Account / Revue

Migrastatin and analogues: New anti-metastatic agents

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Abstract

Migrastatin and some migrastatin analogues are potent anti-metastatic agents. The biological activity as well as the chemical syntheses of migrastatin and its analogues is discussed. *To cite this article: Sé. Reymond, J. Cossy, C. R. Chimie 11 (2008).*
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1. Introduction

Cancer is one of the most severe worldwide health problems. In 2005, 7.6 million of the 58 million deaths in the world were attributed to cancer [1]. Since metastasis is often responsible for fatal outcomes among cancer patients, substantial progress in the ability to treat this disease will critically depend on the discovery of new anti-metastatic drugs and the development of more effective clinical strategies [2].

Recently, the discovery of migrastatin, a new anti-migratory agent, has stimulated the development of a diverse array of analogues with activity against tumor cell migration. This review will present the isolation and structure elucidation of migrastatin, as well as the syntheses and applications of migrastatin and its analogues.

2. Isolation and structure elucidation

In 2000, Imoto et al. reported the first isolation of migrastatin **1** from a cultured broth of the strain *Streptomyces* sp. MK929-43F1 which was collected in Japan [3]. The gross structure of migrastatin was proposed to be a 14-membered macrolactone incorporating three double bonds and featuring a pendant alkyl glutarimide side-chain. Later, in 2002, the absolute configuration of migrastatin was assigned by X-ray crystallographic analysis of the *N-p*-bromophenacyl derivative **2**, and the absolute configuration was also confirmed by the modified Mosher's method [4]. The macrocyclic core of migrastatin features an interesting *syn−syn* stereotriad at C8−C10 with the (8*S*, 9*S*, 10*R*) configuration and incorporates a (*Z*)-trisubstituted double bond (Fig. 1).

The same year, in 2002, Licari et al. isolated migrastatin as well as *iso*-migrastatin **3** from a culture of *Streptomyces platensis* NRRL 18993 [5]. This strain was already known for producing dorrigocins A **4** and B **5**, which are linear isomers of migrastatin (Fig. 2). More recently, Shen et al. used gene-inactivation of the *S. platensis* polyketide synthase to demonstrate that

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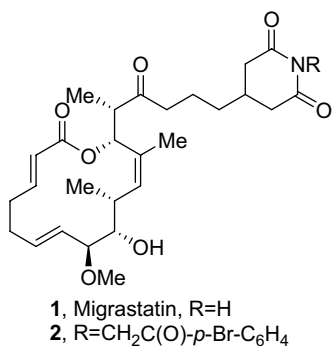
1, Migrastatin, R=H
2, R=CH₂C(O)-*p*-Br-C₆H₄

Fig. 1.

migrastatin and dorrigocins were actually shunt metabolites of *iso*-migrastatin [6].

3. Biological activity of migrastatin and analogues

In earlier studies, Imoto et al. reported that migrastatin inhibited the migration of esophageal cancer EC17 cells and mouse melanoma B16 cells with IC_{50}s of 1.0 μg/mL and 3.0 μg/mL, respectively, in wound healing assays [3]. Although other glutarimide containing natural products possess antibiotic activities [7], migrastatin has no effect on the biosyntheses of proteins, RNA, or DNA. However, Imoto et al. found that in their original isolation of migrastatin, tele-ocidin-related impurities were present. As teleocidin-related compounds are well known to inhibit tumor cell migration, the study of the inhibition of tumor cell migration by pure migrastatin was carried out, and it was shown that migrastatin actually inhibited the migration of EC17 cells with an IC_{50} of 10 μg/mL [8]. In this study, the authors also found that migrastatin displayed low cytotoxicity, and it was a weak anti-proliferative agent on a variety of tumor cells with IC_{50}s around 100 μg/mL or higher. Furthermore,

Danishefsky et al. showed that migrastatin had a modest IC_{50} of 29 μM on the migration of 4T1 mouse breast tumor cells in a chamber cell migration assay [9]. The metabolic stability of migrastatin in mouse plasma was verified, and no lactone opening was observed [10]. The migration of human umbilical vein endothelial cells was also moderately inhibited with an IC_{50} of 65 μM [10].

More recently, Imoto et al. reported that migrastatin was capable of suppressing multidrug resistance [11]. Indeed, migrastatin inhibits P-glycoprotein and consequently sensitizes drug resistant P-glycoprotein-overexpressing tumor cells to anticancer drugs like taxol, vinblastine, and vincristine. It was proposed that migrastatin interacts with P-glycoprotein at the azidopine- and vinblastine-binding site. In a recent study, Nakae et al. revealed that migrastatin acts as a muscarinic acetylcholine receptor antagonist [12]. However, the biological target and mode of action of migrastatin remain unknown.

Inspired by the anti-metastatic potential of migrastatin, a variety of simplified analogues, the syntheses of which will be presented later (*vide infra*), were evaluated for structure–activity relationship studies (Fig. 3). Danishefsky et al. have screened the biological activity of analogues **6**–**21** and they have reported that macrolactones **8** and **9** were 1000 times more active than migrastatin itself on the migration of 4T1 cells with IC_{50}s of 22 nM and 24 nM, respectively (Table 1) [9,10]. Whereas **1** was reported to be stable in mouse plasma, lactones **8** and **9** showed rapid lactone opening. Hydroxy-acid **14**, which is the hydrolyzed form of lactone **9**, still possesses an IC_{50} of 378 nM [10]. When macroketone **11**, which was stable in mouse plasma, was tested on 4T1 cell migration, an IC_{50} of 100 nM was obtained [10].

When analogues **8**, **9**, and **11** were evaluated on human endothelial cell migration (HUVECs), lower

3, *iso*-migrastatin   **4**, dorrigocin A   **5**, dorrigocin B
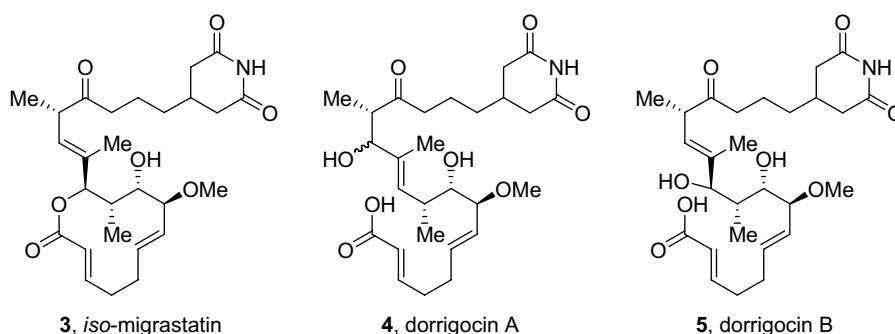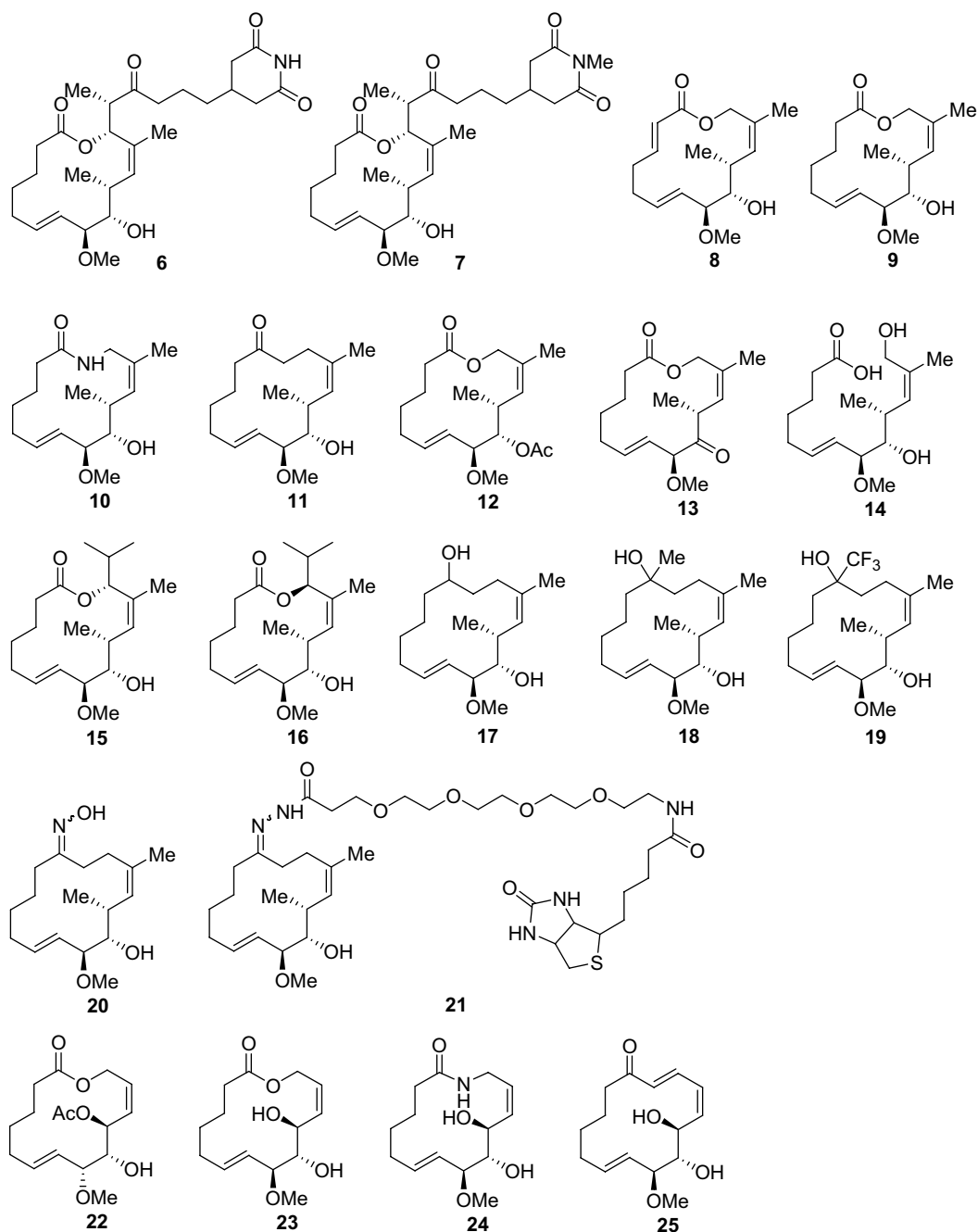
Fig. 2.

