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4-Hydroxy-2-Pyridone Alkaloids: Structures and Synthetic Approaches

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4-Hydroxy-2-pyridone alkaloids exert diverse biological effects, ranging from antifungal, antibacterial, insecticidal and cytotoxic activity to the induction of neurite outgrowth in different cell assays. For this reason, this class of compounds has attracted much attention in the scientific community, resulting in the elucidation of the biosynthesis of some members which are formed by fungal polyketide synthases via tetramic acids by fungal polyketide synthases as well as different total synthesis approaches. This article will give a summary of the so far known structures, overview the different activities of the compounds and disclose the synthetic attempts since 1982.

1 Introduction

4-Hydroxy-2-pyridone alkaloids constitute a family of natural products that are extremely rich in diversity and biological activity. In the last decades, new compounds with intriguing architectures have been unveiled and different synthetic approaches towards these compounds have been developed. Despite the increasing knowledge of the 2-pyridone alkaloid family, many unanswered questions remain concerning their biosynthesis, unknown congeners, biological targets and absolute configuration.

The history of the pyridone alkaloids dates back to the 19th century, when Tuson isolated from castor beans a poisonous crystalline substance which he called ricinine (1).¹ The structural elucidation was accomplished in 1904 by Maquenne and Philippe,² who proposed the 2-pyridone core structure. Many decades later, after the first preliminary data³ of two yellow pigments isolated from the insect pathogenic fungi *Beauveria bassiana* and *Beauveria tenella* in 1968 had been published, the structural features of the two fungal biochromes tenellin (6) and bassianin (7) were unraveled in 1974 by McInnes et al.⁴ In the meantime, more pyridone alkaloids were isolated, e.g. flavipucine⁵ (29) (1968), funiculosin⁶ (26) (1969), ilicicolin H⁷ (14) (1971) and the antibiotic kirromycin (45) as a representative of the elfamycins.⁸ These findings enriched the chapter of pyridone alkaloids in natural product chemistry that was opened in 1864 and continues until today, as still novel fascinating structures are being discovered. In this review, we will summarize the wealth of information about the different structures, biological effects, biosynthesis and synthetic approaches. This review will focus on 2-pyridones bearing an oxygen atom in the 4-position, while quinoline based structures will not fall within the scope of this article. The elfamycins will only be taken into consideration for the sake of completeness and not in full detail. General approaches to substituted 2-pyridones have been reviewed.⁹ In this article we will focus on the approaches that have been

applied in the total synthesis of natural products.

2 Structures, natural sources and known bioactivities

Due to the diversity of the pyridone natural products, they will be discussed with respect to the linkage in the 3-position, *i.e.* 3-acyl-, 3-ether- and 3-alkyl-modified 2-pyridones. The following schemes will summarize the known structures. Although the elfamycin-type pyridones also contain a 3-acyl modification, these compounds have been grouped separately for reasons of clarity.

Scheme 1 4-hydroxy-3-acyl-2-pyridones and ricinine (1)

The first group contains all 4-hydroxy-3-acyl modified 2-pyridones and ricinine (1) (Scheme 1). Ricinine (1) is an insecticidal and hepatotoxic alkaloid produced by *Ricinus communis* which is present in high concentrations in the whole plant (ca. 1 mg / g fresh weight).¹⁰ The cytotoxic aspyridones A (2) and B (3) were discovered in the filamentous fungi *Aspergillus nidulans* as the product of a silent PKS-NRPS cryptic gene cluster. This gene cluster was activated by ectopic expression under control of an inducible promoter. With this technique the best producer strain generated 2 and 3 from 0.5 to 1 mg / L of culture broth, enough to determine the relative configuration.¹¹ This discovery bears the implication that different pyridone alkaloids may still be found hidden in silenced gene clusters in many other species. Aspyridone B (3) is the only known pyridone alkaloid containing a catechol moiety, whereas the *p*-hydroxyphenyl moiety of 2 is found in many other pyridone alkaloids. Pyridovericin (4) is one of the many examples featuring this substitution pattern. Originally isolated from the entomopathogenic fungus *Beauveria bassiana* in 1998, it was found to inhibit protein tyrosine kinase at high concentrations (100 µg/mL) in crude cell homogenates from NIH3T3/v-src1.¹² Its absolute configuration was determined by a very interesting quasiracemic synthesis in 2002,¹³ that will be presented in more detail later. A group of similar pyridone alkaloids are the yellow biochromes tenellin (6) and its congeners pre-tenellin (5), bassianin (7) and

farinosone A (**8**) and B (**9**). Tenellin (**6**) was first isolated from the entomopathogenic fungus *Beauveria tenella* in 1968 and later also found in *Beauveria bassiana*.¹⁴ Along with bassianin (**7**) it was found to be an inhibitor of ATPase in isolated membranes.¹⁵ Studies to unravel the biosynthesis of tenellin (**6**) have been performed, which are beyond the scope of this article.^{16,17} Generally, an oxidative ring expansion of tetramic acids to 2-pyridones is discussed. Two racemic syntheses of tenellin (**6**) have been developed in 1982 and 1989 but the absolute configuration still remains unknown.^{18,19} Pre-tenellin B (**5**) was isolated after knockout of one of the two open reading frames (ORF) encoding for a cyp450 oxidase using RNA silencing techniques. Therefore, pre-tenellin B (**5**) was found to be the direct precursor of tenellin (**6**).¹⁷ More recently, the tetraene 2-pyridones farinosone A (**8**) and B (**9**) along with the biosynthetically related farinosone C have been isolated from the entomopathogenic fungus *Paecilomyces farinosus* by bioassay guided fractionation.^{20,21} Farinosone A (**8**) induced neurite outgrowth in the PC-12 assay, whereas farinosone B (**9**) was inactive. The absolute configuration of these natural products remains unknown. Other closely related natural products are the militarinones (**10-12**) isolated from the mycelium of the entomogenous fungus *Paecilomyces militaris* or *Paecilomyces farinosus* in the years 2002 to 2006.²²⁻²⁴ These natural products induced neurite outgrowth in the PC-12 assay at low concentrations by persistently activating the PI3-K/PKB and the MEK/ERK pathways. Militarinone A (**12**) was also capable of inducing apoptosis in the Murine neuroblastoma cell line N2a by nuclear translocation of the apoptosis inducing factor (AIF).²⁵ Deoxymilitarinone A (**11**) was cytotoxic in human neuronal IMR-32 cells at concentrations of 100 μ M. It is interesting to note that **11** and its hydroxamic acid **12** isolated from two different strains differed in their signs of optical rotation, although homochirality of the compounds may not generally be assumed. The relative configuration however has been tentatively assigned as *syn*. Pyridomacrolidin (**13**) is the only known pyridone alkaloid containing a 10-membered cyclic lactone. It was isolated in 1998 from *Beauveria bassiana* along with pyridovericin (**4**) and found to be a weak inhibitor of protein tyrosine kinase.¹² The absolute configuration is unknown and there is only one recent study towards a biomimetic synthesis.²⁶ The antifungal antibiotic ilicicolin H (**14**) was isolated in 1971 from the mycelium of the imperfect fungus *Cylindrocladium ilicicola*.²⁷ Its absolute configuration and biosynthesis have been investigated.^{28,29} Additionally, in 1985 a racemic total synthesis using an intramolecular Diels-Alder strategy was presented.³⁰ Harzianopyridone (**15**) has been isolated in 1989 from the fungus *Trichoderma harzianum* as a racemic mixture and reported to be an antifungal agent.³¹ Later on, a levorotatory sample was also found to be inhibitory towards etiolated wheat coleoptiles (herbicidal) and an inhibitor of the mitochondrial complex II.^{32,33} It is closely related to the atpenins (*vide infra*). A racemic total synthesis has been published in 1995 leaving the absolute configuration of this molecule undetermined.³⁴ Fischerin (**16**), a complex oxidized hydroxamic acid was first isolated in 1993 from the invasive fungal pathogen *Neosartorya fischeri*. It was toxic to mice by causing peritonitis.³⁵ Only parts of the stereostructure have been solved but it is reminiscent of apiosporamide (**17**) and YM-215343 (**18**), structures that have been determined by an elegant total synthesis and proven to be homochiral.³⁶ Apiosporamide (**17**) was isolated from the fungus *Apiospora montagnei* in 1994, the oxidized congener YM-215343 (**18**) was found in the fungus *Phoma sp.* a decade later.^{37,38} Apiosporamide (**17**) was active against the

