An Alternative Approach to Mevinic Acid Analogues from Methyl (3*R*)-(−)-3-Hydroxyhex-5-enoate and an Extension to Unambiguous Syntheses of (6*R*)-(+)- and (6*S*)-(−)-Goniothalamin

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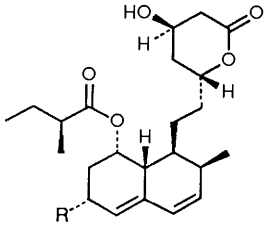
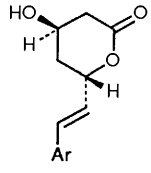
Ozonolysis of the 3-silyloxyhexenoate **12**, derived from the yeast reduction product methyl (3*R*)-(−)-3-hydroxyhex-5-enoate **6** and having an enantiomeric enrichment of 78%, followed by Wittig homologation and selenolactonization leads to the unsaturated mevinic acid analogues **17** and **18**. Subsequent dehydration gives both enantiomers of the natural product goniothalamin **20** and **21**.

The ability of the mevinic acids, exemplified by (+)-compactin **1**[1] and (+)-mevinolin **2**,[2] to specifically inhibit HMGCoA reductase[3] and hence block cholesterol biogenesis has resulted in a great deal of interest in both the total synthesis of these compounds[4] and of simpler, more readily available and possibly more biologically active analogues. In this latter respect, the most promising types of derivatives are the 6-arylvinyl- and 6-arylethyl-lactones **2** and **3** which reflect both the stereochemistry and the central two-carbon link in the natural materials.[5] One of the more bioactive compounds in this series is the chiral biphenyl derivative **4** which, in its open chain form, exhibits 2.8 times the activity of natural compactin.[6] There is therefore a need to develop rapid and efficient methods for the elaboration of lactones **2** and **3** into which a wide variety of aryl as well as other types of substituent can be readily incorporated. Such approaches should also deliver chiral products as, not unexpectedly, those analogues which possess the same absolute stereochemistry as the natural mevinic acids show considerably more biological activity than the alternative *trans* enantiomers or the racemic mixtures.[5,6]



1a; R = H[(+)-compactin]
b; R = Me[(+)-mevinolin]



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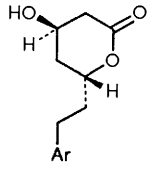

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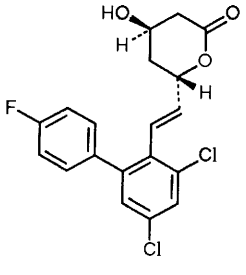

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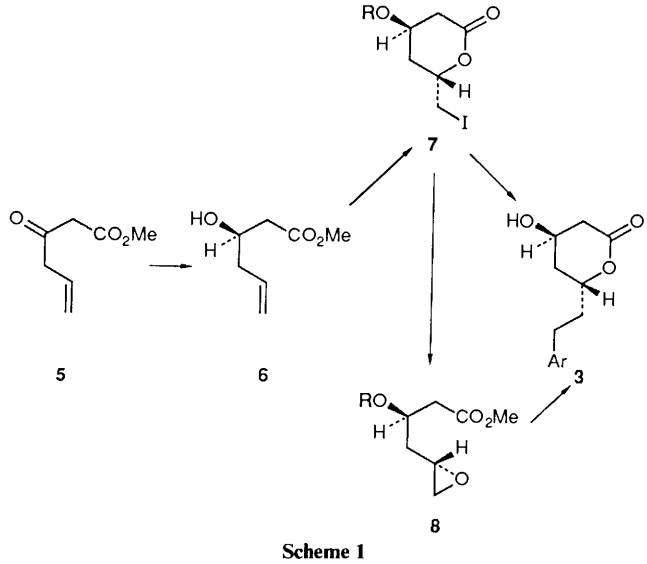
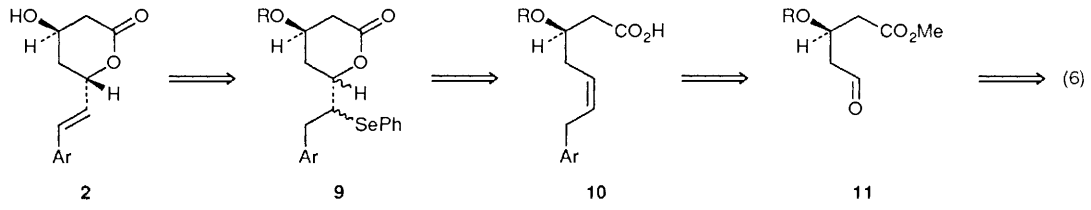
We have found that baker's yeast reduction of the keto ester **5** gives the hydroxy ester **6** with 78% enantiomeric enrichment (Scheme 1).[7] This compound is readily converted into the iodolactones **7** and the epoxy esters **8**, both of which are useful as advanced precursors to the mevinic acid analogues **3**. However, a limitation in the utility of these intermediates is their unsuitability for the elaboration of the unsaturated analogues **2** wherein the aryl substituent is connected to the lactone function by a *trans* ethylene link. We felt that such derivatives could be prepared from the hydroxy ester **6** if the side chain were to be introduced before the cyclization step (Scheme 2). Thus, protection of the hydroxy function and cleavage of the terminal alkene group should lead to the aldehydes **11** which could then be homologated to the unsaturated acids **10** by using a Wittig reaction or a related process. A selenolactonization appeared to offer the best option for effecting the cyclization as the intermediate selenides **9** should undergo facile oxidative elimination to give the targets **2**. This sequence, if successful, also represents a brief approach to a number of natural products containing a pyrone function. Herein, we report in full on the realization of both of these possibilities.[8]

