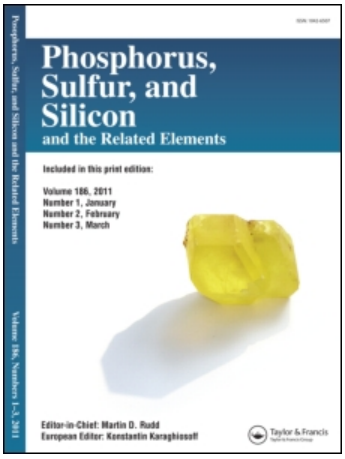

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A NEW GENERAL METHOD FOR THE PREPARATION OF CARBOXYLIC ACID ESTERS

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A NEW GENERAL METHOD FOR THE PREPARATION OF CARBOXYLIC ACID ESTERS

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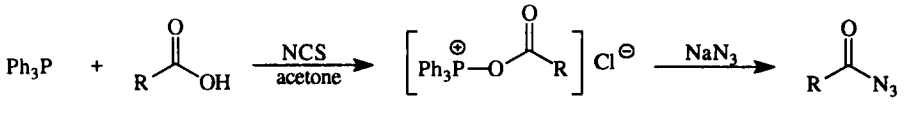
Esters can be generated directly in good yields under mild conditions from the corresponding carboxylic acid and alcohol in the presence of equivalent amounts of pyridine, triphenylphosphine and N-halo-succinimide.

Key words: Carboxylic acids, esterification, triphenylphosphine, N-halo succinimides.

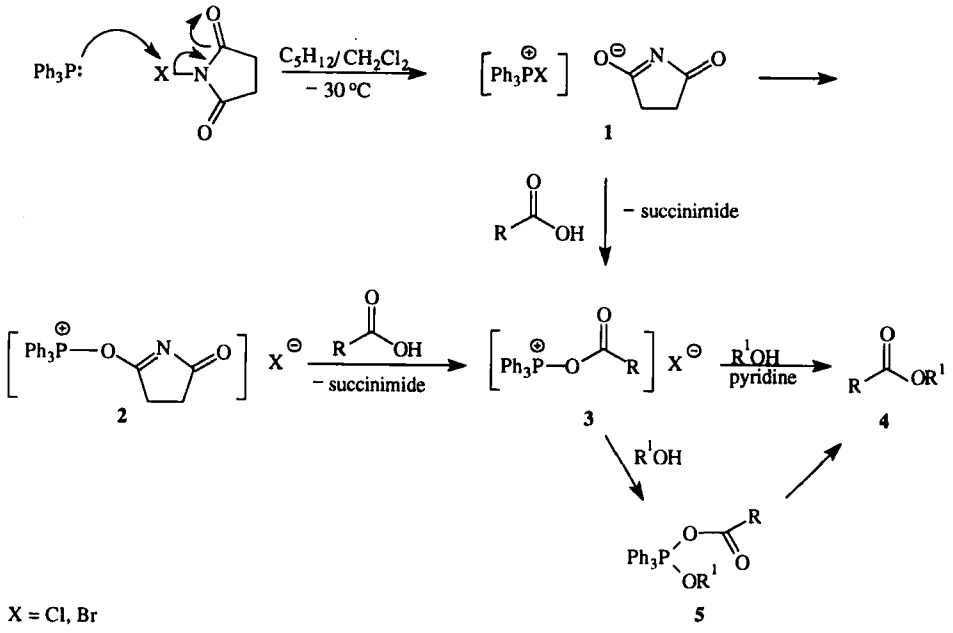
Carboxylic acids can be converted to esters by a variety of methods.[1,2] Nevertheless, there is still some demand for mild and convenient procedures to generate these compounds. The more recent esterification methods include the activation of the carboxylic acids towards nucleophilic attack by transforming the acid into some other functional group such as anhydride,[3,4] metal carboxylate,[5] thio ester,[6] acyloxyphosphonium salt,[7,8] or via in situ activation of the carboxylic acid by reagents which are expensive and/or not readily available, such as azodicarboxylates[9] (the Mitsunobu reaction), 2-halopyridinium salts or other, related compounds applied by Mukaiyama *et al.*[10] In this line it has recently been reported that Appel's salt, in the presence of 2,6-lutidine, converts an equimolar mixture of a carboxylic acid and alcohol to the corresponding ester under extremely mild conditions.[11] During the course of some research[12] regarding the preparation of iminophosphoranes from carboxylic acids by means of NCS in combination with phosphines, e.g. triphenylphosphine, we considered the possibility of applying the same reagents for transforming carboxylic acids into esters. We were aware from our previous work[12] that inorganic azides readily transform acyloxyphosphonium salts (Scheme I) to acyl azides. The method works well at or below room temperature, is simple to use and employs readily available chemicals.

