Optically Active Heteroaromatic Compounds. Part 8.† A Synthetic Approach to (*S*)-2-s-Butylfuran

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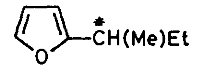
The palladium-catalysed decarbonylation of (*S*)-2-s-butyl-5-ethoxytetrahydrofuran-2-carbaldehyde, obtained by oxidative rearrangement of (*S*)-2-ethoxy-5-s-butyl-3,4-dihydro-2*H*-pyran, yields (*S*)-2-s-butylfuran with a 26% maximum racemization.

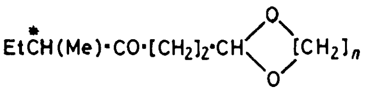
Our interest in developing effective methods[1,2] for the synthesis of optically active monoalkylfurans of high enantiomeric purity, bearing the asymmetric centre directly bound to the nucleus, led us to attempt the preparation of (*S*)-2-s-butylfuran (1) from (*S*)-5-methyl-4-oxoheptanal (2) or its cyclic acetals (3a, b).



(1)

$Et\overset{*}{C}H(Me)\cdot CO[CH_2]_2\cdot CHO$

(2)



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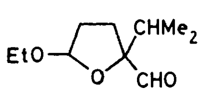
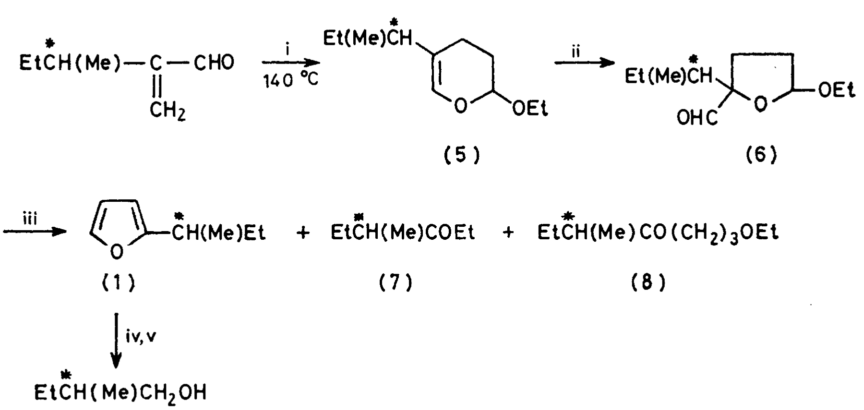


(4)

a; *n* = 2
b; *n* = 3

Compounds (2) and (3a, b) were prepared in satisfactory yield (64—67%) from (*S*)-2-methylbutanoic acid following (i) Stowell's[3] and (ii) Kondo and Tunemoto's[4] procedures. Attempted cyclization of (2) or (3a) either failed or afforded only traces of (1): the treatment of (3b) with oxalic acid afforded (25% yield) an almost completely racemized (1).



Scheme Reagents: i, EtO·CH=CH$_2$, 140 °C; ii, MCPB, 0 °C; iii, Pd–C; iv, O$_3$; v, LiAlH$_4$

Recently it was found that 2-alkoxy-3,4-dihydro-2*H*-pyrans undergo a peracid oxidative rearrangement to 5-alkoxytetrahydrofuran-2-carbaldehydes.[5] Therefore, we converted (*S*)-2-ethoxy-5-s-butyl-3,4-dihydro-2*H*-pyran (5), readily available through a cycloaddition reaction[6] of (*S*)-2-s-butylacrolein[7] to ethyl vinyl ether, into (*S*)-2-s-butyl-5-ethoxytetrahydrofuran-2-carbaldehyde (6) (see Scheme). The best conversion (⩾85%) of (*S*)-2-s-butylacrolein into (5) was achieved at 140 °C using an acrolein–vinyl ether molar ratio of 1 : 5 in order to reduce the isomerization and dimerization products of 2-alkylacrolein (20—22 and 7—8% respectively) which were found at a lower acrolein : vinyl ether (1 : 2) molar ratio.[6]

The oxidative rearrangement of (5) into (6) turned out to be useful because it occurs in high yield (78—88%) and, further, the asymmetric centre in the side-chain should not, on the basis of the proposed mechanism,[5] be involved during the ring contraction of (5). Therefore we devoted our efforts to catalytic conversion of (6) into (1).

