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SYNTHESES OF RHAZINILAM: A COMPARATIVE REVIEW OF FORTY YEARS OF SYNTHETIC ENDEAVORS

Inga Kholod, Olivier Vallat, Ana-Maria Buciumas, and Reinhard Neier*

Department of Chemistry, University of Neuchâtel, Av. Bellevaux 51, CH-2000 Neuchâtel, Switzerland, E-mail: Reinhard.Neier@unine.ch, FAX: +41 (0)32 718 2428

Abstract – *R*-(-)-Rhazinilam is a relatively simple but unusual monopyrrolic product isolated from nature. It is probable that *R*-(-)-rhazinilam is an artifact of the isolation procedure. Seven total syntheses of rhazinilam have been described in the literature. The comparison of the published syntheses clearly demonstrates the sensitivity of the pyrrole ring contained in the rhazinilam structure. Despite the spectacular progress in organic synthetic methods only a few synthetic strategies have been applied to the total synthesis of rhazinilam. Astonishingly the number of steps needed from commercial starting materials has stayed similar over the almost 40 year period since the first synthesis has been reported in 1973.

INTRODUCTION

NATURAL PRODUCTS AS SOURCE FOR NEW DRUGS

The use of natural products for the treatment of human diseases has been documented very early in human history e.g. in the “Ebers Papyrus”, dating back to 1500 B.C.¹⁻⁶ Many widely used drugs have been initially isolated from plants (Figure 1).

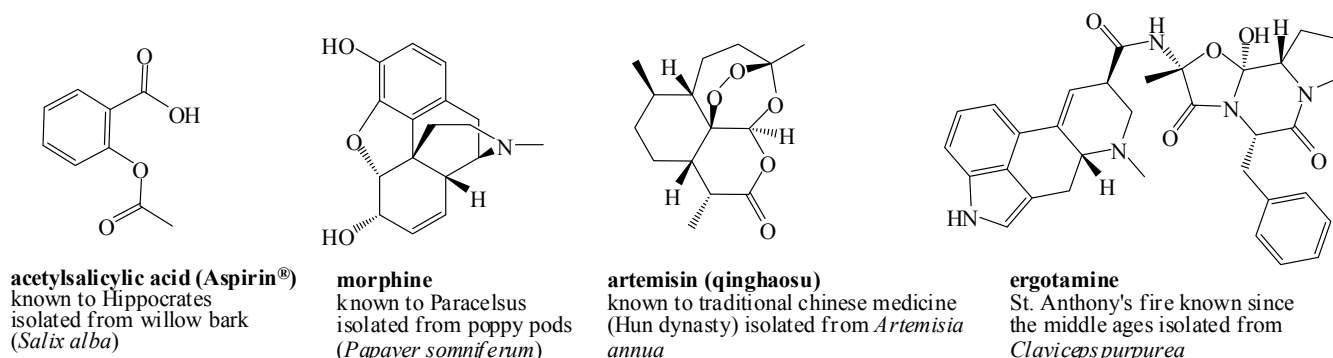


Figure 1. Natural products known for their drug activity

This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

The capacity of chemists to isolate, to identify and to modify drug molecules has been a major driving force for the advancement of chemistry. Until the early sixties of last century, natural products chemistry was undoubtedly one of the central activities of academic and industrial laboratories (Figure 2). Natural products chemistry combined all the activities ranging from the isolation to the synthesis and testing of natural products. Often the problem posed during natural products chemistry was the motivation to develop new and more efficient methods and techniques. Natural products chemistry was undoubtedly a central activity and a field driving the progress of chemistry as a whole. The strong link between synthesis and natural products chemistry was loosened once physical and spectroscopic methods allowed identifying the structures of small quantities of products isolated from natural sources. The structure determination of Vitamin B₁₂ by Dorothy Crowfoot Hodgkin based on X-ray crystallography was an impressive example of the power of physical methods to determine complicated structures.⁷⁻¹⁰

In this process spectroscopic methods gained in importance. Natural products chemistry on the other side lost to a large extent its unique position uniting under one single subject heading, isolation, separation techniques, characterization, identification, studies of reactivities and synthesis. The different subfields became independent and for several decades the importance attributed to natural products and their use was diminished or underestimated. Another factor which influenced the status of natural products chemistry in the canon of chemistry was the development of methods adapted to studies of very important classes of biopolymers like proteins and DNA. Starting from the seminal publication of Watson and Crick¹¹ huge efforts were dedicated to deciphering the secrets of DNA, the essential molecule for the storage of information in living organisms.

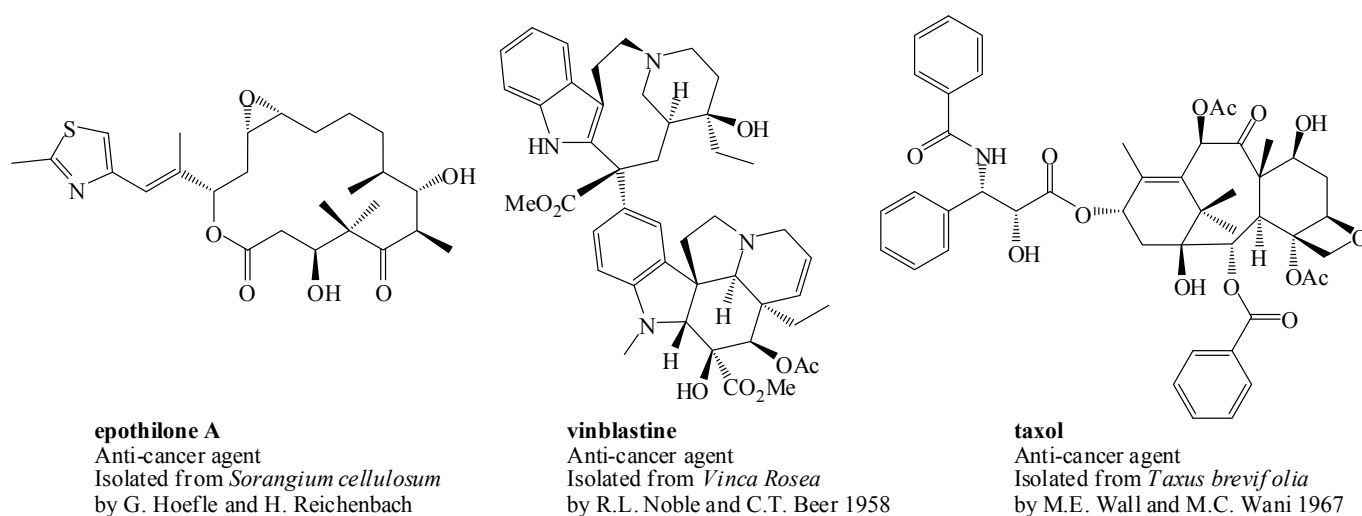


Figure 2. Highly potent natural products widely used in modern medicine

In parallel to the studies of nucleic acids, efforts were devoted to the analysis of peptides,¹² proteins and enzymes and to the determination of their sequence first and then their three-dimensional structure.¹³ The development of solid state synthesis by Bruce Merrifield¹⁴ opened the opportunity to make peptides on demand using automated synthesizer. During a long period the ground work had to be done by many natural products chemists, who had specialized in peptide chemistry.¹⁵ The synthetic transformations, the protecting groups and the analytics had to be optimized before the automated solid state synthesis could become a routine technique. During this period natural products chemistry obviously spread over much wider territory but it lost at the same time its central position. Especially the interest in small natural products diminished or it was overshadowed by the many other activities, which were the focus of important research projects in the field between chemistry, biology and medicine.

Recent years have seen a revival of natural products chemistry in its classical sense. Several factors have contributed to the recovery of the interest in small to medium sized natural products. The challenge of finding new effective drugs has become enormous and the financial risks have put a huge pressure on the pharmaceutical industry. Despite the use of new and efficient scientific, organisational and management methods the number of drugs approved has fallen steadily. The hopes that the increased knowledge (especially from the completion of the human genome project), coupled with more efficient methodologies (synthesis of libraries, parallel synthesis and better separation techniques) would create again higher numbers of drugs have not been fulfilled. Astonishingly in these difficult times natural products have kept their position and many new drugs coming on the market are either natural products or compounds derived from natural products¹⁶⁻²³ (Figure 3).

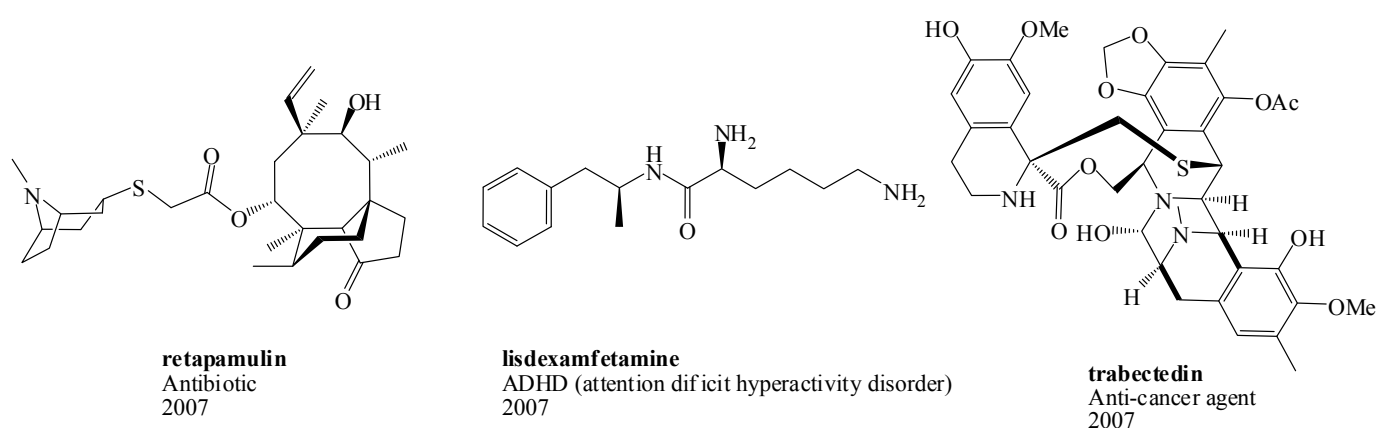


Figure 3. Natural products or natural products derived drugs introduced recently

This is all the more astonishing as searching for drugs from natural sources is the oldest approach to drug discovery. Therefore much hope and huge investments went into new methods, believing that modern science would make the tedious process of finding drug candidates more efficient and faster. Despite

enormous efforts natural products still seem to be one of the best bets, if one wants to find a drug. It is not obvious why nature provides humans with drug molecules. Scientists analyse the natural role of small molecules with the hope to find out why this exquisite class of compounds called natural products have been such an extraordinary source of scientific knowledge and economic wealth.²⁴⁻³⁰ Interesting and important questions are raised about the functions of the collection of these natural products in their natural environment. Many of these questions cannot be answered yet.

A parallel development tries to make use of the biosynthetic machinery, especially in the field of the polyketide biosynthesis, in order to get modified active compounds and/or to find compounds, which are usually synthesized in too tiny amounts to be isolated. Based on the analysis of the genetic information, combined with the knowledge of the function of the individual modules in the biosynthetic machinery modified “natural products” have been obtained.³¹⁻³³

Finding and isolating even delicate natural products has become more efficient and much easier. Thanks to the much milder and faster separation methods available, many natural products, which did not survive the classical, tedious isolation process, can now be found and identified. It is clear, that natural products have gained again the interest of the science community and the pharmaceutical industry. There is still a lot of excitement in all activities related with natural products, as long as small molecules with unusual structures are capable to act and influence important biological processes with unsurpassed selectivity and efficiency.

NATURAL PRODUCTS CONTAINING PYRROLE RINGS

Until the middle of last century a great variety of nitrogen heterocycle containing natural products have been isolated and identified. The number of monopyrrolic natural products isolated was comparatively small³⁴ (Figure 4).

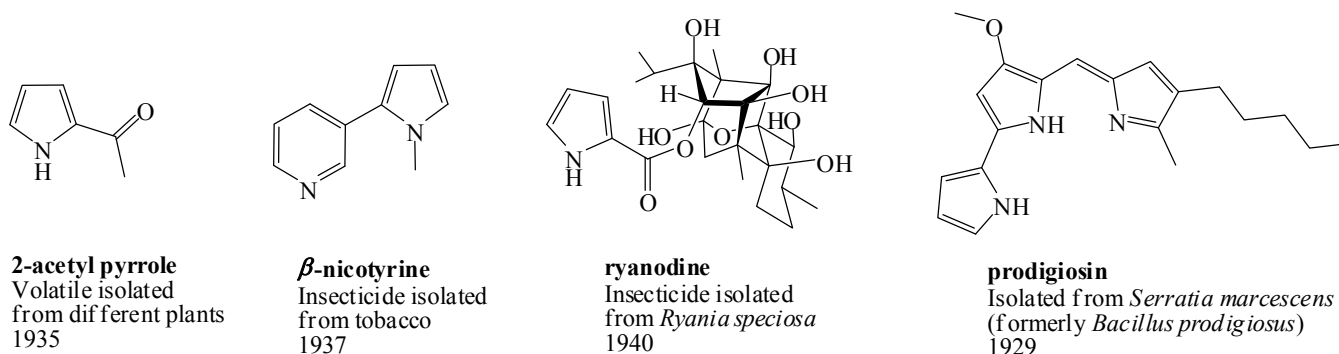


Figure 4. Natural products containing a single pyrrole ring known before 1954

At this point in time the more complex tetrapyrrolic macrocyclic natural products had already been identified and many of their functions had been well recognized. The tetrapyrrolic “pigments of life”

fulfill essential tasks for important processes like oxygen transport, electron transport, catalyzing oxidation processes, catalyzing unique transformations and most importantly playing central roles in photosynthesis. It was also well known that these macrocycles were synthesized in large quantities by nature. The pathways of the biosynthesis and the structures of the simpler precursors were however unknown. The structure of PBG was determined by Cookson and Rimington only in 1954.³⁵ Porphobilinogen (PBG) is the dedicated pyrrolic intermediate for the biosynthesis of uroporphyrinogen III, the precursor of all tetrapyrrolic macrocycles (Figure 5A). In hindsight it is impressive to realize that almost at the same time chemists determined the structure of the universal precursor for the “pigments of life” the structure of a new class of pyrrole containing antibiotics was discovered. Only three years after the discovery of PBG the initial proposals for the structure of netropsin an oligopeptidic antibiotic isolated from *Streptomyces netropsis* were published^{36,37} (Figure 5B). It was only after intensive studies that scientists realized that this class of antibiotics acquires its activity due to the capacity to interact selectively with DNA.

