Rapid Synthesis of an Advanced Functionalized Monocyclofarnesyl Intermediate Using 1,2-Dibromoethyl Ethyl Ether as a Bromoacetaldehyde Equivalent in the Synthesis of Furan-2(5*H*)-ones[1]

F. W. Joachim Demnitz, *[a] Ralph A. Raphael[b]

[a] SANDOZ Pharma AG, Preclinical Research, 350 K06, Basel, CH-4002, Switzerland
Fax +41(61)3243036

[b] University Chemical Laboratory, Lensfield Road, CB2 1EW, Cambridge, England

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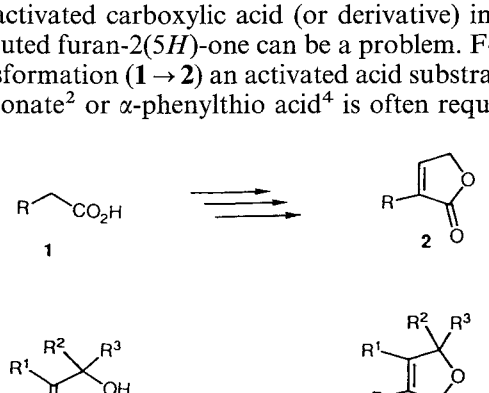
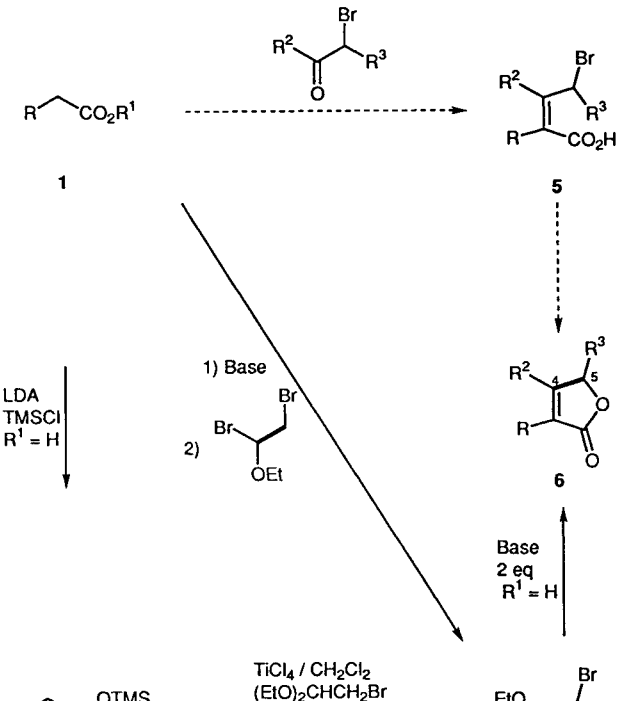
The lithium enolate of the ε-lactone **10** was reacted with 1,2-dibromoethyl ethyl ether to furnish **12**, treatment of which with aqueous K_2CO_3 gave a highly functionalized sesquiterpene of the monocyclofarnesyl skeleton the 3-substituted furan-2(5*H*)-one **13a**.

Whilst a wealth of methods exist for the synthesis of furan-2(5*H*)-ones, (butenolides) of varying degrees of complexity,[2,3] the theoretically simple transformation of an unactivated carboxylic acid (or derivative) into a 3-substituted furan-2(5*H*)-one can be a problem. For such a transformation (**1** → **2**) an activated acid substrate such as malonate[2] or α-phenylthio acid[4] is often required.