coprophilous fungus *Ascobolus furfuraceus* and showed antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*, while YM-215343 (**18**) showed antifungal activity against the pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus* (MIC values of 2-16 µg/ml) and was cytotoxic against HeLa S3 cells (IC₅₀ = 3.4 µg/mL). In 1988, the three antifungal antibiotics atpenin B, A4 and A5 (**19-21**) were isolated from *Penicillium sp.* followed by the total structural elucidation in 1990 for atpenin A4 (**20**) by X-ray crystallography.^{39,40} Like harzianopyridone (**15**), the atpenins were found to be mitochondrial complex II

inhibitors.³³ Atpenin B (**19**) has been obtained in racemic form from a total synthesis in 1994,⁴¹ whereas atpenin A5 (**21**) was stereoselectively synthesized in 2009.⁴²

Scheme 2 4-oxy-3-alkoxy-2-pyridones

The second group comprises the 4-oxy-3-alkoxy-2-pyridones shown in scheme 2. TMC-69 (**22**) is an antitumor antibiotic from *Chrysosporium sp.* that induced prolongation of the survival time of mice transplanted with B16 melanoma and P388 leukemia. The absolute configuration of the THP-moiety could be determined by degradation studies, while the stereogenic center of the side chain remains unassigned.⁴³ Because **22** was labile, Kohno et al. transformed it into its stable hexahydrogenated form TMC-69-6H and reported that this molecule was a selective inhibitor of the dual specificity phosphatases Cdc25A and B. Fürstner and coworkers presented a stereoselective total synthesis of TMC-69-6H in 2003 but they also were not able to assign the absolute configuration of the side chain stereogenic center. In contrast to the report by Kohno *et al.*, they found a different phosphatase inhibition profile with low inhibition of Cdc25A but high inhibition of other phosphatases, e.g. PTP1B and VHR.⁴⁴ Fusapyridon A (**23**) and its dimethylketal fusapyridon B (**24**) were isolated in 2007 from *Fusarium sp.* and **23** exhibited antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.⁴⁵ Their structures are resembling 4,6'-anhydro-oxysporidinone (**25**) from an endophytic strain of *Fusarium oxysporum*, with fusapyridone A (**23**) being the methylether of **25**.⁴⁶ The absolute stereostructure and parts of the relative configuration remain to be solved. 4,6'-Anhydrooxysporidinone (**25**) has so far not been found to exert any biological activity in laboratory systems. Funiculosin (**26**) was discovered as early as 1969 with broad antifungal properties.⁶ Its absolute stereostructure was solved in 1978 by X-ray crystal structure analysis and hydrogenation experiments.^{47,48} It was the first natural product containing a unique all-*syn*-cyclopentanetetrol moiety. Though Williams *et al.* published a stereoselective approach towards funiculosin (**26**) in 1997, no group has ever managed to finish a total synthesis of this structurally

intriguing compound.⁴⁹ The mycotoxin sambutoxin (**27**) was isolated in 1994 from the potato parasite *Fusarium sambucinum*. It caused toxic effects in rats including weight loss, feed refusal and hemorrhage and was lethal to chicken embryos at concentrations of 30 µg per egg.^{50,51} Its analog *N*-demethylsambutoxin (**28**) was discovered in 2006 from extracts of *Fusarium oxysporum* along with other pyridone alkaloids.⁵² Up to now, no biological activity has been assigned to **28**. (+)-Sambutoxin (**27**) has been obtained in totally synthetic form and was shown to be the antipode of the naturally occurring product.⁵³ It is interesting to note, that the dimethyl arrays in group 2 are in an *anti*-fashion, whereas for the militarinones (**10-12**) a *syn*-relation has been proposed in the original isolation report. Flavipucin (**29**),⁵ also known as fruit rot toxin B, contains an interesting spiro-epoxid that has been proposed to be responsible for the activity. It shows antibiotic activity both against gram-positive and gram-negative organisms and phytotoxicity.⁵⁴ A *cis*-fusion at the epoxide has been proposed and verified by a racemic total synthesis in 1979 and X-ray diffraction.^{55,56} Oxysporidinone (**30**) is an oxidized congener of sambutoxin (**27**), that was discovered in 1997 by Breinholt *et al.* in *Fusarium oxysporum* during a screening for natural products inhibiting phytopathogenic fungi such as *Aspergillus niger*, *Botrytis cinerea*, *Alternaria alternata* and *Venturia inaequalis*. Its relative configuration has been solved independently for the ring-systems.⁵⁷ Both (+)- and (-)-oxysporidinone (**30**) and the 6-epimer have been isolated from different strains of *Fusarium oxysporum*. In addition, the 6-deoxygenated product (-)-6-deoxyoxysporidinone (**31**) has been identified.^{46,52} No total synthesis has been reported up to now. The isolation and Ca²⁺-signalling inhibition properties of YCM1008A (**32**) from *Fusarium sp.* in a *Saccharomyces cerevisiae* mutant have been reported in 2007.⁵⁸ In the same year, a racemic total

synthesis and the structural determination of the absolute configuration have been published.⁵⁹

Scheme 3 4-oxy-3-alkyl-2-pyridones

The third group contains all 4-oxy-3-alkyl-2-pyridones shown in scheme 3. Tricyclic biaryl leporins A (**33**) and B (**34**) have been isolated from *Aspergillus leporis* in 1991 and 2003, respectively. Leporin A (**33**) shows activity against the corn earworm *Helicoverpa zea* and moderate antibacterial activity against *Bacillus subtilis*. The relative stereostructure of leporin A (**33**) has been solved and verified in a racemic total synthesis in 1996.^{60,61} Leporin B (**34**) is an inducer of the hexokinase II gene (HKII). It was identified with a rat myoblast cell construct expressing the reporter gene luciferase under control of the HKII promoter. Thus,

