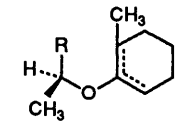
Yeast Reduction of Some Four-Carbon Chlorinated Ketones. A Convenient Synthesis of (*S*)-(+)-But-3-en-2-ol

Tuncel Ibrahim, Timothy J. Grattan and John Stanley Whitehurst
Department of Chemistry, The University, Exeter, EX4 4QD, UK

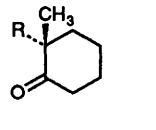
The action of fermenting yeast on various four-carbon chlorinated ketones has been studied. (*S*)-(+)-But-3-en-2-ol is conveniently prepared from (±)-3-chlorobutan-2-one which yields a 1:1 mixture of (2*S*,3*S*)-and (2*S*,3*R*)-3-chlorobutan-2-ols. Conversion of the mixture into the dimethylmethoxymethyl ethers followed by dehydrohalogenation and hydrolysis then gives (*S*)-(+)-but-3-en-2-ol.

The enol ether **1a** undergoes rearrangement[1] regiospecifically to yield compounds **2a** and **3a** (80.5:19.5). The ether **1b** on rearrangement gives regiospecifically and almost enantioselectively **2b** and **3b** (97:3). If, as seems likely, the allyl (as

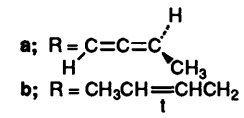


1

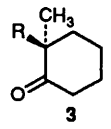
a; R = C≡CH
b; R = CH=CH$_2$
c; R = CCl=CH$_2$
d; R = CH=CHCl
t



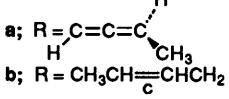
2



a; R = C=C=C(H)CH$_3$
b; R = CH$_3$CH=CHCH$_2$
t



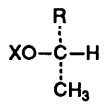
3



a; R = C=C=C(H)CH$_3$
b; R = CH$_3$CH=CHCH$_2$
c

4

a; R = CHClCH$_3$(±)
b; R = CH$_2$CH$_2$Cl
c; R = CHClCH$_2$Cl(±)
d; R = CH$_2$CHCl$_2$
e; R = CCl=CH$_2$
f; R = CH=CHCl
t



5

a; R = CHClCH$_3$(±), X = H
b; R = CHClCH$_3$(±), X = C(CH$_3$)$_2$OCH$_3$
c; R = CH=CH$_2$, X = C(CH$_3$)$_2$OCH$_3$
d; R = CH=CH$_2$, X = H
e; R = CHClCH$_2$Cl(±), X = H
f; R = CH$_2$CHCl$_2$, X = H

against propargyl) ether system is necessary to achieve high specificity then the compounds **1c** and **1d** might also be valuable intermediates because the side chains formed after rearrangement should be more easily modified than that of **2b** for annulation purposes.

The (*S*)-alcohols incorporated in **1a** and **1b** were prepared[1] by resolution of their racemates. In seeking more efficient routes to these alcohols and routes to those corresponding to **1c** and **1d** we turned to the yeast (*Saccharomyces cerevisiae*) fermentative reduction of some possible four-carbon precursors. Compounds of type **4**, if accepted by yeast would be expected[2] to yield predominantly or exclusively (*S*)-alcohols of type **5** (X = H). Santomauro[3] reported that (±)-3-chlorobutan-2-one was reduced by yeast to a laevorotatory 3-chlorobutan-2-ol. Since there is no recorded case of optical inversion occurring at carbon alpha- to single carbonyl groups in substrates under fermentation conditions, we expected that only one enantiomer of the ketone was being reduced. In practice we found that commercially available **4a** was accepted by yeast in relatively massive quantities and was transformed into a separable 1:1 mixture of chlorobutanols **5a** in 54–64% yield with less than 4% of ketone being recovered. Etherification of this mixture with 2-methoxypropene (oxalic acid dihydrate as catalyst) gave the ethers **5b** in quantitative yield. The ethers were unreactive to DBU but underwent smooth dehydrohalogenation with potassium t-butoxide in dimethylformamide[1] to yield compound **5c** (81%). Hydrolysis then gave pure (*S*)-(+)-but-3-en-2-ol,[1] proof that reduction at the carbonyl group had been stereospecific and had given a mixture of the (2*S*,3*S*)- and (2*S*,3*R*)-compounds. Also the elimination of hydrogen halide must have been essentially of Hofmann-type as no butan-2-one was detected in the product, and this points to the advantage of bulk in the protecting group and the base.

