# A Facile Chiral Synthesis of the Lactone Moiety of Compactin and Mevinolin from (*R*)-*O*-Benzylglycidol

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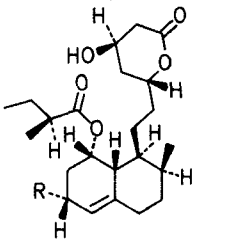
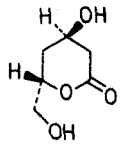
A facile chiral synthesis of (4*R*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydro-2-pyrone (**3**) a key synthon for the lactone portion of compactin and mevinolin, is established using (*R*)-O-benzylglycidol as starting material.

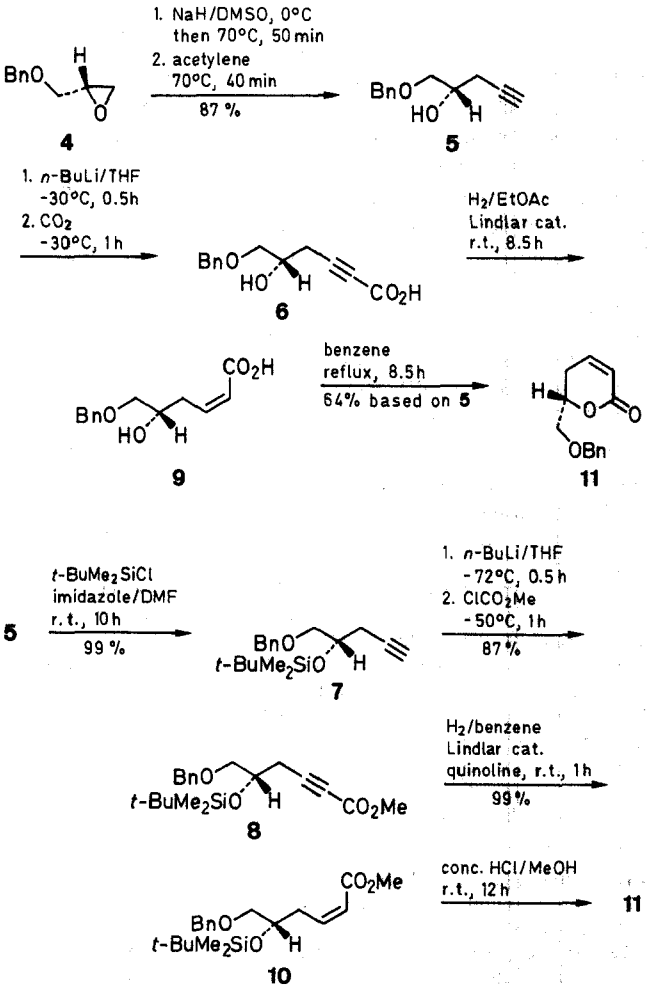
The lactone moiety of compactin[1] (**1**) and mevinolin[1] (**2**) is an essential structural feature associated with their biological activity.[2] Despite its rather simple structure, the synthesis of the (4*R*,6*R*)-tetrahydro-2-pyrone ring system has proven to be challenging.[3] We wish to report here a facile enantiocontrolled synthesis of (4*R*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydro-2-



**1**, compactin: R = H
**2**, mevinolin: R = $CH_3$

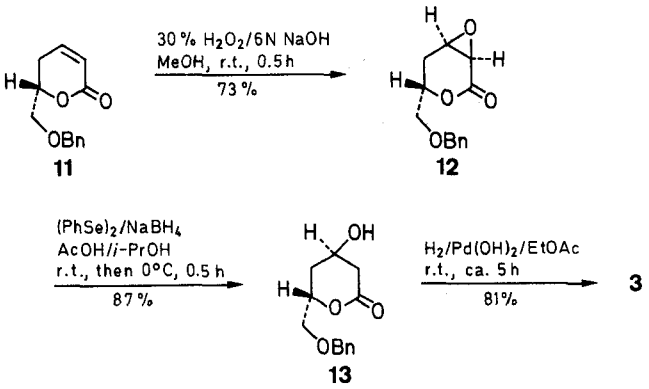


**3**



pyrone (3), potentially useful as a key synthon for the synthesis of compactin (1) and mevinolin (2) as well as their analogues, using (*R*)-*O*-benzylglycidol[4] (4) as starting material.

