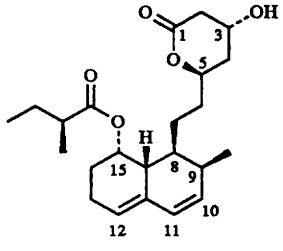
Total synthesis of (+)-compactin by a double Michael protocol

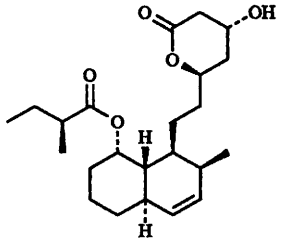
Hisahiro Hagiwara,* Takashi Nakano, Masakazu Kon-no and Hisashi Uda
Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-ku, Sendai 980, Japan

The total synthesis of (+)-compactin **1** has been achieved by employing a double Michael reaction of (*R*)-1-acetyl-3-(*tert*-butyldimethylsiloxy)cyclohexene **16** with methyl crotonate as the key reaction.

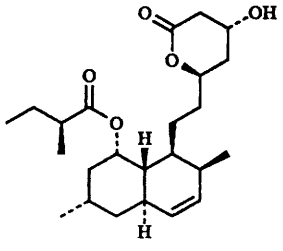
The control of cholesterol biosynthesis is of importance in connection with the prevention of heart disease in humans.[1] Therefore, the discovery of (+)-compactin (ML-236B) **1**,[2,3] isolated from *Penicillium brevicompactum*, and, subsequently dihydrocompactin **2** and mevilonin **3** along with other congeners,[4] was of importance since these compounds effectively inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in endogeneous cholesterol biosynthesis. Mevilonin (lovastatin) **3** and pravastatin **4** which is a derivative of compactin **1**, are already used for this purpose in various countries. Because of their bioactivity and intriguing



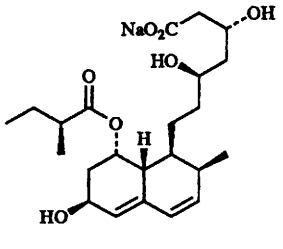
1



2



3

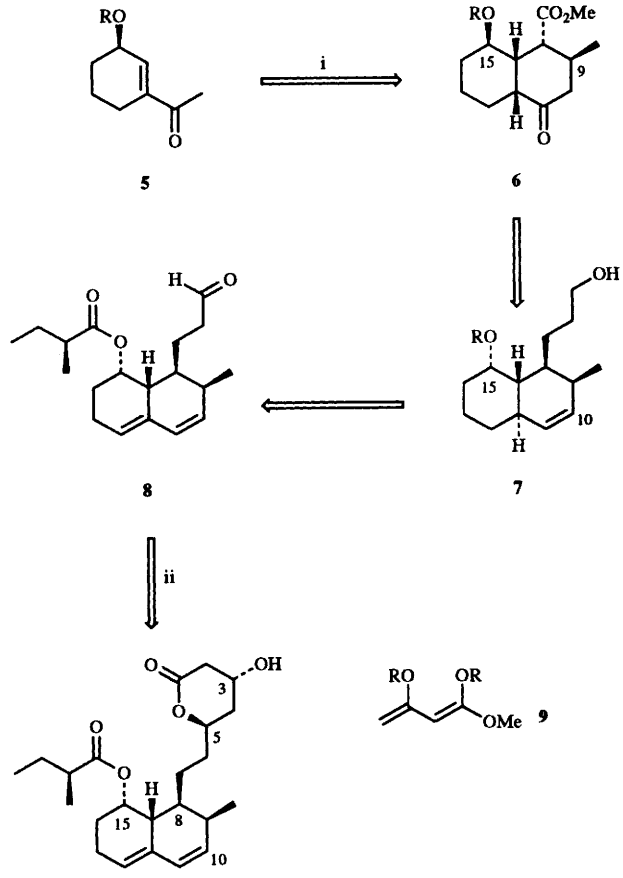


4

structure, these compounds have attracted attention, both physiologically and chemically. Since then, many synthetic efforts[5] have been devoted, mainly by employing Diels–Alder strategies, to the construction of the decalin portion. As a part of our study to demonstrate the synthetic utility of the double Michael reaction,[6] we have reported earlier the successful total synthesis of (+)-dihydrocompactin **2**;[5f] here we now describe an alternative synthesis of (+)compactin **1** by employing a double Michael reaction as the key step.

Results and discussion

Our synthetic strategy is outlined in Scheme 1. Double Michael reaction of acetylcyclohexene **5** and methyl crotonate gave the decalone **6**[5f] having a *cis*-steroidal stereostructure and sufficient functional groups for further transformation into compactin **1**. In particular, the stereochemistry of the methyl group at C-9† and a proton at C-15a of **6** were held in a syn relationship to each other so that two of four contiguous asymmetric centres of the decalin portion of compactin **1** were satisfied. The *cis*-steroidal stereostructure was easily isomerised

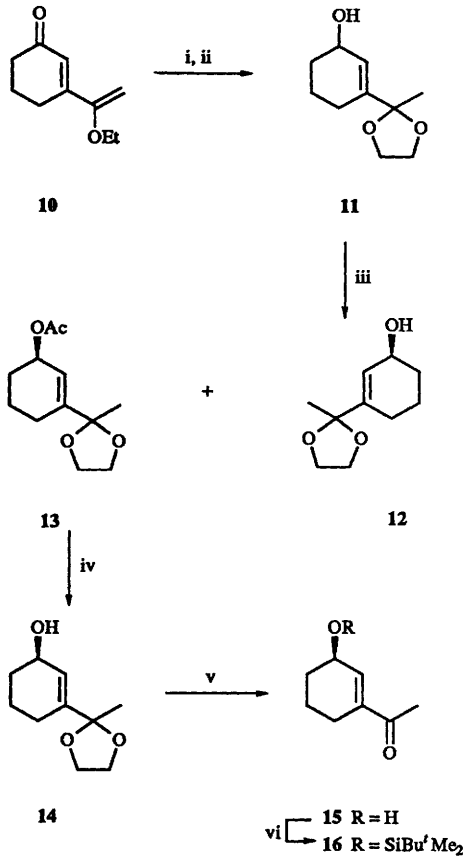


Scheme 1 *Reagents:* i, $MeCH{=}CHCO_2Me$; ii, **9**

into a *trans*-decalone[5f] whose axial methoxycarbonyl group could isomerise into the desired equatorial orientation. Introduction of a double bond at C-10 and inversion of the configuration at C-15 would then furnish the alcohol **7**. After introduction of an extra double bond at C-11a in **7**, functional group manipulations would lead to the aldehyde **8**. Finally, the lactonic portion of compactin **1** would be fixed by aldol condensation of methyl acetoacetate or its equivalent **9**[7] to the aldehyde **8**.

In order to synthesise (+)-compactin **1**, (*R*)-alkoxyacetyl-

† Non-systematic numbering is used in this text, except in the Experimental section.

