Personal Account

THE CHEMICAL RECORD

DOI: 10.1002/tcr.202000066

α-Aminonitriles: From Sustainable Preparation to Applications in Natural Product Synthesis

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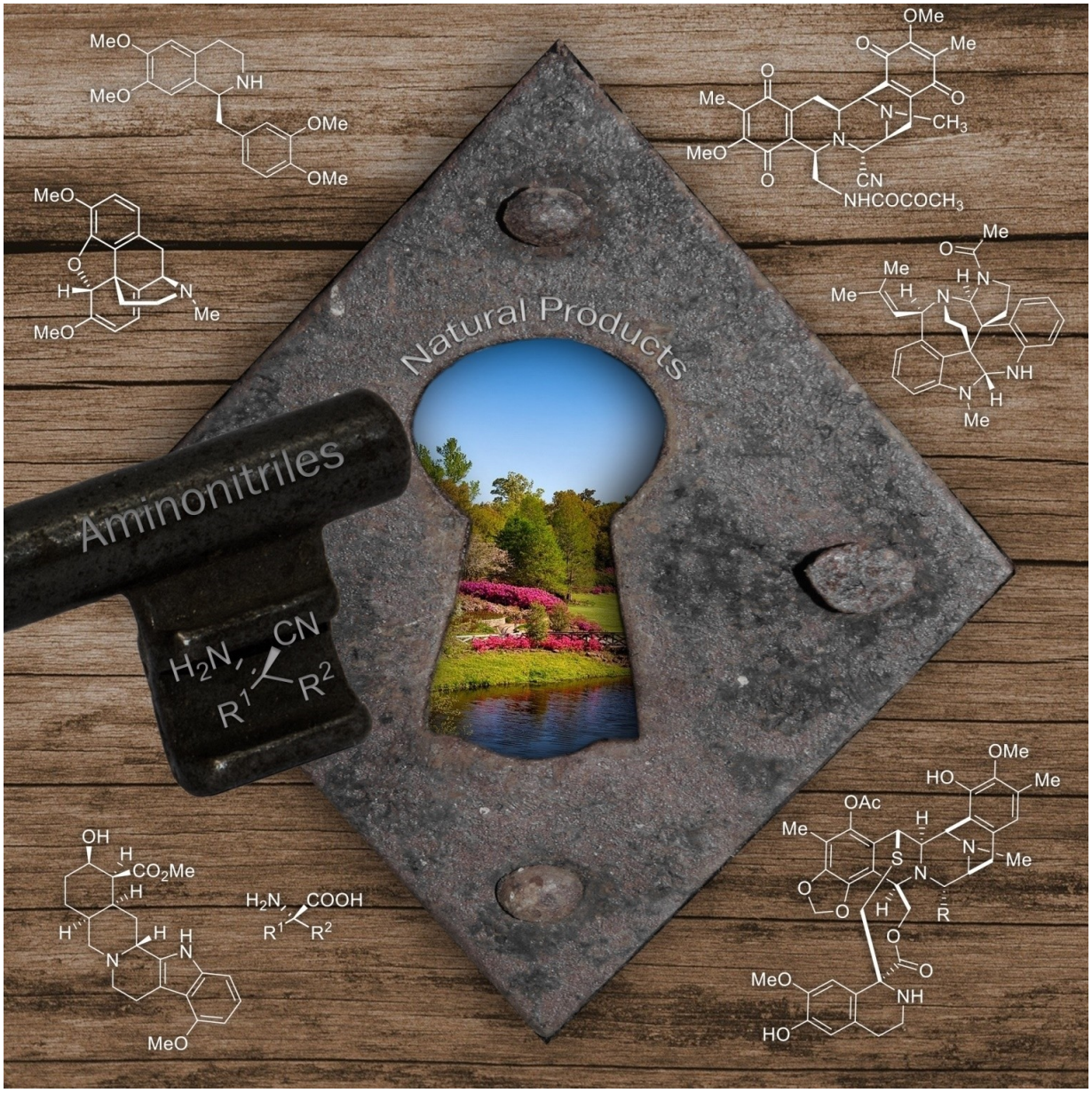
Dedicated to the memory of Professor Dieter Enders, pioneer of α-aminonitrile chemistry.



Abstract: Due to their numerous reactivity modes, α-aminonitriles represent versatile and valuable building blocks in organic total synthesis. Since their discovery by Adolph Strecker in 1850, this compound class has seen a wide dissemination in synthetic applications from laboratory to million-ton industrial scale and was extensively used in the syntheses of various classes of natural products. As these compounds provide a multitude of reactivity options, we feel that a broad overview of their multiple reaction modes may reveal less familiar opportunities for successful total synthesis planning. This personal account article will thus focus on α-aminonitriles used as key intermediates in selected natural product synthesis sequences which have been reported in the two decades since Enders' and Shilvock's seminal review. Natural α-aminonitriles will also briefly be treated.

Keywords: α-aminonitriles, natural products, total synthesis, amines, sustainable chemistry

1. Introduction

Since the first description of a condensation between amines, carbonyl compounds and hydrocyanic acid in 1850 by Adolph Strecker,[1] the chemistry of α-aminonitriles has been subject to a multitude of research and review articles as this compound class provides a number of unique synthetic opportunities.[2] Numerous methods for their synthesis have been developed during the past decades, involving classical Strecker chemistry,[3] metal-catalyzed[4] and metal-free syntheses,[5] electrochemical approaches,[6] as well as various photochemical pathways.[7] Besides the use of light as an ecologically ideal source of energy for chemical synthesis, a variety of other procedures involving non-toxic reagents like ferro-/ferricyanides, thiocyanates and α-amino acids as cyanide sources, have been developed.[8] In addition, attempts were made to release cyanide only upon mechanochemical, photochemical or thermal activation.[9] Moreover, numerous asymmetric approaches to chiral non-racemic α-aminonitriles and α-amino acids have been reported.[1,2c,d,3a,d,10] The arrangement of the amine and the nitrile functionality in α-aminonitriles entails different modes of reactivity, an overview of which is shown in Figure 1. Rather obvious is the hydrolysis of the nitrile group to afford either α-amino acids or α-amino amides first described by Strecker himself. Furthermore, α-aminonitriles can be considered as "cyanide-protected" or masked iminium ions, which can be either reacted with various carbon- or heteroatom nucleophiles or converted back into their parent carbonyl compounds upon decyanation (e.g. induced by Ag^{+} or Cu^{2+}) and hydrolysis.[2a,3b,11] Complementary, α-aminonitriles are also capable of polarity inversion (*Umpolung*) through α-deprotonation. Depending on the work-up, their conjugate anions can react as α-amino carbanion or as acyl anion equivalents.[2b,12] α-Aminonitriles are also easily converted into nitrile-stabilized ammonium ylides, which undergo various types of rearrangements as outlined in a review by Opatz in 2014.[2f] Removal of the cyano group through substitution by hydride in an elimination/addition sequence affords simple amines. This topic has recently been reviewed by Mattalia and will therefore not be discussed in detail here.[13] Additionally, the full reduction of the nitrile moiety leads to 1,2-diamines while classical amine and nitrile chemistry can be performed as well.[14] Their attractive, multifaceted reactivity therefore renders α-aminonitriles highly useful and versatile building blocks in the synthesis of nitrogen-containing heterocycles, drugs[2e,3d,10b,13a,14] and natural products as will be demonstrated in various case reports.

2. Selected Examples of Routes to α-Aminonitriles

Among the numerous approaches developed for the synthesis of α-aminonitriles during the past decades, a selection of procedures from the Opatz group may illustrate the use of photochemical pathways as well as the usage of non-toxic cyanide sources (see Scheme 1).

Originating from work on alternative energy sources in chemistry, different photocatalytic protocols to permit visible and even infrared light induced C–H bond activation have been developed. Together with the Tremel lab, the Opatz group reported the first oxidative photocyanation of tertiary amines with both visible and near-infrared light using TiO_2-nanoparticles functionalized with a self-developed sensitizer providing a strong electronic coupling to the semiconductor.[7c] Another example is recent work with the Heinze lab using their chromium(III) sensitizer $[Cr(ddpd)_2]^{3+}$ which again permits the transformation of tertiary amines to

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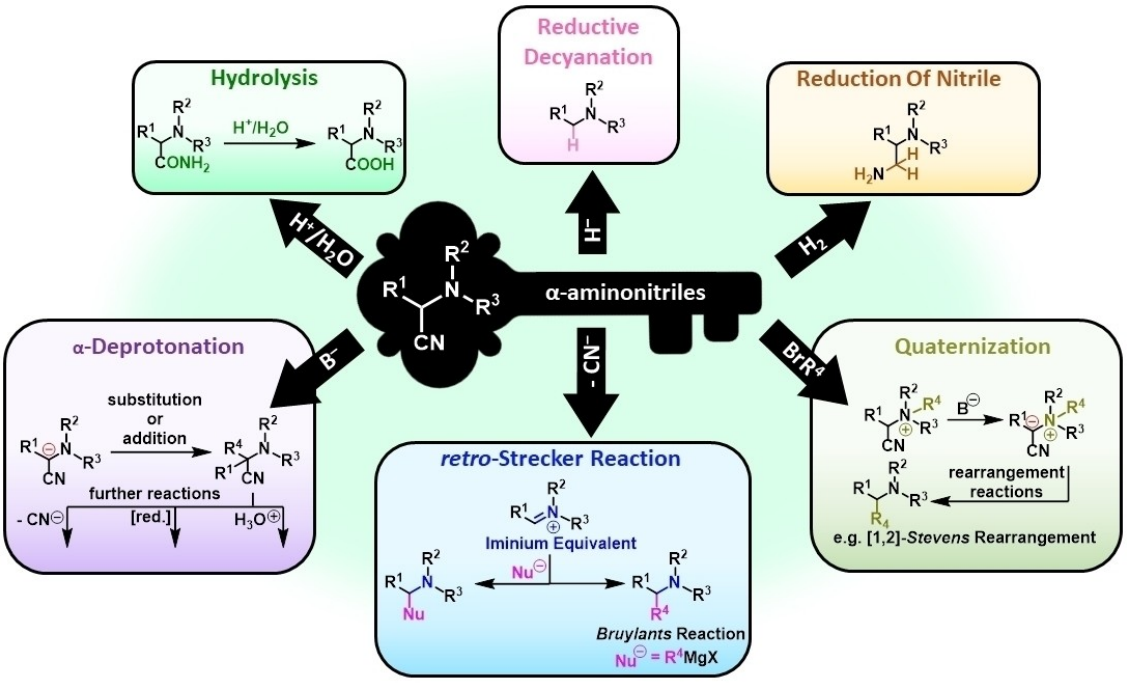

Figure 1. Modes of reactivity of α-aminonitriles.

aminonitriles.[7g] In the latter case, the use of the abundant chromium instead of the common ruthenium- or iridium-based sensitizers provides an ecological and economical benefit. Photoorganocatalytic protocols were developed[7b,d] as well as an inexpensive and simple flow reactor using sunlight.[15]

In the search for non-toxic cyanide sources, it was found that ferro- and ferricyanides, known to release cyanide at elevated temperatures, can be directly employed in a Strecker-reaction, furnishing aminonitriles in a one-pot, biphasic green solvent system.[9b] Moreover, a catalytic procedure for the

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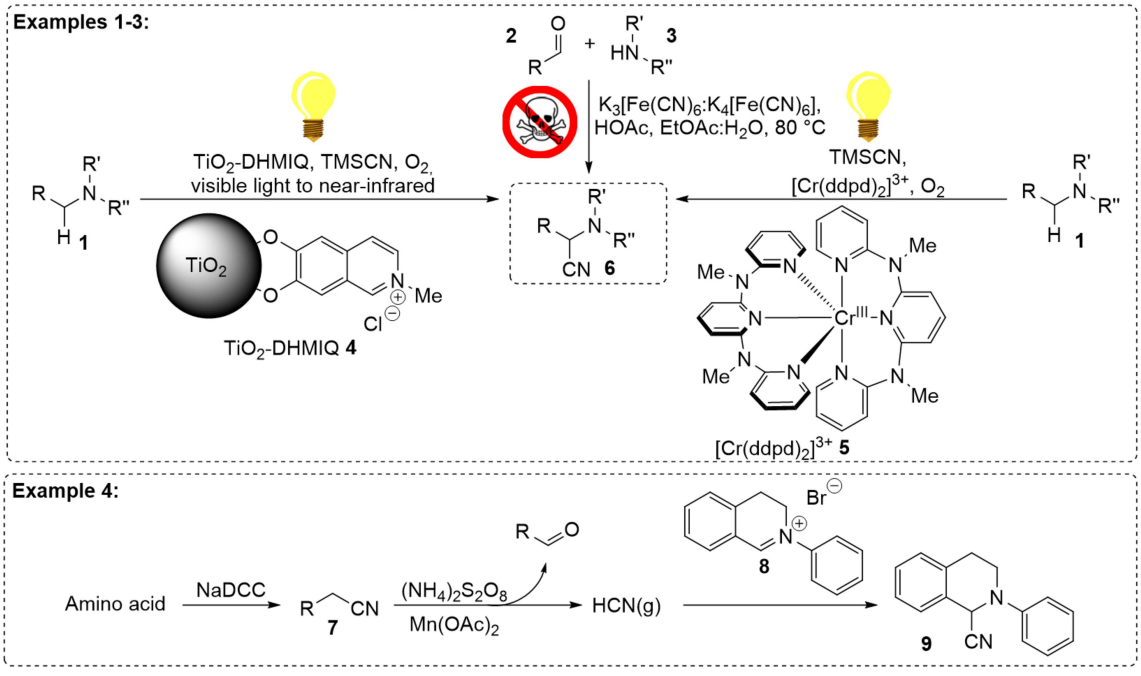
Nina Vierengel received her bachelor's degree in biomedicinal chemistry at JGU Mainz in 2016. After finishing her master's degree in 2018, she started working as a graduate student in the Opatz lab. Her research interests mainly focus on the total synthesis of natural products, in particular of macrolactones, as well as on natural product structure elucidation.

Prof. Till Opatz graduated from Frankfurt University in 1997 and completed his PhD at JGU Mainz with Prof. Horst Kunz in 2001. After a postdoctoral stay in Utrecht with Prof. Rob Liskamp, he returned to JGU for his habilitation (2006). In 2007, he was appointed associate professor at Hamburg University and returned again to JGU as a full professor in 2010. His research focuses on new synthetic methods, bioactive compounds, natural products and sustainable chemistry.



Scheme 1. Selected preparation methods of aminonitriles by the Opatz group.

conversion of biomass-derived α-amino acids to HCN has been developed.[8c] This and further examples of non-toxic cyanide sources were summarized in a 2019 review article.[8b]

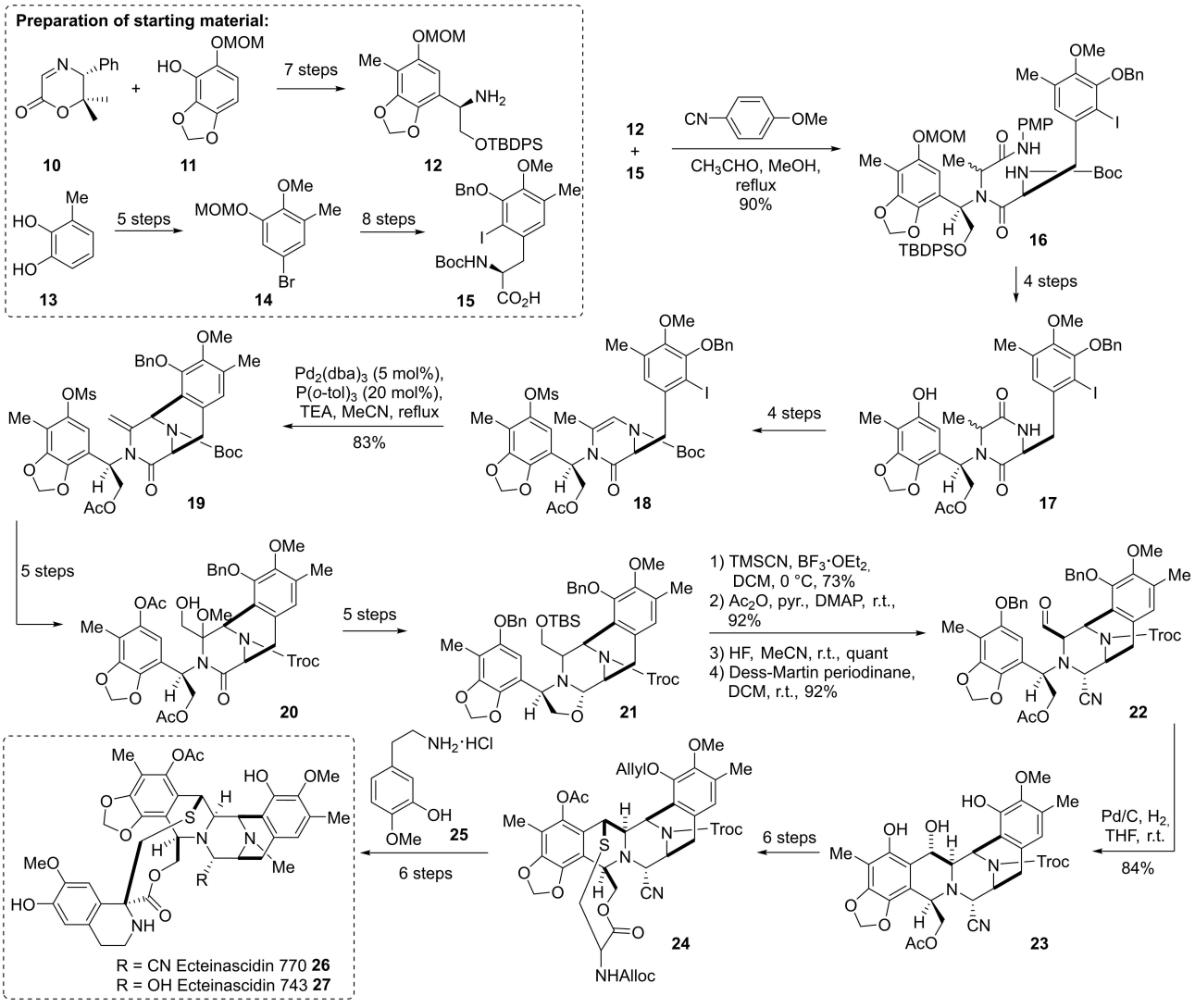
3. α-Aminonitriles as Key Intermediates in Natural Product Syntheses

3.1. Reactions as Masked Iminium Equivalents

α-Aminonitriles can be regarded as masked iminium equivalents as they easily undergo *retro*-Strecker reactions (HCN elimination) upon decyanation with either Brønsted- or soft Lewis acids such as copper- or silver salts.[16] This iminium ion reactivity was employed in numerous syntheses of natural products, some selected examples of which will be described in the following section.

