

ENANTIOSELECTIVE TOTAL SYNTHESSES OF (4R,6R)-(+)-4-HYDROXY-6-PENTYLVALEROLACTONE, ex *Cephalosporium recifei*, AND OF (6R)-(-)-MASSOIALACTONE

Frank Bennett and David W. Knight*

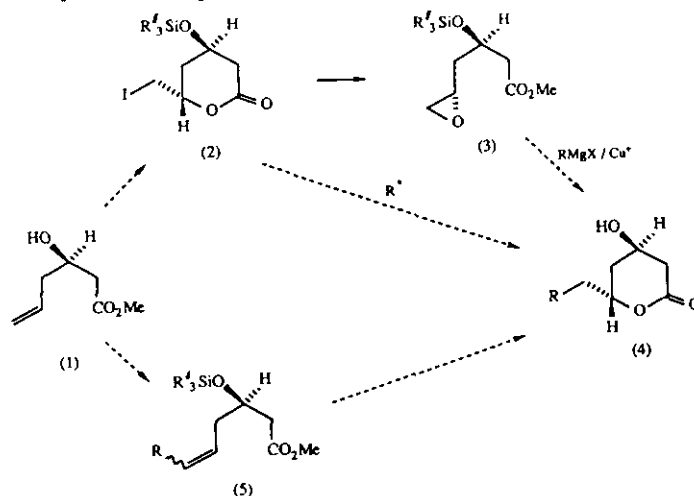
Department of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, U.K.

Garry Fenton

Rhône-Poulenc, Dagenham, Essex, RM10 7XS, U.K.

Abstract - Total syntheses of (4R,6R)-(+)-4-hydroxy-6-pentylvalerolactone (6) and (6R)-(-)-massoialactone (7) have been achieved, starting from the yeast reduction product methyl (3R)-3-hydroxyhexenoate (1).

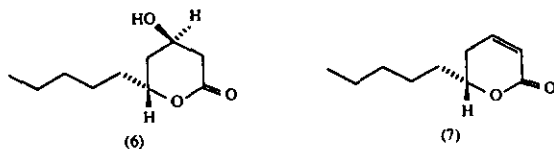
Our recent studies¹ have shown that the (R)-hydroxy-ester (1), available with ca. 76% enantiomeric enrichment by baker's yeast reduction of the corresponding β -keto-ester, can be used to prepare mevinic acid analogues (4) in two ways, one option being conversion into the iodo-lactone (2), or the



corresponding epoxide (3), followed by addition of a 6-substituent using radical coupling or modified Grignard reactions, respectively. Alternatively, the substituent can be incorporated by sequential ozonolysis and Wittig coupling of

protected derivatives of ester (1); the resulting unsaturated esters (5) can then be saponified and subjected to seleno-lactonisation leading to analogues (4) after removal of the seleno group and finally deprotection. As the absolute configuration of hydroxy-ester (1) has been firmly established¹ and because the relative stereochemistries of 4,6-disubstituted lactones (4) can be determined with certainty from ¹H nmr data, these methods should be particularly useful for the unambiguous synthesis of natural valerolactones and 2-pyrones, in addition to the mevinic acids, and hence for the assignment of absolute stereochemistry to such compounds. Herein, we illustrate these features by the first asymmetric syntheses of a naturally occurring enantiomer of 4-hydroxy-6-pentylvalerolactone (6) and of natural (-)-massoialactone (7), by using iodo- rather than seleno-lactonisation.

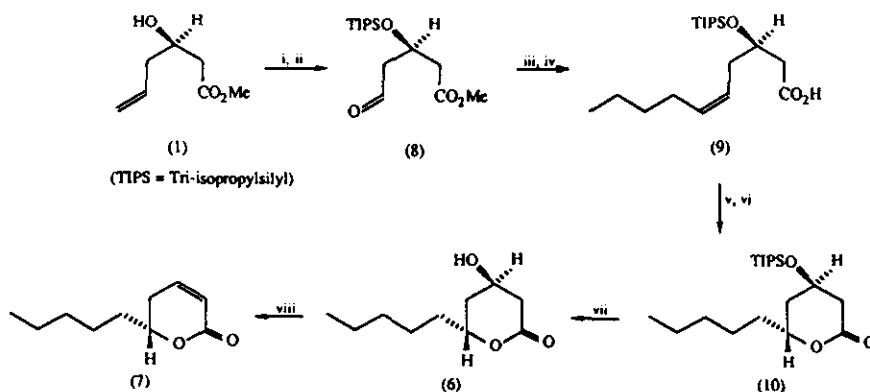
4-Hydroxy-6-pentylvalerolactone, $[\alpha]_D^{25} +27.4^\circ$ (c 11.7, CHCl₃), has been isolated from the fungus Cephalosporium recifei; while the spectral data exhibited by this compound support a trans relative stereochemistry, the absolute configuration has not been established.² By contrast, massoialactone (massoialactone) occurs in a number of plant sources including the bark oil of Cryptocarya massoia,³ cane molasses,⁴ in which it contributes to the flavour, and jasmine flowers⁵ as well as in the defence secretion of two species of formicin ants of the genus Camponotus.⁶