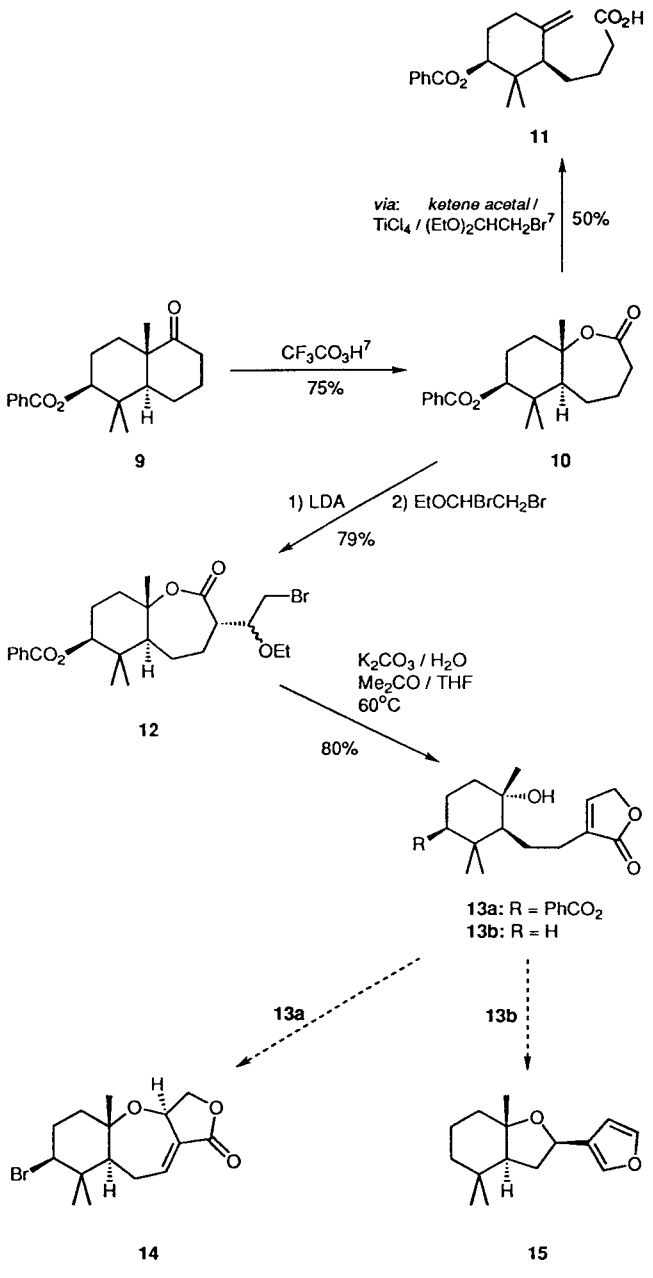
The condensation of acyloins **3** with active methylene compounds to give furan-2(5*H*)-ones **4** is known,[2] but we found that it fails for glycolaldehyde-derived simple 3-monosubstituted furan-2(5*H*)-ones, **4** (R^1, R^2, R^3 = H). Recent investigations have addressed the conversion of **1** into **2**, providing some solutions,[3,5] although the procedures together with the preparation of starting materials can be lengthy. Some years ago we provided a simple solution to this problem, which formally represents a Knoevenagel condensation of a carboxylic acid with an α-halo carbonyl compound followed by cyclisation (Scheme 1, **1** → **5** → **6**).[6]

The rationale in its simplest variant involved the Lewis acid mediated Mukaiyama reaction of a ketene(bistrimethylsilyl) acetal (KBTMSA) with bromoacetaldehyde diethyl acetal giving β-alkoxy-γ-bromo acids (**7** → **8**) which were converted to furan-2(5*H*)-ones **6** (R^2 = R^3 = H) by reaction with two equivalents of a base. We wish to report that in a small number of cases we have found a *base-mediated strategy* using 1,2-dibromoethyl ethyl ether as a two carbon alkylating agent at the bromoacetaldehyde oxidation level to prepare the intermediate **8**, a superior or alternative method for the same overall



Scheme 1

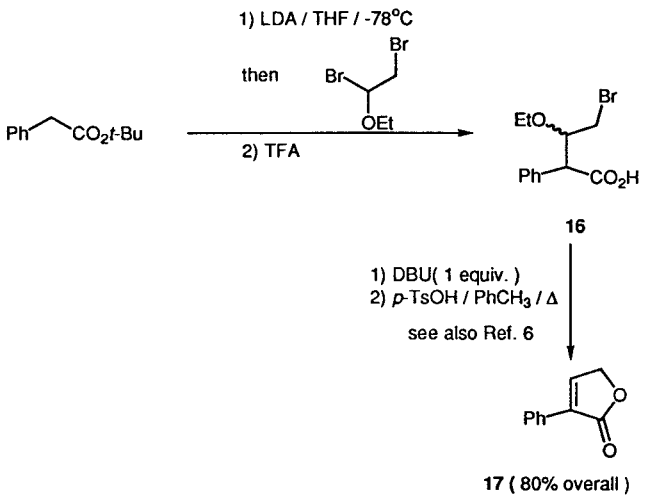
transformation. This method nicely complements our Lewis acid/KBTMSA procedure.[6] Thus, whereas our KBTMSA approach failed in the attempted synthesis of the α-(2-bromo-1-ethoxyethyl)lactone **12** from **10**, giving instead the *exo*-olefin **11**,[7] treatment of the lithio derivative of **10** (LDA/THF/TMEDA/ −78 °C) with 1,2-dibromoethyl ethyl ether gave exclusively the α-epimer **12** in 79% yield (1.4:1 diastereomer mixture).[8] Reaction of this product in K_2CO_3/H_2O/THF/acetone at 60 °C provided the hydroxyfuran-2(5*H*)-one **13a** (80%) in a one-pot procedure involving ε-lactone hydrolysis, γ-lactone ring closure and β-elimination of ethanol. Thus the highly functionalized monocyclofarnesyl skeleton and possible advanced natural product intermediate **13a** is available from the known ketone **9** in just 3 steps in 47% overall yield.[7] Compounds **13a** and **13b** have been envisaged by us as key intermediates for the syntheses of aplysistatin[9] **14** and ancistrofuran[10] **15**, respectively (Scheme 2).