It appeared likely that under appropriate conditions, preferably in some volatile, non polar solvent, the acyloxyphosphonium salt **3** (Scheme II) might react also with alcohols, yielding the corresponding esters **4**. The esterification could proceed either via some pentacoordinated species such as **5**, through direct nucleophilic attack of the alcohol at the carbonyl carbon of **3**, or via an intermediate acid halide.

It would not be necessary or desirable to isolate the intermediate phosphonium salts **2** and **3** (Scheme II). Indeed, we found after some initial experiments with



SCHEME I



SCHEME II

dichloromethane as a solvent, that when N-bromosuccinimide (NBS) was added to an equimolar mixture of ethanol, diphenylacetic acid, triphenylphosphine and pyridine in pentane/dichloromethane, a vigorous reaction ensued and the expected ester, ethyldiphenylacetate could be isolated in 70% yield after 0.5 h at ambient temperature.

A number of different acids and alcohols were thereafter studied and the scope and generality of the reaction investigated. The results are shown in Table I. The reaction conditions are very mild and the method works excellent with aliphatic acids, saturated along with unsaturated, and with phenol as well as alcohols.

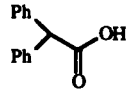
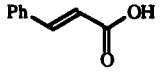
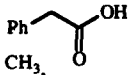
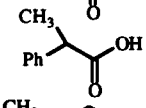
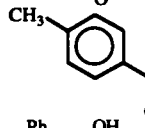
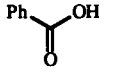
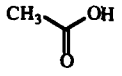
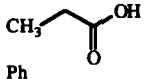
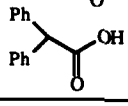
Primary and secondary alcohols react equally well, whereas tertiary alcohols, e.g. tert-butyl alcohol, not unexpectedly, give poor yields.

It should also be mentioned that the abovementioned reaction conditions, where a 12:1 mixture of pentane/dichloromethane is applied as a solvent, apparently are unsuitable for the preparation of phenol esters and for esters of benzoic acids. Thus, yields from the reaction of *p*-toluic acid with alcohols are uniformly below 2% when the reaction is performed as above in (pentane/dichloromethane).

We found, however, that the abovementioned reactions of *p*-toluic acid and reaction between phenol and aliphatic as well as aromatic carboxylic acids gave good yields of ester in other solvents, e.g. dichloromethane, when the phenol was added as the last component, that is after the NBS had reacted with the triphenylphosphine and the carboxylic acid for a couple of minutes. This behaviour bears some analogy to the action[7] of the PPh_3/CCl_4 system, which is reported to lead to good yields of ester only when the alcohol is added as the last component after a prereaction of the three-component system (triphenylphosphine/carbon tetrachlo-

TABLE I

Conversion of carboxylic acids to esters by means of triphenylphosphine and NBS[a]

