A number of 10-membered lactones have been isolated as secondary metabolites, and many of them have interesting and potent activities. Because of synthetic and biological interests, many synthetic studies of these compounds have been made. This review summarizes synthetic approaches to three natural 10-membered lactones, mueggelone, microcarpalide, and Sch 642305. Mueggelone is an inhibitor of fish development, microcarpalide is a microfilmament disrupting agent, and Sch 642305 is an inhibitor of bacterial DNA primase.

Key words: 10-membered lactone; mueggelone; microcarpalide; Sch 642305; total synthesis

Many 10-membered lactones have been isolated as secondary metabolites of terrestrial and marine organisms, such as bacteria, fungi, and plants. Synthetic studies on these compounds are meaningful, as well as biological studies, because their bioactivities are frequently concerned with structure. The first naturally occurring 10-membered lactone is jasmine ketolactone, which was isolated in 1942 as a component of essential oil of *Jasminum grandiflorium*, and whose structure was confirmed in 1964. Diplodialide A is the first bioactive 10-membered lactone isolated from a fungus as a steroid hydroxylase inhibitor, in 1975. After that, this class of compounds attracted many organic chemists, and many synthetic studies have been reported. In synthesizing these compounds, the key reaction is the construction of a 10-membered ring. Lactonization was most common as a ring-closing step before the development of ring-closing metathesis (RCM). Recently, construction of the lactone ring by RCM has been increasing remarkably. This review centers on synthetic approaches to three 10-membered lactones, mueggelone, microcarpalide, and Sch 642305. All of three lactones were found as microbial secondary metabolites, and synthetic approaches have been reported by many groups, including us, motivated by their potent activities.

I. Synthetic Approaches to Mueggelone

Mueggelone has attracted the keen interest of scientists for its unique activity and structure since it was isolated from a bloom-forming strain of *Aphanizomenon flos-aquae* in 1997. With mueggelone at a concentration of 10 µg/ml, zebra fish larvae showed 45% mortality, and the surviving larvae showed edema in the heart region and thrombosis. This compound is thought to play an ecologically important role in inhibition of the development of herbivorous fish. Mueggelone was found to have a 10-membered lactone and *trans*-epoxide by spectroscopic analysis; however, no information has been reported on the absolute configuration of the three stereocenters. This compound was re-isolated from blue-green alga, *Gloeotrichia sp.*, in 1998 by another group, but stereochemistry was not mentioned.

I. Our first synthesis of mueggelone

The first synthesis of mueggelone was accomplished by our group in 2000 (Scheme 1 [1]). We undertook the synthesis of all four possible stereoisomers of mueggelone, which have *trans* epoxide, to determine the absolute configuration. In order to prepare the four stereoisomers efficiently, we selected the key intermediate 4, which can be transformed into any of the four stereoisomers *via* asymmetric reduction of a ketone, macro lactonization, and finally epoxide formation. The side chain part was synthesized from alcohol 1, which was obtained from D-arabinose according to the established procedure. Alcohol 1 was converted to aldehyde 2 *via* construction of Z-olefin by Wittig reaction. The best ratio (*E*/Z = 1:10) in this Wittig reaction was provided using NaHMDS as a base, and these isomers were easily separated by AgNO3-impregnated silica gel column chromatography. Aldehyde 2 was subjected to the Horner–Wadsworth–Emmons reaction to give the key intermediate 4. Under a condition using n-BuLi as a base, the *E*/Z ratio was 96:4; however, partial epimerization (25%) of the TBSO group was observed. On the other hand, the procedure employing DBU–LiCl resulted in very little epimerization (1–2%) with excellent *E*/Z selectivity (*E*/Z = >99:1). Now that the key intermediate was obtained enantioselectively, we tried several conditions for asymmetric reduction of the enone 4, and the best selectivity (α/β = 9:1 or 9:1) was obtained with the (S)- or (R)-CBS-reagent and borane–THF complex. After confirmation of the stereochemistry of each isomer by the modified Mosher’s