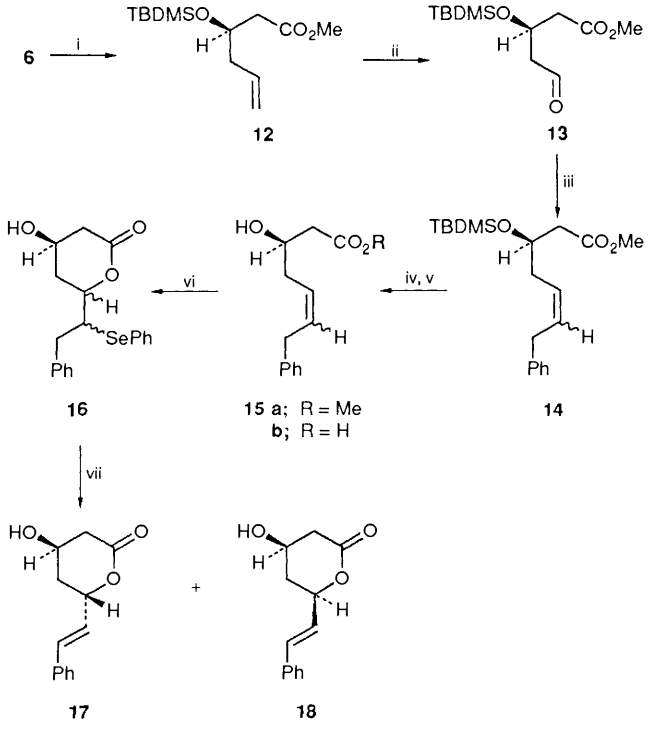


Scheme 1

The initial yeast reduction product **6**[7] was protected as the t-butyldimethylsilyl (TBDMS) ether **12**, which, upon sequential treatment with ozone and dimethyl sulphide, delivered an excellent yield of the aldehyde **13** (Scheme 3). Although we had our doubts about the stability of this compound, especially in respect of facile β-eliminations, these proved to be unfounded; aldehyde **13** could be purified by column chromatography although this was unnecessary as the material was produced in a sufficiently pure state to be used directly in the subsequent step. The intermediate ozonide **19** could also be isolated by column



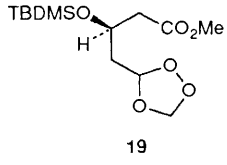
Scheme 2



Scheme 3 *Reagents and conditions:* i, TBDMSCl, imidazole, DMF, 20 °C, 24 h; ii, O_3, CH_2Cl_2, −78 °C, then Me_2S, 40 °C, 48 h; iii, CH_2=$CHPPh_3$·Br, PhLi, THF, 20 °C; iv, 40% aq. HF, CH_3CN, 0 °C, 3 h; v, 2M aq.NaOH, 20 °C, 16 h; vi, PhSeCl, THF, −78 °C→20 °C, 1 h; vii, $NaIO_4$, THF–MeOH–H_2O (2:2:1), 20 °C, 1 h