Although heating of 5-ethoxy-2-isopropyltetrahydrofuran-2-carbaldehyde (4) in the presence of [RhCl(CO)(PPh$_3$)$_2$] gave no reaction, stoicheiometric decarbonylation of aldehyde occurred, in the presence of [RhCl(PPh$_3$)$_3$] in benzonitrile,[8] affording [RhCl(CO)(PPh$_3$)$_2$] (almost quantitative yield) together with 2-methylpentan-3-one (80% yield); no furan was produced.

Better results were achieved when (4) was heated at 130—200 °C in the presence of a catalytic amount of Pd–C (10%)[9] when 2-methylpentan-3-one (33%) and 2-isopropylfuran (67%) were obtained (g.l.c.).

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† Part 7, ref. 6.

Analogous treatment of (6) in the presence of Pd–C (5%) produced (1) (60%), 4-methylhexan-3-one (7) (20%), and small amounts of (*S*)-1-ethoxy-5-methylheptan-3-one (8).*

Compound (1) was isolated by preparative g.l.c. in 10—15% overall yield (see Scheme). The best experimental results were obtained carrying out the reaction on small amounts of (6) (10 mmol) and distilling the products as soon as formed.

It should be noted that the catalyst recovered after the reaction and washed with pentane always displayed the same activity in this reaction. Compounds (1) and (7) were both optically active: for the ketone (7) an (*S*)-configuration and a rather low optical purity (12%)[10] were found.

In order to determine its absolute configuration and optical purity, (1) was cleaved by ozone: the reduction of the resulting ozonide with $LiAlH_4$ gave (*S*)-2-methylbutan-1-ol (73% optical purity).†,[11] On this basis a 26% racemization with respect to (*S*)-2-s-butylacrolein[7] was evaluated (Scheme).

Samples of (*S*)-2-s-butylfuran (1) with higher optical purity (up to 84%) were obtained in successive runs, the stereochemical course of this reaction depending on the features of the catalytic process (heterogeneous conditions) and on the distillation rate of the products from the reaction vessel.

EXPERIMENTAL

B.p.s are uncorrected. G.l.c. analyses were performed on a Perkin-Elmer F-30 or a C. Erba Fractovap model GT gas chromatograph, using the columns and the temperatures specified. N.m.r. spectra were recorded with a Varian T-60 or a JEOL PS 100 spectrometer, on pure liquids unless otherwise specified with $SiMe_4$ as internal standard. I.r. and mass spectra were obtained with a Perkin-Elmer 225 spectrophotometer and a Varian Mat CH 7 mass spectrometer respectively. Optical rotations were taken either with a Perkin-Elmer 142 or a Schmidt–Haensch polarimeter and refer to pure liquids unless otherwise stated. THF refers to tetrahydrofuran and MCPB to *m*-chloroperbenzoic acid.

(S)-2-(4-*Methyl*-3-*oxohexyl*)-1,3-*dioxan* (3b).—A solution of 2-(2-bromoethyl)-1,3-dioxan (21.2 g, 0.11 mol) in THF (65 ml) was treated with magnesium turnings (3.4 g, 0.14 mol) in THF (20 ml) and refluxed for 10 min after the addition was completed. After cooling to room temperature, the resulting mixture was filtered under nitrogen into a dropping funnel. This solution was then added with stirring to freshly distilled (*S*)-2-methylbutanoyl chloride (12.1 g, 0.11 mol), α_D^{25} (*l* 1) +17.2° (96% optical purity), in THF (80 ml) at −70 °C.