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method,[13] hydrolysis was followed by Yamaguchi lactonization[14] to give 10-membered lactone 5 and 6 in satisfactory yield, together with a small amount of a dimeric lactone (5–10%). On the other hand, the Corey–Mukaiyama method[15] was found to give only several unidentifiable compounds. In the following epoxide formation stage, we succeeded in controlling the stereochemistry of the epoxide by the direction of elimination, that is, mueggelone and (9S,12R,13R)-isomer were obtained from 5 by changing the position of the leaving group. In the same way, (9S,12S,13S)- and (9S,12R,13R)-isomer were synthesized from 6. With the four stereoisomers in hand, we analyzed the NMR spectra and specific rotations carefully. It was hard to distinguish these isomers by 1H NMR, but in the 13C NMR spectra an obvious difference was observed. In addition, the sign of specific rotation (natural: +28.3, synthetic: +28.7) showed that natural mueggelone had an absolute configuration of 9S.[16] This compound acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells.[21] Because of the large difference between the effective concentration for antimicrofilament activity and for cytotoxicity, it is thought that this compound

2. Synthesis of mueggelone by Yadav et al.

Yadav et al. reported the synthesis of mueggelone in 2008 (Scheme 1[2]).[16] introducing all three stereocenters by Sharpless asymmetric epoxidation (AE).[17] Their key reaction was olefin cross metathesis between side chain moiety 10 and lactone moiety 15 in the final step of synthesis. The side chain moiety was synthesized from propargyl alcohol. Diyne 7 was partially reduced to allylic alcohol 8, and was subjected to Sharpless AE[17] and Lindlar hydrogenation to afford epoxide 9. C1-homologation gave terminal olefin 10. On the other hand, lactone moiety 15 was synthesized from allylic alcohol 11, which was prepared from 1,9-nonanediol in several steps. After Sharpless AE, it was converted to the corresponding epoxy iodide 12. Terminal olefin was introduced by a reductive epoxide opening in the presence of zinc[18] to afford 13, which was converted to the corresponding hydroxy acid 14. Yamaguchi lactonization[19] of hydroxy acid 14 gave lactone 15. Olefin cross metathesis[4,19] between precursors 10 and 15 in the presence of the 2nd-generation Grubbs catalyst[20] gave mueggelone with complete E selectivity, but the yield was not very high (40%) because undesired homodimer was generated.

II. Synthetic Approaches to Microcarpalide

Microcarpalide is a 10-membered lactone, isolated from the fermentation broth of an unidentified endophytic fungus by Hemscheidt and co-workers in 2001.[21] This compound acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells.[21] Because of the large difference between the effective concentration for antimicrofilament activity and for cytotoxicity, it is thought that this compound

Scheme 1. Synthetic Approaches to Mueggelone.
will be an effective tool in studies of cell motility and metastasis, and will be a potential lead structure to selective, nontoxic antiactin agents. Since the isolation of microcarpalide, a number of syntheses have been reported in the past few years.

1. First synthesis of microcarpalide by Marco et al.

The first synthesis of microcarpalide was achieved by Marco and co-workers in 2002 (Scheme 2 [1]). Their key reaction was the RCM of ester 18 to form 10-membered lactone, and four stereocenters were derived from commercially available chiral pools. (R)-Glycidol was converted to alcohol 16 by epoxide opening with n-pentyl cuprate and subsequent chelation-controlled allylation. Alcohol 16 was coupled with acid 17, which was derived from (S,S)-tartaric acid, to afford diene ester 18, the precursor for RCM. Treatment of 18 with 1st-generation Grubbs catalyst under high dilution conditions (1 mM) provided a 2:1 E/Z mixture of 10-membered lactone 19. On the other hand, it is worth mentioning that the use of 2nd-generation Grubbs catalyst resulted in the exclusive formation of undesired (Z)-19. Their theoretical calculations showed that (Z)-19 is more stable than (E)-19, by about 2 kcal/mol. The authors supposed that the E/Z ratio was no longer kinetically controlled but rather the result of a chemical equilibrium, and that it caused a marked enhancement in the percentage of (Z)-isomer. After isolation of (E)-isomer from the 2:1 mixture (19), deprotection gave microcarpalide. Although there was a small problem with E/Z selectivity at the ring-closing step, they achieved short and efficient synthesis of microcarpalide.

2. Other syntheses of microcarpalide employing RCM

Since Marco et al. achieved the first synthesis of microcarpalide, a number of syntheses have been reported. Similarly to Marco’s synthesis, most of them also featured RCM of a diene ester of type 18. In their synthetic approaches, construction of the four stereocenters and selection of protecting groups, which influence the total efficiency and E/Z selectivity of RCM, are important.

