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GENERAL SYNTHESIS OF OPTICALLY ACTIVE 4-ALKYL (OR ALKENYL)-γ-LACTONES FROM GLUTAMIC ACID ENANTIOMERS

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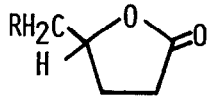
We report a general synthesis of optically active 4-alkyl-γ-lactones (1a), and of 4-alkenyl-γ-lactones in which the double bond may be two or more carbon atoms removed from the ring (1b).



1a R is alkyl

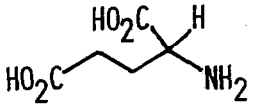
1b R is alkenyl

As examples, we have prepared both enantiomers of 1a in which R is methyl or n-butyl, and of 1b in which R is $-CH^{Z}{=}CH(CH_2)_4CH_3$.

4-Alkyl-γ-lactones have been reported as flavor components[1], and as a component of *Trogoderma* insect pheromones[2], and 1b (R is $-CH^{Z}{=}CH(CH_2)_4CH_3$) is a social pheromone of the black-tailed deer[3]. Several insects discriminate between enantiomers, and in all cases reported are more responsive to the naturally occurring enantiomer[2,4]. Humans can perceive striking differences in flavors of some pairs of enantiomers[5]. Availability of the lactone enantiomers will allow structure-activity studies of these chiral compounds. We are particularly interested in the enantiomers of the deer lactone.

The key intermediate, the lactone tosylate (8), was prepared from either of the commercially available enantiomers of glutamic acid (2↔8). We have found that the reaction of 8 with lithium dialkylcuprate or dialkenylcuprate proceeds selectively with tosylate displacement, rather than ring opening, to give 1a or 1b. It has been reported that tosylates react preferentially with lithium di-n-butylcuprate in the presence of an ester group[6].

On treatment with nitrous acid, (S)-(+)-glutamic acid (2)($[\alpha]_D^{23}$ + 29°, C=1, 6N HCl, Aldrich) gave the (S)-(+)-lactone acid (3)(mp 71-73°, $[\alpha]_D^{20}$ + 15.6°, C=2, EtOH; 55%. lit[7] mp 71-72°, $[\alpha]_D^{28}$ +10.6°, C=5.0, MeOH). (R)-(-)-glutamic acid (2)($[\alpha]_D^{23}$ -31.2°, C=5, 5N HCl, Aldrich) gave (R)-(-)-3



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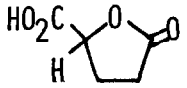

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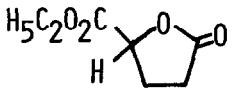

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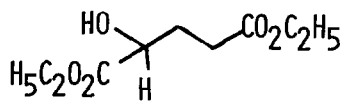

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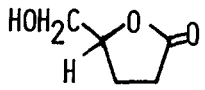

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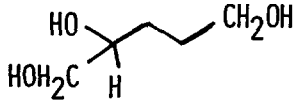

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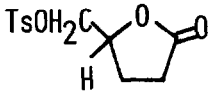
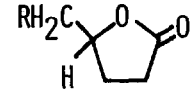


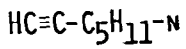
8

R_2CuLi

9 R IS ME
10 R IS N-BU
11 R IS 



1A R IS ME OR N-BU
1B R IS $CH \overset{(Z)}{=} CH\text{-}C_5H_{11}\text{-}N$



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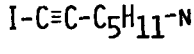

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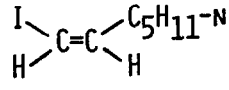

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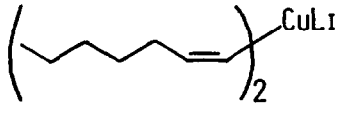