4-Chlorobutan-2-one **4b** (prepared from methyl vinyl ketone and hydrogen chloride[4]) was reduced by yeast but not stereospecifically; the chlorobutanol produced was of low optical rotation and its behaviour in NMR spectroscopy with the chiral shift reagent tris-3-(trifluoromethylhydroxymethylene)-(+)-camphoratoeuropium(III) was similar to that of the racemic alcohol. 3,4-Dichlorobutan-2-one **4c** (prepared[5] from methyl vinyl ketone and chlorine) was reduced as for the 3-chloro compound to a 1:1 mixture of compounds, presumably the (2*S*,3*S*)- and the (2*S*,3*R*)- diastereoisomeric alcohols **5e**. 4,4-Dichlorobutan-2-one **4d** was prepared[6] from acetyl chloride and vinyl chloride in the presence of aluminium chloride. As the compound lost hydrogen chloride on storage it was treated with yeast immediately. The product was a single optically active alcohol as judged by NMR spectroscopy with the aid of chiral shift reagent. Purification from unchanged ketone (10–20%) was effected by chromatography. Treatment of compound **4c** with potassium carbonate in a two-phase chloroform–water system furnished compound **4e** (84%). Previous methods for preparing this compound[7] have given very low yields. Compound **4d** was similarly converted (85%) into **4f**[6] for which the *trans* configuration is established by the coupling constant (*J* 22 Hz) between the two olefinic protons. Unfortunately neither **4e** nor **4f**, the intended progenitors of **1c** and **1d**, were accepted by yeast; fermentation ceased (although the yeast was

not killed) even at concentrations of substrate as low as 0.5 g dm^{-3} of vigorously fermenting suspension. These results were totally unexpected in view of examples given by Sih and Rosazza[8] for similarly constituted compounds. The bromine analogue of **4c** as well as methyl ethynyl ketone and methyl vinyl ketone were also not accepted.

Experimental

Petroleum refers to light petroleum (b.p. 40–60 °C) which had been stirred with concentrated sulphuric acid for *ca.* 3 h and then washed with water, aqueous sodium carbonate, and water again before being dried and distilled. IR spectra refer to liquid films. NMR spectra were taken in deuteriochloroform solution. Coupling constants *J* are given in Hz. Evaporations were conducted below 30 °C.