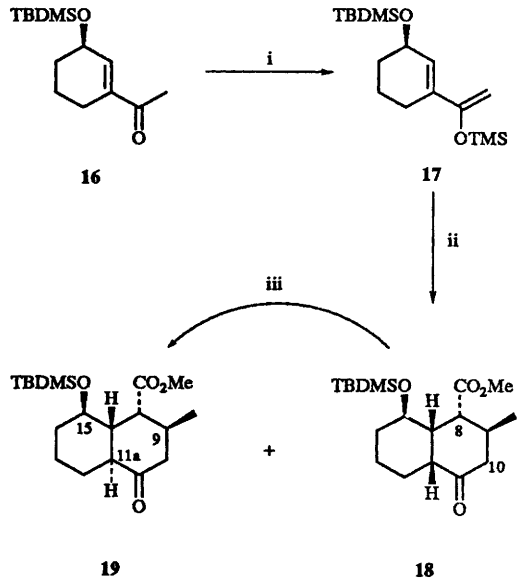


Scheme 2 *Reagents and conditions:* i, 2-ethyl-2-methyl-1,3-dioxolane, $(CH_2OH)_2$, CSA; ii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; iii, Lipase Amano AK, vinyl acetate, hexane; iv, K_2CO_3, MeOH; v, PTSA·H_2O, aq. acetone, reflux; vi, *tert*-butyldimethylsilyl chloride, DMAP, DMF

cyclohexene **5** was required (Scheme 2). Attempted catalytic asymmetric reduction of the enone **10**[5f,8] gave a poor result when the oxazaborolidine complex was employed.[9] Resolution of the racemic alcohol **15** by host-guest complexation was successful,[10] although not compatible with large scale resolution. We then turned our attention to a bio-organic method. As we reported previously,[11] the (*R*)-cyclohexenol acetate **13** (98% ee) was obtained easily by enantioselective kinetic acetylation using Lipase Amano AK in vinyl acetate and hexane in the presence of ground molecular sieves 4 Å; such a kinetic resolution was sufficiently efficient as to allow the resolution of 20 g of racemic alcohol **11** in a short period of time.

The reaction of the kinetic enolate of (*R*)-1-acetyl-3-*tert*-butyldimethylsiloxycyclohexene **16** (generated from the trimethylsilylenol ether **17** by treatment with methyllithium) with methyl crotonate in the presence of 2 equiv. of hexamethylphosphoric triamide (HMPA) afforded a mixture of the *cis*-decalone **18** (major isomer) and *trans*-decalone **19** (minor isomer) in 96% yield (for detailed discussion on stereochemical course of the reaction, see ref. 5*f*) (Scheme 3). Without separation, treatment of a mixture of the decalones **18** and **19** with sodium methoxide resulted in complete isomerisation (in 91% yield) of the major *cis*-decalone **18** into the *trans*-decalone **19** having an axial ester.

Prior to inversion of the stereochemistry at C-15, the decalone **19** was transformed into the xanthate **21** in order to elaborate unsaturation at C-10 (Scheme 4). Thus, reduction of the decalone **19** with sodium borohydride ($NaBH_4$) at 0 °C gave in 84% yield the axial alcohol **20** which was converted into the xanthate **21** in 95% yield. Deprotection of the *tert*-butyldimethylsilyl group at C-15 in 83% yield followed by Swern oxidation[12] afforded the



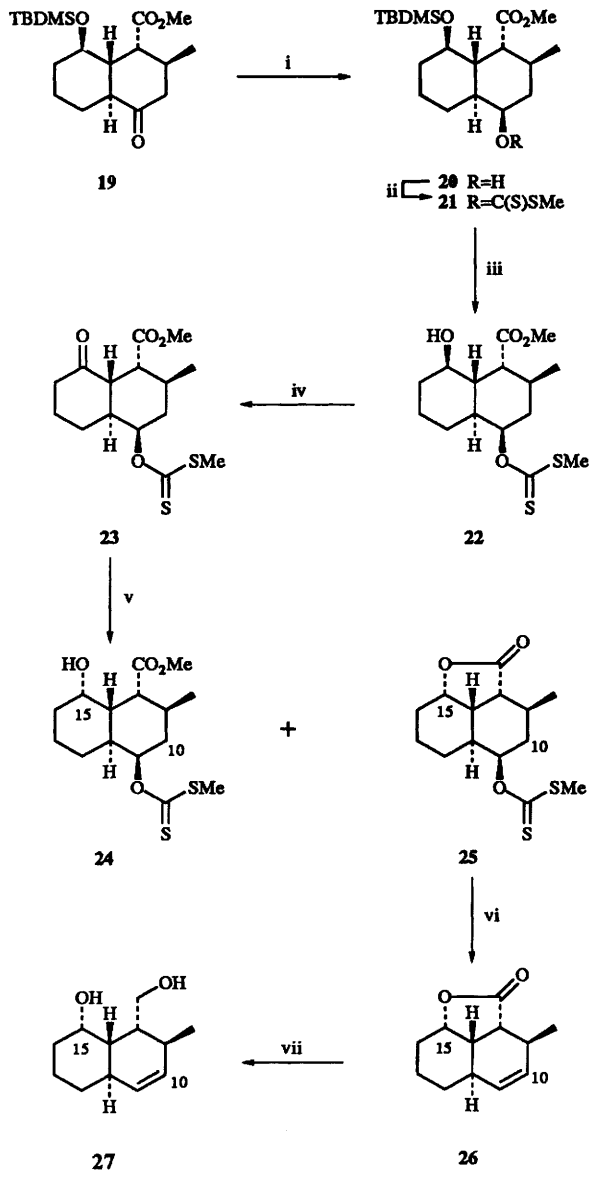
Scheme 3 *Reagents and conditions:* i, LDA, THF, −78 °C then trimethylsilyl chloride, −78 °C to 0 °C; ii, MeLi, THF, −78 °C then methyl crotonate, HMPA, −78 °C to −20 °C; iii, MeONa, MeOH, reflux, 2 h

ketone **23** in 74% yield. Reduction of the ketone **23** with $NaBH_4$ at −40 °C gave a mixture of hydroxy ester **24** and the lactone **25** with the required stereochemistry at C-15; upon warming up to room temperature the hydroxy ester **24** cyclised to the lactone **25**. The lactone **25** was heated at 210 °C in 1-methylnaphthalene to introduce the double bond at C-10. Without work-up, the resulting olefinic lactone **26** was reduced with lithium aluminium hydride (LAH) to give the diol **27** in 73% yield (3 steps).

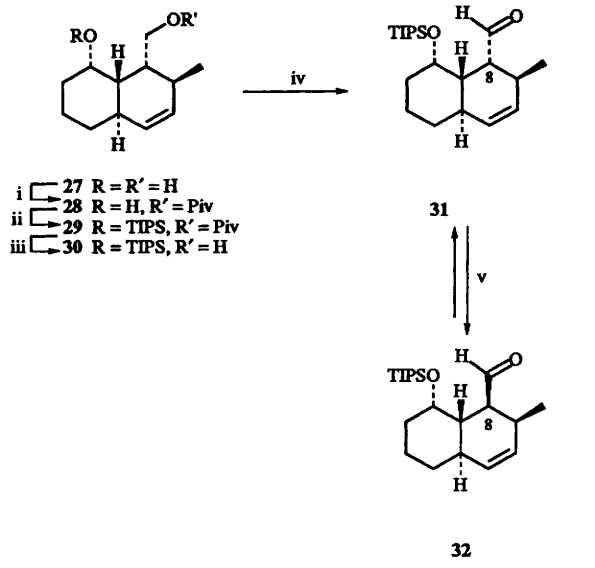
Control of the stereochemistry at C-8 was accomplished by base-catalysed isomerization of the aldehyde **31** utilising 1,3-steric repulsion imposed by the alkoxy group at C-15 (Scheme 5). Molecular mechanics calculations[13] for the aldehydes **31** and **32** suggested that the energy difference was larger (ΔE 1.3 kcal mol^{-1},‡ with a 63:37 distribution in favour of **32**) when a triisopropylsilyl (TIPS) group was employed as a protecting group at C-15 rather than other groups such as trimethylsilyl, *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl. The primary alcohol of the diol **27** was then selectively protected as the pivalate ester to afford **28** (99%) and, thereafter, the secondary alcohol as the TIPS ether to give the silyl ether **29** (99%). Removal of the pivaloyl group with LAH in 99% yield followed by Swern oxidation[12] gave the aldehyde **31** (80%). Treatment of the aldehyde **31** with potassium carbonate in methanol[5d,f] provided an equilibrium mixture of the isomeric aldehyde **32** (55%) along with the recovered aldehyde **31** (45%). These two aldehydes, **31** and **32**, were easily separable by medium-pressure liquid chromatography (MPLC) enabling easy recycling.

