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Total Synthesis of the Monoterpenes (−)-Mintlactone and (+)-Isomintlactone

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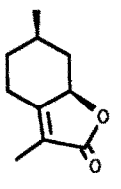
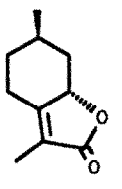
Abstract: The first total, stereodirected synthesis of the monoterpenes (−)-mintlactone and (+)-isomintlactone from the same chiral starting product is described. A stereoselective, radical-mediated ring closure was the key step in both syntheses.

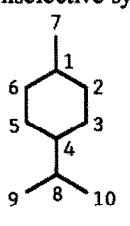
The essential oil of *Mentha piperita* L. (peppermint oil), one of the most important commercial flavouring materials, is produced in many countries. Its chemical composition has been thoroughly investigated, more than 300 components having been reported. Among the minor constituents, the menthane derivatives (−)-mintlactone **1** and (+)-isomintlactone **2** were isolated from a sample of American peppermint oil.[1] Before their first description as natural products, the formation of these compounds in the course of synthetic processes[2-4] had been reported. Racemic **1** was also an intermediate in a total synthesis of menthofurane.[5] More recently, a further, nonselective synthesis of



(-)-Mintlactone **1**



(+)-Isomintlactone **2**

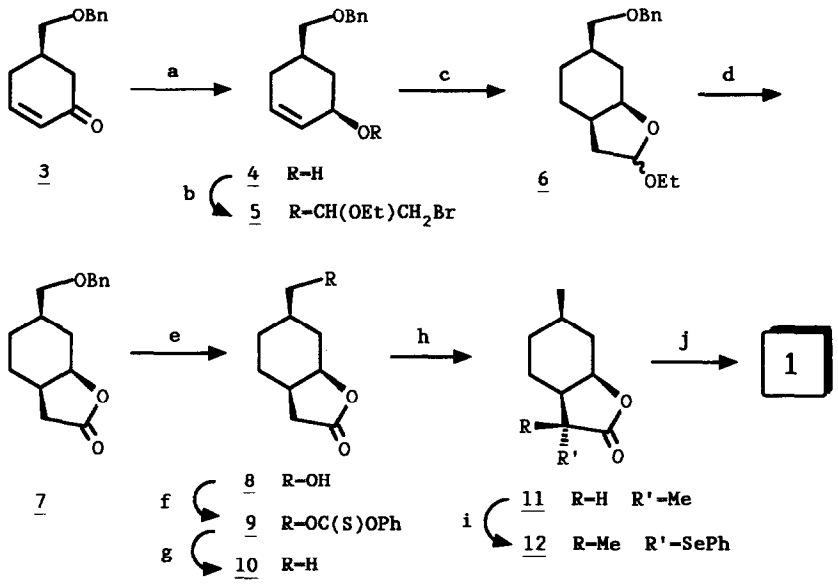


Menthane

racemic **1** and **2** has been published.[6] We recently reported[7] the first stereodirected synthesis of optically active **1**, using the chiral enone **3**[8] as the starting material. We now wish to report the full results of our syntheses of both monoterpene lactones in their naturally occurring, optically active form. Furthermore, the successful completion of the syntheses constitutes the definitive confirmation of the absolute configuration of chiron **3**.[8b]

(−)-Mintlactone **1** was initially synthesized according to the procedure described in Scheme 1.[7] Hydride reduction of ketone (−)-**3** (>95% ee)[8] gave stereoselectively the allylic alcohol **4** in almost quantitative yield. For the creation of the five-membered lactone ring, we selected a well established homolytic protocol.[9,10] After transformation of alcohol **4** into the bromoacetal **5** by reaction with NBS

and ethyl vinyl ether at -40 °C,[10] the crude product was subjected to homolytic reductive ring closure with tri-*n*-butyltin hydride.[9,10] This procedure afforded acetal **6** as a diastereoisomeric mixture. Oxidation of **6** with Jones reagent proved superior to alternative procedures[11] and gave the stereochemically



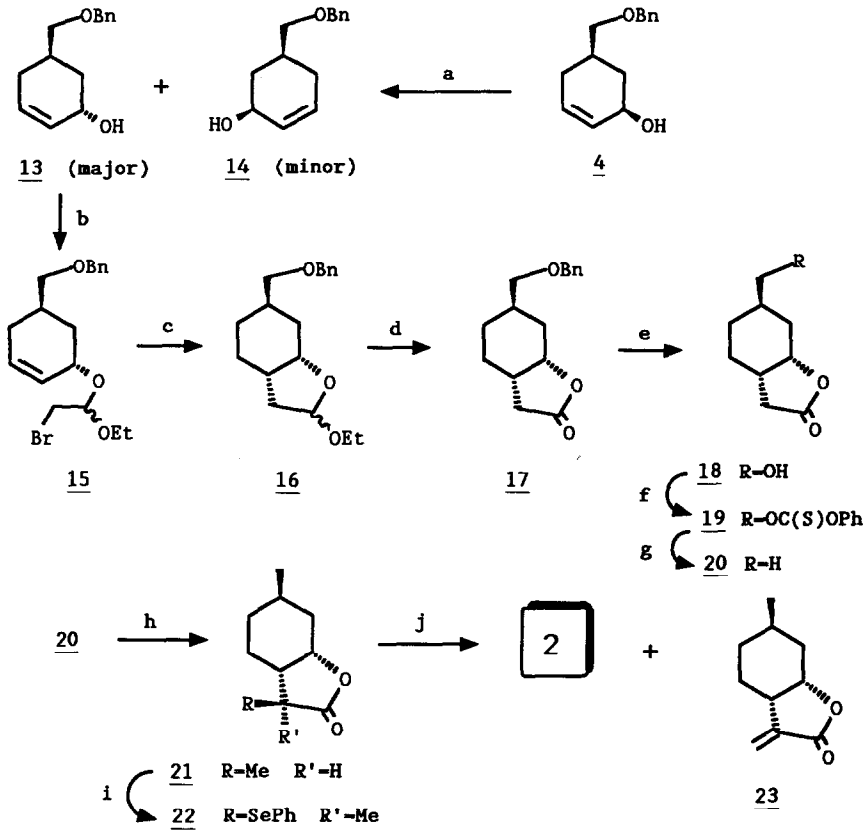
Reagents and reaction conditions. a: $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 45 min, 99%. **b**. NBS, excess $EtOCH=CH_2$, -40 °C, 4 h, 90%. **c**: Bu_3SnH, AIBN, C_6H_6, Δ, 4 h, 92%. **d**: Jones reagent, acetone, 0 °C, 15 min, 84%. **e**: H_2, $Pd(OH)_2$, EtOAc, 30 min, 98%. **f**: ClC(S)OPh, DMAP, MeCN, r.t., 15 h, 83%. **g**: Bu_3SnH, AIBN, Tol, Δ, 3 h, 88%. **h**: LDA, THF, -78 °C, 1 h, then MeI/HMPA/THF, 1 h at -78 °C and 40 min at -50 °C, 60%. **i**: LDA, THF, -78 °C, 1 h, then PhSeCl/HMPA/THF, 40 min at -78 °C and 40 min at -50 °C, 40%. **j**: H_2O_2/THF/AcOH, 0 °C, 1 h, 80%.

Scheme 1. Synthesis of (−)-mintlactone.

homogeneous lactone **7** in a very good yield. Debenzylation of the latter compound to hydroxy lactone **8** could be performed by hydrogenolysis with either $Pd(OH)_2$ or Pd/C, but the former catalyst was more reactive and gave better yields. The reductive elimination of the hydroxyl group in compound **8** was carried out through a radical method, due to the presence of the lactone ring. Acylation of **8** with O-phenyl chlorothionoformate[12] gave thiocarbonate **9**, which was then treated with tri-*n*-butyltin hydride and AIBN in refluxing toluene. This furnished lactone **10** in 73% overall yield from **8**. The remaining C-methyl group was then introduced by methylation of the enolate of **10**, generated with LDA at −78 °C. Although the stereoselectivity of this step was inconsequential for the future course of the synthesis, the attack of the electrophilic reagent MeI took place exclusively from the less hindered α face of the molecule, to yield compound **11**, a dihydro derivative of (−)-mintlactone. As expected, selenylation of the enolate of **11** gave only the phenylselenenyl derivative **12**. Finally, oxidation of **12** with hydrogen peroxide afforded (−)-mintlactone **1** (32% overall yield from **11**), identical in its spectral and physical properties (IR, NMR, optical rotation) with the product described in the bibliography.[1-5]

The synthesis of the epimeric (+)-isomintlactone **2** was then executed alongside the same lines as **1** (Scheme 2). Epimerization of the *cis*-substituted cyclohexenol **4** was performed via Mitsunobu's procedure.[13] This yielded the expected *trans* cyclohexenol **13** as the major product but also a small

percentage (ca. 10%) of the *cis* isomer **14**. Since we were not able to separate both components, we carried out the following steps with this isomer mixture until lactone **17**, which could be separated from its minor counterpart by HPLC (expectedly, this minor compound was identical by NMR with lactone **7**). All the steps were performed in a way analogous to that in Scheme 1, and proceeded also with similar yields. As in the previous instance, the methylation step took place from the least hindered convex side of the lactone enolate, yielding **21** as a single isomer. The oxidative deselenenylation step furnished, however, not only the desired isomintlactone **2** but also its exocyclic double-bond isomer **23**.

