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REGIO- AND STEREOSELECTIVE HYDROGENATION OF METHYL SUBSTITUTED PENTADIEN-1-OLS BY BAKER'S YEAST[†]

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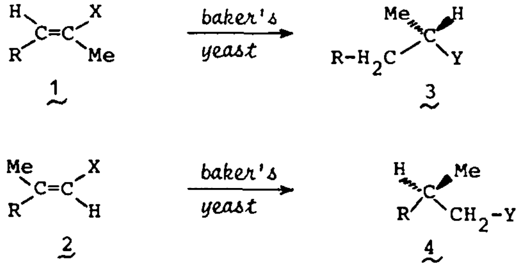
ABSTRACT. *(E)-2-methyl- and (E)-3-methyl-2,4-pentadien-1-ols are reduced to (S)-2-methyl- and (S)-3-methyl-4-penten-1-ols, respectively, using baker's yeast as a regio- and stereoselective reagent. This microbiological conversion provides an efficient route to bifunctional and enantiomerically pure C₆-building blocks containing the C'-CH(Me)-C'' grouping.*

It is now well known that baker's yeast is able to hydrogenate Michael activated CC double bonds[1-6]. A number of syntheses of enantiomerically pure natural products[1b,4a,c-e] have been reported, which take advantage of the high stereoselectivity of this reaction.



X=CHO Y=CH_2OH

X=Y= NO_2, CO_2Et, CH_2OH

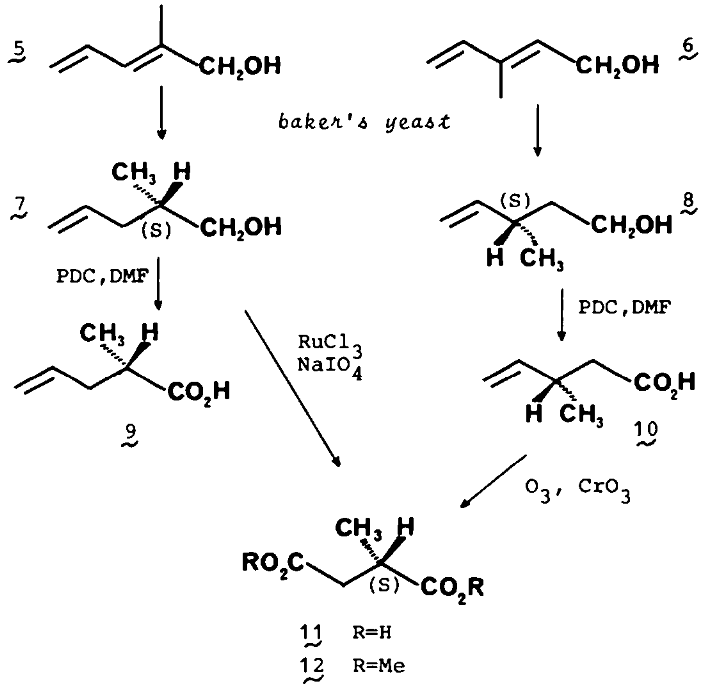
In considering that a chiral building block must have different functionalities at the ends of a short aliphatic chain, in order to be widely applicable, we saw the possibility of obtaining chiral synthons of type 3 and 4 with R= $-CH=CH_2$. The vinyl group is a very versatile function. In addition, having the double bond in α,β-position to a CH_2OH (or a COOH), such synthons represent a potential route to δ- and γ-cyclic ethers or lactones[7].

In this paper we wish to report that the enantiomerically pure chiral building blocks 7 and 8 can easily be obtained by baker's yeast reduction of the central double bond in the corresponding dienic alcohols 5 and 6 (Scheme).

5 was synthesized by Wittig condensation between acrolein and ethyl α-bromopropionate followed by lithium aluminium hydride reduction of the resulting ester. Only the desired (E)-configuration resulted from this Wittig reaction[8]. 6 was prepared by selective catalytic hydrogenation (Pd Lindlar and quinoline) of the commercial (E)-3-methyl-2-penten-4-in-1-ol.

Baker's yeast reductions of 5 were performed at 32 ° C and pH=8 for seven days. In contrast, the microbiological reduction of 6 was slower: after ten days the reaction had gone to 80% completion. The reduction products were isolated in 25-30% yields by steam-distillation in diethyl ether and subsequent flash chromatography. Care must be taken in the recovery of the fermentation products, because of the high volatility of these alcohols.

