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An Alternative Approach to Mevinic Acid Analogues from Methyl (3R)-3-Hydroxy-5-Hexenoate and an Extension to Rational Syntheses of (+)-(6R)-Goniothalamin and its Non-natural (-)-(6S)-Enantiomer

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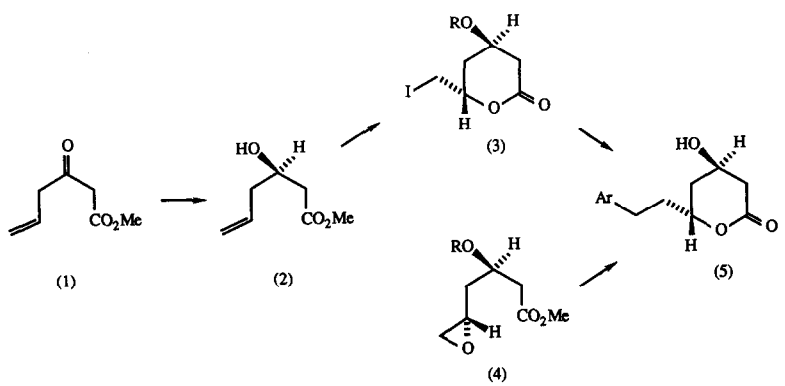
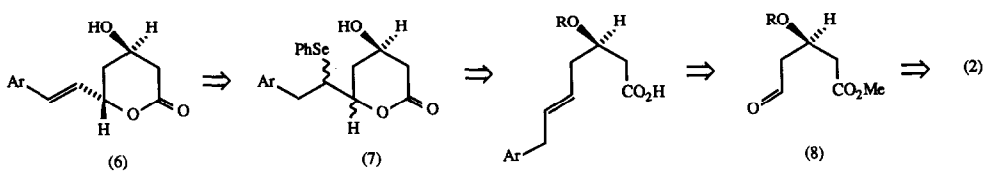
Summary: The chiral mevinic acid analogues [(15) and (16)] have been prepared from the yeast reduction product (2) by homologation and selenolactonistion and subsequently converted into both enantiomers of Goniothalamin [(17) and (18)].

We have recently shown[1] that Baker's yeast reduction of the keto-ester (1) produces largely the (R)-hydroxy-ester (2) (76% ee) which can readily be converted into the (4R,6S)-valerolactone (3) and the (4R,6S)-epoxy-ester (4) (Scheme 1). Both of these synthons are valuable as precursors to hypocholesterolemic Mevinic acid analogues (5),[1-3] and related higher homologues. A limitation of these synthons, according to our own experiments,



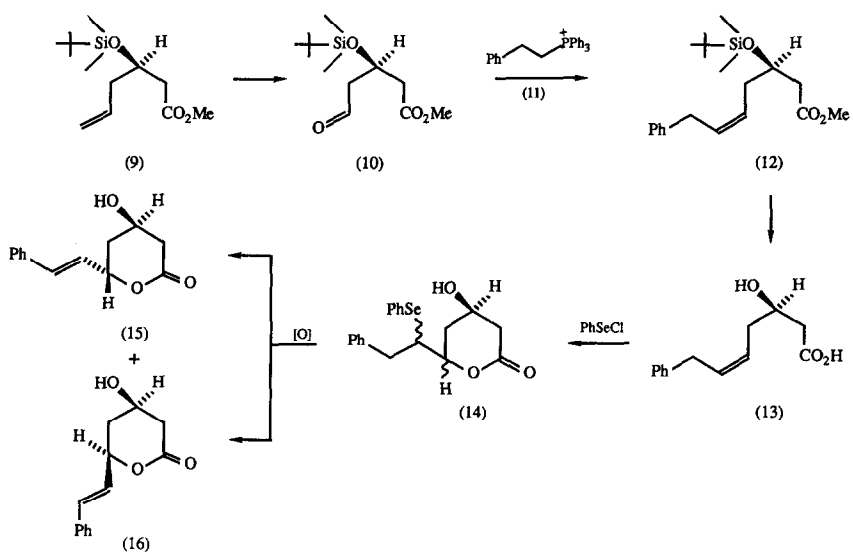
Scheme 1.



Scheme 2.

is their lack of suitability as precursors to Mevinic acid analogues (6) wherein the aryl group and valerolactone function are connected by a trans-ethylene bridge. Extensive studies involving many analogues of types (5) and (6) have shown that the presence of this unsaturated linkage is often necessary if useful levels of activity against cholesterol biosynthesis are to be obtained.[4] One such analogue of type (6) has ca. 2.8 x the activity of natural Compactin, the parent member of the Mevinic acids. A suitable precursor to the styryl-lactones (6) would be the selenolactones (7); an expedient way to prepare these from the chiral alcohol (2) is to incorporate the 6-substituent before the lactonisation step, as depicted in Scheme 2, by a Wittig homologation or relative, using the aldehyde (8) which in turn should be readily available from the hydroxy-ester (2). In addition, the final products (6) should be useful in the preparation of other naturally occurring pyranones and related systems. Herein, we report the successful outcome of the route depicted in Scheme 2, and illustrate the flexibility and potential of the methodology in total syntheses of both enantiomers of the natural product Goniothalamin (18).