3.1.1. Various Nucleophiles

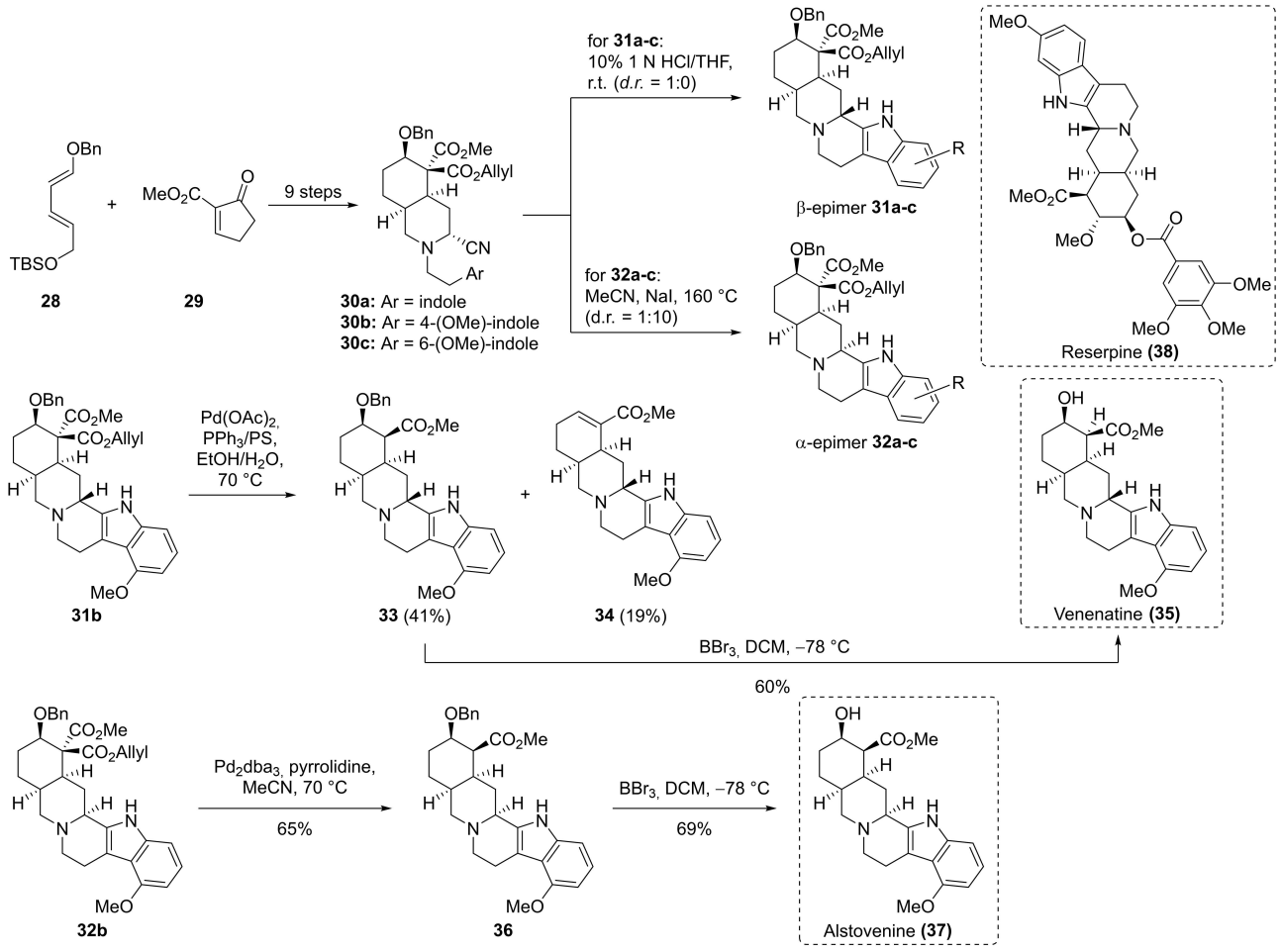
In 2002, the Fukuyama group reported the enantioselective total synthesis of ecteinascidin 743,[17] a complex trimeric tetrahydroisoquinoline (THIQ) alkaloid, which is known for its potent *in-vitro* and *in-vivo* antitumor activity against a variety of cancers and cancer cell lines and was isolated from the caribbean tunicate *Ecteinascidia turbinate* in 1969.[17–18] In 2007, this compound received marketing authorization of the EU for the treatment of advanced soft-tissue sarcomas.[19] Its first total synthesis was reported by the Corey group in 1996; however, the α-aminonitrile approach by Fukuyama presented herein is more efficient (see Scheme 2).[17,20] The highly functionalized (*R*)-arylglycinol starting material **12** could be obtained in seven steps starting from a chiral iminolactone template **10**. As a second starting material, phenylalanine derivative **15** was synthesized via previously reported bromide **14**[21] in 13 steps starting from commercially available 3-methylcatechol (**13**). With these two building blocks in hand, the next step was the transformation into dipeptide **16** by heating **12** and **15** in MeOH together with *p*-methoxyphenylisocyanide and acetaldehyde. An Ugi four-component reaction afforded diketopiperazine **17**, which was subjected to a four-step sequence involving mesylation, Boc-protection, regioselective reduction of one of the the ring carbonyls using $NaBH_4$ and dehydration of the resulting hemiaminal. Intramolecular Heck reaction proceeded under mild conditions to yield tricycle **19**. Oxidation with dimethyldioxirane and immediate treatment with camphorsulfonic acid (CSA) after switching the protecting groups afforded methoxy alcohol **20** in five steps. This was converted to oxazolidine **21** in five further steps involving acidic reduction, silylation, several protecting group operations and partial reduction of the lactam carbonyl using Red-Al. Ring opening of **21** with trimethylsilyl cyanide (TMSCN) afforded aminonitrile **22** as a single diastereomer. Due to its potential reactivity and lability, side reactions might



Scheme 2. Total synthesis of ecteinascidin 743 (**27**) by Fukuyama et al..

have been expected as soon as the aminonitrile moiety was introduced. However, multiple transformations like oxidation, hydrogenolysis and allylation were tolerated well. This showcases the potential of this compound class which provides synthetic options as well as a sufficient stability when carefully taken into consideration during synthesis planning. After isolation of compound **23** with the correct oxidation state at C-4, attention was focused on preparation of the ten-membered thioether ring **24**. Completion of the total synthesis was performed through construction of the missing THIQ moiety by deprotection and biomimetic transamination reaction as well as subsequent Pictet-Spengler reaction to furnish ecteinascidin 770 (**26**). Being a natural product itself, the latter shows potent cytotoxic and antitubercular activities.[22] The aminonitrile moiety was ultimately converted through the iminium ion to the labile hemiaminal by decyanation with $AgNO_3$ to give ecteinascidin 743 (**27**). Enamine formation is prohibited by Bredt's rule in this case.[17]

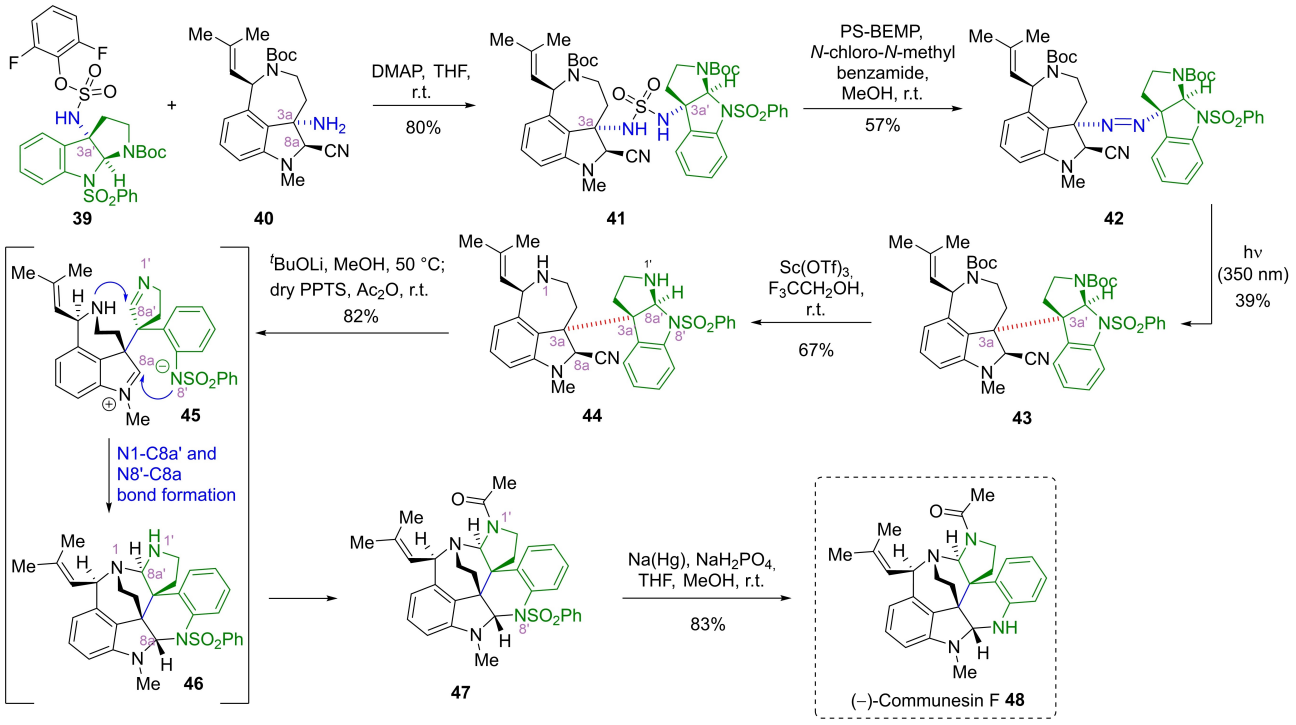
Yohimbinoid alkaloids represent popular targets for total syntheses. In 2013, Sarpong and co-workers developed a new approach towards this compound class which resulted in the first total synthesis of venenatine (**35**) and alstovenine (**37**) by applying α-aminonitrile intermediates to effectively control the stereochemistry at C-3 in a Pictet-Spengler cyclization (Scheme 3).[23] This work was built on Woodward's pioneering synthesis of reserpine (**38**) in 1958, which led to the undesired epimer, and the ingenious solution of Stork, who used an aminonitrile to regiospecifically produce an iminium ion to solve the reserpine C-3 problem.[24] As starting materials, the readily available diene **28** and enone ester **29** were employed.



Scheme 3. Total synthesis of venenatine (**35**) and alstovenine (**37**) by the Sarpong group.

After a sequence of Diels-Alder reaction, hydrogenation, silyl ether cleavage, sulfonation of the resulting primary alcohol and subsequent α-hydroxylation, oxidative cleavage and treatment with potassium cyanide, the desired aminonitriles **30a–c** could be obtained as single diastereomers. Extensive optimization studies of the following Pictet-Spengler cyclization revealed that the nucleophilicity of the indole moiety played a significant role in the inherent diastereoselectivity. Furthermore, the use of an exogenous nucleophile like sodium iodide led to a complete reversal of the diastereoselectivity. The exact mechanism of this thermal Pictet-Spengler cyclization and the role of the iodide additive however remained unclear. The authors assumed that a rapid exchange of the cyanide to the iodide could produce a reactive iodo species which would block the α-face and lead to the α-diastereomer instead. With C-3 epimers **31b** and **32b** in hand, the total synthesis was completed by removal of the allyl ester through deallylation/decarboxylation and debenzylation to furnish venenatine (**35**) and alstovenine (**37**).

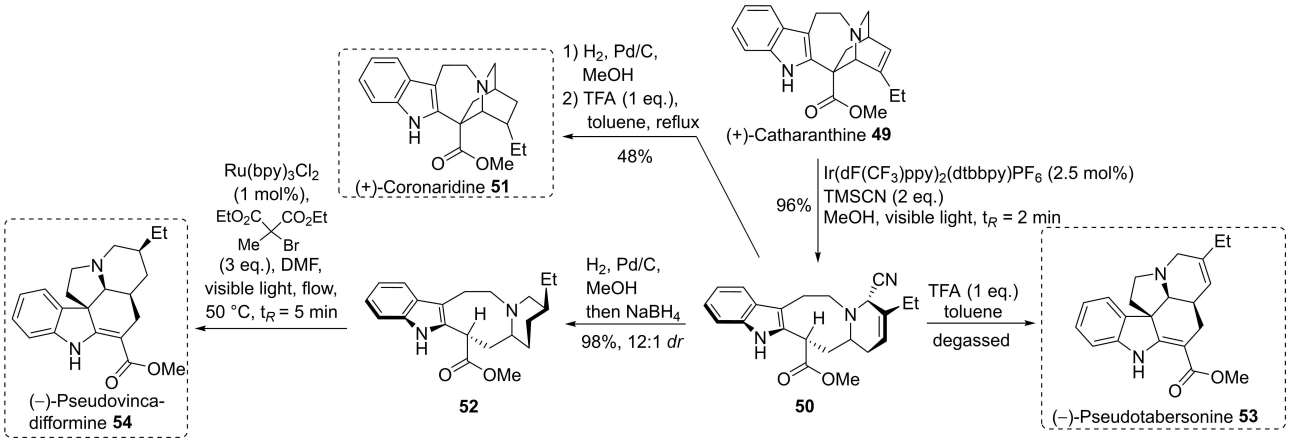
Another example for aminonitriles as masked iminium ions in natural product synthesis was reported by the Movassaghi group in 2016 (Scheme 4). They published the hitherto shortest biomimetic enantioselective total synthesis of (−)-communesin F based on a late-stage heterodimerization and aminal exchange.[25] (−)-Communesin F is a member of the highly complex communesin alkaloids, which were first isolated in 1993 from a marine *Penicillium* fungus.[26] To date, various interesting solutions towards these special molecules have been reported including approaches from Ma, Weinreb and Stoltz.[27] However, Movassaghi's approach reflects the latest insights concerning the biogenesis of these structures.[28] Gram quantities of starting material **39** were synthesized via a three step sequence involving mild reduction followed by subsequent decarboxylation and Rh-catalyzed C–H amination starting from a readily available bromo-substituted cyclotrypt-



Scheme 4. Total synthesis of (−)-communesin F (**48**) by Movassaghi et al..

amine derivative.[25] To access tricyclic aminonitrile **40**, the group developed two different approaches involving an oxyamination route or a sulfinimine allylation sequence. The first approach provided flexibility for a late-stage introduction of various substituents at N-8 and established the C-3a configuration but led to an oxazolidine substructure which was difficult to elucidate. Instead, the second approach yielded C-8a aminonitrile which served as an ideal latent iminium source for late-stage hemiaminal formation while retaining the required stability for further transformation.[25] After extensive optimization, stereoselective C3a-C3a' bond formation was achieved through complex fragment assembly based on the formation of diazene **42** from sulfamate **39** and tricylic aminonitrile **40** in two steps via dissolution of the two fragments in THF/DMAP, followed by chemoselective oxidation of sulfamide **41** using *N*-chloro-*N*-methylbenzamide in conjunction with PS-BEMP (polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine).[25] The remarkable diastereoselectivity at C-3a is assumed to be due to a rapid radical combination in conjunction with an additional stereoinduction enforced through the C-8a aminonitrile moiety. After selective removal of the N1 and N1' amine protecting groups of heterodimer **43** with $Sc(OTf)_3$ while preserving the sensitive C-8a nitrile moiety, final-stage biomimetic aminal reorganization could be achieved at the C8a'-aminal with the electron withdrawing N8'-sulfonamide being the respective leaving group. This allowed for a selective opening of the cyclotryptamine substructure. The resulting iminium intermediate **45** could then be rapidly trapped by the N1 amine to undergo N1-C8a' and N8'-C8a bond formation, only forming the desired heptacycle **46**. After two additional steps, (−)-communesin F (**48**) was obtained.

