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Fifteen years of biological and synthetic studies of decarestrictine family

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1. Introduction

Decanolides have attracted special attention over the last years[1–3] and an important class of compounds is the decarestrictine family. The decarestrictines are secondary metabolites that were isolated from various *Penicillium* strains and identified as bioactive compounds by chemical screening.[4–6] Among them, several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol.[4,6]

It is worthy of note that maintenance of cholesterol blood level is of considerable interest for the control of coronary diseases, which are responsible for about 40% of morbidity in developed countries. Efficient drugs are now in the market and most of these compounds, known as statines or mevinic acids, are more or less related to a family of lactonic compounds derived from the lead compounds pravastatin and mevinolin (Fig. 1).[7] The structural difference between decarestrictines and these well-known cholesterol inhibitors suggests another mode of action to be operative. In addition, decarestrictines exhibit no other effects such as antibacterial or antifungal activities. Taking together their strong and selective biological profile, decarestrictines are attractive compounds for developing a new class of cholesterol-lowering drugs.

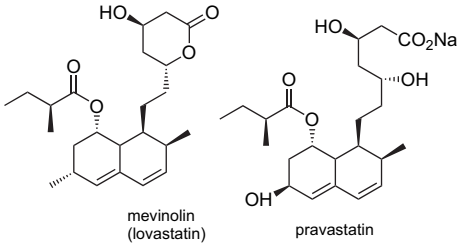

Figure 1. Commercial drugs used for lowering cholesterol level in the blood.

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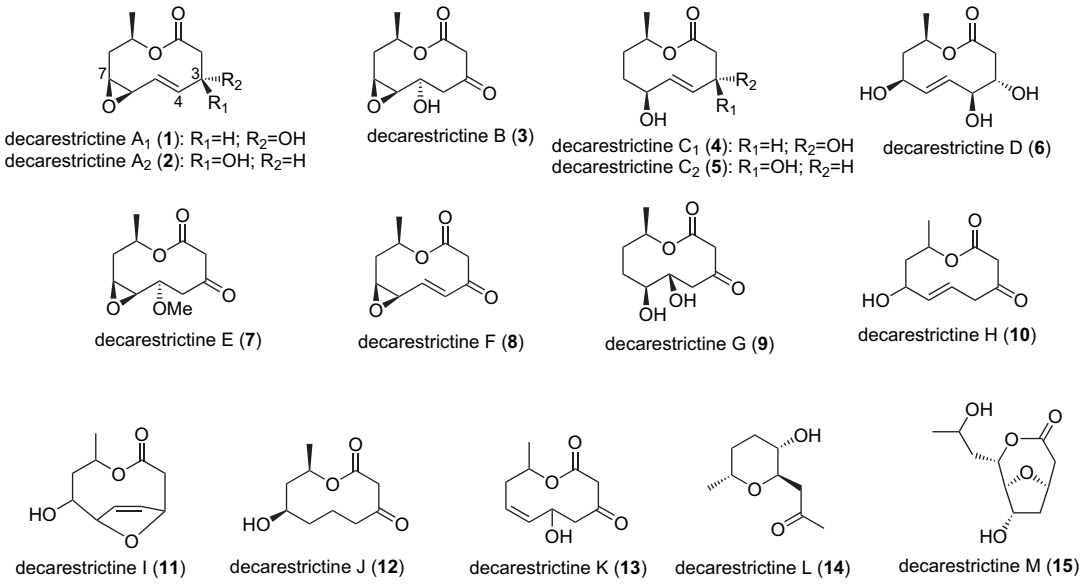


Figure 2. Structure of decarestrictine family of natural products.

2. Isolation and structural features

Decarestrictines A–D (A_1 (**1**), A_2 (**2**), B (**3**), C_1 (**4**), C_2 (**5**), D (**6**)—Fig. 2) are secondary metabolites that were isolated from different strains of *Penicillium simplicissimum* and *Penicillium corylophilum*.[4] Independently, decarestrictine D (**6**) was isolated from the Canadian tuckahoe fungi *Polyporous tuberaster*[8] and named as tuckolide. They are readily soluble in methanol, ethyl acetate or chloroform, but insoluble in water or *n*-hexane. With the exception of the crystalline decarestrictine D (**6**), most of the decarestrictines appear to be colorless oils. The structural elucidation of these fungal metabolites is based mainly on 1D and 2D NMR spectroscopy and additional information concerning the stereochemistry was obtained by X-ray analysis.[5] The absolute stereochemistry of decarestrictine B (**3**) was established by X-ray diffraction analysis of the crystalline bromobenzoate derivative. Decarestrictine A and decarestrictine C seemed to be homogeneous on TLC, however, their ^{1}H NMR spectra revealed that both decarestrictines actually consist of two components: A_1 and A_2 (**1** and **2**), and C_1 and C_2 (**4** and **5**) in 3:1 and 1:1 ratios, respectively. The structural elucidation of both components of each diastereomeric mixture was possible because of the well separated signal patterns in their ^{1}H NMR spectra, and the absolute stereochemistries were tentatively proposed. In contrast to A and C, decarestrictine D (**6**) is homogeneous. It is the most polar component among the decarestrictines due to three hydroxyl groups. Its relative stereochemistry was provided by X-ray analysis.

Subsequent research by the same group on cultures of *P. simplicissimum* led to the further discovery of decarestrictines E–M (**7**–**15**—Fig. 2) as minor components of this class of fungal metabolites.[6]

The decarestrictines E–K (**7**–**13**) and A–D (**1**–**6**) exhibit the typical structural elements of these fungal metabolites: (i) 10-membered lactone ring, (ii) exocyclic methyl group, and (iii) additional variations in the oxygenation pattern ranging from C-3 to C-7. Seven components (**1**, **2**, **4**–**6**, **8** and **10**) display *E*- and two (**11** and **13**) *Z*-configured double bonds. It is remarkable that decarestrictine I (**11**) possesses a bicyclic ring system in which the 10-membered lactone is bridged forming an ether linkage between C-3 and C-6. With the exception of decarestrictines H, I, and K (**10**, **11**, and **13**), the relative configurations were determined from NMR data.

Lack of the 10-membered lactone ring was observed for the remaining decarestrictines L (**14**) and M (**15**). As the biosynthetic pathways leading to the decarestrictine family start from a common decaketide precursor, decarestrictines L (**14**) and M (**15**) may be shunt products on the way to the 10-membered lactones.

More recently, Gloer and co-workers isolated decarestrictines A_1 (**1**) and I (**11**) as minor components from an organic extract from solid-substrate fermentations of the mycoparasitic fungus *Humicola fuscoatra* NRRL 22980, originally isolated as a colonist of *Aspergillus flavus* sclerotia.[9] They were identified by comparison of their data with literature values.[5,6]

Rukachaisirikul and co-workers isolated three new 10-membered macrolides (**16**–**18**—Fig. 3) from the entomopathogenic fungus *Cordyceps militaris* BCC 2816.[10] Compound **16** had the structural elucidation based mainly on 1D and 2D NMR spectroscopies and the relative stereochemistry was confirmed by X-ray crystallographic analysis. This macrolide is

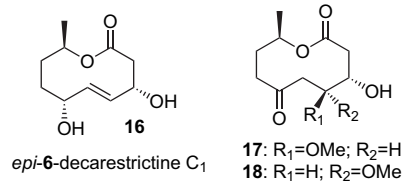


Figure 3. Three new 10-membered macrolides isolated by Rukachaisirikul and co-workers.

closely related to decarestrictine C_1 (**4**), differing only in the configuration at C-6. The structural elucidation and the relative configurations of **17** and **18** were determined form NMR spectroscopy data. These compounds exhibit the typical structural elements of decarestrictine family and are C-4 epimers, but compound **18** was assigned by similarity of NMR data as a C4 *O*-methoxy cepharosporolide C,[11] while **17** as its C4 *O*-methoxy epimer.

3. Biosynthesis

Biosynthetic studies on the main metabolites, decarestrictines B (**3**) and D (**6**), revealed that the carbon skeleton of 10-membered lactones derives from an acetate polyketide starter unit (C-10/C-9), which is subsequently elongated by four malonate building blocks via the polyketide pathway (Fig. 4).[12] The unusual oxygenation pattern was investigated by feeding experiments with sodium [1−^{13}C, $^{18}O_2$]acetate resulting in ^{18}O-incorporation into the lactone moiety at C-1 and C-3 in both, decarestrictines B (**3**) and D (**6**). A fermentation performed under an $^{18}O_2$-enriched atmosphere indicated that the oxygen atoms of the oxirane ring in **3** as well as the oxygen at C-7 in **6** are introduced via oxygenase catalyzed steps. The whole family of decarestrictines seems to arise from a common pentaketide precursor, which is formed by a single polyketide synthetase performing reduction, dehydration, and finally lactonization steps. Subsequently, the proposed intermediate undergoes further post-polyketide modifications to result in the various members of the decarestrictine family.

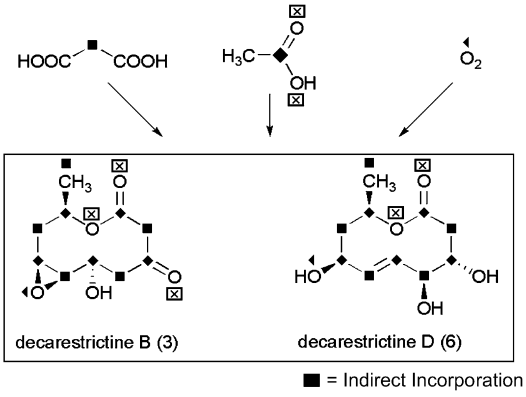


Figure 4. Biosynthesis of decarestrictines B (**3**) and D (**6**).

Besides subsequent enzymatically catalyzed reactions, an unexpected non-enzymatic conversion was found to be the key step in the biosynthetic sequence leading to decarestrictine D (**6**).[13] Under acidic conditions during fermentation, decarestrictines A_1 and A_2 (**1** and **2**) are converted mainly to decarestrictine D (**6**), as the major product, and the new decarestrictines N (**19**) and O (**20**) (Fig. 5). In combination, the results from the analysis of the fermentation time course, the experiments with stable isotope-labeled precursors, the pH-static cultivations as well as non-enzymatic conversions of the different decarestrictines illustrate the biosynthetic relationships in the decarestrictine family, depicted in Figure 5.

These experiments illuminate new mechanistic aspects of polyketide synthase, showing that the oxidation level and stereochemistry of polyketide chains are adjusted prior to each step of chain elongation. Subsequent hydroxylations and methylation steps, as well as further modifications of the carbon skeleton or non-enzymatic reactions finally generate the bioactive metabolites.

4. Approaches to total synthesis

4.1. Decarestrictine L

The relative configuration of natural (+)-decarestrictine L was established by mass spectral data and extensive 2D

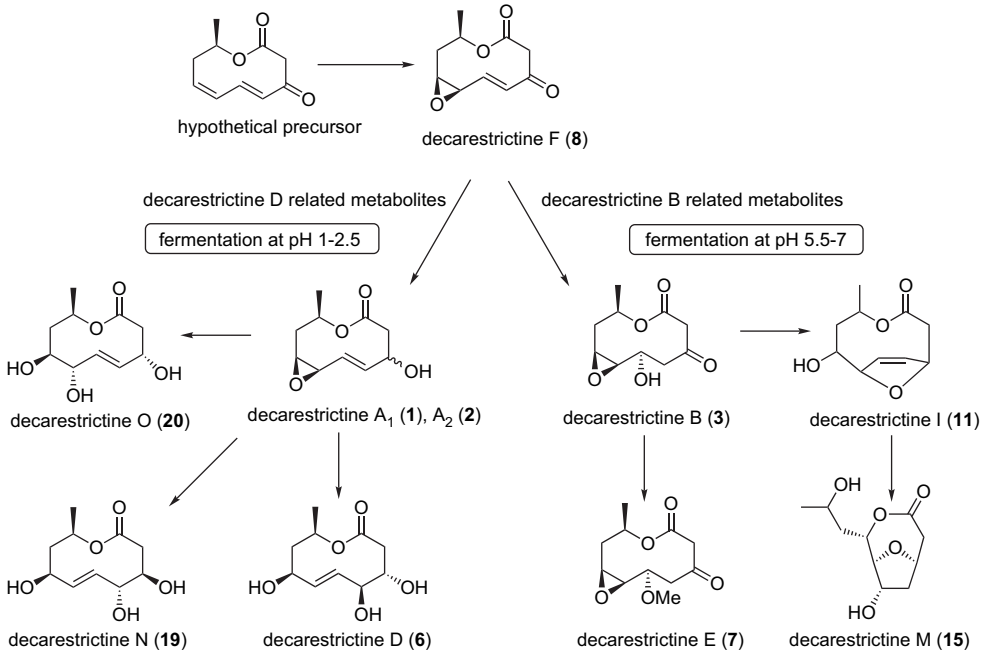


Figure 5. Biosynthetic relationships of the decarestrictine family.