Entry	Acid	Nucleophile	Ester. Yield (%)
1		CH_3CH_2OH	72
2		$(CH_3)_2CHOH$	76
3		$(CH_3)_3COH$	21
4		$(CH_3)CHCH_2CH_2OH$	88
5		$PhCH_2CH_2OH$	83
6		$PhCH_2OH$	81
7		CH_3CH_2OH	63
8		CH_3CH_2OH	64
9		CH_3CH_2OH	63
10		CH_3CH_2OH	0
11		CH_3CH_2OH	58[b]
12		CH_3CH_2OH	60[b]
13		PhOH	67[b]
14		$PhCH_2CH_2OH$	91
15		PhOH	0
16		PhOH	68[b]
17		$PhCH_2CH_2OH$	93
18		S-(+)-$CH_3CH_2CH(OH)CH_3$	72

[a]The reactions were carried out using pentane/dichloromethane as a solvent. [b]Dichloromethane was used.

ride/carboxylic acid) for about 2 hours. It is believed that this different behavior of alcohols/phenol and aliphatic/aromatic carboxylic acids, may be due mainly to solubility differences, partly of the reacting compounds, and, more importantly, of the various intermediates formed as the reaction proceeds.

The new synthesis can be performed under very simple experimental conditions. Unlike the PPh_3/CCl_4 system, the present method appears not very sensitive to air, moisture, or other impurities. Nearly all reactions were performed in vessels

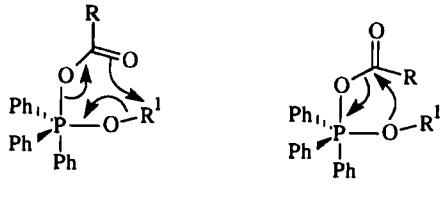
open to the atmosphere and rigorous anhydrous conditions were found to be inessential for the yield.

Very likely this convenient method can be applied also to substrates having more complex structures than that of the simple off the shelf chemicals available for the present investigation.

Several mechanisms may be postulated for the present transformation. Presumably the reaction proceeds by way of the acyloxyphosphonium salt **3** (Scheme II). Nucleophilic attack at this species by halide ion might lead to **4** via an intermediate acyl halide. A control experiment performed without any alcohol and pyridine added to the reaction mixture established, however, that under the abovementioned reaction conditions, acyl halides are not formed. Furthermore, the intermediate **3** may be attacked by the alcohol either directly at the carbonyl carbon in a rate determining step to give **4** via acyl-oxygen cleavage (path a), or via nucleophilic attack at phosphorus forming an intermediate phosphorane (path b).

In carbon as well as in phosphorus chemistry, reaction mechanisms and rates are greatly affected by the nature of the leaving group, although the relationship between structure and reactivity is not well understood. In the present case the oxyphosphonium group is a very good leaving group, and nucleophilic attack by the alcohol at the carbonyl carbon of **3** is hence possible. Owing to the rather low nucleophilicity of alcohols towards the carbonyl group, we believe, however, that the reaction proceeds along the path b mechanism, via the pentacoordinated intermediate **5** (Scheme II), probably by way of the four-membered cyclic transition state **7** (Scheme III). In the case of aliphatic alcohols there is additionally the possibility of a six-membered transition state as depicted in **6** (Scheme III). Steric considerations predict that **6** would lead to inversion at the secondary carbon atom, whereas **7** would preserve the stereochemistry of the alcohol.

The conversion of secondary alcohols to the corresponding halides by the Ph_3P/CCl_4 system is reported to lead to inversion of configuration at the secondary carbon atom.[13] Likewise Ramaiah[8] working at a modified version of the Ph_3P/CCl_4 method for the preparation of esters, utilizing carboxylic acid salts instead of the free acids, found that the esterification proceeds with inversion and racemization at the secondary carbon atom. Based on this evidence the author[8] suggested that the reaction proceeds either by way of a tight ion pair, or via the six-membered transition state **6** (Scheme III). In confirmation of the path b mechanism, via **7** (Scheme III), we investigated the reaction of diphenylacetic acid with S(+)-2-butanol in the presence of triphenylphosphine, pyridine and NBS as described in



6 **7**

SCHEME III

the experimental section. The reaction gave 72% of the expected ester, 2-butyl diphenylacetate **19**, whose $[\alpha]_D^{20}$ (40 mg/ml, $CHCl_3$) was +16.5°.

