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A. Pelss[1], A. M. P. Koskinen[1]*

STEREOCONTROLLED CONSTRUCTION OF DECAHYDROQUINOLINE RING SYSTEMS: THE CASE OF LEPADIN ALKALOIDS

(REVIEW)

In this review the marine derived decahydroquinoline alkaloid chemistry and biology is described. A proposal is made for the biosynthetic relationships between acyclic and cyclic C-18 aminoalcohol natural products.

Keywords: aminoalcohols, decahydroquinolines, asymmetric synthesis, biosynthesis, total synthesis.

Decahydroquinoline (DHQ) alkaloids are unique natural products which can be divided into three distinct sets. The first group (more than 50 members) of these alkaloids are simple 2,5-disubstituted DHQs isolated from dart poison frogs and ants with the parent member being alkaloid *cis*-195A also known as pumiliotoxin C [1]. These diverse *cis*- or *trans*-fused decahydroquinolines are equipped with various short alkyl and alkenyl side chains. The structurally related but biologically different lepadins **1**–**8** (Fig. 1) are on the other hand marine alkaloids isolated from three distinct ascidians: *Clavelina lepadiformis* (found in the North Sea), *Didemnum* and *Aplidium tabascum* (both found in the Great Barrier Reef) [2–5]. The third group consists of more complex polycyclic alkaloids which besides the DHQ ring system can contain several other heterocyclic ring systems fused into one molecule. Representative members of this group are gephyrotoxin and *Lycopodium* alkaloids [6, 7].

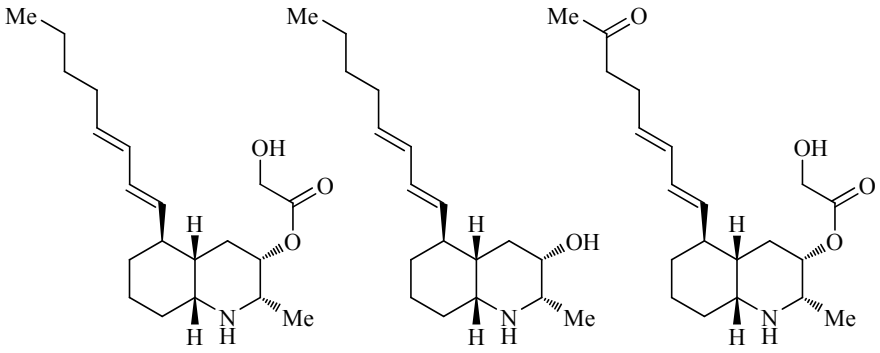
This review will focus solely on the second group of DHQ alkaloids which distinct to the other two groups of DHQ containing alkaloids have not been reviewed in full so far [8]. Lepadin alkaloids differ from dendrobatin frog alkaloids in additional oxygenation at the position 3, where substituent may be hydroxy or acyloxy group, as well as having an eight carbon long side chains of variable oxidation level at the position 5 of DHQ ring. There are three stereochemical groups of lepadins each derived from distinct tunicate species (Fig. 1). Lepadin F makes an exception, being present in both ascidians from the Great Barrier Reef. Lepadins possess some interesting biological activities: lepadins A and B – cytotoxicity against cancer cell lines, lepadins D–F – antiplasmoidal and antitrypanosomal activity. Lately, lepadin B together with pictamine was found to block neuronal nicotinic acetylcholine receptors α4β2 and α7. However, the availability of only small quantities of these natural products has precluded further studies on the development into potential leads for nicotinic based therapies [9].

Biosynthetic considerations

The diverse marine tunicates found in various waters of the Earth are rich sources of both acyclic and cyclic aminoalcohol lipids of variable length carbon chains. Particularly interesting are the C-18 aminoalcohols. The acyclic highly

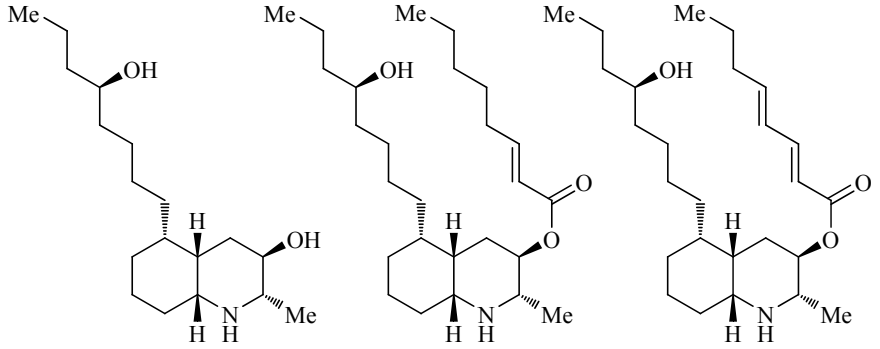
unsaturated crucigasterins **9**–**12** and obscuraminol A **13** (Fig. 2) are supposed to be biosynthetically derived from L- or D-alanine and the corresponding unsaturated fatty acids *via* a pathway similar to that of sphingosine biosynthesis [10–12].

Group 1



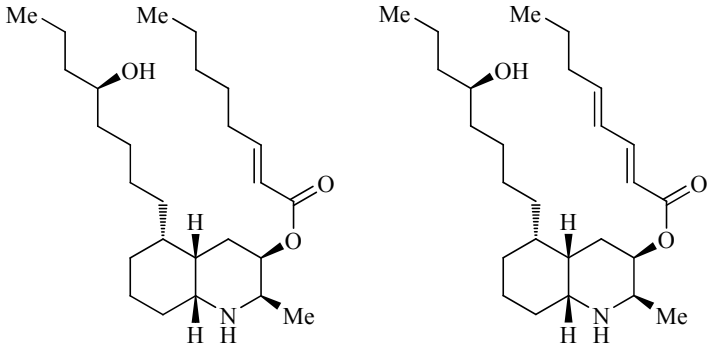
Lepadin A (**1**) Lepadin B (**2**) Lepadin C (**3**)

Group 2



Lepadin D (**4**) Lepadin E (**5**) Lepadin H (**6**)

Group 3



Lepadin F (**7**) Lepadin G (**8**)