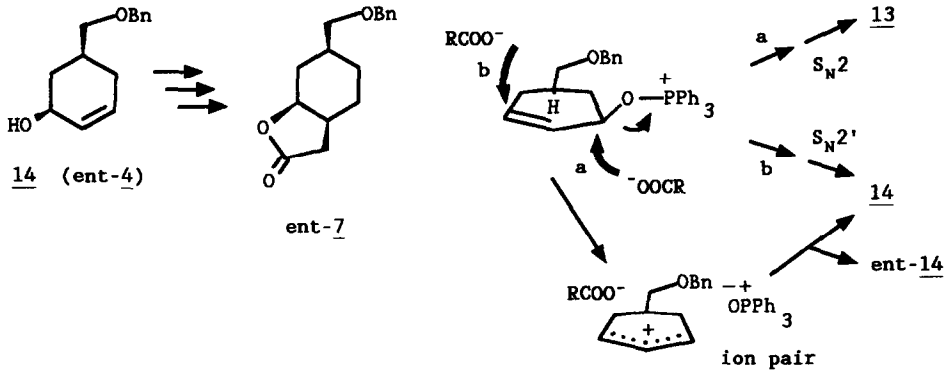


Reagents and reaction conditions. **a**: 1) DEAD, PPh_3, PhCOOH, THF, 4 h, r.t. 2) NaOH, aq MeOH, reflux, 40 min., 78% overall. **b**. NBS, excess $EtOCH=CH_2$, -40 °C, 4 h, 78%. **c**: Bu_3SnH, AIBN, C_6H_6, Δ, 4 h, 89%. **d**: Jones reagent, acetone, 0 °C, 15 min, then HPLC, 84% in **17**. **e**: H_2, $Pd(OH)_2$, EtOAc, 30 min, 98%. **f**: ClC(S)OPh, DMAP, MeCN, r.t., 15 h, 81%. **g**: Bu_3SnH, AIBN, Tol, Δ, 3 h, 73%. **h**: LDA, THF, -78 °C, 1 h, then MeI/HMPA/THF, 1 h, -78 °C, 40 min at -50 °C, 76%. **i**: LDA, THF, -78 °C, 1 h, then PhSeCl/HMPA/THF, 1 h, -78 °C, 40 min at -40 °C, 50%. **j**: H_2O_2/THF/AcOH, 0 °C, 1 h, **2** (28%), **23** (20%).

Scheme 2. Synthesis of (+)-isomintlactone.

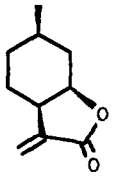
As stated above, the Mitsunobu reaction gave a ca. 9:1 mixture of the expected alcohol **13** and the *cis* isomer **14**. While **13** results from the normal course of the Mitsunobu reaction (Scheme 3), compound **14** is probably formed through a S_N2' reaction type, which is expected to take place in the *syn* mode.[13,14] It may be easily deduced from Scheme 3, however, that the latter stereochemical course should lead to

the enantiomer of alcohol **4** (**14** ≡ ent-**4**). The absolute configuration and optical purity of **14** was deduced by conversion, as commented above, to a lactone identical by NMR with **7**. This lactone had an optical rotation of $-3.1°$, to be compared with the value $+10.4°$ of the almost enantiomerically pure **7** (>95% ee). While this confirms the absolute configuration of **14**, its lowered optical purity may be explained if we assume that it is formed, at least in part, through a tight, asymmetric ion pair (Scheme 3) which then collapses in two possible ways to give either **14** or its enantiomer.[13,14]



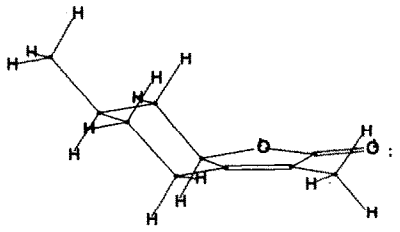
Scheme 3. Alternative mechanistic pathways for the Mitsunobu reaction.

We have performed molecular mechanics calculations for the four lactonic products **1**, **2**, **23** and **24** (the exocyclic double-bond isomer of **1**, not formed in detectable amounts) with Still's MacroModel program.[15] The results are summarized in Scheme 4. For the three former compounds, the coupling constants predicted by the program agree well with the experimental values.[15] The thermodynamic stabilities of all four products have been estimated by two independent theoretical ways. Both of them predict a higher *difference* in the enthalpy contents within the pair **1**/**24** when compared with the pair **2**/**23**.[16] This may be invoked to explain the different outcome of the oxidative deselenenylation reactions, where **22** yields the two possible elimination products **2** and **23**, while **12** gives only the endocyclic isomer **1**. Since the elimination step [selenoxide → olefin] is a concerted process proceeding through a cyclic, transition state,[17] we can reasonably follow that the activation energy of the process is proportional to the stability of the obtained olefin. In other words, the more stable olefin should be formed through the less energetic transition state. If we assume that a part of the aforementioned energy difference between the final products is already present in the corresponding transition states leading to them, we can predict that **22** is more prone than **12** to give both posible regioisomers, as the former product evolves towards transition states closer in energy than in the case of the latter.



24

The lactone methylation step could be obviated by placing the future α-lactone methyl group from the beginning. The reaction series described above were thus repeated by using ethyl propenyl ether (mixture of E + Z isomers) instead of ethyl vinyl ether. Scheme 5 presents the modified syntheses of (−)-mintlactone and (+)-isomintlactone, the individual steps being carried out as in Schemes 1 or 2. Due either to the fact that we used a mixture of the geometrical isomers of ethyl propenyl ether, or to lack of stereoselectivity in the homolytic cyclization steps, compounds **26** and **32** were mixtures of



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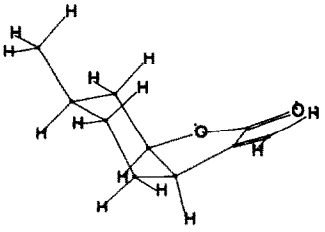

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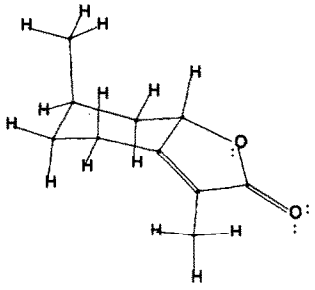

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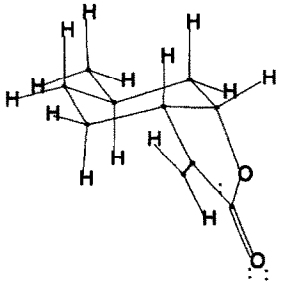

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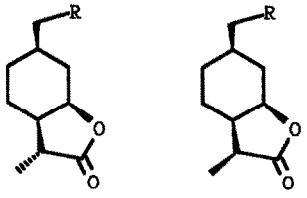
Scheme 4. Optimized conformations of lactones **1**, **2**, **23** and **24** (calculated by MacroModel).