Our syntheses began with protection of the initial yeast reduction product (1) as its tri-isopropylsilyl ether; subsequent ozonolysis provided the aldehydo-ester (8), $[\alpha]_D^{20} -6.7^\circ$ (c 1.2, CHCl₂) (76% ee) in excellent yield (Scheme). Wittig homologation using n-pentyltriphenylphosphorane followed by saponification then gave the unsaturated acid (9) contaminated with ca. 6% of the corresponding (E)-isomer. The crucial lactonisation step occurred smoothly when acid (9) was treated with three equivalents of iodine and an excess of sodium bicarbonate in acetonitrile (0°C/3 h);⁷ subsequent de-iodination using tri-n-butyltin hydride led to a 10:1 mixture of valerolactones in favour of the

trans-isomer (10). Our previous studies¹ revealed that increasing the steric bulk of the 3-silyloxy group gave greater trans selectivity in kinetic iodolactonisations leading to lactones (2). This present example indicates that the presence of a 6-substituent in the lactonisation substrate, in this case acid (9), further enhances the trans selectivity, at least with cis-unsaturated acids.

The major lactone (10) was separated by column chromatography and deprotected using 40% aq. HF in acetonitrile to give the hydroxy-lactone (6) which exhibited spectral data identical with that reported for the natural material isolated from *C.recifei*.² Proton chemical shift and coupling constant data^{1,8} clearly established the trans relative stereochemistry; the synthetic sample showed $[\alpha]_D^{24} +29.4^\circ$ (c 1.4, CHCl_3) corrected to $+38.7^\circ$ on the basis of 76% ee in the starting ester (1). The natural material is reported to have $[\alpha]_D^{25} +27.4^\circ$ (c 11.7, CHCl_3)² and therefore has the (4R,6R) absolute configuration shown in formula (6).



Reagents: (i) $i\text{-Pr}_3\text{SiCl}$, imidazole, DMF, 20°C , 48 h (87%); (ii) (a) O_3 , CH_2Cl_2 , -78°C , (b) Me_2S , 40°C , 40 h (91%); (iii) $n\text{-C}_6\text{H}_{11}\text{P}^+\text{Ph}_3\text{Br}^-$, $n\text{-BuLi}$, THF, 20°C , 0.5 h (85%); (iv) KOH, MeOH, 20°C , 16 h (86%); (v) I_2 , NaHCO_3 , CH_3CN , 0°C , 3 h (93%); (vi) $n\text{-Bu}_3\text{SnH}$, THF, reflux, 3 h (ca. 80%); (vii) 40% HF, CH_3CN , 0°C , 7 h (85%); (viii) POCl_3 , pyridine, 65°C , 5 h (92%).

Scheme

Subsequent dehydration of lactone (6) using phosphorus oxychloride in

pyridine then gave, in excellent yield, natural (-)-massoialactone (7), $[\alpha]_D^{36}$ -82.4° (c 2.7, CHCl₃) corrected to -108.4° based on a 76% ee. The natural material is reported to have $[\alpha]_D^{25}$ -91° (c 1, CHCl₃),^{3,6} or -99.4 (c 1.035, CHCl₃);⁵ the absolute configuration has been established as (R) by ORD studies,⁹ by a synthesis of the (S)-enantiomer ($[\alpha]_D^{22}$ +82.5° (c 0.63, CHCl₃)³ and by a preparation of the (R)-enantiomer ($[\alpha]_D$ -110.5° (c 2.5, CHCl₃)) from racemic methyl 5-hydroxy-2-decynoate by hplc separation of the (R)- α -naphthylethyl carbamate derivative.^{10,11} Other spectral and analytical data exhibited by our synthetic sample were identical to those reported for the natural material.³⁻⁶ Using this methodology, it should thus be possible to both synthesis and to assign absolute stereochemistry to a range of related hydroxy-valerolactones and reduced pyrones.

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