(S)-(+)-*But*-3-*en*-2-*ol*.—Fresh yeast (100 g) was dispersed in 3 dm^3 of deionised water in a 5 dm^3 conical flask. Sucrose (250 g) was added, the flask shaken and then fitted with a gas bubbler outlet; it was then placed in a constant temperature (30 °C) water bath. After 30 min 3-chlorobutan-2-one **4a** (Fluka AG; 25 g) was added to the vigorously fermenting liquid. Two days later all visible signs of fermentation had ceased and the clear yellow supernatant liquid was decanted and extracted thoroughly with ether (4 dm^3). The extracts after drying ($MgSO_4$) and evaporation yielded a weakly laevorotatory pale brown oil (16–18.5 g). GC (10% OV-101, 50 °C) showed the presence of unchanged ketone (2–4%) and the two diastereoisomers of 3-chlorobutan-2-ol **5a** with retention times of 6.0, 8.2 and 9.4 min respectively. Distillation gave *compounds* **5a**, b.p. 59–61 °C/40 mmHg (14–16.2 g, 55–64%) (Found: C, 44.2; H, 8.7. C_4H_9ClO requires C, 44.24; H, 8.31%); ν_{max}/cm^{-1}: 3380, 2975, 2930, 1445, 1378, 1154, 1118, 1082, 1010, 975, 922 and 806; δ_H 1.25 (6 H, d, *J* 10, CH_3CHOH, both isomers), 1.47 (3 H, d, *J* 10, CH_3CHCl), 1.52 (3 H, d, *J* 10, CH_3CHCl), 3.05 (2 H, s, exchangeable with D_2O, OH) and 3.5–4.4 (4 H, m, $CHOHCHCl$); δ_C 18.2 (intensity 36.4), 19.4 (37.4), 19.7 (28.3) and 21.3 (26.7) (methyl carbons), 63.7 (47.3), 64.7 (39.1), 71.1 (53.2) and 71.8 (40.5). The mixture of chlorobutanols (28 g) in ether (10 cm^3) was added dropwise to a stirred solution of oxalic acid dihydrate (0.2 g) in 2-methoxypropene (28 g) under nitrogen. After 1 h, evaporation gave the dimethylmethoxymethyl ethers **5b** in quantitative yield. A sample was purified by short column chromatography on Grade I alumina in petroleum; ν_{max}/cm^{-1}: 2982, 2935, 2825, 1445, 1375, 1206, 1180, 1150, 1080, 1060, 1014, 988, 910, 840, 828 and 682; δ_H 1.1–1.6 (12 H, complex), 3.25 (3 H, s, OCH_3) and 3.6–4.4 (2 H, m, CHC*H*. The above acetal **5b** (45 g) was added dropwise during 15 min to a stirred solution of potassium t-butoxide (42 g) in dimethylformamide (240 cm^3) under nitrogen. The solution darkened and became warm. After 90 min water (50 cm^3) was added and the solution extracted thoroughly with petroleum (2.5 dm^3). The combined extracts were washed with water (2 × 50 cm^3), dried (potassium carbonate), evaporated (finally at 50 mmHg) and distilled to yield the *acetal* **5c**, b.p. 75 °C/75 mmHg (29 g, 80%) (Found: C, 66.7; H, 11.4. $C_8H_{16}O_3$ requires C, 66.63; H, 11.18%); ν_{max}/cm^{-1}: 3070, 1452, 1378, 1258, 1207, 1070, 1055, 994, 853, 826 and 680; δ_H 1.25 (3 H, d, *J* 10 Hz, CH_3CH), 1.35 (6 H, s, CH_3CCH_3), 3.20 (3 H, s, OCH_3), 4.40 (1 H, m, CH_3CH), 5.12 (2 H, m, $C{=}CH_2$) and 5.88 (1 H, m, $CH{=}CH_2$).

To the stirred acetal **5c** (25 g) under nitrogen was added water (3.1 cm^3) and then oxalic acid dihydrate (0.3 g). After 20 min, GC (10% PEGA, 30, 70 and 90 °C) showed complete conversion to the butenol. No butan-2-one was detected. (*S*)-(+)-But-3-en-2-ol **5d** was isolated by distillation from a small amount of potassium carbonate, b.p. 97 °C/755 mmHg (10.35 g, 83%), $[\alpha]_D^{25}$ +25.4° (ether, *c* 1.2).[1] The methyl doublet at δ_H 1.28, *J* 7, remained a doublet in the presence of 0.10 molar proportion of tris-3-(trifluoromethylhydroxymethylene)-(+)-camphorato-europium(III), as against the two equal intensity doublets given by racemic but-3-en-2-ol.

4-*Chlorobutan*-2-*ol*.—A stirred solution of methyl vinyl ketone (35 g) in chloroform (500 cm^3) at −10 °C was treated with hydrogen chloride (18.2 g) during 1 h. The resulting dark brown liquid was washed with saturated aqueous sodium hydrogen carbonate (3 × 500 cm^3), evaporated, and distilled. 4-Chlorobutan-2-one **4b** (21.5 g, 50%) was collected at 47 °C/14 mmHg; GC (10% OV-1, 80 °C) showed one peak; δ_H 2.19 (3 H, s, CH_3CO), 2.91 (2 H, t, *J* 7, CH_2CO) and 3.74 (2 H, t, *J* 7, CH_2Cl). The ketone (2.13 g) in ethanol (5 cm^3) was added to a stirred solution of sodium borohydride (0.38 g) in ethanol (50 cm^3) to yield after work-up (±)-4-chlorobutan-2-ol (1.49 g, 69%) as a colourless liquid. A sample was purified by GC (10% OV-1, 80 °C) (Found: C, 44.4, H, 8.1. C_4H_9ClO requires C, 44.24; H, 8.31%); ν_{max}/cm^{-1}: 3540, 1373, 1330, 1289, 1242, 1170, 1128, 1075, 1014, 951, 932, 909, 880, 850, 729 and 660; δ_H 1.26 (3 H, d, *J* 8, CH_3CHOH), 1.75–2.05 (3 H, m, includes exchangeable OH), 3.55–3.84 (2 H, m, CH_2Cl) and 4.08 (1 H, m, CH_3CHOH). Treatment of 4-chlorobutan-2-one with yeast gave, after chromatography (silica gel; ether–petroleum 1:1) 4-chlorobutan-2-ol, $[\alpha]_D^{25}$ +3.5° (ether, *c* 0.8) (16%). The ^1H NMR spectrum in the presence of tris-3- trifluoromethylhydroxy-methylene)-(+)-camphoratoeuropium(III) showed that this material was virtually racemic.