enhancement of HKII transcription enhanced the luciferase signal.⁶² After the isolation of fusaricide (**35**) in 1996 from *Fusarium sp.* Snider and coworkers embarked on a total synthesis program that was finished in 2001.⁶³ The relative configuration was solved by X-ray diffraction. It was active in the Rev binding assay rendering it a potential antivirally active substance and also active against *Candida albicans* and *Penicillium chrysogenum* (MIC's 16 and 8 µg/ml, respectively). Its antitumoral potency was found *in vitro* but not *in vivo* against Madison lung carcinoma cell line M109 (1 µg/ml).⁶⁴ Epipyridone (**36**) is the *p*-hydroxyphenyl modified derivative of fusaricide (**35**). Its natural source is the endofungal filamentous fungus *Epicoccum sp.* The authors suggest an interesting biosynthetic proposal for the side chain via an intramolecular hetero Diels-Alder reaction, which would also be valid for construction of the structures of e.g. fusaricide (**35**) and PF1140 (**38**). No bioactivity has yet been assigned for epipyridone (**36**) and only the relative configuration is known.⁶⁵ The wide spectrum fungicide PF1140 (**38**) has been isolated in 1996 and published along with its relative stereostructure.⁶⁶ In 2005 the absolute stereostructure was unraveled by X-ray crystallography of a derivative.⁶⁷ Also in 2005, feeding experiments in *Eupenicillium sp.*, the natural source of PF1140 (**38**), led the authors to propose a novel biosynthetic pathway to 2-pyridones.⁶⁸ Its deoxygenated congener deoxy-PF1140 (**37**) was found in the culture broth of *Penicillium sp.* along with PF1140 (**38**) and deoxyakanthomycin (**40**). Formation of **40** was also explained with the newly proposed biosynthetic route.⁶⁹ Interestingly, whereas PF1140 (**38**) was active in antimicrobial assays against *Bacillus subtilis* and *Candida albicans* and modestly active in the murine leukemia bioassay (P388), deoxy-PF1140 (**37**) lacked activity in these screenings suggesting an important role for the hydroxamic acid. Akanthomycin (**39**) and its recently discovered congener deoxyakanthomycin (**40**) (*vide supra*) exist as atropisomers stemming from hindered rotation around the axis of the pyridone and a stereochemical complex seven-membered ring. Both compounds were discovered in different fungal strains. The producer of Akanthomycin (**39**) is the entomopathogenic fungus *Akanthomyces gracilis*, while *Penicillium sp.* generated (**40**). The relative structure of (**39**) was solved by X-ray crystal structure analysis of one of the atropisomers in 2002. Direct application of **39** (both isomers) on agar plates inhibited the growth of *Staphylococcus aureus* at 250 ng.⁷⁰ In a screening assay for radical scavengers of microbial origin in 1991, the fungus *Acremonium sp.* was found to produce a rotameric mixture of pyridoxatin (**41**), that was about 20 times as active as vitamin E (inhibition of lipid peroxidation in rat liver microsomes).⁷¹ This activity was proposed to originate from tight iron chelation of the hydroxamic acid. Interestingly, a (pyridoxatin)₃Fe – complex has been isolated from another source and the absolute configuration determined by X-ray diffraction and CD-spectroscopy (antipode of that shown for **41**).⁷² A racemic total synthesis was presented in 1994 by Snider and Lu.⁷³ The first report on 8-methylpyridoxatin (**42**) dates back to 1999, when it was discovered in a screening for EPO-inducing compounds based on a luciferase reporter technology in the fungal strain *OS-F61800*.⁷⁴ Confusingly, it was later found in another entomopathogenic fungal strain *Cordyceps nipponica* and both atropisomers renamed to cordypyridone A (**42a**) and B (**42b**).⁷⁵ In this isolation procedure, potent antimalarial activity against *Plasmodium falciparum* was reported (IC₅₀ = 0.066 and 0.037 µg/mL) in addition to the unveiling of the absolute stereostructure. In 2009 a racemic synthesis of cordypyridones A (**42a**) and B (**42b**) with separation of the atropisomers was

reported.⁷⁶ In the same publication presenting the structures of **42a** and **42b** also the relative stereostructures of cordypyridones C (**43**) and D (**44**) were disclosed.⁷⁵ Both compounds showed no antimalarial activity against *Plasmodium falciparum*.

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Scheme 4 Elfamycin type 2-pyridones

Only a few examples of the elfamycin type 2-pyridones are shown in scheme 4. The most famous of these antibiotics are kirromycin (**45**), aurodox (**46**), elfamycin (**47**) and factumycin (**48**). The elfamycins inhibit the bacterial elongation factor EF-Tu.⁷⁷ Both aurodox (**46**) and elfamycin (**47**) have been prepared by a stereoselective
10 total synthesis in 1985 by Nicolaou and Dolle.^{78,79} A detailed discussion of these compounds is beyond the scope of this article. Further information can be found in a recent article by Wohlleben et al. and the references cited therein.⁸⁰

Table 1 Overview of pyridone alkaloids, their primary biological source and year of isolation

Natural Product	Source	Isolation	Total synthesis
Ricinine (1)	<i>Ricinus communis</i>	1864	1923
Aspyridone A (2)	<i>Aspergillus nidulans</i>	2007	
Aspyridone B (3)	<i>Aspergillus nidulans</i>	2007	
Pyridovericin (4)	<i>Beauveria bassiana</i>	1998	Quasiracemic in 2002
Pre-Tenellin B (5)	<i>Beauveria bassiana</i>	2008	
Tenellin (6)	<i>Beauveria tenella</i>	1968	Racemic in 1982 / 1989
Bassianin (7)	<i>Beauveria bassiana</i>	1968	
Farinosone A (8)	<i>Paecilomyces farinosus</i>	2004	
Farinosone B (9)	<i>Paecilomyces farinosus</i>	2004	
Militarinone D (10)	<i>Paecilomyces militaris</i>	2003	
N-Deoxymilitarinone A (11)	<i>Paecilomyces farinosus</i>	2006	
Militarinone A (12)	<i>Paecilomyces militaris</i>	2002	
Pyridomacrolidin (13)	<i>Beauveria bassiana</i>	1998	
Ilicicolin H (14)	<i>Cylindrocladium ilicicola</i>	1971	Racemic in 1985
Harzianopyridone (15)	<i>Trichoderma harzianum</i>	1989	Racemic in 1995
Fischerin (16)	<i>Neosartorya fischeri</i>	1993	
Apiosporamide (17)	<i>Apiospora montagnei</i>	1994	Stereoselective in 2005
YM-215343 (18)	<i>Phoma sp.</i>	2004	Stereoselective in 2005

Atpenin B (19)	<i>Penicillium sp.</i>	1988	Racemic in 1994
Atpenin A4 (20)	<i>Penicillium sp.</i>	1988	
Atpenin A5 (21)	<i>Penicillium sp.</i>	1988	Stereoselective in 2009
TMC-69 (22)	<i>Chrysosporium sp.</i>	2001	
Fusapyridon A (23)	<i>Fusarium sp.</i>	2007	
Fusapyridon B (24)	<i>Fusarium sp.</i>	2007	
Anhydrooxysporidinone (25)	<i>Fusarium oxysporum</i>	2007	
Funiculosin (26)	<i>Penicillium funiculosum</i>	1969	
(+)-Sambutoxin (27)	<i>Fusarium sambucinum</i>	1994	Stereoselective in 2000
<i>N</i> -Demethylsambutoxin (28)	<i>Fusarium oxysporum</i>	2006	
Flavipucine (29)	<i>Aspergillus flavipes</i>	1968	Racemic in 1979
Oxysporidinone (30)	<i>Fusarium oxysporum</i>	1997	
6-Deoxysporidinone (31)	<i>Fusarium oxysporum</i>	2007	
YCM1008A (32)	<i>Fusarium sp.</i>	2007	Racemic in 2007
Leporin A (33)	<i>Aspergillus leporis</i>	1991	Racemic in 1996
Leporin B (34)	<i>Aspergillus leporis</i>	2003	
Fusaricide (35)	<i>Fusarium sp.</i>	1996	Racemic in 2001
Epipyridone (36)	<i>Epicoccum sp.</i>	2007	
Deoxy-PF1140 (37)	<i>Penicillium sp.</i>	2009	
PF1140 (38)	<i>Eupenicillium sp.</i>	1996	
Akanthomycin (39)	<i>Akanthomyces gracilis</i>	2002	
Deoxyakanthomycin (40)	<i>Penicillium sp.</i>	2009	
Pyridoxatin (41)	<i>Acremonium sp.</i>	1991	Racemic in 1994
8-Methylpyridoxatin (42)	<i>fungus OS-F61800</i>	1999	Racemic in 2009
Cordypyridone C (43)	<i>Cordyceps nipponica</i>	2001	
Cordypyridone D (44)	<i>Cordyceps nipponica</i>	2001	
Kirromycin (45)	<i>Streptomyces collinus</i>	1972	
Aurodox (46)	<i>Streptomyces goldiniensis</i>	1973	Stereoselective in 1985
Efrotomycin (47)	<i>Nocardia lactamdurans</i>	1976	Stereoselective in 1985
Factumycin (48)	<i>Streptomyces lavendulae</i>	1982	