Fig. 3.

inhibitory activities were observed, but analogues **8** and **9** still display higher activities than migrastatin **1** (Table 2) [10]. It was also shown that macrolactone **8** had good activity against the migration of human cancer cells such as HT 29, Ovcar3, and RL without interfering with cell proliferation [10].

In another study, Danishefsky et al. demonstrated that macrolactam **10** and macroketone **11** were potent

metastasis inhibitors in *in vivo* mouse models. These simplified migrastatin analogues appear to inhibit Rac activation, thus blocking the formation of lamellipodia and inactivating the metastatic process [13].

More recently, Murphy et al. reported their results in the evaluation of new migrastatin analogues **22**–**25** as potent anti-metastatic agents, but these macrocyclic compounds displayed lower activities than Danishefsky's

Table 1
Chamber cell migration assay with 4T1 cells [10]

Compound	IC_{50}
1	29 μM
6	10 μM
7	7.0 μM
8	22 nM
9	24 nM
10	255 nM
11	100 nM
12	192 nM
13	223 nM
14	378 nM
15	227 μM
16	146 μM
17	8.9 μM
18	3.1 μM
19	101 nM
20	2.3 μM
21	331 nM

26
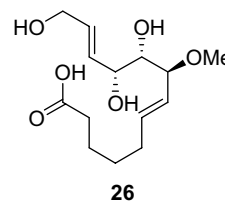
Fig. 4.

analogues [14]. However, during their studies, Murphy et al. disclosed that the simplified dorrigocin analogue **26** was a potent inhibitor of the migration of gastric adeno-carcinoma (AGS) cells at nanomolar concentrations (Fig. 4).

The inhibition of tumor cell migration is an important process that could contribute to the eradication of cancer. Further studies concerning the mode of action of migrastatin and its analogues will probably help the chemists to design improved migrastatin analogues for applications in cancer therapies.

4. Synthesis of migrastatin and analogues

4.1. Total synthesis of migrastatin

To date, two syntheses of migrastatin have been reported in the literature [10,15,16] as well as one semisynthesis achieved from *iso*-migrastatin [17].

4.1.1. Synthesis of Danishefsky et al. [10,15]
The strategy of Danishefsky et al. for the elaboration of migrastatin relied on the preparation and assembly of five subunits **A**, **B**, **27**−**29**. The three stereogenic centers

Table 2
Chamber cell migration assay with HUVECs [10]

Compound	IC_{50}
1	65 μM
8	150 nM
9	125 nM
11	12 μM

present at C8−C10 would be installed through a stereoselective Lewis Acid-Catalyzed Diene Aldehyde Condensation (LACDAC) between chiral aldehyde **27** and substituted butadiene **28**. The obtained C7−C13 fragment would next be elongated by using a condensation with a chiral propionamide of type **B**, which would establish the C13 and C14 stereocenters. The glutarimide side-chain would be attached to the C7−C16 fragment by using a Horner−Wadsworth−Emmons (HWE) olefination with aldehyde **29** followed by the reduction of the generated enone. Finally, a fragment of type **B** would be linked at C13 to introduce the non-conjugated diene moiety, and a RCM (ring-closing metathesis) would establish the macro-lactone core (Scheme 1).

The synthesis of migrastatin started with the preparation of allylic alcohol **34** which possesses three of the five stereogenic centers present in migrastatin as well as the (Z)-trisubstituted double bond (Scheme 2). In order to achieve the chelation-controlled LACDAC, the key aldehyde **27** was prepared from commercially available 2,3-*O*-isopropylidene-L-tartrate (**30**) in four steps. Indeed, diester **30** was reduced with DIBAL-H to the corresponding dialdehyde and subsequently treated with the *in situ* generated divinylzinc to afford a diol which was obtained with a good diastereoselectivity (>90%). After methylation of the obtained diol (NaH, MeI) and removal of the acetonide protecting group (HCl, MeOH), tetraol **31** was obtained in 60% yield from tartrate **30**. The oxidative cleavage of diol **31** was achieved using Pb(OAc)$_4$, leading to aldehyde **27** which was directly engaged in an α-chelation controlled LACDAC with diene **28**. The formation of dihydropyrone **32** (87% yield from diol **31**), as a single diastereoisomer incorporating the *syn−syn* stereotriad required for the synthesis of migrastatin, can be rationalized by an *exo* mode of approach of the diene as a result of the chelation with TiCl$_4$ of both the carbonyl group and the α-methoxy group of the alde-hyde [18]. Dihydropyrone **32** was then transformed to diol **33** in three steps. The carbonyl group was first reduced with LiBH$_4$, the resulting alcohol was subjected to a Ferrier-rearrangement upon treatment
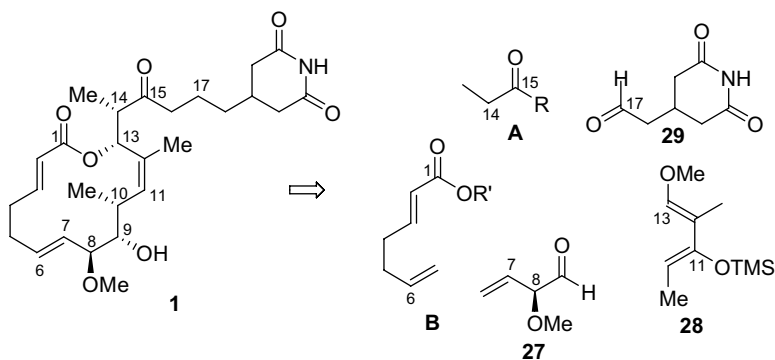
Scheme 1.

with CSA, producing a lactol which was finally reduced with LiBH$_4$ to yield diol **33**.

In their first approach to this fragment, Danishefsky et al. differentiated between the primary versus the secondary hydroxyl groups in diol **33** by using a three-step sequence involving an acetylation of the primary hydroxyl group, a silylation of the free secondary hydroxyl group, and finally, the removal of the acetate at the primary position. Unfortunately, this sequence suffered from low yielding upon scaling-up the synthesis. In contrast, a better procedure involved the protection of both hydroxyl groups with TBSOTf and selective cleavage of the primary silyl ether (AcOH, THF, H$_2$O) yielding alcohol **34** (80% from **33**).

The synthesis of fragment C7–C21, compound **40**, is delineated in Scheme 3. After oxidation of **34** to the corresponding aldehyde, an Evans *anti*-aldol reaction (MgCl$_2$, Et$_3$N, TMSCl) [19] with oxazolidinone **35** allowed the isolation of imide **36** in 67% yield. The

protection of alcohol **36** as a triethylsilyl (TES) ether followed by the removal of the chiral auxiliary led to the formation of primary alcohol **37** (83%) which was transformed to phosphonoacetate **38** after three additional steps. The HWE olefination between **38** and aldehyde **29** under Masamune–Roush conditions [20] installed the glutarimide side-chain of migrastatin, allowing the formation of enone **39** as a single olefin isomer in 57% yield over the last four steps. Fragment C7–C21 **40** was finally obtained in 82% yield after the conjugate reduction of enone **39** with the Stryker reagent {[(Ph$_3$P)CuH]$_6$} and the selective cleavage of the TES silyl ether at C13.