Elongation of the two-carbon unit from C-7 of the aldehyde **32** was performed by a Horner–Emmons reaction leading to the α,β-unsaturated ester **33** (97%) (Scheme 6). The double bond at C-6 was selectively reduced with magnesium[14] in methanol to give the methyl ester **34** (98%) which was reduced with LAH to give the alcohol **35** (92%). Deprotection of the *tert*-butyldimethylsilyl group of the alcohol **35** gave the diol **36** quantitatively. The diene moiety at C-10 and C-11a was introduced by a bromination–dehydrobromination sequence.[15] The diol **36** was titrated with a solution of bromine in $CHCl_3$ (1 mol dm^3) to give the dibromide **37** (91%). The configuration

‡ 1 cal = 4.184 J.



Scheme 4 *Reagents and conditions:* i, $NaBH_4$, MeOH, 0 °C; ii, BuLi, CS_2, MeI, THF, −50 to −25 °C; iii, TBAF, THF; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; v, $NaBH_4$, MeOH, −60 °C; vi, 1-methylnaphthalene, 210 °C, 1.5 h; vii, LAH, Et_2O



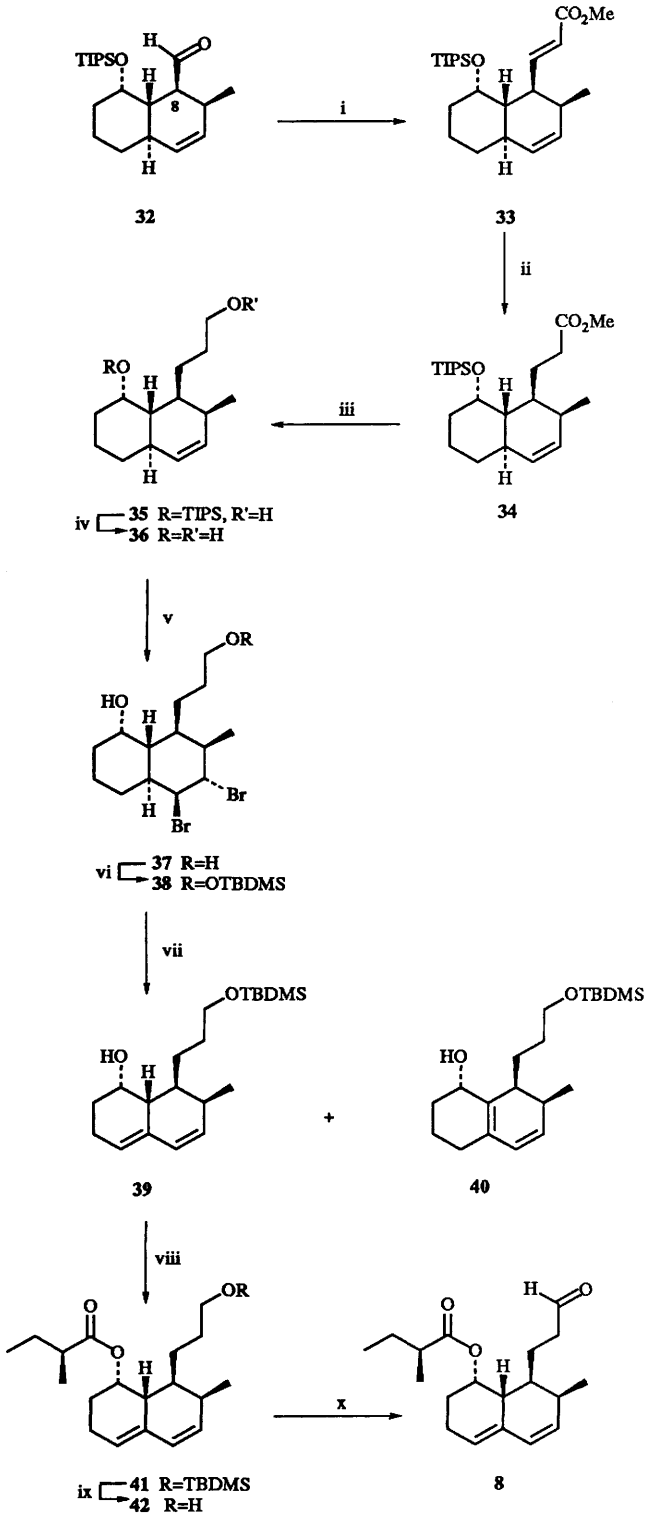
Scheme 5 *Reagents:* i, pivaloyl chloride, pyridine; ii, TIPSOTf, Et_3N, CH_2Cl_2; iii, LAH, Et_2O; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; v, K_2CO_3, MeOH

at C-10 and C-11 of the dibromide **37** was assigned as diaxial from the narrow coupling patterns of the protons at C-10 (δ 4.92, $w_{\frac{1}{2}}$ 4 Hz) and at C-11 (δ 4.58, $w_{\frac{1}{2}}$ 7 Hz). After selective protection of the primary alcohol of the dibromide **37** to give the silyl ether **38** (72%), treatment of the latter with DBU furnished the diene **39** (70%) and the isomeric *endo*-diene **40** (14%). Among substrates investigated for this bromination–dehydrobromination sequence, the diol **36** was the best substrate for bromination, the alcohol function at C-15 then being free for dehydrobromination. Of the bases (Bu^{t}OK, NaH or DBU) and solvents (Bu^{t}OH, xylene, DMSO or HMPA) examined, a combination of DBU and HMPA gave the best result. Esterification with (*S*)-2-methylbutanoic anhydride provided the ester **41** (84%), which was deprotected to give known hydroxy ester **42**[16] quantitatively. Swern oxidation[12] of the latter proceeded to give the aldehyde **8**[16] (95%).