The initial yeast reduction product (2) was converted into the corresponding silyl ether (9) [TBDMSCl, imidazole, DMF, 20°C, 24h] which was then ozonised [O_3, CH_2Cl_2, -78°C] and the resulting ozonide decomposed using



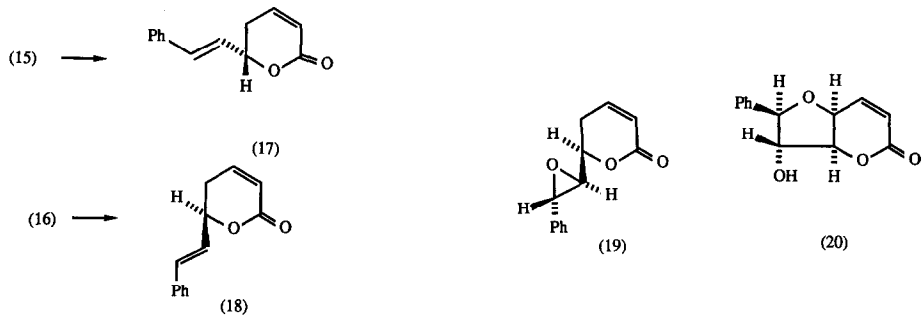
dimethyl sulphide [40°C, 48h] to give the aldehyde (10),[5] $[\alpha]^{24}$ -9.6° (c 1.2, $CHCl_3$),[6] in 94% overall yield from ester (9). Wittig homologation was then achieved using the ylide (11), generated by addition of phenyl lithium to Schweizer's reagent, vinyltriphenylphosphonium bromide[7] in THF at 20°C. By using ca. four equivalents of the ylide, the desired alkene (12) was isolated in 85% yield[8] containing ca. 16% of the corresponding (E)-isomer. Attempts to effect seleno-lactonisation of the carboxylic acid, obtained from ester (12) by saponification, with phenylselenenyl chloride failed to produce more than traces of lactonic products; the selenium reagent appeared to attack the silyl

protecting group instead. We therefore prepared the hydroxy-acid (13) by sequential desilylation [40% HF, CH_3CN, 0°C, 3h] and hydrolysis [2M NaOH, 20°C, 16 h] in 69% overall yield; on treatment with PhSeCl in THF [-78°C → 20°C, 1h] followed by column chromatography, a mixture of rather sensitive selenolactones (14) was isolated in 70-75% yield. These were immediately oxidised [$NaIO_4$, THF-MeOH-H_2O (2:2:1), 20°C, 1h] during which reaction the resulting selenoxides underwent elimination to give the trans- and cis-lactones [(15) and (16)] again in 70-75% isolated yields. The ratio of the two products was 1.2:1 in favour of the less polar trans-isomer (15), m.p. 102-104°C, which was readily separable from the cis-isomer (16), m.p. 66-68°C, by column chromatography [silica gel, ether]. Stereochemical assignments were based on ^1H n.m.r. coupling constants as previously described.[1] The trans-isomer (15) exhibited a narrow multiplet (δ4.44, $W_{\frac{1}{2}}$=ca.8 Hz) for the 4-H and a dddd pattern (J=10.8, 6.5, 3.4, and ca. 1 Hz) at δ5.38 for the 6-H, indicating that the 4-hydroxyl group is axial and hence trans to the equatorial 6-styryl substituent, especially when compared to the corresponding resonances for the cis-isomer (16) [4-H: δ4.34, dddd, J 9.3, 8.1, 5.8, and 5.0 Hz; 6-H: δ4.88, dddd, J 11.6, 6.6, 3.1, and ca. 1 Hz] which clearly show that both of these protons are axial in this isomer. In addition the downfield shift of the 6-H in the trans isomer relative to that in the cis-isomer can be ascribed to its [1.3]-diaxial relationship with the axial 4-OH group.[1] In both isomers, the alkene geometry was clearly trans, (J=15.9 Hz), as expected.

We had therefore achieved our first aim, that of developing a brief route to the Mevinic acid analogues (6). Although the lack of stereoselectivity at the selenolactonisation step is a disadvantage, the very availability of both isomers [(15) and (16)] and the certainty with which their relative stereochemistries can be determined, means that this sequence can be applied to both the unambiguous synthesis and to the determination of the absolute configuration of a wide variety of naturally occurring pyranones. We illustrate this principle by syntheses of both enantiomers of the natural product Goniothalamin.

Originally isolated from Cryptocarya caloneura[9], Goniothalamin was assigned the (6S)-stereochemistry (17) on the basis of a degradation study but this was revised to the (6R)-geometry (18) on the basis of two synthetic studies.[10] Despite this, a very recent paper[11] quoted the (6S)-configuration for the natural material. Dehydration of the trans-lactone (15) [$POCl_3$, pyridine, 70°C, 1h] gave (6S)-goniothalamin (17), which was identical in all respects with the natural material[9] except for the optical rotation: $[\alpha]_D^{20}$ =-130° (c 0.7, $CHCl_3$) which when corrected for the 76% ee of precursor (2)[6] gives a value of -171°; natural Goniothalamin is reported to have $[\alpha]_D$ +179° (c 2, $CHCl_3$)[11] or +135° (0.7% in MeOH).[9] Dehydration of the cis-lactone (16) under the same conditions gave (6R)-goniothalamin, identical in all respects with the natural material, including optical rotation: $[\alpha]_D^{26}$+126° (c 0.5, $CHCl_3$) corrected to +166°. We therefore conclude that natural Goniothalamin is

the (6R)-enantiomer (18), in agreement with the results from previous synthetic work.[10] These results suggest that the recently reported Goniothalamin 7,8-epoxide[11] has the 6R,7S,8S configuration (19) rather than 6S,7R,8R



assignment which was given on the basis of Goniothalamin having a (6S)-configuration. In addition, they support the original absolute configuration assigned to the biosynthetically related tetrahydrofurano-2-pyrone, Goniothalenol (20),[12] rather than the enantiomeric structure mentioned by Sam et.al.[11] Further efforts to exploit this relatively brief sequence to chiral pyrones are in progress.

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