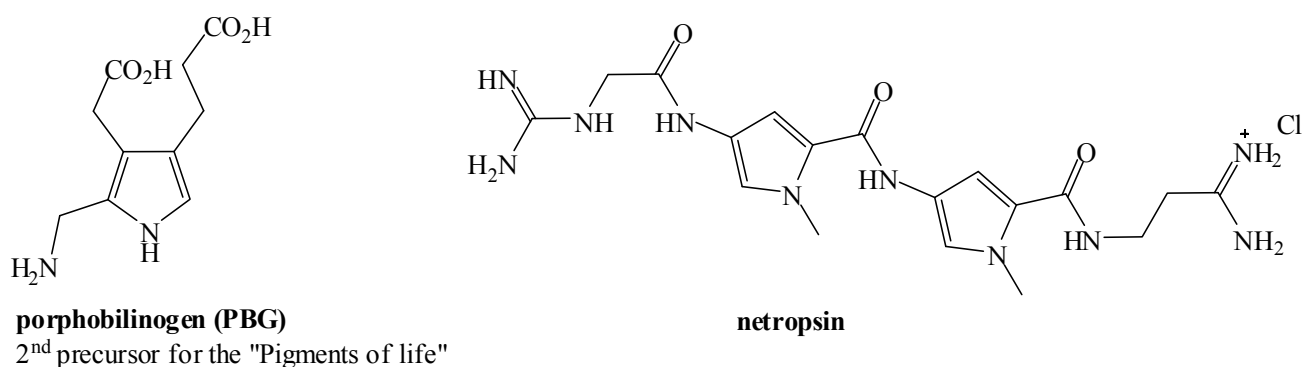


Figure 5. Structures of porphobilinogen and of netropsin, two pyrrole containing natural products with essential functions discovered in the late fifties of last century

Since these two important discoveries the number of monopyrrolic natural products isolated and determined has increased steadily. A systematic overview of all monopyrrolic natural products known before 2003 has been presented by Gossauer in his beautiful review article.³⁴ The monopyrrolic natural products are incorporated in an astonishing variety of different skeletons. Most pyrrole containing natural products are decorated by a functional group stabilizing the electron rich heterocycle against oxidation and degradation. Esters, amides or lactam are directly bond to the heteroaromatic ring. Aromatic rings directly connected to the heterocycle can also stabilize the sensitive pyrrole. Only very few pyrrole containing natural products have not incorporated a stabilizing group into their structure. Pyrroles isolated from ants are a notable exception³⁸ (Figure 6), but it is probably correct to assume that these special natural products are not produced in large quantities.

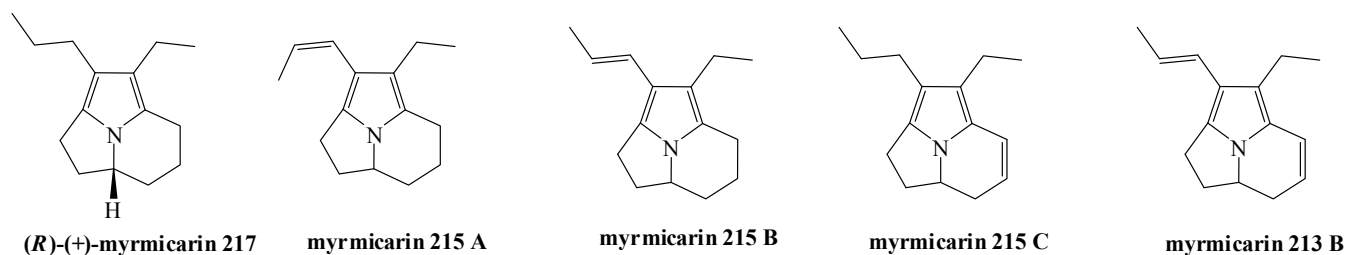


Figure 6. Alkaloids isolated from African ants *Mirmicaria opaciventris*

The other more remarkable exception is PBG, the second dedicated precursor of the tetrapyrrolic natural macrocycles. The amount of PBG synthesized by nature each year is huge. PBG is not accumulated during the biosynthetic process, but is synthesized in the quantities needed for the formation of the adequate quantities of the tetrapyrrolic macrocycles. PBG possesses a high reactivity, which is used for the synthesis of uroporphyrinogen III, the natural precursor of all “pigments of life”. The absence of stabilizing groups on the pyrrole ring of PBG makes sense. The enhanced reactivity is a crucial element for the next step of the biosynthesis. The electron withdrawing groups present in many monopyrrolic natural products increase the stability of these compounds and allow their isolation.

Pyrrole containing natural products have been isolated from many sources. The structural variety is impressive. The role played by the pyrrole ring for the function of these natural products can be crucial as in the case of PBG. In many cases the chemists and biologists are not yet able to attribute a precise function to the pyrrole ring within the skeleton of the natural product. The properties of the electron rich pyrrole ring and its strong hydrogen bond donor capacity bestow unique properties to this small heterocycle, which have been used by nature and which had to be taken into account, when natural products contain monopyrrolic units. It is therefore one of the challenges for chemists with an interest in this type of compounds to disclose the links between the structure of these monopyrrolic natural compounds and their properties. Still one of the best ways to reveal the connections inscribed into the structure of the natural products and to learn about the reactivity of these compounds are studies of the total synthesis.

ISOLATION AND STRUCTURE DETERMINATION OF RHAZINILAM AND ITS STRUCTURAL ANALOGUES

(R)-(-)-Rhazinilam (**1**) was first isolated by Linde from *Melodinus australis* in 1965.³⁹ The isolation from *Rhazya stricta* (1970)^{40,41} some years later lead to the trivial name used today. The natural product has been found in other South-east Asian members of the family Apocynaceae.⁴²⁻⁵⁰ The alkaloid **1** has also been obtained from somatic hybrid intergenic cell cultures.⁵¹ More recently, (R)-(-)-rhazinilam (**1**) was isolated from the plant species *Kopsia arborea* (2007).^{52,53}

The structure of (*R*)-(-)-rhazinilam (**1**) was established in 1972 through spectroscopic analysis, chemical degradation studies⁴¹ and finally confirmed by X-ray crystallographic techniques⁴³ (Figure 7). The complete infra red, mass spectra and ¹H and ¹³C NMR analysis of compound **1** was reported later.⁵⁴ The four rings are identified as rings A to D. The quaternary carbon center at C20 and a phenyl-pyrrole chirality axis are the two stereogenic elements of (*R*)-(-)-rhazinilam (**1**). The dihedral angle between rings A and C is almost 90°. The lactam bond is in the *s-cisoid* conformation. The nine membered ring adopts a boat-chair conformation imposed by the two aromatic bonds and the lactam bond contained in the medium sized ring rigidifying the ring. It was not possible to determine the absolute configuration (*R*, *aR*) by X-ray. The absolute configuration was deduced *via* semi-synthesis from an aspidosperma alkaloid, namely (+)-1,2-didehydroaspidospermidine (**13**) (Scheme 1).⁵⁵

Other alkaloids with the same tetracyclic array as (*R*)-(-)-rhazinilam (**1**) have been isolated from different members of the family Apocynaceae: rhazinicine (**2**),⁶⁰⁻⁶³ 3-oxo-14,15-dehydrorhazinilam (**3**),⁶⁴ (-)-leuconolam (**4**),^{46,48,63,65,66} (+)-*epi*-leuconolam (**5**),^{46,48} *N*-methylleuconolam (**6**),⁶⁷ (*R*)-(-)-rhazinal (**7**),^{63,68} kopsiyunnanines C1 (**8**), C2 (**9**), C3 (**10**)⁵³ (Figure 7). The formation of all these alkaloids is postulated to occur *via* oxidative pathways from 5,21-dihydrorhazinilam (**11**), which is co-isolated with **1**.^{46-48,52,59}

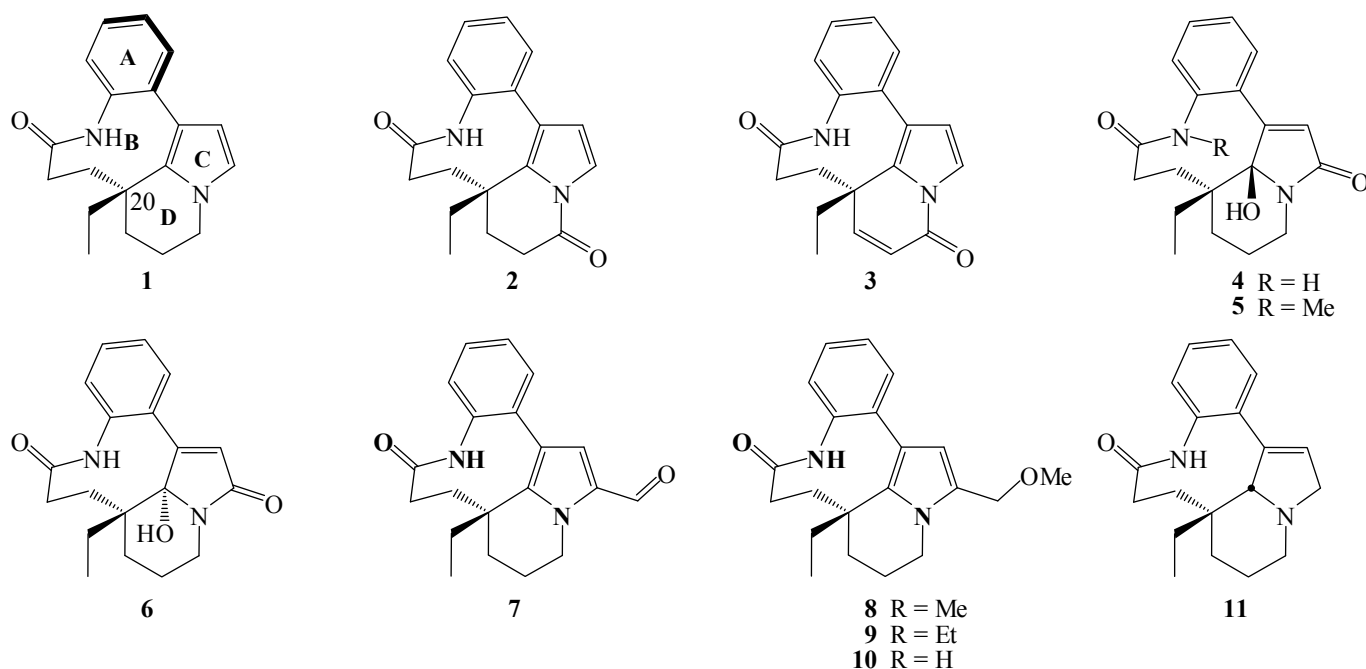
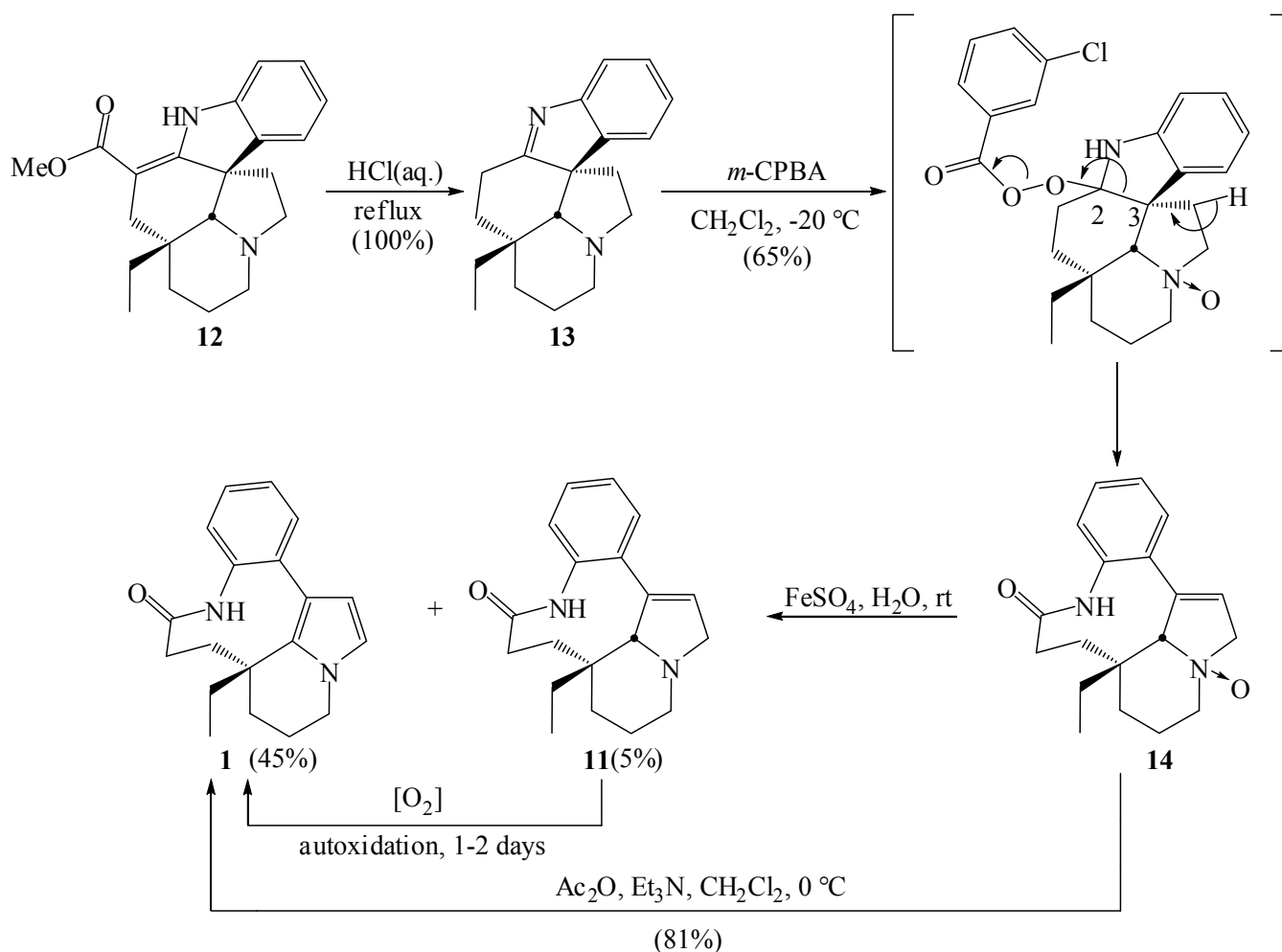