After the addition, the reaction mixture was allowed to warm to room temperature and then maintained at 25 °C for 1 day. The solvent was removed, the residue hydrolysed with a saturated solution of ammonium chloride, and the organic layer extracted with pentane. The solution was washed with sodium carbonate solution, dried (K_2CO_3), and the solvent removed under reduced pressure. Distillation of the residue gave pure (2 m 20% Silicone oil 550 on Chromosorb W column at 180 °C) (3b) (14.2 g, 64%); b.p. 77—78 °C/0.2 mmHg; α_D^{25} (*l* 1) +16.1°; *m/e* 200 (M^+); δ(CCl_4; 60 MHz) 0.7—1.3 (m, 6 H), 1.3—2.0 (m, 6 H), 2.1—2.9 (m, 3 H), 3.3—4.1 (m, 4 H), and 4.48 (t, 1 H) (Found: C, 65.44; H, 9.85. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%).

(S)-2-*s-Butylfuran* (1) *and* (S)-5-*Methyl*-4-*oxoheptanal* (2).—Hydrolysis of (3b) (9.0 g, 45 mmol) according to Stowell[3] gave a 2 : 1 mixture of (2) and (1) (2 m 20% Silicon oil 550 column at 150 °C). Fractional distillation gave (1), b.p. 134 °C, $[\alpha]_D^{25}$ +1.43 (*c* 1.115 in cyclohexane); *m/e* 124 (M^+) (Found: C, 77.3; H, 9.7. $C_8H_{12}O$ requires C, 77.37; H, 9.74), and (2), b.p. 92—93 °C/35 mmHg; α_D^{25} (*l* 0.1) +0.148°; δ(CCl_4; 60 MHz) 0.7—1.9 (m, 8 H), 2.42 (m, 1 H), 2.70 (s, 4 H), and 9.73 (s, 1 H); $\nu_{max.}$(CCl_4) 2 728, 1 732sh, and 1 710 cm^{-1}; *m/e* 142 (M^+).

(S)-2-(4-*Methyl*-3-*oxohexyl*)-1,3-*dioxolan* (3a).—n-Butyllithium (2 mol. equiv.) was added at −78 °C under nitrogen to a stirred solution of 2-(2-phenylsulphonylethyl)-1,3-dioxolan, m.p. 67—68 °C (24.3 g, 0.10 mol), and tetramethylethylenediamine (TMEDA) (23.2 g, 0.20 mol) in anhydrous THF (200 ml). After 2 h at 0 °C, the reaction mixture was transferred, under a nitrogen atmosphere, into a dropping funnel and added slowly at −78 °C to a solution of (*S*)-methyl 2-methylbutanoate (11.6 g, 0.1 mol), $[\alpha]_D^{25}$ +21.62 and hexamethylphosphoramide (20 ml) in THF (100 ml). After 2 h the reaction was completed by stirring the mixture for a further 12 h at room temperature.

The reaction mixture was hydrolysed with a saturated solution of ammonium chloride at 0 °C and extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed; the residual oil (31.0 g) of the crude (*S*)-2-(4-methyl-2-phenylsulphonyl-3-oxohexyl)-1,3-dioxolan, was used without further purification. A solution of this product (30.7 g, 97.6 mmol), propanol (300 ml), and water (30 ml) was treated with aluminium amalgam (*ca.* 15.5 g).[4,12] The mixture was stirred for 5 h, filtered, and the organic product was recovered in ether and dried (Na_2SO_4). The solvent was removed and (*S*)-2-(4-methyl-3-oxohexyl)-1,3-dioxolan (18.0 g, 99%) was obtained; b.p. 111 °C/0.6 mmHg; δ (60 MHz) 2.6 (m, 3 H), 3.8 (m, 4 H), and 4.8 (m, 1 H); *m/e* 186 (M^+) (Found: C, 64.2; H, 9.65. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%).

Attempted Cyclization of (S)-2-(4-*Methyl*-3-*oxohexyl*)-1,3-*dioxolan to* (1).—A sample of (3a) (2.5 g, 13.4 mmol) was boiled with 2N-sulphuric acid. The reaction product was steam-distilled and extracted with n-pentane. G.l.c. analysis [2 m 10% butanediol succinate (BDS) on Chromosorb W column at 100 °C] showed only traces of (1). Similar results were obtained with 0.1N and concentrated sulphuric acid. In a further experiment with the same 1,3-dioxolan (4.5 g, 24.2 mmol) in ethanol (3 ml), water (100 ml) and hydrochloric acid (3 drops) were added. The reaction product was recovered and identified as (2), whose treatment with toluene-*p*-sulphonic acid in refluxing benzene led only to polymeric products.