Fig. 1. Structure of lepadins A–H

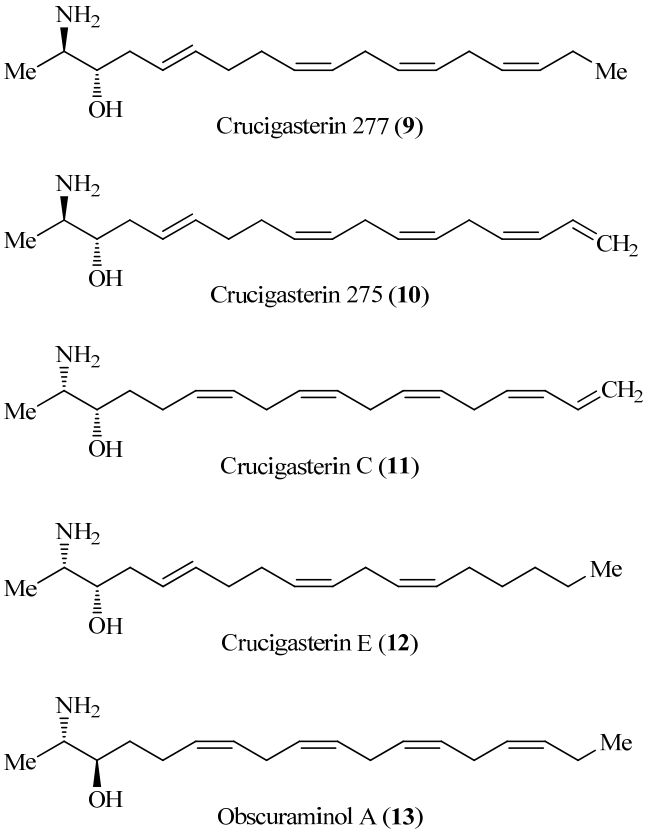
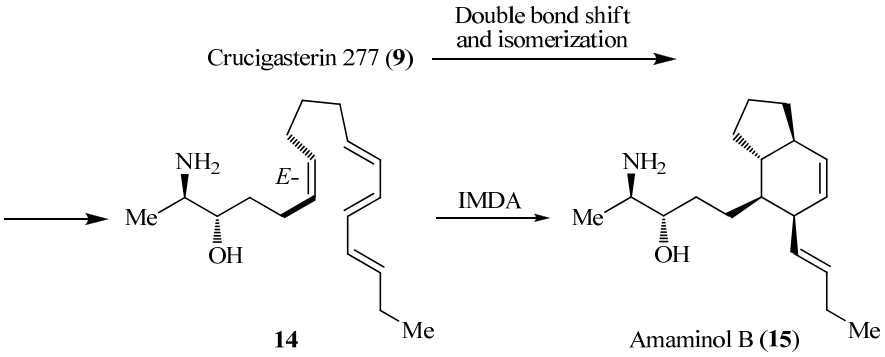
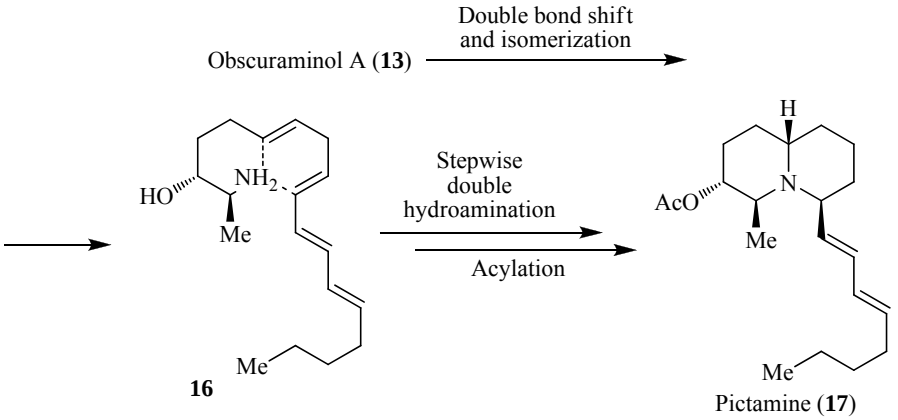


Fig. 2. Structure of some crucigasterins and obscuraminol A

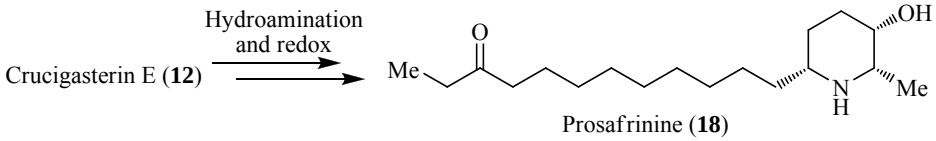
It is reasonable to assume that these linear compounds as well as other as of yet unisolated and unknown aminoalcohol lipids are engaged in the biosynthetic machinery that produces a set of diverse cyclic C-18 aminoalcohols: the tetrahydroindane based amaminols A and B, the decahydroquinoline based lepadins **1**–**8**, the quinolizidine based pictamine (**17**) and piperidine based, plant derived prosafrinine (**18**) [13–15]. Isomerization and shift of four skipped double bonds of *E*,*Z*,*Z*,*Z*-configuration in crucigasterin 277 (**9**) to the triple conjugate *all-E*-configuration as in the structure **14** can lead to enzymatic asymmetric intramolecular Diels–Alder (IMDA) cyclization to produce amaminol B (**15**). Such a bio-inspired but two building block approach was realized in our laboratory total synthesis of amaminol A, differing from amaminol B by configuration of stereocenter at the amino group [16].



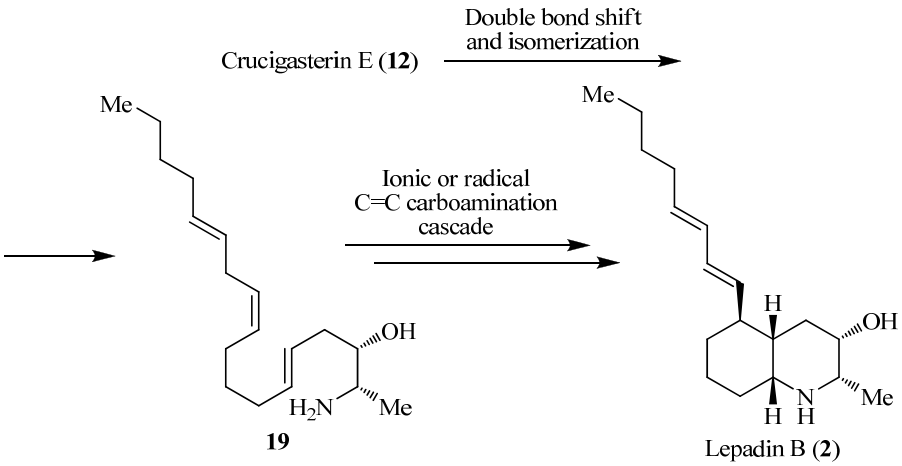
Isomerization and shift of the *all-Z*-configuration double bonds in obscuraminol A (**13**) to *all-E*-isomer and conjugation of three of them could produce precursor **16**, which would be ready for a stepwise double hydroamination delivering pictamine (**17**) after acylation. Double hydroamination could take place either by the first generating the piperidine ring and then fusing the second ring. Alternative transannular cyclization of the preformed ten-membered aza-macrocycle could take place. It is possible that only the first two double bonds of compound **13** could be isomerized to pre-organize the C–N bond formation events. The final isomerization of the remaining double bonds could then occur afterwards.