Figure 7. (*R*)-Rhazinilam (**1**) and its naturally occurring analogues

POSTULATED FORMATION OF (*R*)-(-)-RHAZINILAM FROM INDOLE ALKALOIDS

(*R*)-(-)-Rhazinilam (**1**) is now considered to be an artifact of the extraction procedure. The unstable 5,21-dihydrorhazinilam (**11**)⁴¹ aromatises spontaneously on exposure to air.^{46,47} The dihydro-derivative **11**

is believed to be the immediate natural precursor of (*R*)-(-)-**1**. More significantly the natural product **1** can also be synthesized starting from (+)-vincadifformine (**12**) (Scheme 1).⁵⁵ The mechanism of the stepwise conversion was proposed by Smith⁵⁵ and later experimentally confirmed by Guenard.^{56,57} The sequence starts from (+)-**12** and comprises an acid-catalysed ester hydrolysis and decarboxylation followed by an oxidation-reduction-oxidation sequence. The key step in this sequence is the MCPBA-promoted oxidative cleavage of the C2-C3 indoline bond in (+)-**13** producing the *N*-oxide **14**. The *N*-oxide **4** was reduced with Fe(II) to give a 9 : 1 mixture of (*R*)-(-)-**1** and (*R*)-**11**. The conversion of (*R*)-(**11**) to (*R*)-(-)-**1** was slow. This observation suggests that the formation of **1** from *N*-oxide **14** occurred *via* a Polonovsky-type reaction.^{57,58} This is further circumstantial evidence for this hypothesis. (+)-1,2-Didehydroaspidospermidine (**13**) has never been detected *in vivo* together with **11** or (*R*)-(-)-**1**. If (+)-1,2-didehydroaspidospermidine (**13**) is the precursor of (*R*)-(-)-rhazinilam (**1**) remains an open question.



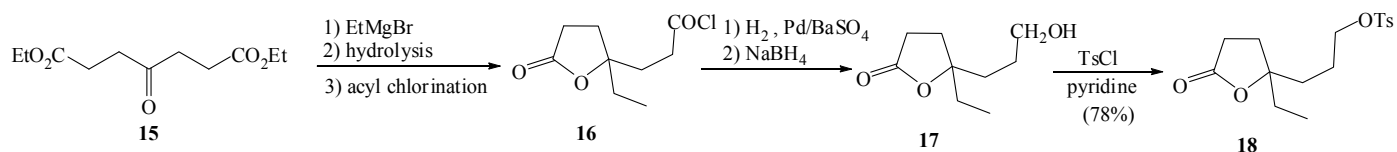
Scheme 1. Semi-synthesis of (*R*)-rhazinilam (**1**) from (+)-vincadifformine (**12**)

TOTAL SYNTHESSES OF *rac*-RHAZINILAM

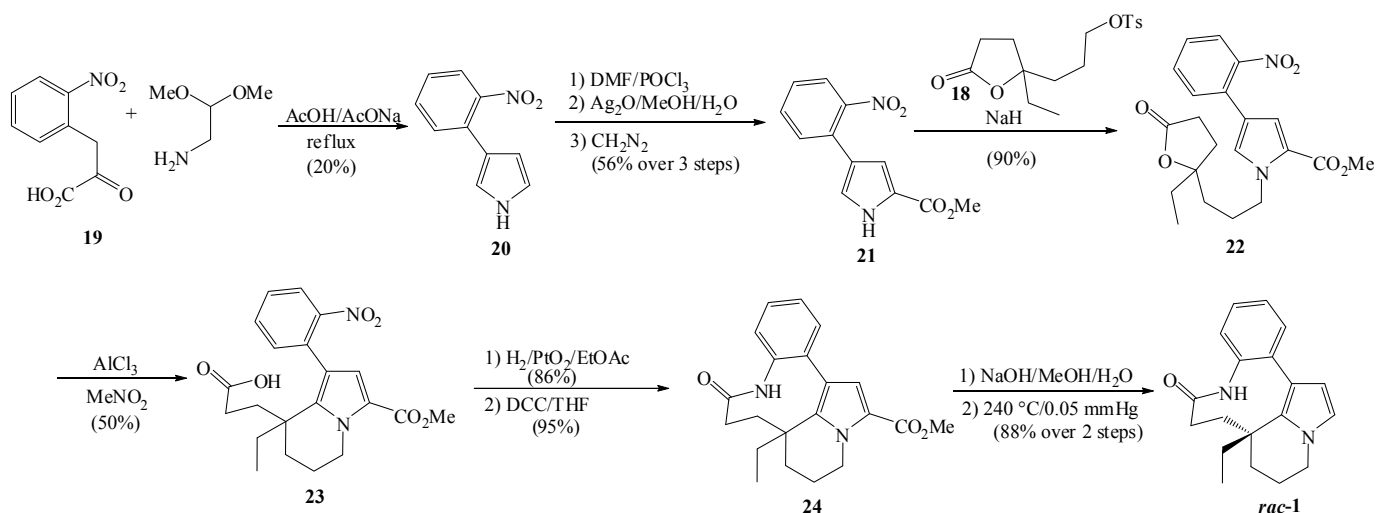
Four total syntheses of racemic rhazinilam (**1**) have been reported. The main motivation for these studies was the unusual structure of (\pm)-**1**. Over the almost forty years different strategies were applied to create the challenging elements contained in (\pm)-**1**: the direct A-C biaryl link, the nine-membered lactam B ring, and the quaternary-carbon at C20.

FIRST TOTAL SYNTHESIS OF *rac*-RHAZINILAM BY SMITH

The first total synthesis of the racemic rhazinilam (**1**) was reported by Smith and co-workers in 1973.⁵⁵ Reacting ethyl magnesium bromide with diethyl 4-ketopimelate (**15**) gave the lactone in good yield, (Scheme 2). The resulting γ -lactone **16** was reduced in a two-step sequence: Rosenmund reduction followed by NaBH₄ reduction. Tosylation of **17** with tosyl chloride in pyridine provided the desired tosyl derivative of γ -lactone **18** in 22% over six steps from commercially available **15**.



Scheme 2. Synthesis of intermediate **18**



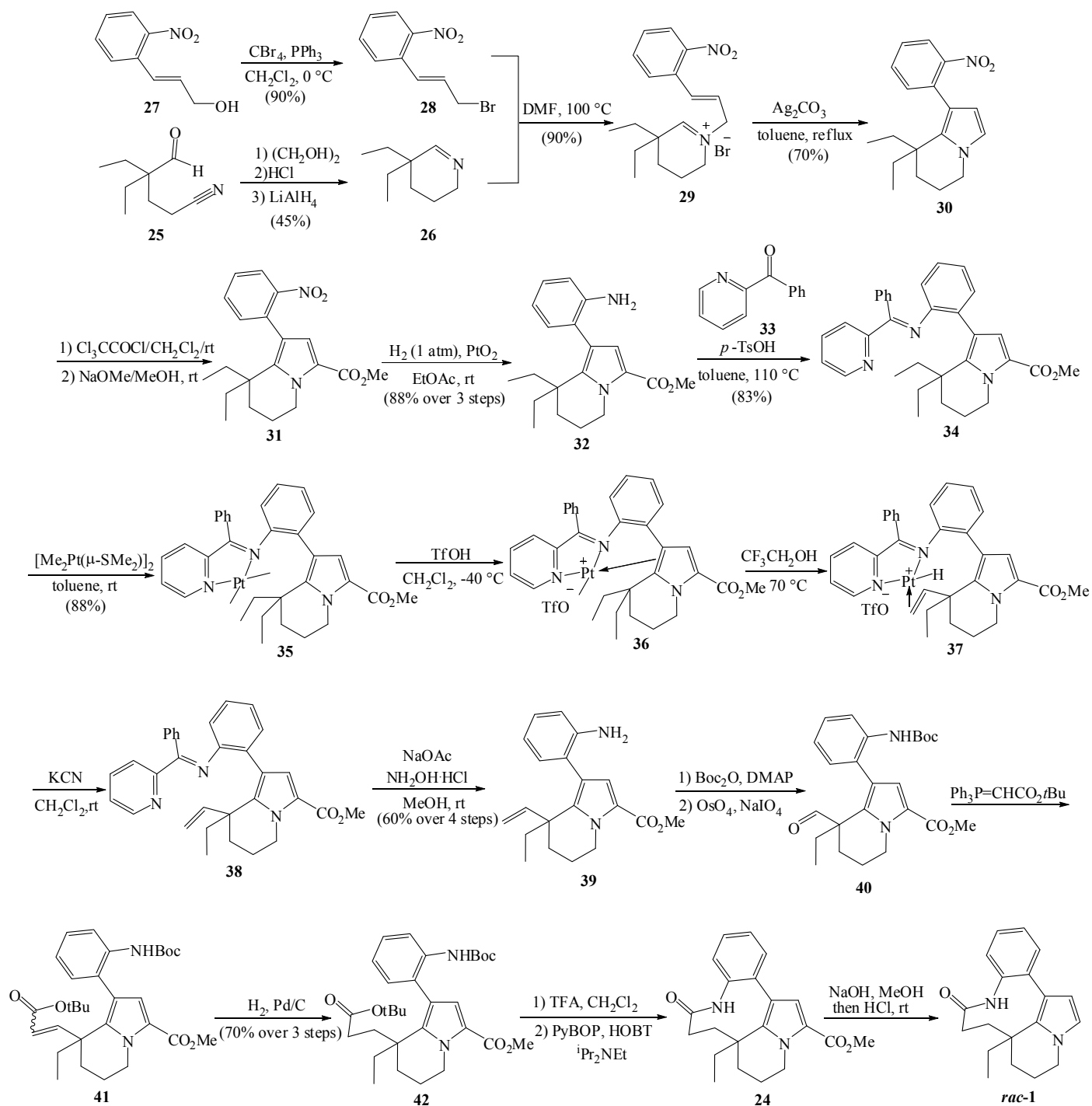
Scheme 3. Smith's total synthesis of *rac*-rhazinilam (**1**)

The pyrrole **20** was prepared *via* Knorr-type condensation (Scheme 3). Vilsmeier formylation of compound **20** followed by silver oxidation and subsequent esterification with diazomethane generated the pyrrole **21** in 11% yield over four steps from **19**.

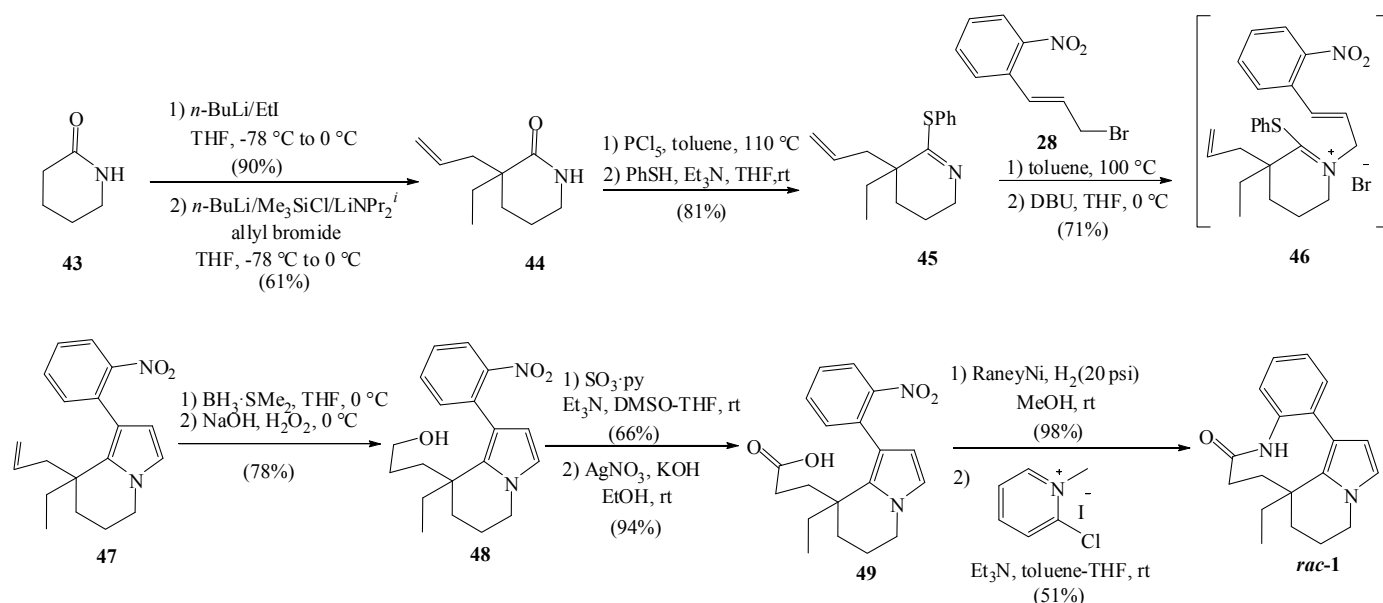
The crucial combination of the two intermediates was achieved by the *N*-alkylation of the sodium salt of the pyrrole **21** with the tosyl derivative of the lactone **18**. The intramolecular Friedel-Crafts cyclisation of the pyrrole **22** gave the tetrahydroindolizine derivative **23** in 50% yield. Catalytic reduction of the nitro group followed by lactamisation afforded compound **24**. A two step sequence had to be applied to produce *rac*-rhazinilam (**1**) under harsh conditions but in good overall yield. The synthesis proceeds through ten steps starting from the commercially available acid **19** in a remarkable 3.6% overall yield.