In 2014, Stephenson used the diversity of α-aminonitrile chemistry in the syntheses of (−)-pseudotabersonine (**53**), (−)-pseudovincadifformine (**54**) and (+)-coronaridine (**51**) (see Scheme 5).[29] Therein, commercially available (+)-catharanthine (**49**) was fragmented through photoredox catalysis in a formal *retro*-Mannich reaction in the presence of TMSCN to yield α-aminonitrile **50**. While previous attempts to preserve catharanthine's chirality failed,[30] due to rapid racemization upon chemical conversion, this protocol completed the task by using a flow reactor with a residence time of only 2 minutes in 96% yield. When α-aminonitrile **50** was refluxed with one equivalent of TFA in degassed toluene, (−)-pseudotabersonine (**53**) was obtained in 90% yield in a Pictet-Spengler reaction with a 2:1 enantiomeric ratio. The latter could be increased to 20:1 by lowering the temperature to 60 °C, unfortunately at the expense of the overall yield. When **50** was hydrogenated with H_2 over Pd/C and subsequently subjected to the rearrangement conditions applied before, (+)-coronaridine (**51**) was obtained in 48% yield over two steps. Hydrogenation



Scheme 5. Total syntheses of (+)-coronaridine (**51**), (−)-pseudotabersonine (**53**) and (−)-pseudovincadifformine (**54**) reported by Stephenson.

of aminonitrile **50** over palladium followed by workup with $NaCNBH_3$ provided a tertiary amine **52** in 98% yield with a 12:1 diastereomeric ratio, favouring the desired β-epimer. When the latter was converted under oxidative photoredox conditions in flow using diethyl 2-bromo-2-methylmalonate as the terminal oxidant, (−)-pseudovinca-difformine (**54**) was obtained in 58% yield.

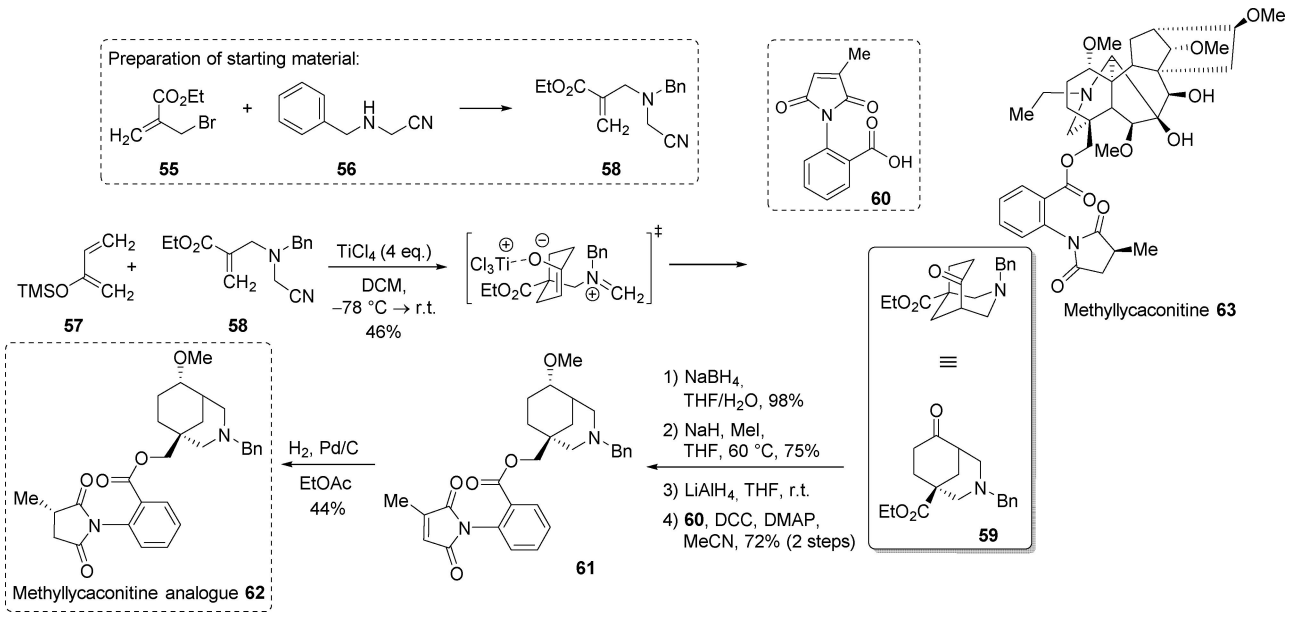
In Barker's synthesis[31] of *Delphinium* and *Aconitum* alkaloid analogues, α-cyanoaminoacrylates were reacted with 2-silyloxy-1,4-butadienes in a $TiCl_4$-catalyzed one-pot Diels-Alder/Mannich reaction to produce bicyclic intermediate **59**. Yields and reaction times were found to depend on the concentration of the $TiCl_4$ solution, on the diene equivalents and on the order of reagent addition. The resulting products can be further transformed into 6-alkoxy-3-azabicyclo[3.3.1] nonanes, which are the common core structure in the natural products of interest. This approach relies on a report by Yang et al.[32] which describes the $TiCl_4$-induced iminium ion cyclizations of α-cyanoamines. For the synthesis of methyllycaconitine analogue **62**, the required α-aminonitrile **58** was synthesized from ethyl 2-(bromomethyl)acrylate (**55**) and 2-benzylamino-acetonitrile (**56**) using standard procedures (Scheme 6). After diastereoselective ketone-reduction and subsequent methylation using standard procedures, the respective ester was reduced with lithium aluminium hydride to afford the corresponding alcohol. Coupling with acid **60** gave the respective maleimide **61**, which was then hydrogenated to produce methyllycaconitine analogue **62**.

As described before, aminonitriles can be obtained through photochemical protocols. The Opatz group reported a highly active catalyst system for the metal-free visible light aerial photocyanation of tertiary aliphatic amines in 2016. This system was applied in the syntheses of the alkaloid (±)-crispine A and both enantiomers of tetraponerines (−)-T7 and (−)-T8 (Scheme 7).[7b] The synthesis of (±)-crispine A, a THIQ alkaloid that was isolated from *Carduus crispus*, a curly plumeless thistle,[7b,33] commenced with commercially available homoveratrylamine (**64**), which was converted to the corresponding pyrrolidine **65** in two steps. Photocyanation afforded α-aminonitrile **66** in 78% yield. *In-situ* generation of iminium ion **67** with $AgBF_4$ and subsequent cyclization in hot trifluoroacetic acid (TFA) afforded (±)-crispine A (**68**) with an overall yield of 70%.[7b] Tetraponerines **74** and **75** are tricyclic alkaloids with an aminal structure isolated from the poison of *Tetraponera (Pseudomyrmecinae)* ants.[34] The synthesis started with the organocatalytic enantioselective preparation of key intermediate **70** in four steps from piperidine **69**. Reductive amination of **70** yielded amine **71**, which was converted to a mixture of the desired targets in a one-pot procedure via chemoselective photocyanation, iminium ion generation and *N*-deprotection. Separation via flash chromatography afforded (−)-T7 (**74**) in 32% and (−)-T8 (**75**) in 13% yield.

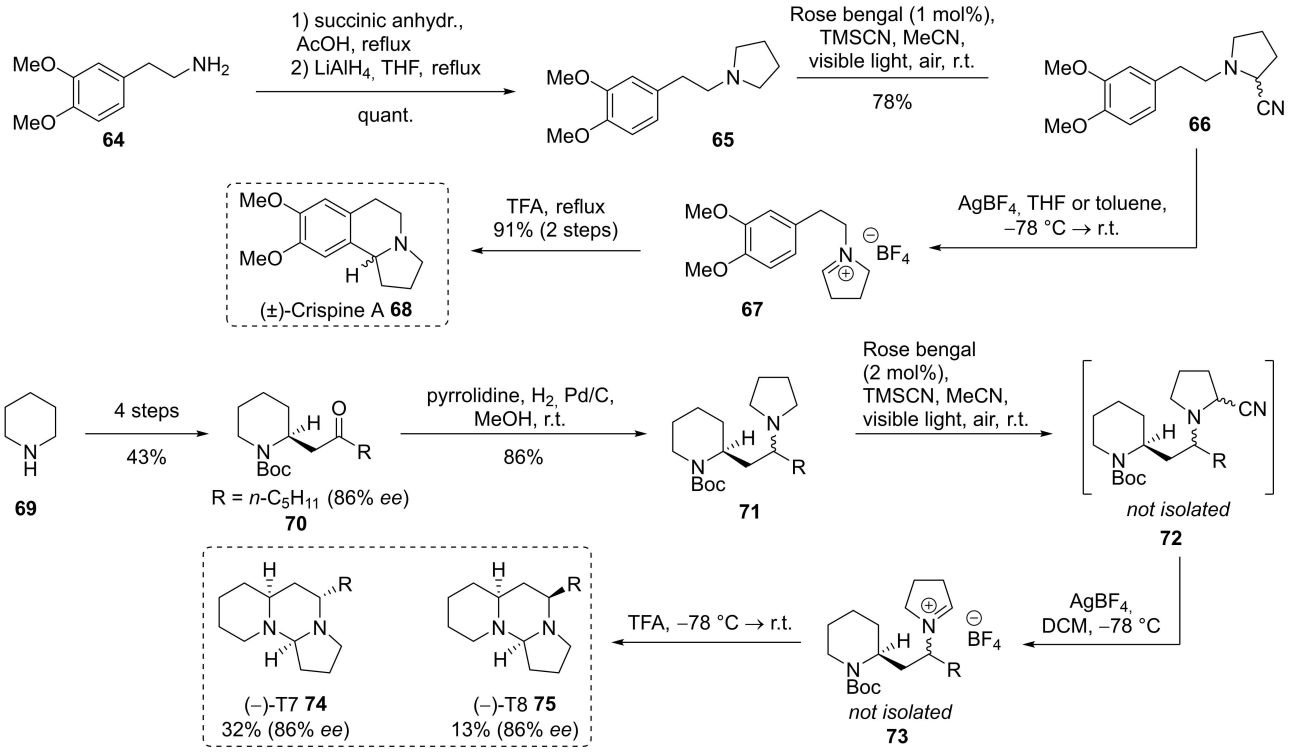
Furthermore, this protocol[7b] was used in the postfunctionalization of natural products as demonstrated in the synthesis of nicotine derivative **78** through photochemically generated 5-cyanonicotine (**77**). This precursor was then subjected to a so-called Bruylants reaction with *n*-pentylmagnesium bromide, providing the formal product of a C–H alkylation (see Scheme 8). The Bruylants reaction will be discussed in the following section.

3.1.2. Bruylants Reaction

The reaction of an α-aminonitrile with a Grignard reagent to obtain an α-substituted amine in a formal cyanide displacement, is known as the Bruylants reaction.[35] Syntheses of aliphatic amines in this fashion are common, but reactions with aryl Grignard reagents[36] to yield tertiary aryl amines or

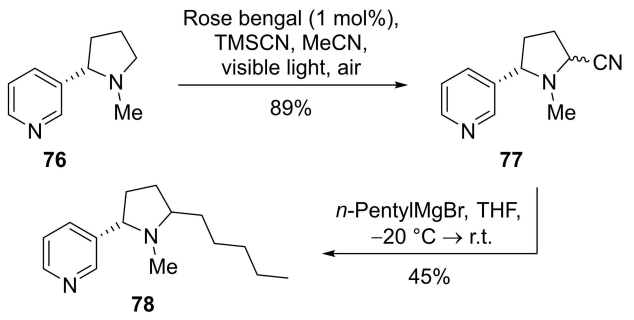


Scheme 6. Total synthesis of methyllycaconitine analogue **62** by Barker et al..

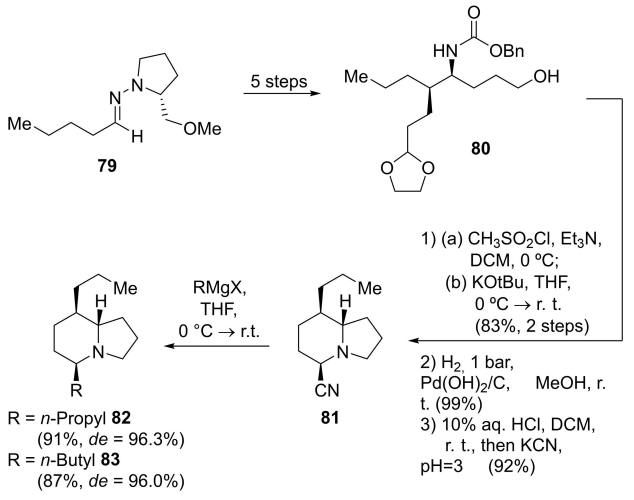


Scheme 7. Total synthesis of (±)-crispine A (**68**) and tetraponerines (−)-T7 (**74**) and (−)-T8 (**75**) by the Opatz group.

vinylic Grignard reagents to furnish allylic amines have also been reported.[37] The Bruylants reaction proceeds through initial elimination of cyanide to give an iminium ion which is trapped through rapid addition of the C-nucleophile (Grignard reagent or organozinc reagent).[37–38] Various total syntheses of natural products using the Bruylants reaction have



Scheme 8. Application of aminonitriles for late-stage modification to afford nicotine derivative **78** by the Opatz group.

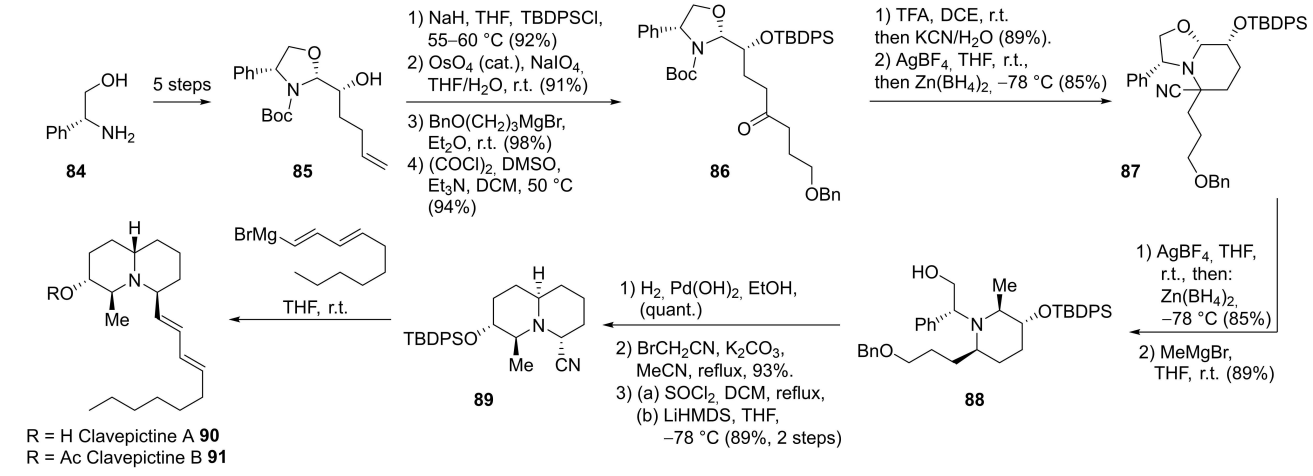


Scheme 9. Bruylants reaction affording alkaloids (−)-209I (**82**) and (−)-223 J (**83**) by Enders.

been reported in the literature, the enantioselective total syntheses of the indolizidine alkaloids 167B, 209D, (−)-205 A and (−)-235B by Polniaszek and Belmont in 1990 and 1991 being prominent historic examples.[39]

Enders and co-workers reported the first enantioselective synthesis of dendrobatid alkaloids (−)-209I and (−)-223 J in 2000, which can be isolated from the skin of members of the *Dendrobatidae* frog family such as the poison dart frog.[40] The sequence started from *n*-pentanal and included an asymmetric alkylation using Enders' *(R)*-1-amino-2-(methoxymethyl)-pyrrolidine (RAMP) auxiliary to furnish aminonitrile **81** (Scheme 9). This precursor was subjected to Bruylants conditions using *n*-propyl and *n*-butylmagnesium bromide to furnish alkaloids (−)-209I (**82**) and (−)-223 J (**83**) in 91% (96.3% *de*) and 87% (96.0% *de*) yield.