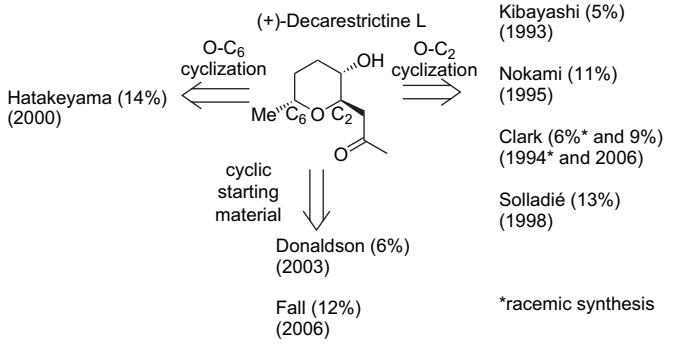
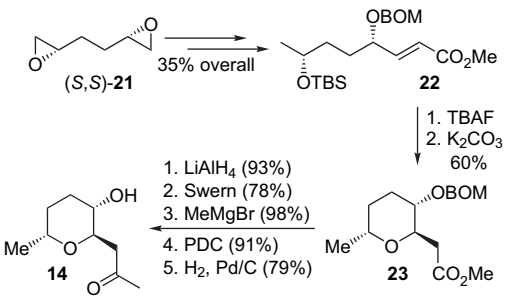


Figure 6. A comparison of main disconnections and yields in the total syntheses of (+)-decarestrictine L.

NMR analysis,[6] and its absolute configuration (+)-(2*R*,3*S*,6*R*) was later confirmed by Kibayashi,[14] who reported the first total synthesis of the natural isomer. The cholesterol inhibitory activity of **14** along with its low abundance continues to make it an appealing synthetic target. Eight total syntheses of decarestrictine L (**14**) can be found in the literature; here these examples are highlighted in order to demonstrate the diverse synthetic methodology that has flourished around **14** (Fig. 6).

The first and enantioselective synthesis reported by Kibayashi[14] stems from the previously known transformation of D-mannitol into 1,2:5,6-diepoxyhexane[15,16] and stereoselective formation of the tetrahydropyranyl nucleus through an intramolecular 1,4-conjugate addition[17] (Scheme 1). The ester **22** is the key intermediate in this approach and was prepared in 35% yield from (*S*,*S*)-diepoxide **21** according a route previously described.[18] Desilylation of **22** furnished the intramolecular 1,4-conjugate adducts in part, which was without isolation subjected to subsequent 1,4-addition under thermodynamically equilibrated conditions (K_2CO_3, THF, reflux, 12 h) to afford **23** in 60% overall yield with exclusive trans (with respect to C-2 and C-3) selectivity. However, when the conjugate addition was conducted for a short period of time (1 h), it resulted in a 1:1 mixture (60% yield) of *trans*:*cis* adducts. Sequential $LiAlH_4$ reduction and Swern oxidation led to the aldehyde derivative, which was then converted to the corresponding ketone by Grignard reaction with MeMgBr followed by PDC oxidation. Hydrogenolytic removal of the BOM protecting group furnished (+)-decarestrictine L (**14**) in 18 steps and 5% overall yield.

The high stereoselectivity observed in the 1,4-addition under thermodynamically equilibrated conditions was reasoned



Scheme 1. Final steps of the Kibayashi synthesis of decarestrictine L.

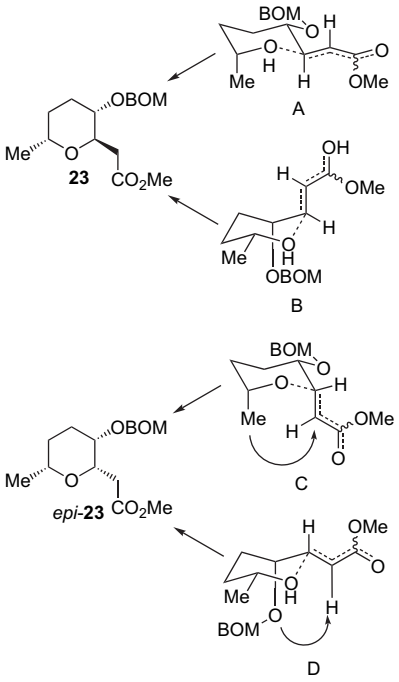
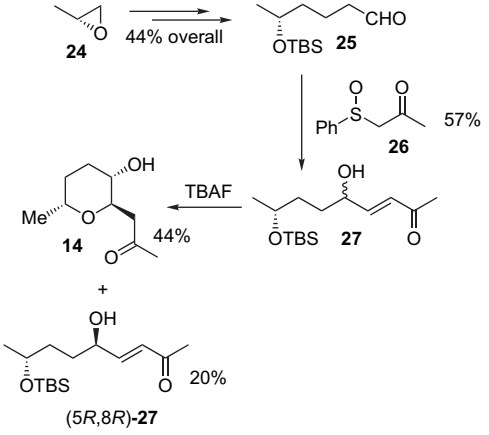


Figure 7. Transition states in the intramolecular 1,4-conjugate addition in the Kobayashi synthesis of decarestrictine L.

from an analysis of the possible chair-like transition states (Fig. 7). The transition states C and D leading to the undesired *cis* adduct *epi*-**23** are destabilized substantially by 1,3-diaxial interaction and 1,3-allylic strain, respectively. In the *trans*-predictive transition states A and B, the latter conformer B would be energetically less favorable since both the sterically larger substituents adopt axial orientation. Finally, the most favorable process would occur via the conformer A, thus providing predominantly the trans adduct **23**.

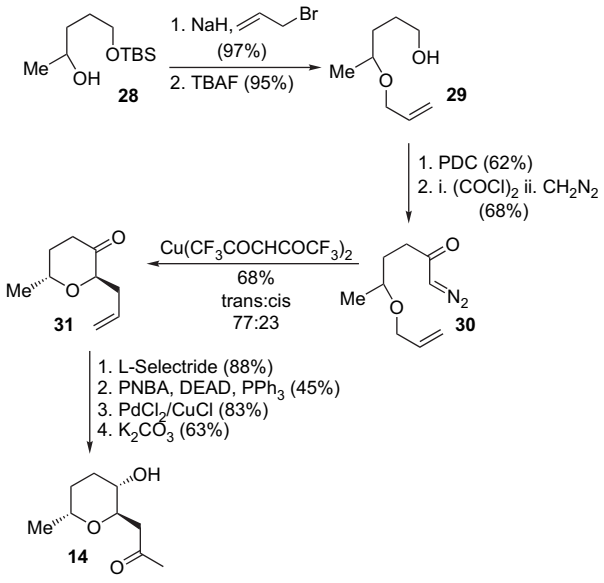
A short and efficient synthesis of **14** was proposed by Nokami and co-workers and was based on the similar cyclization strategy, via introduction of the methyl carbinol moiety from optically active propylene oxide (Scheme 2).[19] Starting with *R*-(+)-propylene oxide **24** and propargyl tetrahydropyranyl ether, *R*-5-*tert*-butyldimethylsilyloxyhexanal **25** was obtained by standard methods in five steps.[20] The aldehyde **25** was



Scheme 2. Nokami's synthesis of decarestrictine L.

treated with sulfoxide **26** in presence of diethylamine in acetonitrile to give **27** in 57% yield as a diastereomeric mixture (5*R*/5*S*=1:1). Desilylation of **27** furnished (+)-decarestrictine L (**14**) and the water soluble diol **27** in 44 and 20% yields, respectively. Although modest yield was obtained from **27** in the cyclization step, total synthesis of **14** was achieved in seven steps and 11% overall yield.

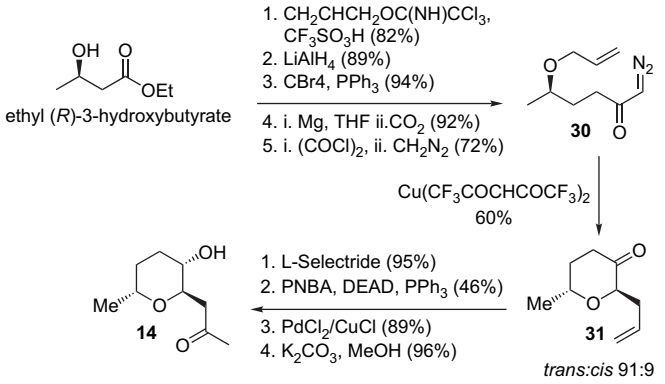
Clark and co-workers described a racemic synthesis of decarestrictine L (**14**).[21] The strategy used for the construction of the heterocyclic ring was based on a tandem intramolecular carbenoid insertion and ylide rearrangement reaction (Scheme 3).[22,23] This synthesis started with O-allylation of mono-



Scheme 3. Racemic synthesis of decarestrictine L by Clark *et al*.

protected diol **28** and deprotection of the primary hydroxyl group affording **29** in 92% yield. This alcohol was oxidized with PDC, the resulting carboxylic acid was converted to the corresponding acid chloride, and treatment of crude acid chloride with diazomethane gave the diazo ketone **30** (42% in three steps). Reaction of **30** with a catalytic amount of copper(II) hexafluoroacetylacetonate afforded the tetrahydropyran-3-one **31** in 68% yield as a chromatographically separable mixture of diastereoisomers (*trans*:*cis* 77:23). Reduction of **31** with L-Selectride® afforded the corresponding alcohol as a single diastereoisomer. Protection of the hydroxyl group as the *p*-nitrobenzoyl ester under Mitsunobu conditions proceeded with inversion of configuration at the 3-position.[24] The methylketone functionality was installed in high yield by palladium-catalyzed oxidation.[25] Finally, basic hydrolysis afforded (±)-decarestrictine L (**14**) in nine steps and 6% overall yield.

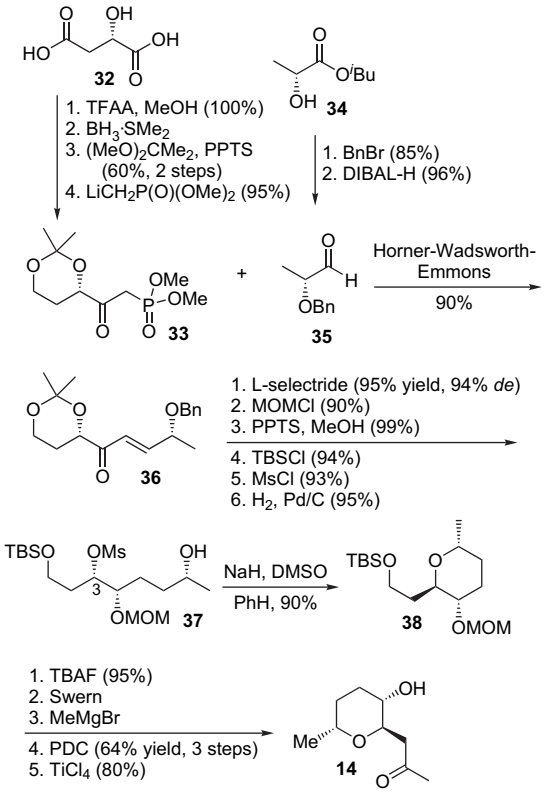
More recently, Clark and co-workers reported a stereoselective synthesis of (+)-decarestrictine L (**14**) from commercially available chiral pool material ethyl (*R*)-3-hydroxybutyrate (Scheme 4).[26] In this approach, they employed the same strategy used for the racemic synthesis.[21] Thus, O-allylation of ethyl (*R*)-3-hydroxybutyrate,[27] followed by $LiAlH_4$ ester reduction gave the corresponding alcohol. This alcohol was



Scheme 4. Non-racemic synthesis of decarestrictine L by Clark *et al*.

used to prepare the corresponding bromide by treatment with carbon tetrabromide and triphenylphosphine, which was converted into the corresponding Grignard reagent. Subsequent treatment with solid carbon dioxide delivered the carboxylic acid, which was converted to the corresponding acid chloride and treated with diazomethane to give the chiral diazo ketone **30** (45% in five steps), the same cyclization precursor of the racemic synthesis. The key ring-forming step was effected by treatment of the diazo ketone **30** with copper(II) trifluoroacetylacetonate.[28] Tandem catalytic carbenoid generation, ylide formation, and rearrangement delivered a mixture of the isomeric pyranones in 60% yield with the required diastereoisomer **31** as the major product. This condition employed in the cyclization step was decisive for the stereoselection and yield obtained. Diastereoisomeric reduction proved to be problematic and a variety of reducing agents were employed. However, use of L-Selectride® as the reducing agent allowed reduction to the desired diastereoisomer in 95% yield. The synthesis of (+)-decarestrictine L (**14**) was finalized via the same synthetic transformations performed in the racemic synthesis, allowing its production in 10 steps and 9% overall yield.