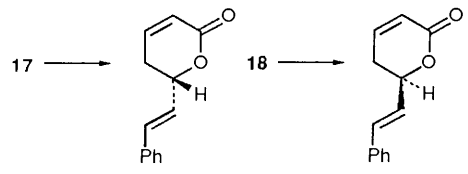
chromatography and this too appeared to be a reasonably stable compound (distillation was not attempted!). Wittig homologation of the aldehyde **13** was then effected by reaction with phenethylidenetriphenylphosphorane, generated[9] by the addition of phenyllithium to Schweizer's reagent, vinyltriphenylphosphonium bromide. Four equivalents of the phosphorane were used to obtain a 67% isolated yield of the desired alkene **14** with a *cis–trans* ratio of *ca.* 5:1. The isomers were not separated at this stage. The reaction proved to be somewhat capricious with yields varying between 20 and 87% under a variety of related conditions; in our hands, the method described in the Experimental section was the most reproducible.

Attempts to effect selenolactonization of the acid obtained by saponification of the ester **14** were unsuccessful as the selenium reagents appeared to attack the silyl function. Therefore, the latter was removed to give the hydroxy ester **15a** which was then saponified, leading to the hydroxy acid **15b** in good overall yield. Upon treatment with phenylselenenyl chloride[10] in tetrahydrofuran [−78→+20 °C], followed by column chromatography, a mixture of sensitive selenolactones **16** was isolated, typically in 70–75% yields. These were immediately oxidized using sodium metaperiodate in aqueous methanol–tetrahydrofuran at ambient temperature for 1 h, during which process the intermediate selenoxides underwent elimination to give the *trans*- and *cis*-lactones **17** and **18** which subsequently proved to be readily separable by column chromatography. According to a ^{1}H NMR spectrum of the reaction product prior to separation, these were formed in a ratio of *ca.* 2:1 in favour of the *trans* isomer **17**. The stereochemical assignments were based on ^{1}H NMR coupling constants.[7] Thus, the less polar *trans* isomer **17**, m.p. 102–104 °C, exhibited a narrow multiplet at δ_H 4.44 ($w_{\frac{1}{2}}$ = 10.6 Hz) for the 4-H and a dddd pattern at δ_H 5.38 (J = 10.8, 6.5, 3.4 and *ca.* 1 Hz) for the 6-H indicating that the 4-hydroxy group is axial and hence *trans* to the 6-styryl function. In contrast, the corresponding resonances in the *cis* isomer **18**, m.p. 66–68 °C, appeared at δ_H 4.34 (dddd, J = 9.3,



8.1, 5.8 and 5.0 Hz) and δ_H 4.88 (dddd, J = 11.6, 6.6, 3.1 and *ca* 1 Hz), data which are consistent with both protons being in axial positions. In addition, the downfield shift of the 6-H in the *trans* isomer **17** relative to that in the *cis* isomer **18** ($\Delta\delta$ = 0.5 ppm) can be ascribed to its [1.3] relationship with the axial 4-hydroxy group.[7] As expected, the alkene geometry in both isomers was *trans* (J, CH_a=CH_b = 15.9 Hz).

The lack of significant stereoselection in the selenolactonization step was a disappointing feature of the scheme; a number of attempts to improve upon this were unsuccessful. Unusually, however, this turns out to be a distinct advantage in two respects. Our first aim was the preparation of analogues of the mevinic acids and it could be considered an advantage to obtain two readily distinguishable isomers for biological evaluation from one sequence of reactions. Given the availability of the appropriate aryllithium species, this sequence should be amenable to the elaboration of a range of analogues **2**. An additional benefit of these requirements is that there is no need to separate the initial isomeric mixture formed in the Wittig homologation step. A second advantage of the lack of stereoselection is that both enantiomers of some natural pyrones should be available from this sequence which can therefore be used to determine unambiguously the absolute stereochemistry of such compounds. This principle is illustrated in the case of the natural pyrone goniothalamin. Originally isolated from the bark of *Cryptocarya caloneura*[11] and from *Goniothalamus andersonii*[12] and assigned the (6*S*) absolute stereochemistry **20**[11,12] on the basis of an apparently unambiguous degradation sequence, subsequent synthetic studies have led to a revision to the alternative (6*S*) stereochemistry **21**.[13] In spite of this, the (6*S*) stereochemistry **20** is quoted for natural goniothalamin in a recent publication.[14] Our approach to the goniothalamin enantiomers simply required dehydration of the mevinic acid analogues **17** and **18**. This was achieved by brief exposure of the separated isomers to phosphorus oxychloride in warm pyridine. Such treatment of the *trans* lactone **17** led to (6*S*)-goniothalamin **20**, which was identical in all respects to the natural product, except for the optical rotation, $[\alpha]_D$ −129.8° (*c* 0.7; $CHCl_3$), corrected to −166.4° on the basis of an enantiomeric enrichment of 78%.[7]



