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SYNTHESIS OF THE ENANTIOMERS OF 4-SUBSTITUTED γ-LACTONES WITH KNOWN ABSOLUTE CONFIGURATION

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Abstract—The highly pure enantiomers of several 4-alkyl (or alkenyl)-γ-lactones of known absolute configuration were synthesized from glutamic acid enantiomers. The key step is selective tosylate displacement rather than ring opening of the lactone tosylate (7→1) by lithium dialkylcuprate or dialkenylcuprate. The enantiomeric purity of synthesized γ-caprolactone was confirmed within the limitations of Pirkle's chiral solvating agent. The enantiomers of synthesized (*Z*)-6-dodecen-4-olide were used for reference to determine the enantiomeric composition of the pheromone isolated from the black-tailed deer.

In a brief communication,[1] we outlined a general synthesis of optically active 4-alkyl-γ-lactones, and 4-alkenyl-γ-lactones whose double bond is two or more C atoms removed from the ring. Retention of the integrity of the chiral center was assumed, but no reliable $[\alpha]_D$ values were available from the literature. Efforts to use the chiral shift reagent, Eu(hfbc)$_3$, in conjunction with PMR or CMR to determine enantiomeric composition were not successful. We report here details of an improved synthetic procedure, and confirmation of optical purity of the enantiomers of γ-caprolactone within the limitations of the chiral solvating agent recently introduced by Pirkle *et al.*[2] Unfortunately this method was successful in our hands only for γ-caprolactone, but the integrity of the chiral center of the other lactones seems a reasonable assumption since they were synthesized by analogous procedures from the same starting materials. As examples, we synthesized both enantiomers of γ-caprolactone (**1a**, R is methyl), γ-nonalactone (**1a**, R is n-butyl) and (*Z*)-6-dodecen-4-olide (**1b**).

4-Alkyl (or alkenyl)-γ-lactones are ubiquitous natural products, and have been found, for example, in: peach,[3,4] apricot,[5] strawberry,[6] tobacco,[7] the flower *Polianthes tuberosa*,[8], cooked lamb,[9] butterfat,[10,11] the pygidal gland of two species of staphylinid beetles,[12] the mandibular gland of the leaf-cutting ant *Atta sexdens rubropilosa*,[13] several species of dermestid beetles of the genus *Trogoderma*,[14] the Japanese beetle,[15] and the black-tailed deer.[16]

Humans can perceive differences in flavor and odor of some pairs of enantiomers.[17–18] Several insects discriminate between enantiomers of pheromone components, and in all cases reported are more responsive to the naturally occurring enantiomer.[15,20–23] In one case,[15] the racemic form showed little or no activity; apparently the "wrong" enantiomer "masked" the active one. We were especially interested in γ-caprolactone (**1a**, *R* is methyl) and (*Z*)-6-dodecen-4-olide (**1b**), since these are, respectively, components of the attractant pheromone of several *Trogoderma* species of dermestid beetles[14] and of the "social scent" of the black-tailed deer.[16] The availability of the pure enantiomers made it possible to determine that *T. granarium* responds to the (*R*)-(+)-enantiomer of γ-caprolactone but to neither the (*S*)-(−)-enantiomer nor the racemic form.[24a] Deer, on the other hand, showed a marginal preference for the predominant enantiomer, (*R*)-(−), of its pheromone, whose enantiomeric composition (89%(*R*)-(−)/11%(*S*)-(+)) was determined by direct comparison of the optical rotation of the naturally occurring material with that of the synthesized enantiomer.[24b] In informal tests, seven people were unable to distinguish between the enantiomers of the γ-lactones described here.

