Specific Isotope Enrichment of Methyl Methacrylate

Thekla M. Werkhoven,[a] Reinier van Nispen,[a] and Johan Lugtenburg*[a]

Keywords: Methyl methacrylate / ^{13}C label / Mass spectrometry / ^{1}H NMR / ^{13}C NMR

A synthetic scheme has been developed to prepare methyl methacrylate specifically ^{13}C-labelled at all different positions and in any combination of positions, from simple, commercially available starting materials. According to this scheme methyl (1-^{13}C)- and methyl (2-^{13}C)methacrylate (**1a** and **1b**) have been prepared with high label incorporation (99%).

Introduction

Methyl methacrylate (MMA) is a monomer that is used in many polymer applications. Its biggest use in material application is in the preparation of artificial glass (Plexiglas or Perspex) which is industrially made at a scale of 1.8×10^6 t/a.[1] Besides applications in which single polymers are used, a trend is to use blends of different polymers in order to obtain as good as possible mixtures that show the desired properties of both components with no or very little interference of the undesired properties.

A very powerful method to study the structure, morphology and dynamics of materials is to use site-directed isotopically labelled materials in conjunction with isotope-sensitive spectroscopic techniques such as solid-state NMR spectroscopy and neutron reflectivity.[2−21] This allows for studying the system at the atomic level without perturbation. ^{13}C-enriched materials are used to study structural[2−9] or dynamic[10] properties. Also ^{2}H-enriched materials are used to obtain structural[11−14] and dynamic[15−17] information from NMR spectroscopy. ^{2}H labelling is also used for neutron reflectivity studies[18][19] and forward recoil spectrometry.[20][21]

In order to achieve our goal, we follow a threefold strategy. First the required highly enriched site-directed isotopically labelled monomers are prepared by organic synthetic schemes starting from simple commercially available isotopically enriched starting materials. Secondly, the isotopically labelled polymers and copolymers are prepared in such a way that they have the same characteristics as the commercial bulk material. In order to minimize the cost for the isotopically labelled materials, this is carried out at a small scale. Third, these isotopically labelled systems are studied with solid-state ^{13}C-NMR techniques and other isotope-sensitive techniques in order to obtain structural and dynamic information at the atomic level that then will be correlated with the bulk properties of the materials.

We recently published this approach for the study of grafting polyethene and ethene-propene copolymers with maleic anhydride[2] and the study of blends and semi-interpenetrating networks of poly(styrene-*co*-acrylonitrile) and poly(styrene-*co*-maleic anhydride).[3] Also crosslinking of EPDM (ethene-propene-diene-monomer copolymer) rubbers has been published.[4]

For those studies we have prepared important monomers in various highly ^{13}C-enriched isotopic forms such as acrylonitrile,[3] ethyl acrylate,[22] maleic anhydride[2][3] and styrene.[3]

The present paper deals with the synthesis of ^{13}C-labelled methyl methacrylate to study polymers, based on methyl methacrylate, at the atomic level with isotope-sensitive techniques.

Here we present a new scheme, which allows for specific labelling of the MMA molecule at any desired carbon position or combination of positions. According to this scheme methyl (1-^{13}C)methacrylate and methyl (2-^{13}C)methacrylate were prepared at a scale of 5 g in 99% isotopically enriched form. These two label positions were chosen to be able to study both the polymeric backbone [polymer from methyl (2-^{13}C)methacrylate] as well as the ester function [polymer made from methyl (1-^{13}C)methacrylate].

By our scheme various other esters can easily be prepared besides methyl esters. Even the preparation of *tert*-butyl esters is possible. Also a host of isotopically labelled methacrylates with different alkyl functions can be prepared and if necessary also with isotope labels in the ester function.

This scheme can also be adapted to introduce deuterium labels at any position and combination of positions, even in combination with ^{13}C labelling. The scheme can also be adapted to prepare many more α,β-unsaturated esters and acids in isotopically labelled form by selecting the required reagents.

Results and Discussion

Synthetic Scheme

For the synthesis of site-directed isotopically labelled molecules the synthetic scheme has to fulfil additional requirements compared to general organic synthesis. First the number of commercially available isotopically labelled starting materials is restricted. Secondly, the scheme should be such that no isotope dilution or scrambling occurs during the synthesis. Also symmetric synthons have to be avo-

[a] Leiden Institute of Chemistry, Gorlaeus Laboratories, P. O. Box 9502, NL-2300 RA Leiden, The Netherlands

  1434−193X/99/1111−2909 $ 17.50+.50/0

ided, e.g. a commercial synthesis for methyl methacrylate using acetone as starting material[1] cannot be used for the site-directed isotope labelling.

Methyl methacrylate is synthesized from acetic acid, methyl iodide, paraformaldehyde and methanol as carbon sources, see Figure 1. Three materials (methyl iodide, methanol and paraformaldehyde) are commercially available in 99% ^{13}C enrichment at reasonable prices. Acetic acid is available in the three ^{13}C-labelled forms, (1-^{13}C)-, (2-^{13}C)- and (1,2- $^{13}C_2$)acetic acid, also at reasonable prices.

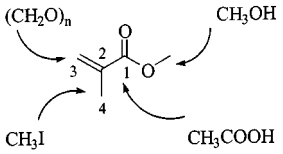
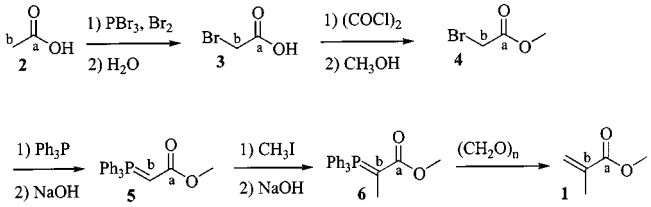


Figure 1. Origin of the carbon atoms in methyl methacrylate (**1**)

In Scheme 1 a method with simple steps to prepare methyl methacrylate is depicted.