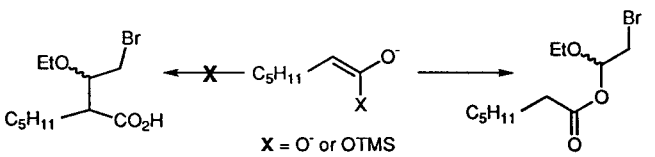


Scheme 2

Application of our masked bromoacetaldehyde reagent to three other cases met with mixed success. *tert*-Butylphenylacetate could be converted in high overall yield (80% without purification of intermediates) to 3-phenylfuran-2(5*H*)-one (**17**).[11] Reaction of heptanoic acid dianion or trimethylsilylheptanoate monoanion with 1,2-dibromoethyl ethyl ether under similar conditions and in direct analogy to our KBTMSA method on the other hand provided a highly unstable, unpleasant and difficult to characterize product for which structure **18** was proposed, based on its chemical and spectroscopic behaviour (Scheme 3).

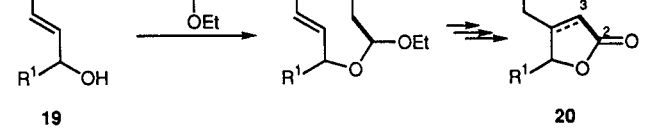
1,2-Dihaloalkyl alkyl ethers such as 2,3-dichlorotetrahydrofuran[12] have been used on rare occasions to alkylate enolate anions, but 1,2-dibromoethyl ethyl ether to our knowledge has not. This readily prepared[13] and storeable reagent has served as an electrophile mainly for





Scheme 3

Grignard reagents[14] and oxygen nucleophiles.[15–18] It is an interesting and useful two-carbon building block and bromoacetaldehyde equivalent, applicable in cases where bromoacetaldehyde itself may be inappropriate, such as the present one.[16] Interestingly this reagent has been used in a different approach to γ-lactones[16–18] and furan-2(5*H*)-ones[18] wherein the two carbons of 1,2-dibromoethyl ethyl ether give rise to carbons 2 and 3 in the final γ-lactone/furan-2(5*H*)-one product (Scheme 4, **19** →**20**), whereas in our case they result in carbons 4 and 5 in the final furan-2(5*H*)-one (Scheme 1, **1** →**8** →**6**).



Scheme 4

Melting points are corrected. ^{1}H NMR spectra (90, 250 MHz) were recorded using internal TMS or residual $CHCl_3$ protons as references. Preparative TLC was carried out using precoated silica gel F_{254} plates. AR grade solvents were used without purification or, where applicable, were purified using standard procedures. All commercial reagents were used without purification. Petrol refers to petroleum ether, bp 40–60°C.

***trans*-Decahydro-7β-benzoyloxy-6,6,9aβ-trimethyl-2-oxo-1-benzoxepin (10):**

A solution of **9**[7] (815 mg, 2.6 mmol) in anhyd CH_2Cl_2 (130 mL) slurried with Na_2HPO_4 (1.63 g) was treated with CF_3CO_3H[7] (2 equiv) in CH_2Cl_2. After stirring for 8 h at r.t. the mixture was

filtered through Celite, washed twice with sat. $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated in vacuo to a clear oil which was crystallised from EtOAc/hexane. Two crops and preparative TLC of the mother liquors (eluent: EtOAc/hexane, 1:1) gave the benzoate lactone **10**; R_f 0.31 (584 mg, 75% based on recovered starting material) as platelets; two recrystallisations from EtOAc provided an analytical sample; mp 146.5–149°C.