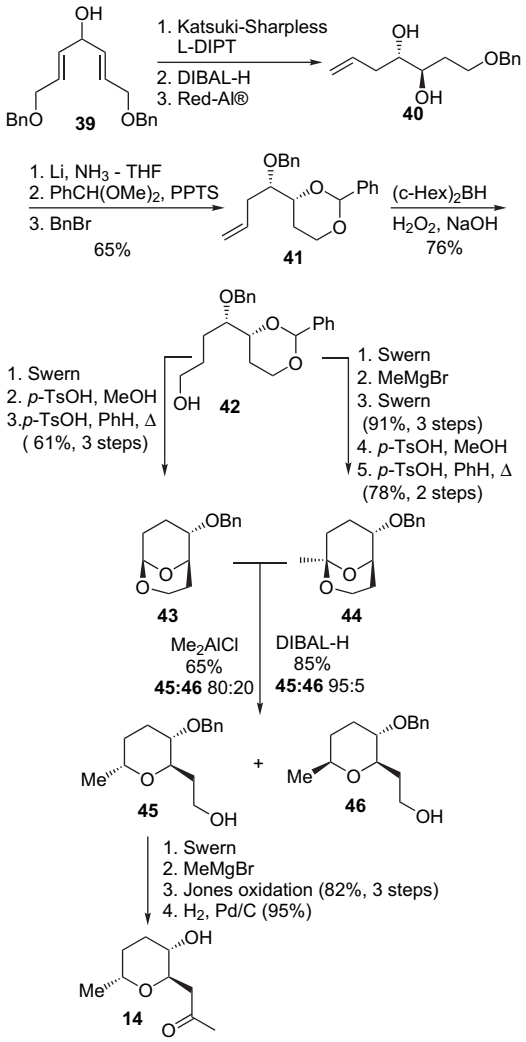
In 1998 Solladié and co-workers contributed with a new synthesis of decarestrictine L (**14**) through an intramolecular S_N2-type reaction allowing the stereocontrolled formation of the tetrahydropyranyl ring (Scheme 5).[29] Compound **33** was synthesized from (*S*)-malic acid (**32**) after monoesterification with MeOH,[30] reduction of the carboxylic acid function at low temperature (−15 °C) with borane dimethyl sulfide, protection of the resulting crude diol with dimethoxypropane in dimethylformamide, and reaction with lithium dimethyl methylphosphonate[31] to afford the intermediate β-ketophosphonate **33** in four steps and 57% overall yield. Aldehyde **35** was prepared from (*R*)-isobutyl lactate (**34**), after benzylation and DIBAL-H reduction of the ester group. The phosphonate **33** was then coupled with aldehyde **35** via a Horner–Wadsworth–Emmons olefination in 90% yield under controlled conditions (control of temperature and slow rate of addition). Treatment of **36** with L-Selectride® afforded a highly stereoselective reduction of the carbonyl group (*syn*/*anti*=97:3). This high stereoselectivity was explained on the basis of the Felkin-Anh model assuming a favored approach of the reducing



Scheme 5. Solladié's synthesis of decarestrictine L.

agent from the less hindered face in a conformation of **36** where the vicinal oxygen is perpendicular to the plane of the carbonyl group. Hydroxyl protection with MOMCl/DIPEA, cleavage of the acetonide with PPTS/MeOH, selective protection of the primary terminal OH with TBSCl/imidazole, and finally mesylation of the OH at C-3 introduced the adequate leaving group for the cyclization. These four steps occurred in 78% overall yield. Removal of benzyl protecting group was followed by cyclization of **35** with NaH in refluxing benzene.[32] This reaction gave the pyran ring **38** in 90% yield with complete inversion of configuration at C-3. Deprotection of the silylated group in **38**, and Swern oxidation led to the aldehyde derivative, which was then converted to the corresponding methylketone by Grignard reaction with MeMgBr and PDC oxidation. Deprotection of the MOM group with $TiCl_4$ in CH_2Cl_2 at 0 °C furnished (+)-decarestrictine L (**14**) in a convergent synthesis in 17 steps and very high overall yield (13%).

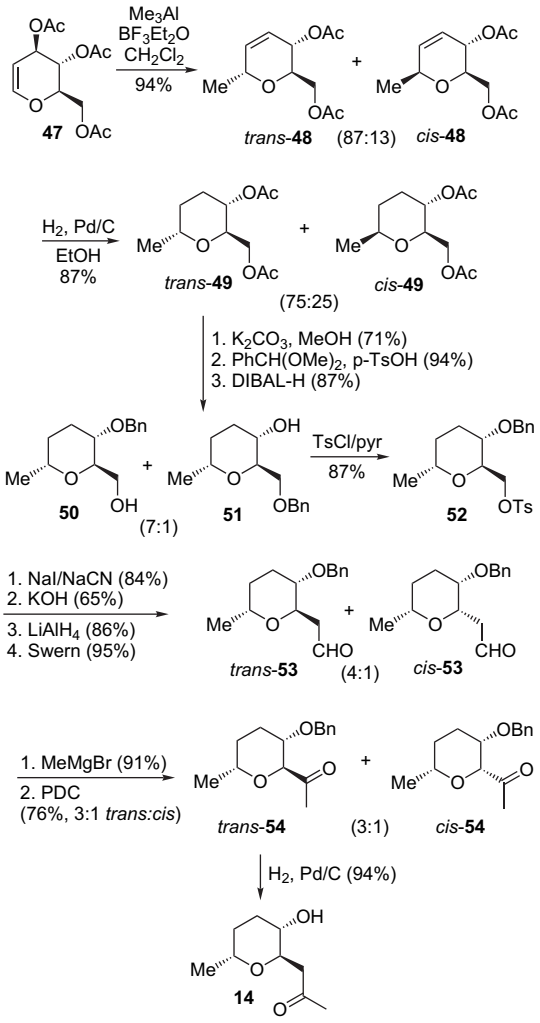
In a very interesting and efficient strategy Hatakeyama described a total synthesis of decarestrictine L (**14**) employing either Me_2AlCl promoted methylative cleavage of bicycle **43** or DIBAL-H promoted reductive cleavage of bicycle **44** (Scheme 6).[33] The chiral building block **40** was prepared from **39** in optically pure form in 64% yield, by combination of catalytic Katsuki–Sharpless asymmetric epoxidation, regioselective DIBAL-H reduction, and Red-Al® promoted reductive cleavage of benzyloxy group.[34] Upon sequential Birch reduction, benzylideneacetal formation and benzylation, **40** afforded benzylidene acetal **41** in 65% overall yield. Hydroboration of **41**, followed by oxidation afforded primary alcohol **42**



Scheme 6. Hatakeyama's synthesis of decarestrictine L.

and the corresponding secondary alcohol in a ratio of 78:22 almost quantitatively. Thus, alcohol **42** was converted into the key intermediate **45** employing two different approaches. Bicycle **43** was prepared from **42**, after Swern oxidation, methanolytic removal under acidic conditions of the benzylidene acetal group, and intramolecular acetalization in 61% overall yield. Alternatively, alcohol **42** was converted to bicycle **44** in 71% overall yield through a five-step sequence involving Swern oxidation, Grignard reduction, Swern oxidation, methanolytic removal of the benzylidene acetal group under acidic conditions, and intramolecular acetalization. Methylative cleavage of **43** with Me_2AlCl afforded the desired pyran **45** and its epimer **46** in a ratio of 80:20 in 65% yield. On the other hand, reductive cleavage[35] of **44** with DIBAL-H took place with excellent diastereoselectivity to give **45** and **46** in a ratio of 95:5 and 85% yield. The sequence is terminated by Swern oxidation, Grignard reduction, Jones oxidation, and hydrogenolytic debenzylation. The total synthesis of (+)-decarestrictine L (**14**) was accomplished in 17 steps and 14% overall yield.

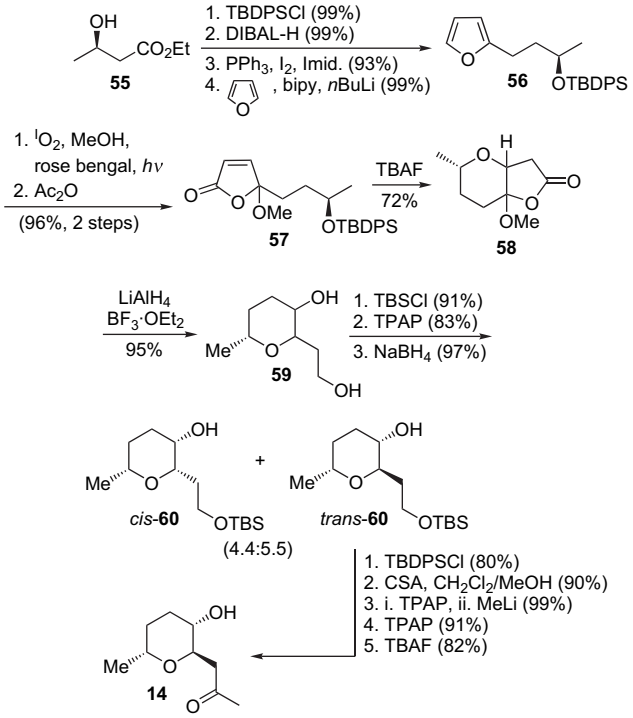
Donaldson and co-workers have proposed a general route to decarestrictine L (**14**) using the commercially available tri-*O*-acetyl-D-glucal **47** as starting material (Scheme 7).[36] Under



Scheme 7. Synthesis of decarestrictine L by Donaldson *et al*.

Lewis acidic conditions, the reaction of glycols with trialkylaluminum reagents generates the corresponding *C*-glycosides,[37,38] and the stereoselectivity of this reaction has been explored by Woerpel.[39] Reaction of **47** with Me_3Al in the presence of boron trifluoride etherate gave a mixture of *trans*-**48** and *cis*-**48** in 94% yield and 83:17 ratio. Separation of the two isomers was not possible and catalytic hydrogenation of the *cis*/*trans* **48** gave a separable mixture of diastereoisomers *trans*-**49** and *cis*-**49** in 94% yield and 75:25 ratio. The decrease in the ratio is attributed to olefin isomerization of **48** prior to reduction. Upon hydrolysis of *trans*-**49**, benzylidene acetalization, and reductive cleavage of benzylidene acetal, a mixture of primary alcohol **50** and secondary alcohol **51** was obtained in 7:1 ratio. Reaction of the mixture of **50**/**51** with tosyl chloride gave only the corresponding primary tosylate **52** in 85% yield. Nucleophilic substitution of the tosylate **52** with sodium cyanide (in the presence of NaI), basic hydrolysis of nitrile, followed by $LiAlH_4$ reduction, and Swern oxidation gave an inseparable mixture of aldehydes *trans*-**53** and *cis*-**53** in 4:1 ratio. The partial epimerization of the C-6 center is attributed to elimination with subsequent re-addition in the basic hydrolysis step. Addition of methylmagnesium bromide followed by oxidation afforded a separable mixture of *trans*-**54** and *cis*-**54** in 3:1 ratio. Finally, removal of benzyl ether furnished (+)-decarestrictine L (**14**) in 13 steps and 6% overall yield. Although not mentioned, the epimeric mixture of alcohols obtained from reduction of nitriles with $LiAlH_4$ in this approach furnished an intermediate already prepared in the total synthesis of Hatakeyama (see **45**, Scheme 6), albeit as a mixture. As described above, the total synthesis of Donaldson was accomplished performing the same synthetic steps as those described by Hatakeyama (except for the oxidation agent: PDC instead of Jones reagent), including the separation of epimers by preparative TLC before the hydrogenolysis of benzyl ether. Due to these facts this synthesis would be better described as a formal total synthesis.

The only synthetic approach to (+)-decarestrictine L (**14**) that has involved the construction of the pyran ring from a furan ring was reported by Fall and co-workers.[40] This route was based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular hetero Michael addition (Scheme 8).[41,42] Starting with commercially available chiral *R*-hydroxyester **55**, the alkylated furan **56** was obtained in 90% yield and four steps.[43] Oxidation of furan **56** with singlet oxygen followed by treatment with acetic anhydride in pyridine afforded the butenolide **57**, the precursor of pyran ring. Removal of the TBDPS group of **57** with TBAF gave bicyclic lactone **58** through an intramolecular Michael addition in 72% yield as a mixture of two diastereomeric compounds. Lactone **58** was opened using $LiAlH_4$, in the presence of $BF_3{\cdot}OEt_2$ to afford **59** as a mixture of diastereomeric diols. Selective protection of primary alcohol in diol **59**, oxidation of secondary alcohol followed by $NaBH_4$ reduction gave a separable mixture of alcohols *trans*-**60** and *cis*-**60** in 5.5:4.5 ratio. The



Scheme 8. Fall's synthesis of decarestrictine L.

sequence is terminated by protection of secondary alcohol of *trans*-**60**, selective removal of the TBS group, TPAP oxidation, MeLi addition, TPAP oxidation, and TBDPS group deprotection. The total synthesis of (+)-decarestrictine L (**14**) was obtained in 17 steps and 12% overall yield.