TOTAL SYNTHESIS OF *rac*-RHAZINILAM BY SAMES

In 2000 a very elegant total syntheses of *rac*-rhazinilam (**1**) was reported by Sames and co-workers.⁷⁰ The key intermediate **32** was synthesized in the efficient sequence depicted in Scheme 4.^{72,73} The Grigg-type 1,5-electrocyclisation reaction⁷⁴ of **29** catalysed by silver carbonate produced the intermediate **30** in 70% yield. The sensitive pyrrole ring was then protected in two steps as methyl ester **31**. Selective reduction of **31** provided the aniline **32** in 25% over seven steps from commercially available nitrile aldehyde **25**. The second key step was the transformation of one of the ethyl groups into ethenyl group. The pivotal platinum complex **35** had to be synthesized, introducing a Schiff base first and treating the Schiff base **34** with the dimethyl platinum reagent $[\text{Me}_2\text{Pt}(\mu\text{-SMe}_2)]_2$ ⁷⁵ providing **35** in 88% yield. Treating the intermediate **35** successively with triflic acid followed by thermolysis in trifluoroethanol at 70 °C and then by decomplexation with potassium cyanide and hydrolysis of the Schiff base **38** provided the racemic alkene **39** in 60% yield over four steps. The total synthesis was then completed *via* a formal one-carbon extension of the vinyl group and the subsequent closure of the medium sized lactam ring in six synthetic steps. Lemieux-Johnson oxidation provided the aldehyde **40** followed by Wittig olefination and selective reduction of the alkene **41** affording the racemic intermediate **42** in 70% over three steps. Reduction and lactamisation of compound **42** gave the previously reported ester **24**, which was transformed to *rac*-**1** according to Smith's methodology.⁵⁵ The synthesis proceeds through twenty steps in 3.5% overall yield starting from nitrile aldehyde **25**. The sequence is considerably longer than the Smith synthesis, but the overall yield is almost identical with the yield of the first synthesis.

Scheme 4. Sames' total synthesis of *rac*-rhazinilam (**1**)TOTAL SYNTHESIS OF *rac*-RHAZINILAM BY MAGNUS

In 2001 Magnus and co-workers published a straightforward and elegant synthesis of *rac*-rhazinilam (**1**)⁷² (Scheme 5).



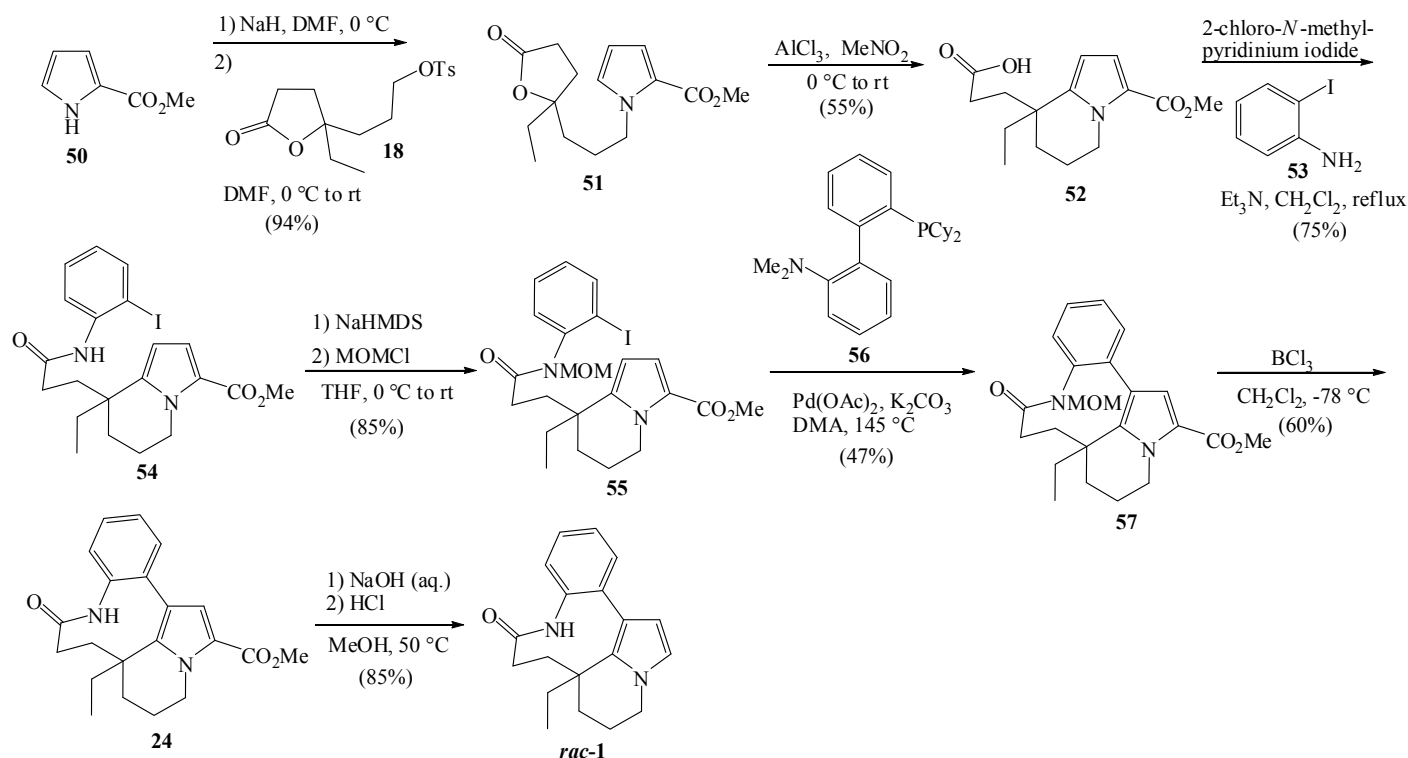
Scheme 5. Magnus' convergent total synthesis of *rac*-rhazinilam (*rac*-1)

The retrosynthetic analysis is very similar to the one used by Sames, with the difference that the two chains on the α -position of the pyrrole ring are already differentiated right from the start of the synthesis. The elegant but lengthy modification of one of the two ethyl groups can thereby be avoided, which reduces the number of steps. Starting from commercially available 2-piperidone **43** the ethyl and allyl group are sequentially introduced in a total of six synthetic operations. *N*-alkylation of this thiophenyl imino ether **45** with 2-nitrocinnamyl bromide **28** gave the corresponding iminium intermediate **46**. This intermediate underwent a Grigg-type 1,5-electrocyclisation/thiophenol elimination reaction⁷⁴ to provide compound **47** in 71% yield. The compound **47** was transformed into the natural product *rac*-1 in a sequence of six steps: hydroboration, Swern-type oxidation with pyridine/sulphur trioxide/dimethylsulfoxide,⁷⁶ exhaustive oxidation using silver nitrate under alkaline condition, Raney nickel reduction and finally lactamisation. The reaction types used in the end game of the Sames and Magnus synthesis are very similar. It is therefore all the more surprising that the Magnus group did not need to introduce any protection on the pyrrole ring. The Magnus group could reduce considerably the number of steps. The synthesis proceeds through nine steps in an impressive 7.6% overall yield.

TOTAL SYNTHESIS OF *rac*-RHAZINILAM OF TRAUNER

The Trauner synthesis published in 2005 forms in the last step *rac*-rhazinilam (**1**) using an intramolecular Heck-type reaction⁷⁷ starting from an intermediate **54** (Scheme 6). The difference to the Sames and Magnus synthesis is the presence of the amide bond directly connecting the A and the D rings. Trauner

group starts with 2-carbomethoxy pyrrole (**50**) which is *N*-alkylated with γ -lactone tosylate **18**. The alkylation and the intramolecular Friedel-Crafts cyclisation of **51** are almost identical to the Smith procedure.⁵⁵ At this point the Trauner synthesis diverges from the Smith synthesis. Amide coupling introduces all the atoms of the rhazinilam skeleton. For the Heck type coupling, the amide had to be protected with the methoxymethyl (MOM) protecting group transforming compound **55**, which was exposed to 10 mol % of Buchwald's "DavePhos" ligand **56**⁷⁸ and Pd(OAc)₂ in the presence of potassium carbonate as base to give the strained nine-membered ring **57** in 47% yield. Removing first the MOM protecting group^{55,70,71} followed by saponification and acid-catalysed decarboxylation produced *rac*-**1**. Only seven steps are needed starting from commercially available pyrrole **50** and an impressive 7.9% overall yield could be obtained. Starting from the commercially available diester **15**, *rac*-rhazinilam (**1**) can be obtained in thirteen steps and in 1.7% overall yield.



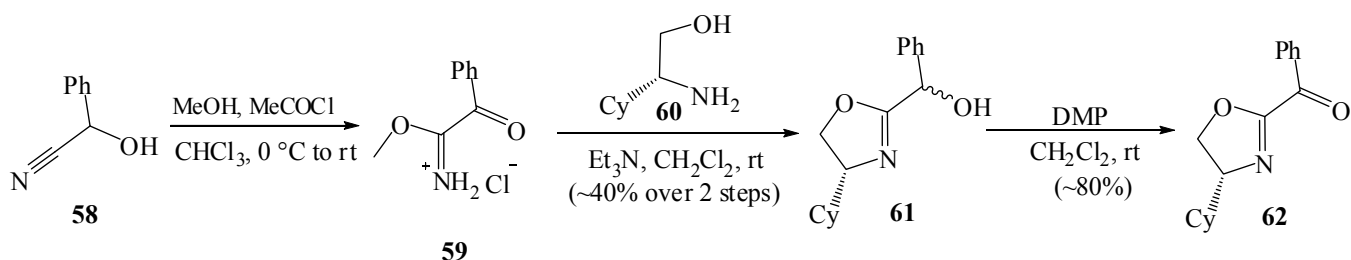
Scheme 6. Trauner's total synthesis of *rac*-rhazinilam (**1**)

TOTAL SYNTHESSES OF *R*-(-)-RHAZINILAM

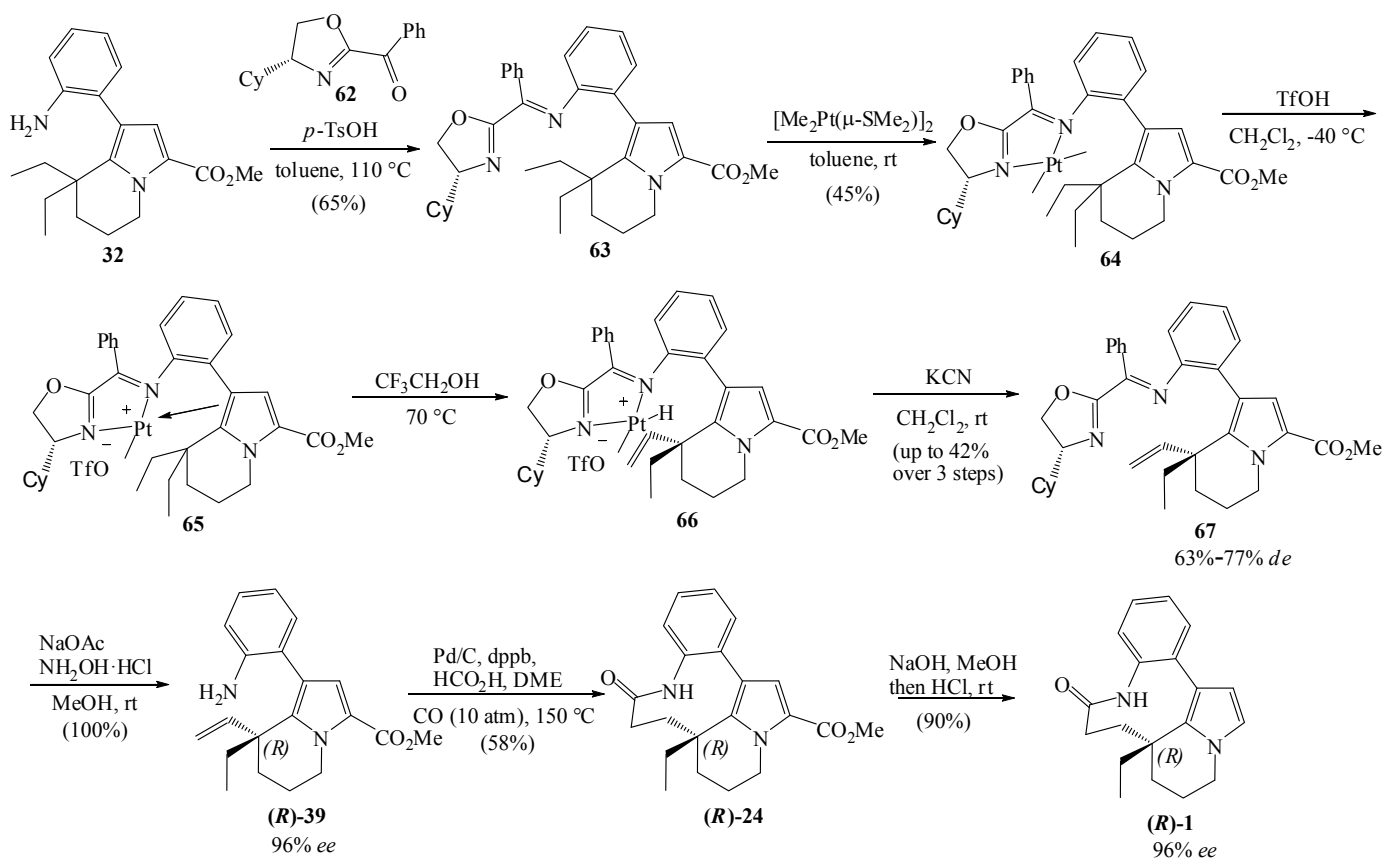
Besides the four syntheses of racemic rhazinilam three of (-)-enantiomer have been reported. The chirality of the A-C biaryl axis is determined by the absolute configuration of the quaternary-carbon at C20. The challenge is therefore to obtain this quaternary center in enantiomerically pure form.