^1H NMR (90 MHz, $CDCl_3$): δ = 8.04 (2H, dd, J = 7.5, 1.5 Hz), 7.63–7.53 (1H, m), 7.51–7.39 (2H, m), 4.85 (1H, dd, J = 12, 4 Hz), 2.79 (1H, br ddd, J = 13, 5, <2 Hz), 2.57 (1H, ddd, J = 13, 13, 3 Hz), 2.12–1.36 (9H, m), 1.57 (3H, s), 1.04 (3H, s), 1.00 (3H, s).

IR ($CHCl_3$): ν = 1715 cm^{-1}.

MS: m/z = 330 (M^+), 315, 208, 193, 105, 77.

$C_{20}H_{26}O_4$ calc. C 72.74 H 7.94 (330.4) found 72.80 7.78.

trans-Decahydro-7β-benzoyloxy-3α-(2′-bromo-1′-ethoxyethyl)-6,6,9aβ-trimethyl-2-oxo-1-benzoxepin (12):

A solution of benzoate lactone **10** (508 mg, 1.54 mmol) in anhyd THF (2.5 mL) was added dropwise over 6 min to LDA (1.1 equiv) in anhyd THF (8 mL) at −78% under an argon atmosphere. The solution was stirred for 30 min after which time TMEDA (0.25 mL, 1.7 mmol, 1.1 equiv) was added and stirring continued for a further 10 min. Then 1,2-dibromoethyl ethyl ether (786 mg, 3.39 mmol, 2.2 equiv) was added dropwise. Stirring was continued at −78°C for 3 h before the solution was allowed to warm to r.t. over 1 h. The mixture was quenched with sat. NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 2M HCl, sat. $NaHCO_3$ solution, brine and dried ($MgSO_4$). Concentration in vacuo gave a yellow gum which was taken up in EtOAc/petrol (1:1) and several drops of $CHCl_3$. Diastereomer-I (the more polar one) of the α-(2-bromo-1-ethoxyethyl)-ε-lactone **12** crystallised as platelets; mp 136–139°C. Preparative TLC of the mother liquor (eluent: EtOAc/petrol, 3:7) gave more of diastereomer-I (**12**); R_f 0.30 (total yield: 270 mg, 46% based on recovered starting material) and diastereomer-II (**12**); R_f 0.35 (192 mg, 33% based on recovered starting material); mp 122–124°C (needles from hexane) and starting material (96 mg, 19%).

Diastereomer-I:

^1H NMR (250 MHz, $CDCl_3$): δ = 8.03 (2H, dd, J = 7.5, 1.5 Hz), 7.63–7.53 (1H, m), 7.51–7.40 (2H, m), 4.84 (1H, dd, J = 12, 4 Hz), 4.00–3.91 (1H, m), 3.75 (1H, dd, J = 10, 3 Hz), 3.71–3.58 (2H, m), 3.35 (1H, dd, J = 10, 8 Hz), 2.92 (1H, ddd, J = 12, 5, <2 Hz), 2.20–1.53 (9H, m), 1.62 (3H, s), 1.24 (3H, t, J = 7 Hz), 1.04 (3H, s), 1.02 (3H, s).

IR ($CHCl_3$): ν = 1714 cm^{-1}.

MS: m/z = 401, 279, 264, 218, 105, 77.

$C_{24}H_{33}BrO_5$ calc. C 59.87 H 6.91 Br 16.60 (481.5) found 59.72 6.71 16.43

Diastereomer-II:

^1H NMR (250 MHz, $CDCl_3$): δ = 8.04 (2H, dd, J = 7.5, 1.5 Hz), 7.64–7.55 (1H, m), 7.52–7.41 (2H, m), 4.83 (1H, dd, J = 12, 4 Hz), 3.84 (1H, dd, J = 9, 2 Hz), 3.79–3.63 (3H, m), 3.50 (1H, dd, J = 9, 7 Hz), 2.94 (1H, ddd, J = 12, 7, <2 Hz), 2.38–1.35 (9H, m), 1.65 (3H s), 1.20 (3H, t, J = 7 Hz), 1.05 (3H, s), 1.03 (3H, s).