4.2. Decarestrictine J

The absolute stereochemistry of decarestrictine J (**12**) itself has not been reported. However, because **12** coexisted with decarestrictine B (**3**), whose absolute configuration had been determined by an X-ray analysis,[5] Yamada and co-workers suggested (7*R*,9*R*)-stereochemistry for natural (−)-decarestrictine J (**12**).[44] Only one total synthesis of the proposed structure of (−)-decarestrictine J (**12**) has been reported in the literature.[44] The synthetic strategy is outlined in Figure 8. This route involves a regioselective epoxy-opening reaction[45,46] of **63** and the formation of a 10-membered lactone by a samarium(II) iodide-promoted Reformatsky reaction of bromoacetoxy aldehyde **61** as the key steps.[47]

The synthesis began by reaction of *R*-(+)-propylene oxide **24** and propargyl tetrahydropyranyl ether **66**, employing lithium amide in liquid ammonia, afforded **67** in a 60% yield (Scheme 9). Benzylation of alcohol **67**, THP group deprotection, and reduction of the triple bond with lithium aluminum hydride gave the corresponding (*E*)-allylic alcohol. Asymmetric Sharpless epoxidation with L-(+)-diethyl tartrate afforded (2*S*,3*S*)-epoxy alcohol **64** in >95% diastereoisomeric excess. Dess–Martin oxidation of **64** and subsequent Horner–Emmons reaction with triethyl phosphonoacetate gave the corresponding γ,δ-epoxy-α,β-unsaturated ester. Epoxy-opening reaction with DIBAL-H afforded the unsaturated diol **62** with high regioselectivity (16:1). Protection of primary hydroxyl group of **62** with TBS and subsequent protection of secondary hydroxyl group with MOM afforded the corresponding protected unsaturated triol. Catalytic hydrogenation of olefin was accompanied by concurrent hydrogenolysis of the benzyl group; subsequent esterification with bromoacetyl bromide gave ester **68**. Fluoride-mediated deprotection of the TBS group of **68** and oxidation with PCC afforded the precursor of 10-membered ring lactone. Cyclization of **61** by Reformatsky reaction gave an inseparable diastereoisomeric mixture (6:4) of 10-membered ring hydroxyl lactones in 70% yield. Finally, Dess–Martin oxidation of hydroxyl group afforded (−)-decarestrictine J (**12**) in 17 steps and 3.9% overall yield.

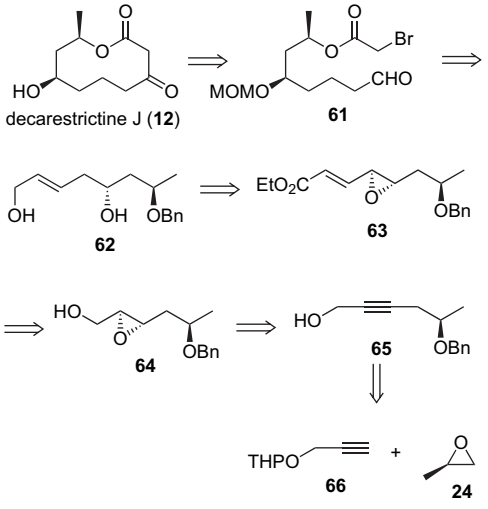
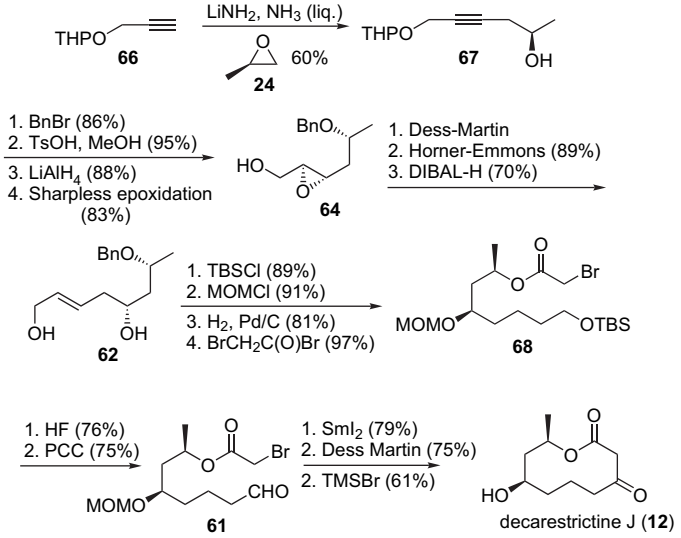


Figure 8. An overview of the retrosynthetic analysis of decarestrictine J by Yamada and co-workers.

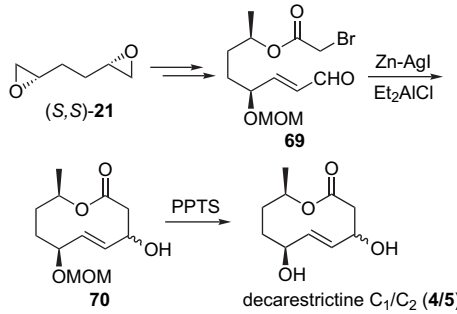


Scheme 9. The Yamada synthesis of decarestrictine J.

4.3. Decarestrictine C_2

Natural decarestrictine C is an inseparable diastereomeric mixture epimeric at C-3 (decarestrictine C_1 (**4**)/decarestrictine C_2 (**5**)=1:1 ratio). The structural elucidation of both diastereoisomers, decarestrictine C_1 (**4**) and decarestrictine C_2 (**5**), was tentatively proposed by NMR spectroscopy.[4] In 1993 Kibayashi reported the synthesis of decarestrictine C_1/C_2 (**4/5**) as an inseparable 1:1 epimeric mixture at C-3 starting with (*S*,*S*)-diepoxide (**21**) (Scheme 10).[48] The synthetic material was found to be identical with a diastereomeric mixture of natural decarestrictines C_1/C_2 (**4/5**).

More recently, Kibayashi published the first enantioselective synthesis of the proposed structure of (−)-decarestrictine C_2 (**5**) using (2*S*,5*S*)-1,2,5,6-hexanetetrol (**73**) as a C_2-symmetric chiral synthon, in which the diastereoselective aldol-type



Scheme 10. Kibayashi's synthesis of epimeric mixture of decarestrictines C_1/C_2.

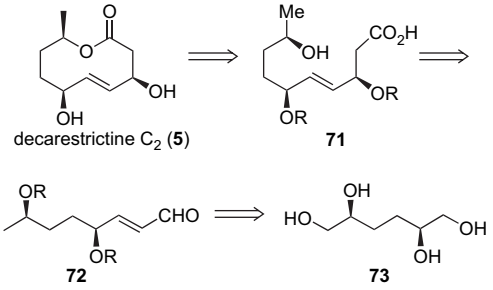
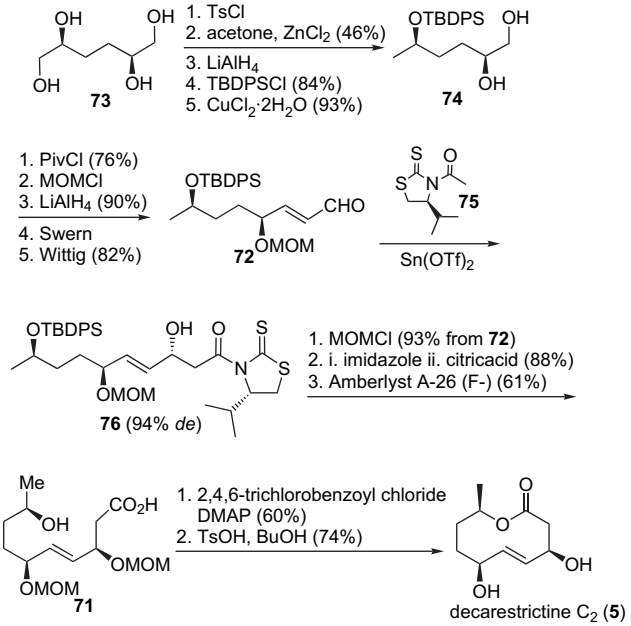


Figure 9. Kibayashi's proposed retroanalysis for the synthesis of decarestrictine C_2.

reaction of a tin(II) enolate of 3-acetyl-(4*S*)-isopropyl-1,3-thiazolidine-2-thione with α,β-unsaturated aldehyde **72** was used as a key step (Fig. 9).[49]

The proposed synthesis of Kibayashi is outlined in Scheme 11. C_2-symmetric tetrol **73** was obtained by standard methods from D-mannitol.[50] The synthesis began with monotosylation of the primary hydroxyl group in **73**, followed by protection of 1,2-diol, reduction of the tosylate using $LiAlH_4$, protection of secondary alcohol with TBDPS group, and cleavage of the acetal group with copper(II) chloride.[51] The diol **74** was obtained in five steps and 36% overall yield. Subsequent selective pivaloylation of primary alcohol, protection of secondary alcohol with MOM group, and $LiAlH_4$ deprotection of the pivaloyl group afforded the corresponding primary alcohol. Swern oxidation followed by Wittig olefination of the resulting aldehyde afforded 2-(*E*)-octenal **72** as a single geometrical isomer. For the diastereoselective introduction of the hydroxyl-bearing asymmetric center, **72** was subjected to diastereoselective aldol-type reaction using tin(II) enolates.[52] Thus, the chiral tin(II) enolate prepared from (*S*)-acetyl-1,3-thiazolidine-2-thione **75** and $Sn(OTf)_2$ in the presence of 1-ethylpiperidine was allowed to react with **72** to provide intermediate



Scheme 11. Synthesis of decarestrictine C_2 by Kibayashi and co-workers.

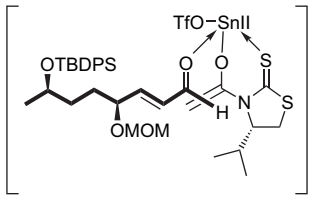


Figure 10. Transition state for diastereoselective aldol-type reaction.

76 with 95% diastereoisomeric excess, which required immediate hydroxyl protection because of its lability. Formation of the new stereogenic center with the desired *R* configuration was explained by consideration of the chelated transition state depicted in Figure 10, where tin enolate of **75** attacks aldehyde **72** at its *Re* face. Removal of the chiral auxiliary by mild aminolysis[53] and deprotection of the TBDPS group afforded the key intermediate **71**. Subsequent lactonization of **71** by the Yamaguchi method afforded the 10-membered lactone in 60% yield. Deprotection of the MOM group furnished (−)-(3*R*,6*S*,9*R*)-decarestrictine C_2 (**5**) in 16 steps and 3% overall yield. Spectroscopic data and X-ray crystallographic analysis for synthetic material unambiguously confirmed the structure and stereochemistry of **5** proposed for decarestrictine C_2. However, there were significant differences between the ^1H and ^{13}C NMR spectral data for this material and the corresponding data for natural decarestrictine C_1/C_2 (1:1 mixture). This discrepancy in the spectral data was attributed to the formation of a 1:1 molecular complex in solution resulting from intermolecular hydrogen bonding between decarestrictine C_1 and C_2.

4.4. Decarestrictine D

Decarestrictine D (**6**) is a potent inhibitor of cholesterol biosynthesis. Considering its selective biological profile, **6** has been identified by many research groups worldwide as an attractive synthetic target toward developing new cholesterol-lowering drugs. Consequently, the syntheses of **6** and its seco-acid have been reported by various research groups, focused on macrolactonization strategies or C–C cyclization (Fig. 11).

The relative stereochemistry of natural (−)-decarestrictine D (**6**) was provided by X-ray analysis[5] and its absolute configuration has been established by total synthesis[54] and X-ray analysis of a chiral derivative.[55]

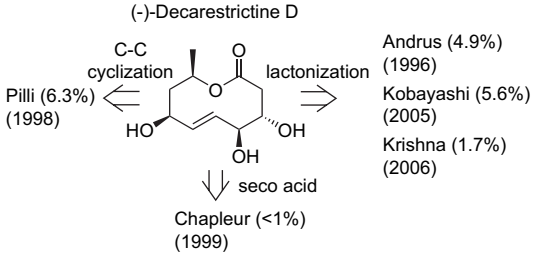


Figure 11. Key bond-forming decanolide moiety and yields in the syntheses of decarestrictine D and its seco-acid.

