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ASYMMETRIC 1,4-ADDITIONS TO γ-MENTHYLOXYBUTENOLIDES. ENANTIOSPECIFIC SYNTHESIS OF CHIRAL 1,4-BUTANEDIOLS.

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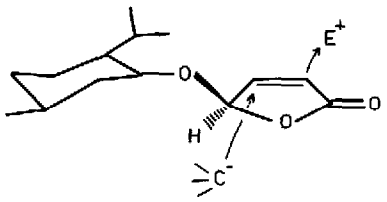
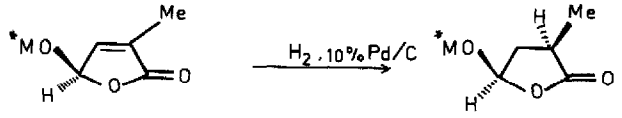
Abstract: Optically active methyl-substituted butanediols and γ-lactones were prepared from γ-menthyloxy-2[5H]-furanone.

Chiral γ-menthyloxybutenolides (1) have served as the basis for our novel asymmetric synthesis strategies[1] due to the excellent stereocontrol by the γ-menthyloxy substituent, the easy way of preparation of these synthons in enantiomerically pure form and the use of cheap d-or l- menthol as chiral auxiliary. Optically active γ-lactones[2] can be particularly advantageous in the formation of acyclic chiral building blocks with arrays of methyl- and hydroxy-substituents at vicinal or remote chiral centers. For instance Hanessian and co-workers[3] reported the use of (S)-4-hydroxymethyl-butyrolactone in the synthesis of several amphotericin B segments.
We now wish to report a stereoselective 1,4-addition-enolate alkylation strategy for the synthesis of optically active methylbutyrolactones as well as 2-methyl- and 2,3-dimethyl-butanediol.

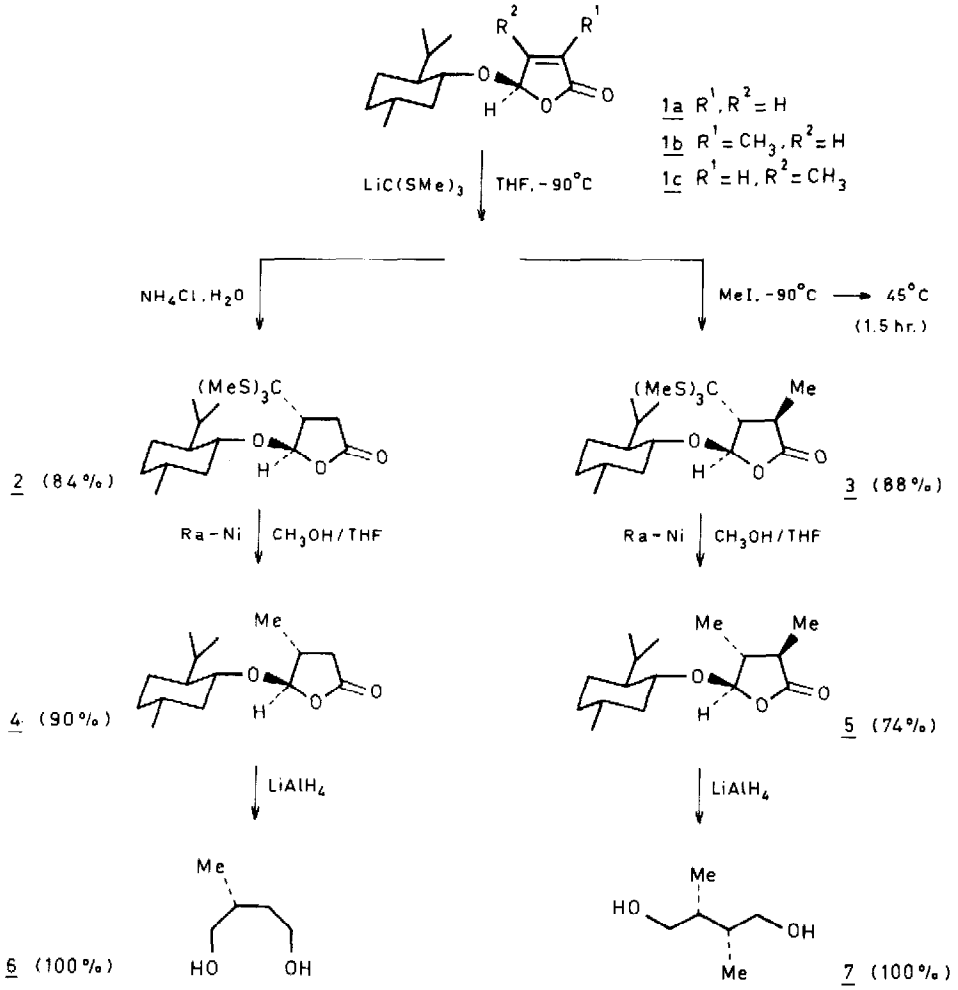


Addition of carbon nucleophiles to the enone moiety proceeds anti to the menthyloxy-group and quenching of the resulting enolate is expected to proceed preferentially anti to the substituent at C_4.
In an alternative approach the diastereoface selective hydrogenation of 3-methyl-(1b) and 4-methyl-butenolides (1c) yield γ-menthyloxy-methyllactones which could be converted into R- and S-2-methyl-1,4-butanediol respectively (eq. 1)[4]. The present route starts with enantiomerically pure