IR ($CHCl_3$): ν = 1712 cm^{-1}.

MS: m/z = 401, 400, 358/360, 278, 263, 217, 105, 77.

$C_{24}H_{33}BrO_5$ calc. C 59.87 H 6.91 Br 16.60 (481.5) found 59.64 6.91 16.78

4β-Benzoyloxy-2β-(2′-(3″-furan-2″(5″*H*)-onyl)ethyl)-1β,3,3-trimethylcyclohexanol (13a):

Diastereomer-I **12** (82 mg, 0.17 mmol) was heated to 60°C in a mixture of 5% aq K_2CO_3 (0.65 mL), acetone (1.95 mL) and THF (1.3 mL) for 13 h. The cooled mixture was acidified with 2M HCl and the layers were separated. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with water and brine. Drying ($MgSO_4$), filtration and concentration in vacuo gave a clear colourless gum which was taken up in hot EtOAc/hexane and cooled for crystallisation. One crop gave **13a**; mp 169.5–170°C and preparative TLC of the mother liquor (eluent: EtOAc/petrol, 7:3) gave more of the desired product; R_f 0.22 (total yield: 50 mg, 80%) together with a small amount of the corresponding β-ethoxy-γ-lactone which could be resubjected to the reaction conditions in order to provide more of the desired **13a**.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.03 (2H, dd, J = 7.5, 1.5 Hz), 7.62–7.54 (1H, m), 7.50–7.40 (2H, m), 7.18 (1H, t, J = 2 Hz), 4.86–4.75 (3H, m), 2.63–2.40 (2H, m), 2.00–1.50 (8H, m), 1.28 (3H, s), 1.02 (3H, s), 1.00 (3H, s).

IR ($CHCl_3$): ν = 3580, 3475, 1755, 1712, 1657 cm^{-1}.

MS: m/z = 357, 354, 250, 235, 232, 105, 77.

$C_{22}H_{28}O_5$ calc. C 70.94 H 7.58 (372.5) found 70.64 7.46

Diastereomer-II of **12** gave an identical result.

4β-Benzoyloxy-2β-(3′-carboxypropyl)-3,3-dimethylmethylenecyclohexane (11):

The benzoate lactone **10** (85 mg, 0.257 mmol) in anhyd THF (1.5 mL) was added dropwise to LDA (1.1 equiv) in THF (2 mL) at −78°C under an argon atmosphere. After 30 min TMSCl (0.12 mL, 0.9 mmol) was added and the mixture allowed to warm to r.t. It was diluted with CCl_4, filtered through Celite and concentrated in vacuo. Repetition of this process gave a pale yellow oil (100 mg) which was dissolved in CH_2Cl_2 (0.5 mL) and added dropwise to a solution of $TiCl_4$ (0.03 mL, 0.27 mmol) and bromoacetaldehyde diethyl acetal (0.04 mL, 0.27 mmol) in anhyd CH_2Cl_2 (2.5 mL) at −78°C under argon. The resulting solution was stirred for 30 min, quenched with a solution of KH_2PO_4 (19 mg) and Na_2HPO_4 (19 mg) in water (2 mL) and allowed to warm to r.t. The mixture was extracted with CH_2Cl_2 and the organic layers were washed with water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow gum (90 mg) which upon preparative TLC (eluent: EtOAc/petrol, 4:6) yielded recovered lactone **10** (37 mg, 44%); R_f 0.25 and olefin acid **11** (40 mg, 50%); R_f 0.38 as a gum.

^1H NMR (90 MHz, $CDCl_3$): δ = 9.98 (1H, br s), 8.07 (2H, dd, J = 7.5, 1.5 Hz), 7.63–7.33 (3H, m), 5.06–4.83 (2H, m), 4.68 (1H, br s), 2.60–1.39 (11H, m), 1.00 (3H, s), 0.90 (3H, s).

IR ($CHCl_3$): ν = 3520, 3400–2400, 1705 cm^{-1}.

MS: m/z = 330 (M^+), 257, 208, 105.

HRMS: m/z (M^+) calc. for $C_{20}H_{26}O_4$: 330.1831; found: 330.1837.