27a-30a 27b-30b

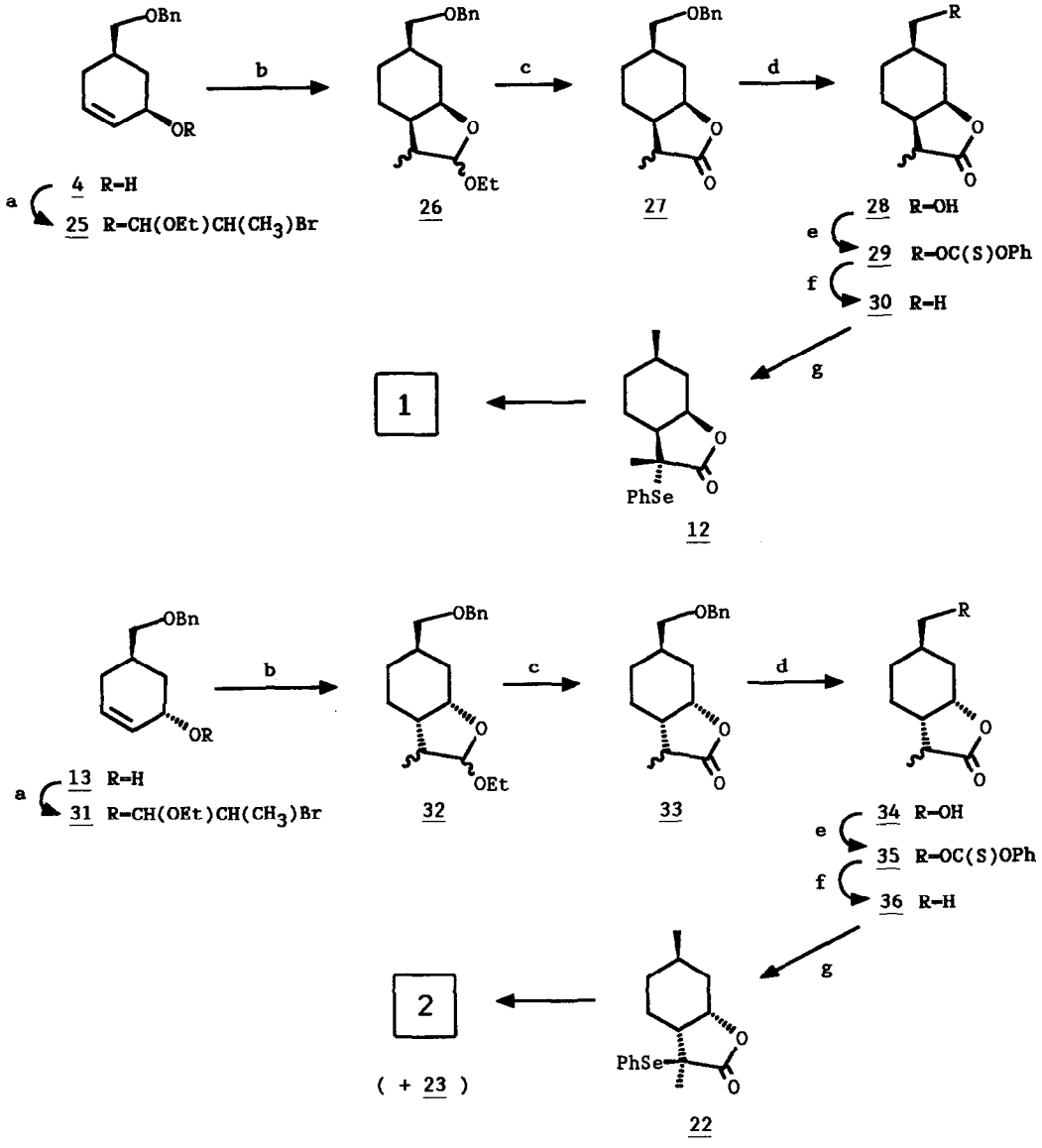
(R = OBn, OH, OCSOPh, H)

epimers at C-8 (see menthane numbering, C-9 is the methyl carbon). In the mintlactone series, the epimers could be separated later at the stage of compound **27** although this was not necessary for synthetic purposes (physical constants for the epimers of **27-30**, depicted in the adjoining diagram, are given in the Experimental). The separation proved impracticable, however, in the case of compounds **32-36** and the reactions were thus carried out with the epimeric mixtures up to compound **22**, which was again configurationally homogeneous.

It is worth mentioning that the measured optical rotations of compounds **1** and **2** (see Experimental) are approximately 96% of the reported values for the enantiomerically pure compounds.[1] This agrees nicely with the optical purity which had been determined for the starting compound **3**, indicating that no loss of stereochemical integrity has occurred during the synthesis.

EXPERIMENTAL

NMR spectra were measured in $CDCl_3$ solution (Varian Unity 400 and Bruker AC-200). Mass spectra were run by the electron impact mode (70 eV) on a Hewlett-Packard 5988A mass spectrometer. IR spectra were recorded as oily films. Optical rotations were measured at 23 °C. Reactions which required an inert atmosphere were carried under argon (Ar) with flame-dried glassware. Commercial reagents (from Aldrich or Fluka) were used as received. Acetonitrile (from SDS) was stored over 4Å molecular sieves. THF was distilled under Ar from sodium-benzophenone ketyl. Benzene and toluene were



Reagents and reaction conditions. **a**: NBS, excess EtOCH=CHMe, -40 °C, 4 h, 83% (**25**), 89% (**31**). **b**: Bu_3SnH, AIBN, C_6H_6, Δ, 4 h, 83%. **c**: Jones reagent, acetone, 0 °C, 15 min, 76% (**27**), 80% (**33**). **d**: H_2, $Pd(OH)_2$, EtOAc, 30 min, 99%. **e**: ClC(S)OPh, DMAP, MeCN, r.t., 15 h, 79% (**29**), 73% (**35**). **f**: Bu_3SnH, AIBN, Tol, Δ, 3 h, 80% (**30**), 61% (**36**). **g**: LDA, THF, -78 °C, 1 h, then PhSeCl/HMPA/THF, 40 min at -78 °C and 40 min at -50 °C, 40% (**12**), 49% (**22**).

Scheme 5. Improved syntheses of (−)-mintlactone and (+)-isomintlactone.

distilled under Ar from sodium. "Usual work-up" means pouring into brine, extraction with Et_2O or EtOAc (indicated), additional washing with 5% aq $NaHCO_3$, if acids had been utilized in the reaction, then again with brine, drying over

anhydrous Na_2SO_4 and elimination of the solvent *in vacuo*. Column chromatography was made on silica gel Merck (40-63 μ). HPLC was performed in the reverse phase mode (LiChrosorb RP-8, 250 x 8 mm).

(R)-5-*Benzyloxymethyl-2-cyclohexenone* (3). Obtained as previously described.[8] IR $\bar{\nu}_{max}$ cm^{-1}: 3084, 3060, 3032, 1673, 1248, 1099, 880, 731, 696; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 6.96 (1H, *ddd*, J = 10, 5.1, 2.7 Hz), 6.01 (1H, *ddd*, J = 10, 1.5, 1 Hz), 4.50 (2H, *s*), 3.41 (2H, *m*), 2.60-2.20 (5H, *m*); ^{13}C NMR (50 MHz): δ 199.54 (*s*), 149.61 (*d*), 138.28 (*s*), 129.78 (*d*), 128.47 (2 x *d*), 127.73 (*d*), 127.58 (2 x *d*), 73.14 (*t*), 73.03 (*t*), 40.89 (*t*), 35.37 (*d*), 28.77 (*t*).

Reduction of enone 3 *to allylic alcohol* 4. A solution of 3 (1.08 g, 5 mmol) in EtOH (70 ml) was treated at 0 °C with $CeCl_3.7H_2O$ (2.67 g, 7.15 mmol) and then with $NaBH_4$ (292 mg, 7.73 mmol). The reaction mixture was then stirred for 1 h at the same temperature and worked-up as usual. Chromatography of the residue (hexane-EtOAc 2:3) gave 4 in almost quantitative yield (1.12 g) as a colourless oil, $[\alpha]_D$ −9.8° ($CHCl_3$; c 1.4); IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 3094, 3065, 3028, 1645, 1451, 1114, 1023, 910, 733, 695; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 5.70 (2H, *m*, ethylenic H), 4.51 (2H, *s*, PhCH_2), 4.30 (1H, *m*, C*H*OH), 3.40 (2H, apparent *d*, J = 6 Hz, CH_2OBn), 2.30-1.70 (4H, *m*), 1.25 (1H, *ddd*, J = 11.5, 10, 10 Hz); ^{13}C NMR (50 MHz): δ 138.54 (*s*), 131.33 (*d*), 128.45 (2 x *d*), 128.15 (*d*), 127.63 (3 x *d*), 74.82 (*t*), 72.98 (*t*), 67.26 (*d*), 35.85 (*t*), 33.25 (*d*), 28.41 (*t*); MS, *m/z* (% rel. int.): 218 (M^+, 1), 200 ($M^+ - H_2O$, 5), 109 (12), 92 (44), 91 (100), 81 (22), 79 (50).

Bromoacetal 5. A solution of alcohol 4 (981 mg, 4.5 mmol) in ethyl vinyl ether (5 ml) was cooled at -40 °C. After addition of NBS (800 mg, 4.5 mmol), the reaction mixture was stirred at the same temperature for 3 h. The crude mixture was then diluted with Et_2O (30 ml), filtered, and the filtrate was washed with 5% aq KOH. Usual work-up and silica gel chromatography (hexane-EtOAc 9:1) gave some starting product (100 mg) and 5 (1.34 mg, 90% based on consumed 4) as a mixture of diastereomers: colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 5.80 (1H, *ddd*, J = 10, 4, 2 Hz), 5.70 (1H, *br d*, J = 10 Hz), 4.81 (1H, *m*, acetal H), 4.52 (2H, *s*, PhCH_2), 4.30 (1H, *m*, C*H*OR), 3.65 (2H, m, OC$H_2$$CH_3$), 3.37 (4H, *m*, BnOC$H_2$ + CH_2Br), 2.30-1.70 (5H, *br m*), 1.24 (3H, *t*, J = 7 Hz, OCH_2*Me*), 1.25 (1H, overlapped *m*).