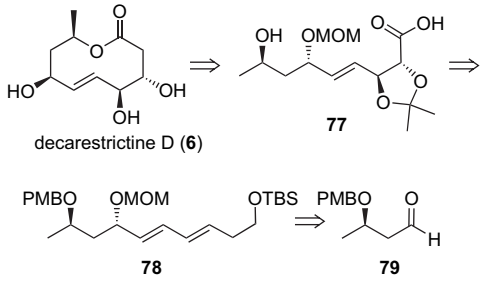
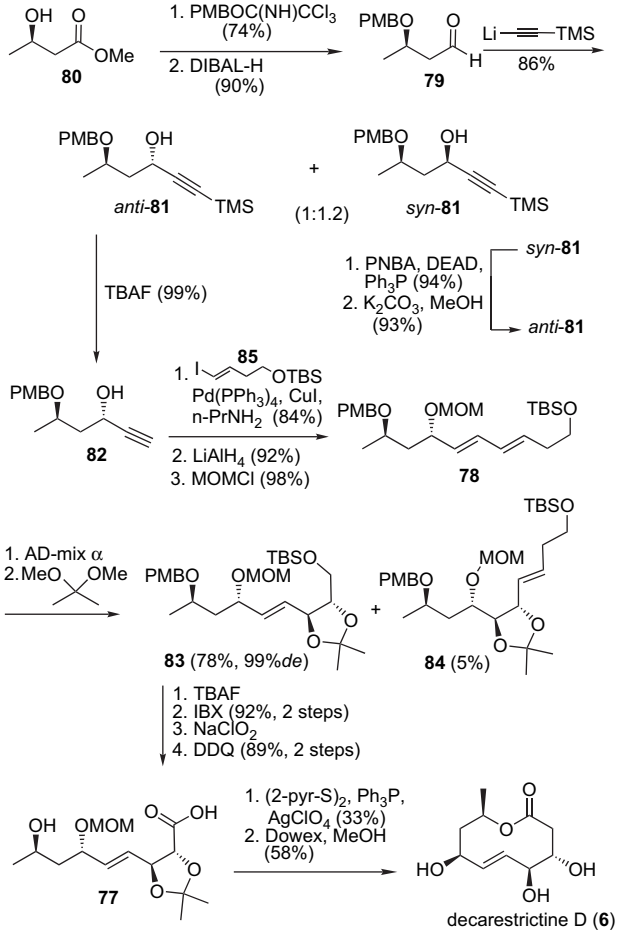


Figure 12. Retrosynthetic analysis of Andrus's synthesis of decarestrictine D.

Andrus and Shih[54] reported the first and enantioselective synthesis of decarestrictine D (**6**). The strategy used for the construction of the 10-membered lactone ring was based on the direct lactonization of the protected seco-acid **77** (Fig. 12). The precursor seco-acid **77** was planned to be prepared using a regioselective Sharpless asymmetric dihydroxylation of the diene intermediate **78**. The nature of the protecting group adjacent to the internal position of diene **78** may prove to be a critical factor for achieving high regio- and diastereoselectivity. MOM group, acetate, *p*-nitrobenzoate, and TBDPS group were screened to optimize the dihydroxylation step.

The synthesis begins with protection of (*R*)-(−)-methyl 3-hydroxybutanoate[56] (**80**) as the PMB ether, followed by reduction with DIBAL-H to give aldehyde **79** in 67% yield in two steps (Scheme 12). Addition of lithio(trimethylsilyl)acetylene proceeded in essentially absence of stereoselectivity and gave a separable diastereomeric mixture *syn*/*anti*-**81** in 1.2:1 ratio. Isomer *syn*-**81** was converted into isomer *anti*-**81** after Mitsunobu inversion followed by basic hydrolysis (80% combined yield of *anti*-**81**). Removal of the TMS group of isomer *anti*-**81** afforded the propargyl alcohol **82** in 99% yield. Coupling of **82** with vinyl iodide **85** using catalytic amount of palladium(0) and cuprous iodide[57] produced the corresponding (*E*)-unsaturated alcohol in 84% yield. $LiAlH_4$ reduction gave the (*E*,*E*)-diene, which was protected as its MOM ether **78**. Sharpless asymmetric catalytic dihydroxylation[58] of **78** generated the desired diol **83** in 78% yield and 99% diastereoisomeric excess. The regioselectivity observed is consistent with the transition state arrangement model proposed by Corey,[59] and has been explained in terms of the nature of protecting groups (both electronic and steric effects). The TBS ether of **83** was removed using TBAF followed by oxidation using IBX[60] to generate the corresponding aldehyde in 92% overall yield. Sodium chlorite oxidation of aldehyde to the corresponding carboxylic acid followed by DDQ removal of the PMB ether afforded the key intermediate **77**. The desired 10-membered protected lactone was obtained in 33% yield after lactonization using 2,2′-dipyridyldisulfide and triphenylphosphine with added silver perchlorate. Finally, one-step removal of the MOM and the acetonide groups furnished first total synthesis of (−)-decarestrictine D (**6**) in 17 steps and 4.9% overall yield.

The synthetic approach to lactones has traditionally focused mainly on the use of fragmentation/ring expansion reactions and on lactonization strategies in order to build the lactone ring.[61] Examples of the construction of lactones through the



Scheme 12. Synthesis of decarestrictine D by Andrus and co-workers.

formation of the C−C bond are scarce[62,63] and the intramolecular Nozaki−Hiyama−Kishi (NHK) coupling reaction stands as a promising protocol.[64–66] Pilli and Victor have investigated some key factors that control the stereochemistry of NHK cyclization in the construction of 10-membered lactone rings[67,68] and demonstrated the utility of this methodology in the total synthesis of decarestrictine D (**6**).[67,69] The synthetic strategy is outlined in Figure 13 and involves the stereoselective construction of the 10-membered lactone and of its stereogenic center at C-7 through an intramolecular NHK coupling reaction with vinylic iodide-aldehyde **86**.

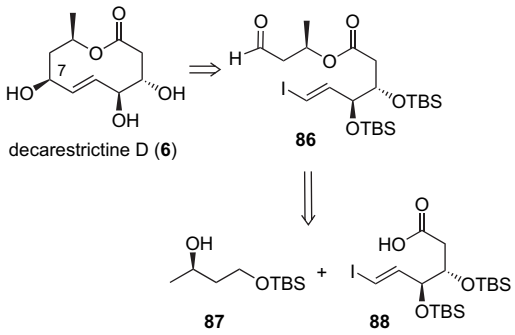


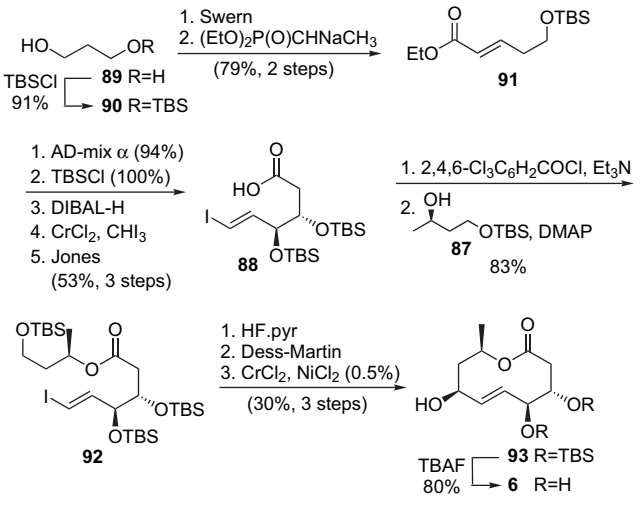
Figure 13. An overview of the retrosynthetic analysis of decarestrictine D by Pilli *et al.*

The synthesis started with monosilylation of 1,3-propanediol **89**, followed by Swern oxidation of **90** and Wittig olefination to give the unsaturated ester **91** as a 22:1 separable mixture of *E* and *Z* isomers (Scheme 13). The *E*-**91** isomer was submitted to Sharpless dihydroxylation and the corresponding diol was formed in 94% yield and 91% ee. Protection of diol with TBS group and DIBAL-H reduction of ester group afforded the corresponding aldehyde. The crude aldehyde was immediately submitted to modified Takai's conditions[67,70] to give the corresponding *E*-vinylic iodide that was submitted to an one-pot desilylation–oxidation step with Jones reagent[71] to afford carboxylic acid **88** in 53% overall yield for four steps.

Alcohol **87** was prepared in 71% yield and 99% ee from natural biopolymer polyhydroxybutyrate (PHB),[72] after reductive depolymerization and selective protection of the primary hydroxyl group with TBSCl. Yamaguchi coupling[73] of carboxylic acid **88** and alcohol **87** afforded the key intermediate **92** in 83% yield. Selective deprotection of primary TBS group of **92**, followed by Dess–Martin oxidation, and NHK coupling reaction gave the 10-membered lactone ring **93** as a single diastereoisomer, in 30% yield over three steps. Finally, deprotection of TBS groups with TBAF afforded (−)-decarestrictine D (**6**) in 13 steps and 6.3% overall yield.

Chapleur and co-workers suggested that decarestrictine D (**6**) would be an inhibitor of cholesterol biosynthesis on the basis of structural similarities between decarestrictine D and mevinolin.[74] These similarities rely on the presence of a lactone moiety and the presence of a hydroxyl group in β position of the carbonyl group. However, the lipophilic part present in mevinolin, which is essential for inhibition, cannot be found in decarestrictine D. The lactone function of 'mevinic acids' is formed upon isolation and it is well know that the free acid is the biologically active form.[75,76] Then, the seco-acid (**94**) of decarestrictine D might be the real inhibitor of cholesterol biosynthesis. On this basis they decided to prepare **94** and evaluate its biological proprieties.

The retrosynthetic analysis of **94** is based on an olefination between two enantiomerically pure building blocks **96** and **97**



Scheme 13. Pilli's steps of synthesis of decarestrictine D.

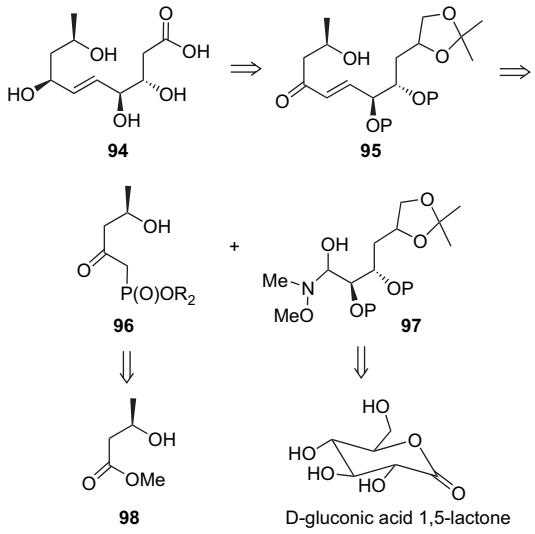
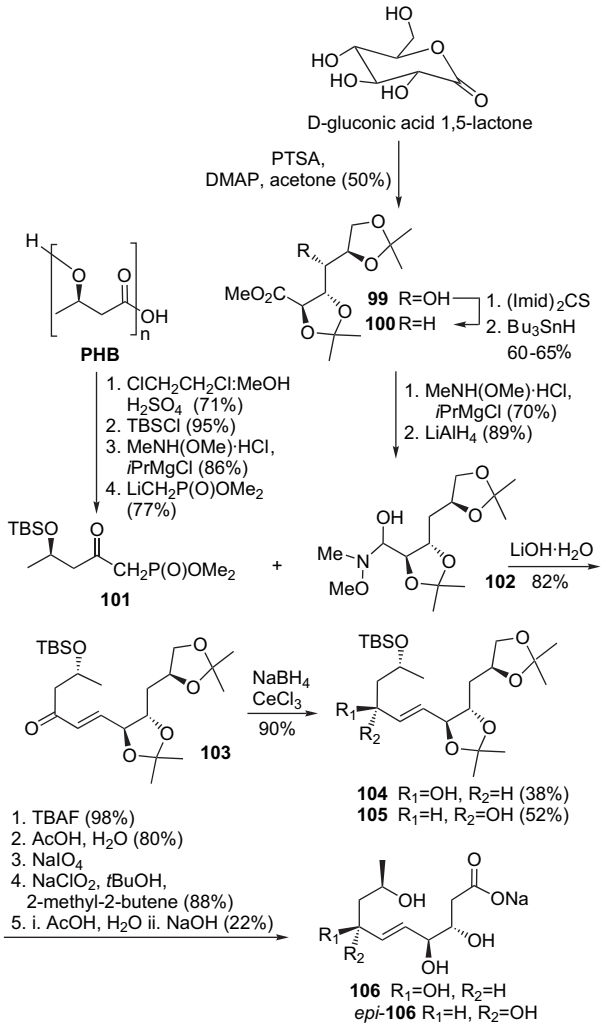


Figure 14. Chapleur's proposed retrosynthesis of the seco-acid of decarestrictine D.

(Fig. 14). The phosphonate moiety **96** was obtained by condensation of a phosphonate anion on a suitable derivative of 3-hydroxy butyric acid and the hemi-aminal **97** was prepared from D-gluconic acid 1,5-lactone.

Phosphonate **101** was prepared from natural biopolymer polyhydroxybutyrate (PHB)[72] (Scheme 14). Depolymerization of PHB afforded the corresponding ester, protection of the primary hydroxyl group with TBSCl and treatment with the magnesium salt of *N*,*O*-dimethylhydroxylamine led to corresponding Weinreb amide,[77] which was condensed with lithiotrimethylphosphonate afforded phosphonate **101** in four steps and 55% overall yield. Ester **99** was obtained from D-gluconic acid 1,5-lactone in 50% yield after treatment with PTSA, DMAP, and acetone.[78] The hydroxyl group of **99** was removed under radical conditions and the ester group was transformed into Weinreb amide after treatment with the magnesium salt of *N*,*O*-dimethylhydroxylamine. Reduction of amide with $LiAlH_4$ afforded the intermediate hemi-aminal **102** in 39% yield from ester **99**. To the delight of the authors, Horner–Emmons olefination between **101** and **102** using Blackwell conditions[79] produced only *E* olefin in 82% yield. The carbonyl group of enone **103** was reduced with $NaBH_4$ in presence of $CeCl_3$ to afford a separable epimeric mixture of **104** and **105** in 90% yield and 1:1 ratio. Desilylation of **104** followed by selective removal of one isopropylidene group led to corresponding tetrol in 80% yield. 1,2-Diol cleavage with sodium periodate afforded the aldehyde, which was oxidized without purification to provide the corresponding carboxylic acid in 88% yield.[80] The final step was the removal of the last isopropylidene group followed by treatment with sodium hydroxide to yield (22% in this step) the target compound **106** in 11 steps and less than 1% yield. The same synthetic steps applied to **105** furnished C7-*epi*-**106** in similar yield.