*MO = l-menthyloxy-

γ-menthyloxybutenolide 1a[1] which is readily available from 5-hydroxy-2[5H]-furanone. Conjugate addition of lithiotrismethylthiomethane to 1a and subsequent quenching with NH_4Cl leads to 2 in 84% yield. Alternatively a tandem[5] 1,4-addition followed by alkylation of the enolate intermediate with methyliodide provides 3 in 88% yield. Both 2 and 3 are obtained as single diastereoisomers[6] (NMR, HPLC).



The bulky γ-menthyloxy-substituent favours attack from the less hindered face in accordance with previous results[1] with thiol and amine additions to 1a, whereas the tris(methylthio)methyl substituent at C4 dictates the anti methylation in 3. ^{1}H NMR established the relative stereochemistry of 2 and 3, in particular $J_{H3,H4}$=2.20Hz in 3 and $J_{H4,H5}$=0Hz in 2 and 3 indicate anti configurations at the vicinal centers. Desulphurization with Raney-Nickel[8] gave lactones 4 and 5[10] and subsequent $LiAlH_4$ reduction resulted in optically pure (R)-2-methyl-butane-1,4-diol (6) and (2R,3R)-2,3-dimethyl-1,4-butanediol (7). The optical purities and absolute configurations were based on comparison with an independent sample[4] (for 6) and the literature preparation of 7. Diol 7 has been previously prepared by resolution of 2,3-dimethylsuccinic acid using brucine[7]. As far as we know the route described here presents the first asymmetric synthesis of 7[9]. In conclusion we found a short asymmetric synthesis of chiral butyrolactones and methyl-substituted diols. Application of this strategy to substituted lactones and acyclic synthons is currently under investigation.

Acknowledgement.
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6. All compounds showed correct ^{1}H- and ^{13}C NMR, high resolution MS and IR data; optical rotations: 2 $[\alpha]_D^T$-88.7° (c 1.9 $CHCl_3$); 3 $[\alpha]_D^T$-102.0° (c 1.0, $CHCl_3$); 4 $[\alpha]_D^T$-146.6° (c 0.9, $CHCl_3$); 5 $[\alpha]_D^T$-173.1° (c 1.1, $CHCl_3$); 6 $[\alpha]_D^T$+13.4° (c 1.0, MeOH)[4]; 7 $[\alpha]_D^T$+5.32(c 10.0, Et_2O); lit.[7] $[\alpha]_D^{23}$ +5.38 (c 5.0, Et_2O); ^{1}H- and ^{13}C NMR data of 4 and 5: 4 ^{1}H NMR ($CDCl_3$, δ, ppm) 5.27 (d, 1H, J = 2.2 Hz), 3.49 (d.t., 1H, J = 12.8 Hz, J = 4.1 Hz), 2.82 (d.d., 1H, J = 17.6 Hz, J = 8.2 Hz), 2.44-2.31 (m, 1H), 2.09 (d.d., 1H, J = 17.6 Hz, J = 4.0 Hz), 1.11 (d, 3H, J = 7.3 Hz), 2.05-0.76 (m, 18H, menthyl H's); ^{13}C NMR ($CDCl_3$) 15.49 (q), 17.05 (q), 20.80 (q), 22.15 (q), 22.97 (t), 25.35 (d), 31.24 (d), 34.20 (t), 35.39 (t), 36.21 (d), 39.76 (t), 76.72 (d), 105.93 (d), 175.94 (s); 5 ^{1}H NMR ($CDCl_3$, δ, ppm) 5.19 (d, 1H, J = 5.8 Hz), 3.50 (d.t., 1H, J = 10.6 Hz, J = 4.4 Hz), 2.27-2.13 (m, 1H), 1.99 (m, 1H), 1.27 (d, 3H, J = 7.3 Hz), 1.14 (d, 3H, J = 6.6 Hz), 2.05-0.76 (m, 18H, menthyl H's); ^{13}C NMR ($CDCl_3$) 13.93 (q), 14.87 (q), 15.55 (q), 20.86 (q), 22.14 (q), 22.88 (t), 25.17 (d), 31.27 (d), 34.17 (t), 40.03 (t), 42.80 (d), 44.24 (d), 47.63 (d), 78.27 (d), 105.38 (d), 176.67 (s).

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