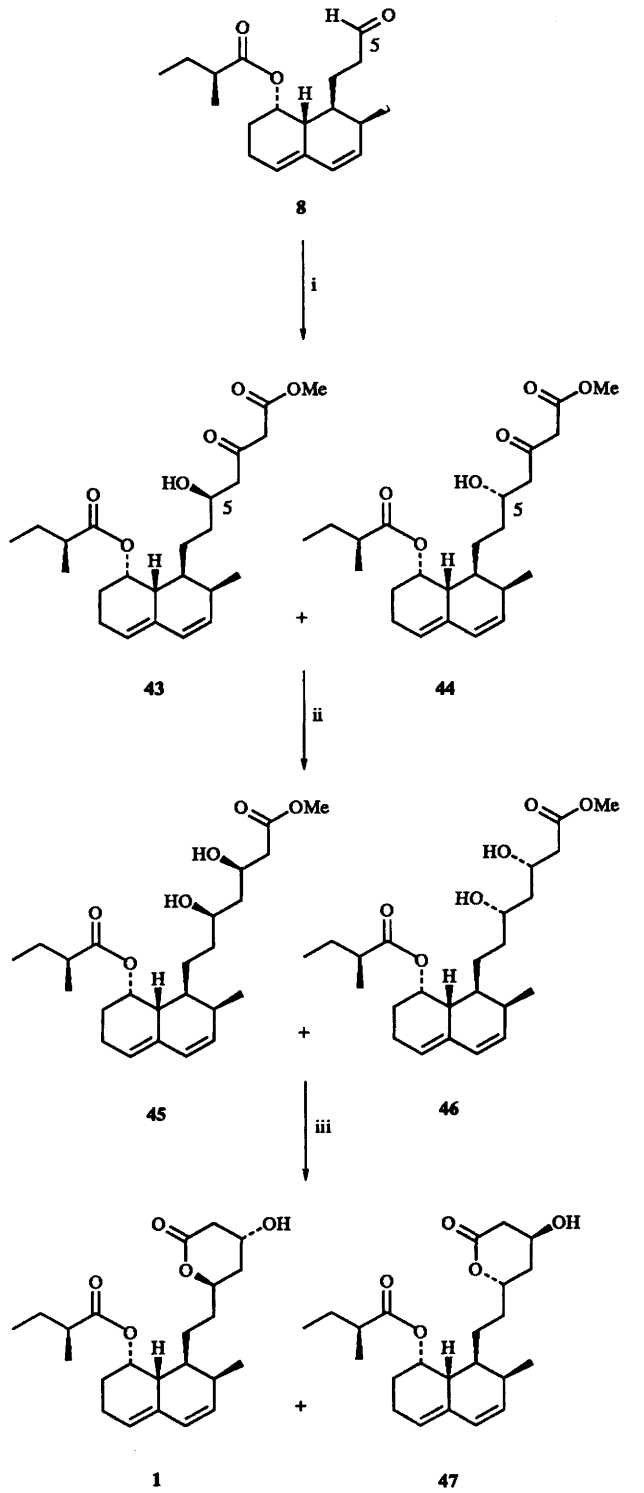
The lactonic portion was introduced according to the procedure of Sih *et al.*[16] with some modifications. Aldol condensation of the dianion of methyl acetoacetate proceeded cleanly in 70% yield to give the aldol products **43** and **44** which were an inseparable mixture of epimers at C-5 (Scheme 7). Since compounds **43** and **44** were indistinguishable chromatographically and spectroscopically, the carbonyl group at C-3 was reduced *syn*-selectively by $NaBH_4$ in the presence of diethylmethoxyborane (Et_2BOMe)[17] to afford, quantitatively, the diols **45** and **46** which were still inseparable. Of the lactonisation conditions involving PTSA/benzene[16] or lipase (PPL or lipase PS), treatment of the diols **45** and **46** with HF–pyridine complex in acetonitrile gave a mixture of (+)-compactin **1** and (+)-3,5-di-*epi*-compactin **47** (92%) which were separable by recycling MPLC. The ratio of (+)-compactin **1** and (+)-3,5-di-*epi*-compactin **47** was 2:1 which indicated that the stereoselectivity of the aldol condensation of the dianion of methyl acetoacetate with the aldehyde **8** was 2:1[16] and the reduction of compounds **43** and **44** was highly *syn*-selective. On the other hand, an aldol condensation of the bis(trimethylsilyl enol ether) of methyl acetoacetate **9**[7] proceeded in the presence of $TiCl_2(OPr^i)_2$ to give the aldol products **43** and **44** in 1:1 ratio (82%). The spectral data (NMR, IR, mass) and behaviour on MPLC of synthetic (+)-compactin **1** were identical with those of natural compactin as well as optical rotational value {$[\alpha]_D$ +258 × 10^{-1} cm^2 g^{-1} (*c* 0.38, acetone), natural $[\alpha]_D$ +265 × 10^{-1} cm^2 g^{-1} (*c* 0.51, acetone)}.

Experimental

All mps were determined with a Mitamura Riken hot-stage apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-8300 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with JEOL-FX 90Q (90 MHz) instrument with tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Specific rotations, $[\alpha]_D$, were determined on a JASCO DIP-370 polarimeter for solutions in chloroform unless otherwise indicated, and are given in 10^{-1} deg cm^2 g^{-1}. UV spectra were obtained on a JASCO Ubest-50 spectrophotometer. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel packed column. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether. Anhydrous sodium sulfate was used for drying organic extracts. THF was distilled from sodium diphenyl ketyl



Scheme 6 *Reagents and conditions:* i, $(MeO)_2P(O)CH_2CO_2Me$, NaH, HMPA, THF, reflux; ii, Mg, MeOH, 0 °C; iii, LAH, ether; iv, aq. HF acetonitrile; v, Br_2, $CHCl_2$; vi, TBDMSOTf, 2,6-dimethylpyridine, CH_2Cl_2; vii, DBU, HMPA, 60 °C; viii, (*S*)-2-methylbutanoic anhydride, DMAP, CH_2Cl_2; ix, TBAF, THF; x, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2



Scheme 7 *Reagents and conditions:* i, BuLi, NaH, **9**, THF, 0 °C or $TiCl_2(OPr^i)_2$, bistrimethylsilyl enol ether **9**, CH_2Cl_2, −78 °C; ii, Et_2BOMe, $NaBH_4$, MeOH, −78 °C; iii, HF·pyridine complex, acetonitrile

prior to use. Upon typical work-up, the product was extracted with solvent (2 × 20 cm^3 for 1–10 mmol scale reaction). The organic layer was washed with water once and brine once. After being dried over sodium sulfate, the solvent was evaporated under reduced pressure.

1-(3-Hydroxycyclohex-1-enyl)ethanone ethylene ketal 11

A solution of the vinyl ether **10** (10.2 g, 61.3 mmol) and camphorsulfonic acid (CSA) (1.44 g, 6.2 mmol) in ethylene glycol (4.1 cm^3, 73.5 mmol) and 2-methyl-2-ethyl-1,3-dioxolane (23 cm^3) was stirred at room temperature for 10 min, after which it was treated with aq. sodium hydrogen carbonate. The product was extracted with ethyl acetate (× 2) and the organic layer was washed with brine and evaporated. Flash column

chromatography [eluent hexane–ethyl acetate (4:1)] of the residue afforded 1-(3-oxocyclohex-1-enyl)ethanone ethylene ketal (8.71 g, 78%); ν_{max}/cm^{-1} 1671, 1375 and 1209; δ 1.51 (3 H, s), 2.33–2.44 (2 H, m), 3.84–4.07 (4 H, m) and 6.17 (1 H, br s).

To a stirred solution of the resulting ketal (17.8 g, 97.5 mmol) and $CeCl_3 \cdot 7H_2O$ (3.64 g, 9.76 mmol) in methanol (120 cm^3) was added $NaBH_4$ (3.763 g, 99.5 mmol) portionwise carefully at 0 °C. After being stirred at 0 °C for 1 h and then at room temperature for 1.5 h, the reaction was quenched by the addition of aq. ammonium chloride to the mixture. The product was extracted with ethyl acetate (×2) and the extract was washed with brine and evaporated. Column chromatography of the residue [eluent hexane–ethyl acetate (2:1)] provided the alcohol **11** (16.96 g, 94%); ν_{max}/cm^{-1} 3464, 1375, 1196, 1043 and 865; δ 1.45 (3 H, s), 1.62–2.04 (7 H, m), 3.8–3.98 (4 H, m), 4.22–4.3 (1 H, m) and 5.91–5.97 (1 H, m); *m/z* 184 (M^+, 3%), 169 (19), 151 (5), 97 (16), 87 (100), 73 (25) and 43 (76).

(*R*)-1-(3-Acetoxycyclohex-1-enyl)ethanone ethylene ketal 13

A mixture of the alcohol **11** (20.02 g, 109 mmol) and ground molecular sieves 4 Å (10.07 g, 0.5 mass equiv.) in dry hexane (1000 cm^3) was stirred at room temperature for 2 h under nitrogen. Lipase Amano AK was added (2.11 g, 0.1 mass equiv.) and stirring was continued for 5.5 h with monitoring of the reaction by TLC. The reaction was quenched by filtering off the enzyme and ground molecular sieves 4 Å. Evaporation of the filtrate followed by column chromatography of the residue gave the (*S*)-alcohol **12** (10.15 g, 50%, 97% ee) and the (*R*)-acetate **13** (10.58 g, 43%, 98% ee). The enantiomeric excess of the product acetate **13** and recovered alcohol **12** were determined according to the literature procedure.[11] The acetate **13** had $[\alpha]_D$ +125.73 (*c* 1.67); ν_{max}/cm^{-1} 1724, 1374, 1251 and 1041; δ 1.46 (3 H, s), 2.05 (3 H, s), 1.67–2.12 (6 H, m), 3.81–4.0 (4 H, m), 5.3–5.39 (1 H, m) and 5.85–5.92 (1 H, m); *m/z* 226 (M^+, 6%), 211 (24), 184 (20), 169 (29), 87 (100), 73 (19) and 43 (54).