The same alcohol when esterified with diphenylacetyl chloride in the presence of an equivalent amount of pyridine with dichloromethane/ether as a solvent gave **19** (79%) with $[\alpha]_D^{20}$ (43 mg/ml, $CHCl_3$) +18.1°.

Thus, it appears that the Ph_3P/NBS esterification proceeds essentially with retention of configuration at the secondary carbon and that the four-membered transition state (**7**) is favoured over the six-membered one (**6**). This finding is consistent with the fact that the method apparently works equally well with phenol as with alcohols, yielding the corresponding esters in about the same yield.

The six-membered transition state can be excluded in the case of phenols, since ester formation via this mechanism, implying S_N2 attack on an aromatic nucleus, is inhibited.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken at operating frequencies of 200 and 50.3 MHz on a Varian Gemini-200 spectrometer. IR spectra were measured as films with a Perkin Elmer 1310 infrared spectrometer. Column chromatography was carried out using Merck No. 9385 silica gel 60. Melting points, determined with a Reichert Thermopan melting point microscope, are uncorrected.

One-flask preparation of esters from diphenylacetic acid. The esters (**1–6**) were prepared from diphenylacetic acid by the following one-flask procedure. To a two-necked flask fitted with an efficient stirrer was added diphenylacetic acid (1.06 g, 5 mmol), triphenylphosphine (1.45 g, 5.5 mol), alcohol (5 mmol), and pyridine (0.4 g, 5 mmol) in a mixture of pentane (12 ml) and dichloromethane (1 ml). To this admixture was added NBS (1.07 g, 5.5 mmol) in small portions. The reaction mixture was vigorously stirred during and after the addition. From the resulting yellow oil, formed almost immediately, crystallized after a couple of minutes triphenylphospine oxide together with succinimide and pyridinium hydrobromide. Stirring was continued for 1–2 h (3 h. in the case of **3**) at ambient temperature. More pentane (10–15 ml) was added and the solids separated by filtration. After washing the solids with pentane, the combined extracts were concentrated in vacuo and the ester distilled under reduced pressure.

Esterification of aromatic acids and of aliphatic acids with phenol. The reactants, triphenylphosphine and acid (5 mmol of each) were dissolved in dichloromethane (10 ml). The mixture was cooled and NBS (1.07 g, 5.5 mmol) added in one portion. The reaction mixture was vigorously stirred for 1–2 min., whereafter a mixture of pyridine and alcohol (or phenol), 5 mmol of each, was added in one portion. Stirring was continued for 1–2 h. at ambient temperature. Pentane was added and the solids (triphenylphosphine oxide, succinimide and pyridinium hydrobromide) separated by filtration as described above. The solvents were removed by evaporation at reduced pressure, and the remaining oil fractionated to give the pure ester.

Preparation of S(+)-2-Butyl diphenylacetate **18** *from diphenylacetyl chloride and S(+)-2-butanol.* To a solution of diphenylacetyl chloride (5 mmol) and S(+)-2-butanol (5 mmol) in ether (10 ml) was added pyridine (0.40 g, 5 mmol). The reaction mixture was stirred for 1 h. Pentane was added and the salt separated by filtration. Evaporation of the solvents, followed by distillation (Kugelrohr) of the remaining oil, yielded S(+)-2-Butyl diphenylacetate (1.06 g, 79%): bp 220°C/0.01 mm; ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, 3H, CH_3), 1.22 (d, 3H, CH_3), 2.45–2.68 (m, 3H, CH and CH_2), 5.00 (s, 1H, CH), 7.20–7.45 (m, 10H, Ph); MS (70 eV): m/z (%) 268 (2.2, M^+), 168 (15.8), 167 (100), 165 (19.5), 152 (10), 57 (10.9); IR (film) 1730 cm^{-1} (C=O); $[\alpha]_D^{20}$ (43 mg/ml, $CHCl_3$) +18.1°.