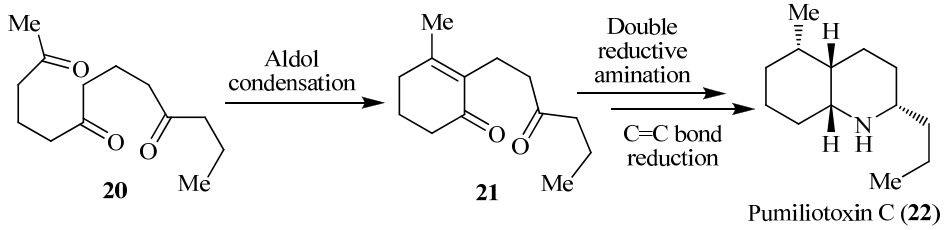
Prosafrinine (**18**) could possibly be biosynthesized from crucigasterin E (**12**) *via* diastereoselective hydroamination type cyclization and following redox transformations.



Three stereochemically distinct groups of lepadin alkaloids could be biosynthetically derived *via* stereoselective carboamination bicyclization reactions of isomerized stereochemically appropriate aminoalcohol lipids. For example, isomerization and shift of two crucigasterin E (**12**) double bonds to the configuration shown in intermediate **19** could be followed by ionic or radical C=C carboamination bicyclization cascade sequence to generate lepadin B (**2**).

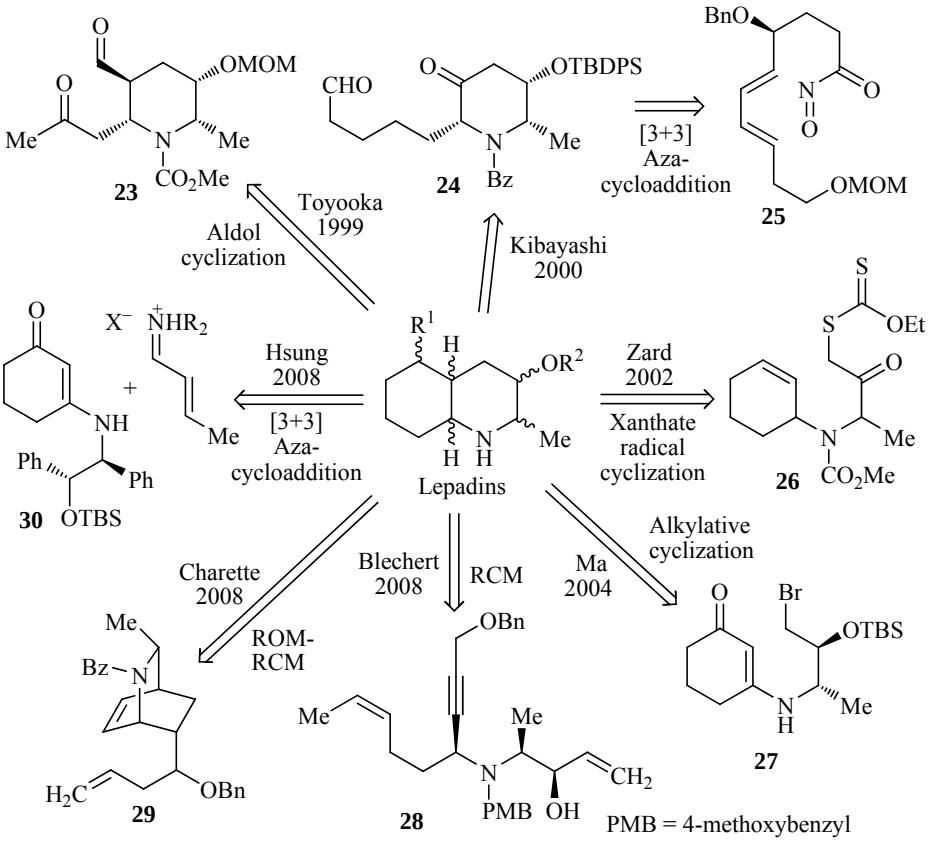


It is interesting to note that for the frog DHQ alkaloid biosynthesis a completely different proposal was put forth in 1979 by Winterfeldt [17]. A polyketide triketone **20** undergoes aldol condensation to produce cyclohexenone **21** and subsequent stepwise double condensation with an ammonia source and reduction gives rise to the DHQ structure **22** exemplified in this case as a pumiliotoxin C. This biosynthetic proposal has been substantiated in the laboratory almost three decades later in 2008 by Amat and Bosch [18].



Synthetic efforts

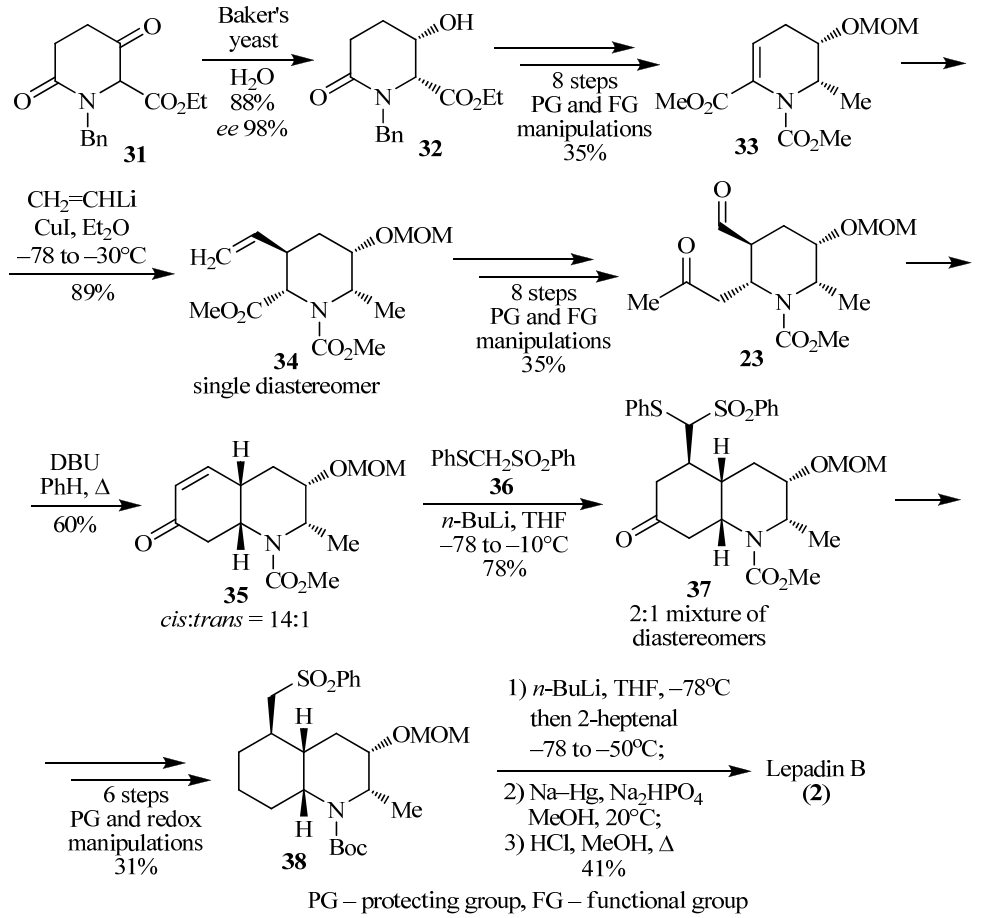
Over the last three decades the syntheses of DHQ alkaloids have generated significant interest. Around 80 publications are dedicated to the pumiliotoxin C synthesis and these have been reviewed previously twice in 1977 and 2002 [19, 20]. In this review we will analyze the synthetic approaches to the lepadin alkaloids with emphasis placed on the strategic disconnections and the key steps used for the stereoselective assembly of the DHQ ring system. The current state of