The Couty group reported a 15-step total synthesis towards clavepictines A and B (see Scheme 10), which were first isolated from the tunicate *Clavelina picta* in 1991 and show potent cytotoxic effects.[41] They relied on a variant of Husson's CN(*R,S*)-methodology[42] and started with an intermediate from the synthesis of (−)-desoxoprosopinine[43] which can be easily prepared from (*R*)-phenylglycinol (**84**) as a chiral auxiliary. After various transformations including treatment with TFA to induce intramolecular condensation, aminonitrile **87** was obtained. Reductive decyanation with $Zn(BH_4)_2$/$AgBF_4$, opening of the cyclic *N,O*-acetal with methylmagnesium bromide, hydrogenolysis using Pearlman's catalyst followed by a sequence of alkylation-cyanomethylation, and intramolecular alkylation furnished bicyclic aminonitrile **89** as a single stereoisomer. This could serve as a precursor for diverse clavepictine analogues as it only had to be subjected to a Bruylants reaction with the corresponding Grignard reagent.



Scheme 10. Total synthesis of clavepictines A (**90**) and B (**91**) reported by the Couty group.

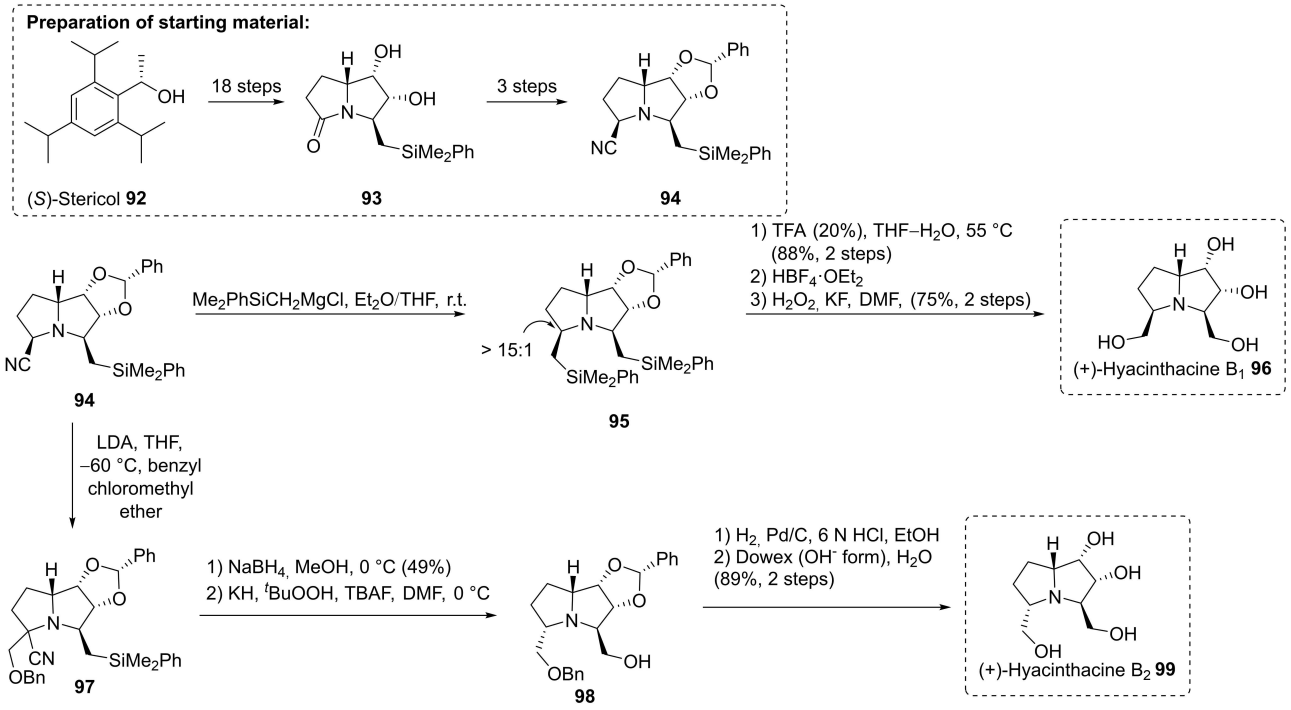
Hyacinthacines are also accessible through aminonitrile chemistry, which was demonstrated in 2013 by Delair and co-workers, who reported the total synthesis of hyacinthacines B_1 and B_2 (Scheme 11).[44] In view of their polyhydroxylated pyrrolizidine structure, they can be considered as imino sugars which are currently among the most extensively studied glycosidase inhibitors for drug development.[45] Hyacinthacines were first isolated in 1999 by Asano from bulbs of the Spanish squill *Scilla campanulata* and show strong biological activities as selective inhibitors of β-glucosidase and β-galactosidase.[44,46] The synthesis of (+)-hyacinthacine B_1 started from the commercial chiral auxiliary (*S*)-stericol® (**92**) which was converted into **93** in 18 steps. Suitable selection of *cis*-hydroxyl protecting groups and reductive cyanation to the corresponding aminonitrile **94** were extensively studied. In the next step, a Bruylants reaction with dimethylphenylsilymethylmagnesium chloride was performed to yield **95**. Acetal cleavage with TFA followed by challenging Tamao-Fleming oxidation, due to potential amino group oxidation, afforded (+)-hyacinthacine B_1 (**96**). For the total synthesis of (+)-hyacinthacine B_2 (**99**), lithiation of **94** with LDA followed by alkylation with BOMCl gave corresponding aminonitrile **97** in high diastereomeric purity. Reduction with $NaBH_4$, subsequent double deprotection through hydrogenolysis in acidic medium and deprotonation with basic ion exchange resin furnished (+)-hyacinthacine B_2 (**99**).

3.2. Deprotonated α-Aminonitriles and their Use as α-Carbanion and Acyl-Anion Equivalents

Pioneering examples of reactions of deprotonated α-aminonitriles were reported by Boekelheide and Popp[47] who described alkylations and addition reactions of deprotonated Reissert compounds in the 1950s. Hauser, Taylor and Ledford[48] then described the α-alkylation of potassium salts of *N,N*-dialkylated α-arylaminonitriles and the subsequent base-induced elimination of HCN from their respective substitution products to form enamines. The latter could be either reduced to tertiary amines or hydrolyzed to form ketones. These works established deprotonated α-aminonitriles as readily available and inexpensive acyl anion equivalents along with the *O*-protected cyanohydrins[12b,49] and the 1,3-dithianes.[50] For a comprehensive overview on the chemistry of deprotonated α-aminonitriles, the reader may be referred to a 2009 review of Opatz.[2b]

3.2.1. α-Carbanion Equivalents

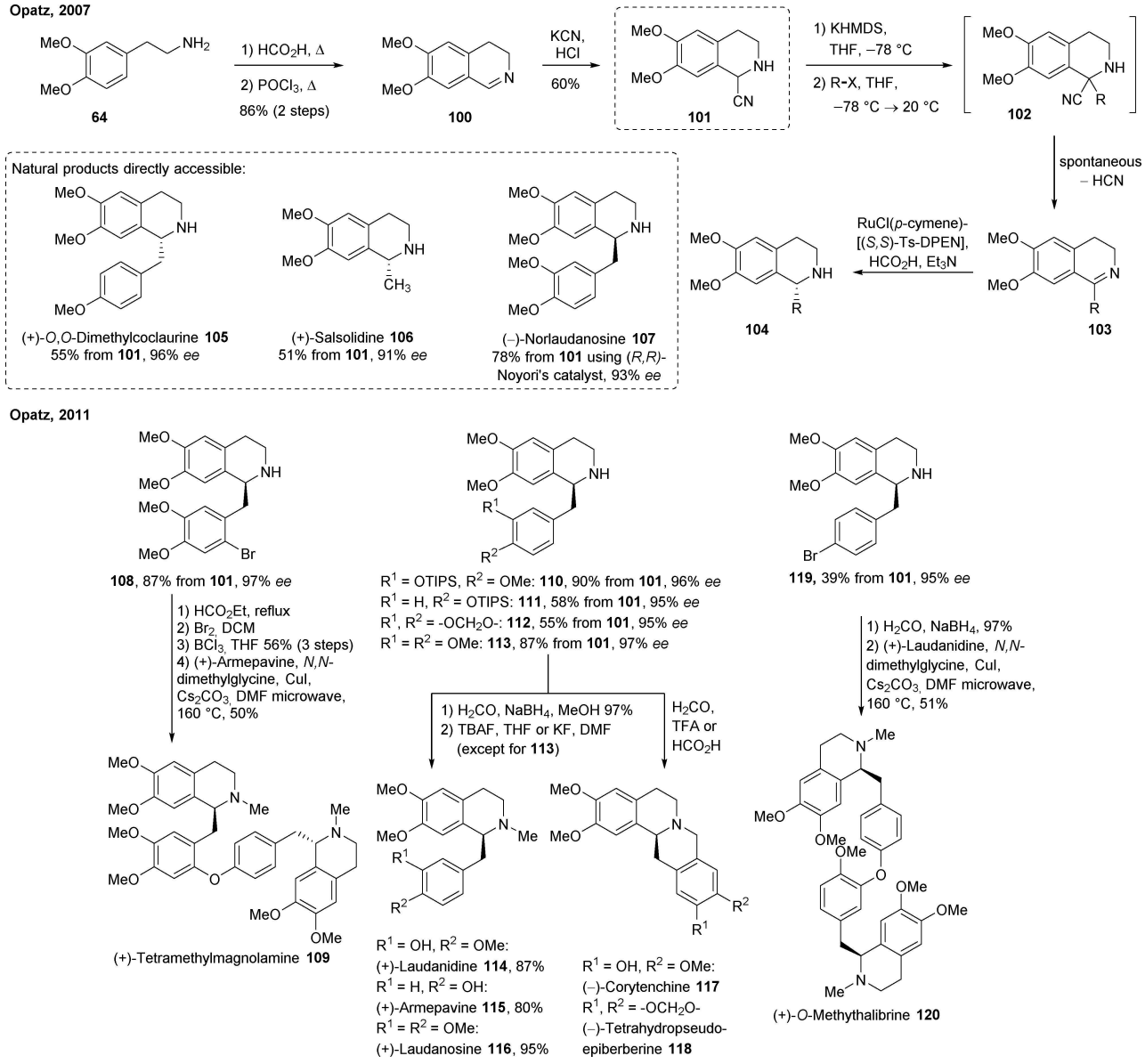
Opatz et al. established a general protocol for the quantitative, non-destructive α-deprotonation of Strecker products derived from aromatic or α,β-unsaturated aldehydes and primary amines or even ammonia. Using this protocol, the readily available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-car-



Scheme 11. Total synthesis of hyacinthacines B_1 (**96**) and B_2 (**99**) by Delair et al.

bonitrile (**101**) could be employed as an α-aminocarbanion equivalent in a number of alkaloid syntheses (see Scheme 12). Compound **101** proved to be very stable against *retro*-Strecker reaction upon deprotonation with KHMDS and subsequent α-alkylation with an electrophilic reagent in THF at −78 °C. Cyanide elimination in the alkylated product occurred spontaneously, yielding the corresponding 3,4-dihydroisoquinolines **103**. The latter could be subjected to an asymmetric transfer hydrogenation with Noyori's catalyst without prior work-up to give highly enantioenriched products **104**.[51] As the tetrahydroisoquinoline scaffold is a recurring motif in a wide range of natural products, the THIQ alkaloids (+)-*O*,*O*-dimethylcoclaurine (**105**), (+)-salsolidine (**106**) and (−)-norlaudanosine (**107**) were directly accessible and *N*-methylated THIQ alkaloids **114**–**116**, tetrahydroprotoberberines **117** and **118** and bisbenzylisoquinolines **109** and **120** were available after a few further transformations.

This reaction sequence was later proven to be useful for the enantioselective synthesis of (−)-dihydrocodeine (**133**) and the formal synthesis of morphinan alkaloids by the same group, which was the most efficient asymmetric approach to morphinan alkaloids reported so far.[52] A xylochemical version



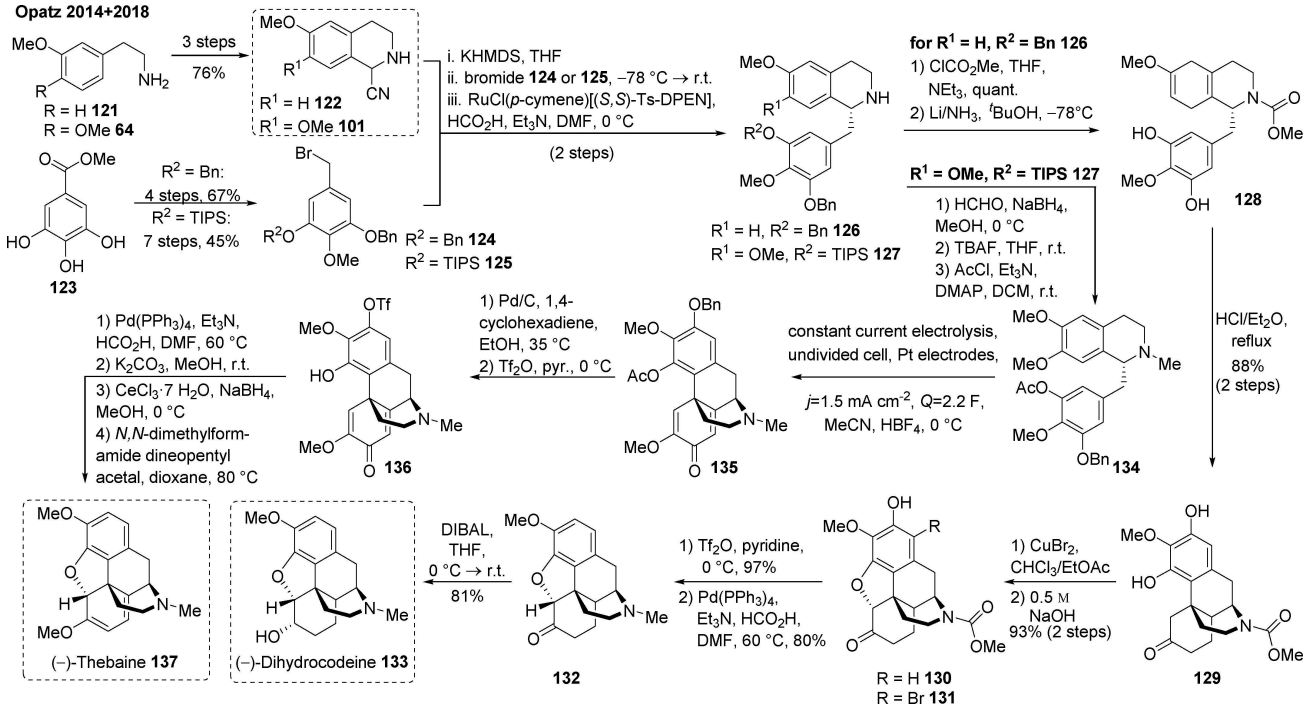
Scheme 12. Overview of accessible natural products from **101** developed by Opatz et al.

of this total synthesis was also developed, which exclusively uses wood-derived starting materials instead of the usual petrochemistry-derived building blocks.[53]

