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Synthesis of Enantiomerically Pure 5-(*l*-Menthyloxy)-3,4-Dibromo-2(5H)-Furanone and Its Tandem Asymmetric Michael Addition-Elimination Reaction

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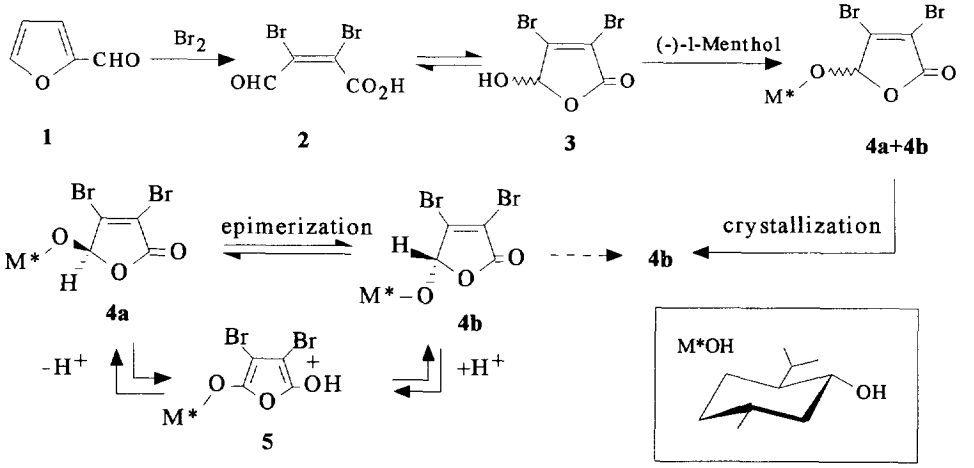
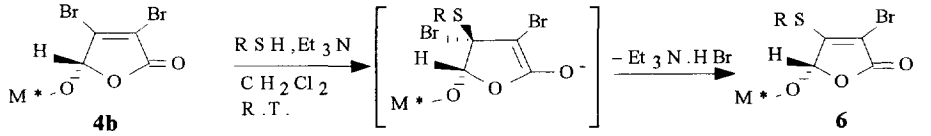
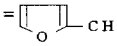
Abstract: *The novel chiral 5-(l-menthyloxy)-3,4-dibromo-2(5H)-furanone* ***4b*** *was prepared in enantiomerically pure form, and its tandem Michael addition-elimination reaction provide the corresponding new chiral sources* ***6a-6d*** *or* ***7a-7e****, respectively in good yield with de>98%.*

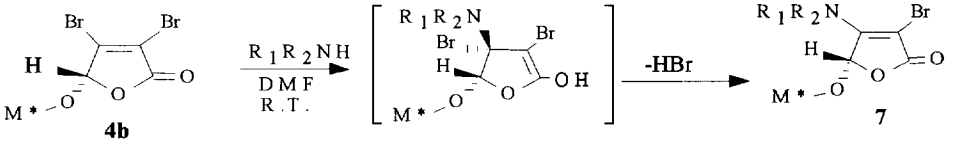
The synthesis and properties of γ-substituted butenolides have recently attracted much attention owing to the unique carbon skeleton of 2(5H)-furanone which is widely present in a variety of biologically active natural products[1] and their utility as valuable synthetic intermediates.[2] Among the various asymmetric transformations studied, chiral auxiliary based methods have afforded very good results.[3] Feringa and coworkers[4] reported the γ -(*l*-menthyloxy)butenolide as a chiral synthon which was efficiently utilized in organic synthesis. As part of our research program on the synthesis and asymmetric reactions of chiral γ-butenolides, we have been particularly interested in the enantiomerically pure preparation of new chiral sources of γ-substituted 2(5H)-furanones and their asymmetric reactions.[5]