(1) Synthesis by Gurjar et al.

Gurjar and co-workers employed diene ester 24, protected with benzyl groups and a methoxymethoxy-methyl (MEM) group, as a precursor for RCM in 2003 (Scheme 2 [2]). Olefinic alcohol 21 was synthesized by Sharpless asymmetric dihydroxylation (AD) of unsaturated ester 20 and the following introduction of a C2 unit. On the other hand, acid 23 was derived from the known compound 22, which was easily obtained from d-mannose. These two fragments were subjected to esterification to give the precursor for RCM. Reaction of 24 (high dilution, 1.6 mM) in the presence of 1st-generation Grubbs catalyst provided E- and Z-isomers of 25 in 10:1 ratio. Finally, removal of the MEM group using TiCl4 resulted in debenzylation to afford microcarpalide. Interestingly, compared with Marco’s synthesis, E/Z selectivity at the ring-closing step was greatly improved by changing the protective groups. Similarly, Ghosh et al. also reported a total synthesis of microcarpalide using the same precursor 24 for RCM in 2005, in which all four stereocenters were derived from d-mannitol (scheme not shown).

(2) Synthesis by Davoli et al.

Davoli and co-workers selected tribenzyl ether as a precursor for RCM in their 2nd-generation synthesis in 2005, a revision of their first synthesis in 2004 (Scheme 2 [3]). In the revised synthesis, they successfully exploited Matteson’s asymmetric homologation to introduce contiguous stereocenters, using (+)- and (−)-pinanediol as chiral directors. Chiral boronate obtained from (+)-pinanediol was subjected to asymmetric homologation to insert the first stereocenter to give α-chloro derivative. After S2/C substitution of the chloride with benzylxoyde, the second asymmetric center was introduced by repeating homologation to give 2-benzoxyl-1-chloroboronate. Treatment with allylmagnesium bromide and subsequent oxidative removal of the boronic scaffold afforded homoallyl alcohol. Similarly, boronate obtained from (−)-pinanediol was transformed into acid 31 by employing Matteson’s asymmetric homologation twice. Alcohol 28 and acid 31 were coupled to provide ester 32. RCM of tribenzyl ether (high dilution, 0.52 mM) with 1st-generation Grubbs catalyst resulted in exclusive formation of E-isomer 33, but with poor conversion (43%). Finally, deprotection was performed using TiCl4 under similar conditions as Gurjar’s to afford microcarpalide. The total yield was not sufficient in their synthesis, but employing Matteson’s asymmetric homologation for construction of all stereochemistry appeared to be a steady and unique approach. In 2007, Prasad et al. reported synthesis of microcarpalide using the same precursor for RCM. They constructed from (S,S)- and (R,R)-tartaric acid in a longer reaction scheme (not shown). Interestingly, they reported that RCM of 32 using 2nd-generation Grubbs catalyst provided an E/Z-mixture with poor conversion (36%).

(3) Synthesis by Sharma and Cherukupalli

In 2006, Sharma and Cherukupalli reported a process of synthesis in which they employed diene ester 38, protected with acetomide and benzyl group, as a precursor for RCM (Scheme 2 [4]). Alcohol 35 was synthesized by epoxide opening of 34, which was prepared from L-ascorbic acid. The other fragment, involving the residual stereocenters, was prepared by Evans aldol reaction using 1,4-butanediol as the starting material. Connection of two fragments 35 and 37 was carried out under the Yamaguchi conditions, and the resulting ester 38 was subjected to RCM using 1st-generation Grubbs catalyst. High dilution conditions (1.4 mM) brought a result similar to Marco’s group, giving a 2:1 E/Z mixture of 10-membered lactone 39 in good yield. After purification of E-isomer, deprotection successfully afforded microcarpalide.

