Evolution of a Strategy for the Total Synthesis of (+)-Cornexistin

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In memory of Professor Klaus Hafner.

Abstract: Herein is given a full account of the evolution of the first total synthesis of (+)-cornexistin. Initial efforts were based on masking the reactive maleic anhydride moiety as a 3,4-substituted furan and on forming the nine-membered carbocycle in an intramolecular Conia-ene or Nozaki–Hiyama–Kishi (NHK) reaction. Those strategies suffered from low yields and were jeopardized by a late-stage installation of the Z-alkene, as well as the stereocenters along the eastern periphery. These issues were addressed by employing a chiral-pool strategy that involved construction of the crucial stereocenters at C2, C3 and C8 at an early stage with installation of the maleic anhydride as late as possible. The successful approach featured an intermolecular NHK coupling to install the Z-alkene, a syn-Evans-aldol reaction to forge the stereocenters along the eastern periphery, an intramolecular allylic alkylation to close the nine-membered carbocycle, and a challenging stepwise hydrolysis of a β-keto nitrile to furnish the maleic anhydride.

Introduction

Cornexistin (1) and hydroxycornexistin (2) are fungal metabolites that belong to the nonadride family of natural products.[1] The term "nonadride" originally referred to natural products that are biosynthetically derived from the dimerization of two C9-building subunits. Today, it refers in a broader sense to compounds characterized by a core structure consisting of a nine-membered carbocycle, to which at least one maleic anhydride moiety is fused. The first two congeners of this class, glaucanic (3) and glauconic acid (4),[2] were isolated in 1931. Over the last decades, several additional members such as byssoschlamid acid (5),[2b, f] rubratoxin A (6),[3] scytalidin (7),[4] heveadride (8),[5] cornexistin, and the phomoidrides A (9) and B (10)[6] have been isolated (Figure 1).

Various members of the nonadride natural product family were shown to exhibit diverse biological activities, such as antifungal, antimicrobial and cholesterol lowering activity.[1d] Cornexistin (1) and hydroxycornexistin (2) belong to a subgroup
of the nonadrides that possess only one maleic anhydride fused to the nine-membered carbocycle. After their isolation in 1991 and 1996, respectively, both natural products were found to display outstanding post-emergence herbicidal activity against numerous weeds growing in combination with corn, whilst maintaining excellent corn selectivity. The observed activities were within the range of commercially available herbicides like bialaphos or glyphosate. These findings, paired with the low toxicity against mammals, plants and fungi have drawn considerable interest from agrochemists to explore the cornexistins as lead compounds for the development of new broad-spectrum herbicides. Herein, we report a full account of the development of a synthetic strategy that enabled us to accomplish the first total synthesis of (+)-cornexistin (1).

**Results and Discussion**

We began our studies with the retrosynthetic analysis of cornexistin (1) and hydroxycornexistin (2). From this, we identified the Z-alkene at C7, the nine-membered carbocycle and the maleic anhydride attached to C4/C5 as the key structural motifs. For the installation of these motifs, chemists have developed several powerful methods and elegant strategies over the past decades. For the introduction of the Z-alkene, Clark and Taylor relied on silyl ether via 1,2-addition chemistry. One of the major challenges for the intermolecular merging of a Z-vinyl iodide and an aldehyde via 1,2-addition chemistry. One of the major challenges for the synthesis of 1 is the construction of the medium-sized nine-membered carbocycle (Figure 2b). The Clark group was able to overcome the enthalpic and entropic factors by initially dissecting the nine-membered ring between C1 and C2. By employing a ring-closing metathesis (RCM) reaction the cyclized product was delivered in good yields. In later studies, they were also able to forge the same carbon-carbon bond by an intramolecular NHK reaction. In contrast to these approaches, the Taylor group reported on a retrosynthetic strategy that relied on the connection of C2 and C7 to give a 5/6-bicyclic precursor. An ozonolytic ring-cleavage then delivered the nine-membered core structure of cornexistin (1). In our earlier approaches, the carbocycle was disconnected between C2-C3 (Conia-ene strategy) or C1-C2 (NHK strategy). However, these approaches eventually had to be abandoned due to a lack of scalability. Alternatively, forging the bond between C5 and C6 via intramolecular allylic alkylation turned out to be highly scalable and delivered the nine-membered carbocycle in good yields.

Due to the chemical instability of the maleic anhydride, all previous efforts towards the nonadrides planned for a late-stage construction of this motif (Figure 2c). Masking the maleic anhydride as a furan IV represents one of the most common strategies for its synthesis. For the unmasking, a two-step oxidation protocol is required. Alkynes V are known for their synthetic versatility and also enable the late-stage introduction of maleic anhydrides. For instance, the nickel catalyzed double carboxylation reported by Sakaki allows for a direct one-step conversion. Ogoshi reported the addition of cyanoformates across alkynes to yield β-cyano acrylates VI, which can be sequentially hydrolyzed to maleic anhydrides. In addition, alkynes can be transformed into furans via a cycloaddition/cycloreversion sequence employing oxazoles at high-temperatures. Alternatively, hexacarbonyldicobalt alkylene complexes VII were shown to undergo oxidative decomplexation upon treatment with ceric ammonium nitrate to give maleic anhydrides in high yields. Hydroquinones VIII were also reported to serve as a useful handle for the introduction of maleic anhydrides, as demonstrated in Stork’s synthesis of (+)-byssoschamic acid. Lastly, palladium mediated carboxylation of β-keto ester IX derived enol triflates represents a powerful method for the direct access of anhydride moieties. This sequence was successfully applied in Wood’s synthesis of phomoidride D.