To complete the synthesis of migrastatin, secondary alcohol **40** was reacted with the previously prepared mixed anhydride **41** under Yamaguchi acylation conditions to give dienic ester **42** [21]. Danishefsky et al. envisioned other acylation conditions, but only the Yamaguchi protocol gave satisfactory results. Finally, the
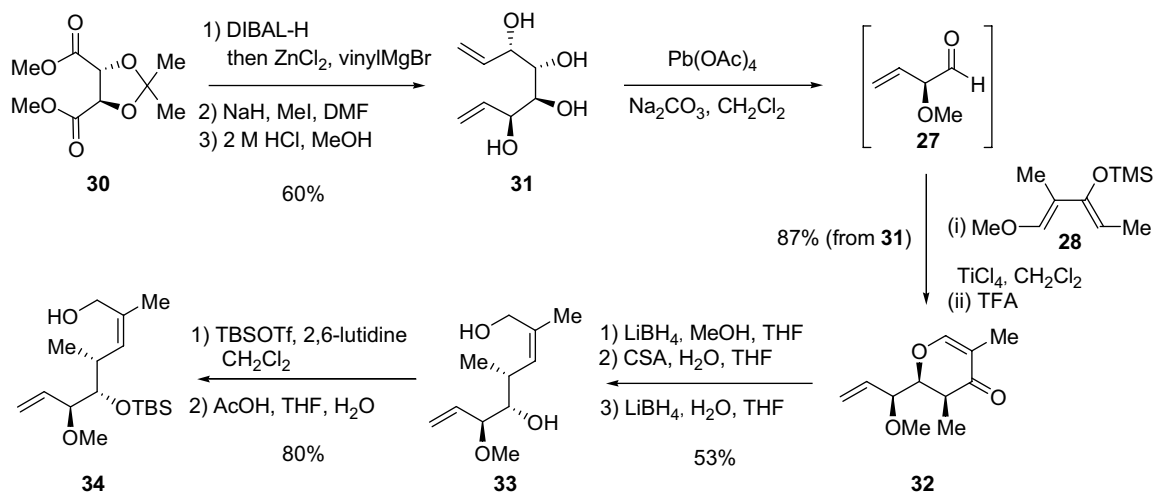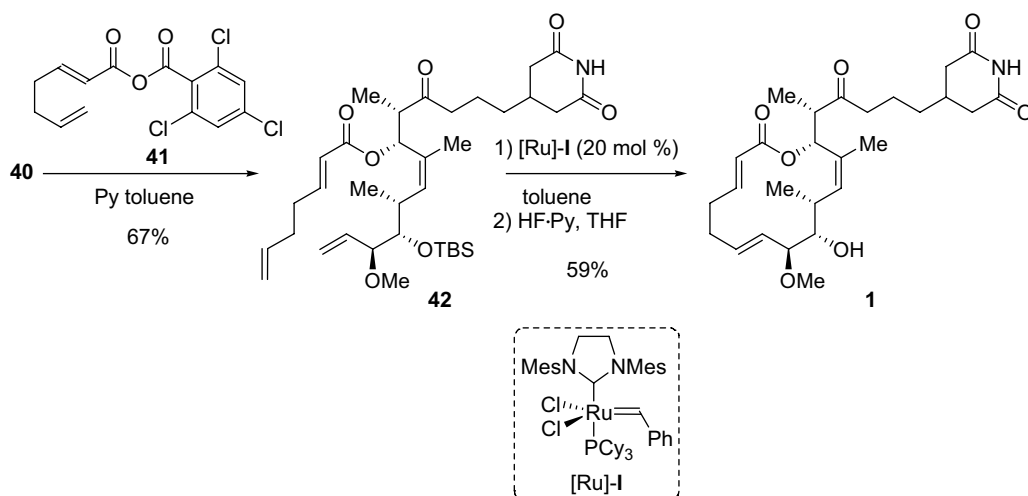

Scheme 2.
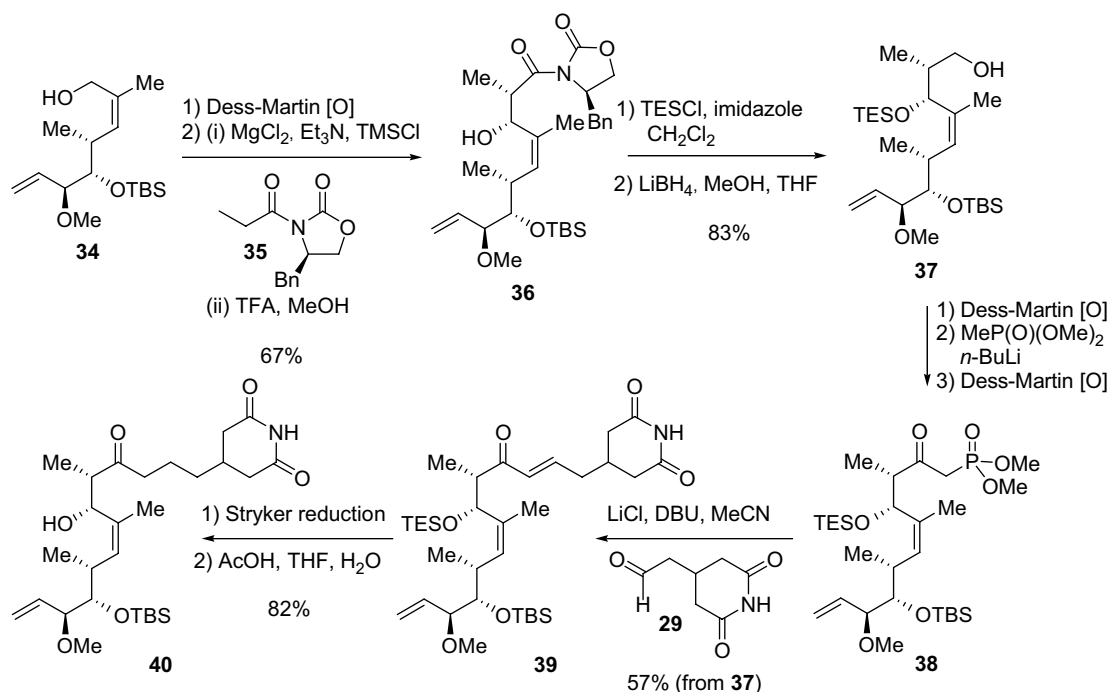
Scheme 3.

macrolactone core of migrastatin was established by applying a RCM to diene **42**, and the final cleavage of the TBS ether at C9 furnished **1** (Scheme 4). Migrastatin was obtained after 23 steps in the longest linear sequence from tartrate **30** with an overall yield of 2.3%.

4.1.2. Synthesis of Cossy and Reymond [16]

In this approach to migrastatin, the macro-lactonization was also envisioned by applying a RCM to a diene of type **C**, which would be in turn prepared by the Yamaguchi acylation of **B** and **D** (Scheme 5). The key step in this synthesis was based on the use of a cross-metathesis (CM) to install the alkyl glutarimide side-chain thus creating the C16—C17 bond. Such CM would eventually be useful for installing other side-chains thereby affording straightforward access to migrastatin analogues. The stereogenic centers at C9, C10 and C13, C14, present in fragment **D**, would be
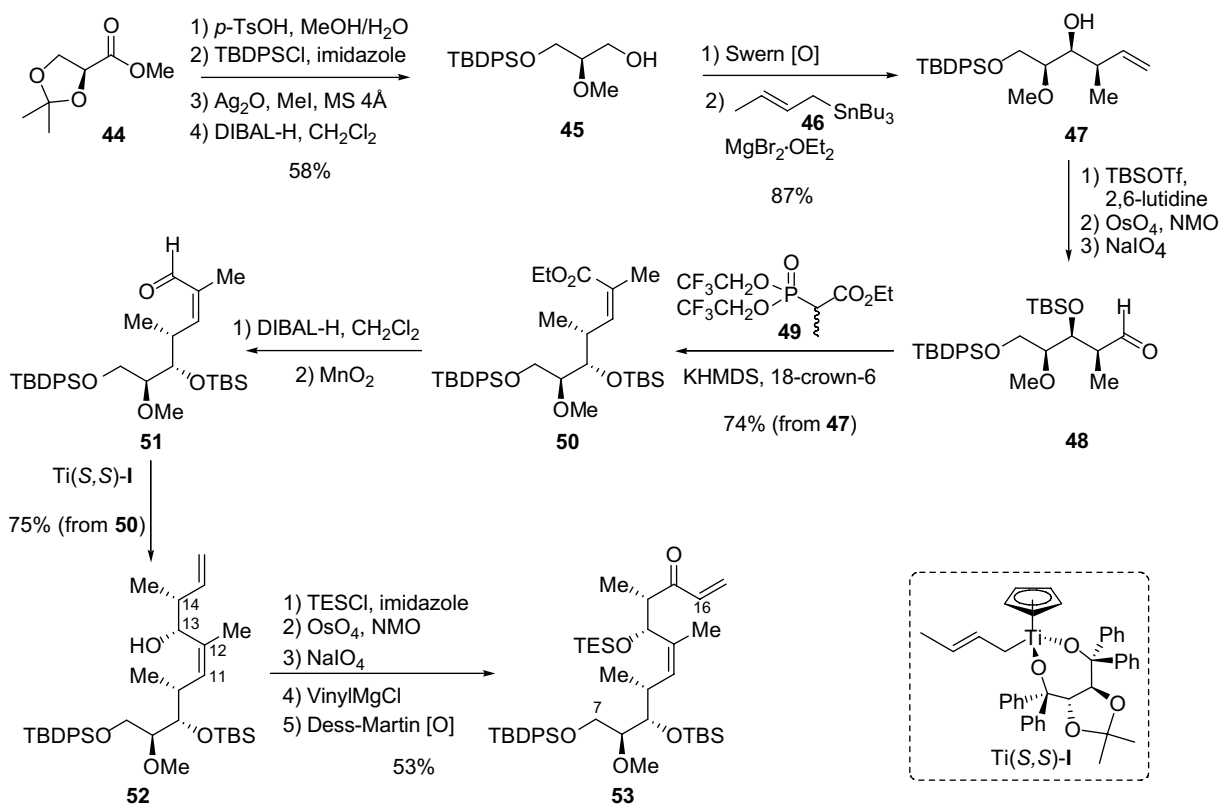

