

3.8 Compactin

Compactin (**1**), Fig. 3.8-1, belongs to a group of diterpenes that attracted attention because of their demonstrated potent inhibition of HMG-CoA reductase [1]. The discovery of compactin coincided with developments in the understanding of the biosynthesis of cholesterol [2]. Cholesterol is biosynthesized in at least 25 steps. The first steps in the pathway involve the successive condensation of three acetyl-CoA units leading to the formation of an important compound, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which is reduced to mevalonate by an enzyme known as HMG-CoA reductase. Mevalonate is then converted to cholesterol through a series of reactions including the formation of squalene. It was shown that the step involving HMG-CoA reductase is rate limiting in the biosynthesis of cholesterol; consequently, the enzyme was considered to be an attractive target for potential cholesterol-reducing agents [2].

Compactin is a fungal metabolite isolated by Endo [1b] (Sankyo Company) from cultures of *Penicillium citrinum*. In an independent effort, Brown [3] of Beecham Pharmaceuticals also reported its isolation from *Penicillium brevicompactum*. Screening of other fungal strains led to the isolation of a fungal metabolite lovastatin (mevinolin) (**3**), a compound having bioactivity similar to compactin [4]. These compounds, along with a number of related semi-synthetic and synthetic compounds, are known as statins. HMG-CoA reductase catalyzes a two-step reduction that requires NADPH. The lactone portion of the statins gives them a structural similarity to HMG-CoA. As a result they bind very tightly to the enzyme and have K_1 values of about 1 nM. They are thus classified as reversible competitive inhibitors of HMG-CoA reductase.

A related structure that also attracted considerable attention is forskolin (**5**), a labdane diterpene that showed therapeutic potential in the cardiovascular area as an activator of adenylate cyclase. Several total syntheses of this compound have been reported. Study of these syntheses would provide insight into the various solutions to the design of the densely functionalized central ring of this interesting compound [5].

There was tremendous activity in synthetic approaches to compactin and related compounds in response to its proven biological activity profile [6]. In addition to the eleven or so total syntheses that have been published, there are many formal approaches and syntheses of the decalin portion of the molecule, which is viewed by most chemists as the core of the architectural challenge. Many preparations of the side chain have also been reported in the literature as its attachment has frequently been one of the last steps in the synthesis of the target.

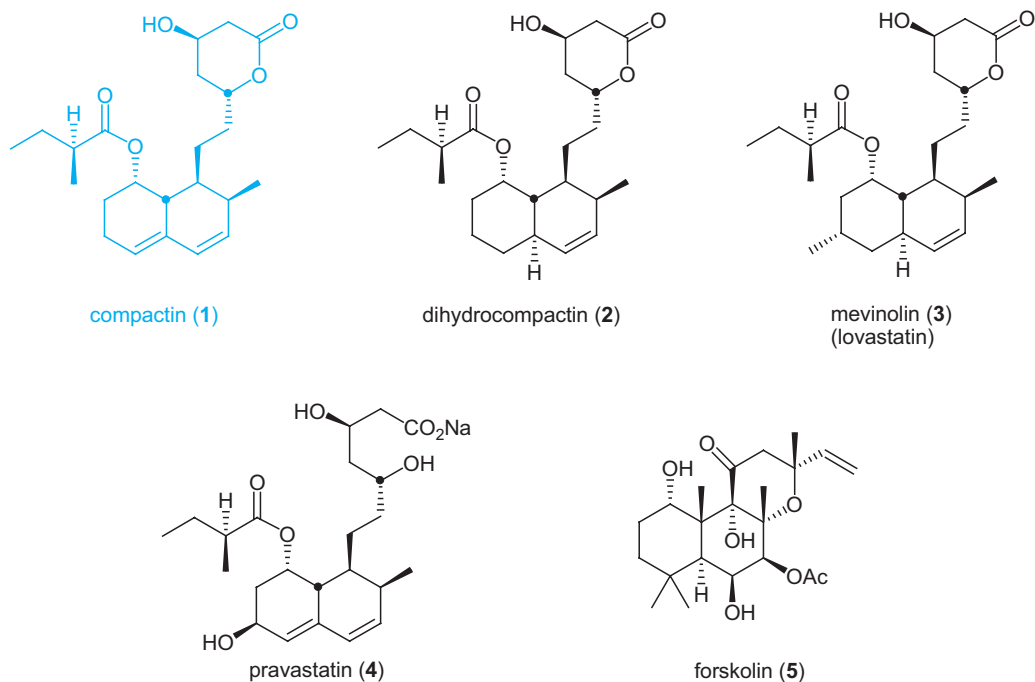


Figure 3.8-1 Compactin and related compounds.

Four approaches are featured here: in addition to the monumental accomplishment by Charles Sih's first attempt, Grieco's and Hagiwara's syntheses are discussed along with Funk's formal synthesis. Sih's synthesis featured an enzymatic step, a very uncommon practice during the 1980s. Funk's approach uses the Diels–Alder reaction, as does Grieco's in his convergent connection of the two halves. Hagiwara's synthesis employs a series of Michael additions to construct the decalin nucleus. The disconnection strategies are indicated in Fig. 3.8-2.

Sih (1981) [7]. One of the pioneers in the use of biocatalysis in synthesis, Sih employed a chemoenzymatic approach to compactin. He chose as the starting material the racemic quinone derivative **6**, whose chemical reductions afforded no selectivity, but whose microbial reduction with *Aureobasidium pullulans* NRRL Y-12610 provided a mixture of products, 33% of which was the optically pure diol **8**. The remaining 67% consisted of various diastereomeric diols **7**, which could be converted back to the starting material by chemical oxidation and recycled further by the enzymatic reduction, Scheme 3.8-1.

After the desired diol **8** was protected as its dibenzyl ether, the olefin was reacted with phenylselenenyl bromide. The issue in this transformation is not stereochemistry but rather the regiochemistry of the introduction of oxygen. Because of its C_2 -symmetry, the product of the selenation, trapped as the acetate, displayed the stereochemistry shown in phenyl selenide **9**. Hydrolysis and oxidation produced an allylic alcohol via a [2,3] sigmatropic rearrangement of the selenoxide. Further oxidation with Jones reagent furnished the required enone **10** in 71% yield. Addition of the side chain as a cuprate reagent followed by trapping with methyl iodide gave **11** in 80% yield but with the incorrect equatorial stereochemistry of the methyl group. To circumvent this problem, the intermediate in the cuprate addition was trapped with formaldehyde, the product converted to its mesylate, and subjected to base-catalyzed elimination to the exocyclic methylene **13**, which was hydro-