Acetal 6. A solution of bromoacetal 5 (1.10 g, 3 mmol) and a catalytic amount of AIBN in dry benzene (125 ml) was heated at reflux under Ar. Tri-*n*-butyltin hydride (1.075 ml, 4 mmol) in dry benzene (15 ml) was then added dropwise within 15 min. After refluxing for 4 h, the reaction mixture was evaporated *in vacuo*, and the residue was dissolved in Et_2O. Usual work-up and silica gel chromatography (hexane-EtOAc 4:1) afforded 6 (800 mg, 92 %) as a mixture of diastereomers: colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (2 x 5H, *m*, Ar*H*), 5.15 (1H, *dd*, J = 6, 5.2 Hz, acetal H), 5.08 (1H, *dd*, J = 5.2, 1.2 Hz, acetal H), 4.50 (2 x 2H, *s*, PhCH_2), 4.17 (1H, *ddd*, J = 9.5, 6.2, 6.2 Hz, C*H*OR), 4.00 (1H, *ddd*, J = 10.5, 6.2, 6.2 Hz, C*H*OR), 3.75 (2 x 2H, *m*, OC$H_2$$CH_3$), 3.50-3.30 (2 x 2H, *m*, BnOCH_2), 2.50-1.20 (2 x 10H, *br m*), 1.20 (2 x 3H, *t*, J = 7 Hz, OCH_2*Me*).

Lactone 7. Jones reagent was prepared by dissolving CrO_3 (1 g, 10 mmol) in H_2O (7 ml) and sulfuric acid (0.87 ml). After cooling at 0 °C, the reagent was added to a solution of acetal 6 (725 mg, 2.5 mmol) in acetone (30 ml) at the same temperature. The reaction was stirred for 15 min and then quenched by addition of 2-propanol (3 ml). Usual work-up (extraction with Et_2O) gave a residue which was chromatographed on silica gel (hexane-EtOAc 3:2). This yielded 7 (546 mg, 84%) as a colourless oil, $[\alpha]_D$ +10.4° ($CHCl_3$; c 1.5); IR $\bar{\nu}_{max}$ cm^{-1}: 3083, 3069, 3030, 1764, 1445, 1359, 1167, 1094, 1003, 736, 696; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 4.56 (1H, *ddd*, J = 10, 6.3, 6.3 Hz, lactone OC*H*), 4.50 (2H, *s*, PhCH_2), 3.38 (1H, *dd*, J = 10, 6.4 Hz, BnOCH_a), 3.29 (1H, *dd*, J = 10, 6.4 Hz, BnOCH_b), 2.70 (1H, *m*), 2.41 (2H, apparent *d*, J = 9.5 Hz), 2.16 (1H, *m*), 1.80-1.50 (4H, *br m*), 1.25 (1H, *m*); ^{13}C NMR (50 MHz): δ 176.91 (*s*), 138.23 (*s*), 128.35 (2 x *d*), 127.58 (*d*), 127.53 (2 x *d*), 78.86 (*d*), 74.13 (*t*), 73.09 (*t*), 34.35 (*d*), 34.28 (*d*), 31.91 (*t*), 31.67 (*t*), 24.06 (*t*), 23.31 (*t*); MS, *m/z* (% rel. int.): 260 (M^+, 4), 169 (3) 139 (11), 107 (9), 92 (25), 91 (100), 79 (16), 65 (15).

Hydroxy lactone 8. A suspension of commercial catalyst $Pd(OH)_2$ (20% Pd, 80 mg) in EtOAc (3 ml) was stirred under H_2 for 10 min. Lactone 7 (520 mg, 2 mmol) in EtOAc (15 ml) was then added via syringe. The mixture was stirred for 30 min at room temperature and ambient pressure. The precipitate was then eliminated by filtration, and the filtrate was conc. *in vacuo* and chromatographed on silica gel. Elution with hexane-EtOAc 1:2 furnished 8 (335 mg, 98%) as a colourless oil, $[\alpha]_D$ +2.9° ($CHCl_3$; c 1.4); IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 1757, 1171, 1083, 1030, 992; ^1H NMR (200 MHz): δ 4.55 (1H, *ddd*, J = 9.5, 6.3, 6.3 Hz, lactone OC*H*), 3.49 (2H, apparent *d*, J = 6 Hz, CH_2OH), 2.68 (1H, *m*), 2.40 (2H, apparent *d*, J = 9 Hz), 2.25-2.00 (2H, *m*), 1.90-1.40 (3H, *br m*), 1.30-1.10 (2H, *m*); ^{13}C NMR (50 MHz): δ 177.22 (*s*), 79.06 (*d*), 66.47 (*t*), 36.13 (*d*), 34.30 (*d*), 32.04 (*t*), 31.08 (*t*), 23.93 (*t*), 22.78 (*t*); MS, *m/z* (% rel. int.): 152 ($M^+ - H_2O$, 1), 140 (31), 122 (33), 111 (13), 110 (10), 95 (20), 93 (35), 80 (100), 67 (30), 55 (31).

Thiocarbonate **9**. O-Phenyl chlorothionoformate (300 μl, 2.25 mmol) and DMAP (366 mg, 3 mmol) were added at once to a solution of alcohol **8** (255 mg, 1.5 mmol) in dry acetonitrile (10 ml). The mixture was stirred for 18 h at room temperature. After elimination of the solvent *in vacuo*, the residue was directly chromatographed on silica gel. Elution with hexane-EtOAc 2:3 afforded **9** (400 mg, 83%) as a colourless oil: IR $\bar{\nu}_{max}$ cm^{-1}: 3058, 1764, 1591, 1485, 1456, 1385, 1282, 1199, 1007, 842, 771, 732, 688; ^1H NMR (200 MHz): δ 7.50-7.00 (5H, *m*, Ar*H*), 4.58 (1H, *ddd*, J = 9.5, 6.3, 6.3 Hz, lactone OC*H*), 4.40 (2H, apparent *d*, J = 6 Hz, CH_2OCSOPh), 2.70 (1H, *m*), 2.40 (2H, apparent *d*, J = 9 Hz), 2.30-1.60 (5H, *br m*), 1.30 (2H, *m*); ^{13}C NMR (50 MHz): δ 194.78 (*s*), 176.50 (*s*), 153.14 (*s*), 129.46 (2 x *d*), 126.54 (*d*), 121.73 (2 x *d*), 78.12 (*d*), 77.10 (*t*), 34.00 (*d*), 32.85 (*d*), 31.83 (*t*), 31.02 (*t*), 23.72 (*t*), 22.88 (*t*).

Lactone **10**. A solution of thiocarbonate **9** (322 mg, 1 mmol) in dry toluene (15 ml) was added dropwise under Ar to a boiling solution of tri-*n*-butyltin hydride (537 μl, 2 mmol) and a catalytic amount of AIBN in dry toluene (50 ml). After refluxing for 3 h, the reaction mixture was evaporated *in vacuo*, and the residue was dissolved in Et_2O and worked-up as usual. Silica gel chromatography (elution with hexane-EtOAc 4:1) provided **10** (135 mg, 88 %) as a colourless oil, $[\alpha]_D$ −6.1° ($CHCl_3$; c 2.6); IR $\bar{\nu}_{max}$ cm^{-1}: 1766, 1450, 1160, 1000, 969, 874; ^1H NMR (200 MHz): δ 4.54 (1H, *ddd*, J = 10, 6.4, 6.4 Hz, lactone OC*H*), 2.67 (1H, *m*), 2.40 (2H, *m*), 2.04 (1H, *m*), 1.90-1.00 (6H, *br m*), 0.96 (3H, *d*, J = 6.5 Hz, *Me*CH); ^{13}C NMR (50 MHz): δ 177.15 (*s*), 79.24 (*d*), 36.90 (*t*), 33.97 (*d*), 31.56 (*t*), 28.77 (*d*), 28.34 (*t*), 24.49 (*t*), 21.79 (*q*); MS, *m/z* (% rel. int.): 154 (M^+, 12), 139 (M^+ − Me, 2), 136 ($M^+ - H_2O$, 3), 125 (4), 111 (10), 95 (75), 94 (40), 82 (40), 81 (100), 67 (68), 55 (71), 41 (73).