More recently, Kobayashi and co-workers described an enantioselective synthesis of decarestrictine D (**6**)[81] using a methodology previously reported, where they employed a nickel-catalyzed coupling reaction between alkenyl



Scheme 14. Synthesis of the seco-acid of decarestrictine D and its C-7 epimer by Chapleur and co-workers.

boronates and highly congested (*Z*)-3-alkoxy-1-alkenyl halides to furnish (2*Z*,4*E*)-alkadienyl alcohol derivatives.[82]

The synthetic strategy is depicted in Figure 15, with seco-acid **107** with properly protected hydroxyl groups at C-3, C-4,

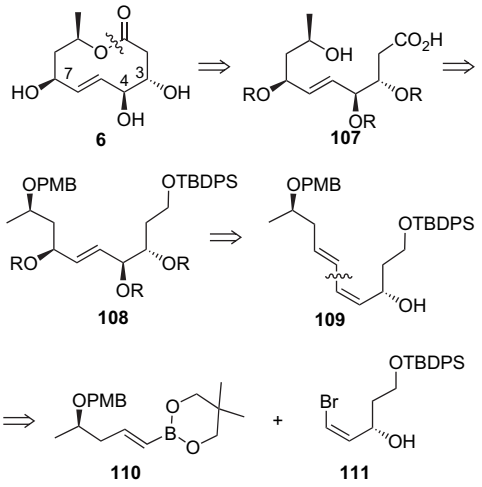
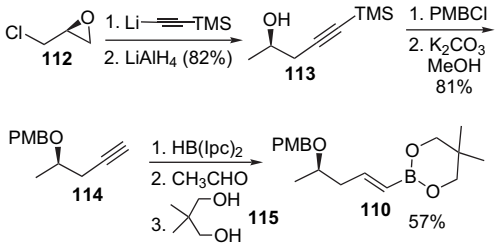


Figure 15. Kobayashi's key strategies in the synthesis of decarestrictine D.

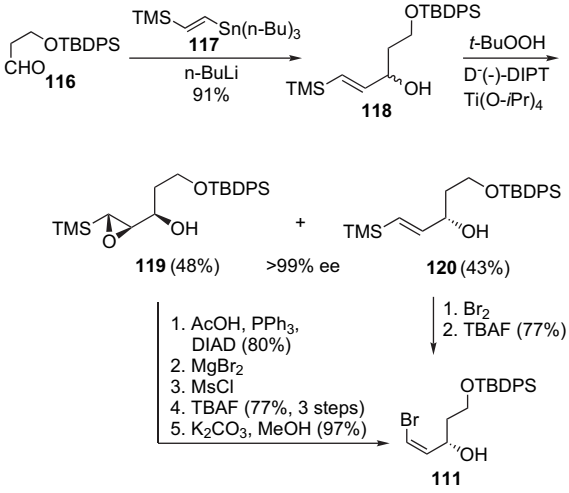


Scheme 15. Kobayashi's synthesis of C6–C10 fragment **110**.

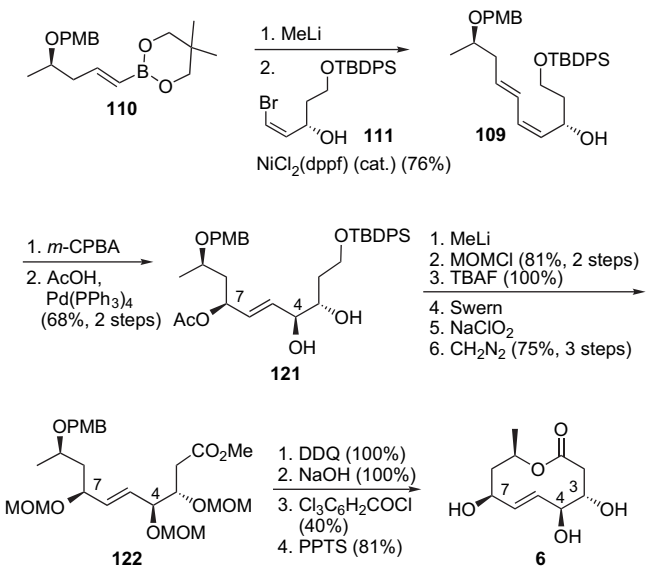
and C-7. Preparation of the C-3–C-7 structure in **107** and its precursor **108** requires the *cis*,*trans* dienyl alcohol **109**, which in turn was disconnected to the borate derived from boronate ester **110** and *cis* bromide **111**.

Synthesis of the boronate **110** was accomplished by a sequence delineated in Scheme 15 starting with epichlorohydrin **112** of 98.9% ee. The first step was the reaction with lithium TMS acetylide, and the resulting chlorohydrin was reduced to **113** in 82% yield from **112**. Protection of **113** with PMBCl under the standard conditions[83] resulted in concomitant removal of the TMS group, though incompletely, to afford a mixture of **114** and a PMB ether of **113** in a 1:2 ratio. Without separation, the mixture was treated with K_2CO_3 in MeOH to produce **114** in 81% from **113**. Finally, the acetylene part of **114** was converted to the vinyl boronate ester moiety of **110** by hydroboration with $(Ipc)_2BH$, ligand exchange with MeCHO,[84] and transesterification with diol **115**.

Another key intermediate **111** was synthesized by taking advantage of the reactivity of vinyl silanes (Scheme 16). Reaction of aldehyde **116** with lithium anion derived from **117** afforded racemic alcohol **118** in 91% yield. Sharpless asymmetric epoxidation of **118** afforded allylic alcohol **120** and epoxy alcohol **119** in >99% ee, which were separated by chromatography and both products were transformed to **111**. Bromination of **120** and subsequent deprotection of TBDPS group afforded **111** in 77% yield. As for **119**, the Mitsunobu inversion with AcOH, followed by reaction with $MgBr_2$ gave the corresponding bromohydrin, which was subjected to mesylation and deprotection of TBDPS group. Methanolysis with K_2CO_3 in MeOH produced **111** from **119** in 60% yield.



Scheme 16. Kobayashi's synthesis of C1–C5 fragment **111**.



Scheme 17. Fragment coupling of the C1–C5 and C6–C10 domains and final steps of Kobayashi's synthesis of decarestrictine D.

Nickel-catalyzed coupling of **110** and **111** (Scheme 17) was executed by addition of MeLi to a mixture of boronate ester **110** and catalytic $NiCl_2$(dppf) followed by reaction with *cis* bromide **111** to furnish dienyl alcohol **109** as the sole product in 76% yield based on **111**. Epoxidation of **109** with *m*-CPBA proceeded in a completely stereoselective manner, and subsequent palladium-catalyzed reaction with AcOH furnished **121** in 68% yield from **109**. At this stage, transformation of **121** in Andrus' seco-acid (see **77**, Scheme 12) led to low yields in the macrolactonization step (17% yield) when performed with Yamaguchi reagent. This obstacle was reasoned as arising from undesired projection of the two reactive sites (CO_2H and OH) into the opposite spaces divided by the acetonide plane. In order to circumvent this energetic barrier for the lactonization, the group projected to construct a different seco-acid. Thus the acetyl group of **121** was removed, and the resulting triol was converted to corresponding MOM ether. After removal of the TBDPS protective group, the resulting alcohol was oxidized to the methoxycarbonyl moiety by the standard method in 61% yield from **121**. The PMB group was then removed with DDQ, and the ester group was hydrolyzed to afford the corresponding seco-acid, which upon Yamaguchi lactonization furnished the 10-membered lactone ring in 40% yield from **122**. Finally, deprotection of MOM group with PPTS[85] in refluxing *n*-BuOH afforded decarestrictine D (**6**) in 81% yield. The total synthesis was reached in 20 steps from **116** and 5.6% overall yield. In addition, Kobayashi has reported a correction of the specific optical rotation values described, due to the use of different solvents ($CHCl_3$ and MeOH) in measurements in others synthetic approaches and isolation.

In 2006, Krishna published a stereoselective total synthesis of (−)-decarestrictine D by a convergent strategy wherein both intermediates are derived from L-malic acid (Fig. 16).[86] The strategy relies on Sharpless asymmetric epoxidation, acetylenic addition onto a chiral aldehyde, 1,2-*syn* selective reduction, and Yamaguchi macrolactonization as the key steps.

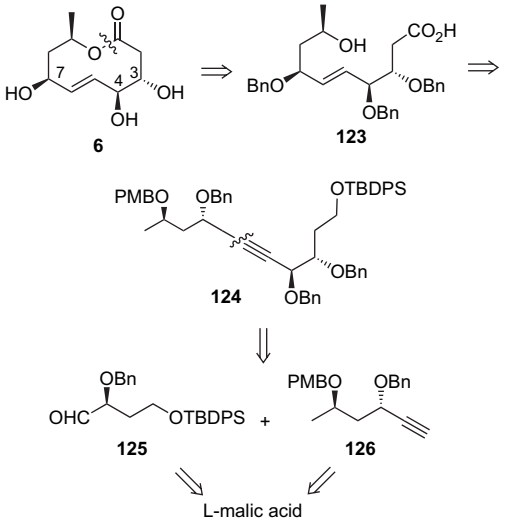
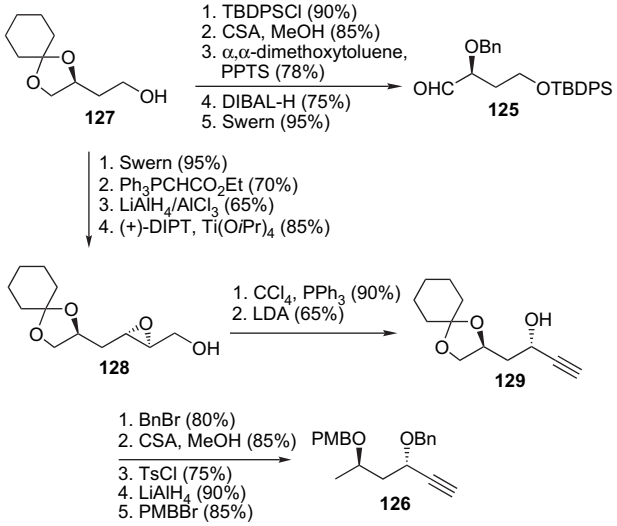


Figure 16. Retrosynthetic analysis proposed by Krishna to the synthesis of decarestrictine D.

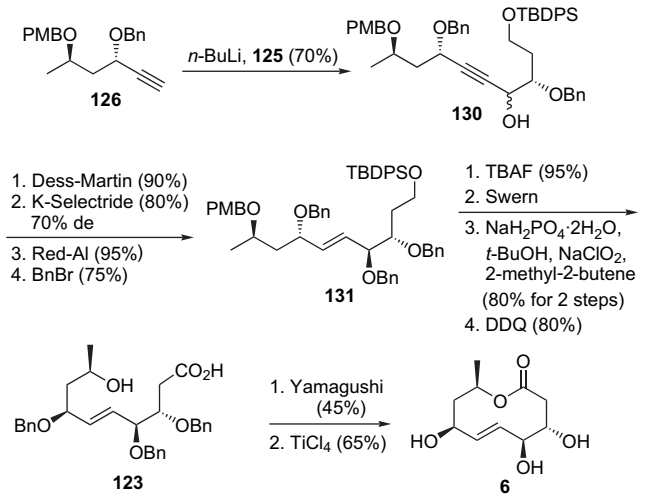
The synthesis starts with compound **127** (Scheme 18), which is readily obtained from L-malic acid. Aldehyde **125** was prepared from **127** in 43% yield, after protection of the primary hydroxyl group with TBDPSCl, methanolytic removal of the acetal group, benzylation of secondary hydroxyl group, and Swern oxidation. To prepare alkyne **126**, alcohol **127** was subjected to Swern oxidation followed by Wittig olefination reaction to afford the corresponding *trans* α,β-unsaturated ester. Reduction with $LiAlH_4/AlCl_3$ and then exposure of the ensuing allylic alcohol to Sharpless epoxidation afforded epoxy alcohol **128** in 37% yield from **127**. Epoxide **128** was chlorinated followed by a base induced double elimination to afford propargylic alcohol **129** in 59% yield. Benzylation of alcohol **129** and methanolytic removal of the acetal group gave the corresponding 1,2-diol. Selective tosylation of primary hydroxyl group, reduction of tosylate group, and PMB



Scheme 18. Synthesis of C1–C4 (**125**) and C6–C10 (**126**) fragments of decarestrictine D by Krishna and co-workers.

protection of secondary hydroxyl group afforded the key intermediate **126** in 39% from **129**.

