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A NOVEL DIASTEREOSELECTIVE SYNTHESIS OF THE LACTONE MOIETY OF COMPACTIN

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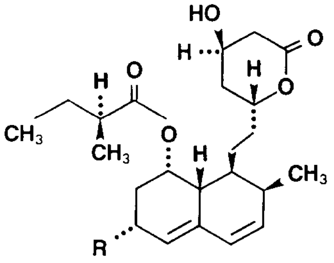
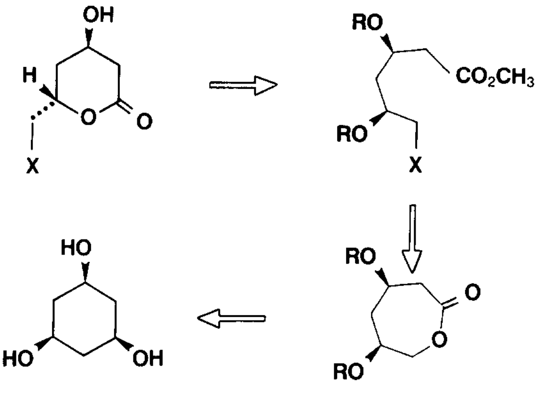
Abstract: A new synthesis of racemic β-hydroxy-δ-lactone 10 with requisite relative stereochemistry as in compactin (1a) is described utilizing *cis*-cyclohexane-1,3,5-triol (3) as the starting material.

Compactin[1] (1a) and mevinolin[2] (1b) have attracted a great deal of interest from synthetic organic chemists[3] because of the high degree of complexity incorporated in their structures and due to their potent inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.[4] We present in this communication a simple and practical stereoselective route to the β-hydroxy-δ-lactone moiety[5] which is the common structural feature essential for the observed biological activity of the above natural products.



1a, R = H
1b, R = CH_3

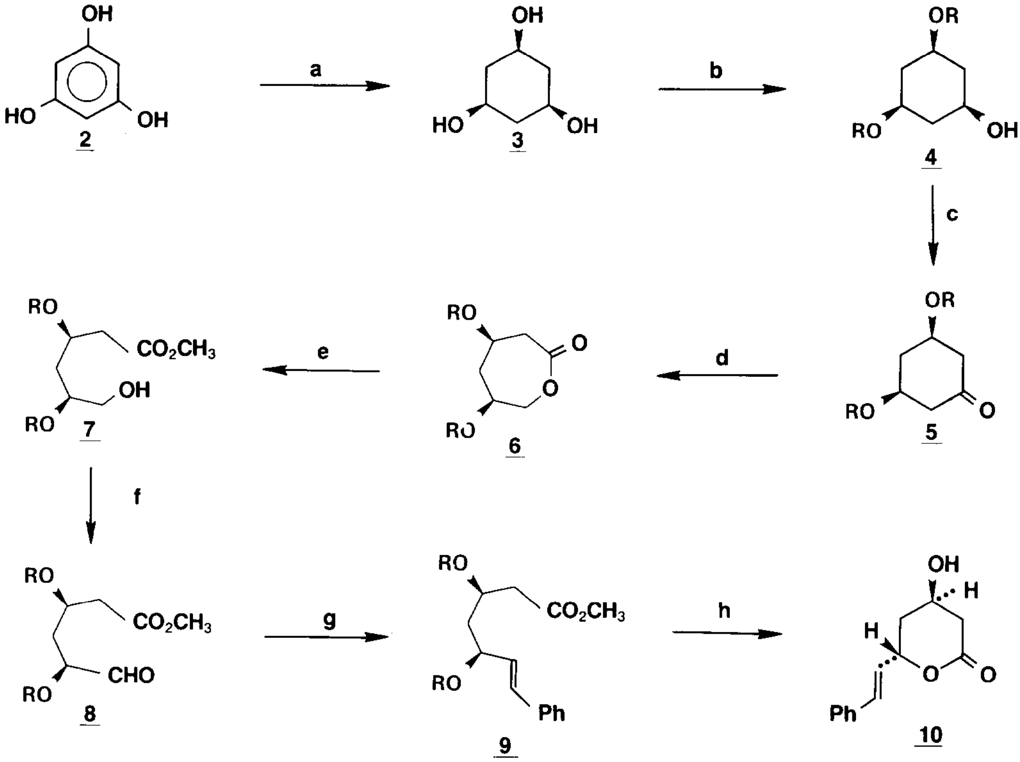
Our synthetic strategy is based upon the retrosynthetic analysis shown below, envisioning that the β-hydroxy-δ-lactone could be derived from *cis*-cyclohexane-1,3,5-triol.



The relative stereochemistry of any two of the hydroxyl groups in the triol would be the same as in the desired product, whereas the remaining hydroxyl group was anticipated to provide a handle for effecting the desired modifications in the carbon framework. cis-Cyclohexane-1,3,5-triol (3) (see Scheme I),[6] obtained readily via the hydrogenation[7] of phloroglucinol (2) using Raney nickel, was converted[8] to the disilyl derivative 4, mp 109-110 °C, in 40% yield using t-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole in dimethylformamide. Oxidation of alcohol 4 (pyridinium chlorochromate, 4-Å molecular sieves, CH_2Cl_2)[9] gave rise to the ketone 5, mp 108-109 °C, in 93% yield.