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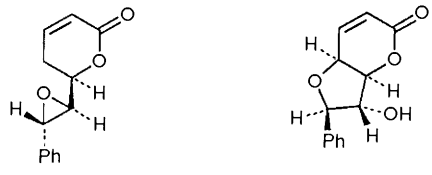
In chloroform solution, the natural product is reported to show $[\alpha]_D$ +170.3° (*c* 1.38)[12] or +178.5° (*c* 2).[14] {The optical rotation value is lower in methanol solution: $[\alpha]_D$ +135° (*c* 0.7; MeOH)[11,13b]}. In similar fashion, dehydration of the *cis* lactone **18** gave (6*R*)-goniothalamin **21**, identical in all respects with the natural material, including optical rotation, $[\alpha]_D$ +126.0° (*c* 0.5; $CHCl_3$), corrected to +162°. We therefore conclude that natural (+)-goniothalamin has the (6*R*) configuration in agreement with previous synthetic studies.[13]



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These results suggest that the recently reported goniothalamin 7,8-epoxide[14,15] is likely to have the (6*R*,7*S*,8*S*) configuration **22** rather than the (6*S*,7*R*,8*R*) assignment which was made on the basis of a (6*S*) configuration for goniothalamin. In addition, these conclusions agree with the original assignment of configuration[16] given to the closely related tetrahydrofurano-2-pyrone (+)-goniothalenol [= (+)-altholactone] **23**, rather than the enantiomeric structure recently proposed.[14] This conclusion is supported by recent synthetic work.[17] Finally, it is possible that the absolute stereochemistries of a series of oxygenated goniothalamin homologues isolated from *Goniothalamus sesquipedalis*[18] should be similarly revised as these were also deduced on the basis of goniothalamin having a (6*S*) configuration.

Experimental

For general details, see reference 7. The enantiomeric enrichment of the methyl (3*R*)-(−)-3-hydroxyhex-5-enoate **6** used in all the following reactions is 78%.[7] All products should therefore be regarded as having this order of optical purity. All *J* values are in Hz.

Methyl (3R)-3-[(*t-Butyl*)*dimethylsilyloxy*]*hex*-5-*enoate* **12**.—Imidazole (5.31 g, 78 mmol) was added to a solution of *t*-butyldimethylchlorosilane (4.70 g, 31 mmol) and methyl (3*R*)-(−)-3-hydroxyhex-5-enoate **6** (3.69 g, 26 mmol) (78% ee)[7] in dry dimethylformamide (40 ml). The resulting solution was stirred at ambient temperature for 24 h then diluted with pentane (70 ml) and washed with water (3 × 20 ml). The organic phase was dried and evaporated and the residue chromatographed over silica gel using ether–hexanes [1:20] as the eluent to give the *ether* **12** (4.75 g, 75%) as a colourless oil, $[\alpha]_D$ −27.5° (*c* 1.1; $CHCl_3$), ν_{max}/cm^{-1} 1733 and 1637; δ_H 0.03 (3 H, s, MeSi), 0.06 (3 H, s, CH_3Si), 0.86 (9 H, s, Bu^t), 2.28 (2 H, br t, *J* 6.3, CH_2=$CHCH_2$), 2.45 (2 H, d, *J* 6.3, CH_2C=O), 3.68 (3 H, s, OMe), 4.24 [1 H, quin, *J* 6.3, C*H*(OSi)], 4.96–5.28 (2 H, m, CH_2=CH) and 5.62–6.13 (1 H, m, CH_2=C*H*); *m*/*z* 217 (26%, $C_{10}H_{21}O_3Si$, M − C_3H_5), 201 (93, $C_9H_{17}O_3Si$, M − Bu^t), and 89 (100, C_3H_9OSi) (Found: $M^+ - C_3H_5$, 217.1262. $C_{10}H_{21}O_3Si$ requires M, 217.1260).