Lactone **11** *by methylation of the enolate of* **10**. An 1.46M solution of *n*BuLi in hexanes (685 μl, 1 mmol) was added at 0 °C under Ar to a solution of di*iso*propylamine (168 μl, 1.2 mmol) in dry THF (2 ml). The mixture was stirred for 30 min at this temperature and then cooled to -78 °C. Lactone **10** (115 mg, 0.75 mmol) dissolved in dry THF (3 ml) was then added dropwise via syringe. After stirring for 1 h at the same temperature, a solution of methyl iodide (75 μl, 1.2 mmol) and HMPA (150 μl) in dry THF (1.5 ml) was added dropwise. The stir was continued for 1 h at -78 °C and then for further 40 min at -40 °C. Quenching by addition of saturated aqueous NH_4Cl (2 ml) was followed by the usual work-up (extraction with Et_2O). Silica gel chromatography (elution with hexane-EtOAc 4:1) afforded **11** (75 mg, 60%) as a colourless oil, $[\alpha]_D$ +40.1° ($CHCl_3$; c 1.5); IR $\bar{\nu}_{max}$ cm^{-1}: 1760, 1443, 1321, 1180, 995; ^1H NMR (200 MHz): δ 4.48 (1H, *ddd*, J = 11, 6.6, 6.6 Hz, lactone OC*H*), 2.47 (1H, *dq*, J = 12.5, 6.8 Hz, MeC*H*CO), 2.30-2.00 (2H, *m*), 1.90-1.50 (5H, *br m*), 1.20 (3H, *d*, J = 6.8 Hz, *Me*CHCO), 1.00 (1H, *m*), 0.95 (3H, *d*, J = 6.5 Hz, *Me*CH); ^{13}C NMR (50 MHz): δ 179.72 (*s*), 77.44 (*d*), 41.65 (*d*), 37.72 (*t*), 35.26 (*d*), 29.42 (*d*), 28.60 (*t*), 23.98 (*t*), 22.03 (*q*), 13.21 (*q*); MS, *m/z* (% rel. int.): 168 (M^+, 1), 139 (1), 124 (6), 109 (28), 95 (48), 81 (100), 67 (50), 55 (16).

Selenylation of lactone **11**. An 1.46M solution of *n*BuLi in hexanes (685 μl, 1 mmol) was added at 0 °C under Ar to a solution of di*iso*propylamine (168 μl, 1.2 mmol) in dry THF (2 ml). The mixture was stirred for 30 min at this temperature and then cooled to -78 °C. Lactone **11** (67 mg, 0.4 mmol) dissolved in dry THF (2 ml) was then added dropwise via syringe. After stirring for 1 h at the same temperature, a solution of phenylselenenyl chloride (115 mg, 0.6 mmol) and HMPA (100 μl) in dry THF (2 ml) was added dropwise. The stir was continued for 1 h at -78 °C and then for further 40 min at -40 °C. Quenching by addition of saturated aqueous NH_4Cl (1 ml) was followed by the usual work-up (extraction with Et_2O). Silica gel chromatography (elution with hexane-EtOAc 9:1) afforded **12** (51 mg, 40%) as a colourless solid: mp 129-130 °C (from hexane-Et_2O): IR $\bar{\nu}_{max}$ cm^{-1}: 3057, 1743, 1444, 1426, 1276, 1211, 1171, 1083, 1061, 955, 745, 688; ^1H NMR (200 MHz): δ 7.70-7.25 (5H, *m*, Ar*H*), 4.93 (1H, apparent *q*, J = 4.8 Hz, lactone OC*H*), 2.25 (1H, *m*), 1.85 (3H, *m*), 1.70-1.30 (4H, *br m*), 1.51 (3H, *s*, *Me*CCO), 1.00 (3H, *d*, J = 7 Hz, *Me*CH), 0.95 (1H, *m*); ^{13}C NMR (50 MHz): δ 177.07 (*s*), 138.00 (2 x *d*), 129.75 (*d*), 129.10 (2 x *d*), 125.81 (*s*), 76.40 (*d*), 50.70 (*s*), 45.00 (*d*), 32.90 (*t*), 28.90 (*t*), 24.79 (*d*), 20.08 (*q*), 19.24 (*q*), 19.08 (*t*).

(−)-*Mintlactone* **1**. A solution of selenolactone **12** (32.3 mg, 0.1 mmol) in THF (2 ml) was cooled to 0 °C. After addition of 30% aqueous H_2O_2 (80 μl) and one drop of glacial acetic acid, the mixture was stirred for 1 h at 0 °C. Usual work-up (extraction with Et_2O) and silica gel chromatography (elution with hexane-EtOAc 4:1) furnished **1** (13.2 mg, 80%) as a colourless oil: $[\alpha]_D$ −50° (c, 2; EtOH), lit.[1] $[\alpha]_D$ −51.8° (c, 10; EtOH); IR $\bar{\nu}_{max}$ cm^{-1}: 2954, 2927, 2862, 1741, 1683, 1445, 1371, 1325, 1296, 1265, 1243, 1094, 1072, 1030, 997, 857, 765, 735; ^1H NMR (400 MHz): δ 4.61 (1H, *br dd*, J = 11.3, 6.1 Hz, H-3), 2.79 (1H, *ddd*, J = 13.5, 4.5, 2 Hz, H-5β), 2.41 (1H, *dddd*, J = 12, 6.1, 2.5, 2.5 Hz, H-2α), 2.20 (1H, *br ddd*, J = 13.5, 13.5, 5.5 Hz, H-5α), 1.93 (1H, *ddddd*, J = 13, 5.5, 2.5, 2.5, 2 Hz, H-6α), 1.79 (3H, *t*, J = 1.6 Hz, H-9), 1.70 (1H, *m*, H-1), 1.00 (3H, *d*, J = 6.6 Hz, H-7), 1.10-0.90 (2H, *m*, H-2β, H-6β); ^{13}C NMR (50 MHz): δ 174.86 (*s*, C-10), 162.32 (*s*, C-4), 119.56 (*s*, C-8), 79.92 (*d*, C-3), 41.94 (*t*, C-2), 34.51 (*t*, C-6), 29.75 (*d*, C-1), 25.44 (*t*, C-5), 21.24 (*q*, C-7), 8.20 (*q*, C-9); MS, *m/z* (% rel. int.): 166.0997 (M^+, 100), 151 (M^+ − Me, 3), 137 (62), 123 (18), 109 (40), 95 (37), 81 (40), 67 (49). Calc. for $C_{10}H_{14}O_2$, M = 166.0994.

Alcohol **13** *by Mitsunobu inversion of* **4**. DEAD (1.42 ml, 9 mmol) was added dropwise under Ar to a solution of alcohol **4** (981 mg, 4.5 mmol), triphenylphosphine (2.36 g, 9 mmol) and benzoic acid (1.1 g, 9 mmol) in dry THF (30 ml). The resulting mixture was then stirred at room temperature for 4 h and worked-up as usual (extraction with Et_2O). Silica gel chromatography (hexane-EtOAc 9:1) yielded a benzoate ester (1.27 g, 88%) as a 9:1 diastereomeric mixture. The obtained product was dissolved in MeOH (40 ml) and treated with 6M aq NaOH (2 ml). The solution was then refluxed for 40 min and worked-up as usual (extraction with Et_2O). Silica gel chromatography (hexane-EtOAc 1:1) afforded **13** (760 mg, 88%) as a colourless oil, which contained ca. 10% of **4**. Colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3380, 3084, 3061, 3027, 1444, 1269, 1113, 1081, 1063, 1026, 735, 695; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 5.85 (2H, *m*, ethylenic H), 4.52 (2H, *s*, PhCH_2), 4.20 (1H, *m*, C*H*OH), 3.40 (2H, *m*, BnOCH_2), 2.30-1.70 (3H, *m*), 1.50 (1H, *ddd*, J = 13.5, 12, 4.2 Hz); ^{13}C NMR (50 MHz): δ 138.50 (*s*), 130.51 (*d*), 128.25 (3 x *d*), 127.46 (3 x *d*), 74.71 (*t*), 73.00 (*t*), 63.80 (*d*), 34.41 (*t*), 29.09 (*d*), 28.84 (*t*); MS, *m/z* (% rel. int.): 187 ($M^+ - 31$, 3), 127 (15), 109 (20), 91 (100), 81 (34), 79 (34), 77 (26), 65 (28).

Bromoacetal **15**. Experimental procedure as for **5**. Yield: 78% (epimer mixture, contaminated with 10% of **5**, see text). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 6.00-5.75 (2H, *m*), 4.80 (1H, *t*, J = 5.5 Hz, acetal H), 4.51 (2H, *s*, PhCH_2), 4.15 (1H, *m*, C*H*OR), 3.80-3.30 (6H, *br m*, OCH_2, BrCH_2), 2.30-1.30 (5H, *m*), 1.20 (two methyl triplets from OCH_2*Me*).

Acetal **16**. Experimental procedure as for **6**. Yield: 89% (epimer mixture, contaminated with 10% of **6**, see text). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 5.15 (2H, *m*, acetal H), 4.50 (2H, *s*, PhCH_2), 4.20-3.20 (5H, *br m*, OC*H*), 2.30-0.80 (*br m* overlapping two methyl triplets from OCH_2*Me*).