2 Synthetic approaches towards pyridone alkaloids

Regarding the strategic construction of the natural products outlined above, there are basically two general approaches towards the pyridone alkaloids, i.e. the modification of a preformed pyridone core structure with (often) electrophilic reagents or a linear route with a late stage cyclization event. Both strategies will be discussed in detail in the following chapter.

2.1 Cyclization strategies for pyridone alkaloids

One of the first synthetic strategies for the construction of pyridone alkaloids dates 10 back to 1982¹⁸ and was developed by David Williams and coworkers, who later disclosed other innovative strategies for the synthesis of these compounds.

2.1.1 Racemic total syntheses of tenellin (6) and ilicicolin H (14) by Dieckmann condensation

15 Preparation of tenellin (**6**) commenced with the condensation of methylester **49** and *N,N*-DMF dimethyl acetal (scheme 5). Subsequent exchange with benzyloxyamine gave the vinylogous carbamate **50** exclusively as the *E*-isomer. As a cyclization would only proceed *via* the *Z*-isomer thus requiring olefin geometry inversion, reduction with sodium cyanoborohydride followed by acylation with diketene
20 afforded β -keto hydroxamic acid **51**. Cyclization occurred after saponification and imidazolyl activation followed by internal acylation after deprotonation with sodium hydride yielding heterocycle **52**.

Scheme 5 Total synthesis of tenellin (**6**). Conditions: a) *N,N*-Dimethylformamide dimethylacetal, 200 °C, 12 h, 87%; b) (Benzyloxy)amine, benzene, CSA, 80 °C, quant.; ethanolic HCl, NaCNBH₃, 4.5 h, 96%; d) diketene, THF, Et₃N, -78 °C, quant.; e) LiOH, THF/H₂O, 99%; f) 1,1-carbonyldiimidazole, THF, 0 °C then g) NaH, 91%; h) Chloranil, ethylbenzene, reflux, 85%; i) H₂/Pd/C, dioxane, then j) dihydropyran, THF, CSA, 0 °C, 94%; k) LDA, THF, -78 °C, 56%; l) Et₃N, CSA, CHCl₃, reflux, then m) CSA, MeOH, benzene, reflux, 82%.

After oxidation with chloranil, the benzyl ether protecting groups had to be
30 exchanged to THP protecting groups. Protected pyridone **53** was used in an aldol
reaction with excess aldehyde giving a complex diastereomeric mixture of alcohol
54. *E*-selective elimination in anhydrous chloroform/triethylamine 4:1 and
deprotection with camphorsulfonic acid gave *rac*-tenellin (**6**) in a good overall
yield.¹⁸

Only three years later, Williams and coworkers published the racemic total synthesis of ilicicolin H (**14**) starting from the known intermediate **52** (scheme 5) after oxidation with chloranil (compound **55**).³⁰ This time, aldol reaction with KOtBu and fourfold excess of the racemic aldehyde **56**, which was obtained from citronellol acetate in eleven steps, gave the addition product that directly eliminated to bis-diene **57**. Interestingly, though this compound had several ways to react under Diels-Alder conditions (heating in dichlorobenzene for five minutes, 80% yield), a facile cycloaddition was observed proceeding through the *exo*-bridged transition state giving *trans*-fused decalins **58** and **59** with the remote C-12 methyl substituent in an equatorial position. The main product **58** and the isomerized conjugated byproduct **59** (5:1 mixture) were utilized as a mixture for the completion of the reaction sequence. First, treatment with excess LDA at -78 °C deprotonated the benzylic position of the hydroxamic acid benzyl ether leading to loss of benzaldehyde and net reduction at N-1. Hydrolysis of the reaction produced the desired configuration at C-8. Cleavage of the remaining benzyl ether with boron trichloride then furnished racemic ilicicolin H (**14**). The yield for the penultimate conversion c) is not reported in the publication.

Scheme 6 Total synthesis of ilicicolin H (**14**). Conditions: a) 4 eq. **56**, 4 eq. KOtBu, -40 °C, THF, 20 4h, 72 %; b) *o*-dichlorobenzene, reflux, 5 min, 80% **58+59** (5:1); c) excess LDA, THF, -78 °C, 20 min, then HOAc/H₂O; d) BCl₃, DCM, -78 °C, 1 min, then MeOH, 60 %.

2.1.2 Racemic total syntheses of tenellin (6) via cyclocondensation of an isocyanate with a β -keto ester enolate

Another convergent synthesis of *rac*-tenellin was reported by Rigby and Qabar.¹⁹ The reaction began with the preparation of a cinnamate derived isocyanate **61** starting from aldehyde **60**, that was protected, elongated with a Horner-Wadsworth-Emmons reaction followed by hydrolysis of the ester. The resulting carboxylic acid was then transformed into the isocyanate either by generating an intermediate acylazide with diphenyl phosphorazidate⁸¹ followed by several hours of refluxing or by using the Weinstock⁸² mixed anhydride protocol.

10

Scheme 7 Total synthesis of tenellin (**6**). Conditions: a) MEMCl, DIPEA, rt; b) (EtO)₂POCH₂CO₂Et, NaH, THF; c) LiOH/H₂O, rt, (95 % over three steps); d) EtOCOC(=O)Cl, Et₃N, NaN₃, toluene, reflux, 90%; e) NaH, THF, 0 °C, then *n*BuLi, 0°C, then aldehyde, 75 %; f) NaH, THF, then g) **61**, Ph₂O, 250 °C, 3 min, 70 %; h) TMS-Cl, NaI, MeCN, 85 %; i) TMS₂NH, cat. TMSCl, reflux, then MoO₅·py·HMPA, DCM, rt, 42%.

The sodium salt of β -keto ester **63**, obtained from the dianion of phosphonate **62** in a HWE-reaction, reacts smoothly *via* an enolate addition with the isocyanate **61**, giving an intermediate enamide that is immediately cyclized at 250 °C in diphenylether. MEM cleavage followed by oxidation of TMS-protected pyridine with Vedejs reagent⁸³ furnished *rac*-tenellin (**6**) in 42% yield. Despite the interesting construction of the pyridone structure, this method surely suffers from the harsh conditions that have to be applied to initiate the cyclization reaction. On the other hand it provided quick access to racemic tenellin (**6**) in good overall yield.