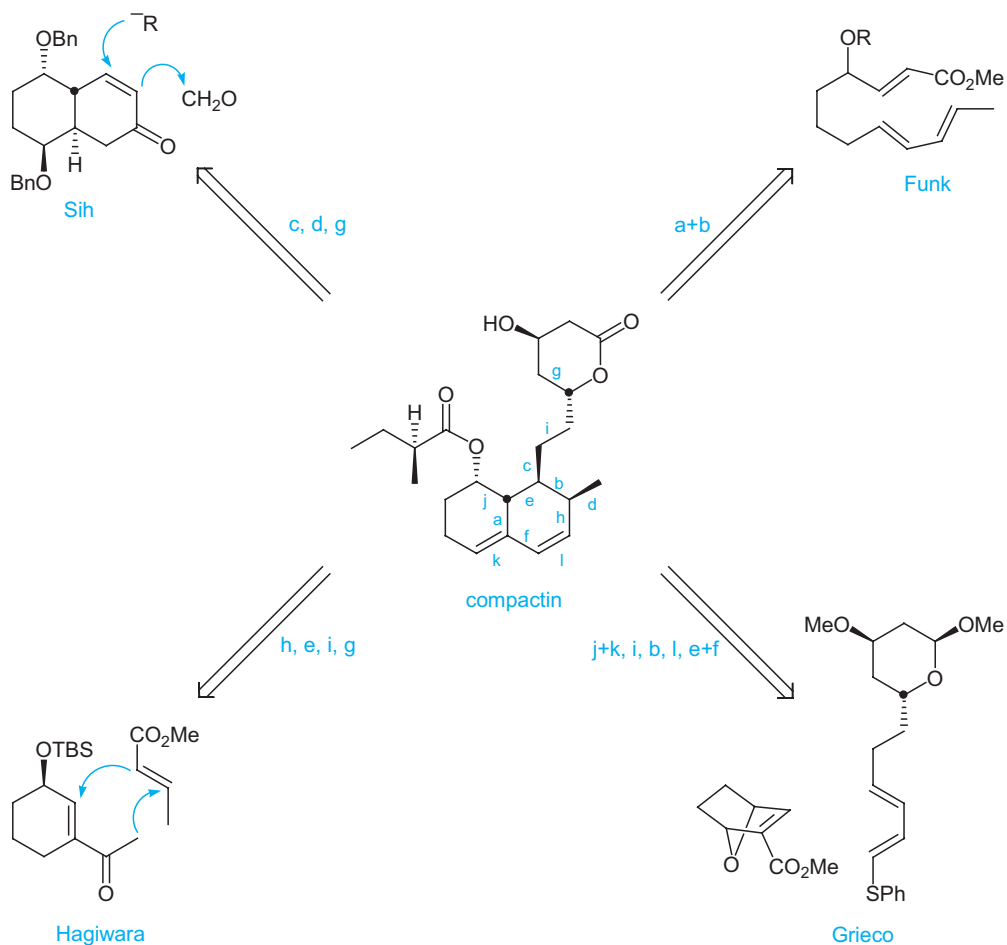


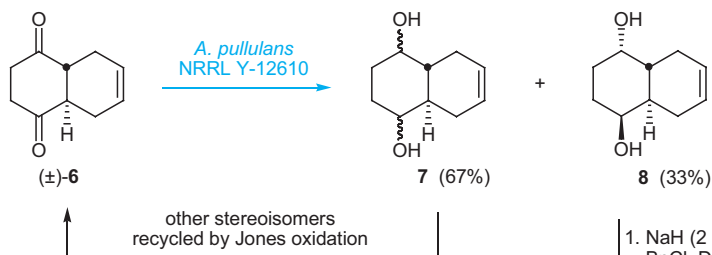
Figure 3.8-2 Disconnections used in the featured syntheses of compactin. (Bond labels are listed in the order of the bond formation.)

generated to provide **11** and **12** in almost equal ratio (55:45), accompanied by 10% yield of the material resulting from isomerization of **13** to the endocyclic olefin. Each epimer equilibrated in sodium methoxide in methanol to a 9:1 mixture of the epimers in favor of the undesired equatorial isomer **11**. Fortunately Sih found that when the hydrogenation was conducted in the presence of pyridine an 81% yield of **12** was produced with only 10% contamination by the equatorial epimer.

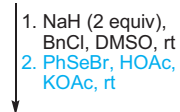
Ketone **12** was converted to its tosylhydrazone and subjected to the conditions of the Shapiro reaction to yield olefin **14**, which was debenzylated by dissolved metal reduction to the corresponding diol. Attempts at selective mono functionalization with (*S*)-2-methylbutyric anhydride failed and consistently delivered as the major product the ester at the undesired hydroxyl. Clearly this was indicative of the increased steric availability of this hydroxyl group. Sih took advantage of this fact by converting the diol to the diester, whose selective hydrolysis furnished monoester **15** in 63% yield, accompanied by 6.6% of the undesired isomer, 6.5% of the diester, and a trace of the diol. Such a strategy is an example of clever thinking (possibly derived from Sih's biochemical

Key Tactics

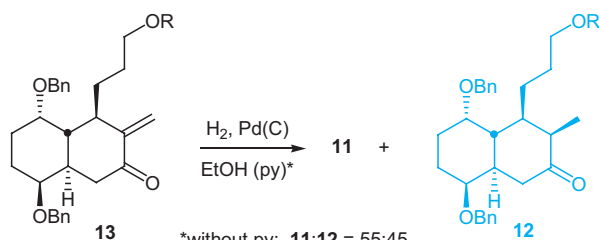
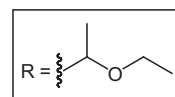
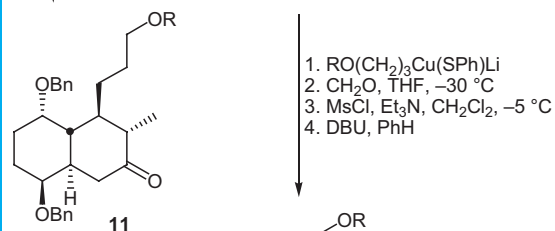
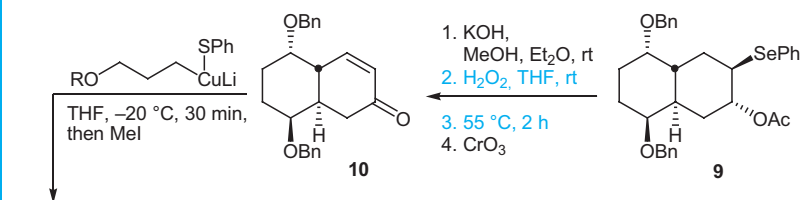
- asymmetric microbial reduction



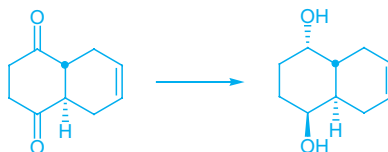
- oxyselenation of olefin



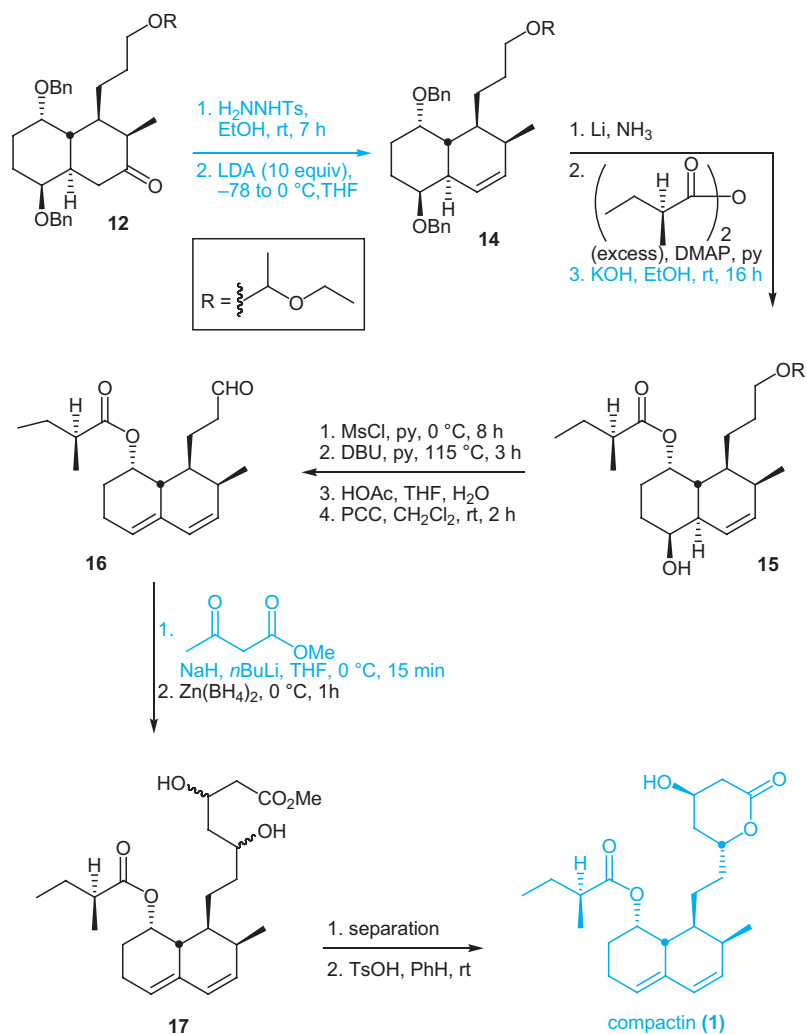
- thermal selenoxide elimination (enone synthesis)



Key strategy: enzymatic desymmetrization (biocatalysis)



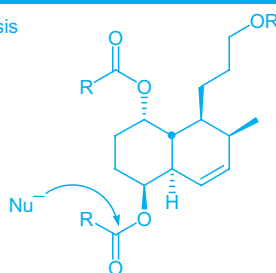
Scheme 3.8-1 Sih (1981)



Key Tactics

- Shapiro reaction
- selective hydrolysis of less hindered ester
- γ -alkylation of keto ester dianion

Key strategy: selective mono-esterification via hydrolysis of a less hindered diester



Scheme 3.8-1 Sih (1981), continued

background as this kind of hydrolysis operates in enzymatic desymmetrization of meso diesters) in exploiting steric hindrance of a functional group by changing the reaction type and thus the outcome.