Lactone **17**. Experimental procedure as for **7**. Yield: 84%. Separation from the minor contaminant **7** was performed by HPLC (MeOH-H_2O 1:1). Colourless oil, $[\alpha]_D$ −33.3° (c, 0.45; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 3084, 3060, 3029, 1758, 1445, 1360, 1230, 1155, 1092, 954, 928, 798, 737; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 4.54 (1H, apparent *q*, J = 3.5 Hz, lactone OC*H*), 4.47 (2H, *s*, PhCH_2), 3.31 (2H, apparent *d*, J = 5.5 Hz, BnOCH_2), 2.65 (1H, *dd*, J = 16.6, 6.5 Hz, CH_aCO), 2.30 (2H, *m*), 2.17 (1H, *d*, J = 16.6 Hz, CH_bCO), 1.80 (3H, *m*), 1.50-0.90 (3H, *br m*); ^{13}C NMR (50 MHz): δ 177.26 (*s*), 138.36 (*s*), 128.22 (2 x *d*), 127.40 (3 x *d*), 79.35 (*d*), 74.62 (*t*), 72.76 (*t*), 38.40 (*t*), 34.75 (*d*), 31.55 (*d*), 30.74 (*t*), 26.97 (*t*), 26.85 (*t*); MS, *m/z* (% rel. int.): 260 (M^+, 6), 169 (6), 151 (5), 139 (6), 92 (38), 91 (100), 79 (15), 65 (15), 55 (10).

Hydroxy lactone **18**. Experimental procedure as for **8**. Yield: 98%. Colourless oil, $[\alpha]_D$ −49° (c, 3; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 1753, 1414, 1230, 1163, 1045, 942, 882; ^1H NMR (200 MHz): δ 4.55 (1H, apparent *q*, J = 3.4 Hz, lactone OC*H*), 3.40 (2H, apparent *d*, J = 6 Hz, CH_2OH), 2.70 (1H, *s*, OH), 2.65 (1H, *dd*, J = 16.7, 6.6 Hz, CH_aCO), 2.25 (2H, *m*), 2.15 (1H, *d*, J = 16.7 Hz, CH_bCO), 1.90-1.50 (3H, *br m*), 1.35-0.90 (3H, *br m*); ^{13}C NMR (50 MHz): δ 177.64 (*s*), 79.51 (*d*), 67.02 (*t*), 38.37 (*t*), 34.67 (*d*), 33.52 (*d*), 30.31 (*t*), 26.87 (*t*), 26.30 (*t*); MS, *m/z* (% rel. int.): 169 (M^+-1, 2), 152 (M^+-H_2O, 80), 137 (8), 108 (12), 95 (23), 93 (100), 79 (60), 67 (41), 55 (38).

Thiocarbonate **19**. Experimental procedure as for **9**. Yield: 81%. Colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3058, 1769, 1591, 1485, 1386, 1291, 1200, 1156, 1017, 935, 771, 728, 687; ^1H NMR (200 MHz): δ 7.50-7.00 (5H, *m*, Ar*H*), 4.57 (1H, apparent *q*, J = 3 Hz, lactone OC*H*), 4.36 (2H, apparent *d*, J = 6 Hz, CH_2OCSOPh), 2.68 (1H, *dd*, J = 16.7, 6.3 Hz, CH_aCO), 2.35 (2H, *m*), 2.18 (1H, *d*, J = 16.7 Hz, CH_bCO), 2.10-1.70 (3H, *br m*), 1.55-1.00 (3H, *br m*); ^{13}C NMR (50 MHz): δ 194.93 (*s*), 176.81 (*s*), 153.11 (*s*), 129.37 (2 x *d*), 126.45 (*d*), 121.69 (2 x *d*), 78.56 (*d*), 77.87 (*t*), 38.23 (*t*), 34.41 (*d*), 30.46 (*d*), 30.30 (*t*), 26.61 (*t*), 26.39 (*t*).

Lactone **20**. Experimental procedure as for **10**. Yield: 73%. Colourless oil, $[\alpha]_D$ −41.4° (c, 1.54; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 1767, 1445, 1414, 1231, 1161, 958, 932, 879; ^1H NMR (200 MHz): δ 4.51 (1H, apparent *q*, J = 3.4 Hz, lactone OC*H*), 2.64 (1H, *dd*, J = 16.7, 6.6 Hz, CH_aCO), 2.20 (2H, *m*), 2.16 (1H, *d*, J = 16.7 Hz, CH_bCO), 1.90-1.50 (3H, *br m*), 1.30-1.00 (2H, *br m*), 0.90 (1H, *m*), 0.88 (3H, *d*, J = 6.5 Hz, *Me*CH); ^{13}C NMR (50 MHz): δ 177.46 (*s*), 79.90 (*d*), 38.42 (*t*), 35.93 (*t*), 34.38 (*d*), 31.95 (*t*), 27.51 (*t*), 25.69 (*d*), 21.76 (*q*); MS, *m/z* (% rel. int.): 154 (M^+, 2), 139 (M^+ − Me, 9), 125 (14), 95 (45), 94 (35), 82 (36), 81 (100), 67 (68), 55 (71).

Lactone **21** *by methylation of the enolate of* **20**. Experimental procedure as for **11**. Yield: 76%. Colourless solid: mp 45-46 °C (hexane); $[\alpha]_D$ −36.8° (c, 1.08); IR $\bar{\nu}_{max}$ cm^{-1}: 1759, 1445, 1267, 1161, 948; ^1H NMR (200 MHz): δ 4.66 (1H, apparent *q*, J = 3.9 Hz, lactone OC*H*), 2.33 (1H, *br q*, J = 7.6 Hz, MeC*H*CO), 2.14 (1H, *dddd*, J = 14.9, 3.9, 2.5, 2 Hz), 2.00-1.50 (4H, *m*), 1.20 (2H, *m*), 1.25 (3H, *d*, J = 7.6 Hz, *Me*CHCO), 0.90 (1H, *m*), 0.89 (3H, *d*, J = 6.5 Hz, *Me*CH); ^{13}C NMR (50 MHz): δ 180.46 (*s*), 77.51 (*d*), 44.03 (*d*), 41.09 (*d*), 35.80 (*t*), 31.51 (*t*), 27.23 (*t*), 25.88 (*d*), 21.42 (*q*), 13.98 (*q*); MS, *m/z* (% rel. int.): 168 (M^+, 1), 153 (M^+ − Me, 1), 124 (9), 109 (39), 95 (66), 81 (100), 67 (71), 55 (44).

Selenylation of lactone **21**. Experimental procedure as for **11**. Yield of **22**: 50%. Colourless solid: mp 115-116 °C (from hexane-Et_2O); IR $\bar{\nu}_{max}$ cm^{-1}: 1747, 1428, 1370, 1199, 1168, 1111, 1095, 949, 744, 688; ^1H NMR (200 MHz): δ 7.70-7.25 (5H, *m*, Ar*H*), 5.05 (1H, apparent *q*, J = 3.2 Hz, lactone OC*H*), 2.25 (2H, *m*), 1.90-1.50 (5H, *br m*), 1.48 (3H, *s*, *Me*CCO), 1.40-1.10 (2H, *m*), 0.91 (3H, *d*, J = 6.5 Hz, *Me*CH), 0.90 (1H, *m*); ^{13}C NMR (50 MHz): δ 176.98 (*s*), 137.98 (2 x *d*), 129.65 (*d*), 129.02 (2 x *d*), 125.45 (*s*), 76.71 (*d*), 51.53 (*s*), 45.16 (*d*), 36.01 (*t*), 32.02 (*t*), 26.34 (*d*), 25.03 (*t*), 21.83 (*q*), 18.78 (*q*).