Ethyl diphenylacetate **1**: distilled (Kugelrohr) at about 250°C/3 mm; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* 7.0 Hz, 3H, CH_3), 4.22 (q, *J* 7.0 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 7.25–7.35 (m, 10H, Ph); MS (70 eV): m/z (%) 240 (18.5, M^+), 212 (12.9), 168 (18.3), 167 (100), 166 (17.7), 165 (38.1), 152 (12.3); IR (film) 1725 cm^{-1} (C=O).

2-Propyl diphenylacetate **2**: distilled (Kugelrohr) at about 270°C/3 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, J 6.2 Hz, 6H, CH_3), 4.98 (s, 1H, CH), 5.02–5.15 (m, J 6.2 Hz, 1H, CH), 7.20–7.35 (m, 10H, Ph); MS (70 eV): m/z (%) 254 (4.5, M^+), 168 (7.8), 167 (100), 166 (7.9), 165 (21.4), 152, (7.4); IR (film) 1725 cm^{-1} (C=O).

2-Methyl-2-propyl diphenylacetate **3**: distilled (Kugelrohr) at about 250°C/3 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H, CH_3), 4.92 (s, 1H, CH), 7.20–7.35 (m, 10H, Ph); MS (70 eV): m/z (%) 268 (1.0, M^+), 254 (1.0), 168 (22.5), 167 (100), 166 (7.4), 165 (14.8), 152 (8.2), 57 (66.4); IR (film) 1725 cm^{-1} (C=O).

3-Methyl-1-butyl diphenylacetate **4**: distilled (Kugelrohr) at about 220°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (d, J 6.2 Hz, 6H, CH_3), 1.49–1.70 (m, 3H, CH and CH_2), 4.19 (t, J 6.6 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 7.25–7.40 (m, 10H, Ph); MS (70 eV): m/z (%) 282 (9.2, M^+), 168 (16.5), 167 (100), 166 (8.2), 165 (15.5), 152 (8.1); IR (film) 1730 cm^{-1} (C=O).

2-Phenethyl diphenylacetate **5**: distilled (Kugelrohr) at about 250°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.93 (t, J 6.9 Hz, 2H, CH_2), 4.42 (t, J 6.9 Hz, 2H, CH_2), 5.01 (s, 1H, CH), 7.20–7.66 (m, 15H, Ph); MS (70 eV): m/z (%) 212 (8.6, $M^+ - C_8H_8$), 168 (15.9), 167 (100), 166 (10.6), 165 (24.7), 152 (12.7), 105 (28.8), 104 (61.6); IR (film) 1725 cm^{-1} (C=O).

Benzyl diphenylacetate **6**: distilled (Kugelrohr) at about 230°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.08 (s, 1H, CH), 5.20 (s, 2H, CH_2), 7.20–7.36 (m, 15H, Ph); MS (70 eV): m/z (%) 302 (1.1, M^+), 212 (1.2), 168 (14.8), 167 (100), 166 (7.9), 165 (20.5), 152 (9.3), 91 (22.7); IR (film) 1730 cm^{-1} (C=O).

Ethyl cinnamate **7**: distilled (Kugelrohr) at about 110°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J 7.1 Hz, 3H, CH_3), 4.31 (q, J 7.1 Hz, 2H, CH_2), 6.44 (d, J 16.0 Hz, 1H, CH), 7.37–7.56 (m, 5H, Ph), 7.70 (d, J 16.0 Hz, 1H, CH); MS (70 eV): m/z (%) 176 (36.2, M^+), 148 (12.4), 147 (10), 132 (12.6), 131 (100), 104 (11.3), 103 (37.8), 77 (23.4); IR (film) 1705 cm^{-1} (C=O).

Ethyl phenylacetate **8**: distilled (Kugelrohr) at about 100°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J 7.1 Hz, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.15 (q, J 7.1 Hz, 2H, CH_2), 7.26–7.42 (m, 5H, Ph); MS (70 eV): m/z (%) 164 (25.6, M^+), 91 (100), 65 (10.4); IR (film) 1730 cm^{-1} (C=O).