Now we would like to report a new synthetic route to enantiomerically pure **4b** through the following process. 4-Hydroxy-3,4-dibromobutenolide **3** was easily prepared by bromination of furfural and further transformation of the open chain to the cyclic structure of this mucobromic acid. By employing *l*-menthol as a chiral auxiliary, γ-(*l*-menthyloxy)dibromobutenolide (**4a+4b**) was obtained in 93% yield via acetalization of 4-hydroxy-3,4-dibromobutenolide with *l*-menthol in benzene as a solvent contained 1-2 drops of concentrated H_2SO_4 at reflux for 10h. The epimeric mixture (**4a+4b**) was checked by ^1H NMR analysis, **4a:4b**=1:1, $\delta_{4a}(CCl_4)$=5.77ppm, s, 0.5H, C_5-H_{4a}; $\delta_{4b}(CCl_4)$=5.70ppm, s, 0.5H, C_5-H_{4b}. Enantiomerically pure **4b** as white needles was obtained in 33% yield after two crystallizations from petrol (30-60°C). ^1H NMR spectra showed a single epimer **4b**, $\delta_{4b}(CCl_4)$=5.70ppm, s, 1H, C_5-H_{4b} and lost the characteristic shift of **4a**. The combined mother liquiors which contained more **4a** than **4b** were evaporated to dryness. The remaining solid was redissolved in benzene and heated at reflux for 8 hours in the presence of a catalytic amount (0.3-0.5 mol%) of 20% H_2SO_4 or p-toluenesulphonic acid ,and shown a mixture of the epimers , **4a:4b**=1:1. It meant that a remarkable second-order asymmetric transformation of **4a** to **4b** in solution had occurred under reflux . The solvent was removed in vacuo and the residue crystallized twice from petrol as described above to afford additional enantiomerically pure **4b** (combined yield 64%). Our results have proved that the crystallization induced epimerization occurs by removal of the major crystalline epimer **4b** after reflux of a benzene solution of **4a+4b** with protonic acid as a catalyst. It is possible for epimerization to be explained by the presence of protonic acid which catalyze enolization of **4a** to the unstable 5-(*l*-menthyloxy)-2-hydroxyfuran intermediate **5** which is achiral except for the *l*-menthyloxy moiety[6] and then consequently the epimerization into **4b**. The results of our investigation have shown clearly that enantiomerically pure **4b** can be reversed to the corresponding epimer **4a** by proton catalysis induced epimerization.[7] It has also stated that enantiomerically pure **4b** or a epimeric mixture **4a+4b** should be stable and could not be in equilibrium with **4a** or **4b**, if this solution of **4b** or **4a+4b** without a catalytic amount of protonic acid was heated at reflux for long time.[8] **4b** was identified on the basis of its satisfactory elemental analytical data and spectroscopic data (IR, UV, ^1H NMR, ^{13}C NMR and Mass).[9] The absolute configuration at the acetal carbon of **4b** was proved to be S by means of an X-ray stucture analysis of its asymmetric reaction product with R-(+)-α-methylbenzylamine.[10] However, the absolute configuration at the acetal carbon of 5-(*l*-menthyloxy)-2(5H)-furanone with crystalline enantiomerically pure was proven to be R.[11]



R : a = Ph , b = Ph CH$_2$, c =  , d = n-C$_5$H$_{11}$



R_1R_2N- : a =  , b =  , c =  , d = Ph CH$_2$NH-, e = (R)-Ph CH(CH$_3$)NH-

Unexpected novel tandem Michael addition-elimination reaction of **4b** with thiols and amines provide a series of new homochiral compound in good yield under mild conditions.

On basis of literature precedent (see ref. 4) most probably the nucleophile attacks stereoselectively the γ-position of **4b** from the side opposite to the menthyloxy group, namely the less hindered face, after that a mole of salt of hydrogen bromide with triethyl amine or a mole of hydrogen bromide has been eliminated to offer the novel chiral compounds **6a-d** respectively in 40-69% yield or **7a-e** respectively in 54-68% yield with de>98%. **6a-d** and **7a-e** were identified on the basis of their elemental data and spectroscopic data.[12] Application of this strategy to substituted chiral butenolides in asymmetric synthesis is currently under investigation.

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References and Notes

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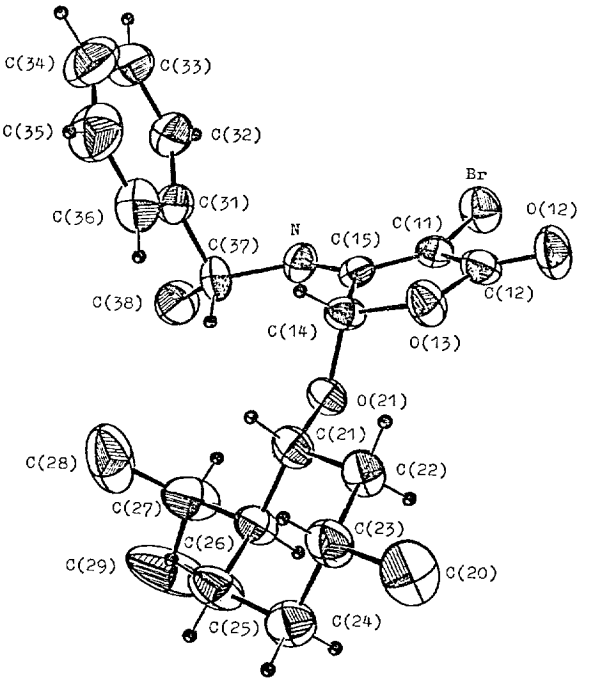
7. ^{1}H NMR study has shown that when the solution of **4b** in CCl_4 with a catalytic amount of protonic acid was heated in sealed tube of ^{1}H NMR at 115-120°C for 13h, the proton induced epimerization of **4b** took place, resulting in an equilibrium mixture of the epimers, **4a**: δ_H=5.77ppm, s, 0.5H, C_5-H_{4a}; **4b**: δ_H =5.70ppm, s, 0.5H, C_5-H_{4b}.
8. After heating the corresponding sealed tube of ^{1}H NMR at 115-120°C for 24h respectively, it was no change in the ^{1}H NMR spectra. Singal ^{1}H NMR absorption for the acetal hydrogen was observed for **4b**: $\delta_H(C_6D_6)$=5.26, 1H, C_5-H_{4b}; and for **4a+4b**: $\delta_H(C_6D_6)$=5.37, 0.5H, C_5-H_{4a}; 5.26, 0.5H, C_5-H_{4b}, respectively.
9. 5-(*l*-menthyloxy)-3,4-dibromo-2(5H)-furanone **4b**: m.p. 146-147°C, $[\alpha]_{589}^{20}$ = +40.0 (c=1.0, $CHCl_3$); UV: λ_{max}=241nm, lgε=3.91 ; Anl. for $C_{14}H_{20}O_3Br_2$: calcd. C, 44.22, H, 4.23; Found: C, 44.24, H, 4.05; IR (KBr,cm^{-1}) : 2951-2921(C-H), 1762(C=O), 1621(C=C), 1313(C-O, lactone), 1145(C-O-C, γ_{as}), 953(C-O-C, γ_s); ^{1}H NMR (300MHz, $CDCl_3$): 0.83(3H, d, J=7.2Hz, H-15), 0.95(6H, m, H-12, H-14), 1.10(3H, m,

