Facile Access to Chiral 5-Hydroxy-2-methylhexanoic Acid Lactones (Pheromones of the Carpenter Bee)

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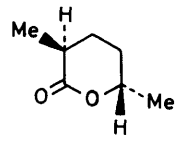
Summary Alkyl 2-acyloxy-3-deoxy-D-*erythro*-hex-2-enopyranoside diesters are converted into the corresponding alkyl 2-*C*-methylene-3,4-enopyranosides upon treatment with methylenetriphenylphosphorane and, depending on the nature of the aglycone, hydrogenation of the dienes can lead to 2-*C*-methyl derivatives with (*R*)- or (*S*)-stereochemistry, which can be easily converted into isomeric chiral 2,5-dimethylvalerolactones.

THE major component of the carpenter-bee sex-pheromone[1] has been identified as (5*S*)-hydroxy-(2*S*)-methylhexanoic acid lactone (**1**). Since the assignment of its constitutional structure, several syntheses of this substance, as well as of its three other isomers, have been reported.[2,3] Because insect pheromones are normally isolated in limited quantities, their availability in optically pure form by synthetic means has proved advantageous, particularly for configurational correlations and subsequent biological evaluation.[4]

Previous syntheses of chiral 5-hydroxy-2-methylhexanoic acid lactones have relied on the methylation of optically active δ-methyl-δ-valerolactones, in turn obtained by automated high-pressure liquid chromatography (h.p.l.c.) separation of the appropriate diastereoisomeric precursors,[2] or by methylation of 4-hydroxy-6-methyl-5,6-dihydro-2-pyrone, followed by dehydration and hydrogenation.[3]



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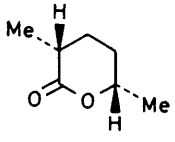
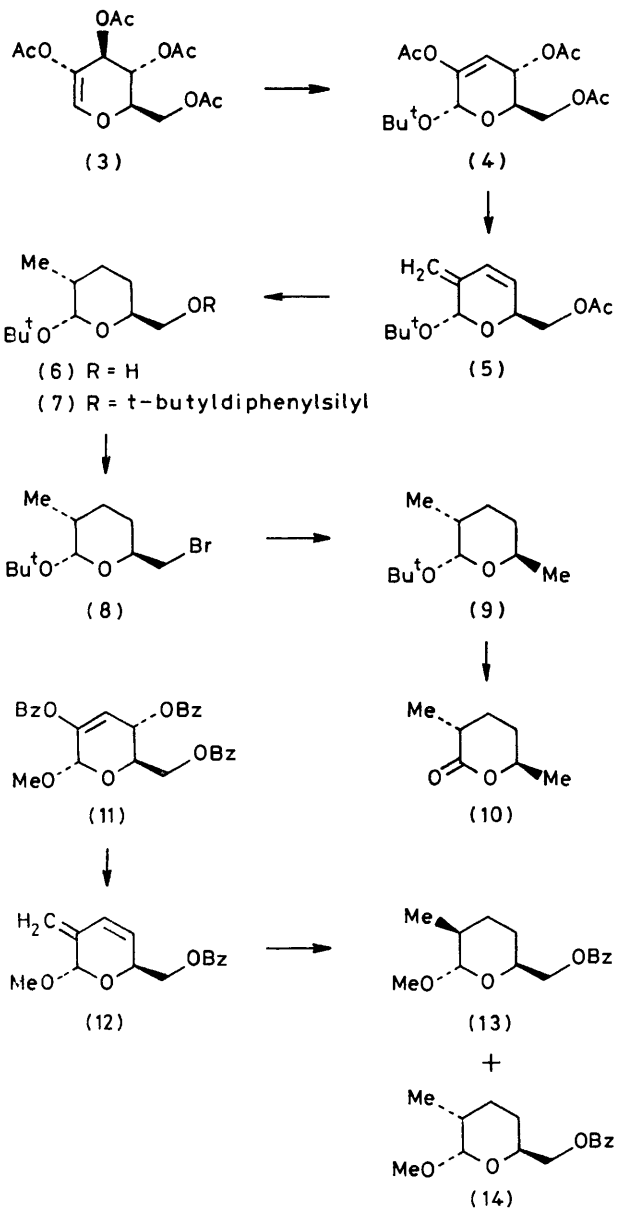