Scheme 4.
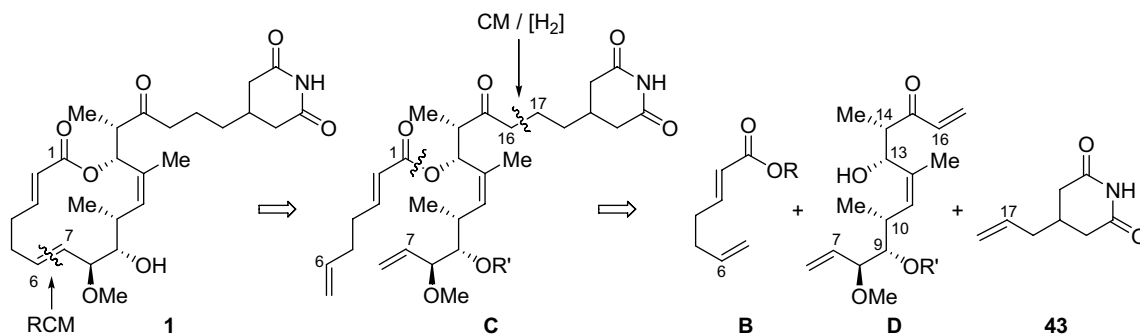
Scheme 5.

controlled by using two enantio- and diastereoselective crotylmetalations. The use of these reactions implies the synthesis of a fragment of type **D** and allylglutarimide **43** (Scheme 5).

The synthesis of fragment **D** started from the commercially available methyl ester **44**, which was transformed to alcohol **45** in four steps (58%). After oxidation of **45** under Swern conditions, the obtained crude aldehyde was treated with but-2-enyl-[(tri-*n*-butyl)]stannane **46** in the presence of MgBr$_2$·OEt$_2$ to give the *syn–syn* stereotriad **47** with a good stereocontrol (dr = 9/1) and in 87% yield for the last two steps [22]. After protection of the secondary alcohol as a silyl ether and oxidative cleavage of the double bond, **47** was transformed to aldehyde **48** which was directly treated with Still–Gennari phosphonate **49** to produce unsaturated ester **50** in 74% yield with good (*Z*)-stereocontrol of the C11–C12 double bond (*Z*/*E* = 97/3) [23]. In order to introduce the last two stereogenic centers at C13 and C14, ester **50** was transformed into α,β-unsaturated aldehyde **51** in two steps (DIBAL-H then MnO$_2$), and then directly treated with the highly face-selective crotyltitanium complex Ti-(*S*,*S*)-**I** leading to **52** in 75% yield (from **50**) with a good diastereoselectivity (dr = 9/1) [24]. In order to install the glutarimide side-chain by CM, alcohol **52** was transformed in five steps to the vinyl ketone **53**. At this stage, a chemoselective oxidative-cleavage of the terminal C15–C16 double bond was required while leaving untouched the internal C11–C12 double bond. To protect the internal double bond from osmylation, the hydroxyl group present at C13 in compound **52** was first protected with TESCl, and then the C15–C16 double bond was selectively transformed into an aldehyde (OsO$_4$, NMO then NaIO$_4$) which was easily transformed to vinyl ketone **53** after two additional steps (vinylMgBr then Dess–Martin oxidation). Enone **53** was obtained in 53% yield from alcohol **52** (Scheme 6).

Worthy of note is the great importance of the triethylsilyl protecting group at C13 which shielded the internal C11–C12 double bond from osmylation (**52** to **53**) [25]. As well, this protecting group masked the C11–C12 double bond from the following CM and hydrogenation steps that had to be used to complete the synthesis of migrastatin. Enone **53** was first coupled with allylglutarimide **43** by using a chemoselective CM reaction catalyzed by the Hoveyda–Grubbs catalyst [Ru]-**II** (53% corrected yield, 60% conversion), and the resulting cross-product was chemoselectively hydrogenated (96%) at C16–C17 to produce **54**. With **54** in hand, the endgame was clear as a diene of type **C** had to be prepared. First, the TES ether was selectively cleaved to afford a secondary alcohol, which was acylated using the mixed anhydride **41** under the conditions described previously by Danishefsky et al. to yield ester **55** in 59% yield for the last two steps. The latter was transformed to diene **42** in 44% yield after three steps that included a selective cleavage of the primary silyl ether at C7 with NH$_4$F in methanol, a Dess–Martin oxidation of the obtained alcohol to an aldehyde, and a Takai methylenation [26]. As described previously, the total synthesis of migrastatin was completed with the RCM of diene **42** and removal of the TBS protective group (24% yield) (Scheme 7). Migrastatin **1** was obtained in 26 steps (longest linear sequence) from the commercially available ester **44** with an overall yield of 0.5%.

4.1.3. Semisynthesis of Shen et al. [17]

Shen et al. demonstrated that migrastatin and the structurally related dorrigocins were actually shunt metabolites of *iso*-migrastatin **3** [6], which is the primary metabolite biosynthesized by *S. platensis*. *Iso*-migrastatin **3** is not stable in aqueous solutions and undergoes isomerization to a mixture of **1**, **4** and **5**. More recently, Shen et al. showed that the thermal

Scheme 6.
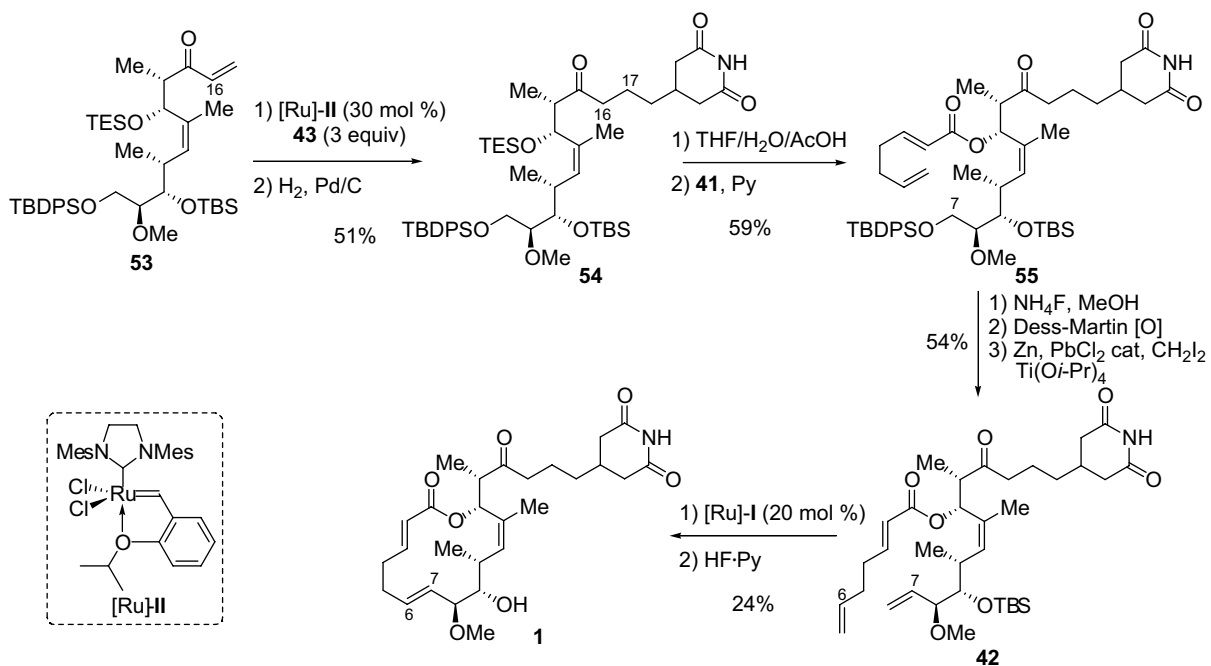
Scheme 7.

rearrangement of *iso*-migrastatin **3** was able to produce the natural product migrastatin **1** regio- and enantio-specifically in 62% yield (Scheme 8) [17]. They suggested that this rearrangement was based on a [3,3]-sigmatropic process. A series of *iso*-migrastatin analogues were also transformed to rearranged migrastatin analogues.