Treatment of sodium acetylide generated *in situ* by introducing acetylene into the dimethyl sulfoxide solution containing sodium methylsulfinylmethanide[5] with (*R*)-*O*-benzylglycidol (4) affords the terminal acetylene[6] 5 in 87% yield, without migration of the acetylene bond.[6] Addition of carbon dioxide to a solution of the lithium acetylide generated from 5 gives the carboxylic acid 6. Hydrogenation of 6 on Lindlar catalyst gives the *Z*-olefin 9 which on brief heating affords the $\alpha,\beta$-unsaturated $\delta$-lactone 11 in 64% overall yield from 5. Since it is difficult to purify the carboxylic acid intermediate 6, an alternative route was also examined. Treatment of 5 with *tert*-butyldimethylsilyl chloride in the presence of imidazole affords the silyl ether 7 which is sequentially lithiated and methoxycarbonylated to give the ester 8 in 87% yield. Hydrogenation of 8 on Lindlar catalyst followed by brief exposure of the resulting olefin 10 to acid furnishes the same $\alpha,\beta$-unsaturated $\delta$-lactone 11 in 86% overall yield with spontaneous desilylation and cyclization.




Epoxidation of 11 using alkaline hydrogen peroxide proceeds stereoselectively from the less hindered face of the molecule to give the epoxide 12 as single product in 73% yield. Treatment of 12 with sodium phenylseleno(triisopropyloxy)borate[7] allows regioselective cleavage of the epoxide bond to furnish the $\beta$-ketol 13 in 87% yield. Finally, the benzyl group of 13 is removed by hydrogenolysis to afford the lactone diol 3 in 81% yield.

Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Mass spectra were recorded with a JEOL-01SG-2 instrument, IR spectra with a JASCO A-102 spectrophotometer, and $^1$H-NMR spectra on JEOL-JNM-FX 90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers.

Reactions, other than hydrogenation, were carried out under argon.

**(*S*)-5-Benzyloxy-4-hydroxy-1-pentyne (5):**
NaH (60% in oil, 5.0 g, 126 mmol) is added portionwise to DMSO (50 mL) at 0°C with stirring, the solution is warmed to 70°C for 50 min, and cooled to r.t. To this solution is introduced dry acetylene for 40 min, (*R*)-*O*-benzylglycidol (4; 5.9 g, 36 mmol) in DMSO (5 mL) is added dropwise, and stirring is continued for 40 min at the same temperature. To the reaction mixture, after cooling to 0°C, is added $H_2O$ (50 mL), and the mixture is extracted with $Et_2O$ (3 × 100 mL). The combined extracts are washed with 5% aq. $NaHCO_3$ (50 mL), and brine (50 mL), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (200 g) using a mixture of $Et_2O$/hexane (3:1 *v/v*) as eluent to give pure 5 as a colorless oil; yield: 5.92 g (87%). Spectral and chromatographic properties are identical in all respects with those of an authentic sample.[6]

**(*S*)-6-Benzyloxymethyl-5,6-dihydro-2-pyrone (11):**
To a stirred solution of the acetylene (5; 1.81 g, 9.5 mmol) in THF (50 mL) is added *n*-BuLi [10% hexane solution (*w/v*), 14.6 mL, 22.8 mmol] dropwise at −30°C and, after 30 min, $CO_2$ is introduced to the mixture at the same temperature for 1 h. Brine (80 mL) is added to the mixture, and the resulting mixture is washed with $Et_2O$ (100 mL). The aqueous layer is acidified to pH = 3 ~ 4 by careful addition of conc. HCl, and the mixture is extracted with $Et_2O$ (2 × 100 mL) and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves the crude acid (6; 2.27 g, 102%) which is used for next reaction without purification.

The above crude acid (6; 1.72 g) is hydrogenated in EtOAc (30 mL) under atmospheric pressure of hydrogen in the presence of Lindlar catalyst (150 mg) for 8.5 h at r.t. After filtration of the catalyst, the solution is evaporated under reduced pressure to leave the crude olefin (9; 1.57 g), which is used for the next reaction without purification.