2.1.3 Quasiracemic total syntheses of pyridovericin via the isocyanate approach

Quasiracemic synthesis tries to combine the advantages of racemic and stereoselective synthesis, i.e. making both enantiomers at the same time but starting and finishing with enantiopure material.⁸⁴ This is achieved by tagging both enantiomers with different but very similar protecting groups, mixing them to a quasiracemate, conducting the synthesis on both quasienantiomers and finally by demixing taking advantage of the tag. After removal of the tag, both quasienantiomers are converted to pure enantiomers. Ideally, both quasienantiomers should have very similar, preferably identical physical properties but there should be at least one orthogonal method for resolution of the tags. The use of this concept has been demonstrated in the quasiracemic total synthesis of pyridovericin (**4**) in 2002

using a fluororous tagging strategy.¹³ In this synthesis different perfluorinated protecting groups as the tags were attached to a β -keto ester-fragment that was used in a cyclocondensation as described in 2.1.2.

Scheme 8 Quasiracemic total synthesis of pyridovericin (**4**). Conditions: a) (COCl)₂, DMSO, then b)

- 5 Ph₃PC(CH₃)CO₂Et, 80 % (2 steps); c) DIBAL, d) see a), 72 %; e) LDA, 78 %; f) NaH; g) Ph₂O, 250 °C, 32 % (two steps); h) TMS-Cl, NaI, MeCN, 90 %.

The differently tagged quasi-enantiomers **65** and **66** were mixed resulting in a quasiracemic mixture that was converted to the aldehyde **67** via Swern oxidation, Wittig reaction, DIBAL reduction followed by another Swern oxidation. At this stage the authors stated that they detected racemization (only after completion of the synthesis) of the quasiracemate from enantiopure material to a purity of about 64% *ee*. They showed that both Wittig reaction and reduction caused this decrease in optical purity. Preparation of the β -keto ester **68** followed by enolate addition/cyclization as in 2.1.2. gave the quasiracemate of **69**, that was now separated by using fluororous HPLC, thus resolving the quasiracemate. Deprotection gave (*R*) and (*S*)-pyridovericin (**4**), in low enantiomeric excess due to the racemization of the quasiracemic mixture in the reaction sequence. However, because no complete racemization had taken place, comparison of the optical rotation allowed to assign the absolute configuration of natural pyridovericin (**4**) being (*R*). In the original publication, the authors also showcased the use of this technique on a compound, which is not prone to racemization.¹³ In this case, better results were obtained.

2.1.4 Construction of (+)-sambutoxin with an enol-ester approach

In 2000 Williams and Turske presented a novel approach towards the construction of densely functionalized pyridone core structures.⁵³ This was exemplified in the enantioselective total synthesis of (+)-sambutoxin (**27**), the antipode of the natural product.

Scheme 9 Enantioselective total synthesis of sambutoxin (**27**). Conditions: a) Mg, CuBr·DMS, THF, -78 °C, then **71**, 75 %; b) LiBH₄, wet Et₂O, 84%; c) PPh₃, imidazole, I₂, 96 %; d) LiEt₃BH, then H₂O₂, NaOH, 98%; e) 10% Pd/C, 10% HCO₂H in MeOH, 93%; f) Swern oxidation, then addn. of Ph₃P=C(CH₃)CO₂Et, 82%; g) DIBAL, DCM, -78 °C, 97%, h) MnO₂, DCM, 91%; i) Hex₂BCl, Me₂Net, -78 °C to -20 °C, then H₂O₂, MeOH, pH 7 buffer, 78 %; j) Me₂tBuSiOTf, collidine, 98 %; k) LiBH₄, THF, -78 °C, then NaIO₄; l) NaBH₄, MeOH, 92 %; m) see c), 96 %; n) *homo*-allyl-MgBr, CuBr·DMS, THF, -78 °C to -20 °C, then o) catecholborane, THF then aq. H₂O₂ at 0 °C, 53% over 2 steps; p) PDC, wet DMF, then CH₂N₂, 82 %; q) LDA, THF, then **80**, HMPA, 71 %; r) DMSO, DCC, pyr-HCl, 89 %; s) DBU, DCM, rt, then BrCCl₃, 0 °C, 92 %; t) TBAF, THF, then u) Pd(OAc)₂, K₂CO₃, MeCN, 44 % over 2 steps; v) NaI, HCl, acetone, 82%.

Bromide **70** (available in 4 steps from (2*R*)-methyl 3-hydroxy-2-methylpropionate) was transformed into its organocopper complex and used in an asymmetric conjugate addition to oxazolidinone **71**,⁸⁵ to yield the 1,3-*anti* dimethyl array **72**. Reductive cleavage of the auxiliary, reduction and cleavage of the benzyl ether yielded alcohol **73**, that was homologated to aldehyde **74**. Interestingly, the authors of this paper do not comment on racemization in the α -position,⁸⁶ which has been discussed under 2.1.3. Further elaboration of the side chain utilizing an *anti*-aldol process as described by Paterson⁸⁷ with an (*S*)-ethyl lactate derived auxiliary **75** proceeded smoothly via the *E*(*O*)-boron enolate and a closed transition state. After TBS-protection of the alcohol, the auxiliary was reductively removed and then periodate cleavage of the *vic*-diol, followed by iodination giving iodide **77**. The chain was then elongated to the ester **78**. In the original report, this chain elongation is depicted using allyl magnesium bromide, however, the *homoallyl* Grignard

reagent was used in this synthesis. The enolate of this ester was condensed with amino aldehyde **80**, which is available from starting material **49** in nine steps (see also scheme 5). Immediate oxidation provided enol ester **81**. Removal of the Fmoc protecting group with DBU triggered the spontaneous cyclization to an intermediate 5,6-dihydropyridone (see also compound **52**, scheme 5), that was oxidized upon addition of bromotrichloromethane, yielding **82** after TBS deprotection. The key step of this reaction sequence is the oxidation of **82** under buffered Saegusa⁸⁸ conditions with palladium acetate. The intermediate quinone methide reacts in an intramolecular conjugate addition leading exclusively to tetrahydropyran **84**.
 10 Cleavage of the MOM-ether releases (+)-sambutoxin (**27**) in overall 35 steps with 26 steps in the longest linear sequence. This sequence combines an interesting and high yielding cyclization strategy via enol ester **81** with a 1,4-addition to a quinone methide after Saegusa oxidation. It was shown that this strategy is also applicable for the synthesis of funiculosin dimethyl ether.⁸⁹

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2.1.5 Total synthesis of (+)-apiosporamide and YM-215343 using a β -lactam precursor

In 2005 Williams *et al.* disclosed a stereoselective total synthesis of (+)-apiosporamide (**17**) and YM-215343 (**18**) based on a further development of their
 20 acylation/cyclisation technique already discussed for tenellin (**6**) (scheme 5) and ilicicolin H (**14**) (scheme 6).³⁶

Scheme 10 Enantioselective total synthesis of (+)-apiosporamide (**17**) and YM-215343 (**18**).
 Conditions: a) **86** + KHMDS, THF, -78 °C, then **85**, 97%, d.r. 1.6:1 ; b) TBS-protection; c) TBAF, 0 °C, 98 %; d) *m*CPBA, DCM, NaHCO₃, 54%; e) TBSCl, imidazole, DCM, quant.; f) *n*BuLi, allyl
 25 alcohol, -78 °C to rt, 80%; g) cat. TEMPO, PhI(OAc)₂, DCM, 70%; h) **92**, K₂CO₃, MeOH, rt, 82%; i) cat. OsO₄, K₃Fe(CN)₆, K₂CO₃, *t*BuOH/H₂O, 94%, then NaIO₄, aq. THF, then H₃CC(O)CH₂P(O)(OMe)₂, K₂CO₃, 91%, E/Z 13:1; j) Cp₂Zr(H)Cl, DCM, rt, then I₂, 77%; k) (*E*)-BrZnCH=CHCH₃, THF/Et₂O/pentane, -30 °C to rt, 74%; l) DMP, py, DCM, 90%; m) EtAlCl₂, toluene, -78 °C to rt, 72%, >97:3 d.r.; n) LiHMDS, THF, -78 °C to 0 °C, then HMPA at -78 °C, then
 30 MeOC(O)CN, 62%; o) KOH in aq. MeOH, 0 °C, 81%; p) BOP, Et₃N, MeCN, 99%; q) Pd(PPh₃)₄, pyrrolidine, DCM, 85%; r) BOP, DCM, DBU, 56%; s) Sml₂, THF, 98%; t) BrCCl₃, tetramethylguanidine, 65% then HF*pyr, THF, 75%; u) DMP, DCM, 92%.