11

(mp 71-72°, $[\alpha]_D^{20}$-15.7°, C=2.4, EtOH. lit.[8] mp 73.5-74° $[\alpha]_D^{20}$-15.9°, C=1.1, EtOH). This reaction proceeds with full retention of configuration[7,9]. The ester (4), together with the by-product (5) was formed from (3) on esterification with EtOH, benzene, p-TsOH. (S)-(+)-4, $[\alpha]_D^{20}$+15.1°, C=0.6, EtOH. lit.[10] $[\alpha]_D^{32}$+11.5°, C=2.93, EtOH. (R)-(-)-4, $[\alpha]_D^{20}$-14.7°, C=0.4, EtOH; 77%. The lactone alcohol (6) and the triol (7) formed by reduction ($NaBH_4$, EtOH, 20-25°, 1.5 hr.) of the mixture of 4 and 5 were separated by silica-gel chromatography. (S)-(+)-6, $[\alpha]_D^{20}$+ 29.6°, C=0.4, EtOH. lit[10] $[\alpha]_D^{26}$+ 31.3°, C=2.92, EtOH. (R)-(-)-6, $[\alpha]_D^{20}$-33.1°, C=0.1, EtOH; 70%. lit.[8] $[\alpha]_D^{30}$ -33.5°, C=3.12, EtOH. Tosylation of 6 (p-TsCl, pyridine, 0-5°, 22 hrs.) gave 8. (S)-(+)-8, mp 85-87°, $[\alpha]_D^{20}$+ 47.0°, C=1.6, $CHCl_3$. lit.[11] mp 84-85°, $[\alpha]_D^{23}$+ 46.2°, C=1.63, $CHCl_3$. (R)-(-)-8, mp 84.5-86°, $[\alpha]_D^{20}$-45.55°, C=1.2, $CHCl_3$; 58%. lit.[11] mp 85-86°, $[\alpha]_D^{23}$-46.3°, C=1.33, $CHCl_3$. Addition of a benzene solution of 8 to an ether solution of lithium dimethylcuprate (9)(2 eq., -70° 2 hrs., -30° 0.5 hr., 0° 0.5 hr) gave 4- hexanolide (1a, R is Me). (R)-(+)-1a-Me, $[\alpha]_D^{20}$+ 42.7°, C=0.1, MeOH; 66%. (S)-(-)-1a-Me, $[\alpha]_D^{20}$-46.3°, C=0.05, MeOH. Addition of a CH_2Cl_2 solution of 8 to an ether solution of lithium di-n-butylcuprate (10) (5 eq. -70°, 1 hr.) gave 4-nonanolide (1a, R is n-Bu). (R)-(+)-1a-n-Bu, $[\alpha]_D^{20}$+42.9°, C=0.15, MeOH. (S)-(-)-1a-n-Bu, $[\alpha]_D^{20}$-37.4°, C=0.2, MeOH; 41%. Addition of CH_2Cl_2 solution of 8 to an ether solution of lithium di [(Z)-1-heptenyl] cuprate (11) (5 eq., -30 to -40° 1.75 hr.) gave (Z)-6-dodecen-4-olide (1b). (S)-(+)-1b, $[\alpha]_D^{20}$ +15.0°, C=0.1, MeOH. (R)-(-)-1b, $[\alpha]_D^{20}$-16.1°, C=0.3, MeOH; 12%. No E-isomer was observed.

The alkenyl cuprate (11) was synthesized by the following steps: metalation[12] of 1-heptyne (12) (n-BuLi, Et_2O, -50 to -20°, 30 min.) and iodination of the 1-lithio-1-heptyne (I_2, Et_2O, -70°, 2.5 hrs. at 0°) to give 1-iodo-1-heptyne (13) (bp 67-68°/0.6 mm; 76%). Addition[13] of dicyclohexylborane to 13 (THF, 0°, 20-30° 30 min.) gave (E)-α-iodo-vinylborane, which was protonolized (AcOH, 10-15°; 20-30°, 2 hrs.) without isolation, to give (Z)-1-iodo-1-heptene (14), (54%). Treatment of 14 with n-BuLi (hexane, -70°, 0.5 hr.) produced (Z)-1-lithio-1-heptene, which on addition to an ether suspension of CuI (0.5 eq. -40°, 1 hr) yielded 11. Spectral data of our products (1a) and 1b) were congruent with those of the natural pheromones reported in the literature[2,3], and with those of the racemic synthetic lactones[14].

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