SAMES' SECOND ENANTIOSELECTIVE TOTAL SYNTHESIS OF (*R*)-(-)-RHAZINILAM

The Sames group adapted their synthesis of *rac*-rhazinilam so that they could obtain the (*R*)-(-)-rhazinilam⁷¹. Sames chose to introduce a chiral auxiliary **62**, so as to functionalize diastereoselectively the intermediate **63** to the product **67** (see Scheme 8). The chiral auxiliary phenyl-(5*R*)-cyclohexyl-2-oxazolinone **62** was prepared in three steps from commercially available mandelonitrile **58** in 32 % overall yield (Scheme 7).



Scheme 7. Synthesis of chiral oxazolyl ligand **62**

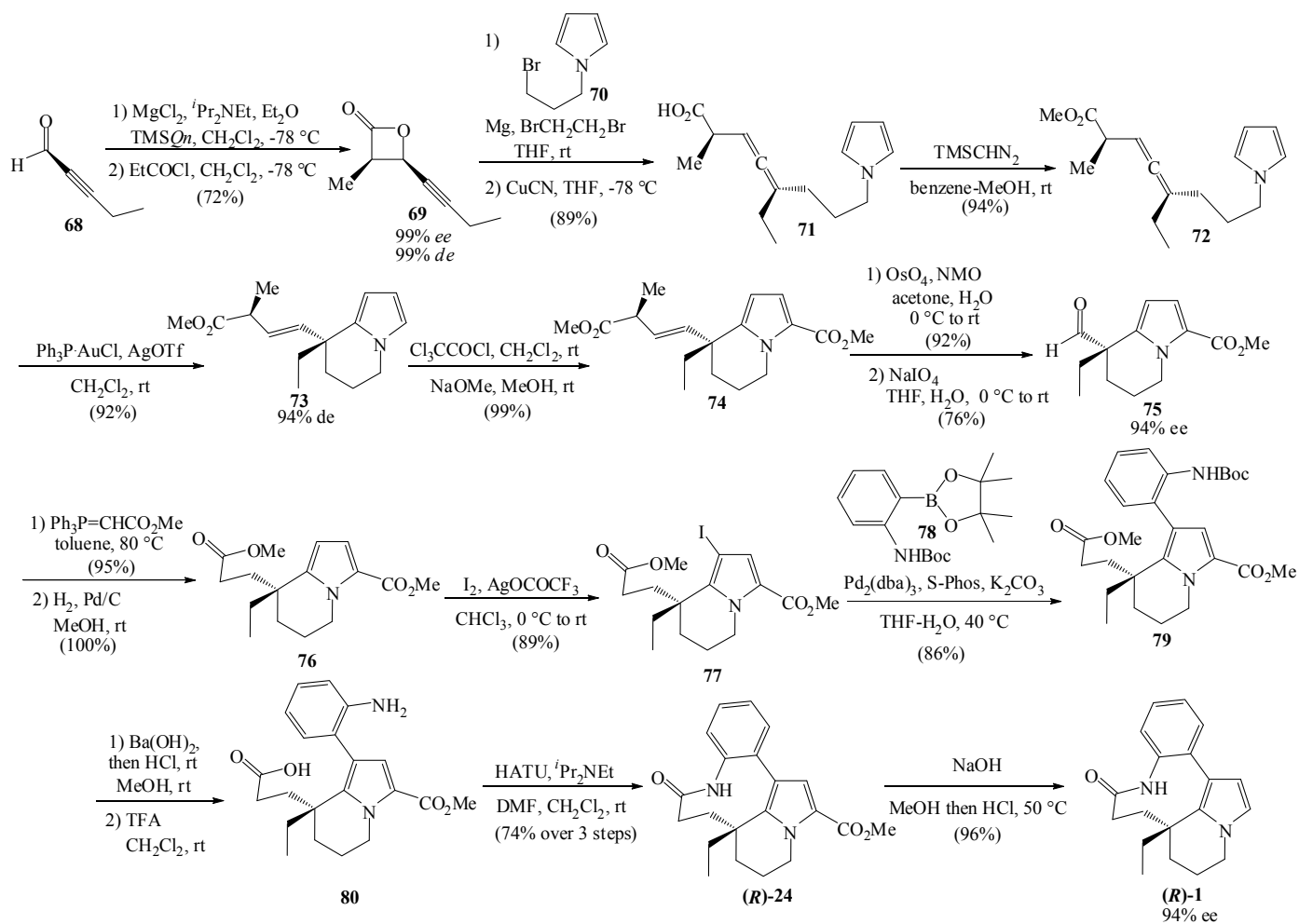


Scheme 8. Sames' total synthesis of (*R*)-(-)-rhazinilam using the chiral auxiliary **62** and separating the diastereoisomers by HPLC

The desymmetrisation of the two enantiotopic ethyl groups in compound **32** was achieved by metal-induced C(*sp*³)-H activation *via* the six steps sequence leading to the alkene **39** (96% *ee*) (Scheme 8). After decomplexation of the platinum with potassium cyanide a mixture of the diastereomers of **67** were obtained with a *de* of 63-77%. In this sequence the diastereomers were separated by preparative HPLC to give after removal of the ligand the alkene (**R**)-**39**. The palladium-catalysed carbonylation of the alkene (**R**)-**39** gave directly in 58% yield the required nine-membered lactam (**R**)-**24** which had been reported^{55,70} previously in its racemic form. This metal catalysed transformation replaced favourably the five step sequence used in the synthesis of the racemate. The enantiomerically pure (*R*)-(-)-rhazinilam (**1**) was finally obtained in 90% yield and 96% *ee* following the procedure described by Smith.⁵⁵ The synthesis proceeds through fifteen steps starting from nitrile aldehyde **25** in 1.6% overall yield.

TOTAL SYNTHESIS OF (*R*)-(-)-RHAZINILAM BY NELSON

In 2006 Nelson and co-workers reported an elegant, enantioselective total synthesis of (*R*)-(-)-rhazinilam (**1**) (Scheme 9).⁷⁹ The enantioselective synthesis of the almost enantiopure β -lactone **69** via a cyclocondensation⁸⁰⁻⁸² using a quinine derived asymmetric catalyst installed the two chiral centers⁸³ with high selectivity. From the β -lactone **69** the enantioenriched allene **72** was obtained by ring opening using the Grignard reagent of **70** *via* an S_N2'-type reaction followed by a methylation with trimethylsilyldiazomethane. The intramolecular asymmetric Au(I)-catalyzed pyrrole addition to the allene installed the quaternary carbon stereocenter with good control and formed **73** including the ring D of rhazinilam. To make the pyrrole ring C resistant to the following reaction steps a methyl ester group was introduced first giving **74**. In a four step sequence **74** the functionalized side chain was first degraded and then reconstructed to obtain **76**. Electrophilic iodination⁸⁴ followed by Suzuki-Miyaura cross-coupling⁸⁵ of compound **77** with the commercially available 2-(*N*-Boc-amino)phenylboronic acid pinacol ester **78** using Buchwald's S-Phos ligand⁸⁶ afforded the 3-aryl pyrrole **79** containing rings A, C and D of rhazinilam. Chemoselective ester saponification and TFA-mediated aniline *N*-deprotection resulted in the formation of the amino acid **80**, the precursor for the formation of the B ring. Lactamisation of this compound was carried out with the HATU coupling reagent to produce the previously described^{55,70,71,77} ester (**R**)-**24** in 74% yield. Removal of the methyl ester group in pyrrole (**R**)-**24**, as previously reported by Smith,⁵⁵ furnished (*R*)-(-)-rhazinilam (**1**) in 96% yield and 94% *ee*. Thus, the synthesis proceeds through fifteen steps starting from commercially available acyl aldehyde **68** in an impressive 19.8% overall yield.

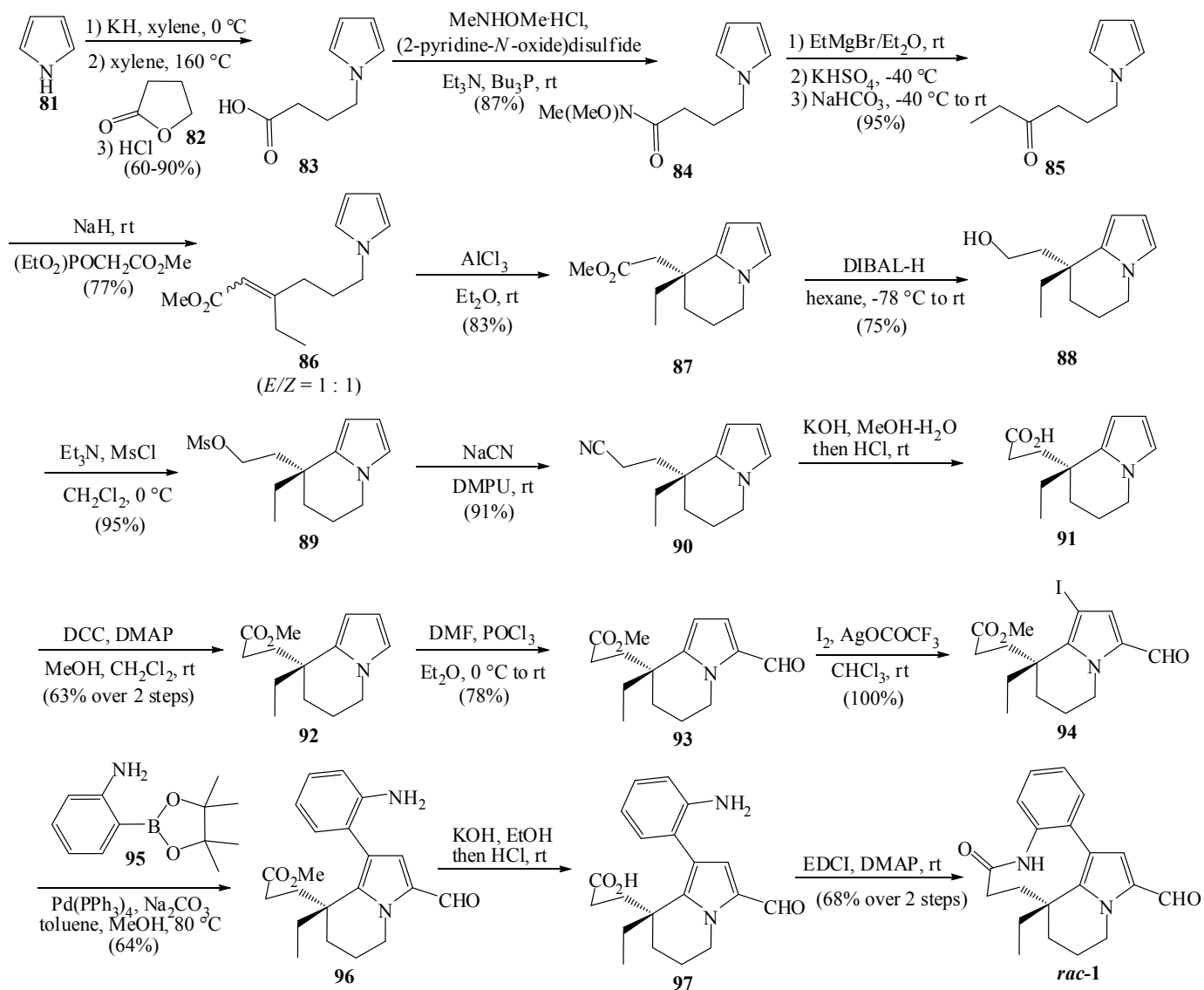


Scheme 9. Nelson's total synthesis of (*R*)-(-)-rhazinilam (**1**)

