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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 strategies¹ 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 -lactones² 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-workers³ 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 C₄.

In an alternative approach the diastereoface selective hydrogenation of 3-methyl-(**1b**) and 4-methyl-butenolides (**1c**) yield γ -menthyloxy-methylactones which could be converted into R- and S-2-methyl-1,4-butanediol respectively (eq. 1)⁴. The present route starts with enantiomerically pure

γ -menthyloxybutenolide 1a¹ 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 tandem⁵ 1,4-addition followed by alkylation of the enolate intermediate with methyl iodide provides 3 in 88% yield. Both 2 and 3 are obtained as single diastereoisomers⁶ (NMR, HPLC).

The bulky γ -menthyloxy-substituent favours attack from the less hindered face in accordance with previous results¹ with thiol and amine additions to 1a, whereas the tris(methylthio)methyl substituent at C4 dictates the anti methylation in 3. ¹H NMR established the relative stereochemistry of 2 and 3, in particular $J_{H3,H4}=2.20\text{Hz}$ in 3 and $J_{H4,H5}=0\text{Hz}$ in 2 and 3 indicate anti configurations at the vicinal centers. Desulphurization with Raney-Nickel⁸ gave lactones 4 and 5¹⁰ 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 sample⁴ (for 6) and the literature preparation of 7. Diol 7 has been previously prepared by resolution of 2,3-dimethylsuccinic acid using brucine⁷. As far as we know the route described here presents the first asymmetric synthesis of 7⁹. 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.

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6. All compounds showed correct ^1H - and ^{13}C NMR, high resolution MS and IR data; optical rotations: 2 $[\alpha]_{\text{D}}^{\text{RT}} - 88.7^\circ$ (c 1.9 CHCl_3); 3 $[\alpha]_{\text{D}}^{\text{RT}} - 102.0^\circ$ (c 1.0, CHCl_3); 4 $[\alpha]_{\text{D}}^{\text{RT}} - 146.6^\circ$ (c 0.9, CHCl_3); 5 $[\alpha]_{\text{D}}^{\text{RT}} - 173.1^\circ$ (c 1.1, CHCl_3); 6 $[\alpha]_{\text{D}}^{\text{RT}} + 13.4^\circ$ (c 1.0, MeOH)⁴; 7 $[\alpha]_{\text{D}}^{\text{RT}} + 5.32$ (c 10.0, Et_2O); lit.⁷ $[\alpha]_{\text{D}}^{23} + 5.38$ (c 5.0, Et_2O); ^1H - and ^{13}C NMR data of 4 and 5: 4 ^1H 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 ^1H 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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