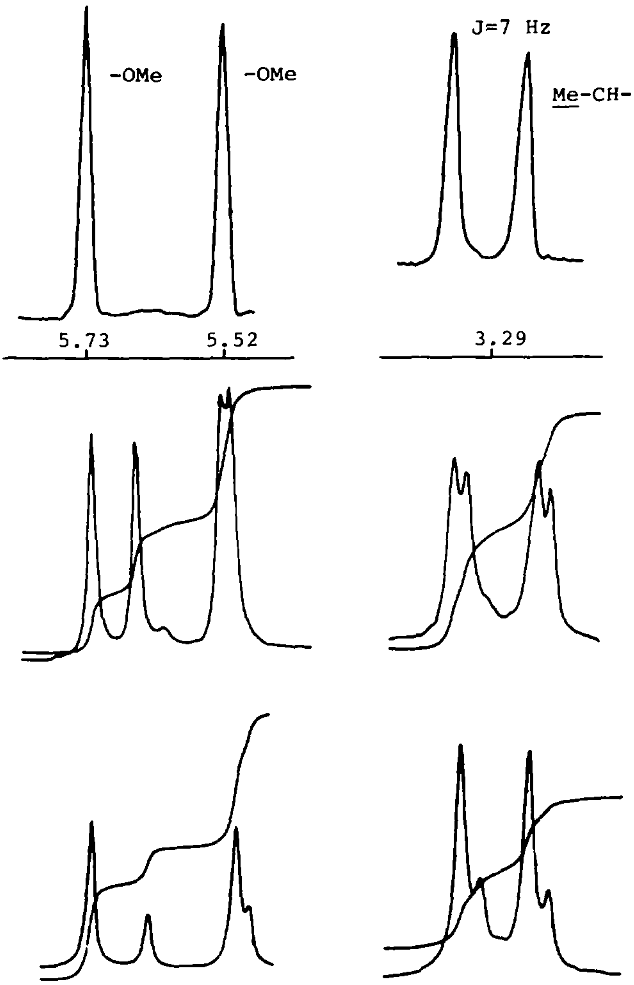
[†] Part 5 of the series "Microbial-mediated syntheses of EPC". For Part 4 see ref.4e.



SCHEME

The S-configuration of both the chirons 7 and 8 was established by a comparison of the optical rotations[9] and that of the corresponding acids (9 and 10) with the values reported in the literature for the same compounds prepared in other ways[10] The alcohols, resulting from microbial reduction, were transformed into (S)-2-methylsuccinic acid (11) (see Scheme) in order to determine their enantiomeric purity. This chemical correlation further confirmed the above assignment of configuration. (S)-(-)-2-Methylsuccinic acid was obtained in two different ways: by sodium periodate oxidation of alcohol 7, catalyzed by rutenium trichloride[11] and by oxidative (CrO_3) ozonolysis of acid 10. In both cases the acid 11 was converted into its dimethylester 12 by reaction with diazomethane and checked for enantiomeric purity by analysis of its ^1H-NMR spectrum with a chiral shift reagent.
The NMR spectrum of 12, when recorded in the presence of $Eu(hfc)_3$, exhibited two singlets due to methoxy group protons and a doublet due to the methyl group (Fig. 1a). Four singlets and two doublets were shown by the NMR spectrum of the racemic ester 12 recorded under the same conditions (Fig. 1b). This comparison indicated unequivocally the high enantiomeric purity of 2-methylsuccinic acid (~100%) and as a consequence demonstrates that baker's yeast hydrogenation of both 5 and 6 occurs with total enantioselectivity.

When the preparation of the (R)-enantiomer of 8 was attempted via yeast reduction of (Z)-6 or its corresponding aldehyde, the (S)-alcohol (8) was obtained, characterized by a slow enantiomeric excess ($<$ 25%). This result can be interpreted, as previously suggested for analogous microbial reductions[4a,12], in terms of: i) a (rapid) double bond isomerisation at the level of the intermediate aldehyde, and ii) probably, an enzymatic hydrogenation occurring at a slower rate for the (Z)- than for the (E)-configurated double bond.



a) (S)-ester, from 7 obtained by baker's yeast fermentation

b) (R,S)-ester

c) 1:1 mixture of (S)-ester (a) and (R,S)-ester (b)

FIGURE 1: ^{1}H-NMR spectra of dimethyl 2-methylsuccinate (12) with Eu(hfc)$_3$ (shift reagent/product molar ratio = 0.6)

It can be pointed out that the chirons 7-10, now readily available by the procedure described here, appear to be of great utility in the syntheses of natural products containing the stereogenic group C'-CH(Me)-C" with definite configuration. Thus, 7 has already been used in racemic form to prepare (±)-dihydro-β-santalol[13] (a sesquiterpene possessing the powerful, woody fragrance of East Indian sandalwood oil), while both the stereoisomer of 9, isolated by resolution of the racemic acid with quinine, were used to synthesize insect pheromones[10a] or analogues[10b] and a part of steroidal sapogenins (kryptogenin, diosgenin and yamogenin)[10c].