A solution of the above crude olefin (9; 1.10 g) in benzene (30 mL) is heated at reflux for 8.5 h with azeotropic removal of the generated $H_2O$ using a Dean-Stark apparatus. The mixture is washed with 5% aq. $NaHCO_3$ (20 mL), and $H_2O$ (10 mL), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (30 g) using a mixture of $Et_2O$/hexane (1:1 *v/v*) as eluent to give pure 11 as a colorless oil; yield: 650 mg (64% overall yield from 5); $[\alpha]_D^{27}$ −115.07° (*c* = 1.008, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_{13}H_{14}O_3$ | calc. | C 71.54 | H 6.47 |
| (218.3) | found | 71.60 | 6.64 |

IR (film): $\nu = 1720\ cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.36–2.65 (m, 2H); 3.70 (d, 2H, *J* = 6.3 Hz); 4.60 (s, 2H); 4.78–4.36 (m, 1H); 5.90–6.20 (m, 1H); 6.78–7.08 (m, 1H); 7.38 (s, 5H).

MS (70 eV): *m/z*(%) = 219 ($M^+ + 1$); 91 (100).

**(*S*)-5-Benzyloxy-4-*tert*-butyldimethylsiloxy-1-pentyne (7):**
A mixture of 5 (3.5 g, 18.4 mmol), *tert*-butyldimethylsilyl chloride (3.6 g, 23.9 mmol), and imidazole (5.0 g, 73.6 mmol) in DMF (30 mL) is stirred at r.t. for 10 h. The mixture is diluted with $Et_2O$ (60 mL) and $H_2O$ (30 mL), and the aqueous layer is separated. The organic layer is washed with 5% aq. $NaHCO_3$ (10 mL), and brine (10 mL), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (150 g) using a mixture of $Et_2O$/hexane (1:20) as eluent to give 7 as a colorless oil; yield: 5.51 g (99%); $[\alpha]_D^{24}$ +10.98° (*c* = 1.038, benzene).

| | | | |
|---|---|---|---|
| $C_{18}H_{28}O_2Si$ | calc. | C 71.01 | H 9.28 |
| (304.2) | found | 71.23 | 9.29 |

IR (film): $\nu = 3310, 2260\ cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 0.08 (s, 3H); 0.10 (s, 3H); 0.78 (s, 9H); 1.95 (t, 1H, *J* ≈ 3 Hz); 2.90 (m, 2H); 3.48 (m, 2H9; 3.95 (m, 1H); 4.55 (s, 2H); 7.35 (s, 5H).

MS (70 eV): *m/z* (%) = 304 ($M^+$); 91 (100).

**Methyl (*S*)-6-Benzyloxy-5-*tert*-butyldimethylsiloxy-2-hexynoate (8):**
To a stirred mixture of 7 (400 mg, 1.32 mmol) in THF (6 mL) is added *n*-BuLi [10% hexane solution (*w/v*), 1.07 mL, 1.71 mmol)] at −72°C. After stirring for 30 min at the same temperature, the temperature is raised to −50°C, and a solution of methyl carbonochloridate (0.152 mL, 1.97 mmol) is added. Stirring is continued for 1 h at the same temperature. The reaction mixture is diluted with $Et_2O$ (10 mL) and sat. aq. $NH_4Cl$ (4 mL), and the aqueous layer is separated. The organic layer is washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The resulting crude ester (470 mg) is purified by chromatography on a silica gel column (15 g) using a mixture of $Et_2O$/hexane (1:30) as eluent to give the pure ester 8 as a colorless oil; yield: 414 mg (87%); $[\alpha]_D^{27}$ −7.14° (*c* = 1.036, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_{20}H_{30}O_4Si$ | calc. | C 66.26 | H 8.34 |
| (362.2) | found | 66.40 | 8.47 |

IR (film): $\nu = 2325, 1720\ cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 0.08 (s, 3H); 0.1 (s, 3H); 0.88 (s, 9H); 2.58 (m, 2H); 3.45 (d, 2H, *J* = 6 Hz); 4.25 (s, 3H); 4.01 (m, 1H); 4.55 (s, 2H); 7.35 (s, 5H).

MS (70 eV): *m/z* (%) = 362 ($M^+$); 91 (100).