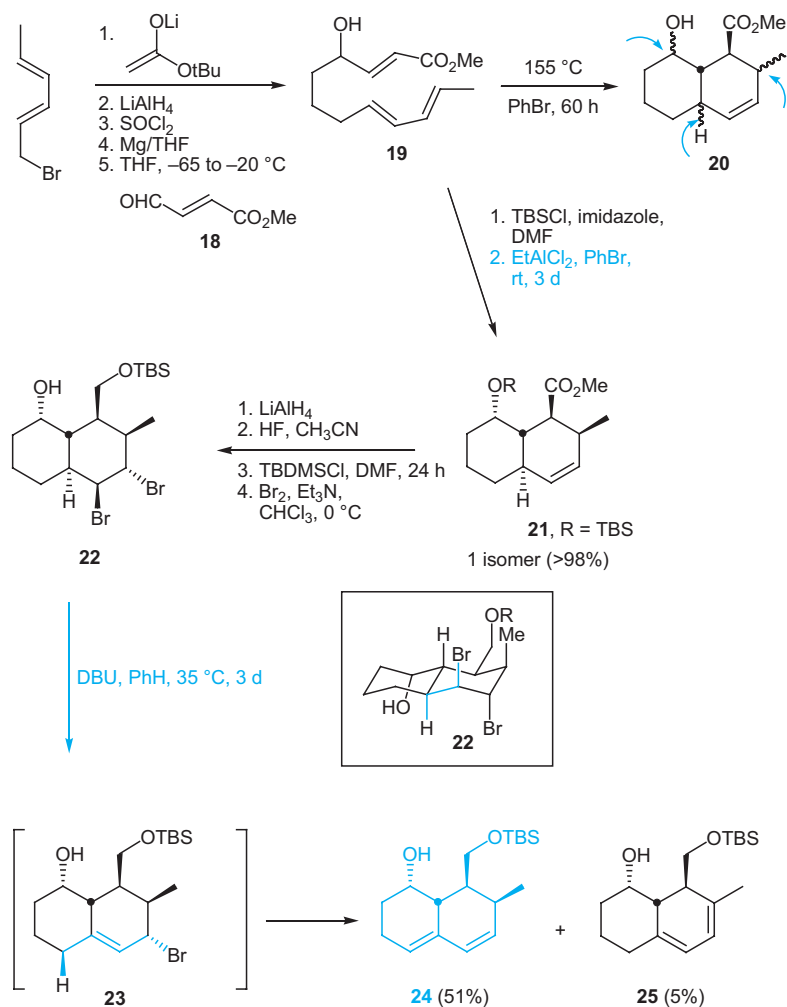
To introduce the required diene, alcohol **15** was converted to its mesylate and subjected to base-catalyzed elimination. The side chain was prepared for the final steps by removal of the protecting group and oxidation of the resulting free alcohol to aldehyde **16**. Its condensation with the dianion derived from methyl acetoacetate followed by reduction of the keto ester gave **17** as a mixture of diastereomeric diols. From this mixture Sih was able to separate two pairs of diols, the less polar of which provided two hydroxylactones upon treatment with TsOH. Compactin was isolated by HPLC from this final mixture. This completed the first asymmetric total synthesis in 23 steps.

Funk (1982) [8]. The approach to the hexahydronaphthalene unit of compactin undertaken by Funk's group involved the use of a Lewis acid-catalyzed Diels–Alder cycloaddition. It provides an interesting and efficient solution to the stereochemical issues associated with the decalin nucleus. The synthesis begins with the alkylation of the anion of *tert*-butyl acetate with sorbyl bromide followed by the reduction of the ester to an alcohol and conversion to an eight-carbon chloride containing the 1,3-diene unit, Scheme 3.8-2.

The addition of the Grignard reagent derived from the dienyl halide to methyl 3-formylacrylate (**18**) gave the functionalized hydroxybutyrate **19**, the intermediate for the intramolecular Diels–Alder reaction. Thermolysis of **19** was conducted in bromobenzene for 60 hours resulting in the mixture (47:41:12) of stereoisomers of **20**, formed in 53% yield, with the major component having a *cis* ring junction and the hydroxyl and methyl groups in the opposite configuration than that required for compactin. However, in the Lewis acid-catalyzed cycloaddition in the presence of ethyl aluminum dichloride at room temperature, the major product (55% yield) was the correctly fused *trans* ring system with the α -hydroxyl, β -ester, and methyl groups as required for compactin (55:45:1). These discouraging results were ameliorated by performing the Diels–Alder reaction on the *tert*-butyldimethylsilyl ether derived from **19** in which the secondary center could impose more steric control in the cycloaddition. Under thermal conditions (140 °C, 120 h) the desired isomer **21** was present to the extent of 65% of a mixture (65:13:22) obtained in 65% yield. At room temperature and under Lewis acid catalysis the reaction provided **21** in 65–73% yield and in a 98:2 ratio with the isomer possessing β -stereochemistry of the silyloxy group. In this fashion all the chiral centers of the compactin nucleus were established in the correct relative configuration.

The ester was converted to an alcohol, the silyl ether deprotected, and the resulting diol was selectively mono-protected and treated with one equivalent of bromine to provide stereoselectively dibromide **22**. Note that the antiperiplanar bond alignment in **22** favors, upon 1,2 elimination, the formation of only the intermediate mono olefin **23** and that further elimination of the bromide represents the reverse mode of HBr 1,4 addition to butadiene under “thermodynamic” conditions. This is a very simple yet elegant solution to the regioselective installation of the diene system as the product of the competing 1,2 elimination, proceeding via *syn* elimination of the halide, makes up only about 5% of the mixture. The synthesis of the compactin nucleus required twelve steps and constituted a formal total synthesis as **24** is equipped with sufficient functionality to attain the target.

Grieco (1983) [9]. An interesting strategy to (+)-compactin by Grieco's group resulted in a convergent synthesis by the union of two optically pure fragments by means of a Diels–Alder reaction, Scheme 3.8-3. The Diels–Alder reaction of nitroacrylate **26** with furan provided the known racemate **27** [10], which was reduced with diimide and hydrolyzed to the nitro acid **28**. Reaction of this compound with homochiral phenylglycinol provided two diastereomeric amides, which were separated by HPLC. The less polar component was esterified with HCl and methanol and subjected to DBU-promoted elimination of the nitro group to furnish the optically pure ester **29**, the dienophile partner in the design.