the art for the construction of these molecules is still in its infancy requiring long reaction sequences. The key disconnections of the majority of the syntheses are based on C–C bond formation rather than C–N bond formation as the strategic disconnection. This is due to the lack of stereoselective methods for direct formation of the DHQ ring *via* C–N bond formation. A wide range of C–C bond formation approaches have been adopted in the lepadin syntheses including aldol cyclization, xanthate radical cyclization, alkylation, ene-yne-ene ring closing metathesis and ring opening – ring closing metathesis (ROM, RCM). Aza-cycloadditions employed in two syntheses represent examples of the C–N bond formation. Due to the length of the syntheses and the use of large amount of concession steps we will restrict this review on the strategic construction steps used to set up the ring system and stereochemistry. Other transformations will mainly be indicated as the number and nature of steps used to convert one intermediate into another.

In 1999, Toyooka reported the first total synthesis of lepadin B using aldol cyclization as the key step [21, 22]. The synthesis began from the racemic triketo compound **31**, which was reduced with baker's yeast in high enantiopurity correctly setting two stereocenters in one step. Further eight steps were necessary to reductively transform the ethoxycarbonyl function of compound **32** into a methyl group as well as to introduce the enoate moiety suitable for the introduction of the next two stereocenters. Organocuprate addition of the vinyl group to dehydropyridine **33** proceeded with exclusive selectivity. The transformation of

Toyooka 1999

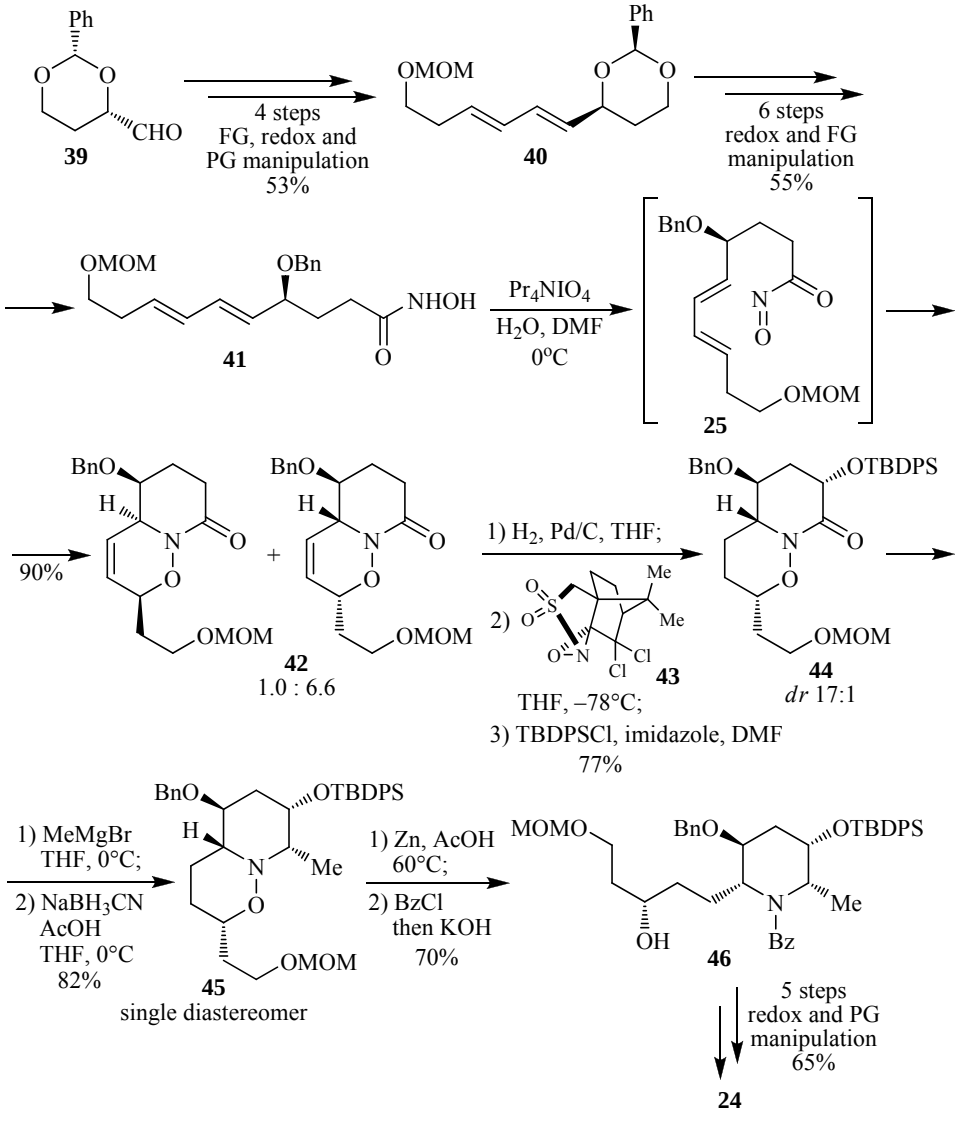


PG – protecting group, FG – functional group

compound **34** to the key cyclization precursor **23** required eight additional steps. The key epimerizative aldol cyclization under the influence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) took place with a reasonable yield and high selectivity to produce the *cis*-fused aza decalin system **35**. At this stage the remaining ring stereocenter was introduced *via* conjugate addition of the active methylene compound **36** albeit in low selectivity. Six further steps were used to cut off unnecessary functionality and produce compound **38**, to which side chain was attached *via* a two stage Julia olefination reaction. Deprotection produced lepadin B in a total of 30 steps and 3.3% overall yield from the triketo compound **31**. This synthesis also proved the absolute stereochemistry of this natural product.