Methyl (3R)-3-[*t-Butyldimethylsilyloxy*]-5-*oxopentanoate* **13**.—A solution of the foregoing ether **12** (1.00 g, 3.88 mmol) in dichloromethane (50 ml) was cooled in a solid CO_2–acetone bath and treated with ozonized oxygen until the solution was blue in colour. The excess ozone was removed in a stream of nitrogen then dimethyl sulphide (0.6 ml) was added and the mixture warmed to ambient temperature. Following the addition of a further aliquot of dimethyl sulphide (2.0 ml), the solution was kept at 40 °C for 48 h then cooled, diluted with pentane (40 ml) and washed with water. The separated organic phase was dried and evaporated to leave the *aldehyde* **13** (0.94 g, 94%) as a pale yellow oil which was pure according to TLC and ^{1}H NMR data and which showed $[\alpha]_D$ −9.6° (*c* 1.2; $CHCl_3$); ν_{max}/cm^{-1} 1726; δ_H 0.09 (6 H, s, 2 × CH_3Si), 0.88 (9 H, s, Bu^t), 2.60 (2 H, d, *J* 6.3, CH_2=CO), 2.70 (2 H, dd, *J* 6.3 and 1.8, CH_2CHO), 3.73 (3 H, s, OMe), 4.70 [1 H, quin, *J* 6.3, C*H*(OSi)] and 9.92 (1 H, t, *J* 1.8, CHO); *m*/*z* 245 (4%, $C_{11}H_{21}O_4Si$, M − CH_3), 203 (97, $C_8H_{15}O_4Si$, M − Bu^t), 161 (31, $C_6H_{13}O_3Si$) and 101 (39, C_4H_9OSi) (Found: M^+ − Bu^t, 203.0735. $C_8H_{15}O_4Si$ requires 203.0740).

If the reaction was worked up after a briefer period of contact with dimethyl sulphide, varying amounts of the intermediate ozonide **19** were present which could be isolated by column chromatography over silica gel eluted with ether–hexanes [1:20], as a less polar material than the aldehyde. The *ozonide* **19**, a colourless oil, showed ν_{max}/cm^{-1} 1730; δ_H 0.08 (6 H, s, 2 × MeSi), 0.89 (9 H, s, Bu^t), 1.97 (2 H, t, *J* 5.4, $CHCH_2CH$), 2.05 (2 H, d, *J* 6.3, CH_2CO), 4.34–4.54 [1 H, m, C*H*(OSi)], 5.12 (1 H, m, OCH_aH_bO), 5.19 (1 H, m, OCH_aH_bO) and 5.36 [1 H, dt, *J* 5.4 and 1.5, O(O)C*H*CH_2].

Methyl (3R)-[(Z) *and* (E)]-3-[(*t-Butyl*)*dimethylsilyloxyl*]-7-*phenylhept*-5-*enoate* **14**.—Phenyllithium (1.8 ml of a 2.0M solution in ether–cyclohexane [3:7], 3.6 mmol) was added dropwise to a stirred suspension of vinyltriphenylphosphonium bromide (1.31 g, 3.6 mmol) in dry tetrahydrofuran (30 ml) at ambient temperature. After a further 20 min, a solution of the aldehyde **13** (0.89 g, 0.9 mmol) in tetrahydrofuran (2 ml) was added in one portion and after a similar period the mixture was poured into water and extracted with pentane (3 × 30 ml). The combined extracts were dried and evaporated and the residue chromatographed over silica gel eluted with ether–hexanes [1:20] to give the *alkenes* **14** (0.21 g, 67%) as a pale yellow oil, $[\alpha]_D$ −20.6° (*c* 1.0; $CHCl_3$), ν_{max}/cm^{-1} 1729; δ_H 0.02 (6 H, s, 2 × MeSi), 0.83 (9 H, s, Bu^t), 2.17–2.66 (4 H, m), 3.35 (2 H, br d, *J* 6.3, $PhCH_2CH$), 3.60 (3 H, s, OMe), 4.22 [1 H, quin, *J* 6.3, C*H*(OSi)], 5.33–5.87 (2 H, m) and 7.02–7.51 (5 H, m); *m*/*z* 291 (27%, $C_{16}H_{23}O_3Si$, M − Bu^t), 217 (24, $C_{14}H_{17}O_2$, M − OsiBu^{t}Me$_2$), 203 (44, $C_9H_{19}O_3Si$), 201 (14, $C_9H_{17}O_3Si$) and 89 (100, C_3H_9OSi) (Found: M − Bu^t, 291.1409. $C_{16}H_{23}O_3Si$ requires M, 291.1416).