(2-Bromo-1-ethoxyethyl)phenylacetic Acid (16):

A solution of *tert*-butyl phenylacetate (2 g, 10.4 mmol) in anhyd 1,2-dimethoxyethane (DME, 3 mL) was added dropwise to a solution of LDA (1.1 equiv) in anhyd DME (8 mL) at −78°C under an argon atmosphere. More DME (5 mL) and Et_2O (5 mL) were added to the resulting suspension. After 15 min 1,2-dibromoethyl ethyl ether (3 mL, 2.1 equiv) was added dropwise and the mixture stirred at −78°C for 45 min before allowing to warm to r.t. over another 30 min. The mixture was diluted with Et_2O and washed with cold 0.5M HCl, water and brine. Drying (Na_2SO_4) and concentration in vacuo gave a brown oil (3.42 g, 96% crude) which was used without further purification.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.23 (5H, br s), 4.14–2.97 (6H, m), 1.43 (9H, s), 1.63 and 0.83 (3H, 2 t, J = 7 Hz).

IR ($CHCl_3$): ν = 1720 cm^{-1}.

MS: m/z = 344/342 (M^+), 288/286, 271/269, 153/151.

HRMS: m/z (M^+) calc. for $C_{16}H_{23}BrO_3$: 344.0810; found: 344.0838.

This *tert*-butyl ester (7.7 g, 22.4 mmol) was stirred at r.t. in TFA (100 mL) for 1 h. Removal of the solvent in vacuo gave a grey solid which was filtered through a short plug of silica gel (eluent: EtOAc/petrol, 7:3 and a trace of AcOH) and concentrated in vacuo again to give the acid **16** as an off-white solid (1:1 mixture of diastereomers) (5.92 g, 92%) which was pure by TLC.

^1H NMR (90 MHz, $CDCl_3$): δ = 9.05 (1H, br s), 7.43 (5H, br s), 4.32–2.91 (6H, m), 1.20 and 1.04 (3H, 2 t, J = 7 Hz).

IR ($CHCl_3$): ν = 3490, 3400–2300, 1745 cm^{-1}.

MS: $m/z = 288/286$ (M^+), 242/240, 206, 153/151.

HRMS: m/z (M^+) calc. for $C_{12}H_{15}BrO_3$: 286.0205; found: 286.0206.

3-Phenylfuran-2(5*H*)-one (17):

The crude γ-bromo acid **16** (5 g, 17.4 mmol) in anhyd CH_2Cl_2 (200 mL) at −5°C was treated dropwise with DBU (2.6 mL, 0.99 equiv). After stirring for 75 min the solution was concentrated in vacuo and triturated with EtOAc/hexane. The DBU · HBr salt was filtered and the filtrate passed through a plug of silica gel. Removal of solvents in vacuo gave β-ethoxy-α-phenylbutyrolactone as a yellow oil (3.52 g, 98%) (1:1 mixture of diastereomers).

^1H NMR (90 MHz, $CDCl_3$): $\delta = 7.35$ (5H, br s), 4.65–4.13, 3.93–3.75 and 3.66–2.82 (6H, m), 1.12 and 0.89 (3H, 2 t, $J = 7$ Hz).

IR ($CHCl_3$): $\nu = 1778\ cm^{-1}$.

MS: $m/z = 206$ (M^+), 160, 118.

HRMS: m/z (M^+) calc. for $C_{12}H_{14}O_3$: 206.0942; found: 206.0942.

A solution of this crude butyrolactone (512 mg, 2.48 mmol) in anhyd toluene (8 mL) containing $TsOH \cdot H_2O$ (118 mg, 0.25 equiv) was heated at reflux for 4 h. The cooled solution was diluted with $CHCl_3$, washed twice with sat. $NaHCO_3$ solution and concentrated in vacuo. The residue was crystallised from isopropyl ether to give **17** (370 mg, 93%. 80% overall for 3 steps) in two crops, mp 85–87°C [Lit.[19] mp 89°C (benzene/petroleum ether)].

^1H NMR (90 MHz, $CDCl_3$): $\delta = 7.78$–8.03 (2H, m), 7.69 (1H, t, $J = 1$ Hz), 7.45 (3H, m), 4.93 (2H, d, $J = 1$ Hz).

IR ($CHCl_3$): $\nu = 1761, 1646\ cm^{-1}$.

MS: $m/z = 160$ (M^+), 132, 103.

$C_{10}H_8O_2$ calc. C 74.99 H 5.03 found 75.19 4.97

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(1) This work was carried out as part of a Ph. D. Thesis at the University Chemical Laboratory, Lensfield Road, CB2 1EW, Cambridge, England.

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