Ethyl 2-phenylpropanoate **9**: distilled (Kugelrohr) at about 110°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.70 (m, 9H, H(1,3,5)), 7.75–8.00 (m, 6H, H(2,6)), 9.09 (d, J 0.9 Hz, 1H, H(8)), 9.45 (d, J 2.1 Hz, 2H, H(10,11)); MS (70 eV): m/z (%) 178 (26.1, M^+), 150 (7.5), 106 (21.2), 105 (100), 104 (11.9), 103 (16.1), 86 (13.7), 84 (19.5), 79 (19.7), 77 (22.7); IR (film) 1730 cm^{-1} (C=O).

Ethyl p-toluate **11**: distilled (Kugelrohr) at about 110°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, J 7.1 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.36 (q, J 7.1 Hz, 2H, CH_2), 7.22–7.96 (m, 4H, Ph); MS (70 eV): m/z (%) 165 (10.1), 164 (42.8, M^+), 136 (39.4), 120 (37.8), 119 (100), 92 (14.3), 91 (40.1), 90 (10.8), 89 (16.3); IR (film) 1710 cm^{-1} (C=O).

Ethyl benzoate **12**: distilled (Kugelrohr) at about 250°C/3 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (t, 3H, CH_3), 4.40 (q, 2H, CH_2), 7.37–7.62 (m, 3H, Ph), 8.05–8.10 (m, 2H, Ph); MS (70 eV): m/z (%) 150 (31.2, M^+), 122 (42.5), 105 (100), 78 (40.8); IR (film) 1720 cm^{-1} (C=O).

Phenyl benzoate **13**: Isolated by silica gel chromatography, m.p. 71–72°C. Lit.[14] 71°C; MS (70 eV): m/z (%) 198 (4.2, M^+), 106 (8.2), 105 (100), 77 (39.5), 76 (2.0), 65 (3.2), 51 (10.8); IR (film) 1745 cm^{-1}, strong (C=O).

2-Phenetyl acetate **14**: The raw product was isolated by silica gel chromatography and distilled (Kugelrohr) at about 85°C/0.01 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3), 3.94 (t, 2H, CH_2), 4.30 (t, 2H, CH_2), 7.15–7.38 (m, 5H, Ph); MS (70 eV): m/z (%) 104 (100, $M^+ - C_8H_8$), 91 (17.4), 77 (11.2), 65 (12.5), 51 (10.5), 43 (56.2); IR (film) 1755 cm^{-1}, strong (C=O).

Phenylacetate **16**: distilled (Kugelrohr) at about 250°C/3 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3) 7.05–7.48 (m, 5H, Ph); MS (70 eV): m/z (%) 136 (14.8, M^+), 94 (100), 66 (8), 65 (6.7); IR (film) 1755 cm^{-1} (C=O).

2-Phenethyl propanoate **17**: The product was isolated by silica gel chromatography and distilled (Kugelrohr) at about 250°C/3 mm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, 3H, CH_3), 2.32 (q, 2H, CH_2),

2.95 (t, 2H, CH_2), 4.30 (t, 2H, CH_2), 7.15–7.60 (m, 5H, Ph); MS (70 eV): m/z (%) 104 (100, $M^+ - C_8H_8$), 91 (10.2), 57 (42.1); IR (film) 1730 cm^{-1} (C=O).

S(+)-2-Butyl diphenylacetate **18**: distilled (Kugelrohr) at about 220°C/0.01 mm; ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, 3H, CH_3), 1.22 (d, 3H, CH_3), 2.45–2.68 (m, 3H, CH and CH_2), 5.00 (s, 1H, CH), 7.20–7.45 (m, 10H, Ph); MS (70 eV): m/z (%) 268 (2.2, M^+), 168 (15.8), 167 (100), 165 (19.5), 152 (10), 57 (10.9); IR (film) 1730 cm^{-1} (C=O); $[\alpha]_D^{20}$ (40 mg/ml, $CHCl_3$) +16.5°.

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