The isomer ratio could not be determined accurately at 90 MHz but a (*Z*)–(*E*) ratio of 83:17 was evident from the NMR data for the corresponding alcohol [see below]. It is therefore likely that the above mixture has a similar composition.

Methyl (3R)-[(E) *and* (Z)]-3-*Hydroxy*-7-*phenylhept*-5-*enoate* **15a**.—Aqueous hydrogen fluoride (15 ml of a 40% solution) was added dropwise to a stirred solution of the foregoing alkenes **14** (1.02 g, 2.93 mmol) in acetonitrile (100 ml) maintained at 0 °C. The mixture was stirred at this temperature for 3 h, then evaporated and the residue partitioned between water (50 ml) and chloroform (100 ml). The organic portion was separated, dried and evaporated to give a residue which was chromatographed on silica gel eluted with ether–hexanes [3:7] to give the

alcohols **15a** (0.52 g, 77%) as a colourless oil with an isomer ratio of 83:17 [(*Z*)-(*E*)], $[\alpha]_D$ −14.1° (*c* 1.0; $CHCl_3$); ν_{max}/cm^{-1} 3450 and 1721; δ_H (400 MHz) 2.32–2.58 (4 H, m, 2 × CH_2), 3.03 (1 H, br s, OH), 3.38 [0.34 H, br d, *J* 6.7, (*E*)-PhCH_2], 3.41 [1.66 H, br d, *J* 7.4, (*Z*)-PhCH_2], 3.70 [0.51 H, s, (*E*)-OMe], 3.71 [2.49 H, s, (*Z*)-OMe], 4.40–4.72 (1 H, m, C*H*OH), 5.52–5.58 (1 H, m), 5.71–5.76 (1 H, m) and 7.16–7.38 (5 H, Ph); δ_C 29.7 (*E*), 33.6 (*Z*), 34.3 (*Z*), 38.6 (*E*), 40.5 (*Z*), 41.1 (*E*), [all CH_2], 51.8 [(*E*) and (*Z*) OMe], 67,8 (*E*), 69.7 (*Z*), 125.4 [(*E*) and (*Z*)], 126.0 (*Z*), 126.6 (*E*), 128.1 (*E*), 128.3 (*Z*), 128.5 (*Z*), 128.6 (*E*), 131.5 [(*E*) and (*Z*)], 140.6 [(*E*) and (*Z*)], [all CH] and 173.2 [(*E*) and (*Z*)]; *m/z* 216 (59%, $C_{14}H_{16}O_2$, M − H_2O), 156 (22, $C_{12}H_{12}$), 142 (100, $C_{11}H_{10}$) and 129 (44, $C_{10}H_9$) (Found: C, 71.8; H, 7.9. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%).

(3R)-[(E) *and* (Z)]-3-*Hydroxy*-7-*phenylhept*-5-*enoic Acid* **15b**.—Aqueous 2M sodium hydroxide (10 ml) was added to the foregoing alcohols **15a** (0.35 g, 1.5 mmol) and the resulting mixture stirred at ambient temperature for 16 h then washed with chloroform. The aqueous solution was then acidified to pH 2 using dilute hydrochloric acid and extracted with chloroform (3 × 15 ml). The combined extracts were dried and evaporated to give the *hydroxy acids* **15b** (0.29 g, 89%) as a viscous, colourless oil, $[\alpha]_D$ −14.2° (*c* 1.0; $CHCl_3$), ν_{max}/cm^{-1} 3390 and 1716; δ_H 1.97–2.89 (4 H, m, 2 × CH_2), 3.37 (2 H, br d, *J* 5.4, PhCH_2), 3.88–4.29 (1 H, m, CHOH), 5.26–5.96 (2 H, m, 2 × =CH) and 7.07–7.78 (5 H, Ph); *m/z* 202 (12%, $C_{13}H_{14}O_2$, M − H_2O), 142 (34, $C_{11}H_{10}$), 131 (25, $C_6H_{11}O_3$), 129 (34, $C_{10}H_9$) and 91 (100, C_7H_7) (Found: $M^+ - H_2O$, 202.0978. $C_{13}H_{14}O_2$ requires M, 202.0994) (Found: C, 70.6; H, 7.1. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%).