(2S,3S)- *and* (2S,3R)-3,4-*Dichlorobutan*-2-*ols* **5e**.—Chlorine (35.5 g) was passed during 3 h through a stirred solution of methyl vinyl ketone (35 mg) in carbon tetrachloride (250 cm^3) at −20 °C. The dark brown solution was evaporated and distilled. 3,4-Dichlorobutan-2-one **4c** was collected as a pale yellow oil (21.6 g, 31%), b.p. 66 °C/14 mmHg. GC (10% OV-1, 100 °C) showed one peak; ν_{max}/cm^{-1}: 2978, 2920, 1720, 1422, 1358, 1280, 1204, 1170, 1150, 1014, 978, 926, 716 and 660; δ_H 2.39 (3 H, s, CH_3CO), 3.85 (2 H, m, CH_2Cl) and 4.30 (1 H, m, $CHClCH_2Cl$). Treatment with yeast (2 g per dm^3 of fermenting liquid) gave a pale yellow oil (44%), GC (10% OV-1, 100 °C) showed unchanged ketone (5–10%) and two resolved peaks of equal intensity. Preparative GC did not separate the components completely; the mixture of *dichlorobutanols* **5e** was an oil (Found: C, 33.5; H, 5.9. $C_4H_8Cl_2O$ requires C, 33.56; H, 5.59%); ν_{max}/cm^{-1}: 3400, 2975, 2922, 1380, 1180, 1122, 1090, 912, 845, 820, 735 and 702; δ_H 1.31 (3 H, br d, *J* 10, CH_3CHOH of both isomers), 3.40 (1 H, s, exchangeable OH) and 3.6–4.7 (4 H, envelope).

3,4-*Dibromobutan*-2-*one*.—A stirred solution of methyl vinyl ketone (14 g) in carbon tetrachloride (100 cm^3) at −10 °C was treated with bromine (32 g) in carbon tetrachloride (100 cm^3) during 1 h; evaporation and distillation gave the title compound as a pale yellow oil (29 g, 63%), b.p. 65 °C/2 mmHg. GC (10% OV-1, 140 °C) showed one peak; ν_{max}/cm^{-1}: 2980, 2930, 2825, 1715, 1445, 1378, 1202, 1151, 1060, 970 and 832; δ_H 2.38 (3 H, s, CH_3), 3.85 (2 H, m, CH_2Br) and 4.61 (1 H, m, CHBr).

(S)-(+)-4,4-*Dichlorobutan*-2-*ol* **5f**.—A stirred suspension of powdered anhydrous aluminium chloride (66 g) in chloroform (100 cm^3) was treated at 5 °C with acetyl chloride (39 g) during 5 min and then acetic acid (0.5 g). Vinyl chloride (58 g) was then passed through the mixture during 90 min. After 15 min the brown viscous liquid was quenched with ice (500 g) and the organic layer removed, washed with water (50 cm^3), dried, evaporated, and then distilled through a 20 cm packed column. 4,4-Dichlorobutan-2-one **4d** was collected as a colourless liquid, b.p. 40 °C/2 mmHg (34 g, 48%); ν_{max}/cm^{-1}: 2980, 1720, 1582,