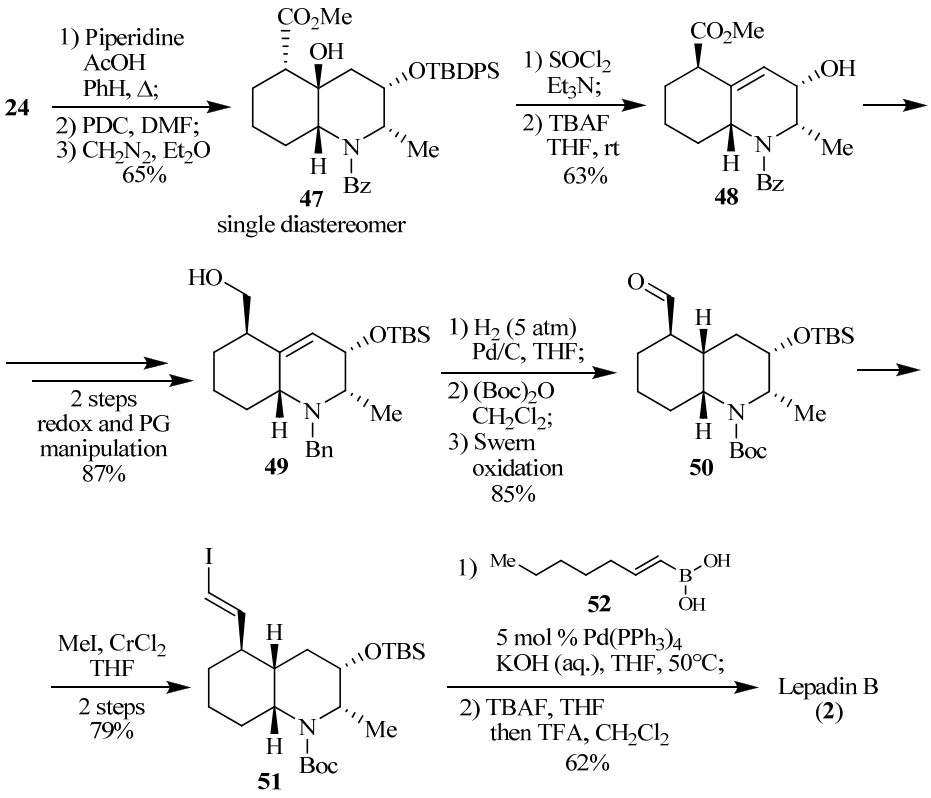
The second and even longer *tour de force* synthesis of lepadin B (**2**) came from the Kibayashi group in 2000 [23, 24]. The synthesis started with the *S*-malic acid derived chiral aldehyde **39**, which was elaborated to compound **40** in four steps *via* two sequential olefination reactions. Six further steps were used to achieve one carbon homologation and produce *N*-hydroxy amide **41** – a precursor for the stra-

Kibayashi 2000

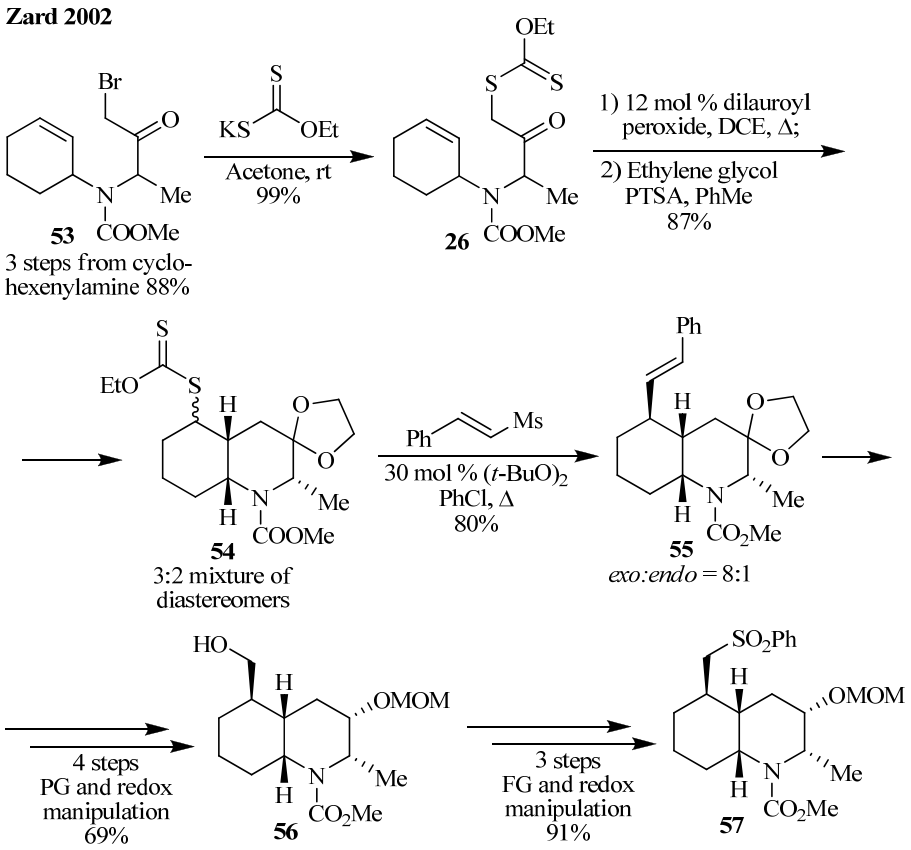


tegic acylnitroso Diels–Alder reaction. The reactive intermediate **25** was formed by oxidation of compound **41** with tetrapropylammonium periodate. Subsequent [4+2]-cycloaddition reaction produced bicycles **42** in reasonable diastereoselectivity. Hydrogenation of the stereochemically pure compound **42** and highly diastereoselective α-oxidation with the Davis sulfonyloxaziridine **43** followed by protection of the newly generated hydroxyl function gave intermediate **44**. At this stage the methyl group was installed in high stereoselectivity *via* a one-pot Grignard addition-reduction protocol. Reductive opening of the oxazine bicycle **45** followed by benzoylation produced compound **46**, which was transformed into aldehyde **24** *via* a five step sequence. Hence the original hydroxyl stereocenter, which was used to stereocontrol the key bicyclization reaction, was excised.

Intramolecular aldol cyclization of compound **24** followed by oxidation by pyridinium dichromate (PDC) and methylation gave decahydroquinoline **47** as a single diastereomer [23, 24]. Elimination of the hydroxyl group followed by tetrabutylammonium fluoride (TBAF) mediated deprotection and iterative epimerization of the stereocenter at the position 5 produced intermediate **48**. Final ring stereocenter was introduced *via* catalytic hydrogenation of compound **49**. Protection and oxidation produced aldehyde **50**, the precursor for chromium mediated Takai olefination reaction to produce alkene **51**. All that was left to finish the synthesis was a Suzuki coupling reaction with boronic acid **52** and global deprotection. The total synthesis of lepadin B was completed in total of 38 steps and less than 1% overall yield from *S*-malic acid. A serious drawback of these first two syntheses is the domination of large number of concession steps over a small number of strategic construction steps.