Compounds 8 and 10, obtained by chemical degradation of (R)-citronellate[7c,10d] or (R)-citronellene[9c], have also been widely employed as chiral building blocks in the synthesis of biologically active products: e.g. lasalocid A[9c] and monensin[7a] (antibiotics), ambruticin[7b] (antifungal agent), aplidiasphingosine[10d] (antimicrobial and antitumor marine terpenoid), eldanolide[7c] (pheromone of Eldana saccharina) and patchouli alcohol[9b] (an odorous compound).

Finally, it must be noted that in compounds 5 and 6 only the double bond contiguous to the alcoholic (or aldehydic) function is hydrogenated by baker's yeast. This high regioselectivity, uncommon with chemical reagents, could have relevant applications, for instance in the preparation of partially reduced polyenes.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker WP80 SY. Chemical shifts are reported in δ from internal Me$_4$Si. Optical rotations were measured in a 1.0 dm cell on a Perkin-Elmer Model 241 polarimeter. MS spectra were recorded on a Varian MAT 112 mass spectrometer. TLC were carried out on silica gel Merck 60 F$_{254}$ plates, normally using hexane-ethyl acetate as eluent. Flash chromatography was performed on silica gel Merck 60 (230-400 mesh). Baker's yeast was "Distillerie Italiane" brand from Eridania (San Quirico-Trecasali (Parma, Italy)).

(E)-2-Methyl-2,4-pentadien-1-ol (**5**). **5** *was prepared by* LiAlH$_4$ *reduction of the corresponding ester as reported in ref.14: IR (liquid film): 3500-3000, 2965, 1600* cm^{-1}*;* ^{1}*H-NMR as in ref.14; GC-MS (FFAP,* T=120°C, N$_2$=1.6 atm, R$_t$=3.84 min*): 98 (*M$^+$*, 38), 97 (7), 83 (42), 81 (5), 80 (24), 79 (24), 67 (11), 43 (100), 41 (95).*

General procedure for fermentations: *The substrate (3 g) in EtOH (5 ml) was gradually added to a suspension of baker's yeast (300 g) in preboiled buffer solution (pH=8). The mixture was stirred at 32-35°C for 7 or 10 days, while other baker's yeast (300-500 g) was added in daily portions. Completion of the reduction was monitored by GC analysis (FFAP,* N$_2$=1.6 atm, T=120°C*). After addition of NaCl, the product was steam distilled and continuously extracted by ether for 8 h. Drying with anhydrous* MgSO$_4$ *and cautious evaporation of the solvent (not under vacuum) by the Claisen and subsequently by the Vigreux apparatus gave the desired product, which was then purified by flash chromatography.*

(S)-(-)-2-Methyl-4-penten-1-ol (**7**). **7** *was prepared by baker's yeast fermentation of* **5** *for 7 days (30% yield):* $[\alpha]^{25}_D$ *-2.45° (c=0.3,* CHCl$_3$*) (lit.[9a] -2.62°); IR and* ^{1}*H-NMR data as in ref. 13b; GC-MS (FFAP, T=120°C,* N$_2$=1.6 atm, R$_t$=1.4 min*): 100 (*M$^+$*,1), 85 (1), 82 (25), 69 (20), 67 (75), 58 (35), 41 (100), 31 (50).*

(S)-(+)-2-Methyl-4-pentenoic acid (**9**). **7** *(650 mg, 5.7 mmol) in dry dimethylformamide (50 ml) was oxidized for 20 h at room temperature with pyridinium dichromate (21.33 g, 56.7 mmol) according to the Corey's method[15]:* $[\alpha]^{25}_D$ *+9.15° (c=1.94,* CHCl$_3$*) (lit. +10.5° (c=1.0,* CHCl$_3$*)[10a], +7.9° [10c], +8.24° [9a]); IR, NMR and MS data as in ref. 10a.*

