin film): ν max - 1735, 1685 and 1655 cm^{-1}

^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.02 (d, J = 2 Hz, 3H, $:CCH_3$), 3.68 (d, $J_{H}{}^{*}{}_{C}$ = 4 Hz, 3H, $^{*}COOCH_3$), 4.23 (q, J - 7 Hz, 2H, OCH_2CH_3), 5.85 (m, 1H, :CH).

2-Methylmaleic acid-4-^{13}C 13. A solution of 1-ethyl-4-methyl-2-methylmaleate-4-^{13}C 12. (210 mg, 1.21 mmole), sodium hydroxide 4.0 M (1.0 ml, 4 mmole) and absolute ethanol (2,0 ml) was stirred for 12 hrs at room temperature, in a 25 ml stoppered flask. The reaction mixture was evaporated to dryness under reduced pressure at room temperature. The residue was acidified with 6.0 M HCl until a pH of 0 - 0.6 was obtained (0.8 ml). The resulting solution was evaporated to dryness under reduced pressure at room temperature. The white residue was extracted with ether (4 x 20 ml). The ether extracts were combined, dried, and the ether was evaporated to leave a brownish solid (0.17 g). H NMR analysis showed that 2-methylmaleic acid-4-^{13}C, 13.

^{1}H NMR (acetone-d_6): δ = 2.10 (d, J = 2 Hz, 3H, $:CCH_3$), 6.00 (m, 1H, :CH), 9.32 (br. s, 2H, COOH).

2-Methylmaleic anhydride-4-^{13}C 2. A solution of crude 2-methymaleic-4-^{13}C acid 13 (0.016 g, 1.2 mmole) in acetic anhydride (2.00 g, 18.8 mmole) was refluxed for 2 hrs. The reaction was cooled to room temperature and evaporated under reduced pressure until a weight of 0.16 g was reached. The brownish oil was transferred into a short path distillation apparatus and distilled under reduced pressure to yield pure 2-methylmaleic anhydride-4-^{13}C (90 mg, 64 %) as a pale yellow oil, b.p. 60 - 62°C / 0.025 torr.

IR (thin film): ν max = 1825, 1740 and 1650 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.22 (d, J = 2 Hz, 3H, $:CCH_3$), 6.67 (d q, $J_{GEM\ H^{*}C}$ = 8 Hz, and J = 2 Hz, 1H, $:CH^{*}COO-$).

Synthesis of 2-ethoxymaleic anhydride-4-^{13}C 3

Triethyl phosphonacetate-1-^{13}C 14 was prepared by the modified method of Wolinsky and Erickson (9). A solution of triethyl phosphite (1.00 g, 6.02 mmole) and ethyl bromoacetate-1-^{13}C (1.00 g, 5.95 mmole) was heated to 170^{o}C for 9 hrs, in a 25 ml flask equipped with a condenser through which steam was circulated to allow selective evaporation of bromo ethane. The reaction was cooled and distilled under reduced pressure to yield triethyl phosphonoacetate-1-^{13}C (1.27 g, 95%), as a colourless oil, b.p. 107 - 108^{o}C / 0.80 torr.

IR (thin film): ν max = 1690 and 1260 cm^{-1}

H NMR ($CDCl_3$): δ 1.18 - 1.47 (t t, J = 7 Hz, 9H, 3 x OCH_2CH_3), 2.98 (dd, J_{HP} = 22 Hz and $J_{GEM.H^*C}$ = 8 Hz, 2H, P-CH_{2^*}CO-), 3.90 - 4.40 (t q, J = 7 Hz, 6H, 3 x OCH_2CH_3).

Diethyl-2-ethoxymaleic-4-^{13}C 15 was prepared following the method of Grell and Hans (10). Triethyl phosphonoacetate-1-^{13}C (0.70 g, 3, mmole) was placed in THF (7.0 ml) and cooled to 0^{o}C under nitrogen. A slurry of sodium hydride (75 mg, 3.1 mmole) in THF (5 ml), was added dropwise with stirring. The solution was stirred at room temperature until gas evolution had ceased (about 30 min.) At this point diethyl oxalate (0.45 g, 3.1 mmole) was added and the reaction mixture was refluxed for 12 hours. After cooling, the reaction mixture was diluted with water (5 ml) and extracted with ether (1 x 20 ml and 4 x 25 ml portions). The combined ether extracts were dried and evaporated to leave a pale yellow oil. Chromatography with petroleum ether 30 - 60^{o} / ether (100 : 0 to 75 : 25) as eluent, gave the pure diethyl-2-ethoxymaleate-4-^{13}C, 15 (0.32 g, 48 %) as a colourless oil.

IR (thin film): ν max - 1745, 1675 and 1620 cm^{-1}.

H NMR ($CDCl_3$): δ = 1.10 - 1.53 (t t, J - 7 Hz, 9H, 3 x OCH_2CH_3), 3.75 - 4.52 (t q, J - 7 Hz, 6H, 3 x OCH_2CH_3), 5.20

2-Ethoxymaleic acid-4-^{13}C 16. A solution of the diethyl-2-ethoxymaleate-4-^{13}C 15 (100 mg, 0.46 mmole) in ethanol (2 ml) and 4 M sodium hydroxide (2.0 ml, 8 mmole) was stirred at 25^{o}C for 24 hours, then evaporated to

dryness at room temperature. The white residue was acidifed with 6 N HCl to pH 0 - 0.6 and reevaporated to dryness. The white crystalline solid was then extracted with ether (1 x 25 and 4 x 15 ml portions). Evaporation of the ether extracts left pure 2-ethoxymaleic acid-4- C (70 mg, 95 %) as white needles, m.p. 113 - 115°.

2-Ethoxymaleic anhydride-4-^{13}C 3. A solution of the 2-ethoxymaleic acid-4-^{13}C (70 mg, 0.43 mmole) in acetic anhydride (1.00 g) was heated under reflux for 1 hr, and evaporated until a weight of 70 mg was reached. The residue was transferred to a micro distillation apparatus and distilled under reduced pressure to give 2-ethoxymaleic anhydride-4-^{13}C 3 (57 mg, 92 %) as a pale yellow oil, b.p. 110 - 113°C / 0.25 torr.

IR (thin film): ν max = 3135, 2995, 1835, 1750, 1645 and 1220 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.52 (t, J = 7 Hz, 3H, OCH_2CH_3), 4.27 (q, J = 7 Hz, 2H, OCH_2CH_3), 5.57 (d, $J_{GEM.H*C}$ = 5 Hz, 1H, :CH).

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