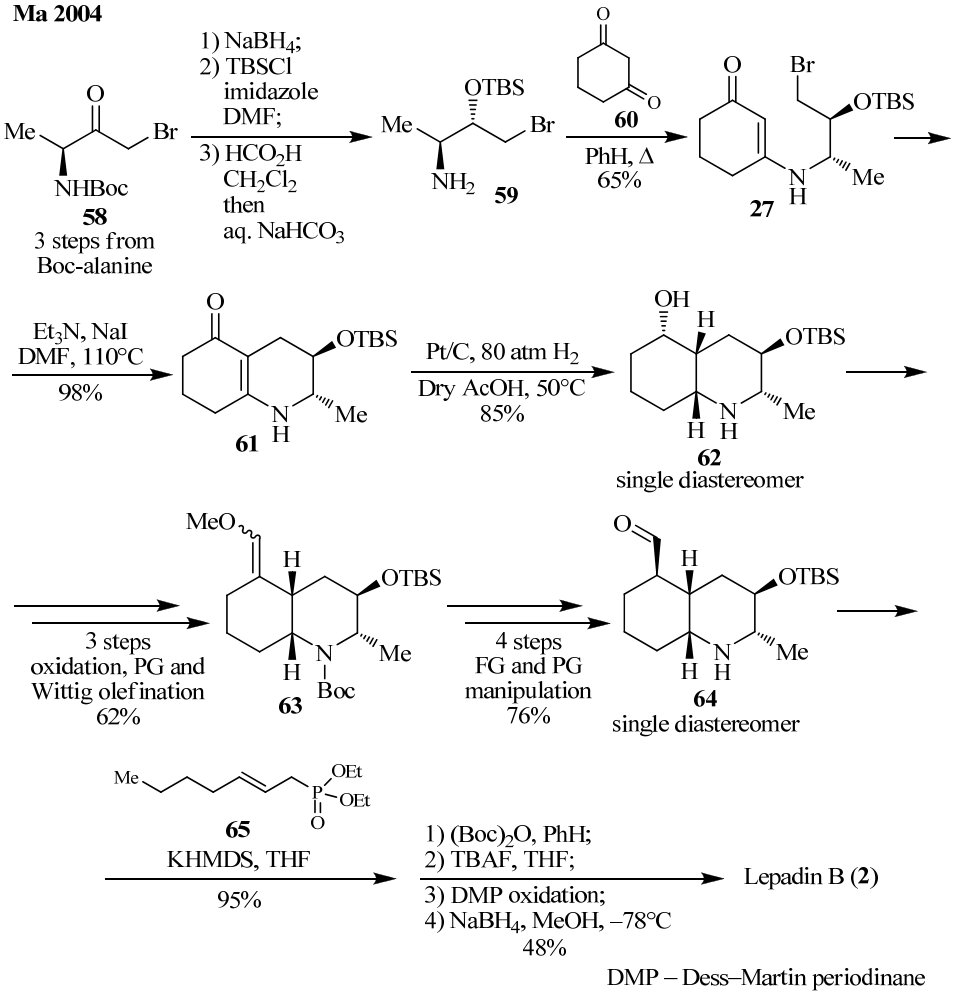


In 2002 Zard reported a formal synthesis of racemic lepadin B [25]. The distinction of this synthesis comes in the use of a remarkably diastereoselective radical based cyclization and side chain attachment strategy. The xanthate radical cyclisation precursor **26** was derived from racemic cyclohexenylamine in four steps and 88% yield. The key radical cyclization was initiated using dilauroyl peroxide in refluxing dichloroethane. Only the *cis* ring junction product was observed albeit as a 3:2 mixture of isomers at the position C-5. However, this did not influence the high stereoselectivity of radical vinylation, which had to be performed on the protected compound **54** to avoid significant reduction of the xanthate group *via* hydrogen transfer [26]. The intermediate **55** was then transformed to compound **57**, an intermediate in the Toyooka synthesis, *via* a seven step redox, FG and PG manipulation sequence hence constituting a formal synthesis of lepadin B (**2**) in a total of 19 steps. Thus, the development and application of the Zard group own radical based methodologies to the synthesis of lepadin B (**2**) achieved significant improvement of step count over the previous two syntheses.



In 2004 Ma and Pu completed the synthesis of several lepadins [27, 28]. Boc-alanine was chosen as the source of chirality and was converted to bromoketone **58** *via* a three step Arndt–Eistert homologation protocol. Highly diastereoselective reduction followed by hydroxyl protection and selective cleavage of Boc group delivered protected bromoaminoalcohol **59**, which was condensed with 1,3-cyclo-hexanedione **60** to give the cyclization precursor **27**. The key alkylative ring forming reaction proceeded at high temperature in high yield. Complete high pressure hydrogenation of ketone **61** took place with remarkable selectivity

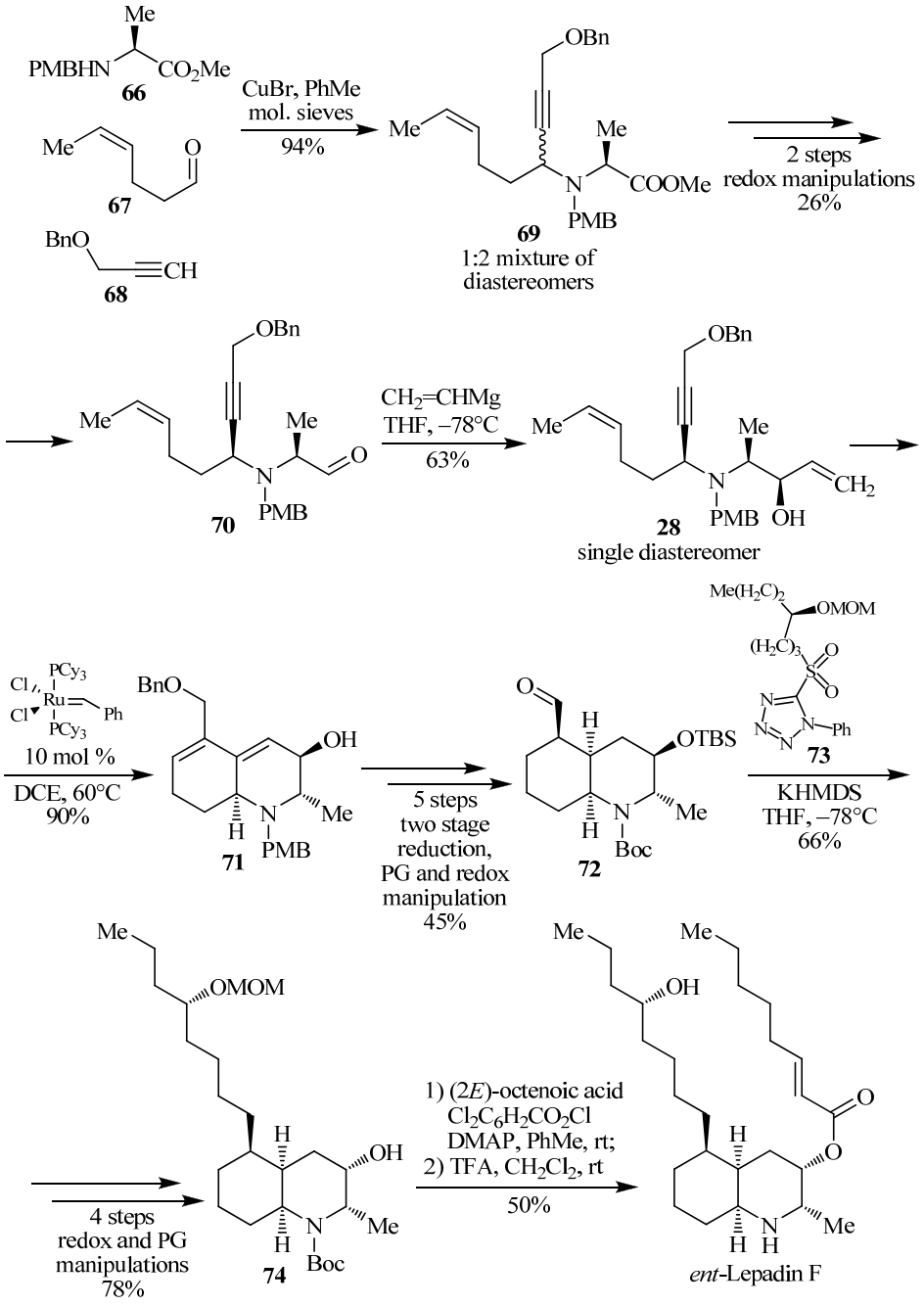
producing three new stereocenters in high yield. A three step oxidation, protection and Wittig olefination reaction sequence delivered the isomeric methyl enol ethers **63** in 62% overall yield. The four step sequence comprising methyl ether hydrolysis to aldehyde, deprotection and equilibration of the newly created stereocenter gave aldehyde **64** as a single diastereomer in 76% overall yield. Side chain was attached *via* Horner–Wadsworth–Emmons reaction (HWE olefination) with phosphonate **65** in high yield. All that remained to complete the synthesis was protecting group and redox manipulations to invert the 2-hydroxyl stereocenter, a sequence which took four steps and proceeded in 48% overall yield. In total, the linear 21 step sequence delivered lepadin B in 5.3% overall yield. In a similar fashion Ma and Pu completed the synthesis of all other lepadins with the exception of lepadins F and G.



