Total Synthesis of (+)-Dihydrocompactin

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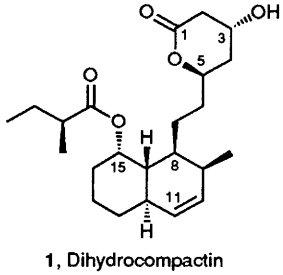
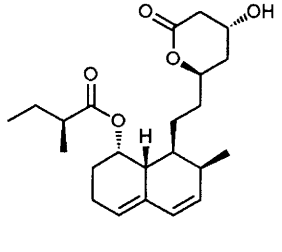
The total synthesis of (+)-dihydrocompactin **1** has been achieved by employing the double Michael reaction of 3-*tert*-butyldimethylsilyloxy-1-acetylcyclohexene with methyl crotonate as a key step.

Hypercholesterolaemia is a major factor in causing coronary heart disease, and its extent is increasing among geriatric diseases. Since more than 70% of the total input of cholesterol is biosynthesised from acetyl CoA in humans, control of the biosynthesis of cholesterol is important in treating and preventing such diseases.[1] Compactin **2**, first isolated from *Penicillium brevicompactum* by Sankyo Co.,[2] efficiently inhibits HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis. Later, a Merck group isolated dihydrocompactin **1**[3] from *Penicillium citrinum*, having bioactivity comparable to that of compactin **2**, among other congeners.[4] Because of their unique bioactivity and structure, these compounds have attracted much attention as synthetic targets.[5] We delineate herein our new synthetic route towards the total synthesis of (+)-dihydrocompactin **1**.

(+)-Dihydrocompactin **1** may be structurally divided into two portions: the octahydronaphthalene and the δ-lactone moieties. The basic framework of the hydronaphthalene portion was synthesised *via* double Michael reaction[6] (Scheme 1). The reaction of the kinetic enolate of 3-*tert*-butyldimethylsilyloxy-1-acetylcyclohexene, generated from the trimethylsilyl enol ether **3** using methyllithium, with methyl crotonate in the presence of hexamethylphosphoric triamide (HMPA) afforded a mixture of the major *cis*-decalone **4** having a steroidal conformation and the *trans*-decalone **5** in 85% yield.† Without separation, treatment of a mixture of the decalones **4** and **5** with sodium methoxide resulted in complete isomerisation of the major *cis*-decalone **4** into the *trans*-decalone **5** in 78% yield. Prior to inversion of the stereochemistry at C-15,‡ the decalone **5** was transformed into the xanthate **7** to elaborate unsaturation between C-10 and C-11. Thus, reduction of the decalone **5** with sodium borohydride ($NaBH_4$) at 0 °C gave the axial alcohol **6** which was converted into the xanthate **7** in 72% overall yield by sequential treatment with butyllithium, carbon disulfide and methyl iodide. Deprotection of the *tert*-butyldimethylsilyl group at C-15 followed by Swern oxidation[7] afforded the ketone **8** in 82% overall yield. Reduction of the ketone **8** with $NaBH_4$ at −40 °C gave a mixture of the hydroxyester **9** and the