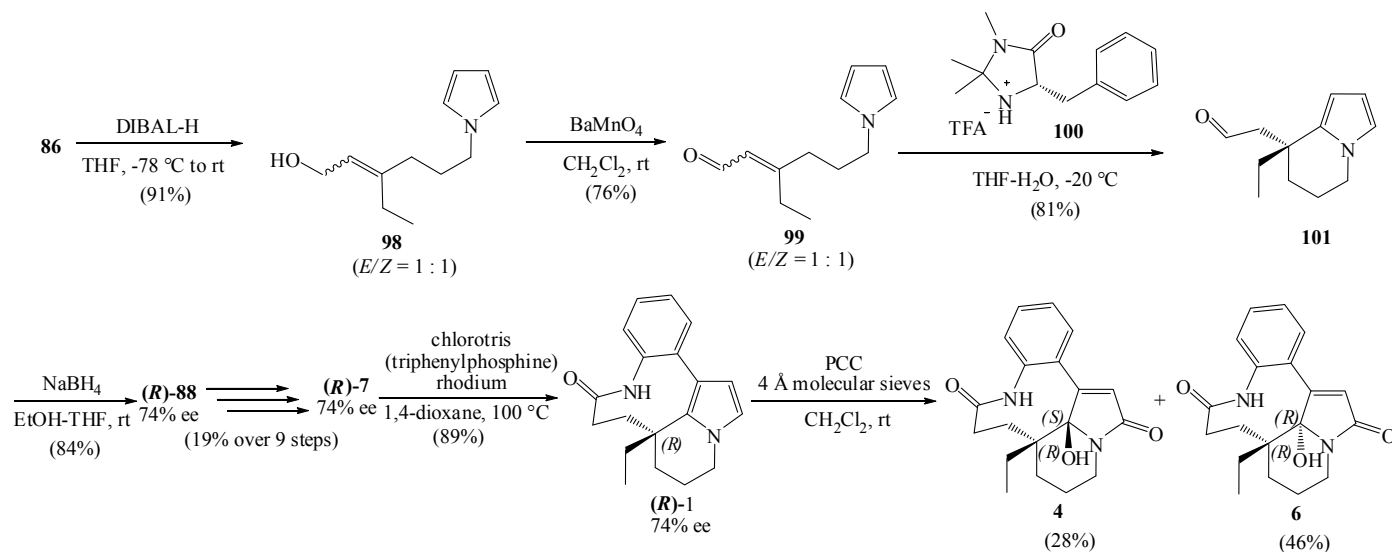
TOTAL SYNTHESIS OF (*R*)-(-)-RHAZINILAM BY BANWELL

Banwell and co-workers reported a synthesis of *rac*-rhazinal (**7**)⁸⁴ (Scheme 10) and based on this chemistry an enantioselective total synthesis of (*R*)-(-)-rhazinilam ((*R*)-**1**)⁸⁷ (Scheme 11). The key step of the enantioselective synthesis is a MacMillan's chiral organocatalyst⁸⁸ promoted intramolecular Michael addition reaction closing the D ring and the quaternary center in 74% enantiomeric excess. The synthetic route to the pivotal intermediate **99** started with the *N*-alkylation of pyrrole with γ -butyrolactone **82** under conditions defined by Li and Snyder.⁸⁹ Conversion into the corresponding Weinreb amide **84** using modified Mukaiyama conditions⁹⁰ and subsequent treatment with ethyl magnesium bromide furnished the ketone **85**. Wadsworth-Horner-Emmons olefination provided the β,β -disubstituted methyl acrylate **86** followed by reduction with excess DIBAL-H to give the corresponding alcohol **98**. The

alcohol **98** was oxidized with barium manganate⁹¹ to the aldehyde **99** obtained in 76% as a roughly 1:1 mixture of *E*- and *Z*- isomers.



Scheme 10. Banwell's total synthesis of (*rac*)-rhazinal



Scheme 11. Banwell's total synthesis of (*R*)-rhazinal, (*R*)-rhazinilam, (*R,S*) (-)-leuconolam and (*R,R*) (+)-*epi*-leuconolam

The pivotal intramolecular Michael addition reaction involved exposure of this mixture of aldehydes to (*5S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate **100** (MacMillan's first generation organocatalyst) resulting in formation of the unstable indolizine aldehyde **101** in 81% yield. Subsequent reduction of compound **101** using sodium borohydride afforded the stable alcohol **88** in 84% yield in 74% *ee*. The completion of the synthesis of (*R*)-(-)-rhazinilam (**1**) involved the one-carbon homologation via S_N2 reaction using nitrile as one carbon nucleophile and the installation of the aniline moiety via by Suzuki-Miyaura cross-coupling.⁸⁵ During this sequence a Vilsmeier-Haack formylation had to be inserted. The aldehyde is at the same time a protecting group for the sensitive pyrrole ring and it dictates the regioselectivity of the following electrophilic iodination to give the iodo-pyrrole **94** in quantitative yield. The final steps were the saponification of the ester followed by lactamisation delivering synthetic (*R*)-(-)-rhazinal (**7**). Conversion of (*R*)-**7** into (*R*)-(-)-rhazinilam (**1**) was achieved by heating of ((*R*)-**7**) with stoichiometric quantities of Wilkinsons "catalyst" in refluxing 1,4-dioxane. The synthesis proceeds through eighteen steps starting from pyrrole **81** and in 4.4% overall yield. Treatment of (*R*)-(-)-rhazinilam (**1**) with an excess of pyridinium chlorochromate (PCC) resulted in the conversion of this substrate into a chromatographically separable mixture of (-)-leuconolam (**4**) (28%) and (+)-*epi*-leuconolam (**6**) (46%).

TOTAL SYNTHESSES OF ANALOGUES OF RHAZINILAM

Several publications describe efforts dedicated to the total syntheses of analogues of rhazinilam. Some publications report the total syntheses of analogues obtained as “side products” of the efforts dedicated to the total synthesis of rhazinilam. Four different analogues isolated from nature have been synthesized so far: rhazinal in its racemic (two synthesis) and in its enantio-enriched form (one synthesis, see Scheme 11), rhazinicine as racemate (one synthesis) and finally leuconolam and *epi*-leuconolam in enantioenriched form (one synthesis leading to the mixture of the two natural products, see Scheme 11).

TOTAL SYNTHESSES OF RHAZINAL

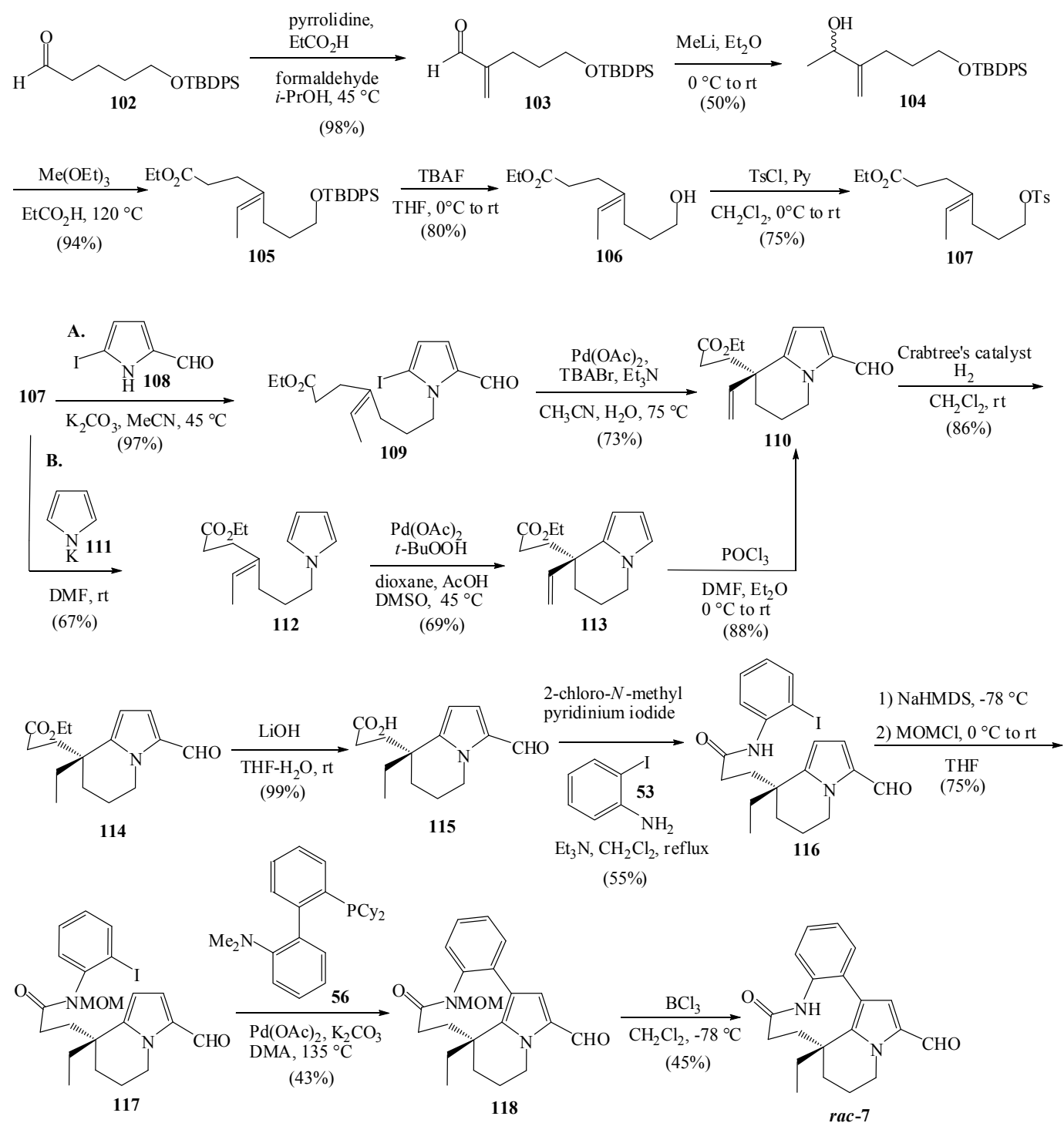
Total Synthesis of *rac*-Rhazinal and of (*R*)-(-)-Rhazinal by Banwell

Both syntheses use an intramolecular Michael addition as key step to form the C-D ring unit (Scheme 10 and 11). In 2003 Banwell and co-workers reported the first total synthesis of racemic *rac*-rhazinal (*rac*-**7**)⁸⁴ achieved in fifteen steps with 6.6% overall yield. In 2006 the Banwell group achieved the synthesis of the natural (*R*)-(-)-rhazinal ((*R*)-**7**)⁸⁷ in seventeen steps with 5.0% overall yield.

Total Synthesis of *rac*-Rhazinal by Trauner

Trauner and co-workers reported⁹² a concise synthesis of *rac*-rhazinal (**7**) using Pd-catalyzed coupling reactions to form the ring D (cyclisation of **112** or alternatively of **109**) and the ring B (cyclisation of **117**) (Scheme 12). The synthesis of the aliphatic part proceeded through the *E*-trisubstituted ester **107** which was constructed from the known aldehyde **102**.⁹³ The α -methylation followed by treatment with methyllithium afforded the allylic alcohol **104**. The Claisen rearrangement of the allylic alcohol produced the ester **105** in 94% yield. Deprotection of silyl ether with tetra-*n*-butylammonium fluoride and subsequent tosylation of **106** afforded the desired intermediate **107**. Reaction of **107** with the potassium salt of pyrrole **111** gave the *N*-alkylated pyrrole **112** in 67% yield.

The oxidative cyclisation of compound **112** using Pd(OAc)₂ in the presence of *t*-BuOOH resulted in the formation of tetrahydroindolizine **113** in 69% yield. The C-D precursor was then protected as aldehyde **110** by subsequent Vilsmeier-Haack formylation (41% over three steps from compound **107**). The intermediate **110** was prepared in parallel by a very similar sequence, where the formyl group was introduced on the pyrrole ring at the desired position from the beginning and where a direct Heck coupling involving the iodopyrrole **108** formed the D-ring.



Scheme 12. Trauner's total synthesis of *rac*-rhazinal

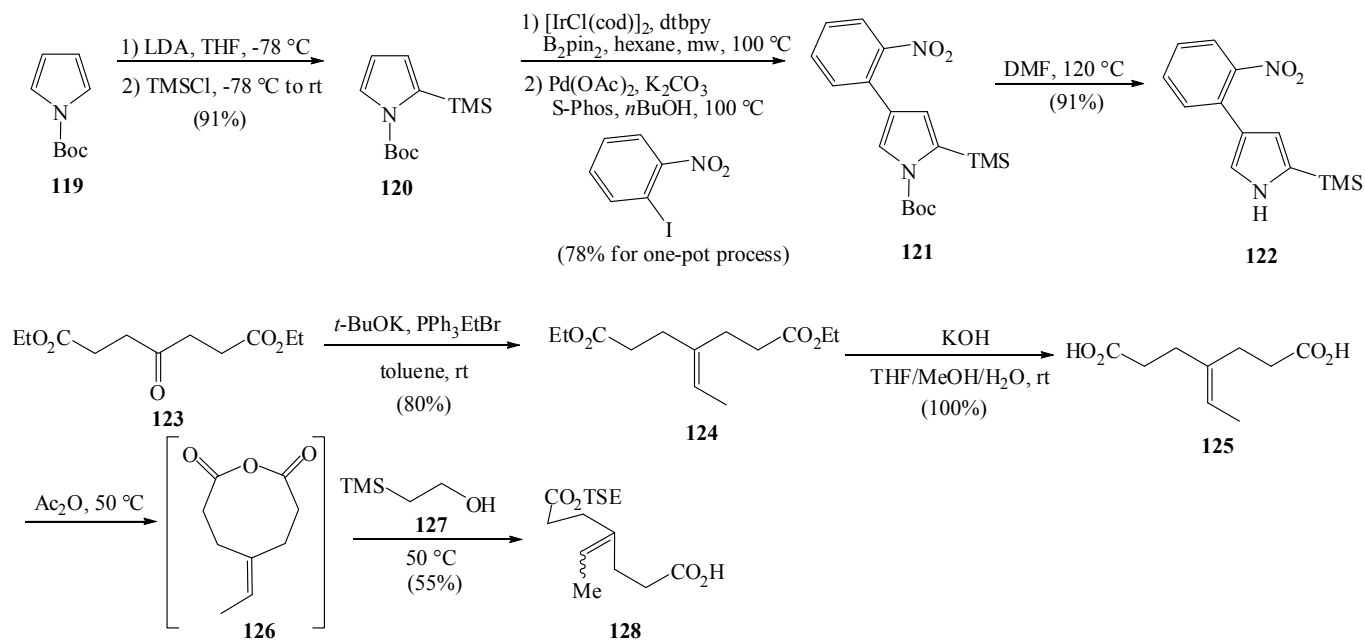
The chemoselective reduction of the double bond using Crabtree's catalyst followed by hydrolysis of the ester yielded the corresponding acid **115** in excellent yield. Coupling of the acid **115** with 2-iodoaniline **53** under Mukaiyama's conditions provided the amide **116**,⁷⁷ which was protected as the methoxymethyl

(MOM) key intermediate **117** in 75% yield. The B-ring was formed using 10 mol % of Buchwald's "DavePhos" ligand **56**⁷⁸ and Pd(OAc)₂ in the presence of potassium carbonate to produce the *N*-MOM rhazinal **118** in 43% yield. After removal of the MOM protecting group with a large excess of boron trichloride racemic *rac*-(±)-rhazinal (**7**) was obtained in 45% yield. The synthesis proceeds through thirteen steps in 1.3% overall yield (Method A) or through fourteen steps in 0.8% overall yield (Method B). We have calculated the yield starting from aldehyde **102** which is not commercial. The method used for the preparation of this aldehyde is not indicated.