5-*Alkyl*-2-*ethoxy*-3,4-*dihydro*-2H-*pyrans*.—In a typical run (*S*)-2-s-butylacrolein (36.5 g, 0.33 mol), $[\alpha]_D^{25}$ +31.21, freshly distilled ethyl vinyl ether (106.5 g, 1.46 mol), and some crystals of hydroquinone were heated in a rocking

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* The outcome of this reaction seems to depend on the nature of the catalyst used: Pd–C (5 or 10%) (Fluka AG or Merck) gave substantially similar results (1) and (7) being the main products. However when Pd–C (5 or 10%) (Engelhard) was used (8) was the main product. A sample of pure (8) showed α_D^{25} (*l* 0.1) +0.34° (neat).

† $[\alpha]_D^{25}$ = −6.66 (3.020, n-heptane).

steel autoclave at 140 °C for 46 h.[6] Evaporation of the solvent and distillation afforded (*S*)-2-ethoxy-5-s-butyl-3,4-dihydro-2*H*-pyran (5) (51.3 g, 85%); b.p. 95—96 °C/15 mmHg; d_4^{25} 0.913 4; $[\alpha]_D^{25}$ +39.71 (Found: C, 71.3; H, 10.9. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.9%); δ (100 MHz) 0.8—1.5 (m, 11 H), 1.9 (m, 5 H), 3.7 (m, 2 H), 4.9 (m, 1 H), and 6.1 (s, 1 H); *m/e* 184 (M^+, 8%), 155 (32), 139 (11), 71 (100), 57 (13), 44 (62), 43 (44), and 41 (32); $\nu_{max.}$ 3 070, 1 665, 1 465, 1 455, 1 380, 1 375, 1 240, 1 165, and 1 070 cm^{-1}. In another run (*S*)-2-s-butylacrolein (19.1 g, 0.17 mol) and ethyl vinyl ether (60.6 g, 0.84 mol) gave (5) (27.0 g, 86%), $[\alpha]_D^{25}$ +43.37, $[\alpha]_D^{25}$ +44.31 (*c* 1.989 in n-heptane).

A similar reaction performed on 2-isopropylacrolein (36.5 g, 0.37 mol) with ethyl vinyl ether (90.0 g, 1.25 mol) afforded 2-ethoxy-5-isopropyl-3,4-dihydro-2*H*-pyran (38.0 g, 60%); b.p. 76—77 °C/10 mmHg; δ(CCl_4, 60 MHz) 1.0 (m, 6 H), 1.18 (m, 3 H), 1.8 (m, 4 H), 4.78 (m, 1 H), and 5.95 (m, 1 H); *m/e* 170 (M^+) (Found: C, 70.5; H, 10.6. $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%).

2-Alkyl-5-ethoxytetrahydrofuran-2-carbaldehydes (6) *and* (4).—To a solution of 70% MCPB (13.7 g, 56 mmol) in methylene chloride (150 ml) at 0 °C, was added dropwise (5) (10.0 g, 54 mmol), $[\alpha]_D^{25}$ +39.71°, dissolved in methylene chloride (20 ml).[5] The mixture was stirred at room temperature for 40 h and treated with a concentrated sodium hydrogencarbonate solution (75 ml). The solvent was removed and the residue diluted with ether. The ethereal solution was washed, dried (Na_2SO_4), and distilled to give (*S*)-5-ethoxy-2-s-butyltetrahydrofuran-2-carbaldehyde (6) (9.2 g, 85%); b.p. 74 °C/0.8 mmHg; δ (100 MHz) 1.35—2.24 (m, 7 H), 3.18—3.91 (m, 2 H), 5.06 (m, 1 H), and 9.33 (m, 1 H); *m/e* 171 ($M^+ - C_2H_5$, 100%), 155 (14), 97 (38), 87 (18), 85 (30), 83 (24), 69 (34), 57 (71), 55 (47), 43 (42), 41 (62), and 29 (51); $\nu_{max.}$ 2 710, 1 730, 1 465, 1 455, 1 375, 1 160, and 1 050 cm^{-1} (Found: C, 66.0; H, 10.05. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%).