**Methyl (*S,Z*)-6-Benzyloxy-5-*tert*-butyldimethylsiloxy-2-hexenoate (10):**
The acetylene (8; 382 mg, 1.06 mmol) is hydrogenated under atmospheric pressure using Lindlar catalyst (20 mg) in benzene (10 mL) in the presence of quinoline (0.2 mL). After uptake of the theoretical amount of hydrogen, the mixture is filtered through Celite, and the filtrate is washed with 5% HCl (5 mL) and 5% aq. $NaHCO_3$ (5 mL), dried with $MgSO_4$, and evaporated under reduced pressure to give the ester 10 as a colorless oil; yield: 380 mg (99%); $[\alpha]_D^{26}$ +6.27° (*c* = 1.02, benzene).

$C_{20}H_{32}O_4Si$ (364.2) calc. C 65.90 H 8.85 found 65.89 9.02

IR (film): $\nu = 1720\ cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 0.05$ (s, 6H); 0.88 (s, 9H); 2.88 (m, 2H); 3.38 (d, 2H, $J = 6$ Hz); 3.95 (m, 1H); 4.55 (s, 2H); 5.82 (dt, 1H, $J = 1.5$, 12 Hz); 6.38 (dt, $J = 7.5$, 12 Hz); 7.35 (s, 5H).

MS (70 eV): $m/z$ (%) = 364 ($M^+$); 91 (100).

**(*S*)-6-Benzyloxymethyl-5,6-dihydro-2-pyrone (11) from the Silyl Ether 10:**

To a stirred solution of the silyl ether (**10**; 9.0 g, 0.025 mol) in MeOH (150 mL) is added conc. HCl (50 mL) dropwise at r.t., and stirring is continued for 12 h at the same temperature. The mixture is diluted with $Et_2O$ (500 mL) and $H_2O$ (300 mL), and the aqueous layer is separated. The organic layer is washed with 5% aq. $NaHCO_3$ (200 mL), and brine (200 mL) and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residual oil is purified by chromatography on a silica gel column (200 g) using a mixture of $Et_2O$/hexane (1:1) $v/v$) as eluent to give the unsaturated lactone **11** as a colorless oil; yield: 4.65 g (86%). Spectral data are identical in all respects with those of an authentic material.

**(3*R*,4*R*,6*S*)-6-Benzyloxymethyl-3,4-epoxy-tetrahydro-2-pyrone (12):**

To a stirred solution of the unsaturated lactone (**11**: 855 mg, 3.92 mmol) in MeOH (20 mL) is added 30% aq. $H_2O_2$ (1.33 mL, 13.2 mmol) and 6N NaOH (0.39 mL, 2.35 mmol) at r.t. After stirring for 30 min at the same temperature, the mixture is diluted with $Et_2O$ (50 mL) and $H_2O$ (50 mL), and the solution is made acidic (pH = 3 ~ 4) by addition of conc. HCl. The organic layer is separated, and the aqueous layer is further extracted with $CH_2Cl_2$ (50 mL). The combined organic layers are washed with brine (2 × 10 mL), dried with $MgSO_4$, evaporated under reduced pressure, and the residual oil in benzene (10 mL) is heated at reflux with azeotropic removal of $H_2O$ to recyclize the seco-acid generated under the epoxidation conditions. After removal of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (45 g) using a mixture of $Et_2O$/hexane (1:2 $v/v$) as eluent to give pure **12** as a colorless oil; yield: 671 mg (73%); bp 190°C/0.3 Torr (Kugelrohr); $[\alpha]_D^{24}$ +48.24° ($c = 1.082$, $CHCl_3$).

$C_{13}H_{14}O_4$ (234.3) calc. C 66.66 H 6.02 found 66.88 6.11

IR (film): $\nu = 1740\ cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 2.30$ (m, 2H); 3.60 (m, 3H); 3.69 (m, 1H); 4.58 (s, 2H); 4.70 (m, 1H); 7.34 (s, 5H).

MS (70 eV): $m/z$ (%) = 234 ($M^+$); 91 (100).