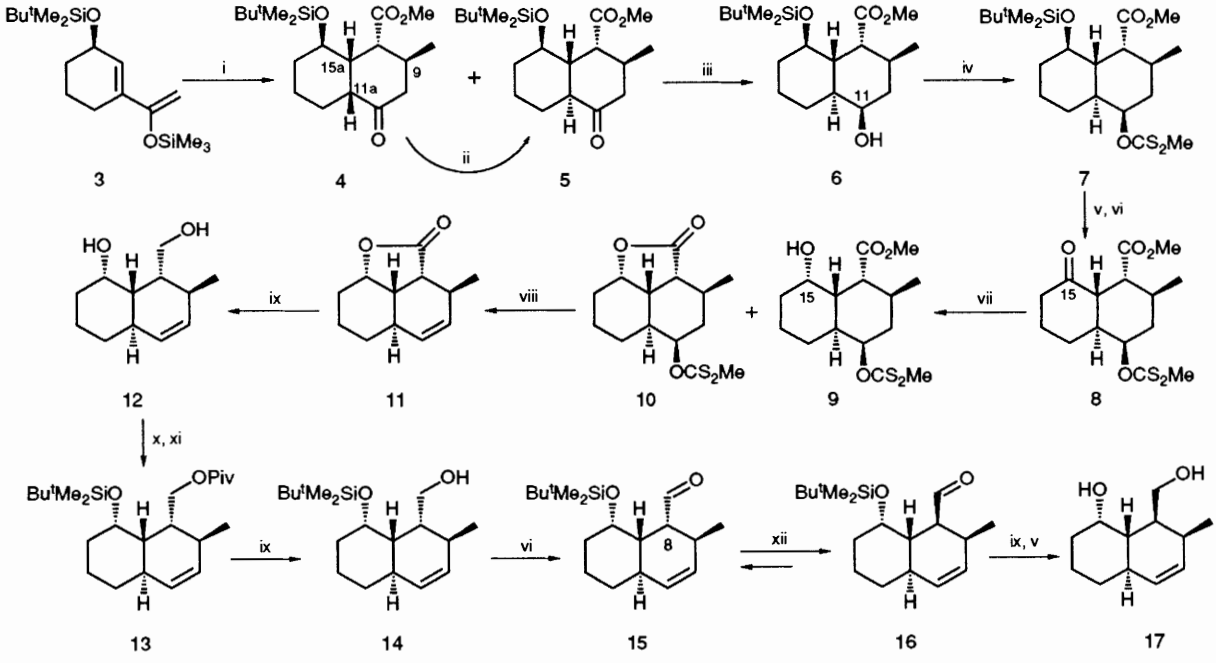
1, Dihydrocompactin



2, Compactin

† All yields refer to pure isolated products, which exhibited satisfactory ^1H NMR, IR and mass spectral and/or elemental analyses.

‡ Non-systematic numbering is used in this publication starting from the lactonic carbonyl carbon atom.

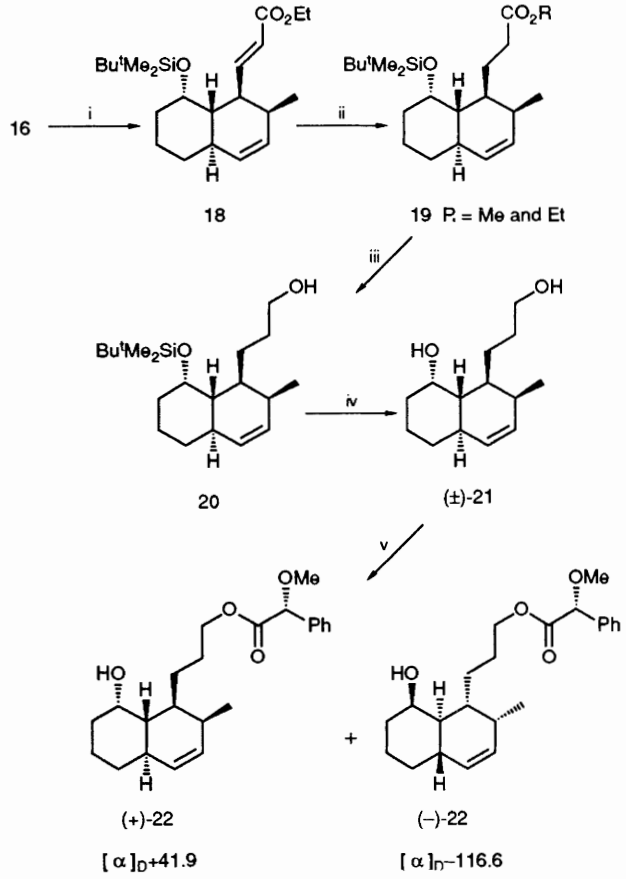


Scheme 1 *Reagents and conditions*: i, MeLi, methyl crotonate, HMPA (2 equiv), THF, −78 to −10 °C; ii, NaOMe–HOMe, reflux, then CH_2N_2; iii, $NaBH_4$, HOMe, 0 °C; iv, BuLi, carbon disulfide, MeI, THF; v, Bu^n_4NF, THF, room temp.; vi, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 to −25 °C; vii, $NaBH_4$, HOMe, −60 to 40 °C; viii, 1-methylnaphthalene, 210 °C; ix, $LiAlH_4$, Et_2O; x, pivaloyl chloride, pyridine; xi, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2; xii, K_2CO_3, HOMe