Scheme 1. Synthetic scheme for the preparation of isotopically labelled MMA (**1**); **1a** = (1-^{13}C)MMA, **1b** = (2-^{13}C)MMA

Before we used the isotopically labelled enriched starting materials (1-^{13}C)- and (2-^{13}C)acetic acid, the scheme was first optimized using unlabelled compounds.

The scheme starts with acetic acid (**2**) which was converted quantitatively into bromoacetyl bromide in a Hell−Volhard−Zelinskii reaction with PBr_3 and Br_2.[23] The reaction mixture was quenched with water to obtain pure bromoacetic acid (**3**) isolated in 98% yield. Bromoacetic acid was treated with oxalyl chloride and 1.2 equivalents of methanol to give methyl bromoacetate (**4**) in 81% yield. This is the procedure that is advised to be used when the methyl ester function has to be isotopically labelled, see Discussion. For preparations where a nonlabelled ester function is required the reaction mixture of the Hell−Volhard−Zelinskii reaction mixture (containing bromoacetyl bromide) can be treated with excess dry methanol (or another alcohol) to give the required ester in one step (72%).[23] Treatment of **4** with triphenylphosphane in ethyl acetate gave the corresponding triphenylphosphonium bromide, which precipitated in quantitative yield. After filtration, this salt was dissolved in dichloromethane and treated with aqueous sodium hydroxide (2 equivalents) resulting in deprotonation to the stable phosphorane **5**. This phosphorane was synthesized in its 1-^{13}C-labelled form before.[24] The solution of **5** was treated with 1.5 equivalents of CH_3I.[23] After this reaction, care has to be taken to remove all excess CH_3I together with the solvent, to avoid unwanted alkylation in the next step. The phosphonium iodide, dissolved in dichloromethane, was once more treated with aqueous sodium hydroxide to give the phosphorane **6**. This product contains 80−85% of the required phosphorane **6** and 7.5−10% of nonconverted **5** (only the iodide instead of the bromide) and 7.5−10% of doubly methylated material (the iodide salt of methyl 2-methyl-2-triphenylphosphanylpropionate).[23] The Wittig reaction between the phosphorane **6** and paraformaldehyde was performed in a two-layer system of water and pentane.[25] The phosphorane **6** reacted in this Wittig reaction to give methyl methacrylate **1** in 42% yield. The 7.5−10% of **5** forms methyl acrylate. Methyl acrylate, however, is not found in the final product, as seen by ^1H NMR. We assume that part of the phosphorane reacts with the methyl acrylate formed in a 1,4-addition giving a water-soluble product. Also the higher volatility of methyl acrylate may cause its absence in the final product. When another synthetic method[26] was used, some methyl acrylate was present in the product (< 1%), therefore the detection limit for its presence in MMA was determined using the olefinic part of the ^1H-NMR spectrum.

The 7.5−10% of dimethylated salt does not undergo a Wittig reaction. Thus, only the required product is soluble in pentane; the impurities and by-product (triphenylphosphane oxide) are water-soluble or insoluble. This leads to a quite easy method for obtaining the MMA in pentane, by filtering off all solids after the reaction.

5.0 g (50 mmol) of methyl methacrylate (**1**) was obtained from 10.0 g (167 mmol) of acetic acid, 5.2 g (164 mmol) of methanol, 25.7 g (180 mmol) of methyl iodide and 4.4 g (147 mmol) of paraformaldehyde. The overall yield of methyl methacrylate (**1**) is thus, based on the starting materials, 30% from acetic acid, 30% from methanol, 28% from methyl iodide and 34% from paraformaldehyde.

After the optimization of this scheme, methyl (1-^{13}C)methacrylate and methyl (2-^{13}C)methacrylate were synthesized from (1-^{13}C)acetic acid and (2-^{13}C)acetic acid. The overall yields were 25% and 30%, respectively.

Characterization

Mass Spectrometry

Mass spectrometry is the technique of choice to establish the isotope incorporation and the molecule composition. The electron impact mass spectrum of methyl methacrylate (**1**) shows the molecular ion peak at *m/z* 100 ($C_5H_8O_2$). The molecular ion peak of methyl (1-^{13}C)methacrylate (**1a**) and methyl (2-^{13}C)methacrylate (**1b**) both occur at 101 ($^{13}C^{12}C_4H_8O_2$). In Table 1 the mass fragmentation is given.

The molecular composition was checked with double focus mass spectrometry. The results are in agreement with the calculated values. For methyl methacrylate (**1**) ($C_5H_8O_2$) a value of 100.0535 was measured (calculated for $C_5H_8O_2$: 100.0524). For **1a** 101.0582 was measured and for **1b** 101.0581 (calculated for $^{13}C^{12}C_4H_8O_2$: 101.0558).

The peak intensities of the mass peaks from *m/z* 99 up to *m/z* 103 for both the unlabelled **1** and the labelled **1a** and **1b**

Table 1. Mass fragmentation of methyl methacrylate, methyl (1-^{13}C)- and methyl (2-^{13}C)methacrylate

m/z (%) MMA	(1-^{13}C)MMA	(2-^{13}C)MMA	Fragment
41 (57)	41 (58)	42 (82)	$[CH_2CCH_3^+]$
59 (6)	60 (7)	59 (8)	$[C(O)OCH_3^+]$
69 (100)	70 (100)	70 (80)	$[CH_2C(CH_3)CO^+]$
85 (8)	86 (6)	86 (16)	$[CH_2C(CH_3)C(O)O^+]$
99 (13)	100 (18)	100 (43)	$[M^+ - H]$
100 (57)	101 (66)	101 (80)	$[M^+]$

were measured. The isotope incorporation was determined using a custom-made computer program. For both methyl (1-^{13}C)methacrylate (**1a**) and methyl (2-^{13}C)methacrylate (**1b**), the isotopic substitution with a ^{13}C atom is 99%. This enrichment is, within experimental error, in agreement with the isotope composition of the starting materials (^{13}C)acetic acid (**2a** and **2b**). This means that during the syntheses no isotope dilution had taken place.