(−)-Isomintlactone **2**. Experimental procedure as for **1**. Silica gel chromatography (hexane-EtOAc 4:1) furnished **2** (28%) and **23** (20%). **2** : colourless solid, mp 69-70 °C, $[\alpha]_D$ +73.5° (c, 1.5; EtOH), lit.[1] solid, mp 77-79 °C, $[\alpha]_D$ +76.9° (c, 5; EtOH); IR $\bar{\nu}_{max}$ cm^{-1}: 2930, 2850, 1741, 1684, 1435, 1375, 1344, 1303, 1291, 1259, 1116, 1088, 1032, 966, 868, 795, 765, 696; ^1H NMR (400 MHz): δ 4.80 (1H, *ddq*, J = 12, 6, 1.5 Hz, H-3), 2.66 (1H, *ddd*, J = 14, 4.5, 2 Hz, H-5α), 2.37 (1H, *dddq*, J = 14, 13.5, 5.5, 1.5 Hz, H-5β), 2.34 (1H, *dddd*, J = 12, 6, 2.5, 2.5 Hz, H-2β), 2.26 (1H, *m*, H-1), 1.79 (3H, *t*, J = 1.5 Hz, H-9), 1.78 (1H, *m*, H-6β), 1.53 (1H, *dddd*, J = 13.5, 13.5, 4.5, 4.5 Hz, H-6α), 1.35 (1H, *ddd*, J = 12, 12, 4.6 Hz, H-2α), 1.12 (3H, *d*, J = 7.6 Hz, H-7); ^{13}C NMR (50 MHz): δ 174.96 (*s*, C-10), 163.00 (*s*, C-4), 119.36 (*s*, C-8), 77.48 (*d*, C-3), 39.57 (*t*, C-2), 31.68 (*t*, C-6), 27.34 (*d*, C-1), 21.76 (*t*, C-5), 17.26 (*q*, C-7), 8.17 (*q*, C-9); MS, *m/z* (% rel. int.): 166.0994 (M^+, 100), 151 (M^+ −Me, 2), 138 (29), 137 (62), 123 (18), 109 (46), 95 (40), 81 (49), 67 (54). Calc. for $C_{10}H_{14}O_2$, M = 166.0994. **23**: colourless oil, $[\alpha]_D$ −120° (c, 0.5; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 3090, 3055, 1758, 1685, 1445, 1260, 1189, 1122, 1039, 1007, 948, 816, 794, 733; ^1H NMR (400 MHz): δ 6.08 (1H, *d*, J = 1.3 Hz, H-9_a), 5.50 (1H, *d*, J = 1 Hz, H-9_b), 4.49 (1H, *ddd*, J = 4.8, 4.8, 2.5 Hz, H-3), 2.82 (1H, *ddd*, J = 11.5, 7, 4.8 Hz, H-4), 2.18 (1H, *dddd*, J = 15, 3, 2.4, 2 Hz, H-2α), 1.83 (1H, *dddd*, J = 14, 7, 3.5, 3.5 Hz, H-5β), 1.70-1.55 (2H, *m*, H-1, H-6α), 1.40-1.20 (2H, *m*, H-2β, H-5α), 0.92 (3H, *d*, J = 6.6 Hz, H-7), 0.90 (1H, *m*, H-6β); ^{13}C NMR (50 MHz): δ 170.94 (*s*, C-10), 142.26 (*s*, C-8), 119.62 (*t*, C-9), 77.18 (*d*, C-3), 39.43 (*d*, C-4), 35.69 (*t*, C-2), 31.24 (*t*, C-6), 28.35 (*t*, C-5), 25.58 (*d*, C-1), 21.76 (*q*, C-7); MS, *m/z* (% rel. int.): 166.0994 (M^+, 59), 151 (M^+ −Me, 4), 138 (78), 137 (39), 123 (43), 120 (45), 110 (51), 109 (65), 96 (49), 95 (81), 94 (100), 82 (70), 81 (89), 73 (71), 67 (77), 55 (93). Calc. for $C_{10}H_{14}O_2$, M = 166.0994.

Bromoacetal **25**. Experimental procedure as for **5**. Yield: 83% (mixture of diastereomers). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 5.75 (2H, *m*, ethylenic H), 4.66 (1H, *m*, acetal H), 4.52 (2H, *s*, PhCH_2), 4.30 (1H, *m*), 4.05 (1H, *m*), 3.65 (2H, m, OC$H_2$$CH_3$), 3.35 (2H, *m*), 2.30-1.70 (5H, *br m*), 1.68 (3H, *d*, J = 7 Hz, *Me*CHBr), 1.24 (3H, *t*, J = 7 Hz, OCH_2*Me*), 1.25 (1H, overlapped *m*).

Acetal **26**. Experimental procedure as for **6**. Yield: 83% (mixture of diastereomers). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (*m*, Ar*H*), 5.00-4.50 (several multiplets, acetal H), 4.48 (*s*, PhCH_2), 4.20 and 4.00 (two multiplets, C*H*OR), 3.90-3.20 (*m*, OC*H*), 2.40-1.20 (*br m*, overlapping methyl signals from OCH_2*Me*).

Lactone **27**. Experimental procedure as for **7**. Overall yield in the epimer mixture: 76%. Separation of **27a** and **27b** could be performed, if desired, by silica gel chromatography (hexane-EtOAc 7:3). Epimer **27a**: colourless solid, mp 49-50 °C, $[\alpha]_D$ +42.3° (c, 1.6; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 3055, 3034, 1755, 1445, 1364, 1174, 1104, 1067, 987, 749, 695; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 4.50 (1H, overlapped *m*, lactone OC*H*), 4.50 (2H, *s*, PhCH_2), 3.32 (2H, apparent *d*, J = 6 Hz, BnOCH_2), 2.46 (1H, *dq*, J = 12.5, 6.8 Hz, MeC*H*CO), 2.25 (2H, *m*), 1.90 (1H, *m*), 1.80-1.55 (3H, *br m*), 1.20 (3H, *d*, J = 6.8 Hz, *Me*CHCO), 1.20-1.00 (2H, *m*); ^{13}C NMR (50 MHz): δ 179.48 (*s*), 138.23 (*s*), 128.36 (2 x *d*), 127.60 (*d*), 127.52 (2 x *d*), 77.08 (*d*), 74.51 (*t*), 73.10 (*t*), 42.08 (*d*), 35.30 (*d*), 35.18 (*d*), 32.59 (*t*), 23.62 (*t*), 23.56 (*t*), 13.20 (*q*); MS, *m/z* (% rel. int.): 274 (M^+, 2), 228 (6), 168 (4), 153 (17), 107 (13), 95 (20), 92 (18), 91 (100), 79 (19), 65 (14). Epimer **27b**: colourless oil, $[\alpha]_D$ +18.3° (c, 1.5; $CHCl_3$); IR $\bar{\nu}_{max}$ cm^{-1}: 3082, 3060, 3029, 1758, 1444, 1353, 1180, 1155, 1095, 957, 738, 696; ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 4.50 (3H, overlapped *m*, lactone OC*H* and PhCH_2), 3.50-3.30 (2H, *m*, BnOCH_2), 2.73 (1H, *dq*, J = 6.9, 6.9 Hz, MeC*H*CO), 2.30 (1H, *m*), 2.05 (2H, *m*), 1.85 (2H, *m*), 1.45 (2H, *m*), 1.18 (1H, *m*), 1.13 (3H, *d*, J = 6.9 Hz, *Me*CHCO); ^{13}C NMR (50 MHz): δ 179.48 (*s*), 138.44 (*s*), 128.34 (2 x *d*), 127.63 (2 x *d*), 127.45 (*d*), 77.13 (*d*), 73.00 (*t*), 71.84 (*t*), 41.25 (*d*), 38.82 (*d*), 30.82 (*d*), 28.63 (*t*), 23.53 (*t*), 17.27 (*t*), 9.41 (*q*); MS, *m/z* (% rel. int.): 274 (M^+, 5), 228 (12), 207 (6), 168 (4), 153 (19), 108 (22), 107 (18), 95 (21), 92 (20), 91 (100), 79 (20), 65 (12).

Hydroxy lactone **28**. Experimental procedure as for **8** with either epimer or with the mixture of both. Yield: 99%. Epimer **28a**: colourless oil, $[\alpha]_D$ +43.9° ($CHCl_3$; c 2.4); IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 1754, 1447, 1373, 1319, 1175, 1100, 1027, 987, 752; ^1H NMR (200 MHz): δ 4.50 (1H, *ddd*, J = 11, 6.5, 6.5 Hz, lactone OC*H*), 3.45 (2H, apparent *d*, J = 6 Hz, CH_2OH), 2.46 (1H, *dq*, J = 12.5, 6.8 Hz, MeC*H*CO), 2.40 (1H, *s*), 2.30-2.10 (2H, *m*), 1.90-1.30 (4H, *br m*), 1.16 (3H, *d*, J = 6.8 Hz, *Me*CHCO), 1.10-0.90 (1H, *m*); ^{13}C NMR (50 MHz): δ 179.80 (*s*), 77.29 (*d*), 66.88 (*t*), 41.98 (*d*), 37.08 (*d*), 35.30 (*d*), 32.07 (*t*), 23.50 (*t*), 22.97 (*t*), 13.11

(*q*); MS, *m/z* (% rel. int.): 184 (M^+, 1), 166 ($M^+ - H_2O$, 2), 154 (24), 122 (19), 109 (35), 107 (100), 94 (23), 93 (67), 91 (21), 82 (11), 81 (50), 80 (35), 79 (79), 67 (74), 55 (54). Epimer **28b**: colourless oil, $[\alpha]_D$ +23.1° ($CHCl_3$; c 2.1); IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 1751, 1441, 1371, 1349, 1177, 1034, 956; ^1H NMR (200 MHz): δ 4.43 (1H, apparent *q*, J = 4 Hz, lactone OC*H*), 3.55 (2H, *m*, CH_2OH), 2.73 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO), 2.55 (1H, *m*), 2.30 (1H, *m*), 2.10-1.70 (3H, *br m*), 1.45 (2H, *m*), 1.15 (1H, *m*), 1.12 (3H, *d*, J = 7 Hz, *Me*CHCO); ^{13}C NMR (50 MHz): δ 179.73 (*s*), 77.30 (*d*), 64.16 (*t*), 41.26 (*d*), 38.75 (*d*), 32.81 (*d*), 28.03 (*t*), 23.17 (*t*), 17.31 (*t*), 9.32 (*q*); MS, *m/z* (% rel. int.): 184 (M^+, 1), 166 ($M^+ - H_2O$, 2), 154 (18), 136 (13), 122 (10), 111 (19), 110 (18), 109 (18), 107 (31), 93 (58), 81 (100), 80 (40), 79 (50), 67 (39), 55 (28).