lactone **10** furnishing the stereochemistry at C-15. The mixture of the hydroxyester **9** and the lactone **10** was heated at 210 °C to furnish the double bond between C-10 and C-11. Without work-up, the resulting unsaturated lactone **11** was reduced with lithium aluminium hydride ($LiAlH_4$) to give the diol **12** in 80% yield (3 steps). The remaining task for the octahydronaphthalene part of dihydrocompactin **1** is to control the stereochemistry at the C-8 substituent. The primary alcohol of the diol **12** was selectively protected as the pivalate and subsequently the secondary alcohol as the *tert*-butyldimethylsilyl ether to give the ester **13**. Removal of the pivalate with $LiAlH_4$ (85% in 3 steps) followed by Swern oxidation gave the aldehyde **15** (80%) which gave the isomeric aldehyde **16** (55%) along with the recovered aldehyde **15** (42%) after treatment with potassium carbonate in methanol.[5d] The structure of the aldehyde **16** was confirmed by transformation into the known diol **17**[8] (68% in 2 steps).

Elongation of two carbon unit from C-7 of the aldehyde **16** was performed by Horner–Emmons reaction leading to the α,β-unsaturated ester **18** in 96% yield (Scheme 2). The unsaturation between C-6 and C-7 was chemoselectively reduced with magnesium[9] in methanol to give a mixture of the methyl and ethyl esters **19** which was reduced with $LiAlH_4$ to give the alcohol **20** (85% in 2 steps). Deprotection of the *tert*-butyldimethylsilyl group gave the diol **21** (92%) whose primary hydroxy group was selectively protected as the (*R*)-*O*-methylmandelate[10] to give a diastereoisomeric mixture of the hydroxyester **22** (85%) which was resolved by medium pressure liquid chromatography.