4.2. Synthesis of migrastatin analogues

4.2.1. Synthesis of iso-migrastatin 3 [27]

Recently, Danishesfy et al. reported the first total synthesis of *iso*-migrastatin **3**. They anticipated the unstability of **3** postulating that it was due to the presence of two (*E*)-disubstituted double bonds in the 12-membered ring macrolactone. They decided to introduce the (*E*)-double bond at C2–C3 in the last stages of the synthesis.

Starting from dihydropyranone **32**, which is also a precursor of migrastatin, epoxide **56** was prepared in three steps (35% yield). Then, the reductive opening of **56** furnished a diol, for which the differentiation of the primary versus the secondary hydroxyl group was achieved by using a three-step acetylation/protection/methanolysis sequence that gave rise to primary alcohol **57** in 69% yield (four steps). Alcohol **57** was treated under Swern conditions, and the obtained aldehyde was reacted with Wittig reagent **58** to produce enone **59** in 83% yield (from **57**). In order to introduce the stereogenic center present at C14, an S_N2' opening of the epoxide was envisaged under Marshall conditions [28]. The stereoselective reduction of the enone carbonyl group was achieved by using a Corey reduction [(*S*)-Me-CBS, $BH_3 \cdot Me_2S$; dr = 10/1], and the obtained alcohol was protected with TBSCl. The S_N2' opening of the epoxide with lithium cyano-methylcuprate provided **60** in 55% yield (from **59**). During this step, the methyl group at C14 was installed

with the expected configuration (*anti* relative to the silyl ether at C15), and the (*E*)-trisubstituted double bond at C11–C12 was established (Scheme 9).

With synthon **60** (C7–C21 fragment) in hand, the completion of the synthesis required the construction of the macrolactone core of *iso*-migrastatin. Acylation of **60** at C11 with the racemic seleno-acid **61** afforded diene **62** with the α-selenoester moiety as the masked C2–C3 double bond. After cleavage of the silyl ether at C15 with HF·Py complex, oxidation to the corresponding ketone, and MOM deprotection, diene **63** was obtained in 68% yield (three steps). When diene **63** was treated with catalyst [Ru]-**I**, the RCM afforded a mixture of two macrolactone isomers with a (*Z*)- and (*E*)-double bond at C6–C7 in a 1.6/1 ratio in favour of the (*Z*)-isomer. After separation by chromatography, the (*E*)-isomer **64** was obtained in 21% yield. The final oxidative deselenylation provided **3** in 93% yield (Scheme 10). *Iso*-migrastatin **3** was obtained after 23 steps from tartrate **30** with a global yield of 0.7%.

4.2.2. Synthesis of the macrolactone core 8

The macrolide core **8** was the first migrastatin analogue reported. It possesses the highest activity against the migration of tumor cells but suffers from its plasma instability that results in lactone cleavage.

The first synthesis of this analogue was reported by Danishefsky and Gaul [29], and an optimized synthesis was later reported by this group [10]. The synthesis starts with a ten-step transformation of tartrate **30** into allylic alcohol **34** (Scheme 2). After Yamaguchi acylation of **34** with the mixed anhydride **41**, diene **65** was obtained in 48% yield. The RCM of diene **65** was achieved by treatment with [Ru]-**I**, and the final deprotection of the silyl ether with HF·Py complex yielded the macrolactone core of migrastatin **8** (36% yield for the last two steps) (Scheme 11). Analogue **8** was obtained in 13 steps from **30** in 4% global yield.

iso-Migrastatin **3**   →   neat, 135 °C / 62%   →   Migrastatin **1**
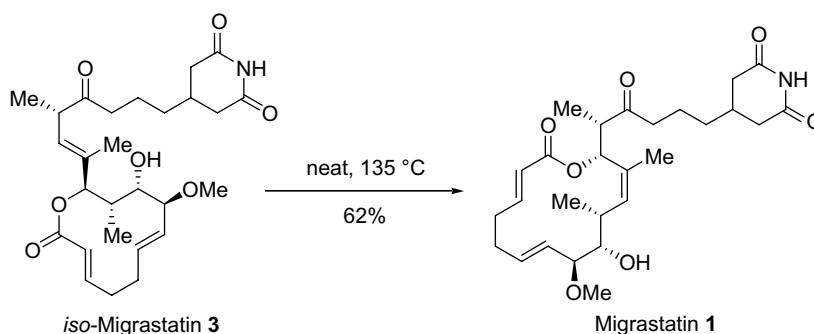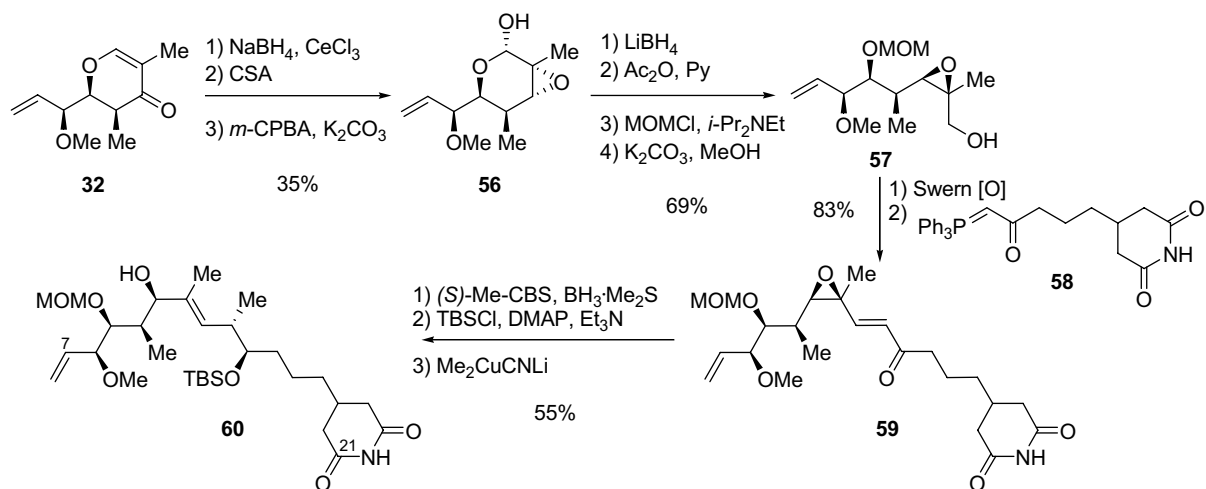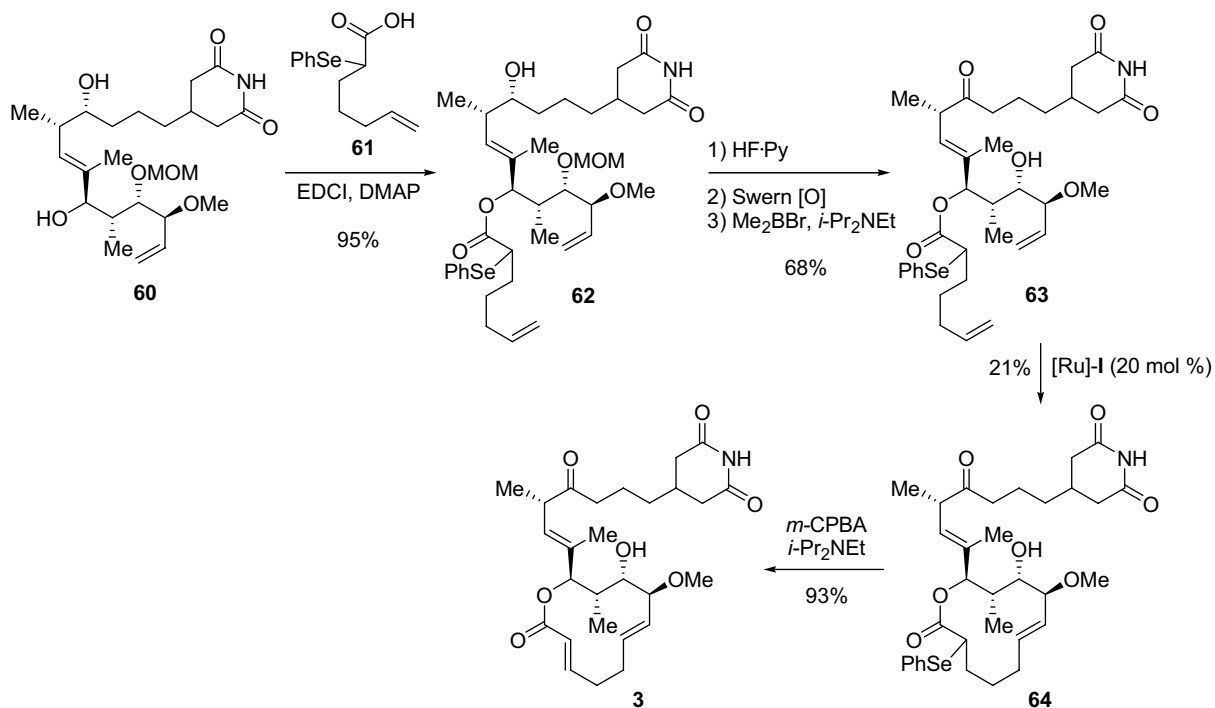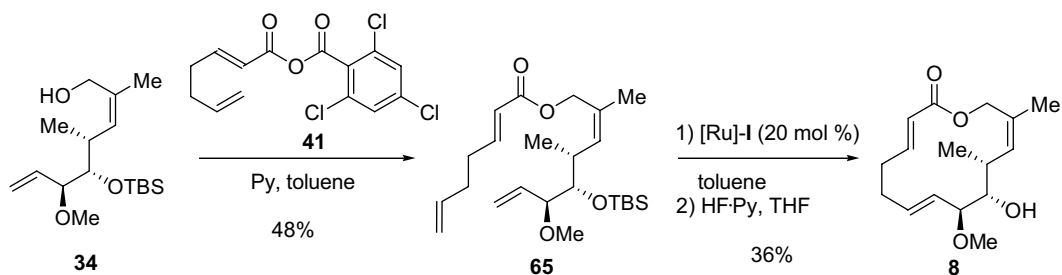
Scheme 8.

