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

Frank Bennett and David W. Knight*

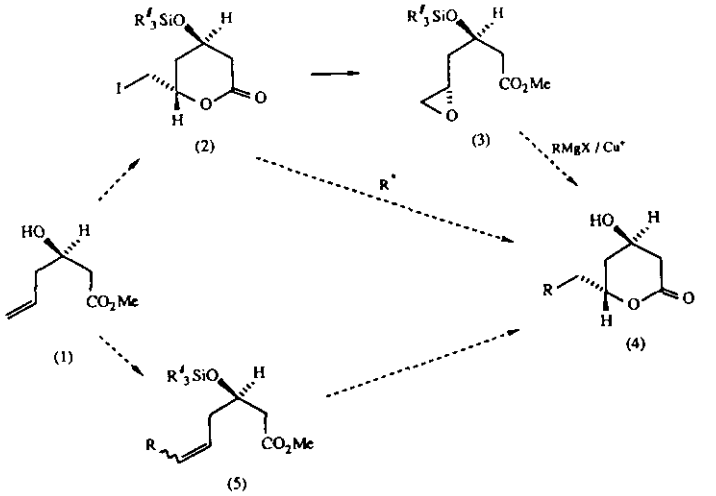
Department of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, U.K.

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).

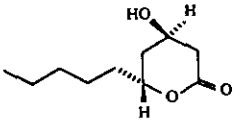
Our recent studies[1] have shown that the (R)-hydroxy-ester (1), available with ca. 76% enantiomeric enrichment by baker's yeast reduction of the corresponding β-keto-ester, can be used to prepare mevinic acid analogues (4) in two ways, one option being conversion into the iodo-lactone (2), or the



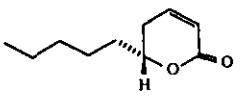
corresponding epoxide (3), followed by addition of a 6-substituent using radical coupling or modified Grignard reactions, respectively. Alternatively, the substituent can be incorporated by sequential ozonolysis and Wittig coupling of

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 established[1] and because the relative stereochemistries of 4,6-disubstituted lactones (4) can be determined with certainty from ^{1}H 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° (c 11.7, $CHCl_3$), 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 (massoilactone) 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 flowers[5] as well as in the defence secretion of two species of formicin ants of the genus Camponotus.[6]



(6)

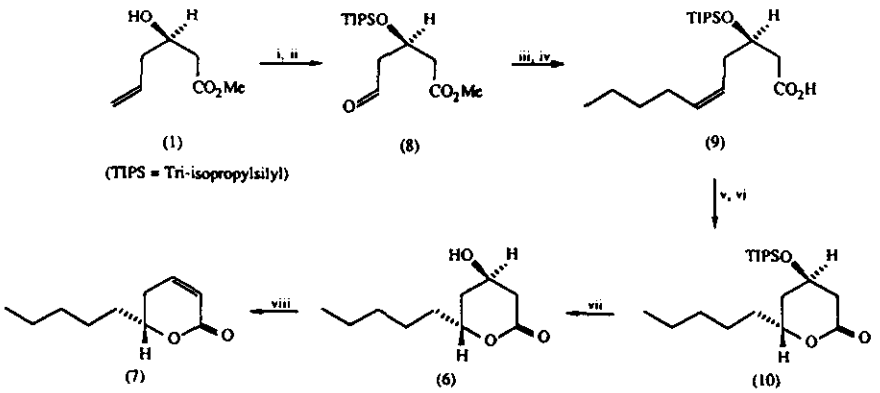


(7)

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° (c 1.2, $CHCl_2$) (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 studies[1] 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° (c 1.4, $CHCl_3$) corrected to +38.7° on the basis of 76% ee in the starting ester (1). The natural material is reported to have $[\alpha]_D^{25}$ +27.4° (c 11.7, $CHCl_3$)[2] and therefore has the (4R,6R) absolute configuration shown in formula (6).



Reagents: (i) $i\text{-}Pr_3SiCl$, 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-$C_6H_{11}\overset{+}{P}Ph_3\bar{B}r$, n-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-Bu_3SnH, 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, $CHCl_3$) corrected to -108.4° based on a 76% ee. The natural material is reported to have $[\alpha]_D^{25}$ -91° (c 1, $CHCl_3$),[3,6] or -99.4 (c 1.035, $CHCl_3$);[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, $CHCl_3$)[3] and by a preparation of the (R)- enantiomer ($[\alpha]_D$ -110.5° (c 2.5, $CHCl_3$)) from racemic methyl 5-hydroxy-2-decynoate by hplc separation of the (R)-α-naphthyl-ethyl 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.

ACKNOWLEDGEMENTS

We thank Rhone-Poulenc (Dagenham) and the SERC for financial support through the CASE Scheme.

REFERENCES

1. F. Bennett, G. Fenton, and D.W. Knight, Tetrahedron Lett., 1988, 29, 4865.
2. R.F. Vesonder, F.H. Stodola, and W.K. Rohwedder, Can.J.Biochem.,1971,50,363.
3. K. Mori, Agric.Biol.Chem., 1976, 40, 1617, and references therein.
4. T. Hashizume, N. Kikuchi, Y. Sasaki, and I. Sakata, Agri.Biol.Chem., 1968, 32, 1306.
5. R. Kaiser and D. Lamparsky, Tetrahedron Lett., 1976, 1659.
6. G.W.K. Cavill, D.V. Clark, and F.B. Whitfield, Aust.J.Chem., 1968, 21, 2819.
7. P.A. Bartlett, D.P. Richardson, and J. Myerson, Tetrahedron, 1984, 40, 2317.
8. Lactone (6): δ_H (400 MHz) ($CDCl_3$) 0.90 (3H, t, J 6.9 Hz, CH_3CH_2), 1.20-1.74 (8H, m, $(CH_2)_4$), 1.73 (1H, ddd, J 14.5, 11.1, and 3.3 Hz, 5α-H), 1.98 (1H, dddd, J 14.5, 3.8, 3.0, and 1.6 Hz, 5β-H), 2.63 (1H, ddd, J 17.7, 3.7, and 1.6 Hz, 3β-H), 2.72 (1H, dd, J 17.7 and 4.9 Hz, 3α-H), 2.81 (1H, br, OH), 4.37 (1H, narrow m, 4α-H), and 4.71 (1H, dddd, J 11.1, 7.8, 4.9, and 3.0 Hz, 6β-H).
9. L. Crombie and P.A. Firth, J.Chem.Soc.(C), 1968, 2852.
10. W.H. Pirkle and P.E. Adams, J.Org.Chem., 1980, 45, 4117.
11. For syntheses of racemic massoialactone, see L. Crombie, J.Chem.Soc., 1955, 1007 and 2535; S. Abe and K. Sato, Bull.Chem.Soc.Jpn., 1956, 29, 88.

Received, 15th Nobember, 1988