The mass spectrum of methyl methacrylate (**1**) shows its main fragments at *m/z* 99 $[M - H]^+$, 85 $[M - CH_3]^+$, 69 $[M - CH_3O]^+$, 59 $[M - C_3H_5]^+$ and 41 $[M - C_2H_3O_2]^+$.[27]

In **1a** the $M - C_3H_5$ peak occurs at *m/z* 60, one unit higher than the unlabelled system, in complete agreement with the location of the ^{13}C isotope in the carbonyl carbon atom. For **1b** the $M - C_2H_3O_2$ peak occurs at *m/z* 42 in agreement with the location of the ^{13}C isotope in the aliphatic part of the molecule.

^{1}H-NMR Spectroscopy

^{1}H-NMR spectroscopy is the method of choice to establish the purity of the material and to determine the position of the ^{13}C isotope clearly when it is bound directly to protons. The ^{1}H-NMR spectra show no peaks of impurities, they are in agreement with the literature values in the case of methyl methacrylate (**1**).[28] For **1a**[15] and **1b** the ^{1}H-NMR spectra show the expected $^2J_{C,H}$, $^3J_{C,H}$ and $^4J_{C,H}$ values. From the couplings it is clear that in **1a** the ^{13}C isotope is at position 1 and in **1b** at position 2, in agreement with the synthetic scheme and the literature values.[15] For **1a** the following $^3J_{C,H}$ values could be determined: $^3J_{C\text{-}1,OCH3}$ = 3.8 Hz, $^3J_{C\text{-}1,3\text{-}Htrans}$ = 12.9, $^3J_{C\text{-}1,3\text{-}Hcis}$ = 6.6 Hz, $^3J_{C\text{-}1,4\text{-}H}$ = 4.1 Hz. The signs could not be determined. The $^3J_{C\text{-}1,OCH3}$ value is in good agreement with that in methyl acetate (3.8 Hz).[29] The $^3J_{C\text{-}1,3\text{-}Htrans}$ and $^3J_{C\text{-}1,3\text{-}Hcis}$ values are in good agreement with the corresponding values for propenoic acid, namely 14.1 Hz and 7.6 Hz, respectively.[30]

For **1b** the following CH coupling constants could be determined: $^2J_{C\text{-}2,4\text{-}H}$ = 6.6 Hz, $^2J_{C\text{-}2,3\text{-}Htrans}$ = 0.6 Hz, $^2J_{C\text{-}2,3\text{-}Hcis}$ = 3.1 Hz, and $^4J_{C\text{-}2,OCH3}$ = 0.4 Hz. These values are in good agreement with those of propenoic acid, namely $^2J_{C\text{-}2,3\text{-}Hcis}$ = −4.6 Hz and $^2J_{C\text{-}2,3\text{-}Htrans}$ = 0.2 Hz, respectively.[30]

^{13}C-NMR Spectroscopy

The ^{1}H-noise-decoupled ^{13}C-NMR spectra give direct information about the location of the ^{13}C label. The spectra of **1a** and **1b** show a very intense signal at δ = 168.0 and 136.2, respectively, in complete agreement with the expected positions. No scrambling has taken place during the syntheses. The other resonances are at δ = 18.3 (C-4), 51.8 (OCH_3) and 125.5 (C-3).[15] From the natural abundance signals in **1a** and **1b** the following ^{13}C,^{13}C coupling constants could be determined: $^1J_{C\text{-}1,C\text{-}2}$ = 70.0 ± 0.2 Hz, $^1J_{C\text{-}2,C\text{-}3}$ = 70.8 Hz, $^1J_{C\text{-}2,C\text{-}4}$ = 44.9 Hz, $^2J_{C\text{-}1,C\text{-}3}$ = 1.8 Hz, $^2J_{C\text{-}1,C\text{-}4}$ = 3.3 Hz and $^2J_{C\text{-}1,OCH3}$ = 2.5 Hz. For **1a** the values are in agreement with the literature values.[15]

Discussion

Methyl (1-^{13}C)methacrylate (**1a**) and methyl (2-^{13}C)methacrylate (**1b**) could be synthesized in good yield, in high purity, with high isotope incorporation (99%) and without isotope scrambling, in a scheme that allows for the isotope incorporation at any position and in any combination of positions. In Figure 1 the source of each atom is indicated. Earlier syntheses have been described for introducing specific ^{13}C labels in methacrylates (positions 1[10,15,31] and 4[31]) and acrylates (position 3[25][32]). These syntheses, however, do not allow labelling at all desired positions and in combinations of positions.

In the Hell−Volhard−Zelinskii reaction an excess of alcohol or water is necessary to quench also the PBr_3 residues. This reaction was studied using 1.05 equivalents of methanol. After stirring of half an hour, ^{1}H-NMR spectroscopy showed complete conversion of bromoacetyl bromide into methyl bromoacetate (**4**). However, workup with water yielded only 30% of methyl bromoacetate, whilst the remainder of the product was converted into bromoacetic acid. A similar experiment consisted of adding ethanol, after the methyl bromoacetate had been formed. In this case 80% of the obtained product was the ethyl rather than the methyl ester. These findings can be explained by the presence of large amounts of HBr in the reaction mixture, which allow for the hydrolysis or transesterification of the methyl ester group. We therefore expect that addition of unlabelled methanol after the reaction with the 1.05 equivalents of labelled methanol would lead to undesired scrambling of the label. Thus, it was necessary to first purify bromoacetic acid (**3**) and subsequently convert this into methyl bromoacetate (**4**).