(4) Synthesis by Banwell and Loong

Three further groups also reported synthesis of this compound using RCM. Banwell’s group (2004, ent-microcarpalide), Chavan’s group (2005), and Fürstner’s group (2007) employed precursor 18 for RCM, the same intermediate as in Marco’s synthesis. Synthesis of ent-microcarpalide by Banwell and Loong is shown in Scheme 2 [5]. They construed the intermediate ent-18 by cross metathesis of α,β-unsaturated ester 44 using 2nd-generation Grubbs catalyst under ethylene, because direct methylation...
of hemiacetal 43 (conversion to ent-18) was not successful, and RCM of α,β-unsaturated ester 44 did not proceed.\(^\text{75}\) Hemiacetal 43 was synthesized from alcohol 41 and acid 42, whose stereocenters originated in Sharpless AD\(^{30,31}\) and (S)-malic acid respectively. In their synthesis, installation of the second double bond for RCM was problematic and lowered synthetic efficiency. Chavan’s group\(^\text{55}\) installed all four stereocenters of 18 by Sharpless AD\(^{30,31}\) while Fürstner’s group\(^\text{66}\) installed them by Sharpless AE\(^{73}\) and AD\(^{30,31}\) (schemes not shown). All of three groups reported that RCM of 18 (or ent-18) resulted in E/Z selectivity similar to that of Marco’s group.\(^\text{22,23}\)

(5) Consideration of the synthesis of microcarpalide by RCM

The majority of syntheses of microcarpalide were based on RCM, as described above. In them, it was most important to construct the desired E-olefin selectively at the ring-closing step. Here, two possible factors influencing E/Z selectivity are discussed.

First, selection of ruthenium catalyst for RCM is important for E/Z selectivity. As reported by Marco, Davoli, Prasad, and Fürstner, the use of 1st-generation Grubbs catalyst\(^\text{59}\) showed moderate or high E selectivity, while the use of 2nd-generation Grubbs catalyst resulted\(^\text{60}\) in enhanced formation of Z-isomer. The similar phenomenon was observed in synthesis of other medium-sized rings\(^\text{67}\) and this must be an important characteristic of RCM. In many syntheses of medium-sized rings by RCM, formation of the E/Z mixture was observed. Generally, olefins formed by RCM were sensitive to the reverse reaction, such as ring opening metathesis (ROM), because of the internal ring strain. 2nd-generation Grubbs catalyst tends to form thermodynamically stable isomers, so Z-isomers are favored in the case of a strained medium-sized ring.\(^\text{27}\)

Second, the selection of protecting groups to be attached to the precursor is also important for reactivity and E/Z selectivity in RCM. In the syntheses of microcarpalide listed above, all the groups employed the same diene esters except for the protecting groups. RCM of the substrates, whose 4-OH and 5-OH were protected with acetoxime (18 and 38), proceeded smoothly in good yield but with moderate E/Z-selectivity (2:1), regardless of the protecting group of 10-OH. The conformational restraint tethered by acetoxime may make both of the reacting sites cyclize easier. On the other hand, when 4-OH and 5-OH were protected as benzyl ether separately (24 and 32), the reaction proceeded with excellent E-selectivity. However, in these cases, the protecting group at C-10 had a great influence on reactivity, that is, MEM protection afforded good yield, while benzyl protection resulted in poor conversion. Careful tuning of protective groups, especially at allylic positions, is necessary for stereoselective construction of medium-sized rings as above by RCM. Recently, Mohapatra et al. reported syntheses of 10-membered lactones by protecting group directed RCM.\(^\text{58}\)