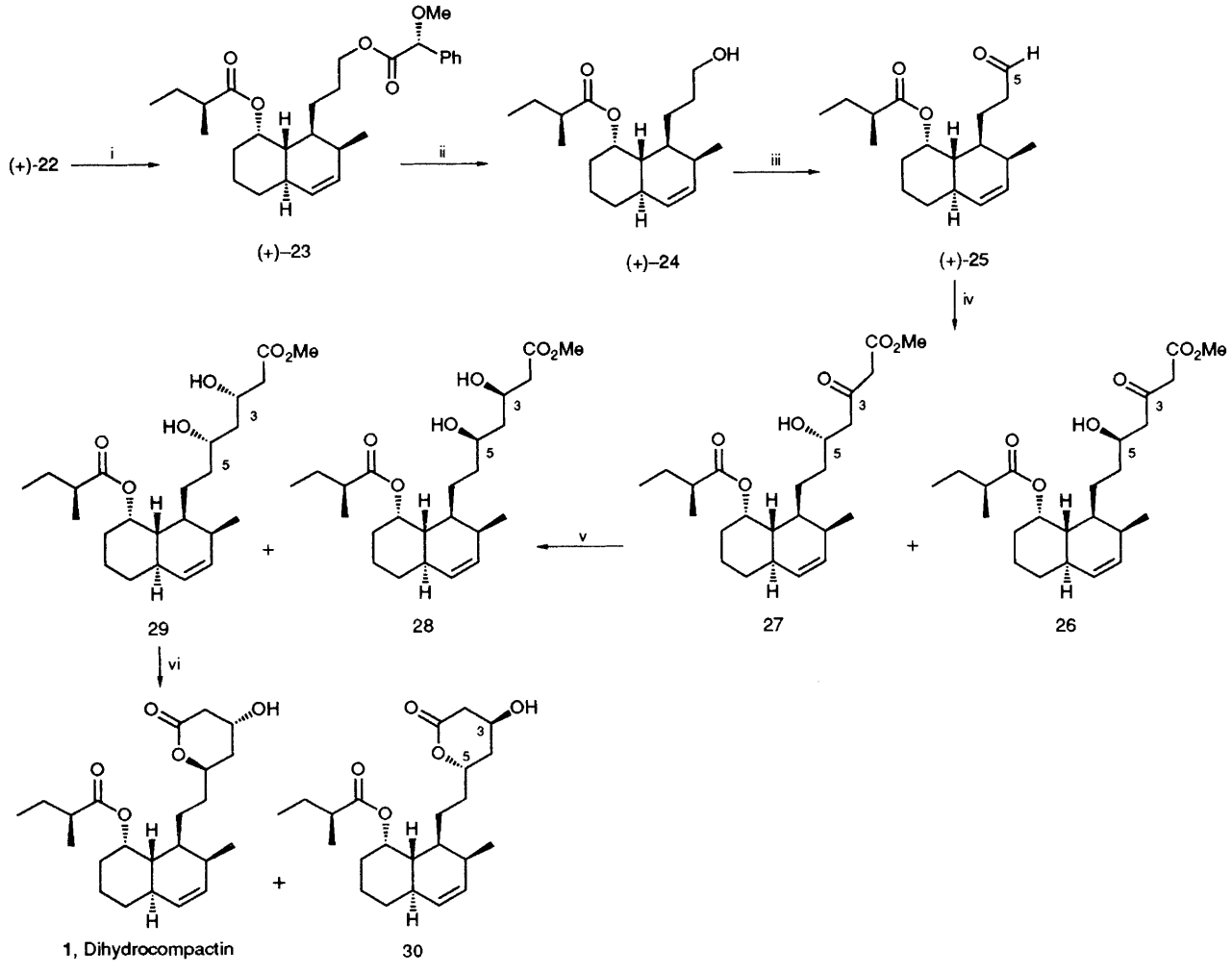
The dihydroxyester (+)-**22**§ having a positive optical rotation value was used for further transformation (Scheme 3). The hydroxy group at C-15 was protected by (*S*)-2-methylbutyric anhydride and the resulting bis-ester **23** was regioselectively hydrolysed to give the hydroxyester **24** (93% in 2 steps). The hydroxyester (+)-**24** was transformed into the aldehyde (+)-**25** by Swern oxidation in 97% yield. The aldol condensation of the aldehyde (+)-**25** with the bistrimethylsilyl enol ether of methyl acetoacetate,[11] in the presence of $TiCl_4$,



Scheme 2 *Reagents and conditions*: i, triethyl phosphonoacetate, HMPA, NaH, THF; ii, Mg, HOMe, 0 °C; iii, $LiAlH_4$, Et_2O; iv, HF (46%), acetonitrile, 0 °C; v, (*R*)-(−)-*O*-methylmandelic acid, dicyclohexylcarbodiimide, 4-dimethylaminopyridine, CH_2Cl_2

afforded the inseparable adducts **26** and **27**. Reduction of a mixture of the adducts **26** and **27** with $NaBH_4$ in the presence of diethylmethoxyborane[12] proceeded with complete *syn*-stereoselectivity to give the 3,5-*syn*-diols **28** and **29** in 59%

§ The absolute stereostructures of the ester (+)-**22** and the lactone **30** were determined by the exciton chirality method. The results will be reported in due course.



Scheme 3 *Reagents and conditions*: i, (*S*)-2-methylbutyric anhydride, pyridine, 40 °C; ii, KOH, HOMe; iii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; iv, $TiCl_4$, bistrimethylsilyl enol ether of methyl acetoacetate, CH_2Cl_2, −90 to −50 °C; v, $NaBH_4$, Et_2BOMe, HOMe, −78 °C to room temp.; vi, HF–pyridine, acetonitrile

yield (2 steps). Treatment of the dihydroxyesters **28** and **29** with hydrogen fluoride–pyridine complex[13] completed the total synthesis of (+)-dihydrocompactin **1** and 3,5-epidihydrocompactin **30**§ (70%) in a ratio of 1 : 1. Separation by medium pressure liquid chromatography afforded pure (+)-dihydrocompactin **1**, $[\alpha]_D$ + 127 (*c* 0.119 in $CHCl_3$) [lit.,[5a] + 129 (*c* 1.3 in $CHCl_3$)]. The spectral data of synthetic (+)-dihydrocompactin **1** were completely identical with reported data.[5a]

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