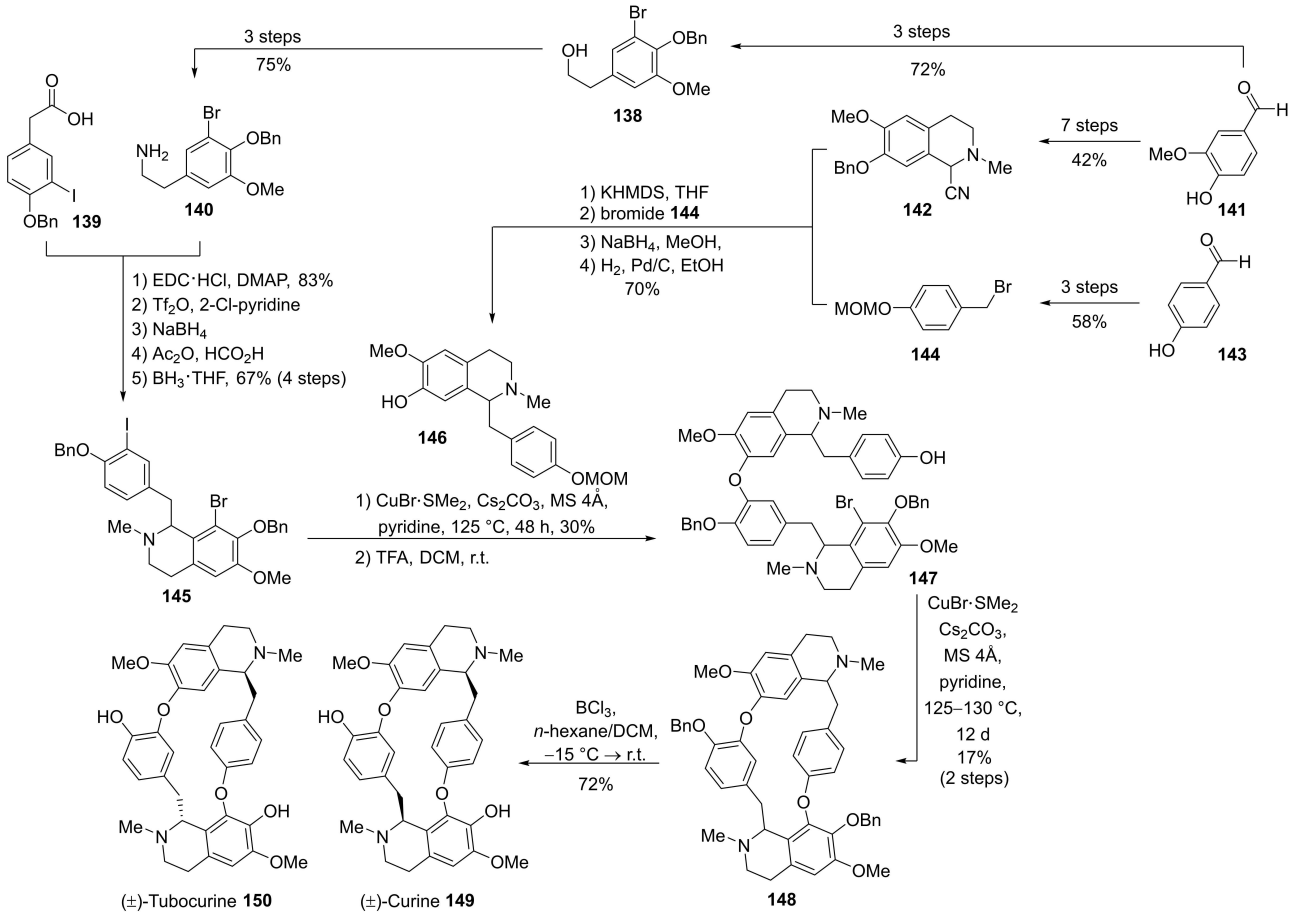
Later, this general route was combined with anodic C–C aryl coupling to provide a biomimetic access to the natural product (−)-thebaine (**137**)[54] and the semisynthetic opioid (−)-oxycodone (see Scheme 13).[55] As starting materials for these syntheses, bromides **126** and **125** were prepared from methyl gallate **123**. Aminonitriles **122** and **101**, available from homoveratrylamine (**64**) and 2-(3-methoxyphenyl)ethylamine (**121**) in three steps, were alkylated according to the established protocol with bromides **124** and **125** to yield the (−)-(*S*)-norlaudanosine derivatives **126** and **127**. (−)-Dihydrocodeine (**133**) was accessible following the Beyerman strategy:[56] After alkoxycarbonylation and Birch reduction of **126** to **128**, Grewe cyclization resulted in the morphinan skeleton of **129** carrying two new stereogenic centers with defined geometry. After bromination of the enolizable ketone, the ether bridge of **130** was closed. Partial bromination of C-1 at this stage was undone by Pd-catalyzed detriflylation/dehalogenation. Final reduction of the carbonyl group in **132** afforded (−)-dihydrocodeine (**133**) in 31% overall yield and 95% *ee* over 12 linear steps.

On the route leading to thebaine, regio- and diastereoselective anodic aryl-aryl coupling established the morphinan ring system of **135**, which was debenzylated and deacetylated employing a transfer hydrogenation with 1,4-cyclohexadiene. The superfluous hydroxy group was removed through Pd-catalyzed transfer hydrogenation of the corresponding triflate **136**. Deacetylation, selective 1,2-reduction of the carbonyl group under Luche conditions and E-ring closure through S_N2'-substitution with *N*,*N*-dimethylformamide dineopentyl acetal[57] yielded (−)-thebaine (**137**) in 93% *ee*. Through variation of the final steps and inclusion of a [4+2] cycloaddition of photogenerated singlet oxygen, the opioid drug (−)-oxycodone is accessible.

In 2016, Opatz et al. reported the first racemic total synthesis of (±)-tubocurine (**150**) and (±)-curine (**149**) starting from vanillin (**141**) (see Scheme 14.).[58] The latter was transformed into both required precursors **140** and **142** in six and seven steps. Alkylation of **140** with bromide **144** according to the established protocol and subsequent debenzylation yielded benzylisoquinoline **146**. Coupling of phenylacetic acid derivative **139** and phenylethylamine **140** gave the cyclization precursor, which was further converted into **145** by sodium borohydride reduction and subsequent *N*-formylation. The final ring closing strategy for the target molecules was build on two subsequent Ullmann couplings of the benzylisoquinoline subunits **145** and **146**. Debenzylation of the coupling products yielded (±)-tubocurine (**150**) and (±)-curine (**149**) after 15 linear steps. As tubocurine can be converted to the arrow poison tubocurarine, the present



Scheme 13. Enantioselective total syntheses of (−)-dihydrocodeine (**133**) and (−)-thebaine (**137**) by Opatz et al..



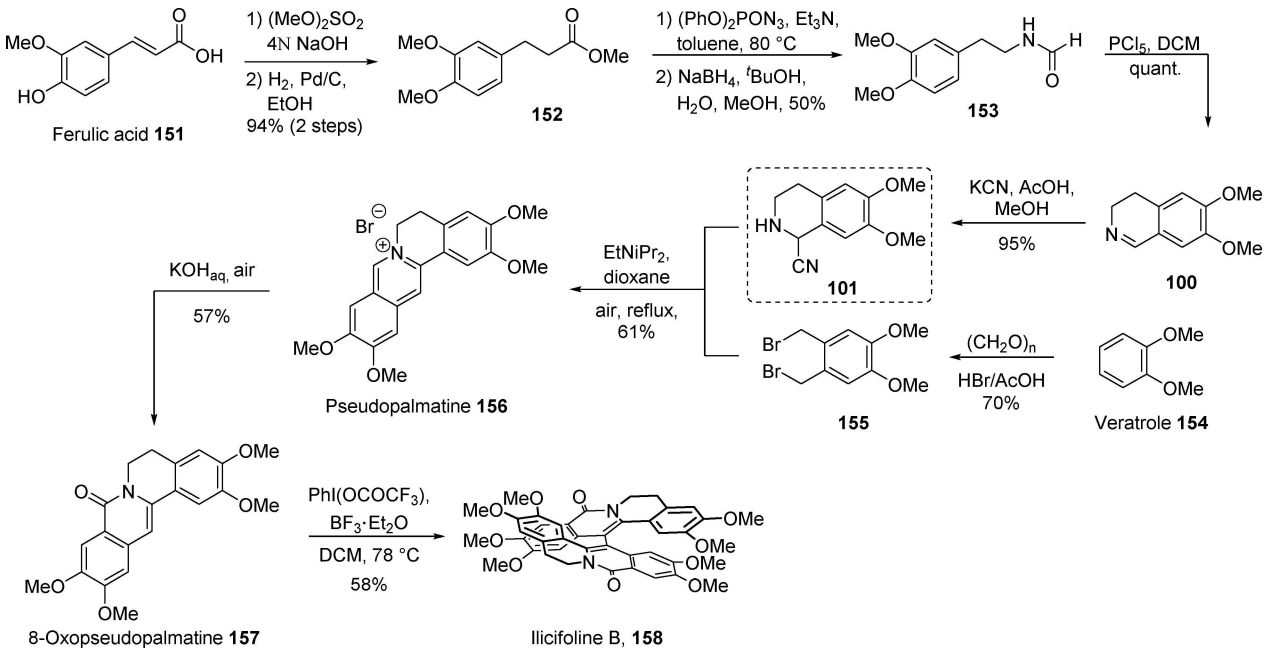
Scheme 14. Total synthesis of (±)-tubocurine (**150**) and (±)-curine (**149**) reported by the Opatz group.

approach represents the first formal total synthesis of this famous alkaloid.

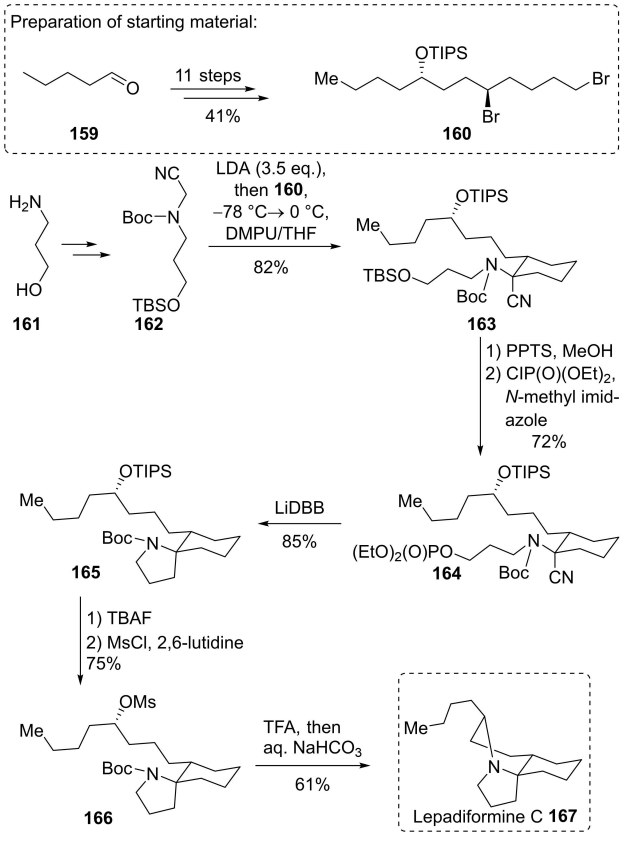
In a xylochemical approach towards ilicifoline B (Scheme 15), the Opatz group converted ferulic acid (**151**), available from various types of biomass, into the well-known α-aminonitrile **101** after a six-step protocol involving a Curtius rearrangement of **152** to form **153**.[53] Veratrole (**154**), a pyrolysis product of wood, was subjected to double bromomethylation with formaldehyde and HBr to produce dibromide **155**.

Compounds **101** and **155** were converted into the berberine alkaloid pseudopalmatine (**156**) in a cascade involving spirocyclization, α-deprotonation, Stevens rearrangement, dehydrocyanation, and oxidation. Aerial oxidation in alkaline solution produced lactam **157**, which was subsequently dimerized with PIFA/$BF_3 \cdot Et_2O$ to yield ilicifoline B (**158**).

Lepadiformine A was first isolated by Biard et al. from the ascidian *Clavelina lepadiformis* in 1994 (see Scheme 16). The synthetic challenge arising from the fused tricyclic structure of the lepadiformine alkaloids and their potential antiarrhythmic properties[59] has inspired several groups[60] to perform synthetic studies on these intriguing natural products. Rychnovsky's strategy[61] for the synthesis of lepadiformines A, B, and C (**167**) envisioned a route where all three rings were introduced in quick succession from similar acyclic dibromides, which were stereoselectively synthesized beforehand. Synthesis of the α-aminonitrile **162** proceeded through TBS-protection of 3-amino-1-propanol (**161**), cyanomethylation and *N*-Boc-protection. The obtained aminonitrile **162** was reacted with dibromide **160** in a one-pot double nitrile anion alkylation. Desilylation of cyclic aminonitrile **163** was followed by *O*-phosphorylation to give cyclization precursor **164**. Spirocyclization to **165** proceeded by diastereoselective ring closure after reductive decyanation with Freeman's reagent (lithium di-*tert*-butylbiphenylide, LiDBB) through the α-lithiated amine. Third and final ring closure proceeded via S_N2-reaction of *N*-deprotected mesylate **166**. Lepadiformine C (**167**) was obtained in 9% overall yield over 18 linear steps. The optical rotation of the hydrochloric salt of the obtained product had the opposite sign compared to the hydrochloric salt of the



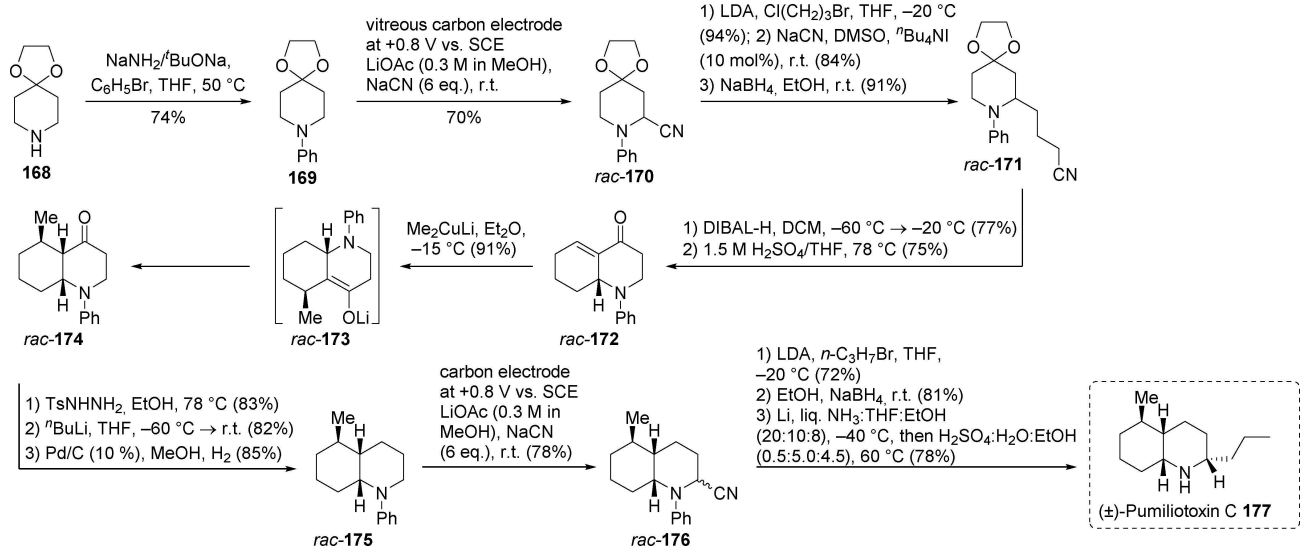
Scheme 15. Total synthesis of ilicifoline B (**158**) by Opatz et al..



Scheme 16. Total synthesis of lepadiformine C (**167**) by Rychnovsky.

natural product, which indicates that the enantiomer of natural lepadiformine C had been synthesized. This disproved the previous assumption that lepadiformine A, B and C were all of the same stereochemistry. A later synthesis of both enantiomers[62] provided further confirmation that lepadiformine C indeed has an enantiomeric core to its congeners, lepadiformines A and B, suggesting that the producing organism is capable of enantiodivergent biosynthesis.

Hurvois and co-workers reported a racemic total synthesis of (±)-pumiliotoxin C (**177**) in 15 steps from commercially available starting materials in 2005 (Scheme 17).[63] Pumiliotoxin C is the most abundant representative of the decahydroquinoline alkaloid class in natural sources, which was first isolated in 1969 from the skin extracts of the Panamanian frog *Dendrobates pumilio*.[64] The α-aminonitrile intermediates, required for C–C bond formation adjacent to the nitrogen atom, were prepared electrochemically. Initiating the synthesis with 4-piperidone ethylene ketal, α-aminonitrile **170** was obtained in two steps via Caubère coupling followed by anodic cyanation. A sequence of deprotonation and alkylation furnished a bifunctional aminonitrile which was further transformed into protected nitrile **171**. Mild reduction of the terminal nitrile group using DIBAL–H, and exposure of the resulting aldehyde to acidic conditions, afforded enone **172**. Conjugate addition of a lithium dimethylcuprate was applied to introduce the C-5 methyl group and furnished octahydroquinoline **174** with excellent diastereoselectivity (*de* ≈ 99 %) in 91 % yield. Removal of the undesired carbonyl moiety at C-4

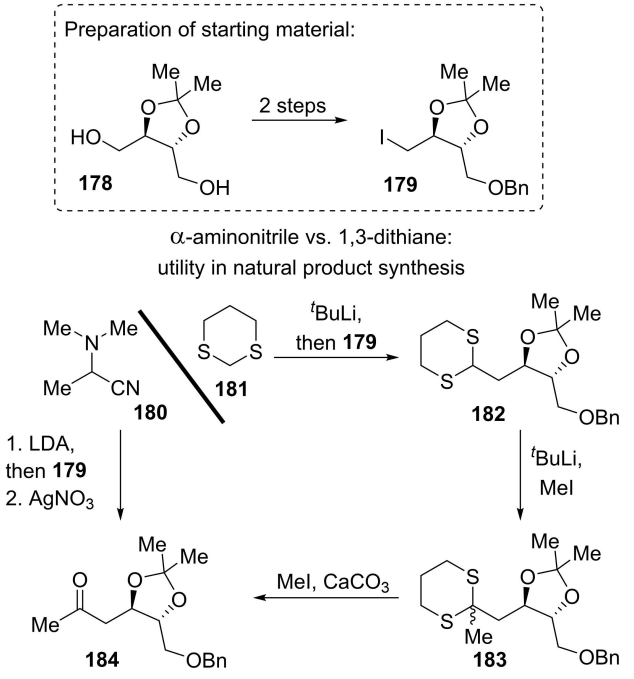


Scheme 17. Total synthesis of (±)-pumiliotoxin C (**177**) reported by Hurvois et al.

through Shapiro reaction and reduction of the resulting alkene afforded decahydroquinoline **175** which was again converted to the corresponding aminonitrile **176** via highly regioselective anodic cyanation. Deprotonation of **176** using LDA, alkylation with propyl bromide, reduction of the aminonitrile moiety under retention of the C-2 configuration followed by *N*-dearylation under Birch conditions afforded (±)-pumiliotoxin C (**177**) in an overall yield of 5 %.