(*R*)-1-(3-Hydroxycyclohex-1-enyl)ethanone ethylene ketal 14

A solution of the (*R*)-acetate **13** (10.58 g, 46.8 mmol) and potassium carbonate (9.77 g, 70.7 mmol) in 20% aq. methanol (100 cm^3) was stirred at 0 °C for 30 min and then at room temperature for 3 h. After addition of aq. ammonium chloride to the mixture, it was extracted with ethyl acetate (×2). The extract was washed with brine and evaporated to dryness. Column chromatography [eluent hexane–ethyl acetate (3:2)] of the residue provided the known[11] (*R*)-alcohol **14** (8.7 g, 100%); $[\alpha]_D$ +47.7 (*c* 0.519).

(*R*)-1-(3-Hydroxycyclohex-1-enyl)ethanone 15

A solution of the ketal **14** (12.94 g, 70.3 mmol) and PTSA·H_2O in 20% aq. acetone (200 cm^3) was heated at 40 °C for 2.5 h. The reaction was quenched by addition of aq. $NaHCO_3$ to the mixture which was then extracted with ethyl acetate. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were washed with brine and evaporated to leave an oil which was used for subsequent reactions without purification.

Since experimental details and spectral data (NMR, IR, mass) of the following compounds have been reported in the earlier work,[5f] only specific rotations and improved yields were noted; **16** $[\alpha]_D$ +50.9 (*c* 1.12) (98% ee); **17** $[\alpha]_D$ +55.8 (*c* 1.12); **18** 96%; **19** $[\alpha]_D$ −41.9 (*c* 1.18), 91%; **20** $[\alpha]_D$ −48 (*c* 1.29), 84%; **21** $[\alpha]_D$ −3.7 (*c* 1.07), 95%; **22** $[\alpha]_D$ −9.2 (*c* 1.01), 83%; **23** $[\alpha]_D$ +28.8 (*c* 1.13), 74%; **25** $[\alpha]_D$ −64.6 (*c* 1.04), 82%; **26** $[\alpha]_D$ +28.6 (*c* 1.29); **27** $[\alpha]_D$ +122.1 (*c* 1.07), 73% overall; **28** $[\alpha]_D$ +68.9 (*c* 1.09), 99%.

(1*R*,2*S*,4a*R*,8*S*,8a*S*)-(2-Methyl-8-triisopropylsiloxy-1,2,4a,5,6,7,8,8a-octahydro-1-naphthyl)methyl pivalate 29

To a stirred solution of the pivaloyl ester **28** (887 mg, 3.2 mmol) in dichloromethane (15 cm^3) at 0 °C under nitrogen was added triethylamine (3.1 cm^3, 22.2 mmol) followed by triisopropylsilyl trifluoromethanesulfonate (1.4 cm^3, 6.3 mmol). After being stirred at room temperature for 3 days, the mixture was treated with aq. ammonium chloride and then extracted with ethyl acetate (×2). The combined extracts were washed with water and brine and evaporated to dryness. The residue was purified by SiO_2 column chromatography [eluent hexane–ethyl acetate (20:1)] to give the TIPS ether **29** (1.37 g, 99%) (Found: C, 71.7; H, 11.3. $C_{26}H_{48}O_3Si$ requires C, 71.5; H, 11.1%); $[\alpha]_D$ +40.1 (*c* 1.28); ν_{max}/cm^{-1} 1716, 1463, 1289, 1176 and 1035; δ 1.02 (3 H, d, *J* 6, Me), 1.09 (18 H, s, *Me*CH × 6), 1.17 (9 H, s, Bu^t), 1.33–1.65 (11 H, m), 2.09–2.41 (2 H, m), 3.97 (1 H, t, *J* 11, C*H*HO), 4.26 (1 H, br s, 8-H), 4.65 (1 H, dd, *J* 11 and 2.8, CH*H*O) and 5.37 (2 H, d like, *J* 13.4, olefinic H); *m/z* 393 ($M^+ - Pr^i$, 19%), 216 (24), 215 (100), 161 (84), 119 (30) and 57 (43).

Since the experimental details for some of the following compounds are almost the same as reported in earlier work,[5f] only yields and spectral data are noted.

(1*R*,2*S*,4a*R*,8*S*,8a*S*)-(2-Methyl-8-triisopropylsiloxy-1,2,4a,5,6,7,8,8a-octahydro-1-naphthyl)methanol 30

99% (Found: C, 71.5; H, 11.4. $C_{21}H_{40}O_2Si$ requires C, 71.1; H, 11.6%); $[\alpha]_D$ +87.5 (*c* 1.198); ν_{max}/cm^{-1} 2868, 1464, 1007 and 883; δ 1.05 (3 H, d, *J* 7.3, Me), 1.12 (18 H, s, *Me*CH × 6), 1.39–1.92 (12 H, m), 2.08–2.45 (2 H, m), 3.4 (1 H, dd, *J* 10.5 and 9.2, C*H*HOH), 4.15–4.32 (2 H, m, CH*H*OH and 8-H) and 5.3–5.47 (2 H, m, olefinic H); *m/z* 309 (6%), 227 (8), 161 (100), 119 (72), 105 (32) and 75 (28).

(1*R*,2*S*,4a*R*,8*S*,8a*S*)-2-Methyl-8-triisopropylsiloxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde 31

86%; mp 40–42 °C (spontaneously solidified in a freezer) (Found: C, 71.7; H, 11. $C_{21}H_{38}O_2Si$ requires C, 71.9; H, 10.9%); $[\alpha]_D$ +44.8 (*c* 1.07); ν_{max}/cm^{-1} 2868, 1712, 1463, 1036 and 883; δ 1.08 (21 H, s, *Me*CH × 6 and Me), 1.51–2.04 (10 H, m), 2.19–2.8 (2 H, m), 2.7 (1 H, br t, *J* 11.9, 4a-H), 4.23 (1 H, br s, 8-H), 5.52 (2 H, br s, olefinic H) and 9.91 (1 H, d, *J* 4.4, CHO); *m/z* 308 (21%), 307 (75), 159 (100), 131 (61), 119 (65), 75 (58) and 61 (93).

(1*S*,2*S*,4a*R*,8*S*,8a*S*)-2-Methyl-8-triisopropylsiloxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde 32

To a stirred slurry of potassium carbonate (985 mg, 7.1 mmol) in methanol (5 cm^3) was added a solution of the aldehyde **31** (2.47 g, 7.1 mmol) in methanol (45 cm^3) under nitrogen. The resulting slurry was stirred at room temperature for 6 days, after which it was treated with hydrochloric acid (1 mol dm^3 solution) and then 50% aq. sodium chloride. The resulting mixture was then extracted with ethyl acetate (×2). Evaporation of the combined extracts followed by column chromatography of the residue [eluent hexane–toluene (1:2)] provided the less polar β-aldehyde **32** (1.365 g, 55%) and the more polar α-aldehyde **31** (1.138 g, 45%); $[\alpha]_D$ +122.8 (*c* 1.08); ν_{max}(neat)/cm^{-1} 2867, 1724, 1464 and 1039; δ 0.91 (3 H, d, *J* 6.6, Me), 1.04 (18 H, s, *Me*CH × 6), 1.46–1.98 (10 H, m), 2.38 (1 H, br t, *J* 11, 4a-H), 2.6 (1 H, br s, 9-H), 2.91 (1 H, ddd, *J* 11, 5.7 and 2.2, 1-H), 4.48 (1 H, br s, 8-H), 5.36–5.66 (2 H, m, olefinic H) and 9.8 (1 H, d, *J* 2.2, CHO).