(S)-(-)-2-Methylsuccinic acid (**11**). **7** *(112 mg, 1.12 mmol) was added to a solution of sodium metaperiodate (8.2 g, 0.0384 eq, 34.3 eq/mol) in water (9 ml), carbon tetrachloride (6 ml) and acetonitrile (6 ml). To this biphasic solution ruthenium trichloride hydrate was added (46.8 mg, 0.2 mmol) and the reaction was stirred vigorously for 3.5 h at room temperature. Then* CH$_2$Cl$_2$ *(20 ml) was added and the phases were separated. The upper aqueous phase was extracted with ethyl ether (30 ml) in a Soxhlet apparatus for 1 day. The ether extract were dried (*MgSO$_4$*) and evaporated. The white residue was recrystallised from ethyl ether:benzene (3:1) to give pure* **11** *(90 mg) in 60% yield:* $[\alpha]^{25}_D$ *-15.55° (c=2.16, abs.EtOH) (lit.[16] -15.0° (c=1.89, abs.EtOH));* ^{1}*H-NMR (*D$_2$O*): δ 1.2 (3H, d, J=7.5Hz, 5-*CH$_3$*), 2.3-3.14 (3H, m.* CH$_2$ *and CH); MS (dis, m/e): 115 (*M$^+$*-17, 26), 114 (88), 88 (20), 86 (100). Anal.Calcd for* C$_5$H$_8$O$_4$*: C,45.45; H, 6.10. Found: C, 46.08; H, 6.12.*

(S)-Dimethyl-2-methylsuccinate (**12**). **11** *(30 mg, 0.227 mmol) in methanol (5 ml) was treated for 2h with 100% excess of diazomethane (istantaneously prepared from N-methyl-N-nitroso-p-toluenesulfonamide (9 g) in ethyl ether (13 ml) and ethylenglycolmonomethylether (13 ml) treated with NaOH 6N (10 ml)). A drop of acetic acid was then added, the solvent was concentrated and the residue treated with ether. The ethereal solution was washed with sodium bicarbonate, then dried and evaporated to give pure* **12** *(35 g, 90% yield): IR (liquid film): 1730* cm^{-1}*;* ^{1}*H-NMR (*CDCl$_3$*): δ 1.2 (3H, d, J=7Hz, 5-*CH$_3$*), 2.13-3.1 (3H, m,* CH$_2$ *and CH), 3.65 (3H, s, 7-*OCH$_3$*), 3.68 (3H, s, 6-*OCH$_3$*); MS (dis, m/e): 160 (*M$^+$*,2), 129 (54), 128 (36), 101 (30), 87 (21), 59 (100). Anal. Calcd for* C$_7$H$_{12}$O$_4$*: C, 52.49; H, 7.55. Found: C, 51.01; H, 7.56.*

(E)-3-Methyl-2,4-pentadien-1-ol (**6**). *(E)-3-Methyl-2-penten-4-yn-1-ol (Merck, 5 g) in ethyl acetate (50 ml) was hydrogenated for 5-6 h in the presence of* Pd/BaSO$_4$ *(870 mg) and quinoline (500 mg). The solution was filtered on celite, washed with HCl 10%, the aqueous layer was washed with ethyl acetate, the combined organic phases were dried (*MgSO$_4$*) and carefully evaporated at room temperature.*

The residue was flash chromatographed (hexane:ethyl acetate 2:1) to give 6 (2.9 g, 90% GC purity, 50% yield): ^{1}H-NMR ($CDCl_3$): δ 1.3-1.7 (1H, broad s, exchanged with D_2O, OH), 1.8 (3H, broad s, CH_3), 4.3 (2H, d, J=7 Hz, $C\underline{H}_2OH$), 5.05 (1H, broad d, J_{BX}=11 Hz), 5.2 (1H, broad d, J_{AX}=16 Hz), 5.66 (1H, broad t, J=7 Hz, $=C\underline{H}CH_2OH$), 6.4 (1H, dd, J_{AX}=16 Hz, J_{BX}=11 Hz); GC-MS (FFAP, T=120°C, N_2=1.6 atm, R_t=3.7 min): 98 (M^+, 22), 97 (6), 83 (56), 79 (18), 70 (25), 69 (75), 41 (100). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.09; H, 10.42.

(S)-(+)-3-Methyl-4-penten-1-ol (8). 8 was prepared by baker's yeast fermentation of 6 for 10 days. The reaction was stopped when the starting material was still present (20%). The purification was performed by $AgNO_3$ (10%)-silica gel flash chromatography (hexane:ethyl acetate 2:1) to give 25% yield of 8: $[\alpha]^{25}_D$ +28.2° (c=0.27, $CHCl_3$) (lit. +29.22° (c=1.54, $CHCl_3$)[9c], +28.9° (c=1.05, $CHCl_3$)[9b]); IR and ^{1}H-NMR data as in ref. 9c; GC-MS (FFAP, T=120°C, N_2=1.6 atm, R_t= 1.2 min): 82 (M^+-H_2O, 31), 67 (100), 31 (14).