After we finished this synthesis we found a better way to effect the Hell−Volhard−Zelinskii bromination using 1 equivalent of trifluoroacetic anhydride instead of PBr_3.[33] This approach leads to quantitative formation of **3** without difficult separations. In our case the hydrolysis of PBr_3 in the product interfered with an efficient ester formation because of HBr formation. Also the use of ^{13}C-labelled diazomethane[34] is studied in our group at the moment. In our scheme all reactions are straightforward, except the alky-

lation step from **5** to **6**. Usually, this type of alkylation gives a 2:1:1 mixture of the required monoalkylated form together with dialkylation and no alkylation. We found reaction conditions in which mainly monoalkylation takes place,[23] however, we could not find conditions where the side reaction was excluded. Proton exchange reactions between the phosphonium salt and the phosphorane[35][36] could not be completely avoided.

As has been discussed above, this problem has been resolved because in the Wittig reaction of **6** the doubly alkylated product cannot undergo a Wittig reaction and the nonalkylated form is so much more reactive towards the products that it undergoes a 1,4-addition with the unsaturated ester. This leads to the required product in pure form with a small lowering of the total yield.

Conclusion

A synthetic scheme has been developed to prepare methyl methacrylate labelled with 99% ^{13}C at any carbon position or in any combination of positions. Using this scheme methyl (1-^{13}C)methacrylate and methyl (2-^{13}C)methacrylate were prepared in good yield. This scheme can also be adjusted to prepare ^{14}C-labelled methyl methacrylate at each position or combination of positions.

The present work complements the isotopically labelled monomers for the study of various polymers and copolymers with isotope-sensitive techniques that give structural and functional information at the atomic level. Besides being monomers for various polymeric materials, methacrylates and the other substances mentioned are very useful building blocks in organic synthesis. These compounds in isotopically labelled form allow many other molecules to be synthesized in isotopically labelled form.

Experimental Section

General Remarks: ^1H-NMR spectra were recorded with a Jeol FX-200, a Bruker DPX-300 spectrometer, or a Bruker DMX-600 using tetramethylsilane (TMS; $\delta = 0$) as internal standard. ^1H-noise-decoupled ^{13}C-NMR spectra were recorded with a Jeol FX-200 at 50.1 MHz and with a Bruker DPX-300 at 75.5 MHz using $CDCl_3$ ($\delta = 77$) as internal standard. Mass spectra were recorded with a Finnigan MAT 900 mass spectrometer, coupled with a Varian GC. The injection temperature was 150°C, the column temperature 80°C and the spectrometer was set in EI mode (70 eV). Double focus mass spectra were performed using a direct insertion probe. The experimental conditions are given for the unlabelled compounds. For labelled compounds, only the changes relative to the corresponding unlabelled compounds are given. (1-^{13}C)- and (2-^{13}C)acetic acid (99% ^{13}C) were purchased from Campro and Cambridge Isotope Laboratories, Inc. All other reagents were purchased from Aldrich or Acros Chimica.

Methyl Bromoacetate (4): A three-necked round-bottom flask, equipped with a reflux condenser with a drying tube with calcium chloride, was flame-dried under nitrogen flow. The flask was charged with 4.00 g (66.6 mmol) of acetic acid (**2**) and 18 g (66.6 mmol) of PBr_3. After cooling the solution to 0°C, 24.4 g (0.17 mol) of bromine was slowly added using an addition funnel. After the HBr evolution had ceased and additional stirring for 15 min at room temperature, the reaction mixture was heated in a water bath of 75°C for 2.5 h. ^1H NMR showed complete conversion of **2** to bromoacetyl bromide (200 MHz, $CDCl_3$, $\delta = 4.45$). After cooling to 0°C, 15 mL (0.37 mol) of dry methanol was added very slowly. After additional stirring for 1.5 h, diethyl ether and water were added for workup. The organic layer was washed with a 1 M $Na_2S_2O_3$ solution, quickly with a $NaHCO_3$ solution of pH = 9 (until neutral), with water and subsequently dried with $MgSO_4$. Concentration in vacuo (not all diethyl ether was evaporated to avoid loss of product) yielded methyl bromoacetate (**4**) (conversion determined after reaction with triphenylphosphane to give **5**). – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3 H, OCH_3), 3.86 (s, 2 H, 2-H). – ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 25.5$ (s, C-2), 53.0 (s, OCH_3), 167.6 (s, C-1).

(1-^{13}C)4 (4a): Similarly, 10.1 g (0.166 mol) of (1-^{13}C)acetic acid was divided in two equal portions and was converted via (1-^{13}C)bromoacetyl bromide [^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.45$ (d, $^2J_{C,H} = 5.15$ Hz, 2-H); ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 160.5$ (s, C-1)] into **4a**. – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$ (d, $^3J_{C,H} = 4.5$ Hz, 3 H, OCH_3), 3.85 (d, $^2J_{C,H} = 4.5$ Hz, 2 H, 2-H). – ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 167.7$ (C-1).

(2-^{13}C)4 (4b): Similarly, two portions of (2-^{13}C)acetic acid (**2b**) (total of 10.3 g; 0.169 mol) were converted via (2-^{13}C)bromoacetyl bromide [^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.45$ (d, $^1J_{C,H} = 157.2$ Hz, 2-H); ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 37.8$ (s, C-2)] into **4b**. – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3 H, OCH_3), 3.85 (d, $^1J_{C,H} = 146.2$ Hz, 2 H, 2-H). – ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 25.5$ (C-2).