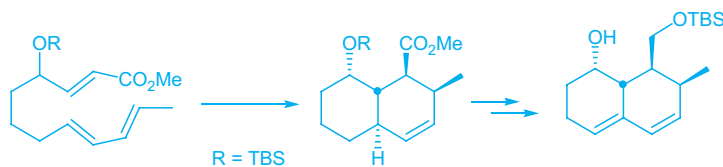


Key Tactics

- Lewis acid-catalyzed Diels–Alder cycloaddition

- dehydrobromination (reverse of thermodynamic 1,4 addition of HX to 1,3-dienes)

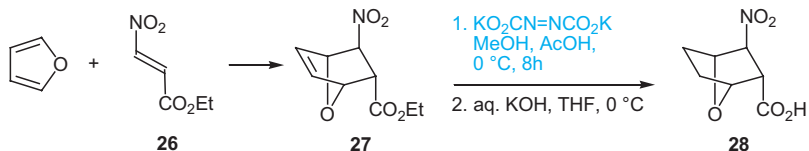
Key strategy: Lewis acid mediated [4+2] cycloaddition; stereospecific generation of a 1,3-diene



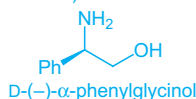
Scheme 3.8-2 Funk (1982)

Key Tactics

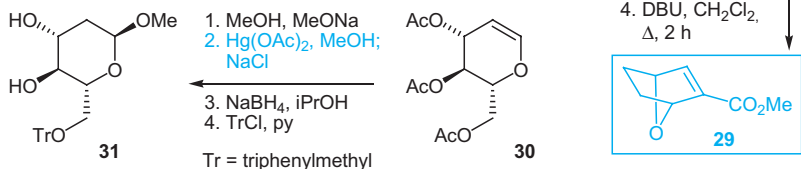
- diimide reduction



- resolution (formation and separation of diastereomeric amides)

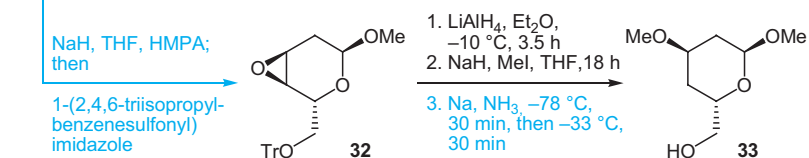


- oxymercuration

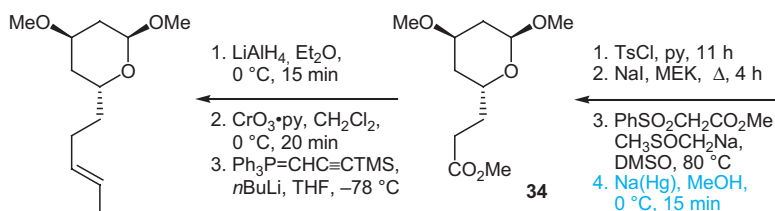


- diol-epoxide transformation

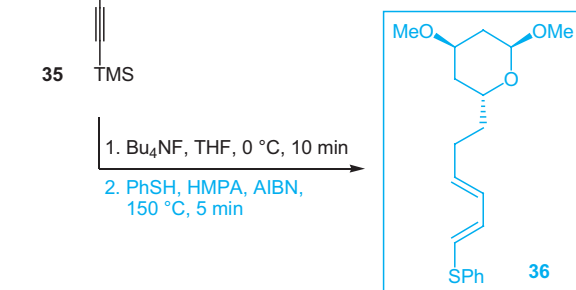
- benzylic hydrogenolysis (trityl group removal)



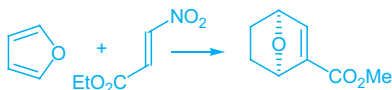
- desulfurization



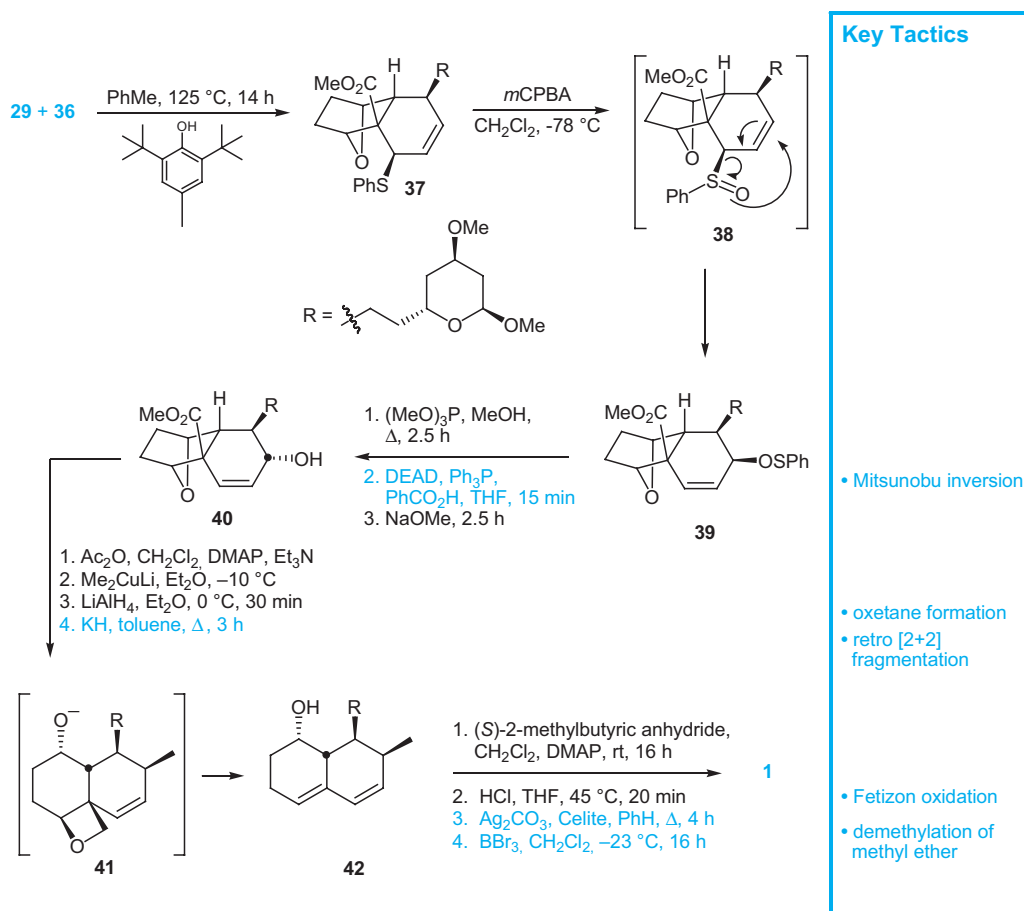
- radical addition to acetylene



Key strategy: Diels-Alder cycloaddition; resolution of acid through diastereomeric amides



Scheme 3.8-3 Grieco (1983)



Scheme 3.8-3 Grieco (1983), continued

The synthesis of the diene component commenced with triacetyl glucal (**30**), which was converted to **31** in a series of steps including oxymercuration to establish the methyl acetal center. Corey [11] used this procedure on a 0.5-mole scale and provided a protocol from trans diol **31** to epoxide **32** during his approach to *N*-methylmaysenine, in which the asymmetry was also incorporated by the use of glucal **30** (see Chapter 5.1, Section 5.1.1). The diol to epoxide conversion is interesting in that it uses an imidazole sulfonamide rather than a tosyl chloride, primarily for steric

reasons. In this transformation the sulfonation of the less hindered hydroxyl is crucial in order to set the correct stereochemistry of the epoxide in **32**.

The epoxide was reduced with lithium aluminum hydride, converted to its methyl ether, and the trityl group removed by means of a dissolved metal reduction to provide the correctly set tetrahydropyranyl unit in **33**. The homologation of the side chain in **33** was accomplished by tosylation, conversion to primary iodide, and alkylation with phenylsulfonyl acetate, which, after desulfurization, provided ester **34**. The yields in this sequence were excellent. The ester was converted in two steps to the aldehyde and its Wittig reaction with propargylic phosphorane generated the trans enyne **35**, which was desilylated and subjected to the radical addition of thiophenol to provide the key partner, thiophenyl diene **36**, for the Diels–Alder coupling with **29**. The crucial cycloaddition was performed in toluene containing 2,4-di-*tert*-butyl-4-methylphenol and gave a 70% yield of the adduct **37**, which clearly results from the endo mode of addition.