The synthetic procedure utilizes the commercial availability of both optically pure enantiomers of glutamic acid, whose absolute configurations are known, and which have been converted to the carboxylic acid lactone (**3**) with complete retention of configuration.[25]

We originally[1] converted **3** by esterification to **4**, which was reduced to the alcohol (**6**) with $NaBH_4$ in accordance with the reported procedure.[26] An alternative sequence, $NaBH_4$ reduction of γ-chloromethyl-γ-butyrolactone has been shown to proceed with full retention of configuration.[27,28] We have found, however, that the more convenient direct reduction of **3** with borane-methyl sulfide[29] gives high distilled yields of **6**; Brown *et al.*[30,31] have shown that carboxylic acids are reduced more rapidly than γ-lactones with borane.

The key step (7→1) in the present synthesis depends on selective tosylate displacement rather than ring opening of the lactone tosylate (**7**) by lithium dialkycuprate or dialkenylcuprate. Preferential displacement of a tosylate in the presence of an ester has previously been demonstrated.[32] In this step of the synthesis of **1b**, the *Z* configuration of the dialkenylcuprate is maintained; no E isomer was detected on three different GC columns.

Synthesis of the alkenylcuprate was straightforward. Metallation[33] of 1-heptyne by treatment with n-BuLi followed by iodination[33] of the 1-lithio-1-heptyne yielded 1-iodo-1-heptyne (**9**). Addition of dicyclohexylborane[34] to the iodoalkyne gave (*Z*)-1-iodo-1-heptenylborane,‡ which was which was protonolized, without isolation, by treatment with acetic acid to give (*Z*)-1-iodo-1-hepten (**10**). Treatment of **10** with n-BuLi in hexane produced (*Z*)-1-lithio-1-heptene, which on addition to an ether suspension of CuI yielded the lithium di-[(*Z*)-1-heptenyl] cuprate.

The optically pure solvating agent (*R*)-(−)-2,2,2-

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‡In our original communication, we mistakenly designated this compound as (*E*) to correspond to the *trans* designation in Ref. 34.

(R)-(−) and (S)-(+)-(Z)-6-dodecen-4-olide (1b)

(R)-(−)-1b. n-BuLi (3.73 mmol, 1.64 ml of 2.3 M soln in hexane) was injected dropwise into a stirred soln of **10** (834.8 mg, 3.73 mmol) in hexane (8 ml) at −70° under argon. The clear soln was stirred for 30 min at −70° and then the (*Z*)-1-lithio-1-heptene was injected into a stirred suspension of CuI (354.3 mg, 1.86 mmol) in dry Et_2O (40 ml) at −70°. The soln was allowed to come to −15 to −20° (40 min), and then was cooled to −35°. A soln of (*R*)-(−)-**7** (99.9 mg, 0.37 mmol) in dry CH_2Cl_2 (15 ml) was injected dropwise to the tan soln of lithium di-[(*Z*)-1-heptenyl] cuprate at −35°, the whole was stirred at −30 to −40° for 1.75 hr and the mixture was poured into a cold (0–5°) soln of 10% NH_4Cl aq. The mixture was filtered by suction (Celite), the organic layer was separated, and the aq. layer was extracted (twice) with Et_2O. The combined organic layers were washed with 10% NH_4Cl aq and H_2O and dried over $MgSO_4$. The solvent was removed and the product (8.85 mg, mg, 12%) was collected by GC (column A, 170°, 60 ml/min, retention time 16 min). $[\alpha]_D^{20}$ −16.1° (*c* = 0.3, MeOH); MS 196 (M^+), 85 (base); IR (neat) cm^{-1} 3018 (), 1778 (lactone C=O), 1176 (C–O); NMR ($CDCl_3$, δ) 0.91 (CH_3, t, 3), 1.4–1.52 (CH_2, m, 6), 1.77–2.70 (CH_2, m, 8), 4.56 (CH–O, m, 1), 5.51 (CH=CH, m, 2).

(S)-(+)-1b. $[\alpha]_D^{20}$ +15.0° (*c* = 0.1, MeOH); $[\alpha]_D^{20}$ +6.3° (*c* = 0.14, $CHCl_3$).

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