Bromoacetic Acid (3): According to the above-mentioned synthesis 4.00 g (66.6 mmol) of acetic acid (**2**) was converted into bromoacetyl bromide. After cooling to 0°C, 10 mL of water was added slowly. After stirring for 15 min at room temperature, diethyl ether and $Na_2S_2O_3$ solution were added. The water layer was extracted four times with 100 mL of diethyl ether. Thorough drying with $MgSO_4$ and evaporation of the solvent yielded 9.11 g (65.5 mmol, 98%) of bromoacetic acid (**3**) as a white solid. – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.90$ (s, 2 H, 2-H), 8.71 (s, 1 H, COOH). – ^{13}C NMR (50.1 MHz, $CDCl_3$): $\delta = 25.2$ (C-2), 172.7 (C-1).

Methyl Bromoacetate (4): 9.11 g (65.5 mmol) of bromoacetic acid (**3**) was placed in a three-necked round-bottom flask, equipped with an addition funnel and a reflux condenser. 6.3 mL (72 mmol, 1.1 equiv.) of oxalyl chloride was slowly added. The reaction mixture was heated for 3 h at 60°C. After cooling to 0°C, 2.69 mL (65.5 mmol, 1.00 equiv.) of dry methanol was added slowly. After additional stirring for half an hour at room temperature, water was added and the mixture was extracted with diethyl ether. Drying with $MgSO_4$ and partial evaporation of the solvent yielded methyl bromoacetate [yield determined after reaction with triphenylphosphane: 8.12 g of **4** (53.1 mmol, 81%)]. – ^1H and ^{13}C NMR: see above.

[(Methoxycarbonyl)methylene]triphenylphosphorane (5): A solution of the methyl bromoacetate (**4**), obtained in the Hell–Volhard–Zelinskii reaction, in 20 mL of ethyl acetate was added to a solution of 17.6 g (67 mmol) of triphenylphosphane in 100 mL of ethyl acetate. After stirring overnight, the white precipitate was filtered off, washed with diethyl ether and dried in vacuo at 40°C for 4 h. 20.0 g (48.0 mmol, 72% from acetic acid) of the phosphonium bromide {[(methoxycarbonyl)methyl]triphenylphosphonium bromide} was obtained. – Decomposition temperature 161–163°C (from H_2O). – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.61$ (s, 3 H, OCH_3), 5.62 (d,

$^2J_{P,H}$ = 15.5 Hz, 2 H, 2-H), 7.6−8.0 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 32.6 (d, $^1J_{P,C}$ = 60.1 Hz, C-2), 53.1 (s, OCH_3), 117.5 (d, $^1J_{P,C}$ = 89 Hz, C-1′), 130.1 (d, $^3J_{P,C}$ = 13 Hz, C-3′), 133.6 (d, $^2J_{P,C}$ = 10 Hz, C-2′), 134.9 (s, C-4′), 164.7 (s, C-1). − A two-layer system of 50.0 g (0.12 mol) of the phosphonium bromide in 300 mL of dichloromethane and 2 equiv. (9.6 g; 0.24 mol) of NaOH in 200 mL water were vigorously shaken in a separation funnel, after which the layers were separated. The water layer was washed twice with dichloromethane. The combined dichloromethane layers were dried with $MgSO_4$ and the solvent was evaporated to yield 40.3 g (0.12 mol; 100%) of the two rotameric forms of **5** as a white solid. − M.p. 167−168°C (from EtOAc). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.90 (25%) + 3.52 (75%) (3 H, OCH_3), 7.4−7.8 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 29.5 (d, $^1J_{P,C}$ = 127.4 Hz, C-2), 49.5 (s, OCH_3), 126.8 (d, $^1J_{P,C}$ = 91 Hz, C-1′), 128.5 (d, $^3J_{P,C}$ = 11.7 Hz, C-3′), 131.7 (s, C-4′), 132.9 (d, $^2J_{P,C}$ = 8 Hz, C-2′), 171.3 (s, C-1).

(1-^{13}C)5 (5a): According to the above procedure, **4a** was converted into 49.1 g (0.12 mol, 71% from **2a**) of phosphonium bromide. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.60 (d, $^3J_{C,H}$ = 4.1 Hz, 3 H, OCH_3), 5.62 (dd, $^2J_{C,H}$ = 7.6 Hz, $^2J_{P,H}$ = 13.4 Hz, 2 H, 2-H), 7.6−8.0 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 165.1 (d, $^2J_{P,C}$ = 2.9 Hz, C-1). − According to the above procedure, 49.1 g of phosphonium bromide was converted into 40.2 g (0.12 mol, 100%) of **5a**. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.92 (23%) + 3.51 (77%) (3 H, OCH_3), 7.4−7.7 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 171.5 (d, $^2J_{P,C}$ = 11.7 Hz, C-1).

(2-^{13}C)5 (5b): According to the above procedure, **4b** was converted into 49.2 g (0.12 mol, 70% from **2b**) of phosphonium bromide. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.61 (s, OCH_3), 5.62 (dd, $^1J_{C,H}$ = 134.4 Hz, $^2J_{P,H}$ = 13.6 Hz, 2 H, 2-H), 7.6−8.0 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 33.1 (d, $^1J_{P,C}$ = 57.1 Hz, C-2). − According to the above procedure, 49.2 g of phosphonium bromide was converted into 39.6 g (0.12 mol, 100%) of **5b**. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.57 (8%) + 3.52 (82%) (3 H, OCH_3), 7.4−7.8 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 29.7 (d, $^1J_{P,C}$ = 127 Hz, C-2).