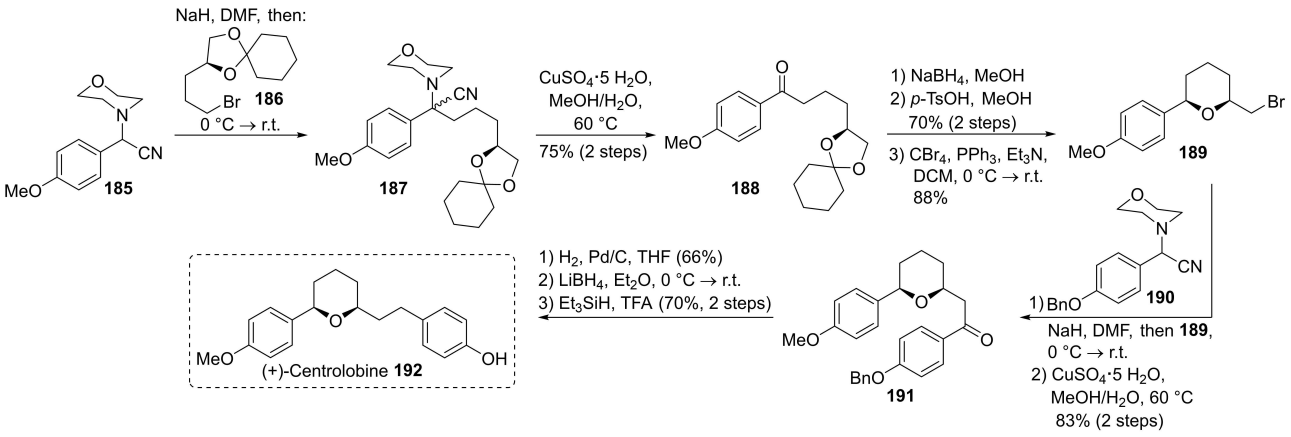
3.2.2. Acyl-Anion Equivalents

The utility of α-(dimethylamino)propionitrile (**98**) in natural product synthesis was demonstrated - among others – in an attempt to synthesize the 1-*epi*-aglycon of cripowellins A and B by Enders et al. in 2005 (see Scheme 18).[65] These amaryllidaceae alkaloids bearing an exceptional [5.3.2]-bicyclic core structure were isolated by researchers of the Bayer company in 1997[66] from bulbs and roots of the lily *Crinum powellii.* One retrosynthetic analysis suggested a keto acid as one of two building blocks for an intramolecular Buchwald-Hartwig arylation precursor to close the ten-membered ring. Even though this specific route eventually did not lead to the desired target compound, it is a good example for how α-aminonitriles might can replace 1,3-dithianes in natural product synthesis as acyl anion equivalents, as both routes were tested in parallel. The authors demonstrated that their reaction sequence was considerably shortened whilst the overall yield of ketone **184** was increased when α-(dimethylamino)-propionitrile (**180**) was employed. This is due to the fact that methylation to afford **183** was no longer required and hydrolysis was possible *in-situ.*



Scheme 18. Comparison of aminonitrile **180** and dithiane **181** approach by Enders to afford the aglycon of cripowellins A and B.

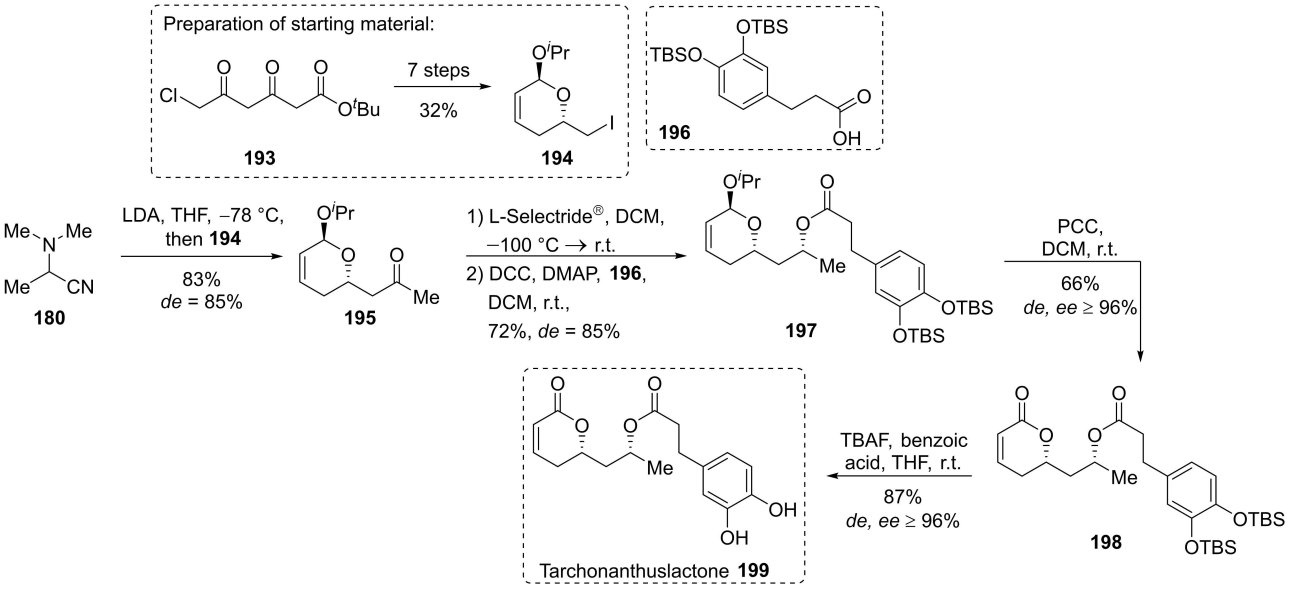
The centrolobines are a group of diarylheptanoids bearing a 2,6-disubstituted tetrahydropyran ring (see Scheme 19). After these compounds raised interest in multiple fields of medicinal chemistry,[67] they became subject to several total synthetic attempts.[68] (+)-Centrolobine (**192**) was first described in 1970 from the tree *Centrolobium tomentosum* by the



Scheme 19. Total synthesis of (+)-centrolobine (**192**) by Aidhen and Sudarshan.

brazilian group around Gottlieb.[67a] Aidhen and Sudarshan presented a versatile and enantioselective synthetic route for (+)-centrolobine (**192**) that differed from the previous ones by making use of acyl anion chemistry.[69] In their total synthesis,[70] an α-aryl-4-morpholin-4-yl-acetonitrile **185** was alkylated in DMF, using sodium hydride as a base, with bromide **186** derived from D-mannitol. After hydrolysis of crude **187** using $CuSO_4 \cdot 5H_2O$ in aqueous methanol at 60 °C, aryl ketone **188** was obtained in 75% yield. In the following step, the latter was reduced to a diastereomeric mixture of benzylic alcohols which underwent stereoconvergent intramolecular cyclization upon treatment with *p*-TsOH to give the *cis*-2,6-disubstituted tetrahydropyran **189**. After Appel bromination, a benzyl protected α-aryl-4-morpholin-4-yl-acetonitrile **190** was used to incorporate the second aryl residue to give **191**. Debenzylation and decarbonylation closed the synthesis of (+)-centrolobine (**192**).

Tarchonanthuslactone (**199**) was isolated by Bohlmann[71] in 1979 from the leaves of *Tarchonanthus trilobus* and was reported to lower plasma glucose levels in diabetic rats.[72] Therefore, it became the target of several total synthesis attempts.[73] In the synthesis of Enders et al. (Scheme 20),[74] α-(dimethylamino)propionitrile (**180**) proved to be a reliable acetyl anion equivalent after deprotonation with LDA and subsequent introduction of previously synthesized iodide **194**. In this case, hydrolysis even occurred during column



Scheme 20. Enders' total synthesis of tarchonanthuslactone (**199**).

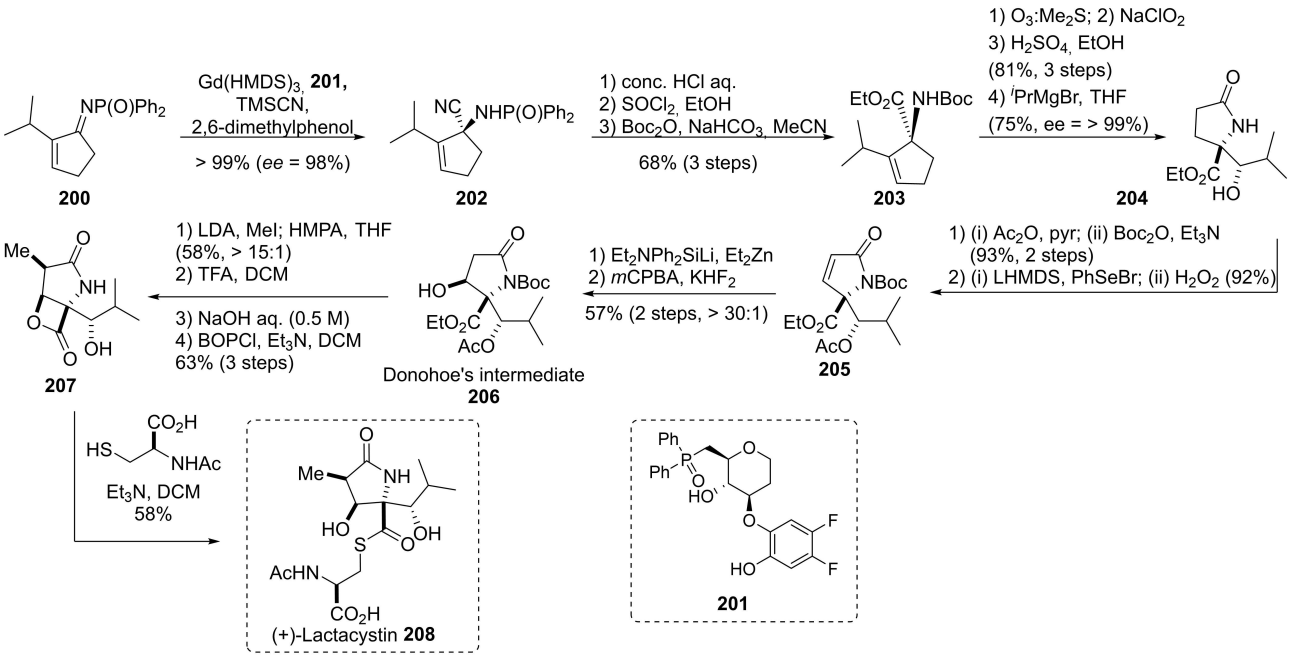
chromatography of the crude alkylated α-aminonitrile product on silica to give the desired alkylation product **195** in 83% yield without the usually required work-up with aqueous $AgNO_3$ or $CuSO_4$. The product thus obtained was *syn*-selectively reduced to an alcohol **197** using L-Selectride® and directly esterified with acid **196** under Steglich conditions. Treatment with pyridinium chlorochromate regenerated the α, β-unsaturated *δ*-lactone moiety of **198**. Final desilylation gave the target compound tarchonanthuslactone (**199**) in a respectable 21% overall yield after twelve linear steps.

3.3. Hydrolysis

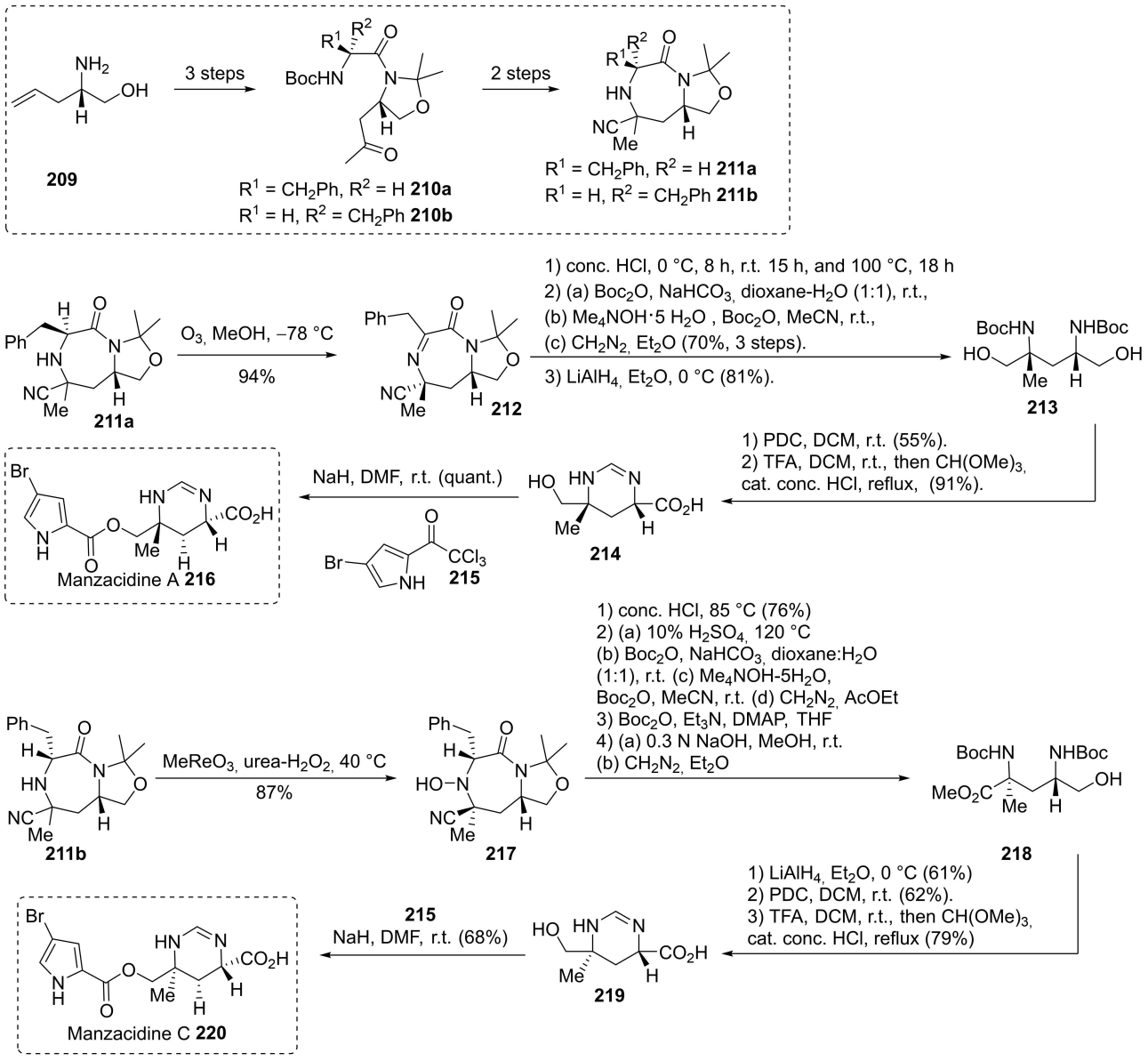
As described before, the Strecker reaction is the earliest multicomponent reaction discovered. The α-amino acid alanine was the first synthesized in this way, even before its isolation from nature.[1] The reaction mechanism involves the formation of an α-aminonitrile, the nitrile moiety of which can be hydrolyzed to either furnish α-amino amides or α-amino acids depending on the conditions applied.[3d,75] Asymmetric Strecker reactions were extensively investigated during the last decades.[2c,d] Hydrolyses of α-aminonitriles were applied for instance in the route to (−)-antirhine[76] in 1986, the major alkaloid of *Antirhea putaminosa*[77] or in the total synthesis of the marine bis(indole)alkaloid (±)-dragmacidin in 1994.[78]

An example for the Strecker reaction applied in natural product syntheses is the total synthesis of the selective and potent 20S proteasome inhibitor (+)-lactacystin (**208**), which was first isolated from *Streptomyces sp.* in 1991.[79] The Shibasaki group reported a catalytic asymmetric total synthesis of (+)-lactacystin in 2006 (see Scheme 21) via catalytic enantioselective Strecker reaction of ketoimines using a gadolinium-based catalyst system.[80] Its three chiral centers on a γ-lactam core render this natural product an attractive target for stereoselective total synthesis. In this protocol, the quaternary C-5 center was constructed in an early stage of the sequence. Starting from commercially available isovaleraldehyde, ring closing metathesis, oxime formation and phosphinoylimine formation yielded ketoimine **200**, which was subject to extensive optimization studies for the enantioselective Strecker reaction to furnish amidonitrile **202**. The latter was further converted to the corresponding amino acid derivative **203** in three steps before being subjected to ozonolysis, oxidation, lactam formation and stereoselective reduction, affording **204** enantio- and diastereoselectively. A four-step sequence involving chemoselective protecting group operations, selenenylation, elimination and silyl conjugate addition followed by Tamao oxidation afforded precursor **205**, which was oxidized by *m*CPBA to furnish Donohoe's intermediate **206**. This could be converted to (+)-lactacystin by removal of the Boc protecting group, hydrolysis of the ethyl ester under basic conditions and lactone formation with BOPCl, as well as treatment with *N*-acetyl-L-cysteine in the last step.