In a further experiment (5) (11.5 g, 62 mmol), $[\alpha]_D^{25}$ +39.71, was added to 85% MCPB (13.8, 68 mmol) dissolved in wet ether (135 ml). The reaction mixture was worked up as usual and (6) (8.8 g, 71%) was recovered; α_D^{25} (*l* 0.1) −1.20°, $[\alpha]_D^{25}$ −11.67 (*c* 4.314 in carbon tetrachloride). Analogously 2-ethoxy-5-isopropyl-3,4-dihydro-2*H*-pyran (25.5 g, 0.15 mol) was treated with MCPB in methylene chloride to yield 5-ethoxy-2-isopropyltetrahydrofuran-2-carbaldehyde (4) (26.5 g, 93%); b.p. 94—97 °C/35 mmHg; δ(CCl_4, 60 MHz) 0.8—1.1 (m, 6 H), 1.10 (m, 3 H), 3.10—3.90 (m, 2 H), 5.16 (m, 1 H), and 9.44 (s, 1 H); *m/e* 157 ($M^+ - C_2H_5$, 100%), 69 (48), 43 (47), 111 (38), 41 (35), 83 (31), 85 (28), 57 (26), 55 (24), and 129 (20) (Found: C, 64.5; H, 9.7. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%).

Attempted Decarbonylation of (4).—(i) *With* $[RhCl(CO)(PPh_3)_2]$. Compound (4) (2.8 g, 15 mmol) and $[RhCl(CO)(PPh_3)_2]$ (0.200 g, 0.3 mmol) were heated with an oil-bath at 180 °C for 1 h, at 200 °C for an additional hour and then at 230 °C for 2 h. No reaction was noticed during this time. G.l.c. analysis of the mixture (2 m 5% Silicone SE 30 on Chromosorb W column at 90 °C) showed that the starting material was unchanged.

(ii) *With* $[RhCl(PPh_3)_3]$. A solution of (4) (0.3 g, 1.6 mmol) and $[RhCl(PPh_3)_3]$ (0.596 g, 0.64 mmol) in benzonitrile (5 ml) was heated, under nitrogen, at 165—170 °C (oil-bath) for 17 h.[13] During this time the deep red colour of this solution slowly turned to yellow.

G.l.c. analysis (2 m SE 30 at 70 °C) performed on the volatile materials, recovered by distillation, showed the presence of 2-methylpentan-3-one (80%), whose structure was determined by comparison of mass spectrum and g.l.c. retention time of an authentic sample. The residual reaction solution (3 ml) was treated with absolute ethanol (20 ml) and kept at −30 °C for 3 h: $[RhCl(CO)(PPh_3)_2]$ (0.430 g, 97%) was recovered upon filtration.

(iii) *With* 10% Pd–C. A sample of (4) (3.0 g, 16 mmol) was added, in a distillation apparatus, to 10% Pd–C (Merck) (0.80 g) at 130 °C. The temperature was raised to 200 °C and the reaction products, distilled as formed, were diluted with n-pentane, washed with water to remove ethanol, dried (Na_2SO_4), and distilled. G.l.c. analysis performed on the distillate showed the presence of 2-isopropylfuran [14] (67%) and 2-methylpentan-3-one (33%). A sample of 2-isopropylfuran, obtained by accurate distillation had b.p. 108 °C, n_D^{25} 1.446 0; δ(CCl_4, 60 MHz) 1.13 (d, 6 H), 2.9 (m, 1 H), 5.8 (m, 1 H), 6.12 (m, 1 H), and 7.18 (m, 1 H); *m/e* 95 (100), 110 (M^+, 34), 57 (23), 41 (18), 39 (15.5), 96 (8.5), 55 (8), and 27 (6.5).