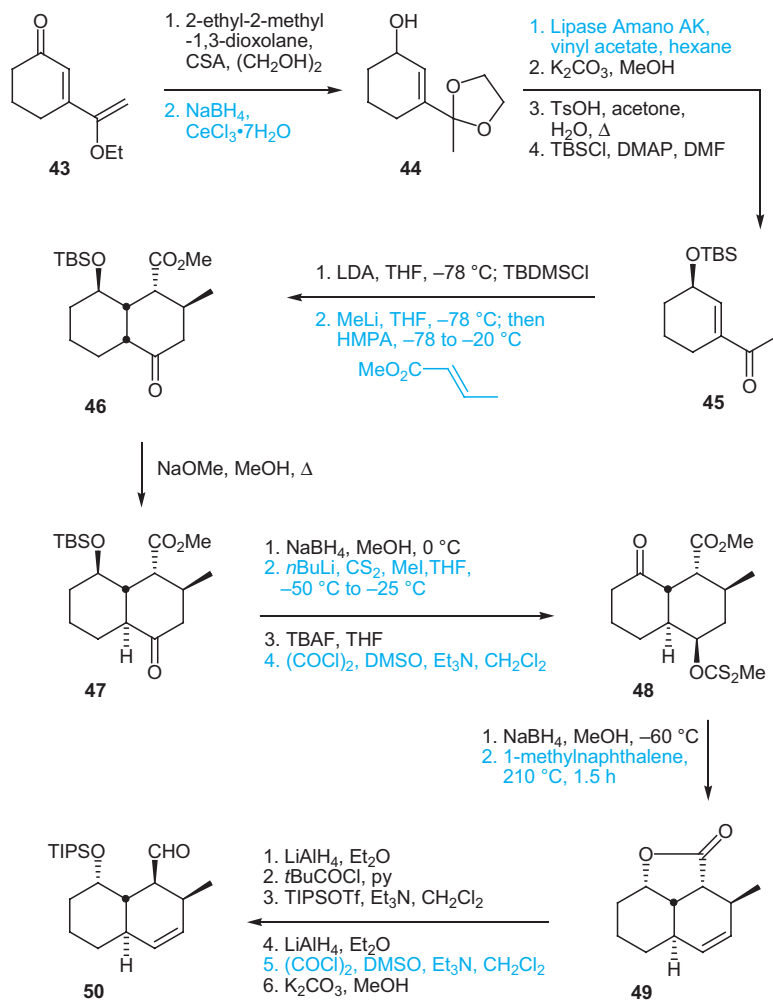
Grieco's strategy called for functionalization of the allylic sulfide via its sulfoxide **38** by an S_N2' displacement; however, on oxidation of this material with *m*CPBA a 2,3-sigmatropic rearrangement occurred to provide the sulfenate **39**. This necessitated an alternative plan for the introduction of the secondary methyl group. The sulfenate was converted to the allylic alcohol with trimethylphosphite, the alcohol subjected to Mitsunobu inversion and the product hydrolyzed to the allylic alcohol **40**.

The next sequence of steps constitutes a unique solution to several issues. First, the alcohol was converted to its acetate and treated with lithium dimethyl cuprate, which generated exclusively the S_N2 product, probably because of the hindrance of approach to the S_N2' site from the bicycloheptane moiety. Reduction of the ester and conversion of the alcohol to its potassium alkoxide led to the fragmentation of the bridge and the formation of the oxetane ring in **41**. The initial displacement of the ether bridge also generated the secondary alcohol center in **42** with the correct relative stereochemistry. The overall yield of this process was 40%. Esterification and final adjustments of the side chain, which included Fetizon oxidation to the lactone and demethylation of the ether with BBr_3 , provided compactin in a total of 31 steps [Note 1].

Hagiwara (1995) [12]. This asymmetric approach is interesting as it exemplifies, in its initial steps, the efficiency of Hagiwara's tandem Michael reaction methodology. The primary Michael donor synthon, enone **45**, was prepared in an optically pure form in six steps from enol ether **43** via enzymatic resolution of the allylic alcohol **44**, as shown in Scheme 3.8-4. The lipase-catalyzed acetylation was performed on a 20 gram scale. The method was superior to catalytic asymmetric reduction methods or chemical resolution; asymmetric reduction with Corey's oxazaborolidine complex [13] gave poor results, and resolution via host–guest complexation was not amenable to large scale.

Enone **45** was converted first to its kinetic enolate, which was protected with *tert*-butyldimethylsilyl chloride and from which the enolate anion was regioselectively regenerated with methyl-lithium. When methyl crotonate was added to the solution of this enolate anion, a double Michael sequence ensued providing in 96% yield the *cis*-fused decalone **46** containing five contiguous chiral centers. It was accompanied by the *trans* isomer **47** as a minor product. Treatment of this mixture with sodium methoxide in methanol furnished 91% yield of *trans* decalone **47**, surprisingly without the isomerization of the axial methyl ester. The efficiency of the Michael cascade is noteworthy as it establishes all the key centers in the compactin nucleus.

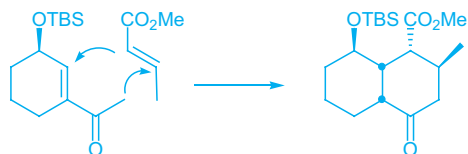
After the ketone in **47** was converted to xanthate **48**, the stereochemistry of the resulting secondary hydroxyl group was adjusted by an oxidation–reduction sequence. Note that both carbonyl groups were reduced stereoselectively from the less hindered face to give axial alcohols and that the intermediate diol ester generated during the reduction to the lactone cyclized on warming to room temperature. Thermolysis of the xanthate at 210 °C generated olefinic lactone **49** in 73% yield. The lactone was reduced and the primary alcohol protected as its pivaloyl ester to allow for a more secure protection of the secondary hydroxyl with a TIPS group. Reduction of the pivaloate was



Key Tactics

- Luche reduction
- enzymatic resolution
- sequential Michael addition
- xanthate synthesis
- Swern oxidation
- xanthate pyrolysis

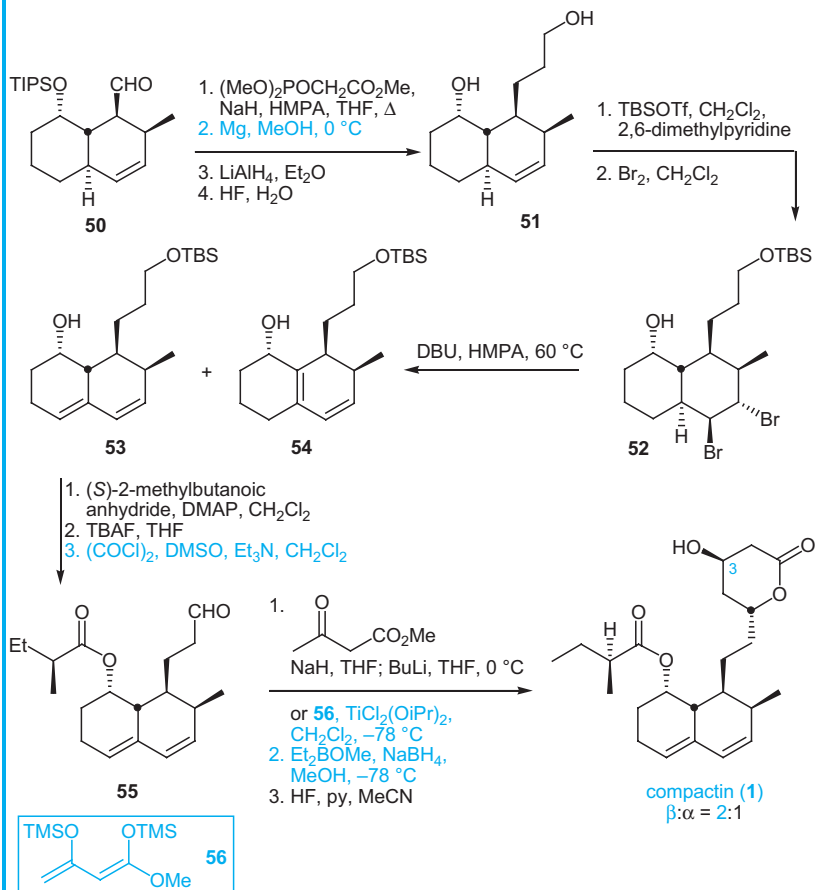
Key strategy: tandem Michael reaction



Scheme 3.8-4 Hagiwara (1995)

Key Tactics

- reduction of acrylates with Mg/MeOH

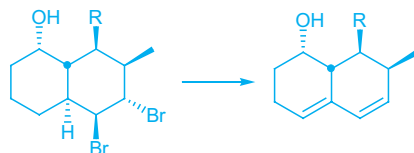


- Swern oxidation

- keto ester alkylation

- directed hydroxy ketone reduction

Key strategy: regioselective diene generation



Scheme 3.8-4 Hagiwara (1995), continued

followed by Swern oxidation and isomerization of the aldehyde to the more stable equatorial position in **50**, in which all of the chiral centers in the decalin portion of the target are correctly set.