Methyl (1′*S*,2′*S*,4a′*R*,8′*S*,8a′*S*)-(*E*)-3-(2′-methyl-8′-triisopropylsiloxy-1′,2′,4a′,5′,6′,7′,8′,8a′-octahydro-1′-naphthyl)-prop-2-enoate 33

97%; mp 50 °C; $[\alpha]_D$ +144 (*c* 2.15) (Found: C, 71.0; H, 10.5. $C_{24}H_{42}O_3Si$ requires C, 70.9; H, 10.4%); ν_{max}/cm^{-1} 1726, 1656,

1463, 1252, 1208, 1159, 1135, 1008, 884 and 680; δ 0.91 (3 H, d, *J* 7, Me), 1.04 (18 H, s, *Me*CH × 6), 0.8–3.0 (13 H, m), 3.72 (3 H, s, MeO), 4.08 (1 H, br s, 8′-H), 5.4–5.7 (2 H, m, olefinic H), 5.95 (1 H, d, *J* 16, 2-H) and 7.04 (1 H, dd, *J* 16 and 10, 3-H); *m*/*z* 363 ($M^+ - Pr^i$, 4%) and 43 (100).

Methyl (1′*S*,2′*S*,4a′*R*,8′*S*,8a′*S*)-3-(2′-methyl-8′-triisopropylsiloxy-1′,2′,4a′,5′,6′,7′,8′,8a′-octahydro-1-naphthyl)propanoate 34

98%, $[\alpha]_D$ +126 (*c* 2.09) (Found: C, 70.7; H, 11. $C_{24}H_{44}O_3Si$ requires C, 70.5; H, 10.85%); ν_{max}/cm^{-1} 1741, 1464, 1436, 1174, 1111, 1095, 885 and 678; δ 0.83 (3 H, d, *J* 7, Me), 1.09 (18 H, s, *Me*CH × 6), 1.2–2.5 (17 H, m), 3.66 (3 H, s, MeO), 4.31 (1 H, br s, 8′-H) and 5.3–5.7 (2 H, m, olefinic H); *m*/*z* 365 ($M^+ - Pr^i$, 100%), 33 (9), 185 (24), 159 (31) and 75 (19).

(1′*S*,2′*S*,4a′*R*,8′*S*,8a′*S*)-3-(2′-Methyl-8′-triisopropylsiloxy-1′,2′,4a′,5′,6′,7′,8′,8a′-octahydro-1′-naphthyl)propanol 35

92%, $[\alpha]_D$ +116.4 (*c* 2.348, $CHCl_3$) (Found: C, 72.6; H, 11.75. $C_{23}H_{44}O_2Si$ requires C, 72.6; H, 11.65%); ν_{max}/cm^{-1} 3639, 3503, 1464, 1383, 1371, 1216, 1094, 1070, 1043, 883 and 677; δ 0.82 (3 H, d, *J* 7, Me), 1.08 (18 H, s, *Me*CH × 6), 1.3–2.5 (18 H, m), 3.66 (2 H, br t, 1-H), 4.3 (1 H, br s, 8′-H) and 5.3–5.7 (2 H, m, olefinic H); *m*/*z* 337 ($M^+ - Pr^i$, 4%), 189 (32), 107 (46), 105 (69), 95 (65), 93 (76), 91 (45), 81 (55), 79 (42), 77 (53), 75 (100), 67 (41), 61 (71), 59 (41) and 55 (44).

(1′*S*,2′*S*,4a′*R*,8′*S*,8a′*S*)-3-(8′-Hydroxy-2′-methyl-1′,2′,4a′,5′,6′,7′,8′,8a′-octahydro-1-naphthyl)propanol 36

To a solution of the TIPS ether **35** (112 mg, 0.3 mmol) in chloroform (1 cm^3) and acetonitrile (4.5 cm^3) was added aq. hydrogen fluoride (46%; 1 cm^3) at room temperature overnight. The reaction was quenched by the addition of aq. sodium hydrogen carbonate and the product was extracted with chloroform (×2). The combined extracts were washed with brine and evaporated to give the diol **36** (70 mg, quant.), mp 102–103 °C (fine needles from hexane) (Found: C, 74.8; H, 10.7. $C_{14}H_{24}O_2$ requires C, 75; H, 10.8%); $[\alpha]_D$ +139.4 (*c* 0.716); $\nu_{max}(CCl_4)/cm^{-1}$ 3615, 3600–3200, 1447, 1437 and 1236; δ 0.84 (3 H, d, *J* 7.1, Me), 0.93–2.38 (16 H, m), 3.61–3.71 (2 H, m, 1-H), 4.16 (1 H, br s, 8′-H) and 5.4–5.7 (2 H, m, olefinic H); *m*/*z* 206 ($M^+ - H_2O$, 28), 147 (100) and 105 (56).

(1′*S*,2′*S*,3′*S*,4′*S*,4a′*R*,8′*S*,8a′*S*)-3-(3′,4′-Dibromo-8′-hydroxy-2′-methyldecahydro-1-naphthyl)propanol 37

To a stirred solution of the olefin **36** (64.8 mg, 0.29 mmol) in chloroform (5 cm^3) was added a solution of bromine (1 mol dm^3 solution in dichloromethane; 0.5 cm^3) until an orange colour persisted. The reaction was quenched by addition of 10% aq. sodium hypochlorite to the mixture. The organic layer was separated and the aqueous layer was extracted with chloroform (×3). The combined organic layer and extracts were washed with brine and evaporated and the residue was purified by MPLC [eluent hexane–ethyl acetate (1:1)] to give the dibromide **37** (101 mg, 91%) (Found: C, 44.0; H, 6.45. $C_{14}H_{24}Br_2O_2$ requires C, 43.8; H, 6.3%), $[\alpha]_D$ +33.3 (*c* 2.05); $\nu_{max}(CHCl_3)/cm^{-1}$ 3618, 3441, 1450, 1385, 1062, 1002, 622 and 542; δ 0.8–2.2 (11 H, m), 1.28 (3 H, d, *J* 7, Me), 2.37 (3 H, m), 3.23 (2 H, br s, $w_{\frac{1}{2}}$ 13, OH × 2), 3.67 (2 H, br t, 1-H), 4.21 (1 H, br s, $w_{\frac{1}{2}}$ 7, 8′-H), 4.58 (1 H, br s, $w_{\frac{1}{2}}$ 7, 4-H) and 4.92 (1 H, br s, $w_{\frac{1}{2}}$ 5, 3-H); *m*/*z* 287 (M^+, 3%), 285 (M^+, 3%), 223 (25), 205 (60), 187 (100), 159 (59), 145 (40) and 105 (27).

(1′*S*,2′*S*,3′*S*,4′*S*,4a′*R*,8′*S*,8a′*S*)-3-(3′,4′-Dibromo-8′-hydroxy-2′-methyldecahydro-1-naphthyl)propyl 1′-*tert*-butyldimethyl silyl ether 38

To a stirred solution of the diol **37** (47.3 mg, 0.12 mmol) in dichloromethane (1 cm^3) at −50 °C under nitrogen was added 2,6-dimethylpyridine (22 mm^3, 0.19 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (34 mm^3, 0.15 mmol). After being stirred at room temperature overnight, the reaction mixture was treated with aq. sodium hydrogen carbonate to quench the reaction. The organic layer was separated and the aqueous layer was extracted with chloroform (×3). The combined organic layer and extracts were washed with brine and evaporated to dryness. The residue was purified by MPLC (eluent ethyl acetate) to give the TBS ether **38** (44 mg, 72%) along with the starting material **36** (11 mg, 24%) (Found: C, 48; H, 7.6. $C_{20}H_{38}Br_2Si$ requires C, 48.2; H, 7.7%); $[\alpha]_D$ +31.1 (*c* 2.26); $\nu_{max}(CHCl_3)/cm^{-1}$ 3462, 1472, 1385, 1258, 1093 and 837; δ 0.06 (6 H, s, Me_2Si), 0.9 (9 H, s, Bu^t), 1.2–2.6 (15 H, m), 1.28 (3 H, d, *J* 7.4, Me), 3.65 (2 H, t, *J* 6, 1-H), 4.2 (1 H, br s, 8′-H), 4.58 (1 H, br s, 4-H) and 4.93 (1 H, br s, 3-H); *m*/*z* 279 (12%), 187 (100), 159 (47), 145 (24) and 75 (27).