Scheme 9.

During their total synthesis of migrastatin, Cossy and Reymond reported the synthesis of macrolide **8** [16b]. To begin, ester **44** was transformed into the α,β-unsaturated ester **50** in ten steps with a global yield of 37%. After reduction of **50** with DIBAL-H (94% yield), the corresponding allylic alcohol was obtained and acylated with **41** providing ester **66** in 67% yield. The latter was converted into diene **65** in three steps: a selective cleavage of the primary TBDPS ether,

a Dess−Martin oxidation of the resulting alcohol, and a Takai methylenation of the aldehyde in 49% yield (three steps). In a manner similar to Danishefsky et al., **65** was transformed into **8** after two steps and in 31% yield. Macrolactone **8** was obtained in 17 steps from **44** in 4% global yield (Scheme 12).

Das et al. also reported a synthesis of macrolactone **8** [30]. Their synthesis started from acrolein **67** which was reacted with Evans oxazolidinone ent-**35**, and after

Scheme 10.

Scheme 11.

cleavage of the chiral auxiliary with LiBH$_4$, allylic alcohol **68** was obtained in 81% yield (two steps) and excellent stereoselectivity. The reaction of diol **68** with *p*-methoxybenzaldehyde dimethyl acetal (**69**) afforded an acetonide which was selectively opened using DIBAL-H, and the obtained primary alcohol was protected as a TBS ether to yield **70** (58% for the three steps). The oxidative cleavage of the double bond in **70** provided an aldehyde which was treated with vinylmagnesium bromide in the presence of MgBr$_2$·OEt$_2$ to yield the *syn–syn* stereotriad **71** in a 7/1 ratio of stereoisomers. After the transformation of alcohol **71** into the corresponding methyl ether, the removal of the TBS group afforded primary alcohol **72** in 58% yield (two steps). This alcohol was first oxidized under Dess–Martin conditions to an aldehyde, which was treated with Ando phosphonate **73** to establish the (Z)-trisubstituted double bond (one isomer formed) [31], and finally, the reduction of the ethyl ester gave rise to allylic alcohol **74** (49% yield, three steps). To complete the synthesis of **8**, alcohol **74** was acylated with **41**, the RCM of the diene was achieved with [Ru]-**I** and the MPM ether was cleaved using DDQ (23%, three steps) (Scheme 13). In summary, macrolide **8** was prepared form acrolein in 15 steps and 2% global yield.

4.2.3. Synthesis of analogues 9–21[10]

Starting from allylic alcohol **34**, Danishefsky et al. designed the synthesis of analogues **9–21**. Upon treatment of **34** with 6-heptenoyl chloride **76** in the

presence of DMAP, diene **77** was obtained in 82% yield. The RCM of diene **77** was then achieved by using [Ru]-**I** (20 mol%), and the removal of the TBS group produced macrolactone **9** in good yield (71%, two steps). From **9**, three new analogues were prepared (Scheme 14). Acetate **12** was obtained after treatment of **9** with acetyl chloride in the presence of DMAP (76% yield), and then the Dess–Martin oxidation of **9** gave rise to ketone **13** (72%). Hydroxy-acid **14**, the opened form of lactone **9**, was obtained in 77% yield when **9** was subjected to NaOH in methanol.

Two other macrolactones, **15** and **16**, both featuring an additional stereogenic center, were prepared from **34** in five steps (Scheme 15). The Dess–Martin oxidation of **34** followed by the treatment of the resulting aldehyde with *iso*-propylmagnesium chloride furnished two separable diastereomeric alcohols **82** and **83** in a 2/3 ratio (86% yield for the mixture). The Yamaguchi acylation of **82** with **84** led to the formation of a diene which was cyclized by a RCM promoted by [Ru]-**I**, and the final cleavage of the TBS ether afforded macrolactone **15** in 46% yield (three steps). By applying the same three-step sequence to alcohol **83**, macrolactone **16** was obtained in 49% yield.
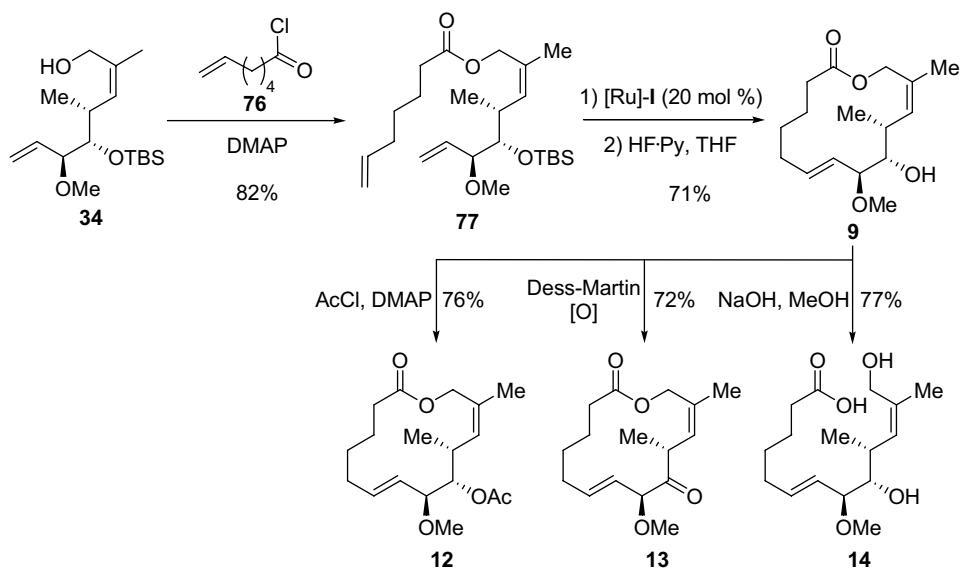
A macrolactam, **10**, was synthesized in five steps from **34** (Scheme 16). Azide **81** was first prepared by using the DBU/diphenylphosphoryl azide (DPPA) method in 87% yield [32]. Azide **81** was then subjected to a Staudinger reduction to afford an amine which was directly coupled with 6-heptenoic acid (**82**) by using
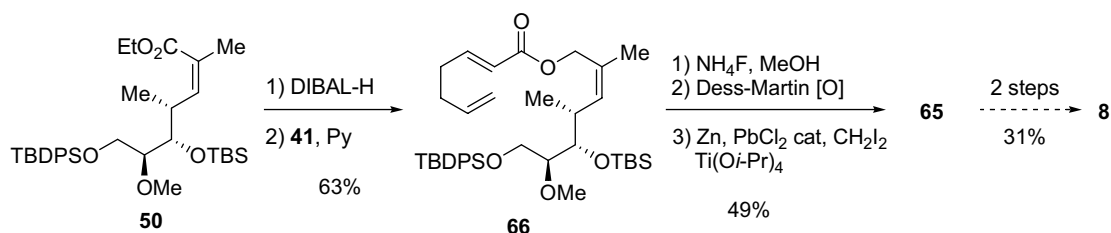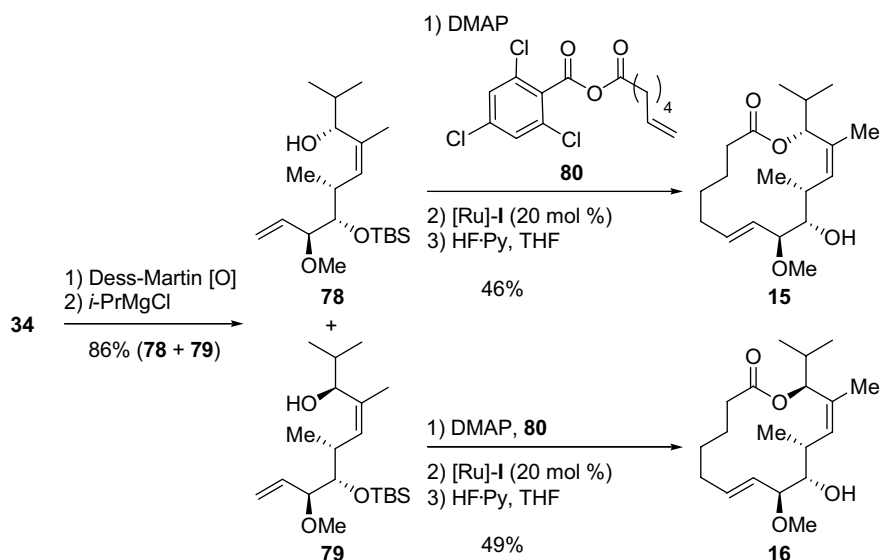