Note: ^{1}H-NMR spectra of phosphorus ylides are known to exhibit special properties.[35−40] Due to internal hindered rotation about the C1−C2 bond, the methoxy protons show two separate signals at moderate temperature, which coalesce at higher temperatures.[35−40] According to the literature, the coalescence temperature of the methoxy signals in the phosphorus ylide **5** in $CDCl_3$ is 30°C[39] or 43°C[37] and in **6** it is 55°C.[40] The methine proton signal of **5** is only visible from the pure compound; in the presence of a proton source, the methine doublet is collapsed.[37] Our spectra are in agreement with these findings. For phosphorane **6** two signals for the methoxy group are found at room temperature in relative amounts of approximately 2:3 for the two rotamers. The phosphorane **5** shows partial coalescence for the two rotameric forms at room temperature, therefore the relative amounts of the two broad signals vary somewhat more.

[1-(Methoxycarbonyl)ethyl]triphenylphosphorane (6): A solution of 40.3 g (0.12 mol) of **5** in 200 mL of dichloromethane in a 250-mL round-bottom flask was cooled to 0°C. 1.5 equiv. (25.7 g, 0.18 mol) of methyl iodide was added and the solution was stirred overnight at room temperature. Evaporation of the solvent and the remainder of the methyl iodide yielded 58.4 g (0.12 mol, 100%, of which 85% monomethylated, 7.5% not methylated and 7.5% doubly methylated) of phosphonium iodide {[1-(methoxycarbonyl)ethyl]triphenylphosphonium iodide} as a yellowish foam. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (dd, $^3J_{P,H}$ = 18.5 Hz, $^3J_{H,H}$ = 7.2 Hz, 3 H, 3-H), 3.58 (s, 3 H, OCH_3), 6.36 (chemical shift depending strongly on concentration) [dq ("sext"), $^2J_{P,H}$ = 14.8 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, 2-H], 7.7−8.1 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 12.8 (s, C-3), 36.6 (d, $^1J_{P,C}$ = 50 Hz, C-2), 53.0 (s, OCH_3), 116.7 (d, $^1J_{P,C}$ = 86.7 Hz, C-1′), 129.9 (d, $^3J_{P,C}$ = 13.2 Hz, C-3′), 133.4 (d, $^2J_{P,C}$ = 8.8 Hz, C-2′), 134.7 (s, C-4′), 167.6 (d, $^2J_{P,C}$ = 1.4 Hz, C-1). − Using the same procedure as for the deprotonation of the C_2-phosphonium salt, 58.4 g (0.12 mol) of phosphonium iodide was deprotonated to give 42.6 g (0.12 mol; 100%) of the two rotameric forms of the yellow phosphorane **6**. − M.p. 153−156°C (from EtOAc). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (d, $^3J_{P,H}$ = 13.7 Hz, 3 H, 3-H), 3.13 (60%) + 3.61 (40%) (3 H, OCH_3), 7.4−7.9 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 12.8 (d, $^2J_{P,C}$ = 10.3 Hz, C-3), 31.7 (d, $^1J_{P,C}$ = 120.1 Hz, C-2), 48.5 + 49.5 (OCH_3), 127.9 (d, $^1J_{P,C}$ = 90.8 Hz, C-1′), 128.2 (d, $^3J_{P,C}$ = 11.7 Hz, C-3′), 131.3 (s, C-4′), 133.2 (d, $^2J_{P,C}$ = 7.3 Hz, C-2′), 170.5 (d, $^2J_{P,C}$ = 13.2 Hz, C-1) + 171.2 (d, $^2J_{P,C}$ = 17.6 Hz, C-1).

(1-^{13}C)6 (6a): According to the same procedure, 40.2 g of the phosphorane **5a** was converted into 56.9 g (0.12 mol, 100%, of which 79% monomethylated) of phosphonium iodide. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (ddd, $^3J_{P,H}$ = 18.3 Hz, $^3J_{H,H}$ = 7.2 Hz, $^3J_{C,H}$ = 5.0 Hz, 3 H, 3-H), 3.58 (d, $^3J_{C,H}$ = 3.8 Hz, 3 H, OCH_3), 6.36 [ddq ("sept"), $^2J_{P,H}$ = 14.8 Hz, $^3J_{H,H}$ = 7.2 Hz, $^2J_{C,H}$ = 6.8 Hz, 1 H, 2-H], 7.7−8.1 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 168.3 (s, C-1). − According to the same procedure, 56.9 g of phosphonium iodide was converted into 42.6 g (0.12 mol, 100%) of **6a**. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (d, $^3J_{P,H}$ = 13.7 Hz, 3 H, 3-H), 3.13 (55%) + 3.59 (45%) (3 H, OCH_3), 7.3−7.9 (m, 15 H, Ph). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8 (d, $^2J_{P,C}$ = 13.3 Hz, C-1) + 171.5 (d, $^2J_{P,C}$ = 11.7 Hz, C-1).

(2-^{13}C)6 (6b): According to the same procedure, 39.6 g of the phosphorane **5b** was converted into 56.9 g (0.12 mol, 100%, of which 83% monomethylated) of phosphonium iodide. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.69 (ddd, $^3J_{P,H}$ = 18.5 Hz, $^3J_{H,H}$ = 7.2 Hz, $^2J_{C,H}$ = 4.1 Hz, 3 H, 3-H), 3.57 (s, 3 H, OCH_3), 6.46 [ddq (d"sext"), $^1J_{C,H}$ = 133.5 Hz, $^2J_{P,H}$ = 16 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, 2-H], 7.6−8.0 (m, 15 H, Ph). − ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 37.1 (d, $^1J_{P,C}$ = 52.7 Hz, C-2). − According to the same procedure, 56.9 g of phosphonium iodide was converted into 41.1 g (0.115 mol, 96%) of **6b**. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.62 (dd, $^2J_{C,H}$ = 4.6 Hz, $^3J_{P,H}$ = 14.2 Hz, 3 H, 3-H), 3.34 (82%) + 3.50 (18%) (3 H, OCH_3), 7.3−7.9 (m, 15 H, Ph). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.6 (d, $^1J_{P,C}$ = 120 Hz, C-2).