Baeyer-Villiger oxidation of compound 5, using m-chloroperbenzoic acid and $NaHCO_3$[10] in CH_2Cl_2, afforded the key intermediate, the 7-membered lactone 6, mp 124-125 °C, in 77% yield. Methanolysis of compound 6 in the presence of a catalytic amount of CF_3CO_2H[11] afforded the hydroxy ester 7 as an oil in nearly quantitative yield. Oxidation of 7 (PCC, 4-Å molecular sieves, CH_2Cl_2)[9] gave the aldehyde 8 (95% yield) which upon treatment with the phosphonium ylide derived from benzyltriphenylphosphonium chloride (n-BuLi in dry THF at -20 °C), yielded the trans olefin 9 in 77% yield. Tetrabutylammonium fluoride (TBAF)-mediated desilylation (AcOH, THF, 20 °C, 18 h; 60 °C, 2 h) gave the desired lactone[12] 10, mp 94-95 °C, in 45% yield.

The chemistry of the 7-membered lactone 6 and the usefulness of aldehyde 8 in preparing analogues of 10 will be reported in due course.



SCHEME I

R = t-butyldiphenylsilyl; a) Raney Ni, EtOH, H_2, 50 °C, 50 psi, 18 h; b) TBDPS-Cl, imidazole, DMF, 20 h; c) PCC, 4-Å mol. sieves, CH_2Cl_2, 3 h; d) m-CPBA, $NaHCO_3$, CH_2Cl_2, 18 h; e) MeOH, CF_3CO_2H, reflux, 20 min; f) PCC, 4-Å mol. sieves, CH_2Cl_2, 4 h; g) $PhCH_2P^+(Ph)_3Cl^-$, n-BuLi, THF, -20 °C, 3 h; h) TBAF, AcOH, THF, 18 h, 20 °C, 2 h, 60 °C.

ACKNOWLEDGEMENT

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1. a) Brown, A.G., Smale, T.C., King, T.J., Hasenkamp, R., Thompson, R.H., J. Chem. Soc., Perkin Trans. 1, **1976**, 1165;
   b) Endo, A., Kuroda, M., Tsujita, Y., J. Antibiot., **1976**, 29, 1346.

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3. a) Hsu, C.-T., Wang, N.-Y., Latimer, L.H., Sih, C.J., *J. Am. Chem. Soc.*, **1983**, *105*, 593;
   b) Hirama, M., Uei, M., *ibid.*, **1982**, *104*, 4251;
   c) Grieco, P.A., Zelle, R.E., Lis, R., Finn, J., *ibid.*, **1983**, *105*, 1403 and references cited therein.

4. Endo, A., Kuroda, M., Tanzawa, K., *FEBS Lett.*, **1976**, *72*, 323.

5. Syntheses of conceptual interest which were reported in the literature recently for the lactone moiety of compactin are as follows:
   a) Cyclocondensation of chiral aldehydes with functionalized dienes: Danishefsky, S., Kerwin, Jr., J.F., Kobayashi, S., *J. Am. Chem. Soc.*, **1982**, *104*, 358.
   b) From *D*-glucose: i. Prugh, J.D., Deana, A.A., *Tetrahedron Lett.*, **1982**, 281; ii. Yang, Y.-L., Falck, J.R., *Tetrahedron Lett.*, **1982**, 4305; iii. Wareing, J.R., Fuller, C.E., Kathawala, F.G., 185th ACS National Meeting in Seattle, Abstract No. 11, March 1983.
   c) From 5-norbornen-2-one: ref. 3a.

6. For the sake of clarity, only one enantiomer is depicted for the structures described in this communication, although *6* - *10* are racemic. Reaction products were purified by column chromatography. Analyses and all the spectral data are in agreement with the proposed structures.

7. Stetter, H., Steinacker, K.H., *Ber.*, **1952**, *85*, 451.

8. In the silylation reaction with two equivalents of *t*-butyldiphenylsilyl chloride, both compound *4* and the corresponding trisilyl derivative were obtained. However, the desired compound was easily separated by chromatography on silica using hexane - EtOAc (4:1) as the eluant.

9. Herscovici, J., Egron, M.-J., Antonakis, K., *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1967.

10. Whitesell, J.K., Mathews, R.S., Helbling, A.M., *J. Org. Chem.*, **1978**, *43*, 785.

11. Under other conditions of methanolysis, compound *6* gave either an incomplete reaction or a complex mixture of products.

12. The relative stereochemistry is confirmed by comparison of NMR chemical shifts with the values obtained for similar protons in analogous compounds reported in the literature. Cf. Stokker, G.E., *U.S. Patent*, **1981**, 4,308,378.

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