Scheme 12.
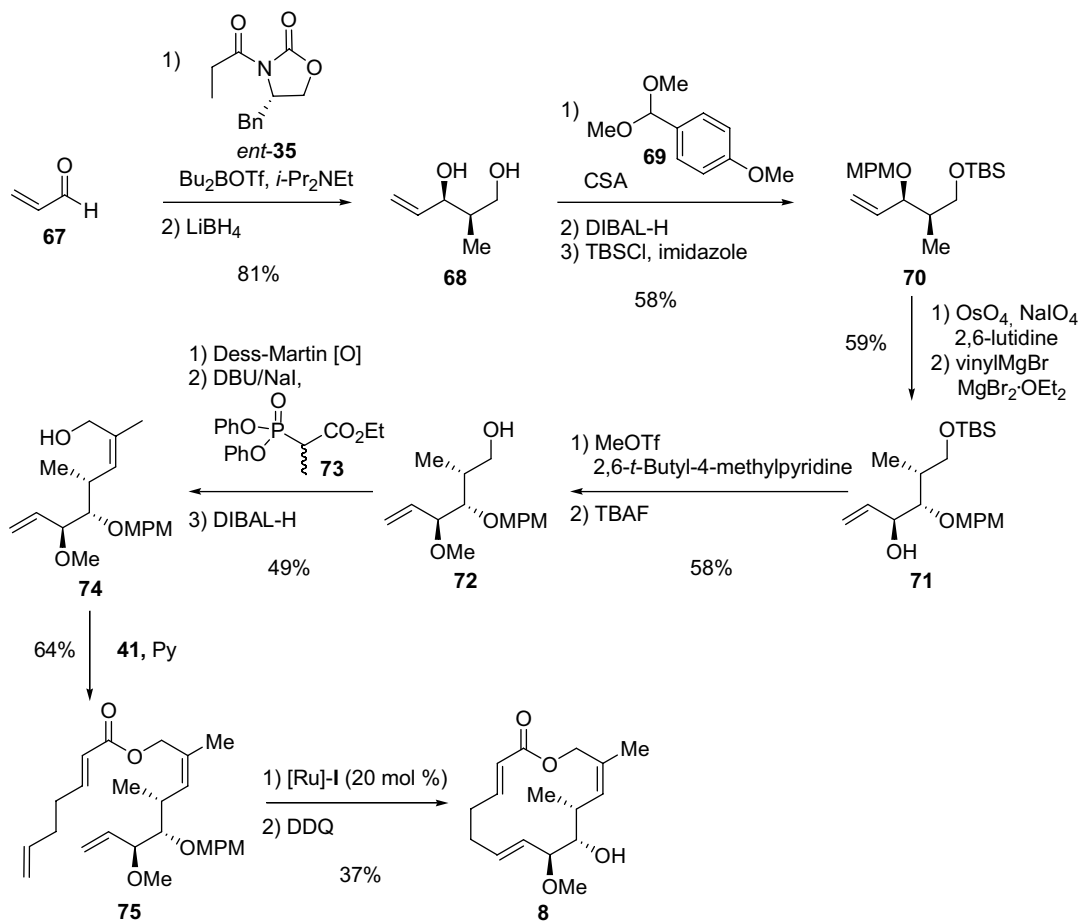
Scheme 13.

Scheme 14.

Scheme 15.

EDC to yield dienic amide **83** (92%, two steps). Finally, the RCM/TBS deprotection endgame furnished lactam **10** in 54% yield.

A synthesis for the preparation of macroketone analogue **11** was also designed. The synthesis of **11** started with the transformation of allylic alcohol **34** into the corresponding allylic bromide, which was displaced by treatment with β-ketosulfoxide **84** in the presence of DBU. After Na/Hg desulfonylation, dienic ketone **85** was obtained in 61% yield (three steps). The RCM/TBS deprotection endgame afforded macroketone **11** in 73% yield (Scheme 17). Starting from this ketone, five additional analogues **17–21** were prepared. Alcohol **17** (diastereomeric mixture, 95% yield) was obtained after NaBH₄ reduction of the carbonyl group in **11**. The addition of methylmagnesium bromide to **11** yielded tertiary alcohol **18** (95%). Reaction of **11** with TMSCF₃ in the presence of

TBAF allowed the formation of **19** bearing a trifluoromethyl group. Finally, **11** was converted to oxime **20** in 70% yield, and the biotin-labeled acylhydrazone **21** was obtained in 75% yield after treatment of ketone **11** with biotin-dPEG4-hydrazide.

4.2.4. Synthesis of analogues 22–25 [14]

Recently, Murphy et al. reported their efforts in the preparation of migrastatin and dorrigocin A analogues. Compared to the analogues described previously, these analogues have no methyl group on the double bond at C12, and at C10, a hydroxyl group is present instead of a methyl group. These analogues were prepared from tri-O-acetyl-D-glucal (**86**) [14a].

After a methanolysis of the acetate groups in **86**, the three hydroxyl groups were protected as TBS ethers by using TBSCl. Then, the selective cleavage of the primary TBS ether with HF·Py complex yielded
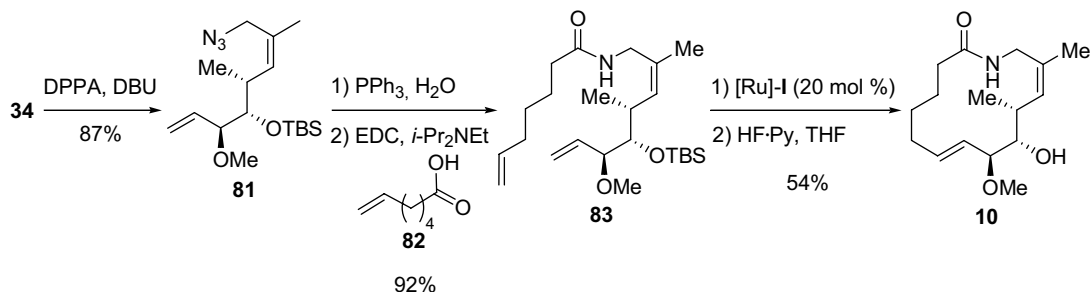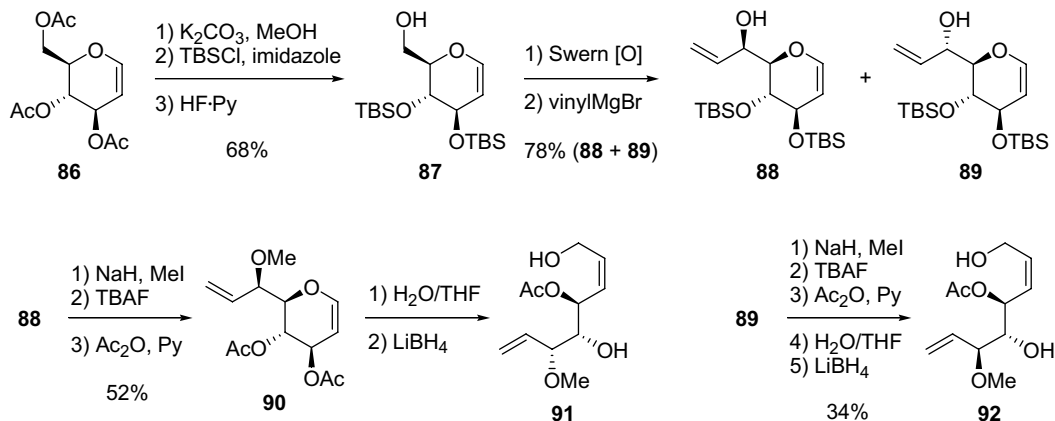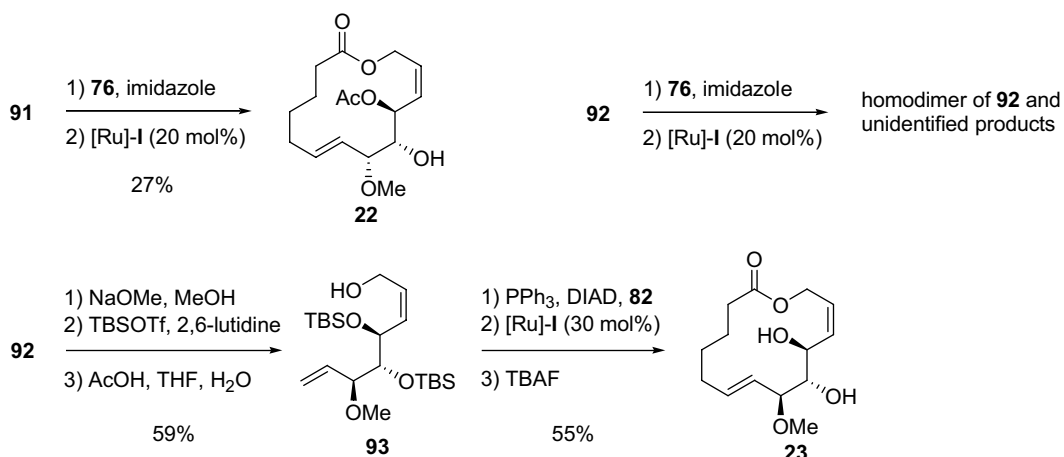

