

An Enantiospecific Route to (6*R*)-(-)-Massoialactone and (4*R*,6*R*)-(+)-4-Hydroxy-6-pentylvalerolactone

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(Received 9 March 1992)

Abstract: An enantiospecific route to two δ -lactone natural products, (6*R*)-(-)-massoialactone and (4*R*,6*R*)-(+)-4-hydroxy-6-pentylvalerolactone, has been developed by using (*R*)-epichlorohydrin as a chiral starting material

The *trans*- β -hydroxy- δ -lactone system is an essential structural feature associated with the HMG-CoA reductase inhibiting activity of compactin and mevinolin.¹ In connection with our synthetic project toward compactin and the related compounds,² we report herewith enantiospecific syntheses of two naturally occurring δ -lactones, (6*R*)-(-)-massoialactone^{3,4} (1) and (4*R*,6*R*)-(+)-4-hydroxy-6-pentylvalerolactone^{4,5} (2), from (*R*)-epichlorohydrin (3) by employing our own strategy^{2,6} for the construction of *trans*- β -hydroxy- δ -lactone system.

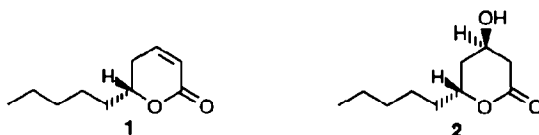
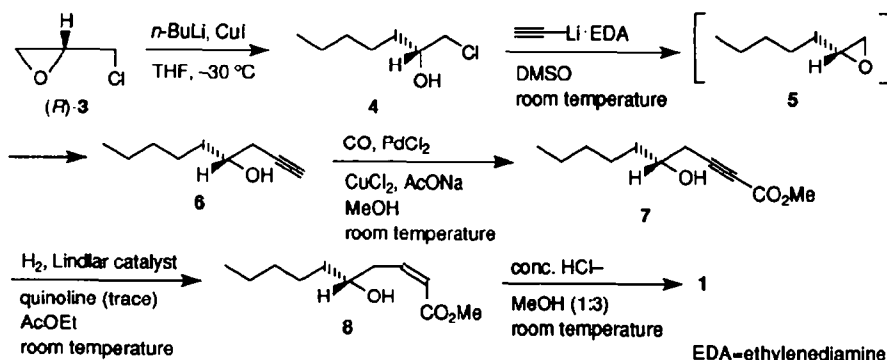


Fig. 1

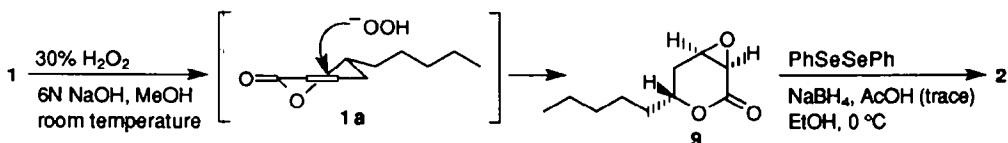
Treatment of (*R*)-epichlorohydrin⁷ (3) with lithium dibutylcuprate, prepared from *n*-butyllithium and copper(I) iodide in the same flask, afforded the chlorohydrin⁸ 4, [α]_D³⁰ -1.47 (*c* 1.0, CHCl₃), in 73.7% yield. Upon exposure to an excess amount (4 equiv.) of lithium acetylide ethylenediamine complex in DMSO solution at room temperature 4 furnished the β -hydroxyacetylene 6, [α]_D²⁸ +22.2 (*c* 1.0, MeOH), in 94.8% yield via a transient formation of the epoxide (5). Since the epoxide (5) was found to be very elusive owing to its high



Scheme 1

volatility, this one-flask procedure was essential for the efficient conversion. In order to introduce the carbomethoxy group, the terminal acetylene **6** so obtained was then stirred with a catalytic amount of palladium(II) chloride (6 mol %) and copper(II) chloride (2 equiv.) in methanol in the presence of sodium acetate (2 equiv.) under atmospheric pressure of carbon monoxide⁹ which gave rise to the expected propiolate ester (**7**), $[\alpha]_{\text{D}}^{29} +11.95$ (*c* 1.8, CHCl_3), in 85.1% yield. Partial hydrogenation of **7** followed by acid-catalyzed cyclization of the resulting (*Z*)-ester (**8**) afforded (*6R*)-(-)-massoialactone (**1**), $[\alpha]_{\text{D}}^{29} -107.52$ (*c* 1.07, CHCl_3) [lit.^{4b} $[\alpha]_{\text{D}} -109$ (*c* 9.1, CHCl_3)], in 75.7% yield.

When optically active massoialactone (**1**) thus obtained was exposed to alkaline hydrogen peroxide,^{2,6} highly diastereoselective epoxidation occurred to give the epoxide (**9**), $[\alpha]_{\text{D}}^{25} +81.3$ (*c* 1.0, CHCl_3), in 83% yield¹⁰ as a single product presumably *via* a stereoelectronically favored transition state¹¹ (**1a**). Subsequent treatment of **9** with the phenylselenolate complex,^{2,6,12} generated from diphenyl diselenide and sodium borohydride in the same flask, allowed facile and regioselective cleavage of the epoxide bond to give the desired natural product, (*4R,6R*)-(+)-4-hydroxy-6-pentylvalerolactone (**2**), $[\alpha]_{\text{D}}^{28} +38.4$ (*c* 1.15, CHCl_3)¹³ [lit.^{5a} $[\alpha]_{\text{D}}^{25} +27.4$ (*c* 11.7, CHCl_3)], in 74.2% yield.



Scheme 2

References and Notes

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- We thank DAISO Co. Ltd., Japan for donation of a large quantity of (*R*)-epichlorohydrin ($\geq 98\%$ ee).
- cf. Takano, S.; Yamate, M.; Takahashi, M.; Ogasawara, K. *Chem. Lett.* **1987**, 2017.
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- Since some of the epoxy-lactone (**9**) was saponified under these conditions, acid workup followed by brief reflux of the crude product in benzene in the presence of a trace of pyridinium *p*-toluenesulfonate was necessitated to revert the contaminated seco-acid into the lactone (**2**).
- Cf. Deslongchamps, P. 'Stereochemical Effects in Organic Chemistry,' Pergamon, Oxford, 1983, p. 209.
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- The synthetic **2** has much higher specific rotation value to the reported value for the natural **2**,^{5a} but was virtually identical to the corrected $[\alpha]_{\text{D}}^{28} +38.4$ ^{4c}; $+37.7$ ^{4e}] calculated by Knight and coworkers based on their asymmetric synthesis of optically enriched **2**.^{4c,e}