(1′*S*,2′*S*,8′*S*,8a′*S*)-3-(8′-Hydroxy-2′-methyl-1′,2′,4a′,7′,8′,8a′-hexahydro-1′-naphthyl)propyl 1′-*tert*-butyldimethylsilyl ether 39

A solution of the dibromide **38** (369 mg, 0.74 mmol) and DBU (0.55 cm^3, 3.7 mmol) in HMPA (2 cm^3) was heated at 60 °C for 5 h under nitrogen to give a white precipitate. After cooling to room temperature, the reaction mixture was treated with aq. ammonium chloride to quench the reacton. The mixture was then extracted with ethyl acetate (×2) and the combined extracts were washed with brine and evaporated. MPLC purification [eluent hexane–ethyl acetate (4:1)] afforded the diene **39** (174 mg, 70%) along with (1′S,2′S,8′S)-3-(8′-*hydroxy*-2′-*methyl*-1′,2′,5,6,7′,8′-*hexahydro*-1′-*naphthyl*)*propyl* 1′-tert-*butyldimethylsilyl ether* **40** (35 mg, 14%). The diene **39** had (Found: C, 71.0; H, 10.6%; M^+, 336.248 66. $C_{20}H_{36}O_2Si$ requires C, 71.4; H, 10.8%; *M*, 336.248 44), $[\alpha]_D$ +201.9 (*c* 1.06); $\nu_{max}(CHCl_3)/cm^{-1}$ 3447, 1472, 1389, 1257 and 1093; δ 0.06 (6 H, s, Me_2Si), 0.88 (3 H, d, *J* 7), 0.89 (9 H, s, Bu^t), 1.1–2.6 (12 H, m), 3.63 (2 H, t, *J* 6, 1-H), 4.22 (1 H, br s, 8′-H) and 5.5–6.0 (3 H, m, olefinic H); λ_{max}/nm 245 (log ε 3.96), 237 (4.12) and 231 (4.07); *m*/*z* 336 (M^+, 21%), 279 (30), 261 (94), 187 (93), 171 (57), 159 (83), 145 (100), 131 (53) and 75 (44).

The *endo*-diene **40** had $\nu_{max}(CHCl_3)/cm^{-1}$ 3006, 1471, 1256, 1100 and 837; δ 0.03 (6 H, s, Me_2Si), 0.88 (9 H, s, Bu^t), 1.07 (3 H, d, *J* 7, Me), 1.2–2.8 (13 H, m), 3.55 (2 H, t like, 1-H), 4.16 (1 H, br s, 8′-H), 5.45 (1 H, dd, *J* 9.4 and 0.97, olefinic H) and 5.65 (1 H, dd, *J* 9.4 and 0.97, olefinic H); *m*/*z* 336 (M^+, 1%), 318 (1), 261 (54), 159 (100), 145 (46) and 75 (33).

(1*S*,2*S*,8*S*,8a*S*)-8-(3′-*tert*-Butyldimethylsiloxypropyl)-7-methyl-1,2,3,7,8,8a-hexahydro-1-naphthyl (*S*)-2-methylbutanoate 41

To a stirred solution of the alcohol **39** (233.4 mg, 0.695 mmol) in anhydrous pyridine (5 cm^3) was added (*S*)-2-methylbutanoic anhydride (0.28 cm^3, 1.4 mmol) and 4,4-dimethylaminopyridine (105 mg, 0.86 mmol). The resulting solution was heated at 40 °C for 2.5 h under nitrogen. The reaction mixture was treated with dilute aq. HCl to quench the reaction and then extracted with ethyl acetate (×2). The combined extracts were washed with brine and evaporated to afford a residue which was purified by MPLC to give the ester **41** (244 mg, 84%) (Found: C, 71.55; H, 10.5. $C_{25}H_{44}O_3Si$ requires C, 71.4; H, 10.5%); $[\alpha]_D$ +219.3 (*c* 0.67); ν_{max}/cm^{-1} 1728, 1462, 1384, 1256, 1181, 1157, 1097 and 838; δ 0.03 (6 H, s, Me_2Si), 0.88 (9 H, Me × 3, m), 0.88 (9 H, s, Bu^t), 1.0–2.6 (14 H, m), 3.57 (2 H, br t, 1-H), 5.27 (1 H, br s, 8-H) and 5.5–6.16 (3 H, m, olefinic H); *m*/*z* 420 (M^+, 5%), 26 (61), 187 (48), 159 (100), 145 (46), 143 (28), 75 (34) and 57 (26).

(1*S*,2*S*,8*S*,8a*S*)-8-(3′-Hydroxypropyl)-7-methyl-1,2,3,7,8,8a-hexahydro-1-naphthyl (*S*)-2-methylbutanoate 42

A solution of TBAF (1 mol dm^3 solution in THF, 1.4 cm^3, 1.4 mmol) was added to the TBS ether **41** (289 mg, 0.689 mmol)

at 0 °C under nitrogen. After being stirred at room temperature for 1 h, the resulting solution was poured into water. The aqueous mixture was then extracted with ethyl acetate (×2) and the combined extracts were washed with brine and evaporated. MPLC purification of the residue [eluent hexane–ethyl acetate (1:1)] provided the alcohol **42** (217 mg, quant), mp 65–66 °C (lit.,[16] 66–67 °C) (fine needles from hexane) (Found: C, 74.3; H, 9.8. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.9%); $[\alpha]_D$ +319 (*c* 1.05) (lit.,[16] +347, *c* 1.06); ν_{max}/cm^{-1} 3638, 3520, 1728, 1461, 1383, 1266, 1241, 1198, 1181, 1165, 1080, 909 and 652; δ 0.88 (3 H, t, *J* 7.2, *Me*CH_2), 0.89 (3 H, d, *J* 7, Me), 1.12 (3 H, d, *J* 6.8, *Me*CH), 1.0–2.7 (15 H, m), 3.56 (2 H, t, *J* 5.3, 1′-H), 5.31 (1 H, br s, 8-H) and 5.5–6.16 (3 H, m, olefinic H); *m/z* 306 (M^+, 2%), 204 (33), 145 (100) and 57 (10).