(S)-(+)-3-Methyl-4-pentenoic acid (10). 10 was obtained as 9 by PDC/DMF oxidation according to the Corey's procedure[15] (77% yield): $[\alpha]^{25}_D$ +13.9° (c=2.90, $CHCl_3$) (lit. +13.55° (c=3.3, $CHCl_3$)[9c], +17.3° (c=2.07, $CHCl_3$)[7c]); IR and ^{1}H-NMR data as in ref. 9c; MS (dis, m/e): 114 (M^+, 13), 96 (17), 87 (7), 73 (33), 69 (100), 60 (98). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.64; H, 8.91.

(S)-(-)-2-Methylsuccinic acid by oxidative ozonolysis of 10. O_3 in oxygen was bubbled into a stirred and cooled solution of 10 (118 mg, 1.05 mmol) in acetone (10 ml) at 78°C until saturation (blue color). To this solution of the ozonide, purged with a stream of nitrogen to remove the excess ozone, Jones reagent (2 ml) was added dropwise when the temperature was gradually raised to 0°C during 1 h. The mixture was diluted with water, water was extracted with CH_2Cl_2 then twice with ethyl ether. The ethereal extracts were dried ($MgSO_4$) and evaporated to give a white residue, which was recrystallised (ethyl ether: benzene 3:1) to obtain pure 11 (74% yield): $[\alpha]^{25}_D$ -14.9° (c=1.69, abs. EtOH).

(Z)-3-Methyl-2,4-pentadien-1-ol (13). 13 was prepared as the corresponding (E)-6, starting from commercial (Z)-3-methyl-2-penten-4-yn-1-ol (working in the dark): IR (liquid film): 3700-3100, 3080, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.3-1.75 (1H, broad s, exchanged with D_2O, OH), 1.85 (3H, broad s, CH_3), 4.25 (2H, d, J=7 Hz, $C\underline{H}_2OH$), 5.15 (1H, dd, J_{BX}=11 Hz, J_{AB}=2 Hz), 5.27 (1H, dd, J_{AX}=17 Hz, J_{AB}=2 Hz), 5.57 (1H, broad t, J=7 Hz, $=C\underline{H}CH_2OH$), 6.73 (1H, dd, J_{AX}=17 Hz, J_{BX}=11 Hz); GC-MS (FFAP, T=120°C, N_2=1.6 atm, R_t=3.97 min): 98 (M^+, 11), 83 (47), 81 (15), 80 (11), 79 (19), 41 (100). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.2; H, 10.1.

(Z)-3-Methyl-2,4-pentadien-1-al (14). 13 (2.35 g, 0.024 mol) in hexane (180 ml) was treated with activated MnO_2 (56.7 g, 0.652 mol) at 0°C for 1 h. Filtration on celite, drying ($MgSO_4$) and evaporation of the solvent gave pure title compound (1.75 g, 62%): IR (liquid film): 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.07 (3H, broad s, CH_3), 5.58 (1H, broad d, J_{BX}=10 Hz), 5.66 (1H, broad d, J_{AX}=17 Hz), 5.9 (1H, broad d, J=9 Hz, $=C\underline{H}CHO$), 7.35 (1H, dd, J_{AX}=17 Hz, J_{BX}=10 Hz), 10.17 (1H, broad d, J=9 Hz, CHO). Anal. Calcd for C_6H_8O: C, 74.97; H, 8.39. Found: C, 74.3; H, 8.09.

Fermentations of 13 and 14. 13 and 14 were reduced with baker's yeast in standard conditions and the fermentation reactions were controlled by GC (FFAP, T=120°C, N_2=1.6 atm). After 10 days the percentage of products was: **(Z)-alcohol fermentation**: 40% starting (Z)-alcohol (13), 3% (E)-alcohol (6), 45% saturated alcohol (8), 12% unknown compounds; **(Z)-aldehyde fermentation**: 20% (Z)-alcohol (13), 5% (E)-alcohol (6), 65% saturated alcohol (8), 10% unknown compounds. The saturated (S)-alcohol (8) was isolated in the usual manner after a flash chromatography on $AgNO_3$ (10%)-silica gel: $[\alpha]^{25}_D$ +6.5° (c=1.02, $CHCl_3$).

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