3. Our synthesis of microcarpalide

Our synthesis of microcarpalide is shown in Scheme 2.\(^\text{6}\),\(^\text{49,50}\) Most synthetic approaches have been based on RCM, whereas we selected lactonization as a ring-closing step and Julia coupling\(^\text{51}\) for the construction of trans-olefin. We also decided to introduce all four stereocenters using Sharpless AD.\(^\text{30,31}\) Starting from the known diol 45,\(^\text{52}\) olefinic ester 46 was prepared by Claisen rearrangement,\(^\text{53,54}\) which was subjected to Sharpless AD. Enrichment of enantiomeric purity was achieved by recrystallization of an intermediate to give aldehyde 47 in an enantiomerically pure form. On the other hand, the sulfone unit was prepared by Sharpless AD of the known olefinic alcohol 48,\(^\text{55}\) and sulfone 49 was also obtained in an enantiomerically pure form via recrystallization of an intermediate. One-pot Julia coupling\(^\text{51,56,57}\) of sulfone 49 and aldehyde 47 using KHMS afforded olefin 50 in good yield, but E/Z selectivity was not very high (E/Z = 2:1). Because the low selectivity appeared to be caused by some chelation effects of oxygen functional groups in sulfone 49 and aldehyde 47 with potassium cation, we tried other conditions employing additives to prevent this chelation. When 18-c-6 was added, trans-olefin 50 was successfully obtained in good yield and high selectivity (E/Z = 10:1). After separation of 50 from cis-isomer, it was converted to the corresponding hydroxy acid, which was subjected to Yamaguchi lactonization\(^\text{52}\) to afford 10-membered lactone in excellent yield (94%). Formation of dimeric lactone was observed at higher concentrations, but not in 1 mM. Finally, deprotection was performed using BF\(_3\)-OE\(_2\) and (CH\(_3\)SH)\(_2\) at −10°C to give microcarpalide successfully. Thus we accomplished a convergent and stereoselective synthesis of microcarpalide with good efficiency employing Julia coupling and Yamaguchi lactonization. Interestingly, acid-catalyzed isomerization of microcarpalide was clarified in the course of our examination. Microcarpalide was found to be partially isomerized by treatment with TsOH, affording a mixture of microcarpalide (10-membered lactone) and 51 (11-membered lactone) in a ratio 6.5:1.

4. Synthesis of microcarpalide by Kumar et al.

In 2005, Kumar and co-workers reported another synthesis using Yamaguchi lactonization as a ring-closing step (Scheme 2).\(^\text{26}\) They also introduced all four stereocenters using Sharpless AD.\(^\text{30,31}\) Acetylene 53 was prepared from α,β-unsaturated ester 52, which was obtained from 1,4-butanediol. Stereocenters were installed by Sharpless AD, and terminal acetylene was constructed by Corey-Fuchs protocol\(^\text{59}\) to give 53. Epoxide 55 was derived from allyl alcohol 54 via Sharpless AD, and Yamaguchi coupling\(^\text{56}\) of acetylene 53 and epoxide 55 provided alcohol 56. Coupled compound 56 was converted to hydroxy acid 57 by Birch reduction\(^\text{51}\) of the triple bond to trans-olefin. Hydroxy acid 57 was the same intermediate as ours, and it was transformed into microcarpalide in a manner similar to our synthesis. Though the reaction scheme was slightly long, the yield of each step was very good.

III. Synthetic Approaches to Sch 642305

In 2003, Chu et al. isolated Sch 642305 from Penicillium verrucosum as a potent inhibitor of bacterial DNA primase.\(^\text{62}\) Because DNA primase is necessary for the replication of chromosomal DNA, this compound is thought to provide an alternative treatment for infectious diseases. In addition, Jayasuriya and co-
workers have reported that Sch 642305 potently inhibits HIV-1 Tat transactivation. Sch 642305 has a bicyclic structure including 10-membered lactone fused with 4-hydroxycyclohexenone. Its unique structure and its significant biological activities have attracted the attention of many organic chemists, and six synthetic approaches, including ours, have been reported in the past few years.

Scheme 2. Synthetic Approaches to Microcarpalide.
1. First synthesis of Sch 642305 by Mehta and Shinde

First synthesis of Sch 642305 was achieved by Mehta and Shinde in 2005 (Scheme 3 [1]). They employed the RCM protocol to construct a 10-membered lactone moiety, and they started from the known endo-tricyclic Diels–Alder adduct of cyclopentadiene and p-benzoquinone. Asymmetric centers were introduced by lipase-mediated enzymatic desymmetrization and via the corresponding meso-diol, which was obtained by reduction of 58.

After oxidation to cyclohexanone 59, zinc-mediated Barbier-type alkylation and subsequent oxy-Cope rearrangement provided the allylated product as a single diastereomer. The norbornyl scaffold was disengaged through a retro-Diels–Alder process to furnish cyclohexenone 60. An ester moiety was introduced by regio- and stereoselective alkylation of 60, and the RCM precursor 61 was obtained via Luche reduction (C-4: \( \alpha/\beta = 1.2:1 \)).

RCM of 61 with the 2nd-generation Grubbs catalyst proceeded smoothly to generate the bicyclic framework. Because it was difficult to reduce the double bond in the lactone ring selectively, catalytic hydrogenation led to fully saturated bicyclic compound 62, in which the enone had to be restored. The restoration was accomplished via the phenylethenation-selenoxide elimination sequence, and finally deprotection with TBAF-AcOH afforded Sch 642305. In this approach, the selectivity of reduction at C-4 was not satisfactory, and the necessity of restoring the enone was a detour.