The aldehyde was homologated to the primary alcohol in **51** by a sequence consisting of a Horner–Emmons–Wittig reaction, reduction of the acrylate with magnesium in methanol, followed by the reduction of the ester and deprotection of the silyl group to provide diol **51**. After the primary alcohol was reprotected, the olefin was subjected to a bromination–dehydrobromination sequence via dibromide **52**, in analogy with the Funk synthesis [8] with one major difference. The DBU elimination gave the required diene **53** in 70% yield but, unlike in the Funk’s case, provided a different

endocyclic diene, namely **54**, in 14% yield. This diene is a product of the alternative 1,4 anti elimination of HBr, unlike Funk's minor isomer, which results from a cis elimination.

To complete the synthesis the secondary alcohol was esterified with the chiral butanoate fragment and the side chain oxidation state adjusted to that of an aldehyde prior to the final steps, which required the introduction of the lactone portion of compactin. Hagiwara followed Sih's strategy by condensing the dianion of methyl acetoacetate with the aldehyde or by performing the acid-catalyzed equivalent of this reaction on the bis(trimethylsilyl) enol ether **56**. The condensation produced an inseparable mixture of hydroxy ketones, which were reduced with syn selectivity to diols by hydroxyl-directed reduction. The diols proved difficult to separate but separation could be effected after the HF-induced lactonization, which produced compactin and its C-3 epimer in a ratio of 2:1.

The synthesis required 34 steps and, like other approaches that involved a linear construction of the hydroxy lactone moiety, was not stereoselective. The key issues of compactin synthesis or the synthesis of its derivatives clearly reside in the manner in which the side chain is introduced into the target. Of the approaches discussed here, only that of Grieco, which was convergent, proceeded with complete control of stereochemistry at all stages.

Other notable syntheses of compactin accomplished in the last 15 years include those of Burke (1991) [14], who constructed compactin in an asymmetric fashion by a cationic vinylsilane cyclization. In 1989 Danishefsky used a variant of the Claisen rearrangement to construct the core of compactin and a Diels–Alder reaction between an aldehyde and the Danishefsky diene to establish the lactone unit [15]. Clive prepared both compactin and mevinolin (**3**) in 1988 by an approach that used a modification of the McMurry coupling between an aldehyde and a ketone performed in an intramolecular fashion [16]. Kozikowski used a nitron addition as a 1,3-diene equivalent in a key step in his 1987 synthesis of compactin [17]. Keck's 1986 synthesis of (+)-compactin featured an intramolecular Diels–Alder reaction of a vinyl allene [18], and Heathcock developed a route to compactin and several analogs in 1985 [19] [Note 2]. A biological route to compactin has been reported; *Penicillium cyclopium* produced 23 grams in 50 days of operation in a bioreactor [20].

Notes

1. [Personal recollection: Paul Grieco] Our approach to compactin, wherein a rigid 7-oxabicyclo[2.2.1]heptene carboxylate was employed as a dienophile, was an extension of our earlier work on psuedoguaianolides. Needless to say, problems arose at every turn despite the simplicity of the strategy on paper. A particularly difficult problem surfaced in the next to the last step wherein the *O*-methyl ether on the lactone ring had to be cleaved. Being unsuccessful in early attempts employing boron tribromide and with backup material being in very short supply, we sought to find a source of natural compactin so that we could methylate the natural material and develop a protocol for converting *O*-methyl compactin into compactin.

I became aware that Professor E. H. Goh of the Department of Pharmacology at Indiana University had some compactin, so I phoned him and asked him if he could spare 10 milligrams. He said no problem and within a few minutes, on his way to lunch, he stopped by the office with his brown bag lunch. Astonished, he handed me his "brown bag lunch" and said here is your compactin. The bag contained 10 grams of compactin. My response to him was, "All we need is a few milligrams to work out the methylation and demethylation of compactin. I said 10 milligrams, not 10 grams!" His response was, "It's all yours. I have no need for it." After his departure I went into the lab with the "brown lunch bag" and presented it to my students. They were as shocked as I had been upon meeting Professor Goh.

With this material Bob Zelle and Randy Lis, both graduate students, proceeded to develop a protocol for methylating the natural material so as to be able to have sufficient *O*-methyl compactin to probe the demethylation. The methylation of compactin proved not to be a trivial task, and an old procedure from the prostaglandin literature employing silica gel and gaseous diazomethane was employed to prepare the methylated compactin. Demethylation was finally accomplished, albeit in only 31% yield, but synthetic compactin was finally in hand. Once again, dedication, hard work, expertise in the laboratory and knowledge of the chemical literature paid off. I also need to acknowledge the work of Dr. John Finn.

2. [Personal recollection: Clayton Heathcock] I first saw the structure of compactin in the summer of 1981 when I was perusing the literature looking for good projects for the new crop of graduate students who were scheduled to arrive in August of that year. Somewhere I happened to run across the 1979 paper in *J. Biol. Chem.* by Brown and Goldstein on the effect of compactin (ML-236B) on cholesterol levels in rats and I knew I had one of my new projects for that fall. I offered the project to all the students I interviewed that fall and two fell in love with it – Terry Rosen and Scott Hecker. Fortunately, by then I had also found the 1980 Merck paper on mevinoxin in *PNAS*. Since I had two rather different ideas on how to approach the mevinoxin acid skeleton, I asked Terry to take up the compactin project by one approach and Scott to tackle the mevinoxin project by the other. Terry and Scott were two really talented experimentalists and they executed the syntheses adroitly. We published the synthesis of compactin in 1985 and of dihydromevinoxin in 1986.

The compactin paper was submitted to *JACS* as a communication, in spite of the fact that several total syntheses of the compound had already been published. The two reviewers returned a split decision and the manuscript was rejected. The negative reviewer said:

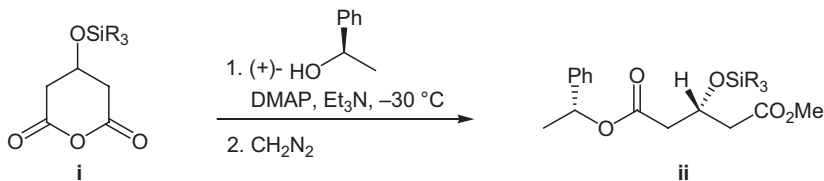
“A considerable interest in the chemical and biological properties of compactin in recent years has resulted in several papers in connection with the total synthesis of this compound as well as its lactone and hexahydronaphthalene portions of the molecule. The present paper also describes such an undertaking – an area which now, in my opinion, lacks the element of urgency”.