(4R,6S,1′E)- *and* (4R,6R,1′E)-4-*Hydroxy*-6-(2′-*phenylvinyl*)-3,4,5,6-*tetrahydro*-2H-*pyran*-2-*one* **17** *and* **18**.—A solution of the foregoing hydroxy acids **15b** (0.234 g, 1.06 mmol) in dry tetrahydrofuran (15 ml) was cooled to −78 °C and treated with phenylselenenyl chloride (0.207 g, 1.08 mmol). The resulting solution was stirred at this temperature for 0.5 h, then warmed to ambient temperature and concentrated under reduced pressure. The residue was adsorbed onto silica gel, the resulting powder placed on a column of silica gel and the products eluted using ether. A mixture of selenides **16** (0.29 g, 73%) was isolated which was immediately oxidized.

The selenides **16** (0.29 g) were dissolved in tetrahydrofuran (8 ml) and a solution of sodium metaperiodate (0.315 g) in methanol–water (7:3) (10 ml) was added. The mixture was stirred at ambient temperature for 1 h, diluted with chloroform (30 ml) and washed with water. The dried chloroform solution was evaporated and the residue chromatographed over silica gel eluted with ether to give: i, the *trans lactone* **17** (0.071 g, 43%) as colourless plates (ether), m.p. 102–104 °C; ν_{max}/cm^{-1} 3410 and 1723; δ_H (400 MHz) 1.95 (1 H, ddd, *J* 14.3, 10.8 and 3.0, 4-H_{ax}), 2.13 (1 H, dddd, *J* 14.3, 3.7, 3.4 and 1.5, 5-H_{eq}), 2.45 (1 H, br s, OH), 2.69 (1 H, ddd, *J* 17.8, 3.6 and 1.5, 3-H_{eq}), 2.79 (1 H, dd, *J* 17.8 and 4.8, 3-H_{ax}), 4.44 (1 H, m, $w_{\frac{1}{2}}$/Hz 10.6, 4-H_{eq}), 5.38 (1 H, dddd, *J* 10.8, 6.5, 3.4 and *ca.* 1, 6-H_{ax}), 6.21 (1 H, dd, *J* 15.9 and 6.5, 1′-H), 6.70 (1 H, dd, *J* 15.9 and *ca.* 1, 2′-H) and 7.25–7.45 (5 H, m, Ph); δ_C 36.4, 38.77, [both CH_2], 62.7, 76.2, 126.6, 126.7(2), 128.3, 128.8(2), 132.6, [all CH], 135.9 (C) and 170.2 (CO); *m/z* 218 (42%, $C_{13}H_{14}O_3$, M^+), 200 (42, $C_{13}H_{12}O_2$, M − H_2O), 172 (28, $C_{12}H_{12}O$, M − CO and H_2O), 133 (25, C_9H_9O), 132 (32, C_9H_8O), 131 (52, C_9H_7O), 130 (53, $C_{10}H_{10}$), 129 (54, $C_{10}H_9$) and 91 (100, C_7H_7) [Found: C, 71.7; H, 6.5. $C_{13}H_{14}O_3$ requires C, 71.4; H, 6.5%]; and ii, [eluted second] the *cis lactone* **18** (0.033 g, 20%), as a white powder (ether–hexane), m.p. 66–68 °C; ν_{max}/cm^{-1} 3420 and 1730; δ_H (400 MHz) 1.82 (1 H, ddd, *J* 13.7, 11.6 and 9.3, 5-H_{ax}), 2.25 (1 H, br s, OH), 2.41 (1 H, dddd, *J* 13.7, 5.0, 3.1 and 1.4, 5-H_{eq}), 2.54 (1 H, dd, *J* 17.2 and 8.1, 3-H_{ax}), 2.98 (1 H, ddd, *J* 17.2, 5.8 and 1.4, 3-H_{eq}). 4.34 (1 H, dddd, *J* 9.3, 8.1, 5.8 and 5.0, 4-H_{ax}), 4.88 (1 H, dddd, *J* 11.6, 6.6, 3.1 and *ca.* 1, 6-H_{ax}), 6.22 (1 H, dd, *J* 15.9 and 6.6, 1′-H), 6.70 (1 H, dd, *J* 15.9 and *ca.* 1, 2′-H) and 7.25–7.45 (5 H, m, Ph); δ_C 38.4, 39.6, (both CH_2), 64.0, 77.5, 126.1, 126.8(2), 128.5(2), 128.8(2), 132.9, (all CH), 135.8 (C) and 170.1 (CO); *m/z* 218 (71%, $C_{13}H_{14}O_3$, M^+), 200 (43, $C_{13}H_{12}O_2$, M − H_2O), 172 (36, $C_{12}H_{12}O$, M − CO and H_2O), 133 (38, C_9H_9O), 132 (33, C_9H_8O), 131 (62, C_9H_7O), 130 (55, $C_{10}H_{10}$), 129 (62, $C_{10}H_9$) and 91 (100, C_7H_7) (Found: C, 71.6; H, 6.6%).