Enone **85** was reacted in an aldol reaction with β -lactam **86** yielding a separable
 1:1.6 mixture of diastereomeric tertiary alcohols **87** and **88**. Compound **88** was TBS-
 35 protected and then selectively deprotected to conduct a Henbest⁹⁰ *cis*-epoxidation,

followed by TBS-reprotection, yielding epoxide **89**. Cleavage of the β -lactam ring with lithiated allyl alcohol resulting in allylic ester **90** which is related to compounds **50** and **51** (scheme 5). Acylation of **90** was conducted after BOP activation of enantiomerically pure acid **95**, which was obtained from (-)-citronellol (**91**) in a nine step sequence. Briefly, homologation with the Ohira-Bestmann reagent⁹¹ **92** after oxidation of the alcohol, bis-hydroxylation, oxidative cleavage and HWE reaction gave ketone **93**, that was hydrozirconated and quenched with iodine with concomitant reduction of the ketone.⁹² Negishi cross coupling delivered the diene, followed by oxidative regeneration of the enone **94**. Diels-Alder reaction and C-acylation according to Mander⁹³ gave acid **95**. After cleavage of the allyl protecting group, ring closure was achieved by activation of the acid in the presence of DBU. Reductive cleavage of the N-protecting group with samarium iodide,⁹⁴ oxidation of the pyridone ring with bromotrichloromethane and TBS-deprotection unveiled (+)-apiosporamide (**17**), which was further oxidized with Dess-Martin periodinane⁹⁵ to YM-215343 (**18**), both being the antipodes of the corresponding natural products. This sequence displays an impressive approach towards pyridone alkaloids. It showcases the utility of β -lactams in the construction of highly functionalized pyridone structures.

2.1.6 Total synthesis of YCM1008A (**32**) by intramolecular *N*-Michael addition-elimination

The total synthesis of YCM1008A (**32**) has been achieved using an internal cyclization strategy giving mixtures of *syn* and *anti* diastereomers that were separated.⁵⁹ Finally, camphanic esters had to be synthesized to facilitate separation of diastereomers due to low selectivity in the transformations. However, using this strategy, the relative and absolute configuration of YCM1008A (**32**) were successfully assigned in the end.

Scheme 11 Total synthesis of YCM1008A (**32**). Conditions: a) TEMPO, NaOCl, KBr, NaHCO₃, DCM, then b) CrCl₃, LiAlH₄, CH₃I, THF, 33% (2 steps); c) (*E*)-CHOCH=CHSn(*n*Bu)₃, Pd(PPh₃)₄, CuI, DMF, 60%; d) (COCl)₂, DMF, DCM, then e) *i*PrNEt₂, MgCl₂, **103**, 74% (2 steps); f) Pd(PPh₃)₄, HCO₂H, Et₃N, THF, 87%; g) **104**, NaH, THF, 25%; h) (*E*)-3-chloroacryloyl chloride, *i*PrNEt₂, MgCl₂, THF, then i) Amberlyst 15, DCM, 34% in two steps, 2,3 *syn* / 2,3 *anti* (1:1); j) TiCl(O*i*Pr)₃, Cl(CH₂)₂Cl, 75% from 2,3 *anti*-intermediate, 34% from *syn*-intermediate; k) DIBAL, DCM, -78 °C, mixture of 4 stereoisomers, 67%; l) (-)-camphanoyl chloride, py, DCM, separation; m) NaOMe, MeOH, 79%.

Alcohol **99** was oxidized and subjected to a Takai reaction.⁹⁶ The vinyl iodide **100** was used in a Stille coupling⁹⁷ giving aldehyde **101** which was further modified in a Horner-Wadsworth-Emmons reaction with phosphonate **104**. Acylation of the intermediate diketo compound resulted in polyene **105** that was directly cyclized to mixtures of *syn*- and *anti*- γ -pyrones. After separation of *syn* and *anti* isomers, deprotection of the hydroxamic acid induced a Michael addition-elimination reaction resulting in both *anti*-isomers **106**. Reduction of the ketone gave a complex mixture of all four possible isomers that were separated after esterification with (-)-champhanoyl chloride. The separated diastereomers were then deprotected and their spectral data compared with those of the natural product. YCM1008A (**32**) was found to be identical in all aspects with (2*R*,3*R*,4*S*,8'*R*) pyridone (**32**). The key steps of this synthesis are the sequential Michael-addition to a γ -pyrone that is subjected to another Michael-addition-elimination reaction to furnish pyridone **106** from starting material **105**. Due to low selectivities, tedious purification procedures and modifications were necessary.

2.2 Modifications of the pyridone core

Different strategies have been developed to modify the pyridone core structure, either by metalation and electrophile quenching, by Knoevenagel-ene cascades or cross couplings.

2.2.1 Total syntheses of atpenins and harzianopyridone by repeated metalation of 2-chloropyridine

The first total synthesis for one member of the atpenins was reported in 1994. It is an interesting reaction sequence featuring a “clockwise” functionalization of 2-chloropyridine **110** via directed metalations, electrophile trapping and the halogen dance reaction (scheme 12).⁹⁸

Scheme 12 Total syntheses of atpenin B (**19**), harzianopyridone (**15**) and atpenin A5 (**21**). Conditions: a) LDA, B(OMe)₃, then CH₃C(O)OOH, 65%; b) MeI, NaH, DMF, rt, 93 %; c) MeOH, NaH, DMF, 80 °C, 86 %; d) *n*BuLi, B(OMe)₃, *m*CPBA, THF, -78 °C, 64 %; e) Ag₂CO₃, ClCON/Pr₂, 70%; f) *n*BuLi, THF, -78 °C, then BrCN, 93 %; g) LDA, THF, -40 °C, cat Br₂, then EtOH, 73 %; h) *n*BuLi, THF, -70 °C, B(OMe)₃, then CH₃COOOH, 63%; i) NaH, SEM-Cl, THF, 84 %; j) *n*BuLi, Diisopropylamine (cat.), then **75**; 80 %; k) PCC, DCM, 70%; l) KOH, MeOH; m) HCl, MeOH, 78 % (2 steps).