Methyl (3*R*,5*R*)-3,5-Dihydroxy-7-{(1′*S*,2′*S*,8′*S*,8a′*S*)-2′-methyl-8′-[(*S*)-2-methylbutanoyloxy]-1′,2′,3′,7′,8′,8a′-hexahydro-1′-naphthyl}heptanoate 45 and methyl (3*S*,5*S*)-3,5-dihydroxy-7-{(1′*S*,2′*S*,8′*S*,8a′*S*)-2′-methyl-8′-[(*S*)-2-methylbutanoyloxy]-1′,2′,3′,7′,8′,8a′-hexahydro-1′-naphthyl}heptanoate 46

To a stirred solution of the mixture of hydroxy ketones **43** and **44** (47.8 mg, 0.114 mmol) in THF (2 cm^3) and methanol (0.5 cm^3) at −78 °C under nitrogen was added diethylmethoxyborane (114 mm^3, 1 mol dm^3 solution in THF; 0.114 mmol). The resulting solution was stirred at room temperature for 30 min and then cooled again to −78 °C. Sodium borohydride (5.3 mg, 0.15 mmol) was added to the solution which was then stored at −78 °C to −10 °C for 3 h. The reaction was quenched by addition of aq. ammonium chloride to the mixture which was then extracted with ethyl acetate (×2). The combined extracts were washed with brine and evaporated to dryness. The residue was dissolved in methanol (3 cm^3) and evaporated. This procedure was repeated three times. MPLC purification (eluent ethyl acetate) of the residue gave inseparable mixture of the diols **45** and **46** (50 mg, quant); ν_{max}/cm^{-1} 3500, 1727, 1647, 1457, 1386, 1180 and 1095; δ 0.88 and 0.89 (total 3 H, d, *J* 7, Me), 0.89 (3 H, t, *J* 7, *Me*CH_2), 1.06 (3 H, d, *J* 7, *Me*CH), 1.0–2.6 (20 H, m), 3.72 (3 H, s, MeO), 3.84 (1 H, m, 5-H), 4.34 (1 H, quintet, *J* 6.6, 3-H), 5.36 (1 H, br s, 8′-H) and 5.5–6.1 (3 H, m, olefinic H); *m/z* 422 (M^+, 3%), 284 (23), 210 (33), 184 (55), 160 (41), 159 (41), 158 (77), 155 (49), 145 (100), 144 (40) and 57 (33) (Found: M^+, 422.2664. $C_{24}H_{38}O_6$ requires *M*, 422.2668).

Compactin 1 and 3,5-di-*epi*-compactin 47

To a stirred solution of the mixture of diols **45** and **46** (50 mg, 0.118 mmol) in acetonitrile in a Teflon bottle (2 cm^3) was added hydrogen fluoride–pyridine complex (0.5 cm^3) at 0 °C. After the mixture had been stirred for 5.5 h, hydrogen fluoride–pyridine complex (0.5 cm^3) was added to it and stirring was continued for a further 40 min. The mixture was then poured into aq. sodium hydrogen carbonate and extracted with ethyl acetate (×2). The combined extracts were evaporated to dryness and the residue was purified by MPLC to afford a mixture of compactin **1** and 3,5-di-*epi*-compactin **47** (41 mg, 92%), which were separated by MPLC after 5 recycles [eluent hexane–dichloromethane (1:1), monitored by UV detector at 245 nm] to give the less polar *epi*-compactin **47** (15.4 mg) and the more polar compactin **1** (15.6 mg). Compactin **1** had $[\alpha]_D$ +258 (*c* 0.38, acetone); ν_{max}/cm^{-1} 3600, 1719, 1457, 1386, 1255, 1221 and 1079; δ§ 0.88 (3 H, t, *J* 7.2, *Me*CH_2), 0.9 (3 H, d, *J* 7, 9-Me), 1.12 (3 H, d, *J* 6.8, *Me*CH), 1.0–2.8 (19 H, m), 4.37 (1 H, quintet, *J* 4.4, 3-H), 4.6 (1 H, m, 5-H), 5.34 (1 H, br s, 15-H) and 5.5–6.1 (3 H, m, olefinic H); λ_{max}/nm 245 (log ε 4.01) 237 (4.19) and 239 (4.15); *m/z* 390 (M^+, 8%), 270 (15), 210 (26), 184 (76), 183 (28), 158 (53), 155 (35), 145 (100), 144 (37), 143 (79), 129 (33), 105 (22), 91 (26) and 57 (55). *epi*-Compactin **47** had $[\alpha]_D$ +152 (*c* 0.77, acetone); ν_{max}/cm^{-1} 3600, 1718, 1260 and 1200; δ 0.89 (3 H, d, *J* 7, 9-Me), 0.89 (3 H, t, *J* 7.2, *Me*CH_2), 1.12 (3 H, d, *J* 7, 9-Me), 1.0–2.8 (19 H, m), 4.4 (1 H, quintet, *J* 3.6, 3-H), 4.7 (1 H, m, 5-H), 5.32 (1 H, br s, 15-H) and 5.5–6.1 (3 H, m, olefinic H); λ_{max}/nm 245 (log ε 4.01), 237 (4.21) and 229 (4.15); *m/z* 390 (M^+, 9%), 270 (14), 210 (20), 184 (63), 183 (25), 158 (52), 155 (33), 145 (100), 144 (39), 143 (79), 129 (33), 105 (22), 91 (24) and 57 (53).

§ Non-systematic numbering.

Acknowledgements

We thank Dr. A. Terahara, Sankyo Co., for the generous gift of natural compactin and Amano Pharmaceutical Co. for Lipase AK. This work was supported in part by Grant in Aid for Scientific Research (No. 02640418) from the Ministry of Education, Science and Culture, Japan.

References

1 For example: Y. Tsujita and M. Arai, *Gendai Kagaku*, 1990, March, p. 19; K. Suckling, *Chem. Ind.* (*London*), 1991, 717; A. Endo and K. Hasumi, *Nat. Prod. Rep.*, 1993, 541.
2 Sankyo Co., Ltd., Jap. P. 50-155690, 1975; A. Endo, M. Kuroda and Y. Tsujita, *J. Antibiot.*, 1976, **29**, 1346.
3 A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp and R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1165.
4 Dihydrocompactin: Y. K. T. Lam, V. P. Gullo, R. T. Goegelman, D. Jorn, L. Huang, C. DeRiso, R. L. Monaghan and I. Putter, *J. Antibiot.*, 1981, 616. Monacolin K (Mevinolin): A. Endo, *J. Antibiot.*, 1980, 334; A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, C. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirshfield, K. Hoogsteen, J. Liesch and J. Springer, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 3957. Dihydromevinolin: G. Albers-Schonberg, H. Joshua, M. B. Lopez, O. D. Hensens, J. P. Springer, J. Chen, S. Ostrove, C. H. Hoffman, A. W. Alberts and A. A. Patchett, *J. Antibiot.*, 1981, 507.
5 Synthesis of (+)-compactin: (*a*) Y.-L. Yang, S. Manna and J. R. Falck, *J. Am. Chem. Soc.*, 1984, **106**, 3811; (*b*) S. D. Burke and D. N. Deaton, *Tetrahedron Lett.*, 1991, **32**, 4651; synthesis of congeners: (*c*) D. L. J. Clive, K. S. K. Murthy, R. George and M. J. Poznansky, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2099; (*d*) S. Hannessian, P. J. Roy, M. Petrini, P. J. Hodges, R. Di Fabio and G. Carganico, *J. Org. Chem.*, 1990, **55**, 5766; (*e*) D. L. J. Clive, K. S. K. Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. da Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze and J. R. Barrie, *J. Am. Chem. Soc.*, 1990, **112**, 3018 and earlier references cited therein; (*f*) H. Hagiwara, M. Kon-no, T. Nakano and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2417.
6 H. Hagiwara, T. Akama, A. Okano and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2173.
7 H. Hagiwara, K. Kimura and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 693.
8 G. A. Kraus and M. E. Krolski, *Synth. Commun.*, 1982, **12**, 521.
9 E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.
10 Unpublished result in collaboration with Prof. Toda, Ehime University.
11 H. Hagiwara, T. Nakano and H. Uda, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3110.
12 A. J. Mancuso, S. L.-Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
13 Molecular modelling was performed using PCMODEL (Serena Software, Bloomington, IN, USA).
14 S. J. Danishefsky and B. Simoneau, *J. Am. Chem. Soc.*, 1989, **111**, 2599.
15 R. L. Funk and W. E. Zeller, *J. Org. Chem.*, 1982, **47**, 180.
16 C.-T. Hsu, N.-Y. Wang, L. H. Latimer and C. J. Sih, *J. Am. Chem. Soc.*, 1983, **105**, 593.
17 T. Hiyama and T. Hanamoto, *Tetrahedron Lett.*, 1988, **29**, 6467.

Paper 4/06863G
Received 10*th November* 1994
Accepted 20*th December* 1994