Thiocarbonate **29**. Experimental procedure as for **9** with either epimer or with the mixture of both. Yield: 74% for **29a** and 83% for **29b** (ca. 79% with the mixture). Epimer **29a**: colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3059, 1760, 1590, 1485, 1382, 1289, 1199, 995, 770, 729, 688; ^1H NMR (200 MHz): δ 7.50-7.00 (5H, *m*, Ar*H*), 4.55 (1H, *ddd*, J = 10.7, 6.6, 6.6 Hz, lactone OC*H*), 4.38 (2H, apparent *d*, J = 6 Hz, $CH_2OCSOPh$), 2.46 (1H, *dq*, J = 12.5, 6.7 Hz, MeC*H*CO), 2.25 (2H, *m*), 2.00-1.60 (4H, *br m*), 1.22 (3H, *d*, J = 6.7 Hz, *Me*CHCO), 1.20 (2H, *m*); ^{13}C NMR (50 MHz): δ 194.85 (*s*), 179.13 (*s*), 153.18 (*s*), 129.51 (2 x *d*), 126.59 (*d*), 121.79 (2 x *d*), 77.48 (*d*), 76.40 (*t*), 41.70 (*d*), 35.22 (*d*), 33.87 (*d*), 32.00 (*t*), 23.35 (*t*), 23.12 (*t*), 13.16 (*q*). Epimer **29b**: colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3070, 1758, 1590, 1484, 1440, 1283, 1198, 1154, 1018, 956, 771, 686; ^1H NMR (200 MHz): δ 7.50-7.00 (5H, *m*, Ar*H*), 4.60-4.40 (3H, *m*, lactone OC*H* + $CH_2OCSOPh$), 2.80 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO), 2.50-1.50 (6H, *br m*), 1.30 (2H, *m*), 1.19 (3H, *d*, J = 7 Hz, *Me*CHCO); ^{13}C NMR (50 MHz): δ 194.83 (*s*), 179.13 (*s*), 153.31 (*s*), 129.47 (2 x *d*), 126.49 (*d*), 121.90 (2 x *d*), 76.57 (*d*), 75.37 (*t*), 41.32 (*d*), 38.77 (*d*), 29.60 (*d*), 28.34 (*t*), 23.49 (*t*), 17.35 (*t*), 9.46 (*q*).

Lactone **30**. Experimental procedure as for **10** with either epimer or with the mixture of both. Yield: 80% in both cases. Epimer **30a** is identical with **11**. Epimer **30b**: colourless oil, $[\alpha]_D$ +6.7° ($CHCl_3$; c 0.7); IR $\bar{\nu}_{max}$ cm^{-1}: 1750, 1445, 1368, 1158, 956; ^1H NMR (200 MHz): δ 4.45 (1H, apparent *q*, J = 4.2 Hz, lactone OC*H*), 2.75 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO), 2.29 (1H, *dddd*, J = 11, 7, 5.5, 4.2 Hz), 2.00-1.75 (2H, *m*), 1.60-1.25 (4H, *br m*), 1.17 (3H, *d*, J = 7 Hz, *Me*CHCO), 1.00 (3H, *d*, J = 7 Hz, *Me*CH), 0.91 (1H, *t*, J = 7.2 Hz); ^{13}C NMR (50 MHz): δ 179.78 (*s*), 77.87 (*d*), 41.27 (*d*), 38.75 (*d*), 32.93 (*t*), 28.76 (*t*), 25.11 (*d*), 19.74 (*q*), 17.26 (*t*), 9.66 (*q*); MS, *m/z* (% rel. int.): 168 (M^+, 1), 139 (1), 124 (12), 109 (25), 95 (100), 82 (37), 81 (50), 67 (81), 55 (48).

Selenylation of lactone **30**. As for **11** with either epimer or with the mixture of both. Yield of **12**: 40%.

Bromoacetal **31**. Experimental procedure as for **5**. Yield: 89% (diastereomeric mixture, contaminated with 10% of **25**, see text). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (*m*, Ar*H*), 6.00-5.75 (*m*, ethylenic H), 4.65 (*m*, acetal H), 4.52 (*s*, $PhCH_2$), 4.10 (*m*, C*H*OR), 3.80-3.40 (*br m*, OCH_2, $BrCH_2$), 2.30-1.30 (*m*), 1.70 (methyl doublets from *Me*CHBr), 1.20 (methyl triplets from OCH_2Me).

Acetal **32**. Experimental procedure as for **6**. Yield: 83% (diastereomeric mixture, contaminated with 10% of **26**, see text). Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (*m*, Ar*H*), 5.10-4.65 (several *m*, acetal H), 4.50 (*br s*, $PhCH_2$), 4.30-3.20 (*br m*, OC*H*), 2.30-0.80 (*br m* overlapping methyl triplets from OCH_2Me and methyl doublets from *Me*CH).

Lactone **33**. Experimental procedure as for **7**. Overall yield in the epimer mixture: 80%. Colourless oil, ^1H NMR (200 MHz): δ 7.40-7.20 (5H, *m*, Ar*H*), 4.71 (1H, apparent *q*, J = 4 Hz, lactone OC*H* of one epimer), 4.49 (*m*, $PhCH_2$, overlapping lactone OC*H* of the other epimer), 3.33 (*m*, CH_2OBn), 2.78 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO of one epimer), 2.40-0.90 (*br m* overlapping methyl doublets at δ 1.27 and 1.15, J = 7 Hz, from *Me*CHCO).

Hydroxy lactone **34**. Experimental procedure as for **8**. Yield: 99% in the epimer mixture. Colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3400, 1739; ^1H NMR (200 MHz): δ 4.65, 4.45 (2 x 1H, apparent *q*, J = 4 Hz, lactone OC*H* of each epimer), 3.40 (*m*, CH_2OH), 2.75 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO of one epimer), 2.40-0.90 (*br m* overlapping methyl doublets at δ1.17 and 1.03, J = 7 Hz, from *Me*CHCO).

Thiocarbonate **35**. Experimental procedure as for **9**. Yield: 73% in the epimer mixture. Colourless oil, IR $\bar{\nu}_{max}$ cm^{-1}: 1752; ^1H NMR (200 MHz): δ 7.50-7.00 (*m*, Ar*H*), 4.72, 4.50 (2 x 1H, apparent *q*, J = 3.5 Hz, lactone OC*H* of each epimer), 4.37 (*m*, $CH_2OCSOPh$), 2.80 (1H, *dq*, J = 7, 7 Hz, MeC*H*CO of one epimer), 2.40-0.90 (*br m* overlapping methyl doublets at δ 1.26 and 1.14, J = 7 Hz, from *Me*CHCO).

Lactone **36**. Experimental procedure as for **10**. Yield: 61% in the epimer mixture. The NMR spectra showed the signals expected for both epimers, one of which was identical with **21**. Substraction of the signals of the latter allowed the assignment of those of its C-9 epimer: ^1H NMR (200 MHz): δ 4.42 (1H, apparent *q*, J = 3.2 Hz, lactone OC*H*), 2.76 (1H, *dq*, J = 7, 7 Hz,

MeCHCO), 2.15 (1H, *m*), 2.00-1.50 (*m*), 1.30-1.10 (*m*), 1.12 (3H, *d*, J = 7 Hz, *Me*CHCO), 0.90 (3H, *d*, J = 6.5 Hz, *Me*CH); ^{13}C NMR (50 MHz): δ 179.81 (*s*), 78.18 (*d*), 42.16 (*d*), 38.97 (*d*), 36.06 (*t*), 31.91 (*t*), 25.14 (*d*), 23.05 (*t*), 21.89 (*q*), 9.05 (*q*).

Selenylation of lactone **36** (epimer mixture). Experimental procedure as for **11**. Yield of **22**: 49%.

All stereochemically homogeneous products gave satisfactory microanalytical data (C, ±0.4%; H; ±0.4%).

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