(6S,2′E)-6-(2′-*Phenylvinyl*)-5,6-*dihydro*-2H-*pyran*-2-*one*, [(6S)-(−)-*goniothalamin*] **20**.—A solution of phosphorus oxychloride (0.06 g, 0.4 mmol) in pyridine (2 ml) was added to a stirred solution of the *trans* lactone **17** (0.056 mg, 0.26 mmol) in pyridine (3 ml), cooled in an ice bath. The resulting solution was stirred without cooling for 15 min, then heated to 70 °C (oil bath temperature) for 1 h. The cooled solution was diluted with ether (40 ml) and washed with 2M hydrochloric acid (2 × 15 ml) and brine (10 ml) then dried and evaporated. Chromatography of the residue over silica gel using ether–hexane [1:1] as the eluent afforded (S)-(−)-*goniothalamin* **20** (0.037 g, 73%) as a colourless solid, m.p. 77–78 °C (acetone–ether) [lit.,[12,14] m.p. 81–82 °C for the (*R*)-enantiomer], $[\alpha]_D$ −129.8° (*c* 0.7; $CHCl_3$), corrected to −166.4° on the basis of an enantiomeric enrichment of 78%,[7] {lit.,[12] $[\alpha]_D$ +170.3° (*c* 1.38; $CHCl_3$); lit.,[14] $[\alpha]_D$ +178.5° (*c* 2.0; $CHCl_3$); lit.,[11] $[\alpha]_D$ +135° (*c* 0.7; MeOH)}; ν_{max}/cm^{-1} 1721, 1654, 1623, 1597 and 1577; δ_H(400 MHz) 2.53–2.56 (2 H, m, C(5)-H_2), 5.11 (1 H, app dq, *J* 7.2 and 1.8, 6-H), 6.10 (1 H, dt, *J* 9.9 and *ca.* 1.5, 3-H), 6.28 (1 H, dd, *J* 16.0 and 6.4, 7-H), 6.73 (1 H, br d, *J* 16, 8-H), 6.93 (1 H, dt, *J* 9.9 and 4.3, 4-H) and 7.26–7.41 (5 H, Ph); δ_C 29.9 (CH_2), 77.9, 121.7, 125.6, 126.7(2), 128.4, 128.7(2), 133.1, [all CH], 135.7 (C), 144.6 (CH) and 163.9 (CO); *m/z* 200 (32%, $C_{13}H_{12}O_2$, M^+), 172 (8, $C_{12}H_{12}O$, M − CO), 156 (6, $C_{12}H_{12}$, M − CO_2), 141 (6, $C_{11}H_9$), 131 (12, H_9H_7O), 115 (9, C_9H_7), 104 (56, C_8H_8), 91 (36, C_7H_7) and 68 (100, C_4H_4O) (Found: C, 77.7; H, 5.9. Calc. for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0%). These data are identical to those reported for the natural product except for the sign of rotation.

(6R,2′E)-6-(2′-*Phenylvinyl*)-5,6-*dihydro*-2H-*pyran*-2-*one*, [(6R)-(+)-*goniothalamin*] **21**.—Using exactly the same procedure as in the foregoing experiment, dehydration of the *cis* lactone **18** (0.008 mg) gave (R)-(+)-*goniothalamin* **21** (0.007 mg, 97%) which showed m.p. 76–78 °C, (acetone–ether) $[\alpha]_D$ +126.0° (*c* 0.5; $CHCl_3$), corrected to +162° (78% ee) together with identical spectral data to that recorded above for the (−)-enantiomer **20**.

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