(2)

We describe herein a synthetically expedient route to *cis*- and *trans*-5-hydroxy-2-methylhexanoic acid lactones with (2*S*, 5*R*) and (2*R*, 5*R*) configurations, respectively, starting with the readily available[5] alkyl 2-acyloxy-3-deoxy-D-*erythro*-hex-2-enopyranoside diesters, such as compounds (**4**) and (**11**) (see the Scheme). Treatment of compound (**3**) with 2-methylpropan-2-ol in the presence of BF_3–Et_2O[6] gave the crystalline α-enoside (**4**) (90%), m.p. 63–64 °C; $[\alpha]_D$ + 84·3°. Upon treatment with methylenetriphenylphosphorane (3 equiv., tetrahydrofuran (THF),



SCHEME

25 °C, 1 h), a remarkable transformation took place to give the diene (**5**) (72%); $[\alpha]_D$ + 108·8°, and the corresponding deacetylated diene (18%), $[\alpha]_D$ + 146·9°. Because of the bulk of the anomeric substituents, catalytic reduction (Pd–C, H_2, EtOAc) gave a mixture of the expected isomers in which the *trans*-isomer was preponderant (9 : 1). The resulting 2-*C*-methyl derivatives were deacetylated and conveniently separated by flash silica gel chromatography ($CHCl_3$–light petroleum, 1 : 4) as the corresponding 6-*O*-t-butyldiphenylsilyl ethers.[7] The *trans*-(2*R*, 5*R*)-isomer (**7**) was thus obtained in 82% yield; $[\alpha]_D$ + 40·7° and the minor *cis*-isomer showed $[\alpha]_D$ + 30·0°. Bromination[8] of compound (**6**) (*N*-bromosuccinimide, Ph_3P, dimethylformamide, 25 °C, 2 h) gave the 6-bromo-derivative (**8**) (75%); $[\alpha]_D$ + 111·9°, which was reduced to compound (**9**) (86%) [$LiEt_3BH$, THF, 25 °C], then hydrolysed (10%, aqueous HCl, THF), and the resulting lactol oxidized (PCC, NaOAc, CH_2Cl_2)[9] to give the target compound (**10**) (74%, 2 steps), (5*R*)-hydroxy-(2*R*)-methylhexanoic acid lactone, m.p. 49—50 °C; $[\alpha]_D$ + 54·9°, (lit.,[2] m.p. 50 °C; $[\alpha]_D$ + 52°).

Since the nature of the aglycone was decisive in determining the stereochemistry of the reduction, an identical series of reactions was performed using the crystalline methyl 4,6-di-*O*-benzoyl-2-benzoyloxy-α-D-*erythro*-hex-2-enopyranoside (**11**)[6] which was expected to provide a higher proportion of the 2,5-*cis*-isomer. Indeed, treatment of compound (**11**) with methylenetriphenylphosphorane followed by catalytic hydrogenation gave a 1 : 1 mixture (86%) of the *cis*- and *trans*-pheromone precursors (**13**), $[\alpha]_D$ + 43·2°, and (**14**), $[\alpha]_D$ + 85·7°, respectively (see the Scheme).

To the best of our knowledge, the Wittig reaction reported here is unique and should find application in related cyclic or acyclic β-acyloxy enol esters. Presumably, it involves initial attack on the 2-acyloxy ester, leading to an intermediate enone, which undergoes the normal reaction with a second equivalent of the reagent. It is also evident that the method can be used with L-glucose as precursor, which would lead to the chiral pheromones (**1**) and (**2**) in the natural series. Alternatively, the intermediates such as compounds (**6**), (**13**), and (**14**) can be inverted at C-5 *via* dehydrobromination of the bromo-derivatives and subsequent reduction.

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