H-11, H-9), 1.40(2H, m, H-8, H-13), 1.68(2H, m, H-10), 2.28(2H, m, H-7), 3.59(1H, bdd, J=4.2Hz, 10.5Hz, 10.5Hz, H-6), 5.82(1H, s, H-5)ppm; ^{13}C NMR (75MHz, $CDCl_3$): 15.94(q), 20.94(q), 22.13(q), 22.96(t), 25.32(d), 31.68(d), 34.01(t), 42.19(t), 48.06(d), 84.41(d), 104.40(d), 118.39(s), 143.30(s), 164.00(s) ppm; m/z: 396(M^+, 2), 241($C_4O_2HBr_2^+$, 45), 138($C_{10}H_{18}^+$, 95), 81($C_6H_9^+$, 100).

10. The stereochemistry of **7e** has been determined by a single crystal X-ray analysis. Crystal data: $C_{22}H_{30}NO_3Br$, M=436.38, othorhombic, space group $p2_12_12_1$, a= 9.842(5), b=12.510(5), c=17.763(6)Å, V=2187(3)Å, Z=4, Dx=1.33g/cm^3, μ=18.79 cm^{-1}, F(000)=912. Monochromated Mo-Kα radiation, λ=0.71073Å, μ=0.8cm^{-1}, R= 0.047 and Rω=0.053 for 1429 with I≥3σ(I).



ORTEP diagram of **7e**

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12. 5-(*l*-menthyloxy)-4-phenylthio-3-bromo-2(5H)-furanone **6a**: m.p. 110-111°C, $[\alpha]_{589}^{20}$=-50.33 (c=2.13, $CHCl_3$), UV: λ_{max}=205nm, lgε=3.91, λ_{max}=250nm, lgε=3.54, λ_{max}=290nm, lgε=3.87; Anl. for $C_{20}H_{25}SO_3Br$: Calcd. C, 56.47, H, 5.92; Found: C, 56.36, H, 5.78; IR (KBr,cm^{-1}) : 2949-2869(C-H), 1764(C=O), 1628(C=C), 1582(Ph, C-H), 1319(C-O, lactone), 1129(C-O-C, γ_{as}), 973(C-O-C, γ_s); ^{1}H NMR (300MHz, $CDCl_3$): 0.60(3H, d, J=6.9Hz, H-15), 0.62(3H, d, J=7.2Hz, H-14), 0.89(3H, d, J=6.6Hz, H-12), 1.03(1H, m, H-11), 1.28(3H, m, H-8,H-9), 1.65(2H, m, H-10), 1.87(1H, m, H-13), 2.08(2H, m, H-7), 3.41(1H, bdd, J=10.8Hz, 10.8Hz, 4.5Hz, H-6), 5.82(1H, s, H-5), 7.47(5H, m, ph)ppm; ^{13}C NMR (75MHz, $CDCl_3$): 15.82(q), 21.15(q), 22.05(q), 22.76(t), 24.85(d), 31.60(d), 33.86(t), 42.11(t), 47.94(d), 83.43(d), 102.46(d), 109.83(s), 126.39(s), 129.31(d), 129.67(d), 134.03(d), 157.60(s), 165.11(s)ppm; m/z: 426(M+2$^+$, 100), 424(M^+, 29), 269($C_{14}H_{21}SO_3^+$, 30), 161($C_4H_2BrO_2^+$, 35), 109(PhS^+, 10).

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