Chloropyridine **110** was first metalated in 3-position followed by trapping with trimethylborate, oxidation to the phenol,⁹⁹ methylation and nucleophilic substitution of the chlorine yielding dimethoxypyridine **111**. Again, selective metalation and subsequent boronation/oxidation gave rise to phenol **112**. Suitable carbamate

protection followed by metalation and trapping with cyanogen bromide gave 5-brominated pyridine **113**. This pyridine was subjected to the halogen dance reaction, generating an equilibrium between the 5-bromo-6-lithio and the 5-lithio-6-bromo species which is shifted towards the more stable 5-lithio-6-bromo compound.⁹⁶

5 Trapping with the trimethylborate/oxidation sequence affords pyridine **114** after SEM-protection. Metalation of pyridine **114**, trapping with aldehyde **115** and oxidation gives the acylated pyridine **116**. Cleavage of the protecting groups releases racemic atpenin B (**19**). The same sequence was also applied to the total synthesis of harzianopyridone (**15**) by trapping of the metallated pyridine **114** with aldehyde
10 **117**.³⁴

A slightly modified but still similar protocol was used for the stereoselective construction of atpenin A5 (**21**).⁴² MOM protecting groups were used insted of the carbamate to avoid strongly basic deprotection conditions which may result in racemization of the α stereogenic center in **21**. However, addition to the aldehyde
15 **120** is conducted under strongly basic conditions. Iodine was used instead of bromine for the halogen dance reaction and metalation of the pyridine core was achieved by lithium halogene exchange in compound **119**. Trapping of metallated **119** with aldehyde **120**, oxidation and deprotection of **121** finished the sequence to atpenin A5 (**21**).

20

2.2.2 Racemic total synthesis of cordypyridones A and B utilizing a Hal-Li exchange

In 2009, a racemic total synthesis of cordypyridones A (**42a**) and B (**42b**) also known as 8-methylpyridoxatin (**42**) was published. The authors presented a short sequence based on a pyridone core modification.⁷⁶

25 **Scheme 13** Total synthesis of 8-methylpyridoxatin (**42**). Conditions: a) Rh-catalyst on β -75 zeolite, H_2 , EtOH, 100 bar, 175 °C, 1h, 82%; b) LDA, TMSCl, THF, -78 °C, 86%; c) $GaCl_3$, THF, ethynyltrimethylsilane, rt, 5 min, 87%; d) NBS, MeCN, reflux, then e) MeI, Ag_2CO_3 , $CHCl_3$, 3d, 42% over 2 steps; f) $nBuLi$, THF, -78 °C, then **112**, then chlorooxoacetate, 1 h, 61%; g) AIBN, Bu_3SnH , toluene, heat, 18 h, 86%; h) $MeMgI$, neat, 165 °C, 2h, 72%; i) HMDS, TMSCl, reflux, 24h
30 then j) $MoO_5 \cdot py \cdot HMPA$, DCM, 24 h; k) Na_4EDTA , $H_2O/EtOAc$, rt, 2h, 61% over three steps.

The reaction started with hydrogenation of phenol **122** with a zeolite-supported rhodium catalyst, giving a *meso*-ketone¹⁰⁰ that was converted into the TMS enolate **123**. The vinyl substituent was then installed *syn* to the other methyl substituents by coupling of **123** with ethynyl-TMS in the presence of gallium trichloride,¹⁰¹ yielding
35 a >9:1 mixture of diastereoisomers **124**. Next, commercially available pyridone **125** was selectively brominated and then converted to the bis-methyl ether **126**. Coupling of the fragments was achieved by Br-Li exchange followed by nucleophilic attack to the ketone. The alcoholate function was directly trapped with chlorooxoacetate producing an oxalate moiety. This was removed in a Dolan-MacMillan

deoxygenation¹⁰² proceeding via a planar C-centered radical, which is intercepted with tributyl tin hydride from the less hindered side (not shielded by axial methyl group). The bis methyl ether **127** was deprotected by heating in neat methyl Grignard reagent yielding pyridone **128** that was *N*-oxidized according to Sammes^{103, 104} giving a separable mixture of the atropisomers of 8-methylpyridoxatin (**42**) (Cordypyridone A (**42a**) and B (**42b**)).

The sequence is certainly attractive due to its shortness combining a fast and efficient coupling of both fragments *via* Li-Br exchange with an interesting access to the functionalized cyclohexyl-moiety by utilizing zeolite assisted hydrogenation.

Key step of this sequence was a lithium halogen exchange and attack of the pyridyl anion on a vinyl ketone terminated by trapping with methyl chlorooxoacetate.

2.2.3 Racemic total synthesis of pyridoxatin, leporin A and fusaricide

In 1994 Snider et al. disclosed their first report on tandem Knoevenagel-electrocyclic reactions to construct functionalized 2-pyridones.⁷³ We have already discussed the useful intermediate *o*-quinone methides¹⁰⁵ in the construction of sambutoxin (**27**) (scheme 9, **28**) that were utilized in this sequence.

Scheme 14 Total synthesis of pyridoxatin (**41**). Conditions: a) LDA, TMSCl, 75%; b) O₃, Me₂S, then c) CH₂N₂, 72%; d) Ph₃P=CHCH₂SiMe₃, 73%; e) DIBAH, 80%; f) Swern oxidation, 80%; g) **113**, piperidinium acetate, EtOH, reflux, 12h, then h) Me₂AlCl, DCM, 12 h, rt, 17% (1:1 mixture of atropisomers); i) HMDS, TMSCl, reflux, 24h then j) MoO₅*py*HMPA, DCM, 24 h, 44% over 2 steps.

Racemic cyclohexanone **129**, obtained by *cis*-hydrogenation of 2,4-dimethylphenol and Jones oxidation, was converted into its TMS-enolate, ozonolyzed and methylated to aldehyde ester **130**, containing ca. 10% of its diastereoisomer. After chain elongation by a Wittig reaction and a reduction oxidation sequence, allylsilane **131** with a nucleophilic double bond was obtained. Condensation of **131** with dihydroxypyridine **125** gave a complex mixture of diastereomers **132**, in which unfortunately the relative relation of the methyl groups was scrambled in the reaction conditions. Treatment of the mixture with excess dimethyl aluminium chloride led to *o*-quinone methides **133** and **134** that reacted in a stereospecific intramolecular ene reaction in **134** giving the desired racemic pyridone **135** with all substituents in the equatorial position. After removal of the undesired product resulting from transition state **133**, the pyridone **135** was oxidized by the Sammes^{103, 104} procedure to the hydroxamic acid pyridoxatin (**41**), that was obtained as a

racemic mixture of atropisomers. This reaction sequence provided a rapid access to racemic 3-cyclohexylpyridones by combining a Knoevenagel and an ene reaction, although in moderate yield.

In 1996 Snider and Lu envisaged to synthesize racemic leporin A (**33**) utilizing a tandem Knoevenagel condensation – inverse electron demand intramolecular hetero Diels-Alder reaction.⁶⁹ Despite extensive investigations on similar reactions by Tietze¹⁰⁵ leading to *trans*-ring fusions, for leporin A (**33**) the Diels-Alder reaction would require to yield a *cis*-ring fusion.

Scheme 15 Total synthesis of leporin A (**33**). Conditions: a) 4d, 25 °C, 58%; b) H₂, Pd/C, EtOH, 60 °C, 98%; c) Et₃N, EtOH, reflux; 35% of **144**; d) HMDS, TMSCl, reflux, 24h then MoO₅·py*HMPA, DCM, 24 h, 57% over 2 steps; e) NaOMe, MeI, 77%.

Condensation of phenylacetonitrile **136** with malonylchloride **137** followed by hydrogenolysis provided pyridone **138**.¹⁰⁶ Aldehyde **140** was obtained from alcohol **139** in four steps. Condensation of pyridone **138** and aldehyde **140** under basic conditions in refluxing ethanol generated intermediate *o*-quinone methide **141**, that reacted amongst other available reaction pathways preferentially to the depicted compounds **144** with the desired *cis*-ring fusion (35 %), **143** with the *trans*-ring fusion (7 %) and different spirocycles **142** (32 %), that were shown to be products of a Claisen rearrangement of **143**, whereas the *cis*-fused pyridone **144** did not rearrange in this manner. *N*-oxidation^{103, 104} followed by methylation yielded leporin A (**33**) in racemic form in only ten steps. This reaction sequence provides rapid access to tricyclic pyridone alkaloids using readily available and inexpensive starting materials combining them in a tandem one-pot Knoevenagel-electrocyclic condensation to obtain *cis*-fused decalin systems.