In 2008 Blechert and coworkers reported the first total synthesis of *ent*-lepadins G and F by employing the ene-yne-ene ring closing metathesis methodology [29]. The synthesis started with a copper mediated three component coupling reaction between PMB-alanine methyl ester (**66**), *cis*-4-hexenal (**67**) and benzyl propargyl ether (**68**) producing the adduct **69** as a 1:2 mixture of diastereomers in favour of the undesired isomer. Chromatographic separation of stereoisomers after reduction of ester group and oxidation of the minor diastereomer produced compound **70**. Further addition of vinylmagnesium bromide proceeded with exclusive selectivity

but moderate yield securing the three stereocenters of the hexahydroquinoline precursor **28**. The subjection of compound **28** to the 1st generation Grubbs catalyst effected impressive cascade ene-yne-ene ring closing metathesis reaction to give hexahydroquinoline **71** with perfectly placed functionality for the introduction of the remaining stereocenters. However, this proved to be not straightforward to accomplish. The reduction of two double bonds in the TBS-protected hexahydroquinoline **71** proceeded stereoselectively from the less hindered face with simultaneous PMB deprotection. However, the hydrogenolytic removal of the *O*-benzyl group required reprotection of the nitrogen functionality as the Boc carbamate and

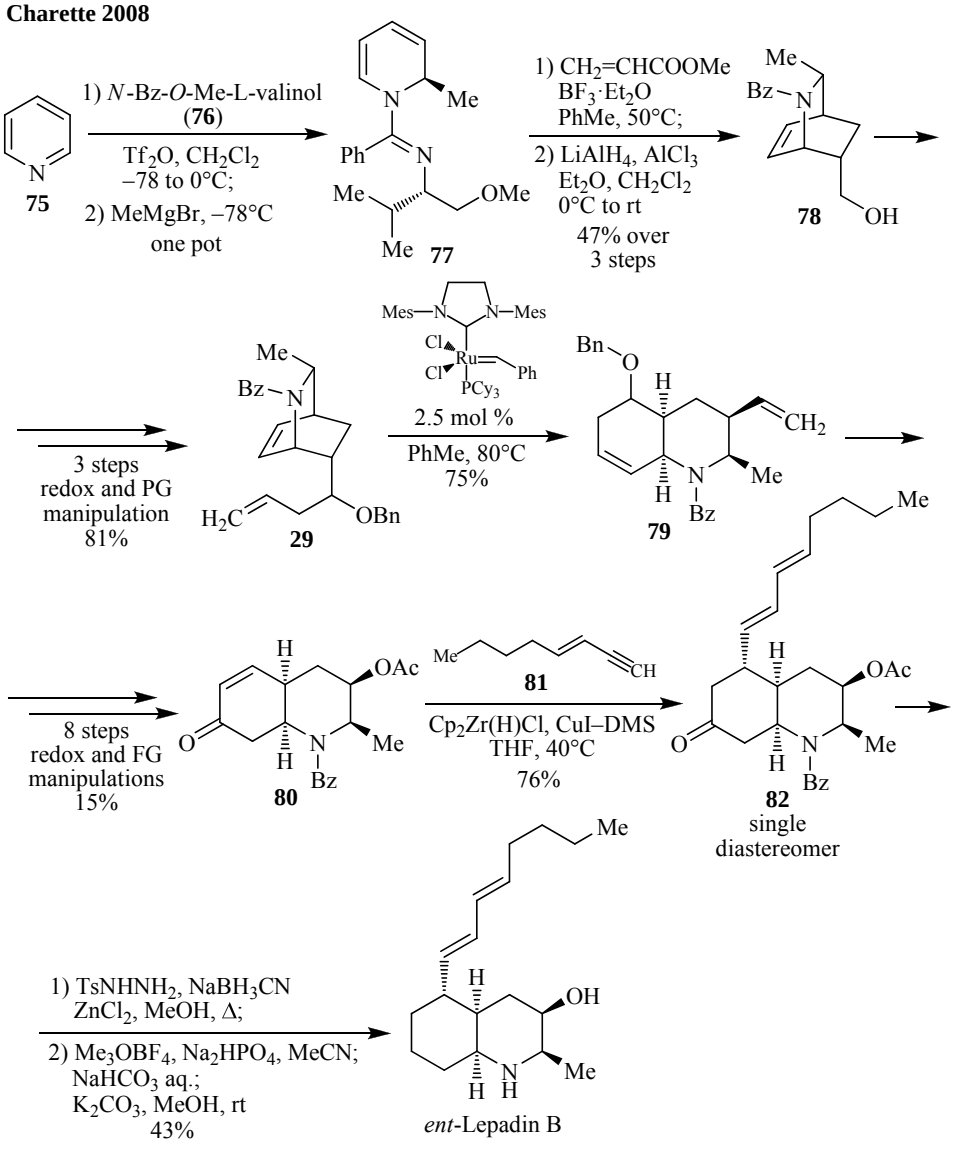
Blechert 2008



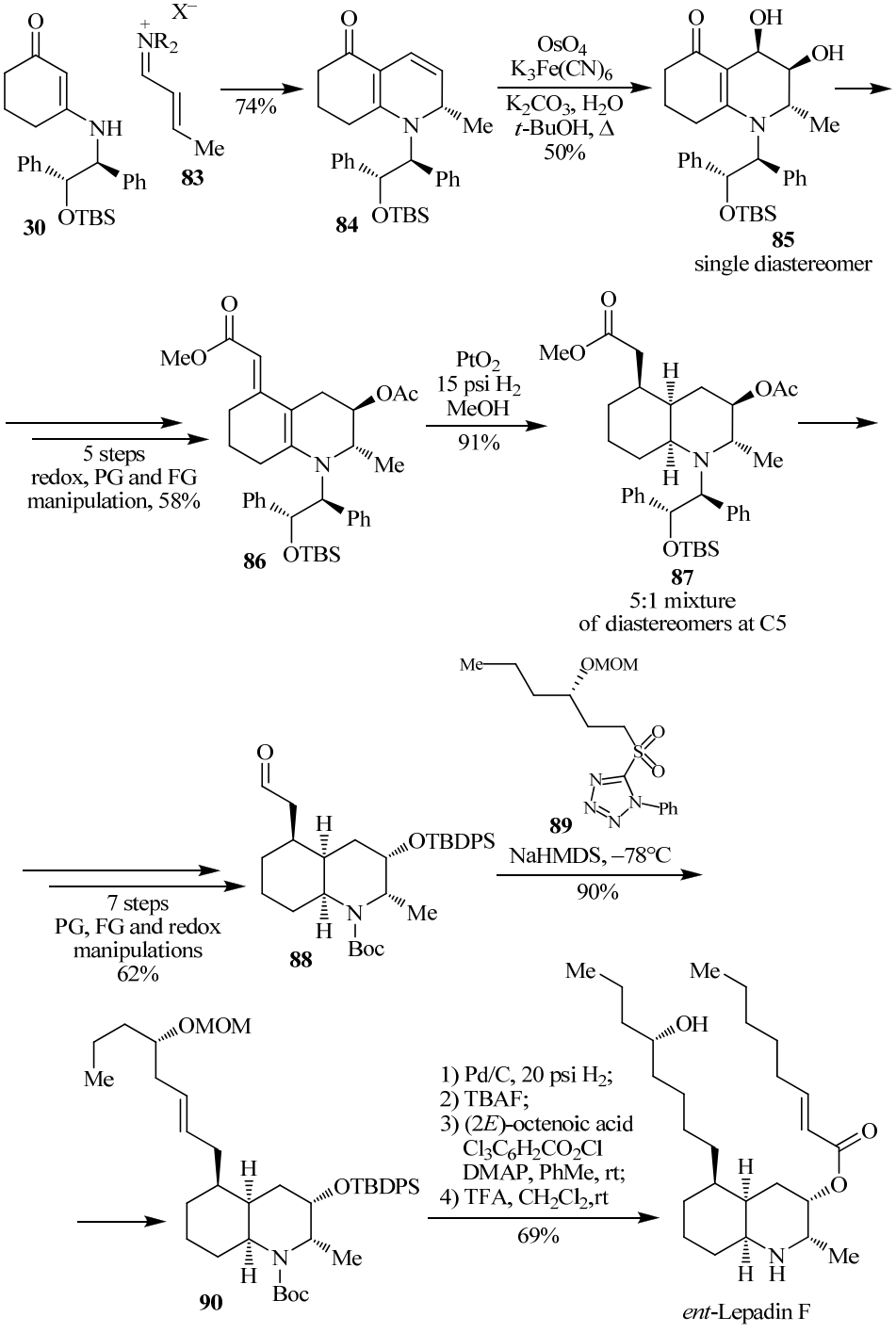
a separate reduction step. Swern oxidation gave the aldehyde **72** ready for side chain attachment *via* Julia–Kocienski olefination with tetrazole **73**. TBS deprotection and redox manipulation inverted the hydroxyl stereocenter and reduced side chain double bond. Acylation of compound **74** with (2*E*)-octenoic acid and deprotection finished the synthesis of *ent*-lepadin F. Similarly *ent*-lepadin G was synthesized using (2*E*,4*E*)-octadienoic acid for the acylation reaction. These syntheses required a total of 19 steps and proceeded in 2% overall yield.

The Charette group started synthesis of *ent*-lepadin B with a diastereoselective 1,2-addition of methyl magnesium bromide to pyridine adduct with the L-valine derived chiral auxiliary **76** [30, 31]. Diastereoselective Diels–Alder reaction with methyl acrylate set the next three stereocenters. Thereby four of five lepadin B stereocenters were very quickly constructed. Reduction of the ester and auxiliary removal gave the aza-bicycle **78** in 47% yield over three steps. Three further steps transformed compound **78** to the key ROM-RCM precursor **29**. An elegant tailor developed ring opening ring closing metathesis of compound **29** using the 2nd generation

Charette 2008



Hsung 2008



Grubbs catalyst furnished octahydroquinoline **79** in good yield. Next the eight step sequence comprising an oxidative transformation of vinyl group into acetoxy group, PG manipulations and Wharton rearrangement gave compound **80** in 15% overall yield. The enone functionality was introduced in compound **81** for the diastereoselective side chain attachment *via* conjugate addition. This was achieved *via* hydrozirconation of alkyne functionality in compound **81** and subsequent