Acetylenic anion of **126** was coupled with aldehyde **125** to give **130** in 70% yield and 20% diastereoisomeric excess. In order to increase the diastereoselectivity and to obtain the requisite stereocenter at the newly created site, propargylic alcohol **130** was oxidized to its corresponding keto compound and selectively reduced with K-Selectride to give the corresponding alcohol with 4*S* stereochemistry in 80% yield and 70% diastereoisomeric excess. After separation of the mixture, the pure diastereoisomer was reduced with Red-Al to give the corresponding olefin, and the resulting allylic hydroxyl group was protected as its benzyl ether to afford **131** in 72% yield. TBDPS deprotection with TBAF afforded the primary alcohol, which was oxidized to the corresponding carboxylic acid by a two-step process. Deprotection of the PMB group with DDQ afforded seco-acid **123** in 60% yield from **131**. According with described by Kobayashi, Yamaguchi macrolactonization of non-cyclic protected **131** yielded the 10-membered lactone ring in moderate yield (45%) and finally global debenzylation gave decarestrictine D (**6**) in 65% yield. In this manner, decarestrictine D (**6**) was produced in 22 steps and 1.7% overall yield (Schemes 18 and 19).



Scheme 19. Coupling of the C1–C5 and C6–C10 fragments and final steps of Krishna's synthesis of decarestrictine D.

5. Derivatization

Over the past decades synthetic modifications of naturally important compounds have become an important tool in altering their pharmacological profile and potency. The construction of hybrid or composite antibiotics, among other strategies, is regarded as an important approach for development of new therapeutic reagents. This concept is based upon the combination of structural fragments commonly found in different antibiotics within one molecule.

Although decarestrictines D (**6**) and B (**3**) have structural resemblance to aglycons with 12- and 14-membered macrolide antibiotics like methymycin and erythromycin A,[87] they do not exhibit antibacterial, antifungal, or antiviral activity.

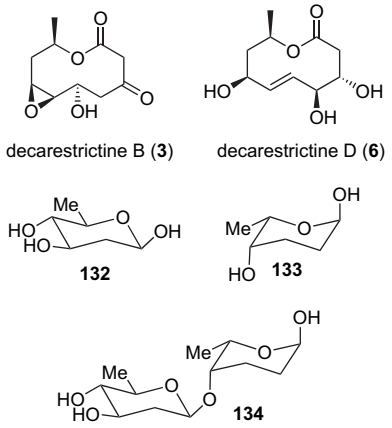


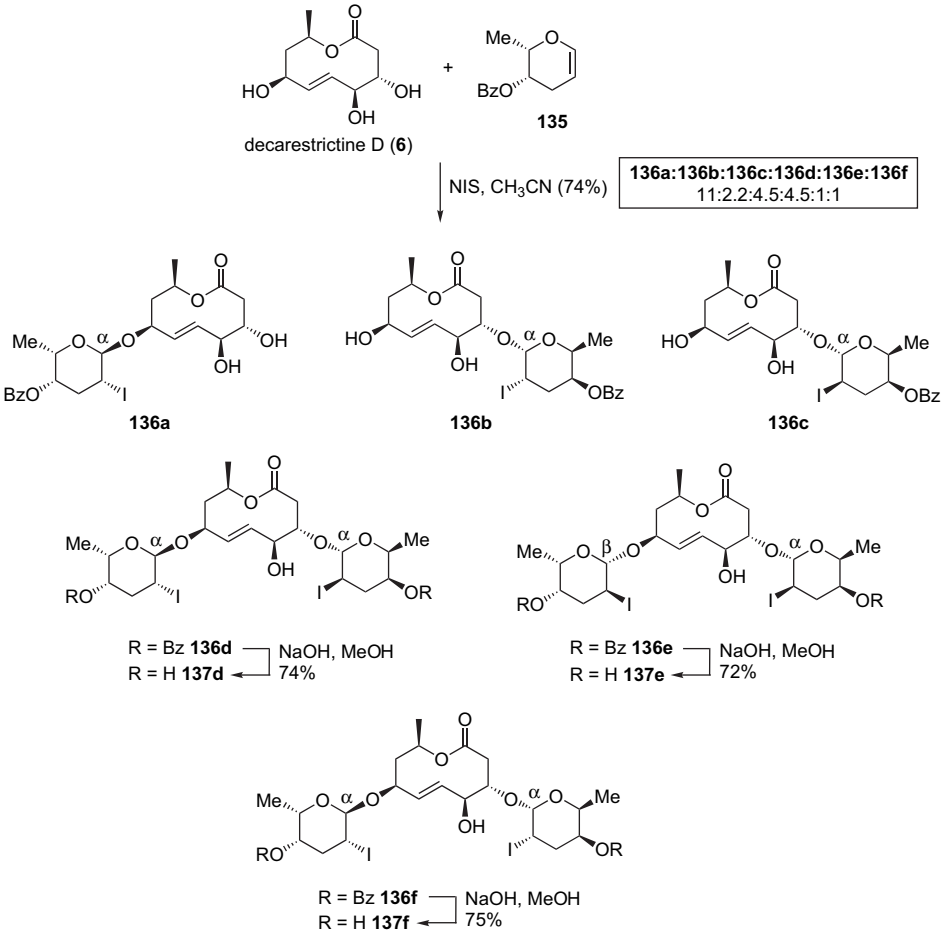
Figure 17. Aglicons and sugar moieties employed by Kirschning in the synthesis of hybrids.

Therefore, combination of the 10-membered lactone moiety of the decarestrictines, which serves as a non-glycosylated secondary metabolite (aglycon), with deoxygenated glycan unit, would lead to promissory hybrid antibiotics.

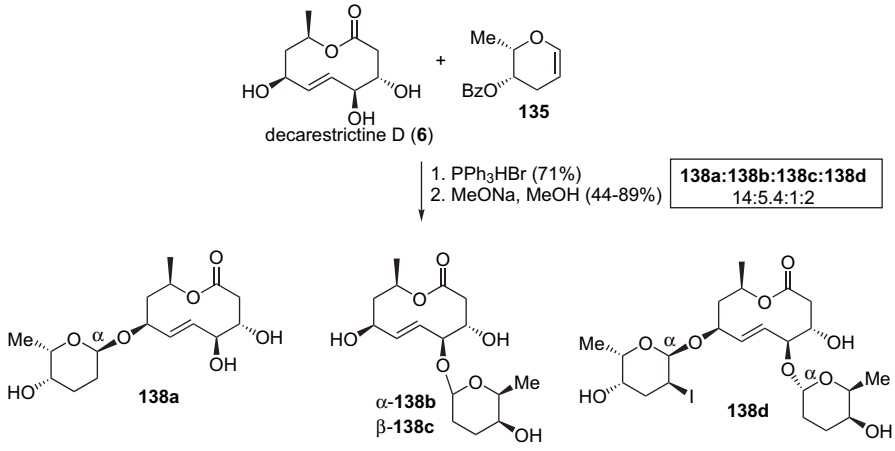
Kirschning and co-workers reported the first synthesis of hybrid structures employing decarestrictines D (**6**) and B (**3**) as an aglycon for the formation of glycol-conjugates.[55] The sugar moieties employed are D-olivose (2,6-dideoxy-D-*arabino*-pyranose, **132**), L-rhodinose (2,3,6-trideoxy-L-*threo*-pyranose, **133**), and the disaccharide **134**, which is composed of **132** and **133** (Fig. 17). These and other rare sugars are commonly found as constituents of angucycline antibiotics,[88] and to a lesser extent in macrolide antibiotics and anthracycline cytostatics. In all these examples the carbohydrate units are essential for biological activity.[87]

In order to gain access to a diverse number of derivatives and to assess the relative reactivity of hydroxyl groups in polyhydroxylated decanolides, decarestrictine D (**6**) was employed as aglycon. Thus **6** was glycosylated with glycal **135** (4-*O*-benzoylated L-rhodinal, obtained from L-rhamnose)[89] employing *N*-iodosuccinimide (NIS) method,[90] to afford a mixture of mono- and bisglycosylated decanolides **136a–f** (11:2.2:4.5:4.5:1:1, 74%) with the expected preference for the α-anomers (Scheme 20). Due to the ratio of the isolated monoglycosylated products, the relative reactivity of the hydroxyl groups in acetonitrile was deduced as 7-OH>3-OH≫4-OH. Debenzoylation of **136d–f** was achieved without substantial cleavage of the lactone ring under mildly basic reaction conditions to afford **137d–f**.

In order to get a more efficient access to a wide number of glycosylated decarestrictines they turned their attention to a proton-induced glycosylation method.[91] Thus, activation of **135** by triphenylphosphane hydrobromide (TPHB), coupling with **6**, followed by debenzoylation furnished three monoglycosylated adducts **138a–c** and one bisglycoside **138d** (14:5.4:1:2) (Scheme 21). Here a reverse preference for the 3-OH and 4-OH glycosylations was disclosed when compared with the NIS-method results. The difference was rationalized on the basis of the difference of hydrogen-bonding capabilities and dielectric constants of the solvents employed.

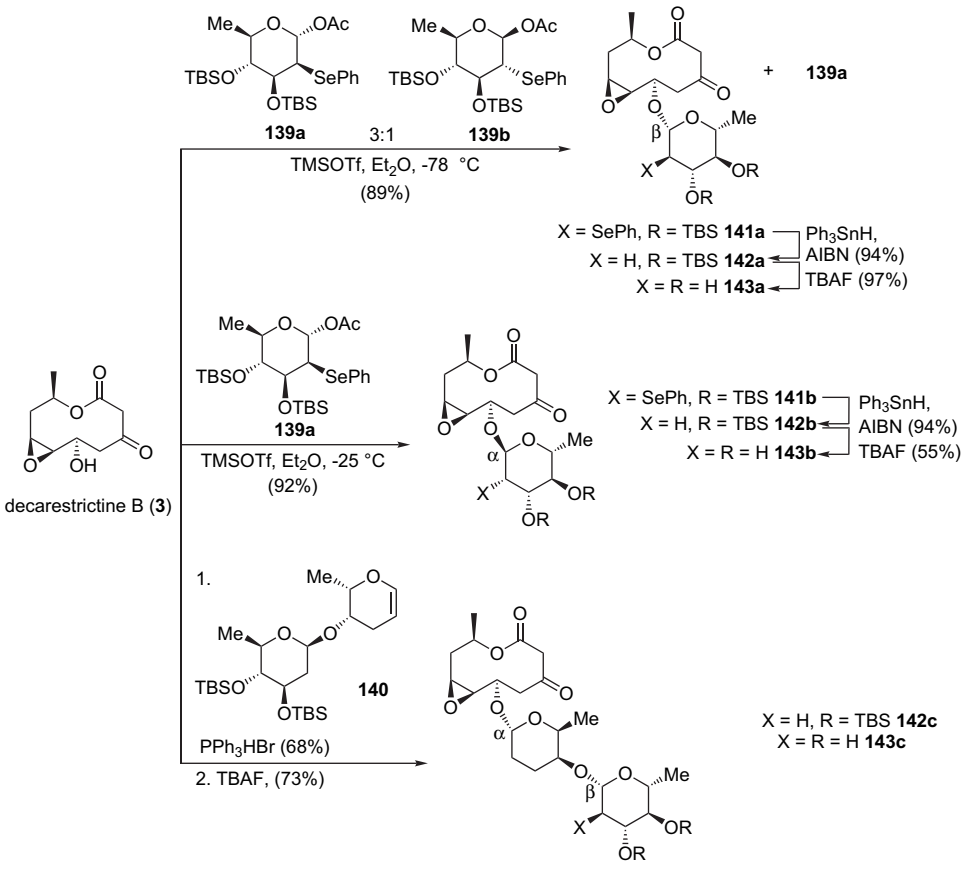


Scheme 20. Kirschning's proposed synthesis of hybrids from decarestrictine D.



Scheme 21. Kirschning's synthesis of hybrids from decarestrictine D by proton-induced glycosylation method.