I appealed to the Editor for reconsideration, as follows: “This is not just another natural product synthesis. As I explain in the introductory paragraph, substances that might be used to regulate *de novo* cholesterol synthesis are of enormous potential importance, both to medicine and to biochemistry. In fact, the impact on society of an effective hypocholesterolemic drug would be far greater than any other known pharmaceutical in human history – greater than penicillin, tagamet, or even valium. Compactin is an exceedingly potent inhibitor of the key enzyme in cholesterol biosynthesis. Clinical trials carried out in Japan have already demonstrated that it is effective in lowering plasma cholesterol levels in humans. However, as is usually the case with new leads, there are problems of long term toxicity, and it is doubtful that compactin itself could be used as a prophylactic drug. Thus, synthetic investigations in the field are still very important. I think that the mevinoxin acids are comparable to the prostaglandins or leukotrienes in their general overall importance. How many *JACS* communications have we had on prostaglandin or leukotriene syntheses?”

“As we point out in the paper, Terry Rosen and I think that our synthetic route to compactin has an element of efficiency and generality that is lacking in prior syntheses. We acknowledge that ours is not the *first* synthesis. However, I think that the attitude that ‘this is not the first compactin synthesis, so it is somehow not important enough for a *JACS* communication’ is symptomatic of what is wrong with organic synthesis these days. It is not whether something is first that is important, but whether it is good science and whether it is likely to be of immediate use to a sizeable segment of the readership. I am convinced that

the disclosures of this manuscript *will* be of interest to the many industrial chemists who are working on the synthesis of mevinic acid analogs.

“Furthermore, our synthesis embodies new synthetic methodology of obvious general utility. The surprisingly high stereoselectivity in reaction of the prochiral anhydride **i** with phenethyl alcohol makes available the useful chiron **ii** and its enantiomer. We have called specific attention to this new methodology in the revised manuscript”.



This argument was sufficient to convince a third reviewer, who recommended publication and the manuscript was accepted. My predictions were largely borne out – our *JACS* communication, even though reporting the sixth total synthesis of the natural product – was cited 35 times in the next five years and more than 70 times to date, far more than the average for *JACS* publications. Furthermore, the mevinic acids *have* become the most important pharmaceuticals, with total sales of more than \$10 billion per year. Indeed, even I take my Lipitor pill every morning with my toast and coffee.

Terry Rosen and Scott Hecker went on to successful careers in the pharmaceutical industry. After brief stints at Abbott and Pfizer, Terry returned to California to work for Tularik, where he is now Vice President in charge of Medicinal Chemistry. Scott began his career at Pfizer and then he, too, returned to California to work for a startup company named Microcide. He soon became Director of Medicinal Chemistry. The company subsequently underwent a merger and is now named Essential Therapeutics; Scott is Vice President, Medicinal Chemistry & Natural Products.

Bibliography: Synthesis of Compactin

1981

- Wang, N. Y., Hsu, C. T., Sih, C. J., Total synthesis of (+)-**compactin** (ML-236B). *J. Am. Chem. Soc.* **1981**, *103*, 6538–6539.

1982

- Deutsch, E. A., Snider, B. B., Synthesis of the hexahydronaphthalene moiety of (\pm)-**compactin** (ML-236B), *J. Org. Chem.* **1982**, *47*, 2682–2684.
- Heathcock, C. H., Taschner, M. J., Rosen, T., Thomas, J. A., Hadley, C. R., Popjak, G., Synthesis and biological activity of the hexalin moiety of **compactin** (ML-236B), *Tetrahedron Lett.* **1982**, *23*, 4747–4750.
- Girotra, N. N., Wendler, N. L., The total synthesis of (\pm)-**compactin** and its natural (+)-enantiomer, *Tetrahedron Lett.* **1982**, *23*, 5501–5504.

1983

- Anderson, P. C., Clive, D. L. J., Evans, C. F., Synthetic studies related to compactin and mevino-
lin: a new synthesis of the hexahydronaphthalene portion of **compactin**, *Tetrahedron Lett.* **1983**, *24*, 1373–1376.

- Grieco, P. A., Zelle, R. E., Lis, R., Finn, J., Total synthesis of the hypocholesterolemic agent (+)-**compactin**, *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404.
- Girotra, N. N., Wendler, N. L., A new route in the sequential total synthesis of **compactin**, *Tetrahedron Lett.* **1983**, *24*, 3687–3688.
- Hsu, C. T., Wang, N. Y., Latimer, L. H., Sih, C. J., Total synthesis of the hypocholesterolemic agent **compactin**, *J. Am. Chem. Soc.* **1983**, *105*, 593–601.

1984

- Funk, R. L., Mossman, C. J., Zeller, W. E., Hypocholesterolemic agent **compactin**. An alternative Diels-Alder strategy for the synthesis of the hexahydronaphthalene portion, *Tetrahedron Lett.* **1984**, *25*, 1655–1658.
- Girotra, N. N., Reamer, R. A., Wendler, N. L., An alternative synthetic route to **compactin** via a Michael-alkylation sequence, *Tetrahedron Lett.* **1984**, *25*, 5371–5372.
- Yang, Y. L., Manna, S., Falck, J. R., Total synthesis of (+)-**dihydrocompactin**, *J. Am. Chem. Soc.* **1984**, *106*, 3811–3814.

1985

- Burke, S. D., Saunders, J. O., Oplinger, J. A., Murtiashaw, C. W., Vinylsilane-mediated polyene cyclization. Synthesis of the octahydronaphthalenol portion of **dihydrocompactin**, *Tetrahedron Lett.* **1985**, *26*, 1131–1134.
- Rosen, T., Taschner, M. J., Thomas, J. A., Heathcock, C. H., Synthetic and biological studies of **compactin** and related compounds. 3. Synthesis of the hexalin portion of **compactin**, *J. Org. Chem.* **1985**, *50*, 1190–1201.
- Rosen, T., Heathcock, C. H., Synthetic and biological studies of compactin and related compounds. 4. Total synthesis of (+)-**compactin**, *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733.

1986

- Grieco, P. A., Lis, R., Zelle, R. E., Finn, J., Convergent, enantiospecific total synthesis of the hypocholesterolemic agent (+)-**compactin**, *J. Am. Chem. Soc.* **1986**, *108*, 5908–5919.
- Keck, G. E., Kachensky, D. F., A highly convergent total synthesis of (+)-**compactin**, *J. Org. Chem.* **1986**, *51*, 2487–2493.

1987

- Kozikowski, A. P., Li, C. S., The isoxazoline route to the hypocholesterolemic agent **compactin**: Use of the isoxazoline as a 1,3-diene equivalent, *J. Org. Chem.* **1987**, *52*, 3541–3552.

1988

- Clive, D. L. J., Murthy, K. S. K., Wee, A. G. H., Prasad, J. S., Da Silva, G. V. J., Majewski, M., Anderson, P. C., Haugen, R. D., Heerze, L. D., Total synthesis of both (+)-**compactin** and (+)-**mevinolin**. A general strategy based on the use of a special TiCl₃/C8K mixture for dicarbonyl coupling, *J. Am. Chem. Soc.* **1988**, *110*, 6914–6916.

1989

- Danishefsky, S. J., Simoneau, B., Total syntheses of ML-236A and **compactin** by combining the lactonic (silyl) enolate rearrangement and aldehyde-diene cyclocondensation technologies, *J. Am. Chem. Soc.* **1989**, *111*, 2599–2604.

1990

- Clive, D. L. J., Murthy, K. S. K., Wee, A. G. H., Prasad, J. S., da Silva, G. V. J., Majewski, M., Anderson, P. C., Evans, C. F., Haugen, R. D., Heerze, L. D., Barrie, J. R., Total synthesis of both (+)-**compactin** and (+)-**mevinolin**. A general strategy based on the use of a special titanium reagent for dicarbonyl coupling, *J. Am. Chem. Soc.* **1990**, *112*, 3018–3028.
- Daniewski, A. R., Uskokovic, M. R., **Compactin** from Hajos (–)-enedione, *Tetrahedron Lett.* **1990**, *31*, 5599–5602; *Bull. Soc. Chim.* **1990**, 849–856.