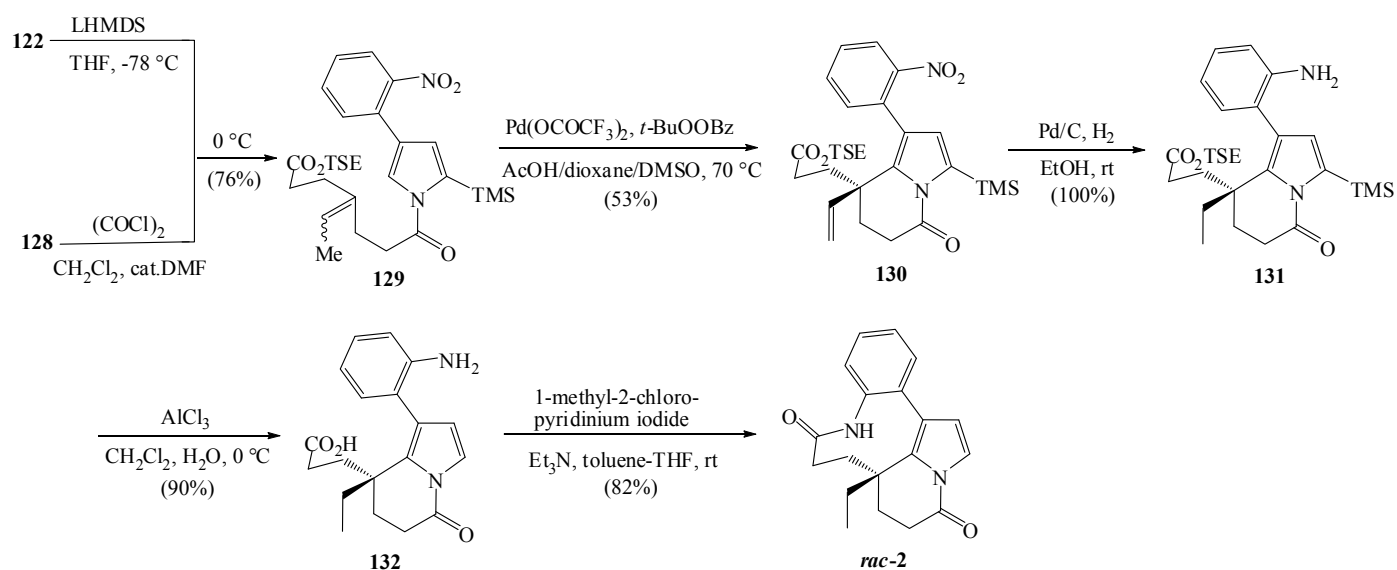
TOTAL SYNTHESIS OF *rac*-RHAZINICINE BY GAUNT

The first total synthesis of the *rac*-rhazinicine (**2**) was reported by Gaunt and co-workers in 2008.⁹⁴ The key steps of this convergent synthesis use modern organometallic reactions to connect the rings A and C first and then to form the D-ring. The B-ring is formed via a lactamization. The connection between the phenyl ring and the pyrrole is achieved by the one-pot Ir^I-catalyzed C-H bond borylation^{95,96} directly followed by subsequent Suzuki coupling reaction.⁹⁷ The oxidative Pd^{II}-catalyzed pyrrole C-H bond cyclisation leads to the formation of the D-ring. The synthesis started with the preparation of the two intermediates **122** and **128** (Scheme 13). For the synthesis of the biaryl intermediate **122** containing the A-C rings Boc and TMS protecting groups had to be introduced to obtain the doubly protected precursor **120**. The one-pot Ir^I-catalyzed borylation/Suzuki coupling formed the 3-arylated pyrrole **121** in 78% yield. Removal of Boc-protecting group under heating afforded the pyrrole **122** containing the A-C rings of rhazinicine.

The alkene monoester intermediate **128** was prepared from the commercially available diethyl-4-oxo-pimelate **123** via Wittig ethenylation followed by functional group manipulation to obtain the intermediate **128** containing all the carbons for the rings B and D. Reacting the lithium anion of **122** with acid chloride of **128** the *N*-acylated pyrrole **129** was obtained in 76% yield (Scheme 14). The intermediate **129** contains all the carbons present in the target molecule. Treating **129** with Pd(TFA)₂ catalyst and *t*-butylperoxybenzoate resulted in cyclisation producing the pivotal tetrahydroindolizine **130** in 53% yield. Simultaneous reduction of the nitro and alkene group of compound **130** followed by AlCl₃-mediated removal of the 2-trimethylsilylethyl and trimethylsilyl protecting groups gave the carboxylic acid **132**. Lactamisation of this compound under Mukaiyama conditions produced the *rac*-rhazinicine (**2**) in 82% yield. The synthesis proceeds through eight steps starting from pyrrole **119** in 1.9% overall yield (through nine steps starting from diester **123** in 1.3% overall yield).



Scheme 13. Synthesis of intermediates **122** and **128** for the total synthesis of the *rac*-rhazinicine by Gaunt



Scheme 14. Total synthesis of *rac*-rhazinicine by Gaunt

TOTAL SYNTEHSIS OF LEUCONOLAM AND *Epi*-LEUCONOLAM BY BANWELL

Banwell and co-workers reported the first total syntheses of (-)-leuconolam (**4**) achieved in nineteen steps with 1.2% overall yield, and (+)-*epi*-leuconolam (**6**)⁸⁷ achieved in nineteen steps with 2.0% overall yield.

Both syntheses involved as a key step an intramolecular Michael addition reaction. They were described in Scheme 11.

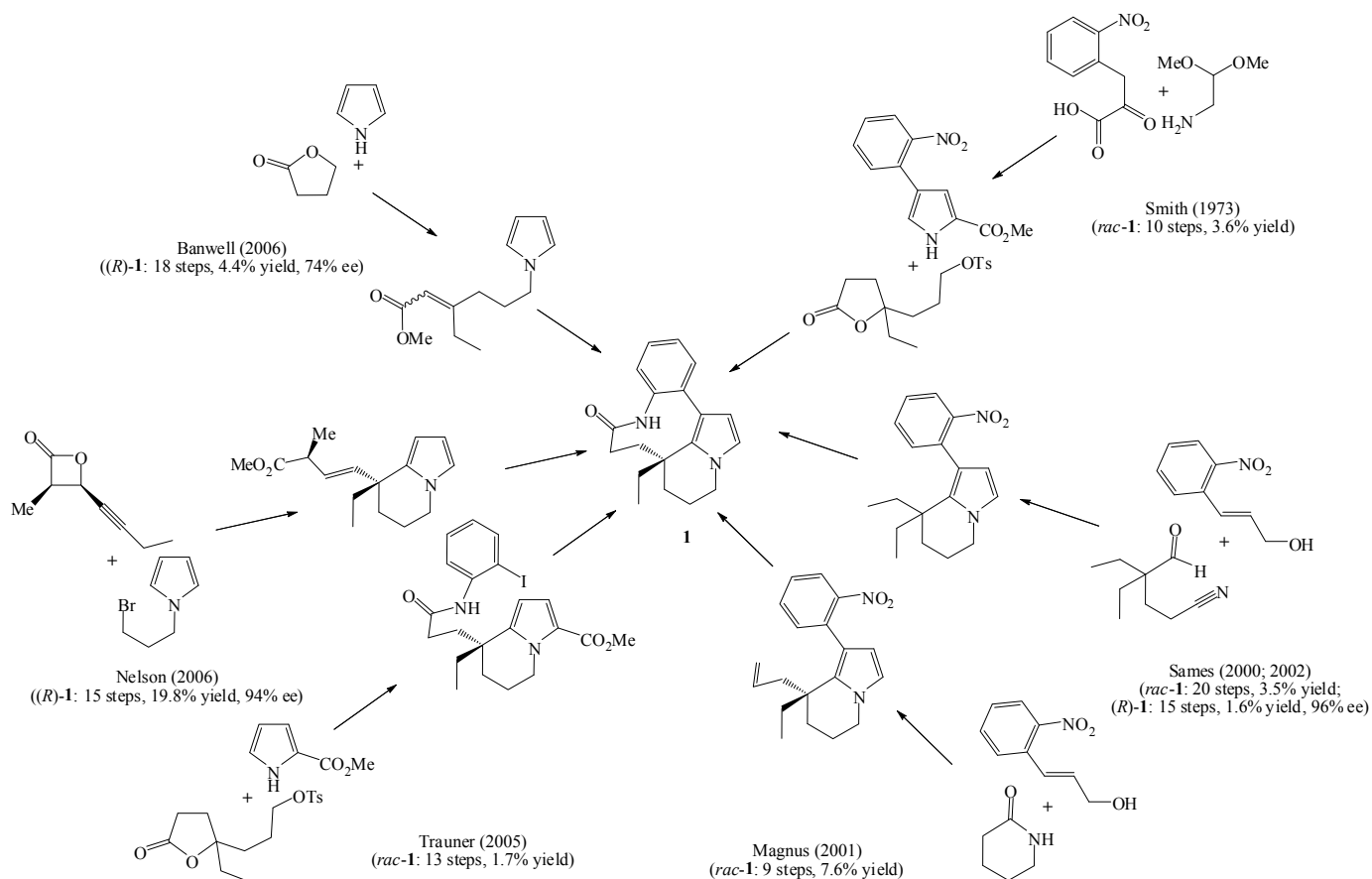
COMPARISON OF THE PUBLISHED RHAZINILAM SYNTHESSES

GENERAL REMARKS

The synthesis of rhazinilam has been studied for now almost 40 years. Seven different syntheses have been reported so far: four of *rac*-rhazinilam and three of (*R*)-rhazinilam. Four analogues of rhazinilam have been synthesized by three different groups using three different approaches: *rac*-rhazinal, (*R*)-rhazinal, *rac*-rhazinicine, (*R*)-leuconolam and (*R*)-*epi*-leuconolam. The methods to construct the rhazinilam skeleton have changed over the years, however the retrosynthetic disconnections for all these syntheses have stayed rather similar. The major difference between the different syntheses is the sequence of the synthetic steps forming the tetracyclic structure and the methods used to create the different rings of rhazinilam. Most of the recent studies reported the synthesis of the enantiomerically enriched natural product (*ee* between 74% and 96%). The research leading to the very first synthesis had clearly been started before the structure of (*R*)-rhazinilam had been ascertained by the structure determination of the crystal by X-ray diffraction. This initial synthesis project follows therefore the logic of structure determination by total synthesis. For almost 30 years no new academic synthesis was reported. The recent syntheses reported since 2000 have been designed around one or several key steps. The goal of these syntheses is to showcase the efficiency of these key steps applying them to a “real” synthetic goal. The use of transition metals for the forming of C-C bonds is illustrated in several of the recent total syntheses. Another important feature illustrating the latest development in organic synthesis is the application of organocatalysis for the asymmetric synthesis of a key intermediate.