2. Our synthesis of Sch 642305

Following first synthesis, our group also succeeded in stereoselective synthesis of Sch 642305 (Scheme 3 [2]). We selected lactonization as a ring-closing step and dianion alkylation for construction of the lactonization precursor. Our starting material 63 (99% ee) was prepared in large quantity via stereoselective reduction of the corresponding \( \beta \)-ketoester with baker’s yeast.

In our laboratory, a number of natural products were successfully synthesized using 63 as a chiral building block. This chiral building block was converted to \( \beta \)-keto sulfoxide 64 after elongation of the side chain. In the step introducing phenylthio group, regioselectivity was 3.5:1, and the undesired minor isomer was easily removed by chromatography after oxidation to 64. On the other hand, iodide 65 was obtained in several steps from (S)-3-hydroxybutylate (98% ee), which could be easily prepared in large amounts from ethyl acetocetate via stereoselective reduction with baker’s yeast and enzymatic improvement of the optical purity.

\( \beta \)-Ketosulfoxide 64 was subjected to regio- and stereoselective alkylation with iodide 65 by the dianion procedure, and subsequent thermal elimination afforded tri-substituted cyclohexenone 66 as a single isomer in moderate yield. As we expected, alkylation occurred selectively from the less hindered \( \beta \)-face of the dianion. After conversion to hydroxy acid 67, it was subjected to Yamaguchi lactonization to afford 10-membered lactone successfully with a small amount of a dimeric lactone. Removal of the TBS group was successful using TBAF-AcOH as in Mehta’s condition, while other conditions resulted in partial epimerization at the C-6 position (\( \beta/\alpha = 3.1:1 \)). Thus we succeeded in stereoselective synthesis of Sch 642305 starting from two chiral sources, which were prepared by stereoselective reduction with baker’s yeast. Alkylation of the \( \beta \)-keto sulfoxide by dianion procedure selectively afforded the desired stereochemistry, and Yamaguchi’s lactonization was also successful in good yield.

3. Synthesis of Sch 642305 by Snider and Zhou

Snider and Zhou also reported the synthesis of Sch 642305 employing Yamaguchi lactonization, but their approach was based on a biomimetic transannular Michael reaction of 14-membered lactone 71 (Scheme 3 [3]). Introduction of the chiral center was performed on olefin 68 by Jacobsen kinetic resolution using oligomeric (salen)Co(III) catalyst to give epoxide 69. After reductive opening of the epoxide, the resulting aldehyde was reacted with acetylide and converted to hydroxy acid 70. Though compound 70 was obtained as an inseparable 1:1 mixture of diastereomers, they were readily separated after the formation of macroolide 71 by Yamaguchi lactonization. Treatment of ketolactone 71 with NaH afforded transannular Michael adduct 72 as a single isomer in good yield, but this bicyclic compound had a cis-fused structure. Their MM2 calculations suggested that Sch 642305 was about 1 kcal/mol more stable than 6-epi-Sch 642305, and so they examined the epimerization of 72. The best result was obtained by microwave irradiation of 72 in the presence of TFA, which gave a separable mixture of 72 and the desired 6-epi-72 (2:7:1). Finally, deprotection of 6-epi-72 provided Sch 642305. In this synthesis, the stereoselectivity at C-4 and C-6 was not satisfactory, but the synthetic approach based on a biomimetic transannular Michael reaction was original and interesting.

4. Synthesis of Sch 642305 by Wilson and Trauner

Wilson and Trauner reported the synthesis of Sch 642305 based on RCM (Scheme 3 [4]). Their approach was similar to Mehta’s first synthesis, but was a very concise synthesis in short steps, starting from the simple building block. Cyclohexenone 73 is known to be preparable from a natural product, quinic acid, as the starting material. A methodology similar to Wilson’s as in Mehta’s condition, while other conditions resulted in partial epimerization at the C-6 position (\( \beta/\alpha = 3.1:1 \)). Thus we succeeded in stereoselective synthesis of Sch 642305 starting from two chiral sources, which were prepared by stereoselective reduction with baker’s yeast. Alkylation of the \( \beta \)-keto sulfoxide by dianion procedure selectively afforded the desired stereochemistry, and Yamaguchi’s lactonization was also successful in good yield.