Methyl Methacrylate (1): 42.6 g of phosphorane **6** was ground and put into a 1-L round-bottom flask. 300 mL of water and 300 mL of pentane were added, as well as 0.7−1.5 mg of 4-methoxyphenol as inhibitor (50−100 ppm). After addition of 1.2 equiv. (4.4 g) of paraformaldehyde, the flask was closed tightly and the mixture stirred overnight. The solids were filtered off and the liquid layers were separated. The water layer was washed with pentane twice; the combined pentane layers were dried with $MgSO_4$. The pentane was distilled off and subsequently the product was distilled under vacuum into a cold trap with liquid nitrogen. This yielded 5.00 g (50 mmol, 42%) of methyl methacrylate (**1**). 100 ppm of 4-methoxyphenol was added as inhibitor. − B.p. 100°C. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.94 (dd, $^4J_{H,H}$ = 1.0 Hz, $^4J_{H,H}$ = 1.6 Hz, 3 H, 4-H), 3.76 (s, 3 H, OCH_3), 5.56 [dq ("quint"), $^4J_{H,H}$ = 1.6 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H_{trans}], 6.10 [dq ("sext"), $^4J_{H,H}$ = 1.0 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H_{cis}]. − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.3 (s, C-4), 51.7 (s, OCH_3), 125.4 (s, C-3), 136.1 (s, C-2), 167.8

(s, C-1). − MS (70 eV); *m/z* (%): 41 (57) [$CH_2CCH_3^+$], 42 (6), 55 (8), 56 (5), 59 (6) [$C(O)OCH_3^+$], 69 (100) [$CH_2C(CH_3)CO^+$], 85 (8) [$M^+ - CH_3$], 99 (13) [$M^+ - H$], 100 (57) [M^+].

(1-^{13}C)1 (1a): Similarly, 42.6 g (0.12 mol) of phosphorane yielded 4.15 g (41 mmol, 34%) of methyl (1-^{13}C)methacrylate (**1a**). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (ddd, $^3J_{C,H}$ = 4.1 Hz, $^4J_{H,H}$ = 1.0 Hz, $^4J_{H,H}$ = 1.6 Hz, 3 H, 4-H), 3.75 (d, $^3J_{C,H}$ = 3.8 Hz, 3 H, OCH_3), 5.56 [ddq (d"quint"), $^3J_{C,H}$ = 12.9 Hz, $^4J_{H,H}$ = 1.6 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H$_{trans}$], 6.10 [ddq (d"sext"), $^3J_{C,H}$ = 6.6 Hz, $^4J_{H,H}$ = 1.0 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H$_{cis}$]. − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.3 (d, $^2J_{C,C}$ = 3.3 Hz, C-4), 51.9 (d, $^2J_{C,C}$ = 2.5 Hz, OCH_3), 125.5 (d, $^2J_{C,C}$ = 1.8 Hz, C-3), 136.2 (d, $^1J_{C,C}$ = 70.2 Hz, C-2), 168.0 (s, C-1). − MS (70 eV); *m/z* (%): 41 (58) [$CH_2CCH_3^+$], 43 (8), 55 (8), 57 (5), 60 (7) [$C(O)OCH_3^+$], 70 (100) [$CH_2C(CH_3)CO^+$], 86 (6) [$M^+ - CH_3$], 100 (18) [$M^+ - H$], 101 (66) [M^+].

(2-^{13}C)1 (1b): Similarly, 42.6 g (0.12 mol) of phosphorane yielded 5.05 g (50 mmol, 43%) of methyl (2-^{13}C)methacrylate (**1b**). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (ddd, $^2J_{C,H}$ = 6.6 Hz, $^4J_{H,H}$ = 1.0 Hz, $^4J_{H,H}$ = 1.6 Hz, 3 H, 4-H), 3.76 (d, $^4J_{C,H}$ = 0.4 Hz, 3 H, OCH_3), 5.56 [ddq (d"quint"), $^2J_{C,H}$ = 0.6 Hz, $^4J_{H,H}$ = 1.6 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H$_{trans}$], 6.11 [ddq (10−12 peaks), $^2J_{C,H}$ = 3.1 Hz, $^4J_{H,H}$ = 1.0 Hz, $^2J_{H,H}$ = 1.7 Hz, 1 H, 3-H$_{cis}$]. − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.3 (d, $^1J_{C,C}$ = 44.9 Hz, C-4), 51.8 (s, OCH_3), 125.5 (d, $^1J_{C,C}$ = 70.8 Hz, C-3), 136.2 (s, C-2), 168.0 (d, $^1J_{C,C}$ = 69.8 Hz, C-1). − MS (70 eV); *m/z* (%): 42 (82) [$CH_2CCH_3^+$], 43 (100), 56 (24), 57 (45), 59 (8) [$C(O)OCH_3^+$], 70 (80) [$CH_2C(CH_3)CO^+$], 71 (39), 86 (16) [$M^+ - CH_3$], 100 (43) [$M^+ - H$], 101 (80) [M^+].

Acknowledgments

The authors wish to thank C. Erkelens and F. Lefeber for recording the NMR spectra and B. Hofte for measuring the mass spectra. This work was supported by the Stichting voor de Technische Wetenschappen (STW) with financial aid from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO).