Decarestrictine B (**3**), also employed in the construction of hybrids, possesses several structural features such as the oxirane ring and the acid–base sensitive β-ketoester functionality that have to be taken into consideration with respect to the glycosylation and subsequent deblocking reactions. Thus, a 1:3 mixture of seleno *O*-silylated glycals **139a** and **139b** was glycosylated with **3** at −78 °C with TMSOTf and afforded the corresponding 2-phenylseleno-β-glycoside **141a** (89% with respect to **139b**), along with unreacted **139a** and **3** (Scheme 22). Reductive removal of the phenylseleno substituent in **141a** under radical conditions provided **142a** in 94% yield. Finally, desilylation with TBAF afforded the desired hybrid structure **143a**. Likewise, pure **139a** was glycosylated with **3** at −25 °C with TMSOTf as promoter to afford **141b** in 92% yield. The target glycoside **143b** was obtained in a two-step sequence through the TBS-protected olivoside **142b**. In

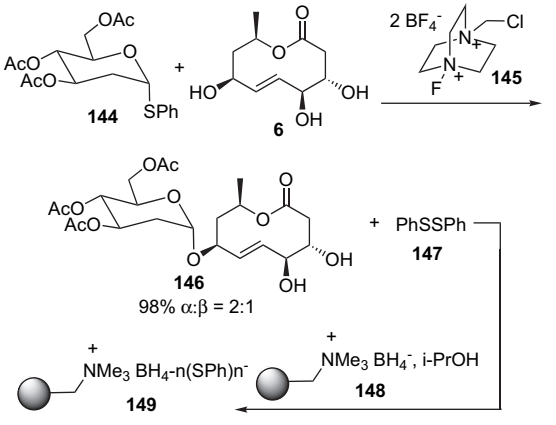


Scheme 22. Synthesis of hybrids of decarestrictine B by Kirschning and co-workers.

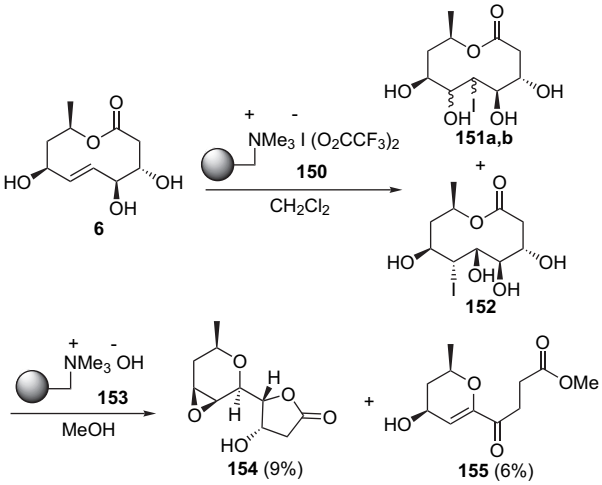
contrast, disaccharide **140** was coupled with **3** in the presence of a catalytic amount of Ph_3PHBr. The primary coupling product **142c** turned out to be very labile and was immediately deblocked to generate glycoconjugate **143c**.

In view of the importance and success of solid-phase chemistry, various polymer-supported syntheses of oligosaccharides including deoxysugar analogs have been developed.[92] Recently, Kirschning and co-workers reported[93] a solid-phase glycosylation of decarestrictine D (**6**) with thioglycoside **144** employing the fluorinating agent Selectfluor[94] **145** (Scheme 23). The desired glycoside **146** was obtained with impurities of **147**. Sequestration of **147** was achieved after treatment with **148** as scavenger in *i*-PrOH, followed by filtration. Concentration under reduced pressure yielded glycoside **146** in 98% and preference for the α-anomer (α/β 2:1).

In another work, Kirschning and co-workers developed a set of polymer-attached hypervalent iodate(I) complexes.[95] The synthetic versatility of these complexes, initially investigated to promote 1,2-functionalization of glycols under very mild conditions,[96] was demonstrated with a one-pot multistep rearrangement of decarestrictine D (**6**) (Scheme 24). This strategy is based



Scheme 23. Solid-phase glycosylation of decarestrictine D by Kirschning and co-workers.



Scheme 24. Polymer-bound rearrangement of decarestrictine D.

in the use of natural products as starting point of cascade-type transformations, which may include rearrangements of the carbon backbone.[97] Consequently, new natural product-like systems with some of the chiral centers kept intact are generated, which lack structural similarity to the natural sources. Choice of decarestrictine D (**6**) emerged from the possibility that olefinic double bond can easily act as a counterpart if approached by an electrophilic species. In this case, either the intermediate cation or the 1,2-addition products could initiate a cascade reaction. Thus, treatment of **6** with polymer-bound bis-trifluoroacetoxy iodate(I) **150** afforded a mixture of 1,2-functionalizated compounds **151a**,**b** and **152**. The crude material was treated with polymer-bound hydroxide **153** in methanol and the two major products **154** and **155** were isolated in 9 and 6%, respectively. The second reaction was accompanied with substantial rearrangement of the decanolide backbone.

The formation of rearranged products **154** and **155** was rationalized by the following proposal. After α-attack of the iodonium cation to the olefinic bond, intermediate **156** can rearrange by two different ways (Scheme 25). In path *a*, the cation was trapped by the hydroxyl group at C-7 to yield oxirane **157**. Deprotonation of the 4-hydroxy group by the polymer-bound hydroxide anion initiated lactonization, followed by ring closure of the intermediate alkoxy anion at C-9. Path *b* begins with trapping of intermediate **156** by the hydroxyl group at C-4 and furnished oxirane **158**. Methanolysis creates the methyl ester, which could cyclize by alkoxyde anion at C-9 to yield tetrahydropyran **159**. The sequence of steps needed to end up with **155** (suggested as two elimination steps and final tautomerization) remains obscure.

6. Biological properties

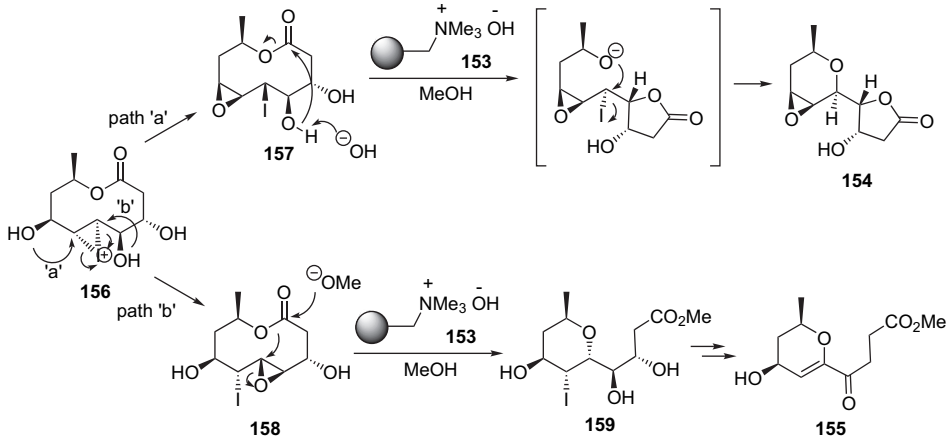
Decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells[98,99] due to an inhibitory effect on cholesterol biosynthesis (Table 1).[4,6] This was tested via sodium ^{14}C-acetate incorporation into cholesterol. The 1×10^{-7} mol/L concentration of each decarestrictine resulted in inhibition effects of about 40% (decarestrictine A), 20 (B), 30 (C) and 50% (D). In this test, the IC_{50} for the standard compound lovastatin is 2.4×10^{-8} mol/L. In normolipemic rats, after oral application of 10 mg/Kg daily for a total of 7 days, the most potent metabolite decarestrictine D showed hypolipidemic activity equivalent to that elicited by daily application of 100 mg/Kg of the commercial product clofibrate (Table 2). Decarestrictines A–D exhibit no significant antibacterial, antifungal, antiprotozoal, or antiviral activity.[4]

Table 1
Incorporation of ^{14}C-acetate into the sterol fraction of HEP-G2 cell-cultures

Compound	Concentration (mol/L)	Number of assays	Incorporation of ^{14}C-acetate (nmol/mg cell protein per 3 h)
Decarestrictine D	10^{-5}	3	8.80
Decarestrictine D	10^{-7}	3	10.16
Control	—	6	19.25

The biological activities of decarestrictines E–M were also investigated.[6] In cell line tests with HEP-G2 cells, the decarestrictines showed more or less potent inhibitory effects on cholesterol biosynthesis. This was tested via sodium ^{14}C-acetate incorporation into cholesterol. The data are presented in Table 3. It is worth mentioning that besides the most potent decarestrictine D (**6**), which exhibits a 10-membered lactone moiety, decarestrictine M (**15**) reveals a good activity in HEP-G2 cell assay. In contrast, evaluation of the activity in normolipemic rats (oral application: 15 mg/Kg[1] a day for a total of 7 days) showed that decarestrictine M is less active than decarestrictine D (antiatherogenic index: HDL/LDL cholesterol=4.63–93% of the control).

More recently, Gloer and co-workers isolated decarestrictines A_1 (**1**) and I (**11**) as minor components of the organic extract from solid-substrate fermentations of the mycoparasitic fungus *H. fuscoatra*, originally isolated as a colonist of *A. flavus* sclerotia.[9] Isolation of anti-*Aspergillus* agents from this colonist of *A. flavus* sclerotia provides support for the concept that fungi that parasitize sclerotia can serve as a source of agents with antifungal activity against host. However, the antifungal activity of crude extract is devoted to the presence of isolated fuscoatroside (18 mm zone of inhibition at 200 μg/disk in disk essays at pure form) and two known compounds reported earlier (monorden and monocillin IV)[100] and not due to the presence of decarestrictines compounds.



Scheme 25. Mechanistic proposal of backbone rearrangement of decarestrictine D.

Table 2
Hypolipidemic activity of decarestrictine D in rats after 7 days of oral application

Number of animals	Compound	Dose (mg/Kg/day)	Total cholesterol			Antiatherogenic index	
			VLDL	LDL	HDL	HDL/LDL	% of control
10	Clofibrate	100	17	68	437	6.43	129
5	Decarestrictine D	10	34	70	601	8.59	172
19	Control	—	45	125	624	4.99	100

Table 3
Incorporation of ^{14}C-acetate into the sterol fraction of HEP-G2 cell-cultures (concentration: 1×10^{-7} mol/L)

Compound	Sodium ^{14}C-acetate incorporation (%) into the cholesterol fraction
E (**7**)	105
F (**8**)	63
G (**9**)	125
H (**10**)	67
I (**11**)	82
J (**12**)	74
K (**13**)	93
L (**14**)	129
M (**15**)	34
Control	100

Although tuckolide **6** (identical to decarestrictine D) has been isolated from the *tuckahoe* ('ground medicine' for the Canadian Plain Indians), which is used as a poultice or for treating rheumatism, the biological activities of the purified compound in these pharmaceutical areas have not been reported.[8] At same direction, antifeedant assays with the corn earworm (*Heliothis zea*) and the fungivorous beetle (*Carpophilus hemipterus*) failed although sclerotia are long-lived and persistent in the soil and seem to be remarkably resistant to other fungi[101] and to insects.[102]

Chapleur and co-workers suggested that the seco-acid (**94**) of decarestrictine D (**6**) might be the real inhibitor of cholesterol biosynthesis. On this basis they decided to prepare the seco-acid **94** and its C-7 epimer and evaluate its biological properties as inhibitor of the rate limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl coenzyme A (**HMGR**).[74] In animal and plant cells, **HMGR** is a highly regulated control point in the biosynthesis of a vast array of isoprenoids and prenyl-lipids. In plants the isoprenoid pathway has additional branches that lead to photosynthetic pigments, growth regulators (abscisic acid, gibberellins, and some cytokinins) and phytoalexins. Therefore, inhibition of **HMGR**-linked isoprenoid biosynthesis would have wide ranging effects on plants growth and development. While mevastatin was a potent inhibitor of pea and rat liver microsomal **HMGR** activity, **94** and its C-7 epimer did not inhibit either the plant or mammalian enzymes. These results show that the reported inhibition of cholesterol biosynthesis by decarestrictine D is likely not related to the inhibition of **HMGR** by the open-chain hydroxyl-acid but is probably related to a subsequent step of the biosynthesis.

It has been demonstrated that DNA-binding agents possess, e.g., antitumor, antiviral, or antimicrobial activity, and certain substances are pharmacological and medical importance. Many antitumor drugs exert their action by interfering with the function of DNA. Preliminary testing for the evaluation of biological activity of some hybrids was conducted,[55] and revealed DNA-binding activity for decarestrictine D (**6**) and the novel glycoconjugates **137d** and **137e** (see Schemes 20 and 21). The essay employed homogenized salmon sperma and the test substance on a RP18 TLC plate and determination of the altered R_f value after development of the chromatogram. The affinity was expressed as the quotient of the R_f in the presence (R_{f1}) and in the absence (R_{f2}) of DNA. Decarestrictine **6** (R_{f1}/R_{f2}=0.1) and **137d** and **137e** (R_{f1}/R_{f2}=0.15) have shown positive results; all other glycosides prepared showed no alterations. The shift of DNA melting points of **6** (ΔT_m=0.7 °C) and **137d** (ΔT_m=0.8 °C) proved DNA affinity and the stabilizing effect on DNA. One possible explanation of this affinity could be the presence of iodine enhancing DNA binding properties.[103] Further investigations with highly sensitive label-free detection technique were used to direct detection of low-molecular weight ligands binding to an immobilized DNA.[104] When compared with more active intercalators (actinomycin D, nogalamycin, doxorubicin, sanguinarine, chelerythrine, and iodesin), the response of decarestrictine **6** was poor either in change in optical thickness with immobilized DNA or shift in DNA melting point. These results proved **6** to be a weak-binding DNA compound.

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