(S)-2-*s-Butylfuran* (1).—In a typical run (6) (3.0 g, 15 mmol) was added at 180 °C to 5% Pd–C (1.0 g) (Fluka AG or Merck); the temperature was raised to 200 °C and the reaction products were recovered as above. G.l.c. analysis (2 m BDS column at 90—200 °C) of the mixture showed at shorter retention time the presence of two products: 2-s-butylfuran (1) (60%), and 4-methylhexan-3-one (7) (20%) identified by comparison with an authentic sample. At longer retention time a further by-product (10%) was detected. This last component was distilled off and (1) was separated from (2) by preparative g.l.c. (3 m 10% BDS on Chromosorb W 60—80 mesh column at 100 °C). From three combined preparations (*S*)-2-s-butylfuran (0.56 g, 10% overall yield) was recovered; b.p. 134 °C, α_D^{25} (*l* 0.1) +1.37°; δ($CDCl_3$, 100 MHz) 0.80 (t, 3 H), 1.25 (d, 3 H), 1.60 (m, 2 H), 2.74 (m, 1 H), 5.82 (m, 1 H), 6.12 (m, 1 H), and 7.12 (m, 1 H); *m/e* 124 (M^+, 20%), 95 (100), 81 (11), 67 (22), 41 (18), and 39 (16); $\nu_{max.}$ 3 180, 2 970, 2 920, 2 870, 1 592, 1 505, 1 465, 1 455, 1 380, 1 160, 882, 728, and 598 cm^{-1}. Analogously a sample of (7), α_D^{25} (*l* 0.1) +0.29°, was recovered too. When the reaction was carried out with 10% Pd–C (Engelhard) the recovered mixture showed, after the usual work-up, (1) (2%), (7) (*ca.* 20%) and the same longer-retained by-product previously noticed (*ca.* 70%); this last component was isolated by accurate distillation and identified as (*S*)-1-ethoxy-5-methylheptan-4-one (8); b.p. 140—142 °C/100 mmHg, α_D^{25} (*l* 0.1) +0.34°; δ (100 MHz) 0.74—1.55 (m, 11 H), 1.70 (m, 2 H), 2.42 (m, 3 H), and 3.25 (m, 4 H); *m/e* 172 (M^+, 9%), 126 (12), 115 (13), 87 (100), 73 (56), 72 (58), 57 (58), 43 (54), 41 (48), 31 (54), and 29 (56); $\nu_{max.}$ 3 970, 3 940, 3 880, 1 710, 1 465, 1 455, 1 380, 1 360, 1 115, and 785 cm^{-1} (Found: C, 69.8; H, 11.67. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%). In repeat runs, starting from (6) (50.1 g, 0.25 mol), obtained from (*S*)-2-s-butylacrolein, $[\alpha]_D^{25}$ +30.70°, after preparative g.l.c. purification, (1) (4.7 g, 15%), α_D^{25} (*l* 1) +15.91°, $[\alpha]_D^{25}$ +18.30° (*c* 3.032 in n-heptane), was recovered.

Reductive Ozonolysis of (1).—A sample of (1) (0.5 g, 4.0 mmol), α_D^{25} (*l* 0.1) +1.37°, was dissolved in anhydrous n-pentane (20 ml) and a stream of ozonized oxygen was allowed to flow into the solution for 3 h at 0 °C. The solvent was evaporated off under reduced pressure and the ozonide, dissolved in dry ether, was reduced with a suspension of lithium aluminium hydride (3.0 g, 79 mmol) in ether (100 ml). The reaction mixture was hydrolysed as usual and (*S*)-2-methylbutan-1-ol (0.075 g, 21%) was recovered after purification by g.l.c. (3 m 8% Carbowax 20 M on Chromosorb W 80—100 mesh column at 100 °C); it showed $[\alpha]_D^{25}$ $-4.83°$ (*c* 4.421 in n-heptane).

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