[1] J. Keijsper, P. Arnoldy, M. J. Doyle, E. Drent, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 248−255.
[2] W. Heinen, C. H. Rosenmöller, C. B. Wenzel, H. J. M. de Groot, J. Lugtenburg, M. van Duin, *Macromolecules* **1996**, *29*, 1151−1157.
[3] W. Heinen, C. B. Wenzel, C. H. Rosenmöller, F. M. Mulder, G. J. Boender, J. Lugtenburg, H. J. M. de Groot, M. van Duin, B. Klumperman, *Macromolecules* **1998**, *31*, 7404−7412.
[4] W. Heinen, L. N. Ballijns, W. J. A. Wittenburg, R. Winters, J. Lugtenburg, M. van Duin, *Polymer*, in press.
[5] P. Wang, A. A. Jones, P. T. Inglefield, D. M. White, J. T. Bendler, *New Polymeric Mater.* **1990**, *2*, 221−234.
[6] A. K. Roy, P. T. Inglefield, J. H. Shibata, A. A. Jones, *Macromolecules* **1987**, *20*, 1434−1437.
[7] M. Linder, P. M. Henrichs, J. M. Hewitt, D. J. Massa, *J. Chem. Phys.* **1985**, *82*, 1585−1598.
[8] G. Tong, Y. Pan, M. Afeworki, M. D. Poliks, J. Schaefer, *Macromolecules* **1995**, *28*, 1719−1720.
[9] M. Afeworki, R. A. McKay, J. Schaefer, *Macromolecules* **1992**, *25*, 4084−4091.
[10] K. Schmidt-Rohr, A. S. Kulik, H. W. Beckham, A. Ohlemacher, U. Pawelzik, C. Boeffel, H. W. Spiess, *Macromolecules* **1994**, *27*, 4733−4745.
[11] N. Zumbulyadis, C. J. T. Landry, T. E. Long, *Macromolecules* **1993**, *26*, 2647−2648.
[12] J. L. White, P. Mirau, *Macromolecules* **1993**, *26*, 3049−3054.
[13] N. Zumbulyadis, M. R. Landry, T. P. Russell, *Macromolecules* **1996**, *29*, 2201−2204.
[14] J. F. Parmer, L. C. Dickinson, J. C. W. Chien, R. S. Porter, *Macromolecules* **1987**, *20*, 2308−2310.
[15] G. Moad, D. H. Solomon, T. H. Spurling, S. R. Johns, R. I. Willing, *Aust. J. Chem.* **1986**, *30*, 43−50.
[16] M. T. Hansen, B. Blümich, C. Boeffel, H. W. Spiess, L. Morbitzer, A. Zembrod, *Macromolecules* **1992**, *25*, 5542−5544.
[17] G.-C. Chung, J. A. Kornfield, S. D. Smith, *Macromolecules* **1994**, *27*, 964−973.
[18] T. P. Russell, S. H. Anastasiadis, A. Menelle, G. P. Felcher, S. K. Satija, *Macromolecules* **1991**, *24*, 1575−1582.
[19] B. Frick, L. J. Fetters, *Macromolecules* **1994**, *27*, 974−980.
[20] K. R. Shull, E. J. Kramer, G, Hadziioannou, W. Tang, *Macromolecules* **1990**, *23*, 4780−4787.
[21] K. R. Shull, A. J. Kellock, V. R. Deline, S. A. MacDonald, *J. Chem. Phys.* **1992**, *97*, 2095−2104.
[22] L. W. Jenneskens, E. M. M. van den Berg, B. Heemskerk, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 627−630.
[23] F. J. H. M. Jansen, M. Kwestro, D. Schmitt, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 552−562.
[24] J. L. Marshall, D. E. Müller, H. C. Dorn, G. E. Maciel, *J. Am. Chem. Soc.* **1975**, *97*, 460−462.
[25] E. M. M. van den Berg, F. J. H. M. Jansen, A. T. J. W. de Goede, A. U. Baldew, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 287−297.
[26] W. A. Nugent, R. J. McKinney, *J. Mol. Catal.* **1985**, *29*, 65−76.
[27] L. O'Toole, R. D. Short, A. P. Ameen, F. R. Jones, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 1363−1370.
[28] L. Jackman, R. H. Wiley, *J. Chem. Soc.* **1960**, 2881−2886.
[29] E. Breitmeier, G. Bauer, *^{13}C-NMR-Spektroskopie*, Georg Thieme, Stuttgart, **1977**.
[30] H. O. Kalinowski, S. Berger, S. Braun, *^{13}C NMR Spectroscopy*, Georg Thieme, Stuttgart, **1989**.
[31] D. O'Hagan, S. V. Rogers, G. R. Duffin, K. A. Reynolds, *J. Antibiotics* **1995**, *48*, 1280−1287.
[32] J. Šmejkal, V. Hanuš, I. Linhart, T. Elbert, *J. Labelled Compd. Radiopharm.* **1990**, 28, 757−761.
[33] J. L. Roberts, C. D. Poulter, *J. Org. Chem.* **1978**, *43*, 1547−1550.
[34] A. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman Inc., New York, **1978**, p. 290.
[35] H. Schmidbar, W. Tronich, *Chem. Ber.* **1968**, *101*, 604−620.
[36] H. J. Bestmann, *Chem. Ber.* **1962**, *95*, 58−63.
[37] F. J. Randall, A. W. Johnson, *Tetrahedron Lett.* **1968**, *24*, 2841−2846.
[38] D. M. Crouse, A. T. Wehman, E. E. Schweizer, *Chem. Commun.* **1968**, 866−867.
[39] H. J. Bestmann, J. P. Snyder, *J. Am. Chem. Soc.* **1967**, *89*, 3936−3938.
[40] H. J. Bestmann, G. Joachim, I. Lengyel, J. F. M. Oth, R. Merényi, H. Weitkamp, *Tetrahedron Lett.* **1966**, *28*, 3355−3358.

Received March 4, 1999
[O99123]