COMPARISON OF THE NUMBER OF SYNTHETIC STEPS AND THE OVERALL YIELD

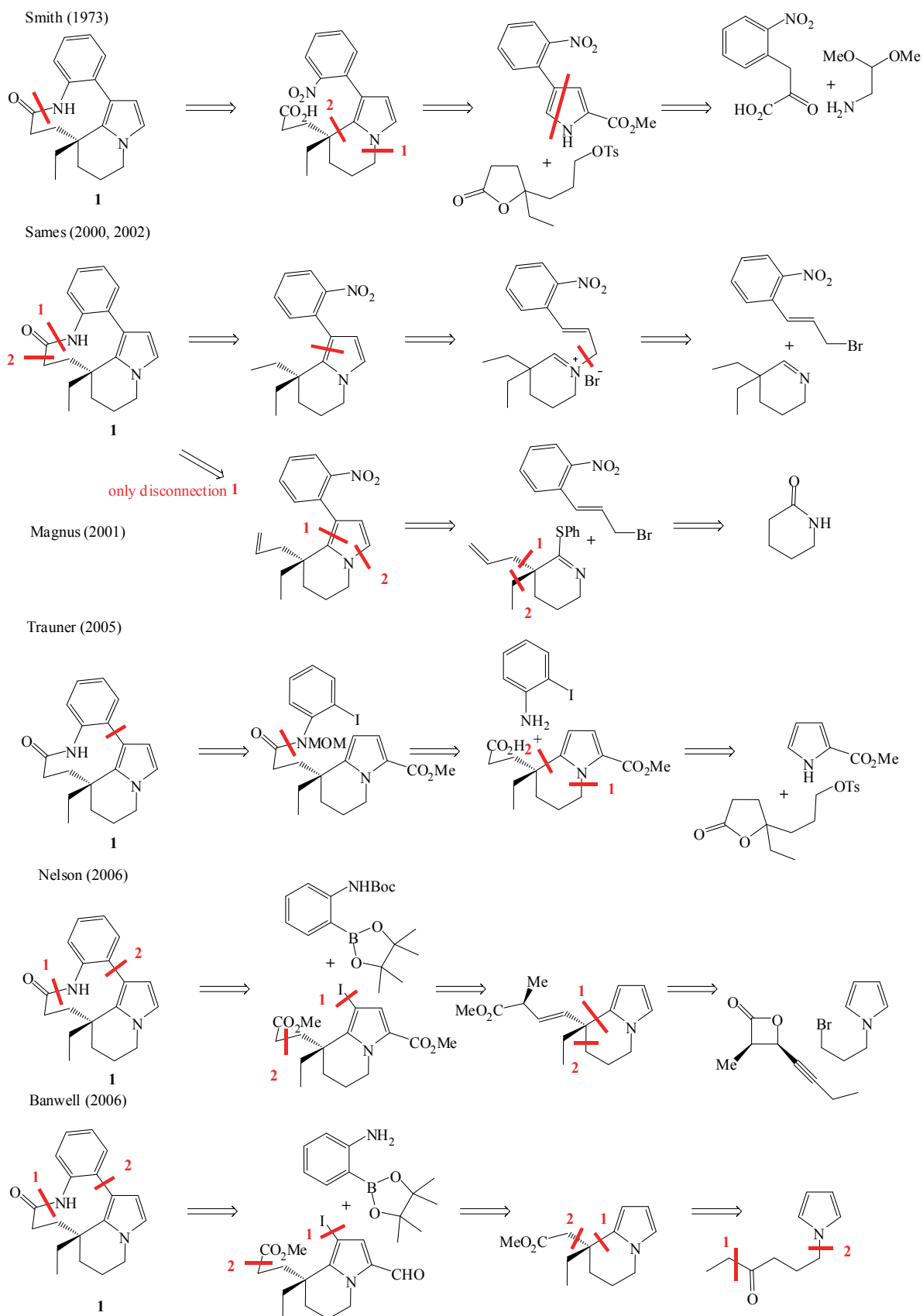
The development of synthetic methodologies since 1973 has been spectacular and it seems almost unfair to compare the first synthesis published in 1973 with the most recent synthesis published in 2006. If one wants to compare the overall yields and the number of synthetic steps from commercially available starting material for all seven syntheses we had in some cases to go back to the literature reports cited by the authors to identify the commercial starting materials. In these cases we assumed that the authors have used the reported procedure and that the authors had obtained the yields of the cited procedures.



Scheme 15. Comparison of the seven total syntheses of rhazinilam reported during the last 37 years. Four syntheses yielded *rac*-rhazinilam and three syntheses gave (*R*)-(-)-rhazinilam

The number of steps from commercial starting material varies from 9 to 20 steps (Scheme 15). The lowest overall yield is 1.6% and the best 19.8%. The average yield per step is more than 70% for all the synthesis reported. The highest yielding synthesis reports an impressive average yield of 90% over 15 steps. The short syntheses tend to be more efficient, but it is interesting to emphasize that five of the seven syntheses have an overall yield between 1.6 and 4.4%, despite the fact that the shortest of these syntheses needs only 10 steps whereas the longest needs 20 steps, twice as many compared with the shortest synthesis. Looking at these syntheses from the standpoint of overall yield the first synthesis is surprisingly efficient. In comparing the four syntheses of *rac*-rhazinilam the shortest synthesis with only 9 steps has been reported by Magnus. In the Magnus synthesis no protecting group on the pyrrole ring was introduced, which shortens the synthetic pathway by at least two steps. The three enantioselective syntheses are all considerably longer, 15 to 18 steps. In one case a chiral auxiliary had to be introduced and to be cleaved. In the enantioselective synthesis by Nelson and by Banwell an enantioselective catalytic process is applied. The overall lengths of these two syntheses are 15 and 18 steps, respectively. Based on the overall yield the synthesis reported by the Nelson group stands out with an overall yield, which is three times higher than the Magnus synthesis and at least a factor of five better than most of the other synthesis.

COMPARISON OF THE RETROSYNTHETIC ANALYSIS USED



Scheme 16. Summary of the retrosynthetic analysis of the seven total syntheses of rhasznilam reported during the last 37 years

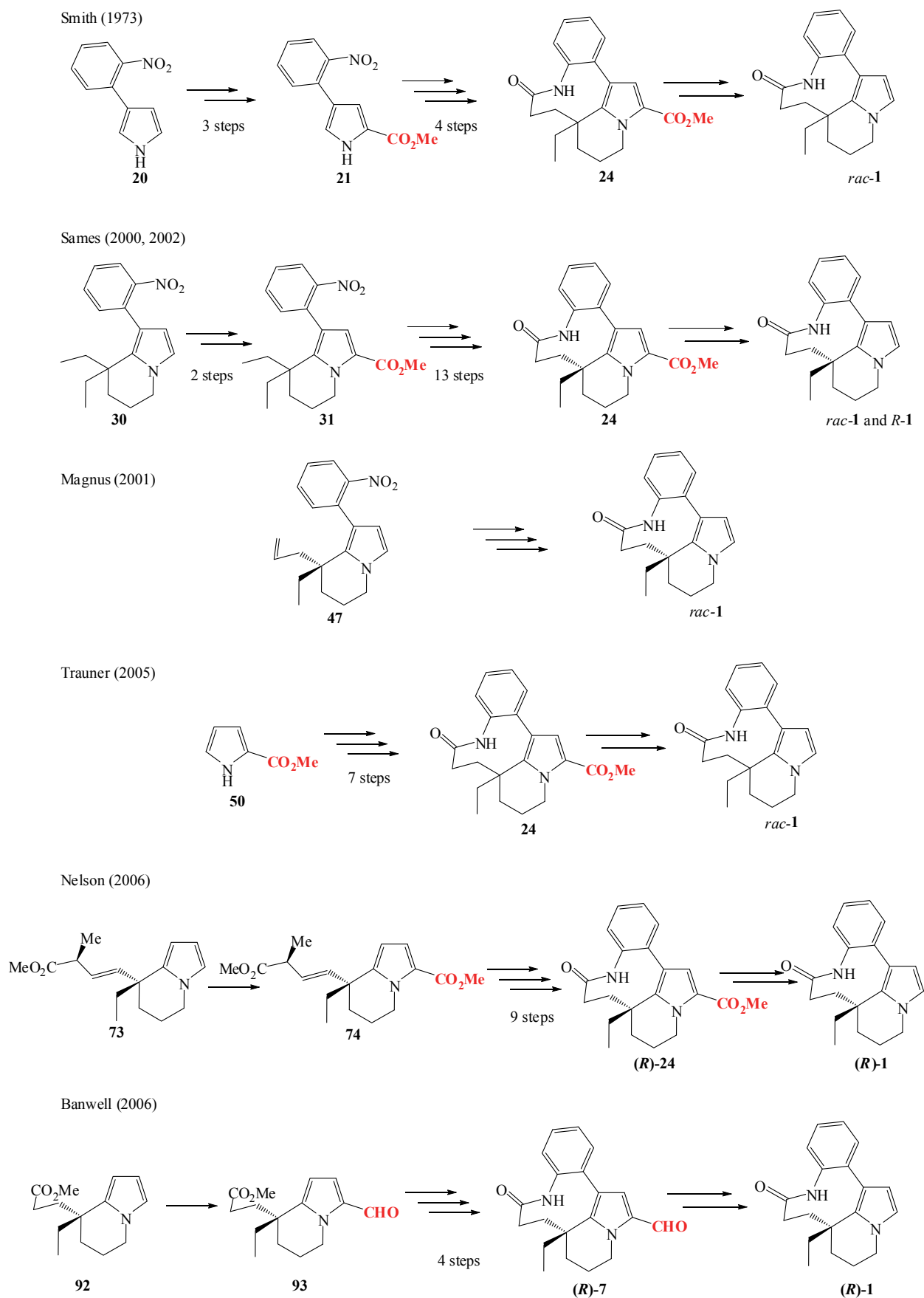
The summary of the retrosynthetic analysis used in the different total syntheses leads to some interesting conclusions (Scheme 16). In all the syntheses the B-ring is formed last. Due to this common retrosynthetic analysis the end game of all syntheses is quite similar. In six of the seven syntheses the lactam formation is the last step finishing the construction of the skeleton of rhazinilam. Only in the Trauner synthesis the B-ring is closed via a Heck type C-C coupling. One has however to mention that the Trauner synthesis is an inversion of the sequence used by Nelson and Banwell. In Trauner's synthesis the amide bond of the B-ring is formed first and the ring closure is achieved via the Heck type coupling second. In the syntheses of Nelson and Banwell the sequence is inverted. The Suzuki coupling is used for the creation of the biaryl unity.

The D-ring is formed in four syntheses just before closing the lactam ring (ring B). In the recent syntheses the aromatic A ring is introduced at the later stage of the synthesis by a coupling reaction (Banwell, Nelson, Trauner syntheses). In the two syntheses by Sames and the synthesis reported by Magnus the D-ring is part of the starting material and stays intact during the whole synthetic sequence.

Three of the seven syntheses use a commercial precursor containing the intact pyrrole ring (Banwell, Nelson, Trauner syntheses). The groups of Smith, Sames and of Magnus have applied synthetic schemes, where the pyrrole ring is constructed during the preparation of rhazinilam. Smith uses a variant of a Knorr-type pyrrole synthesis whereas Sames and Magnus use a Grigg-type 1,5-electrocyclization.

Another observation concerns the use of "protecting" or stabilizing on the pyrrole ring. With one exception, all syntheses have to introduce or to carry on a electron attracting substituent on the pyrrole ring. Most syntheses use an ester group in the α -position (Scheme 17). The Banwell synthesis uses an aldehyde function as protection group of the pyrrole. Very often two steps are needed to introduce the protecting group and one to two steps are again needed for the deprotection. The protecting group is in most of the syntheses carried along a good part of the synthetic sequence. In the Sames synthesis the ester protecting group is present during 14 steps. These substituents have to be removed towards the end of the synthesis. Even if it is not formally stated in most of the publications, their function is clearly to make the intermediates stable enough, that they can be manipulated. The exception is the Magnus synthesis. Despite the fact that the Magnus' group uses an intermediate, which is identical with the one reported in the first synthesis of Sames, the Magnus group was able to avoid the use of electron attracting group on the pyrrole ring.

In summary the synthesis of rhazinilam is still a challenging synthetic problem. The syntheses reported are attractive and incorporate different interesting key steps. Despite the spectacular developments of organic synthesis even the very first reported synthesis is still a valid approach to this fascinating natural product.



Scheme 17. Protecting the α -position of the pyrrole C-ring introducing an electron attracting protecting group during the syntheses of rhazinilam

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Inga Kholod was born in Krasnodar, Russia where she studied medicine at the Kuban State University of Medicine. She received the Master's degree in chemistry from the University of Neuchâtel (Switzerland) in 2007. As an undergraduate she was a trainee at the department "Global Discovery Chemistry" of Novartis Pharma AG. Ms. Kholod is currently completing her PhD research on the total synthesis of rhazinilam and its analogues at the University of Neuchâtel.



Olivier Vallat was born in Fribourg (Canton of Fribourg, Switzerland). He studied chemistry at Federal Technical University Lausanne (EPFL) and at the University of Neuchâtel. He received his diploma degree in chemistry in 2000 from the University of Neuchâtel (Switzerland) working with Professor Helen Stoeckli-Evans. He completed in 2004 his PhD research working on the development of novel methods suitable for the total synthesis of Rhazinilam and its analogues in the group of Professor Reinhard Neier at the University of Neuchâtel. He did his postdoc in 2005-2006 in the group of Professor Viresh Rawal at the University of Chicago working on asymmetric total synthesis of natural product. He is now working as head of Research and Development and quality control laboratory of Febex SA in the Canton of Vaud, Switzerland.



Ana-Maria Buciumas was born in Bogdana (Vaslui), Romania. She studied Chemistry at University "Al. I. Cuza", Iasi, Romania, where she received her Diploma in 2001. After Master Degree in 2003 at the same university, she started her Ph. D. in the group of Professor Reinhard Neier at University of Neuchâtel, Switzerland. After completing her Ph. D. in 2008 in Organic Chemistry, she has joined for two years the group of Professor Alan R. Katritzky, University of Florida, USA, where she studied the Heterocyclic Chemistry as a postdoctoral associate. Her research interests are in the development of biologically important organic compounds.



Reinhard Neier is Professor of organic chemistry and Director of the Chemical Department at the University of Neuchâtel, Switzerland. He was born in Basel where he studied Chemistry. He received his Ph. D. in 1978 at the ETH Zürich working for Professor Albert Eschenmoser on the photochemical seco-corrin to corrin cycloisomerisation. He joined the group of Professor Alan R. Battersby in Cambridge as a postdoctoral fellow to work on the biosynthesis of vitamin B₁₂. He researched and taught at the Universities of Geneva and Fribourg before moving to his present post at the University of Neuchâtel. His research interests encompass application of synthetic methods to mimic biosynthesis, studies of tandem reaction, synthesis of novel ligands and the use of heterocycles as building blocks for liquid crystals. Details on his current and past activities may be found on his home page: <http://www2.unine.ch/cho>