A comparable approach to the fused tricyclic ring system of fusaric acid (**35**) was also developed in the group of Snider, combining a Knoevenagel condensation with a hetero Diels-Alder reaction. Unfortunately, due to the unfavorable substitution pattern of the diene for this type of reaction, the yields were poor (8 % of the desired

adduct).¹⁰⁷

2.2.4 Cross coupling reactions in the construction of functionalized pyridones

Different approaches to modified pyridone alkaloids using palladium catalyzed cross coupling reactions have been described, though none of these approaches has ultimately led to a completed total synthesis of a member of this class of natural products. Two examples will be presented in this section, as they provide interesting chemistry on the way to modified pyridone alkaloids.

The first example is taken from the work of Fürstner *et al.* describing the synthesis of TMC-69-6H (**152**),⁴⁴ the hydrogenated congener of the natural product phosphatase inhibitor TMC-69 (**22**).

Scheme 16 Total synthesis of TMC-69-6H (**152**). Conditions: a) $\{[(\text{allyl})\text{PdCl}_2]\}$ (0.5%), **146** (1.5%) Et_3N , DMF, 65%, 96% ee; b) TBSCl, Et_3N , 18h, 78%; c) Me_2CuLi , THF, -70°C ; d) LiHMDS, **150**, 69% over 2 steps; e) H_2 , Pd/C, EtOH; f) TBAF, THF, 69% over two steps; g) HMDS, TMSCl, reflux, then h) $\text{MoO}_5\cdot\text{py}\cdot\text{HMPA}$, DCM, then sat. aq. EDTA-Na, EtOAc, 61% over 2 steps.

Enantioenriched unsaturated ketone **145** was C-coupled to the enol site of the pyridone **138** in the presence of chiral diphosphane **146**¹⁰⁸ with low catalyst loadings of $\{[(\text{allyl})\text{PdCl}_2]\}$ in high enantiomeric excess. At the same time, a spontaneous 1,4-addition of the hydroxy group to the enone was observed. Retro-Michael reaction in the presence of oxophilic TBS-chloride regenerated the unsaturated ketone that was transformed in a conjugate addition to *trans*-ketone **148**. Julia-Kocienski olefination¹⁰⁹ using sulfone **150** followed by hydrogenation furnished a separable mixture of **151** and its epimer. Deprotection and oxidation according to Sammes procedure^{103,104} furnished TMC-69-6H (**152**) in enantiopure form. The unique palladium catalyzed stereoselective allylation 1,4-addition sequence with a phenol derived substrate followed by the rapid assembly of the target structures constitute the cornerstones of this impressive synthesis, which is certainly amenable to efficiently access other related structures.

The last synthetic approach remaining to be discussed is the nice study towards a biomimetic synthesis published by Robert Adlington *et al.*¹¹⁰ Though the sequence for the preparation of the pyridone core is similar to the one initially conducted by Williams in their tenellin (**6**) synthesis (see scheme 5), we have grouped this approach as a pyridone core functionalization, because a Suzuki-coupling is applied to generate the biaryl axis. Moreover, an acyl nitron intermediate is cyclized with

an enone in a 1,3 dipolar cycloaddition as proposed for the biosynthesis. Interestingly, the dipolarophil in this putative biosynthesis would be cephalosporolide B (**153**), itself a natural product, that has not yet been isolated from *Beauveria bassiana*, from which pyridomacrolidin (**13**) was isolated. It has however been found in the fungus *Cephalosporicum aphidicola*.¹¹¹

Scheme 17 Biomimetic studies towards pyridomacrolidin (**13**). Conditions: a) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , THF, reflux, 12h, 71%; b) H_2 , Pd/C, dioxane, 90 %; c) $\text{PhI}(\text{OAc})_2$, DCM, reflux, 24 h; 60 % **160/161** 1:1.4; 5% other minor isomers; d) **161**, AlCl_3 , toluene, 95 °C, 2d, 40% **160/162/163** 5:2:1.

Parts of the proposed biosynthesis of pyridomacrolidin (**13**) are shown in the upper part of scheme 17. A quinonoid nitrone **154** - obtained by oxidation of *N*-hydroxypyridovericin - would react in a 1,3-dipolar cycloaddition with cephalosporolide B **153** and then rearomatize to give **13**. This interesting proposal was examined using simplified and stabilized analogs of **153** and **154**. First, heterocycle **156** was obtained from starting material **155** in 8 steps using the previously described Dieckmann cyclization strategy in 12% overall yield.¹⁸ **156** was coupled to boronic acid **157** with *tert*-butyl protected *ortho*-positions to prevent side reactions after quinone methide formation. Interestingly, this is one of the rare examples to construct the biaryl axis of e.g. **158** using cross coupling chemistry. Next, oxidation with $\text{PhI}(\text{OAc})_2$ at high temperatures generated a quinonoid nitrone that reacted with model compound **159** regio- and stereospecific generating the *cis*-fused cycloadducts **160** and **161** in 60% yield and *trans*-fused cycloadducts (not shown) in only 5% yield. Addition of the oxygen always occurred on the β -carbon of the enone. It is interesting to note that quinone methide **161** is in fact a tautomer of **160**. Di-*de-tert*-butylation¹¹² was achieved starting from compound **161** under harsh Friedel-Crafts conditions, but no full conversion could be obtained. The same reaction conditions applied to phenol **160** proceeded even more slowly and in lower

yields. However, this study propose that the proposed biosynthesis might be occurring via 1,3 dipolar cycloaddition of quinonoid nitrones to enones resulting in the formation of architecturally intriguing compounds like e.g. pyridomacrolidin (13).

3 Conclusions

Pyridone alkaloids constitute a remarkable class of secondary metabolites. Due to their diversity, many different biological effects of these compounds have been identified, which may however not always be related to their original biological function. Their versatile and diverse structures resulting from different modifications in all positions of the pyridone core render these compounds a fascinating playground for synthetic chemists for many decades. Despite the innovative synthetic approaches that have been developed to obtain these natural products in totally synthetic form, much work remains to be done for synthetic chemists, as many of the known structures have not been determined in full detail. Likewise, the synthesis of derivatives to generate structure-activity-relationships has not found too much attention. The original biological function of these secondary metabolites remains largely unsolved despite speculations about the metal sequestering properties of hydroxamic acids. Thus, some of these compounds may function as siderophores.^{73, 113} Other biological aspects, e.g. the biosynthesis of tenellin, have been clarified in great detail. The oxidative ring expansion mechanism from tetramic acids to generate the pyridone core has been widely accepted.¹¹⁴⁻¹¹⁵ Additionally, hidden pyridone alkaloids have been obtained by activation of silenced gene clusters, coding for PKS-NRPS hybrids.¹¹ For these reasons, many further discoveries in this field of research appear to be possible. At the same time, as can be seen from the known structures, many intermediates and further functionalized pyridone alkaloids remain to be identified in biological sources. In this review, we have only discussed the 4-oxygenated 2-pyridones. Other closely related structures such as for example the lycopodium alkaloids have been reviewed¹¹⁶ and there are many more related structures incorporating the 2-pyridone core. It is also noteworthy that the 2-pyridone structure can be found in approved drugs like e.g. milrinone,^{117,118} making these compounds and the development of versatile synthetic approaches a junction of natural product and medicinal chemistry.

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