5. Synthesis of Sch 642305 by Carda et al.

Carda et al. also succeeded in the short-step synthesis of Sch 642305 using cyclohexenone as the starting material. A methodology similar to Wilson’s
synthesis\(^{91}\) was employed, except for ring-closure (Scheme 3 [5]).\(^{88}\) According to the reported procedure,\(^{89}\) cyclohexene \(73\) was reacted with silyl ketene acetal \(78\)\(^{102}\) to afford silyl enol ether \(79\) as the only product. Treatment of \(79\) with iodide \(80\) in the presence of TASF\(^{95,96}\) provided ester \(81\) as the sole stereoisomer. In the conversion of the ester \(81\) to the corresponding hydroxy acid, ethyl ester was hydrolyzed in the presence of potassium trimethylsilyl anolate\(^{101}\) to avoid epimerization at C-6. The hydroxy acid was subjected to Mitsunobu lactonization\(^{101}\) to give bicyclic lactone \(77\). In the same manner as in Wilson’s synthesis,\(^{91}\) bicyclic lactone \(77\) was converted to Sch 642305 via Saegusa-Ito unsaturation.\(^{97}\) They succeeded in concise synthesis, and the stereoselectivity was excellent.

6. Synthesis of Sch 642305 by Fujioka et al. Recently, Fujioka et al. reported the synthesis of Sch 642305 using chiral auxiliary multiuse methodology (Scheme 3 [6]).\(^{103}\) They used (R,R)-hydrobenzoin not only as a chiral auxiliary, but also as a protecting group and as a template to control regio- and stereochemistry. Bromo acetal \(83\) was synthesized by intramolecular bromoetherification of cyclohexadiene acetal \(82\)\(^{104}\). Hydroboration of \(83\) using tetrabutylborate was followed by oxidation to give a \(\beta\)-bromoketone, from which spontaneous elimination afforded enone \(84\) in moderate yield. While direct alkylation at the \(\alpha\)-position of enone \(84\) was unsuccessful, aldol reaction of \(84\) with \(85\) occurred from a less hindered face of the cyclohexenone ring to give \(86\) in the diastereomerically pure form. After

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[1] Mehta and Shinde (2005) –– 4.3% in 19 steps from \(58\)


[3] Snider and Zhou (2006) –– 1.6% in 17 steps from \(7-octenal\)


[5] Carda et al. (2007) –– 12% in 8 steps from \(enone\)

[6] Fujioka et al. (2007) –– 3.5% in 11 steps from acetal \(83\)

Scheme 3. Synthetic Approaches to Sch 642305.
Michael addition of PhSH to the enone moiety, the secondary hydroxy group was removed by reduction of the corresponding xanthate to afford ketone 87. This ketone was partially deprotected, and was transformed into hydroxy acid 88. Macrolactonization was performed by the modified Corey-Mukaiyama method.15) During this lactonization, β-elimination of PhSH occurred simultaneously to regenerate the enone moiety, and removal of the chiral source provided Sch 642305. Though, chemical yields in some steps were not high, application of the multipurpose chiral auxiliary was interesting and control of regio- and stereochemistry was satisfactory.

IV. Conclusion

We have briefly discussed synthetic studies on three natural 10-membered lactones, mueggelone, microcarpalide, and Sch 642305. Because of their potent activities and their unique structures, these microbial metabolites have fascinated many synthetic chemists, and a number of synthetic approaches have been reported, as described above. Now RCM is the order of the day, and many approaches to these macrolides employ RCM as a ring-closing reaction. In the synthesis of medium-sized lactones, E/Z selectivity and reactivity are greatly influenced by the structure of the product or substrate, and thus it is important to tune up the intermediate of the synthesis. On the other hand, Yamaguchi lactonization is one of the classical methodologies, but it continuously exists as a powerful method for the synthesis of macroide. RCM and Yamaguchi lactonization are alternative and complementary ways in the synthesis of this class of compounds. Inspired by the unique structures and potent activities of natural products, organic chemists will continue to make progress in the synthesis of natural products. It is desirable that synthetic studies on natural products make a contribution to the development of both chemistry and biology.

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References