Ohfune and co-workers described the stereoselective total syntheses of manzacidines A and C (see Scheme 22) in



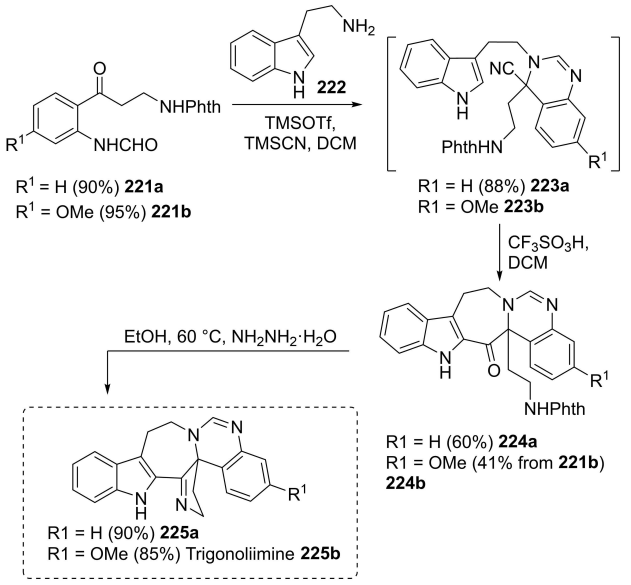
Scheme 21. Total synthesis of (+)-lactacystin (**208**) by the Shibasaki group.



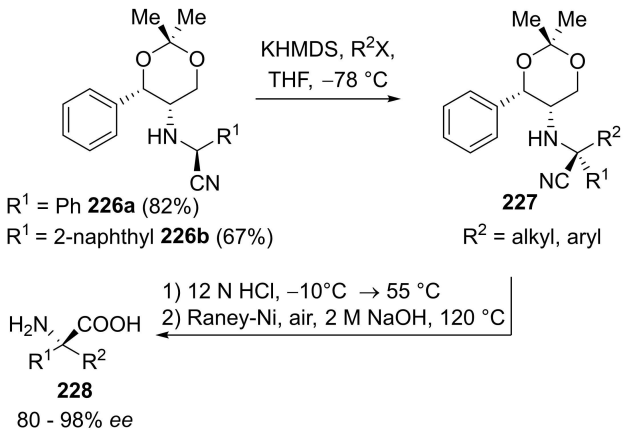
Scheme 22. Total syntheses of manzacidines A (**216**) and C (**220**) by Ohfune et al..

2000.[81] Those bromotetrahydropyrimidine alkaloids were first isolated from an Okinawan marine sponge *Hymeniacidon sp.* in 1991.[82] They possess a unique ester-linked bromopyrrolecarboxylic acid moiety as well as a 3,4,5,6-tetrahydropyrimidine ring and were found to be pharmacologically active as α-adrenoceptor blockers, antagonists of serotonergic receptors as well as actomyosin ATPase activators, which they share with other marine bromopyrrole alkaloids.[81–82] The synthesis started from readily available (2*S*)-allylglycinol (**209**) via chemoselective removal of the Boc group followed by conversion to the corresponding aminonitriles **211a+b**. Further transformations involved oxidation with ozone to imino ketone **212**, which, after hydrolysis of the nitrile group, esterification and reduction, furnished diol **213**. Oxidation and treatment with TFA and methyl orthoformate gave tetrahydropyrimidine **214**, which was esterified with **215** to afford manzacidine A (**216**) in 14 steps and an overall yield of 14%. Manzacidine C (**220**) was obtained starting from aminonitrile **211b** in 15 steps with an overall yield of 3.5%.

A rapid total synthesis via a Strecker/Houben-Hoesch sequence to (±)-trigonoliimine A has been described by the group of Hao in 2013 (see Scheme 23).[83] (±)-Trigonoliimine



Scheme 23. Total synthesis of (±)-trigonoliimine (**225 b**) by the Hao group.

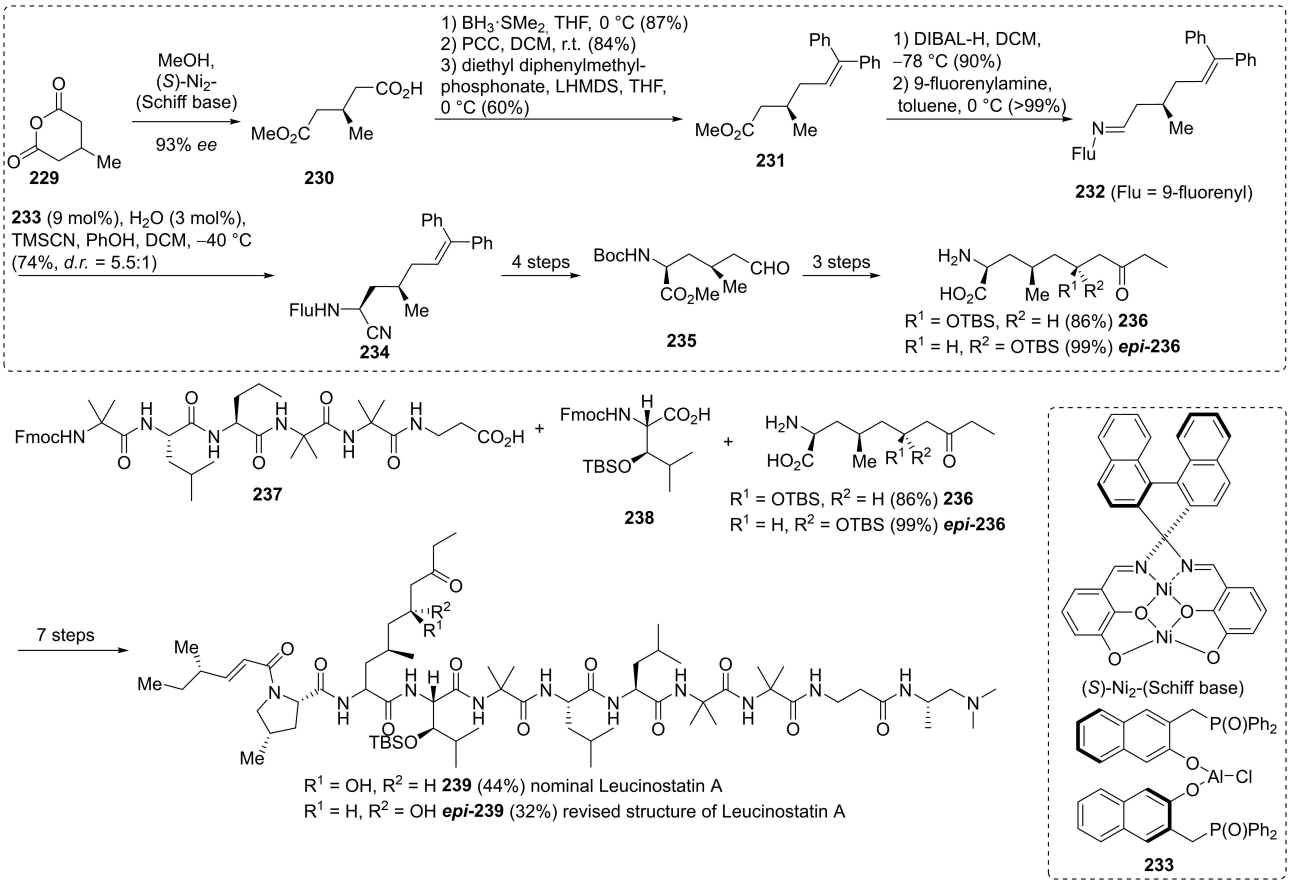


Scheme 24. Total synthesis of α-quaternary amino acids 158 developed by the Opatz group.

A was isolated in 2010 from the extracts of the leaves of *Trigonostemon lii* and shows modest anti-HIV-1 activity.[84] Therefore, it was target of a series of total syntheses including the groups of Tambar, Movassaghi, and others.[85] Ketones **221 a + b** were subjected to Strecker conditions in what turned out to be the most challenging step of this synthesis protocol, as Strecker reactions applied to ketones and aliphatic amines, in contrast to its application to aldehydes, often require the use of preformed imines[86] or high pressure[87] conditions. Unstable aminonitriles **223 a + b** were subjected to Houben-Hoesch-type cyclization affording seven-membered ring ketones **224 a + b**. Treatment with hydrazine in ethanol afforded (±)-trigonoliimine A (**225 b**) in 85 % yield.

As a general approach to α-quaternary amino acids, the Opatz group reported an auxiliary-controlled enantioselective synthesis using a sequence of alkylation of deprotonated α-aminonitriles and their subsequent hydrolysis in 2015 (see Scheme 24).[88] For controlling the stereoselectivity of the alkylation step, the group used Weinges' auxiliary which had already been applied successfully in the diastereoselective crystallization of Strecker products by Weinges and co-workers and was prepared on an industrial scale en route to the antibiotic chloramphenicol from acetone, nitromethane and formaldehyde and subsequent optical resolution. Reaction of its hydrochloride with an aromatic aldehyde and potassium cyanide afforded the aminonitriles **226 a + b** as single diastereomers after crystallization. Subsequent deprotonation and alkylation furnished α-quaternary aminonitriles **227** in high diastereoselectivity, which were then subjected to acidic hydrolysis and oxidative removal of the auxiliary. The products **228** were obtained in high optical purity without the need of intermediary purification.

Even peptide natural products like leucinostatin A, isolated from *Penicilium lilacinum* in 1973,[89] can be stereoselectively synthesized using aminonitrile chemistry. Shibasaki, Watanabe and co-workers reported a synthesis protocol involving a sequence of catalytic asymmetric nitroaldol reaction, diastereoselective thioamide aldol- and Strecker-type reaction as well as catalytic asymmetric alcoholysis in 2017 (see Scheme 25) The first task was the preparation of the 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD) segment (**236**) starting from 3-methylglutaric anhydride (**229**) involving catalytic asymmetric methanolysis[90] to afford half ester **230**. The carboxylic moiety was converted to a formyl group[90b] which was subjected to Wittig-type olefination furnishing trisubstituted olefin **231**. Transformation into imine **232** provided the starting material for a diastereoselective Strecker-type reaction to furnish aminonitrile **234**. Acidic hydrolysis, double protection of the nitrogen atoms and subsequent ozonolysis afforded **235** in four steps. **236** could be obtained in a three-step sequence involving catalytic asymmetric direct thioamide-aldol reaction, subsequent hydrolysis and conversion to the carboxylic acid. After solid-phase synthesis of peptide **237**, *threo*-β-hydroxyleucine (HyLeu) segment (**238**), synthesized from 2-nitroethanol through enantioselective nitroaldol reaction (not shown), and AHMOD segment (**236**) could be attached via standard peptide-coupling procedures, furnishing leucinostatin A (**239**) in four additional steps. After comparison with the reported NMR-data, the group concluded that the correct structure of leucinostatin A is the epimer of the previously reported structure[91] with *R*-configuration at the secondary alcohol moiety of the AHMOD segment.



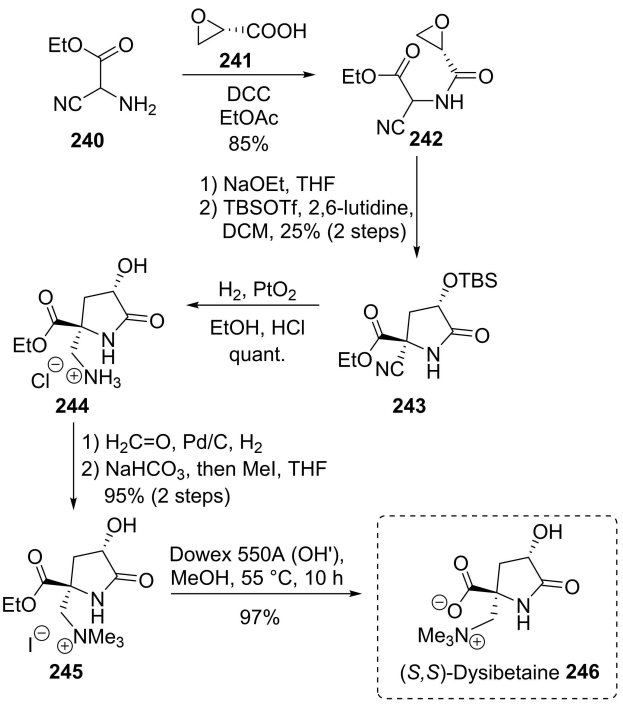
Scheme 25. Total synthesis of leucinostatin A (**239**) and stereochemical revision by Shibasaki and Watanabe.

3.4. Reduction of the Nitrile Moiety

The reduction of nitriles is one of the most economical routes available to produce primary amines. In total syntheses of natural products, the application of α-aminonitriles is a convenient method to selectively transform the available amine function first and after subsequent reduction of the nitrile function, producing a 1,2-diamine with a second amino group for further modification. The main challenge here is to overcome the reductive decyanation as a competing side reaction,[14b,92] which is the reason why catalytic hydrogenation of α-aminonitriles over Pd, Rh or Ni under high hydrogen pressure or the use of lithium aluminium hydride often proved insufficient in this context. Instead, low pressure hydrogenations of *N*-unsubstituted α-aminonitriles in alcoholic HCl over PtO_2[14a] is often the method of choice.

By providing the first total synthesis of both dysibetaine enantiomers (see Scheme 26), Snider and Gu[93] were able to elucidate the stereochemistry of naturally occurring (*S*,*S*)-dysibetaine (**246**) through comparison of the optical rotation of the natural product with that of the synthetic material. This natural product had been isolated by Sakai and co-workers from the marine sponge *Dysidea herbacea*.[94] The synthetic route leading to the (*S*,*S*)-configured product started with condensation of ethyl amino(cyano)acetate (**240**) and (*S*)-glycidic acid **241** under the action of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to yield glycidamide **242**. Intramolecular alkylation of **242** gave a hardly separable mixture of isomers, which were protected with TBDMSOTf to allow chromatographic separation of **243** and its undesired diastereomer. Hydrogenation of **243** over PtO_2 in ethanol containing 3–4 equiv. of conc. HCl allowed clean desilylation and nitrile reduction, affording a quantitative yield of hydroxy amine hydrochloride **244**. Reductive methylation with aqueous formaldehyde and Pd/C under 3.4 bar of H_2 gave an ammonium salt, which was neutralized and subsequently quaternized with excess MeI to afford 95% of trimethylammonium iodide **245**. Hydrolysis with Dowex 550 A resin in the hydroxide form in MeOH at elevated temperature provided 97% of pure (*R*,*R*)-dysibetaine (**246**).

In the 25-step racemic synthesis of dragmacidin E (**258**),[95] completed by Feldmann and Ngernmeesri[96] in 2011, a



Scheme 26. Total synthesis of (*S,S*)-dysibetaine **246**.

Witkop cyclization[97] of indole **248** was the first key step to produce an indole-spanning eight-membered ring **249**, which underwent Dieckmann cyclization[98] to yield ketone-bridged strained product **250** (see Scheme 27). The latter was hydrolyzed to give tricycle **251** as a diastereomeric mixture, which later converged to the same product. The ketone unit could be further transformed into α-aminonitrile **252** in a Strecker-like sequence yielding a 5 : 1 ratio of diastereomers in favour of the desired isomer. After chromatographic separation, the free amine of **252** was protected as its methyl carbamate to prevent *retro*-Strecker reaction. The nitrile was then reduced under Satoh-conditions[99] using a $NaBH_4/CoCl_2$ system and subsequent LiOH-mediated cyclization furnished spiro-2-imidazolone (**253**). For installation of the pyrazinone ring, the benzylic 6 position was oxidized by DDQ to yield a ketone, which was transformed to a mixture of azides using standard procedures. Azide reduction to the primary amine enabled coupling with acid chloride **255**. Pyrazinone formation was achieved through a two-step protocol applied to **256** involving cyclocondensation after deprotection of the primary amine at C-5. The obtained dihydropyrazinone product was oxidized with DDQ to deliver the stable pyrazinone-containing product **257**. The synthesis of **258** was completed by *O*-methylation and subsequent conversion with ammonia of the spiroimidazolone's urea unit into a guanidine-type structure and debenzylation under Stoltz's[100] conditions.