**(4*R*,6*S*)-6-Benzyloxymethyl-4-hydroxy-tetrahydro-2-pyrone (13):**

To a stirred solution of diphenyl diselenide (1.12 g, 3.6 mmol) in *i*-PrOH (10 mL) is added $NaBH_4$ (273 mg, 7.2 mmol) portionwise at r.t., and after a few minutes AcOH (0.07 mL) is added at the same temperature. After 5 min, the mixture is cooled to 0°C, and a solution of the epoxy lactone (**12**; 563 mg, 2.4 mmol) in *i*-PrOH (20 mL) is added dropwise to the mixture. Stirring is continued for 30 min at the same temperature. The mixture is diluted with EtOAc (50 mL), and the organic layer is washed with brine (40 mL) and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (20 g) using $Et_2O$ as eluent to give pure **13** as a colorless oil; yield: 397 mg (87%); $[\alpha]_D^{29}$ +6.59° ($c = 1.032$, $CHCl_3$).

$C_{13}H_{16}O_4$ (236.3) calc. C 66.08 H 6.83 found 65.95 6.96

IR (film): $\nu = 3400$, 1720 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 1.95$ (m, 2H); 2.30 (s, 1H, exchangeable with $D_2O$); 2.68 (d, 2H, $J = 4.15$ Hz); 3.68 (dd, 2H, $J = 4.15$, 1.8 Hz); 4.45 (m, 1H); 4.58 (s, 2H); 4.86 (m, 1H); 7.35 (s, 5H).

$^1$H-NMR (500 MHz) ($CDCl_3$/TMS) of 4-acetoxy derivative of **3**: $\delta = 2.07$ (s, 3H; $CH_3CO$); 2.09 (m, 2H, H-4); 2.72 (ddd, 1H, $J = 17.0$ (gem), 3.75 (with H-$3_{eq}$), 2.0 Hz (with 4-$H_{eq}$); H-$2_{eq}$; 2.78 [dd, 1H, $J = 17.0$ (gem.), 3.75 Hz (with H-$3_{eq}$), H-$2_{eq}$; 3.63 [dd, 1H, $J = 12.0$ (gem), 4.0 Hz (with H-$5_{ax}$, H-6); 3.70 (dd, 1H, $J = 12.0$ (gem), 3.75 Hz (with H-$5_{ax}$, H-6); 4.56 (d, 1H, $J = 12.0$ Hz, $H_{benzylic}$); 4.60 (d, 1H, $J = 12.0$ Hz, $H_{benzylic}$); 4.71 [dq, 1H, $J = 10.0$ (with H-$4_{ax}$), 3.75 (with H-$4_{eq}$, 2 × H-6), H-5]; 5.32 [quint, 1H, 3.75 Hz (with H-$2_{eq}$, H-$2_{ax}$, H-$4_{eq}$, and H-$4_{ax}$, H-5]; 7.35 (m, 5H, $H_{arom}$).

MS (70 eV): $m/z$ (%) = 236 ($M^+$); 91 (100).

**(4*R*,6*S*)-4-Hydroxy-6-hydroxymethyltetrahydro-2-pyrone (3):**

A stirred solution of the benzyl ether (**13**; 100.2 mg, 0.43 mmol) is hydrogenated in EtOAc (3 mL) containing a trace of $CHCl_3$ (5 drops) under atmospheric pressure in the presence of $Pd(OH)_2$ (6.5 mg) at r.t.. After uptake of the theoretical amount of hydrogen (about 5 h), the mixture is filtered through Celite, and the filtrate is evaporated under reduced pressure. The residual oil is purified by chromatography on a silica gel column (5 g) using EtOAc as eluent to give pure **3** as a colorless oil; yield: 50.1 g (81%); $[\alpha]_D^{29}$ +1.81° ($c = 0.992$, MeOH).

$C_6H_{10}O_4$ (146.2) calc. C 49.31 H 6.90 found 49.12 7.14

IR (film): $\nu = 3390$, 1715 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 1.95$ (m, 4H, 2H exchangeable with $D_2O$); 2.70 (d, 2H, $J = 4.2$ Hz); 3.65 (dd, 1H, $J = 12.2$, 4.7 Hz); 3.95 (dd, 1H, $J = 12.2$, 2.7 Hz); 4.48 (quint, 1H, $J = 4.2$ Hz); 4.84 (m, 1H).

MS (70 eV): $m/z$ (%) = 147 ($M^+ + 1$); 115 (100).

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