generation of the reactive organocopper species in one pot. Addition of the *in situ* generated organocuprate to enone **80** proceeded in good yield and exclusive selectivity. Finally, Wolff–Kishner reduction and global deprotection finished the synthesis of *ent*-lepadin B in a total of 18 steps and 1.4% overall yield. Very quick and impressive build-up of complexity in this synthesis was somewhat plagued by large number of concession steps used in the final stages of synthesis.

The 2008 Hsung group total synthesis of *ent*-lepadin F showcased the application of their own aza-cycloaddition methodology [32, 33]. The synthesis started from the chiral aminoalcohol auxiliary derived enamine **30**, which was engaged in an aza-cycloaddition reaction with the crotonaldehyde derived iminium species **83**. The stereocenter at the position 2 of the heterocycle was generated with good selectivity. Next dihydroxylation under forcing conditions proceeded with exclusive selectivity albeit with moderate yield to produce diol **85**. Five steps were used to advance the synthesis of the compound **86**. Manipulations included reductive excision of the superfluous stereocenter at position 4, protection of the remaining hydroxyl function and a 3 step olefination protocol. Medium pressure reduction of the double conjugated system in compound **86** generated exclusively the *cis*-ring junction as well as the correct stereo relationship at the position C-5 with 5:1 selectivity. Compound **87** was converted to aldehyde **88** in seven steps, which included removal of the chiral auxiliary, redox inversion of a stereocenter, PG manipulations and ester to aldehyde conversion. Compound **89** with hydroxylated side chain was attached to aldehyde **88** *via* a Julia–Kocienski olefination. Final deprotection and acylation completed the total synthesis of *ent*-lepadin F in total of 20 steps and 5% overall yield.

Recently, Hsung also reported the synthesis driven proof of the absolute configuration of natural lepadin G to be that as depicted in structure **8** [34].

Total synthesis of lepadin natural products currently requires 18–38 linear steps, which cannot be considered practical. This is in stark contrast to the recent and so far the shortest asymmetric 5 step synthesis of a structurally simpler pumiliotoxin C [35]. It is clear that significant synthetic advances need to be made to achieve more practical syntheses of lepadin alkaloids. Our efforts on the development of a suitable strategy and the required methodologies to bring the synthesis of these natural products closer to the 10 step barrier will be reported in due course.

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[1] *School of Chemical Technology*,
Aalto University,
Kemistintie 1, *Aalto FI-00076*, *Finland*
e-mail: ari.koskinen@aalto.fi

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