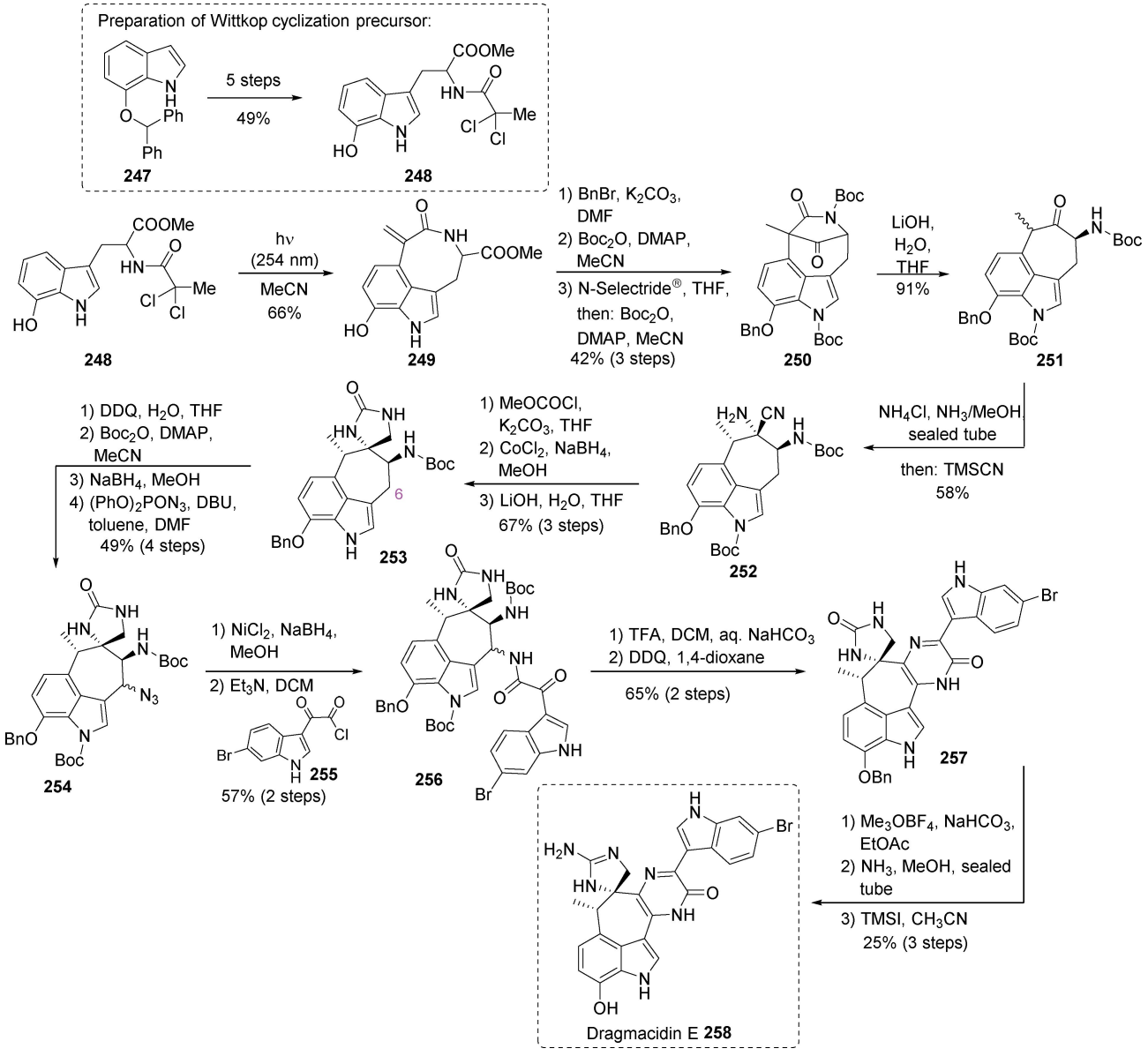
3.5. Rearrangements of α-aminonitriles

Starting from α-aminonitriles, nitrile-stabilized ammonium ylides are readily accessible by quaternization of the amine center and subsequent α-deprotonation. Compounds of this family are known to undergo [1,2]-Stevens[101] or [2,3]-Sommelet-Hauser[102] rearrangements, which proved to be useful in the construction of complex molecules. The Opatz group reviewed applications of these processes in 2014[2f] and applied a [1,2]-Stevens rearrangement in the one-pot synthesis of protoberberine alkaloids, which are characterized by the 5,6-dihydroisoquinolino[3,2-a]-isoquinolinium skeleton (Scheme 28).[103] After double *N*-alkylation of readily accessible 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**101**), the resulting ammonium ylides **155** readily underwent a Stevens rearrangement/decyanation/aromatization cascade when refluxed in 1,4-dioxane with excess of Hünig's base under air, giving the naturally occurring protoberberines pseudoepiberberine (**156**) and pseudopalmatine (**261**) in 44% and 54% yield, respectively.

As this personal account article only covers selected examples of aminonitriles in natural product total synthesis, there are still multiple interesting synthesis approaches not discussed in this respect, like for example the total synthesis of amiclenomycin by Marquet in 2002,[104] the approach to (−)-5,6,11-trideoxytetrodotoxin by the Shinada group in 2006,[105] the synthesis sequence furnishing quinolizidine 217 A by Danheiser[106] and others.[107] For a deeper insight into the topic, the reader may be referred to these references.

4. α-Aminonitriles as Natural Products

In addition to their considerable versatility in total synthesis, α-aminonitrile motifs themselves were identified to be part of highly complex bioactive natural products. Probably the most famous example is saframycin A, a member of the THIQ alkaloid family, which possesses a potent antiproliferative activity against various cancer cell lines as well as activity against gram-positive bacteria.[108] It was first isolated in 1977 from a streptothricin-producing strain of *Streptomyces lavendulae*.[109] Myers and co-workers reported an enantioselective total synthesis of saframycin antibiotics in 1999 using chiral α-amino aldehydes, which were protected at the aldehyde oxidation level through an α-aminonitrile-based *"C*-protecting group" .[110] This example shows that besides their potential reactivity, aminonitriles can also serve as useful protecting groups in long synthesis sequences. In 2018, Oikawa, Oguri and co-workers reported an impressive chemoenzymatic divergent total synthesis of saframycin A (**262**) and other THIQ derivatives with a pentacyclic scaffold such as (−)-jorunnamycin A (**263**) through merging chemical and *in-*



Scheme 27. Total synthesis of dragmacidin E (**258**) developed by Feldmann and Ngernmeesri.

vitro biological synthesis (Figure 2), two disciplines with complementary strengths and weaknesses that have only rarely been combined in natural product synthesis so far.[111] With this new strategy involving enzyme-catalyzed construction of the skeleton, the group gained rapid access (only one single day of reaction time) to such pentacyclic scaffolds needed, without the necessity to isolate and purify every intermediate as compared to chemical multistep approaches.

In 2007, the Garner group[112] reported the total synthesis of cyanocycline A[113] through a set of stereocomplementary metal-catalyzed multicomponent reactions involving azome-

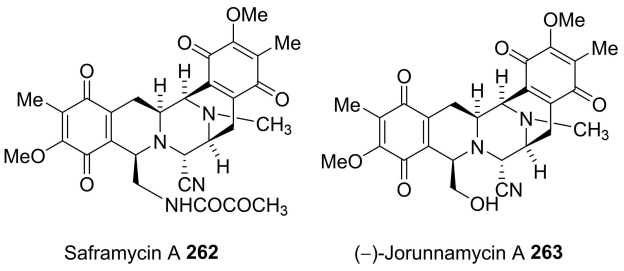
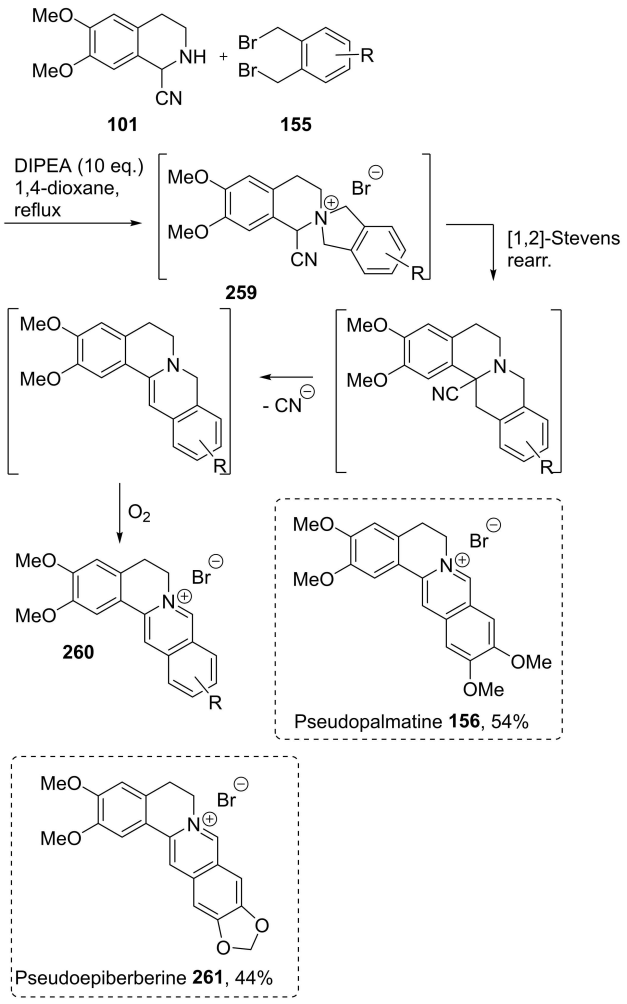
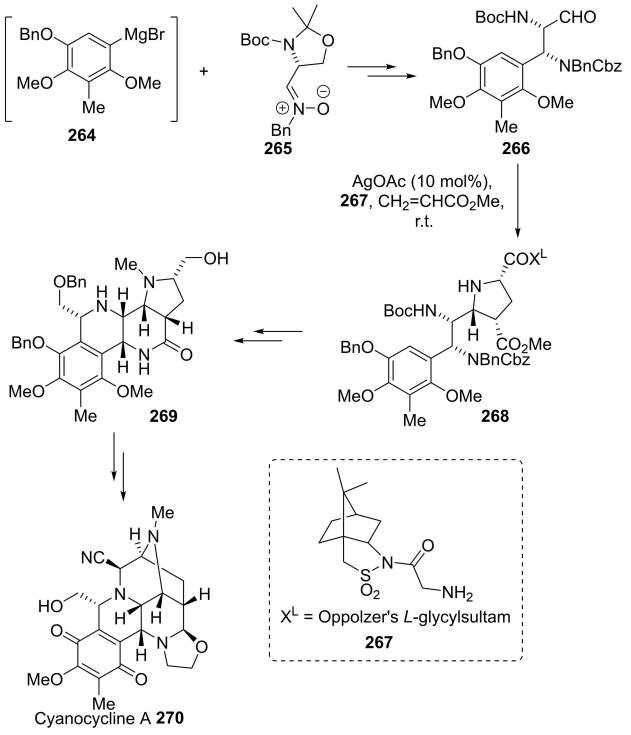


Figure 2. Structures of saframycin A (**262**) and (−)-jorunnamycin A (**263**).



Scheme 28. Total synthesis to pseudopalmatine (**156**) and pseudoepiberberine (**261**) by the Opatz group.



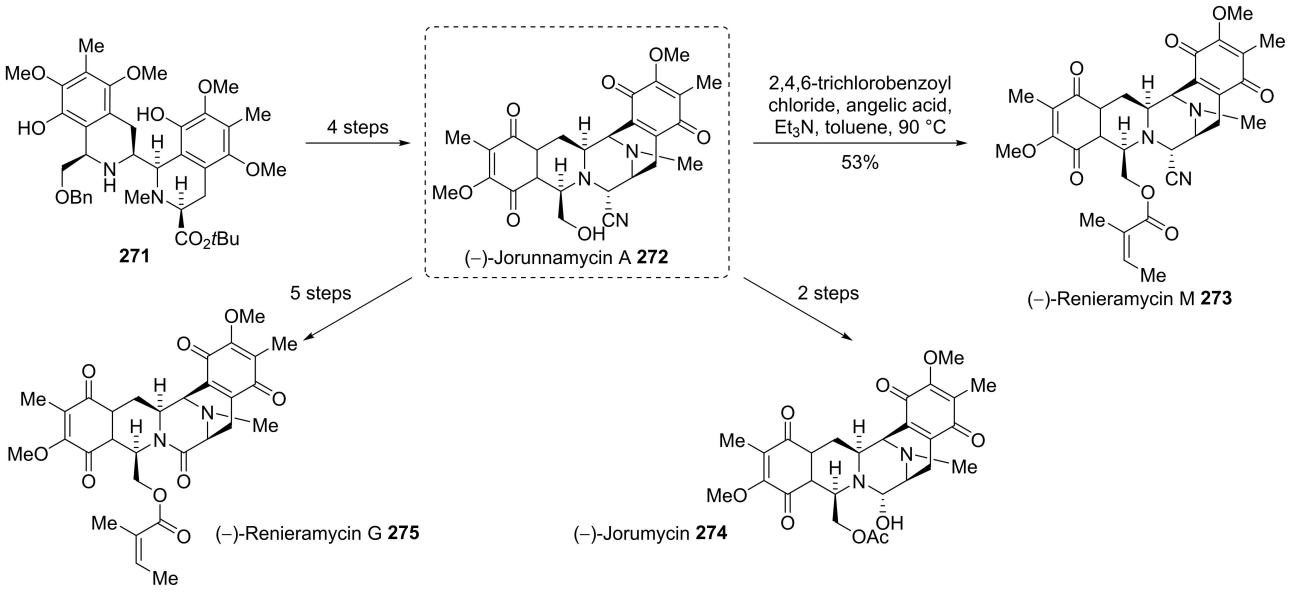
Scheme 29. Schematic route to cyanocycline A (**270**) by Garner et al..

thine ylide cycloaddition, termed [C+NC+CC] couplings, which were developed previously in their laboratory (see Scheme 29).[114] They started their synthesis with a five step sequence to aldehyde **266** which was subjected to the key [C+NC+CC] coupling reaction with Oppolzer's *L*-glycylsultam to afford pyrrolidine precursor **268** in 74% yield. Further transformations including Pd-catalyzed hydrogenolysis, protecting group operations, Pictet-Spengler cyclization and Swern oxidation furnished cyanocycline A (**270**) in 22 linear steps.

After various total syntheses of (−)-renieramycin G from the groups of Liu, Magnus and others,[115] Zhu and co-workers developed the first total synthesis of (−)-renieramycins M and G as well as (−)-jorumycin using aziridines.[116] After the synthesis of precursor **271** from commercially available 2,6-dimethoxytoluene through a series of transformations involving Knochel's methodology,[117] protecting group operations, Pictet-Spengler reaction and Grignard reaction, the group was able to synthesize (−)-jorunnamycin A (**272**) in four additional steps. This compound could be converted to (−)-renieramycin M (**273**) through acylation using modified Yamaguchi-conditions with angelic acid. Similar acylation with acetic anhydride afforded (−)-jorumycin (**274**) in two more steps. Hydrolysis, amide bond formation, hydrogenolysis and selective acylation furnished (−)-renieramycin G (**275**) in five additional steps (Scheme 30). After the development of a series of asymmetric total syntheses of members of the renieramycin family,[118] a stereoselective total synthesis of (−)-renieramycin T was reported by Williams and co-workers in 2016.[119] The key step of this sequence was a Pictet-Spengler cyclization of a bromo-substituted carbinolamine to overcome the regioselectivity problem of the Pictet-Spengler cyclization.

5. Conclusion

During the past two decades, numerous applications of α-aminonitriles in natural product syntheses have been described. Due to their unique reactivity modes and broad applicability, α-aminonitriles continued to defend their role as versatile synthetic tools to yield structurally highly different and in part also very complex products. While exclusively focusing on α-



Scheme 30. Total synthesis of (−)-jorunnamycin **272**, (−)-jorumycin **274** and (−)-renieramycins M **273** and G **275** by Zhu and co-workers.

aminonitriles in syntheses of natural products in the present article, it should become clear that this particular subset of the synthetic chemistry landscape is just the tip of the iceberg and further significant potential lies in syntheses of drugs or performance chemicals using aminonitrile chemistry. α-Aminonitriles are suspected to be intermediates in various biochemical pathways and it is also an important task to develop new, short and especially eco-friendly methods for their preparation which can be applied even in late-stage synthetic approaches.

To conclude this short journey through applications of α-aminonitriles, we propose this extraordinary class of compounds to be considered as a standard tool in retrosynthetic analyses of natural products.

Acknowledgements

We are gratefully to M. Sc. Luca Großmann for designing the cover artwork. Open access funding enabled and organized by Projekt DEAL.

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Manuscript received: May 30, 2020
Revised manuscript received: July 2, 2020
Version of record online: July 24, 2020