Scheme 16.
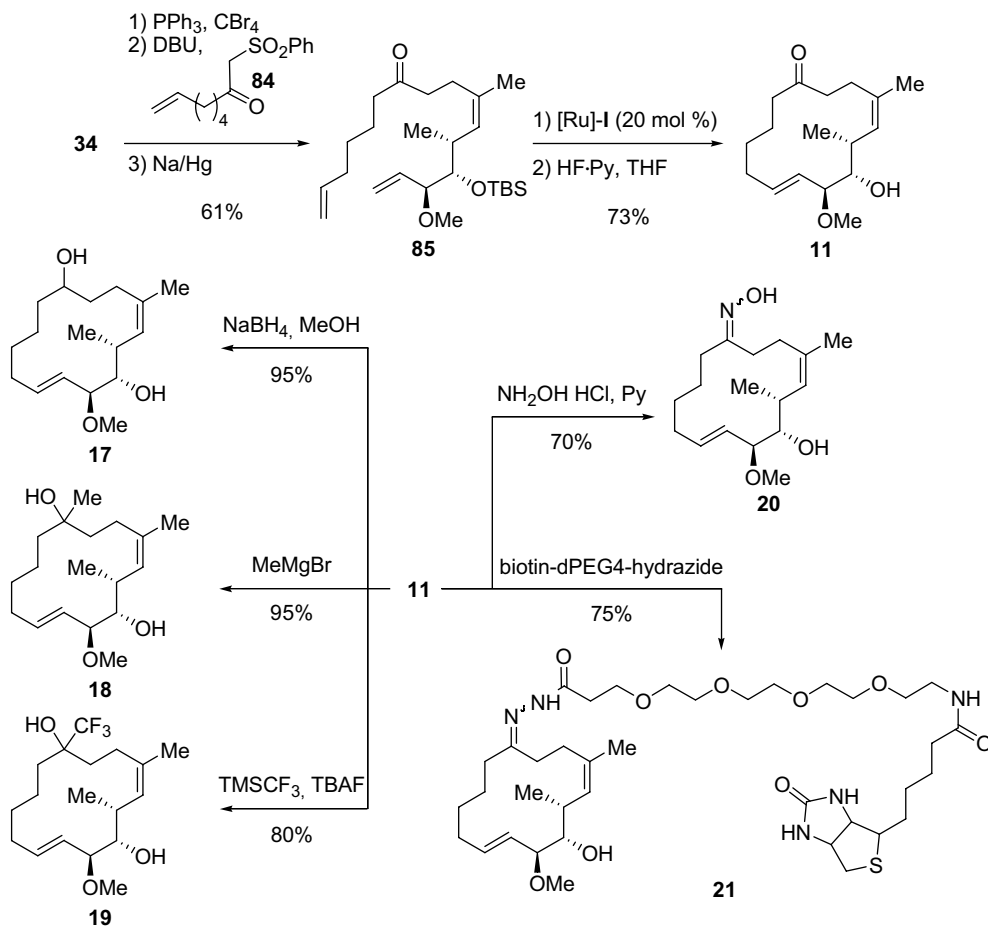
Scheme 17.

primary alcohol **87** (68%, three steps). The oxidation of the latter, under Swern conditions, furnished an aldehyde which was treated with vinylmagnesium bromide to afford a 1/1 mixture of separable

diastereoisomers **88** and **89** (78% yield for the mixture). Both diastereoisomers were used for the preparation of migrastatin analogues. Starting from alcohol **88**, the methylation of the free hydroxyl group
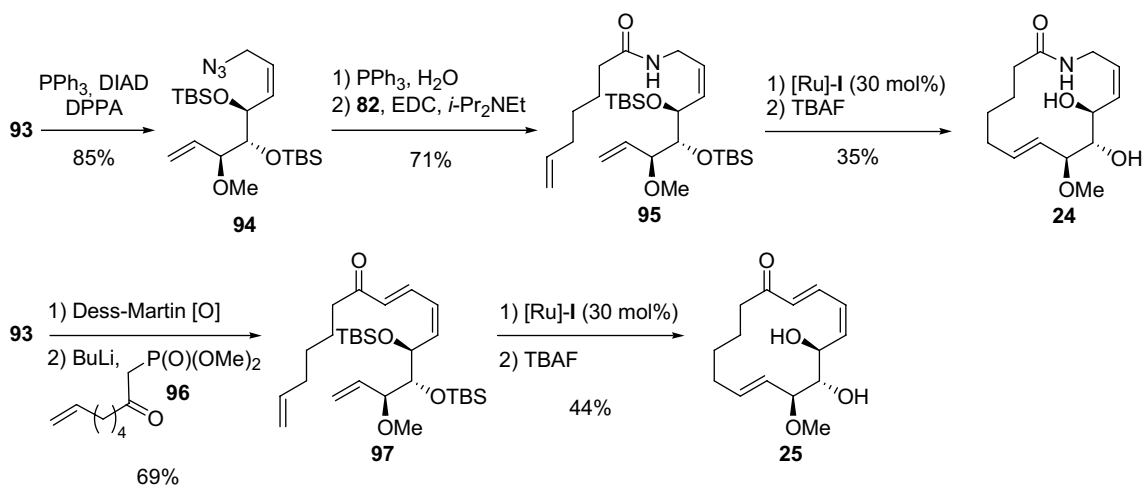

Scheme 18.

Scheme 19.

was performed with NaH and MeI, and the two TBS ethers were exchanged with acetates after TBAF deprotection and acylation with acetic anhydride to provide **90** in 52% yield. Water-mediated allylic rearrangement of **90** then furnished a lactol which was reduced with LiBH₄ to afford allylic alcohol **91** in 68% yield (two steps). The same transformation was applied to **89** thus leading to the diastereomeric allylic alcohol **92** in 34% yield (Scheme 18).

With the key building-blocks **91** and **92** in hand, Murphy et al. prepared four analogues, compounds **22–25**. After selective acylation of **91** with **76** followed by RCM of the obtained diene, macrolactone **22** was obtained in 27% yield. It is noteworthy that the same sequence (acylation then RCM), when applied to **92**, did not lead to the expected

macrolactone but gave homodimerization and unidentified products. Thus, **92** was transformed to **93** after removal of the acetate, protection of the obtained triol with TBSOTf and selective cleavage of the primary TBS ether (59%, three steps). A Mitsunobu reaction of **93** with 6-heptenoic acid (**82**) allowed the formation of a diene which was treated with [Ru]-**I**, thus affording macrolactone **23** in 55% yield after final deprotection of the TBS groups (Scheme 19) [14a].

In order to synthesize macrolactam **24**, allylic alcohol **93** was transformed into an allylic azide **94** by using Mitsunobu conditions with DPPA. After a Staudinger reduction of the azide and EDC coupling of the obtained amine with **82**, amide **95** was obtained in 60% yield. The RCM of **95** with [Ru]-**I** followed by the

Scheme 20.

cleavage of the TBS ethers afforded macrolactam **24** in 35% yield (Scheme 20) [14b].

Finally, the macrocyclic ketone **25** was prepared from allylic alcohol **93**. After Dess–Martin oxidation of **93**, the resulting aldehyde was treated with HWE phosphonate **96** to afford enone **97** (69%, two steps). This compound was then treated with [Ru]-**I** and the obtained macrocyclic ketone was deprotected to provide migrastatin analogue **25** in 44% yield (Scheme 20) [14b].

5. Conclusion

Since the discovery of migrastatin and its unusual anti-metastatic activity, synthetic organic chemists have designed a diverse array of migrastatin analogues. Some of these analogues appeared to have excellent *in vitro* activities, such as the migrastatin macrolactone core **8**. However, as this macrolactone suffers from plasma instability, other analogues such as macrolactam **10** or macroketone **11** were synthesized and have shown to display nanomolar activities and plasma stability. These promising analogues will probably stimulate the design and synthesis of new migrastatin analogues for biological testing and better comprehension of the biological mode of action of this family of compounds.

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