1991

- Burke, S. D., Deaton, D. N., Synthesis of (+)-dihydrocompactin and (+)-**compactin** via vinylsilane terminated cationic cyclization, *Tetrahedron Lett.* **1991**, *32*, 4651–4654.

1992

- Hagiwara, H., Konno, M., Uda, H., Total synthesis of (+)-**dihydrocompactin**, *J. Chem. Soc., Chem. Commun.* **1992**, 866–868.

1993

- Hung, S.-C., Liao, C.-C., A formal synthesis of (±)-**compactin**, *J. Chem. Soc., Chem. Commun.* **1993**, 1457–1458.

1994

- Barco, A., Benetti, S., Bianchi, A., Casolari, A., Pollini, G. P., Romagnoli, R., Spalluto, G., Zanirato, V., Enantioselective synthesis of the hexahydronaphthalene nucleus of (–)-**compactin** from ethyl (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylate and 2-(3-nitropropyl)-1,3-dioxolane as four carbon bifunctional annelating agent, *Tetrahedron* **1994**, *50*, 11743–11754.
- Hagiwara, H., Kon-no, M., Nakano, T., Uda, H., Total synthesis of (+)-**dihydrocompactin**, *J. Chem. Soc., Perkin Trans 1* **1994**, 2417–2430.
- Hung, S.-C., Liao, C.-C., Diels–Alder reactions and synthetic application of 8-trimethylsilyloxy-1,4-dioxaspiro[4.5]deca-6,8-diene. A formal synthesis of (±)-**compactin**, *J. Chinese Chem. Soc. (Taipei)* **1994**, *41*, 817–828.

1995

- Hagiwara, H., Nakano, T., Kon-no, M., Uda, H., Total synthesis of (+)-**compactin** by a double Michael protocol, *J. Chem. Soc., Perkin Trans. 1* **1995**, 777–783.

1996

- Bauer, T., Chapuis, C., Jezewski, A., Kozak, J., Jurczak, J., Stereochemical course of the [4+2] cycloaddition of 1-methoxybuta-1,3-diene to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam. The formal synthesis of **compactin** and **mevinolin**, *Tetrahedron: Asymm.* **1996**, *7*, 1391–1404.

2006

- Robichaud, J., Tremblay, F., Formal enantioselective synthesis of (+)-**compactin**, *Org. Lett.* **2006**, *8*, 597–600.

References

- 1 (a) Endo, A., Kuroda, M., Tanzawa, K., *FEBS Lett.* **1976**, *72*, 323–326; (b) Endo, A., Kuroda, M., Tsujita, Y., *J. Antibiot.* **1976**, *29*, 1346–1348; (c) Endo, A., Tanzawa, K., *Eur. J. Biochem.* **1979**, *98*, 195–201; (d) Brown, M. S., Faust, J. R., Goldstein, J. L., *J. Biol. Chem.* **1978**, *253*, 1121–1128.
- 2 Rodwell, V. W., Nordstrom, J. L., Mitschelen, J. J., *Adv. Lipid Res.* **1976**, *14*, 1–74.
- 3 Brown, A. G., Smale, T. C., King, T. J., Hassenkamp, R., Thompson, R. H., *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–1170.
- 4 Alberts, A. W., Chen, J., Kuron, G., Hunt, V., Huff, J., Hoffman, C., Rothrock, J., Lopez, M., Joshua, H., Harris, E., Patchett, A., Monaghan, R., Currie, S., Stapley, E., Albers-Sconberg, G., Hensons, O., Hirschfield, J., Hoogsten, K., Liesch, J., Springer, J., *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 3957–3961.
- 5 Forskolin total syntheses: (a) Ziegler, F. E., Jaynes, B. H., Saindane, M. T., *J. Am. Chem. Soc.* **1987**, *109*, 8115–8116; (b) Corey, E. J., Da Silva J. P., *Tetrahedron Lett.* **1989**, *30*, 7297–7300; (c) Corey, E. J., Da Silva, J. P., Rohloff, J. C., *J. Am. Chem. Soc.* **1988**, *110*, 3672–3673; (d) Ziegler, F. E., Jaynes, B. H., *Tetrahedron Lett.* **1988**, *29*, 2031–2032; (e) Hashimoto, S., Sakata, S., Sonogawa, M., Ikegami, S., *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672; (f) Delpech, B., Calvo, D., Lett, R., *Tetrahedron Lett.* **1996**, *37*, 1015–1018, 1019–1022. For partial syntheses see: Leclaire, M., Levet, R., Ferreira, F., Ducrot, P.-H., Lallemand, J.-Y., Ricard, L., *J. Chem. Soc., Chem. Commun.* **2000**, 1737, and references therein.
- 6 For reviews of synthetic efforts toward compactin, see: (a) Yadav, V. K., Kapoor, K. K., *Indian J. Chem. B* **1996**, *35*, 1125–1143; (b) Hiyama, T., *Pure Appl. Chem.* **1996**, *68*, 609–612; (c) Clive, D. L. J., Murthy, K. S. K., Wee, A. G. H., Prasad, J. S., da Silva, G. V. J., Majewski, M., Anderson, P. C., in *Studies in Natural Products Chemistry: Stereoselective Synthesis (Part G)*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1992, Vol. 11, pp. 335–377; (d) Rosen, T., Heathcock, C. H., *Tetrahedron* **1986**, *42*, 4909–4951.
- 7 Wang, N.-Y., Hsu, C.-T., Sih, C. J., *J. Am. Chem. Soc.* **1981**, *103*, 6538–6539.
- 8 (a) Funk, R. L., Zeller, W. E., *J. Org. Chem.* **1982**, *47*, 180–182; (b) Funk, R. L., Mossman, C. J., Zeller, W. E., *Tetrahedron Lett.* **1984**, *25*, 1655–1658.
- 9 Grieco, P. A., Zelle, R. E., Lis, R., Finn, J., *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404.
- 10 Just, G., Martel, A., *Tetrahedron Lett.* **1973**, *14*, 1517–1520.
- 11 Corey, E. J., Weigel, L. O., Chamberlin, A. R., Lipshutz, B., *J. Am. Chem. Soc.* **1980**, *102*, 1439–1441.
- 12 Hagiwara, H., Nakano, T., Kon-no, M., Uda, H., *J. Chem. Soc., Perkin Trans. 1* **1995**, 777–783.
- 13 Corey, E. J., Bakshi, R. K., Shibata, S., Chen, C.-P., Singh, V. K., *J. Am. Chem. Soc.* **1987**, *109*, 7925–7426.
- 14 Burke, S. D., Deaton, D. N., *Tetrahedron Lett.* **1991**, *32*, 4651–4654.
- 15 Danishefsky, S. J., Simoneau, B., *J. Am. Chem. Soc.* **1989**, *111*, 2599–2604.
- 16 (a) Clive, D. L. J., Murthy, K. S. K., Wee, A. G. H., Prasad, J. S., da Silva, G. V. J., Majewski, M., Anderson, P. C., Haugen, R. D., Heerze, L. D., *J. Am. Chem. Soc.* **1988**, *110*, 6914–6916; (b) Clive, D. L. J., Murthy, K. S. K., Wee, A. G. H., Prasad, J. S., da Silva, G. V. J., Majewski, M., Anderson, P. C., Evans, C. F., Haugen, R. D., Heerze, L. D., Barrie, J. R., *J. Am. Chem. Soc.* **1990**, *112*, 3018–3028.
- 17 Kozikowski, A. P., L., C.-S., *J. Org. Chem.* **1987**, *52*, 3541–3552.
- 18 Keck, G. E., Kachensky, D. F., *J. Org. Chem.* **1986**, *51*, 2487–2493.
- 19 (a) Rosen, T., Heathcock, C. H., *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733; (b) Heathcock, C. H., Hadley, C. R., Rosen, T., Theisen, P. D., Hecker, S. J., *J. Med. Chem.* **1987**, *30*, 1858–1873.
- 20 Bazaraa, W. A., Hamdy, M. K., Toledo, R., *J. Industr. Microbiol. Biotech.* **1998**, *21*, 192–202.