1365, 1248, 1160, 1028, 946, 940, 750 and 670; δ_H 2.20 (3 H, s, CH_3), 3.37 (2 H, d, *J* 10, CH_2) and 6.11 (1 H, m, *J* 10, $CHCl_2$). The compound lost hydrogen chloride slowly; it was treated with yeast (2 g dm^{-3}) and gave an oil purified from unchanged ketone (10–20%) by chromatography (silica gel, ether:petroleum 1:4) to yield (S)-(+)-4,4-*dichlorobutan*-2-*ol* **5f** (41%) (Found: C, 33.7; H, 5.9. $C_4H_8Cl_2O$ requires C, 33.56; H, 5.59%); $[\alpha]_D^{25}$ +39° (ether); ν_{max}/cm^{-1} 3400, 2960, 2920, 1372, 1262, 1220, 1130, 1029, 932, 900, 848, 752 and 662; δ_H 1.24 (3 H, d, *J* 8, CH_3), 2.28 (2 H, distorted t, CH_2), 3.10 (1 H, br s, exchangeable OH), 4.02 (1 H, sextet, *J* 8, C*H*OH) and 5.90 (1 H, distorted t, $CHCl_2$). The methyl doublet, at δ 1.24, remained a doublet in the presence of 0.1 molar tris-3-(trifluoromethylhydroxymethylene)-(+)-camphoratoeuropium(III).

3-*Chlorobut*-3-*en*-2-*one* **4e**.—3,4-Dichlorobutan-2-one (6 g) was added to a rapidly stirred mixture of chloroform (15 cm^3) and saturated aqueous potassium carbonate (30 cm^3). After 1 h the chloroform layer was separated, dried (K_2CO_3) and evaporated to leave a pale yellow, highly lachrymatory liquid **4e** (3.75 g, 84%); GC (10% OV-1, 80 °C) one peak. The compound was used immediately in an attempted yeast reduction; ν_{max}/cm^{-1}: 3050, 2920, 1695, 1590, 1360, 1252, 1218, 1160, 1090, 968, 932, 818 and 632; δ_H 2.35 (3 H, s, Me), 6.10 (1 H, d, *J* 2, =C*H*H) and 6.41 (1 H, d, *J* 2, =CH*H*).

trans-4-Chlorobut-3-en-2-one **4f** was prepared (85%) from 4,4-dichlorobutan-2-one as for the above 3-chlorocompound; GC (10% OV-1, 80 °C) one peak (Found: C, 45.25; H, 4.9. Calc. for C_4H_5ClO: C, 45.93; H, 4.78%); ν_{max}/cm^{-1}: 3062, 3000, 2918, 1670, 1578, 1420, 1365, 1290, 1250, 1162, 1005, 942, 895, 844, 818, 758, 712 and 670; δ_H 2.26 (3 H, s, Me), 6.49 (1 H, d, *J* 22, C*H*=CHCl) and 7.30 (1 H, d, *J* 22, CH=C*H*Cl).

Acknowledgements

We thank the SERC for financial support.

References

1 T. J. Grattan and J. S. Whitehurst, *J. Chem. Soc., Perkin Trans. 1*, 1990, 11.
2 V. Prelog, *Pure Appl. Chem.*, 1964, **9**, 179; R. MacLeod, H. Prosser, L. Fikentscher, J. Lanyi and H. S. Mosher, *Biochemistry*, 1964, **3**, 838; C. Neuberg, *Adv. Carbohydr. Chem.*, 1949, **4**, 75; D. D. Ridley and M. Stralow, *J. Chem. Soc., Chem. Commun.*, 1975, 400.
3 P. Santomauro, *Biochem. Z.*, 1924, **151**, 48.
4 L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, 1943, **65**, 1276.
5 F. Kienzle and P. Rosen, *Helv. Chim. Acta*, 1979, **62**, 442.
6 V. T. Klimko, V. A. Mikhalev and A. P. Skoldinov, *J. Gen. Chem.*, 1957, **27**, 415.
7 E. M. Kosower and G.-S. Wu, *J. Org. Chem.*, 1963, **28**, 633; A. A. Petrow and E. A. Leporskaya, *J. Gen. Chem.*, 1953, **23**, 1038.
8 J. B. Jones, C. J. Sih and D. Perlman, 'Applications of Biochemical Systems in Organic Chemistry,' Part I, Wiley, New York, 1976, pp. 75–77.

Paper 0/01848A
Received 25*th April* 1990
Accepted 9*th August* 1990