**Nine-membered ring formation via Conia-ene reaction**

In our first approach towards 1, we masked the maleic anhydride as a 3,4-substituted furan and the Z alkene moiety as an oxasililane to give 11 (Scheme 1). Further simplification of 11 by shortening of the propyl chain and removal of the stereocenters at C2 and C3 revealed enone 12 which would be derived from terminal alkyne 13 via a Conia-ene cyclization. This intermediate can be further disected at C5/C6 to provide the allyl bromide 14 and known 3,4-dibromofuran 15. The synthesis of 14 commenced with the TBS protection of 16 (TBSCl, imidazole) followed by a Kulinkovich reaction (Ti(OiPr)4, EtMgBr) (Scheme 2). To obtain high yields, it was crucial to slowly add the ethyl Grignard over a period of four hours maintaining the temperature at 10°C and to use freshly distilled titanium isopropoxide (see the Supporting Information for details).

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*Figure 2. Retrosynthetic analysis of 1 and 2 based on a) the Z-alkene, b) the nine-membered carbocycle and c) the maleic anhydride.*
chloride in the presence ethyl diazoacetate 23. Having secured ample amounts of alkyne 13, we started to investigate the formation of the nine-membered carbocycle via Conia-ene cyclization based on preliminary work by Nakamura (Scheme 3). Treatment of 13 with indium(III) tris(trifluoromethanesulfonimide) (1 mol%) in toluene at 130 °C provided an inseparable mixture of 24 and 25. It is worth noting that catalyst loadings above 3%, exclusively led to decomposition of the starting material. Krapcho decarboxylation of the crude reaction mixture (LiCl, 140 °C) also resulted in partial cleavage of the silyl ether. After full desilylation (HF-pyridine), the free alcohol 26 was obtained in 30% yield over three steps. The structure of 26 was unambiguously confirmed by single crystal X-ray diffraction of the corresponding ferrocene carboxylic ester 27. Unfortunately, all attempts to functionalize the γ-position of the enone via vinylogous deprotonation/alkylation or to realize a Conia-ene cyclization of a non-terminal alkyne were unsuccessful. Efforts on this approach were therefore discontinued, however aldehyde 20 became the starting point for a new approach.

Nine-membered ring formation in a NHK reaction (Part I)

For our second-generation strategy, cornexistin (1) was first traced back to enone 28 which should be readily available from Z-iodide 29 in an intramolecular NHK reaction (Scheme 4). The required cyclization precursor 29 was readily accessible from aldehyde 20, an intermediate of the first-generation route.

 Following the Stork–Wittig protocol, aldehyde 20 was transformed into vinyl iodide 30 in excellent yields and high Z-selectivity (Z/E = 9:1) employing sodium bis(trimethylsilyl)amide as the base. Interestingly, when potassium bis(trimethylsilyl)amide was used as base a 1:1 mixture of (E)–30 and (Z)-30 was obtained. After selective cleavage of the primary silyl ether (py-TsOH), oxidation with Dess–Martin periodinane gave the desired cyclization precursor 29 in 88% yield. To our delight, upon treatment of 29 under standard NHK conditions (CrCl3, NiCl2, DMF) we observed formation of the nine-

After silylation of the primary alcohol (TBSCl, imidazole), the tertiary alcohol of 19 was mesylated (MsCl, Et3N) and a magnesium bromide ethereal promoted fragmentation then provided the allyl bromide 14 (4.5 g in a single batch). The monometalation of furan 15 (nBuLi, MgBr·OEt2) followed by copper(I) catalyzed coupling with 14 afforded 20 in excellent yields (94%). Formylation was accomplished by bromine/lithium exchange followed by addition of N,N-dimethylformamide to give aldehyde 20.

Upon treatment of 20 with the Ohira–Bestmann reagent (21), alkoyne 22 was obtained in 77% yield. The primary TBS-ether was selectively removed (py-TsOH) and the obtained alcohol was oxidized with Dess–Martin periodinane. Transformation into cyclization precursor 13 was achieved under Roskamp conditions involving exposure of 13 to tin(II)
be set at an early stage via a syn-Evans aldol reaction of known aldehyde \(^{36}\)[30] and \(^{37}\)[31].

To begin with, \(^{37}\) was treated with triethylamine and dibutylboron trifluoromethanesulfonate followed by the addition of aldehyde \(^{36}\) (Scheme 6). This highly selective syn-Evans aldol reaction gave \(^{38}\) as a single product. The structure of \(^{38}\) was unambiguously confirmed by single crystal X-ray diffraction. After silyl protection of the secondary alcohol (TBSOTf, 2,6-lutidine), \(^{39}\) was obtained in good yields and large quantities (7.4 g) over two steps.\(^{32}\) The Evans-auxiliary was removed by formation of the thioester (EISH, nBuLi) which was then reduced to the corresponding aldehyde applying Fukuyama’s conditions (Et\(_2\)SiH, NaHCO\(_3\), Pd/C).\(^{33}\) To prevent cleavage of the benzylidene acetal during the reduction step, it was crucial to buffer the reaction mixture with sodium bicarbonate. Attempted homologation with the Ohira–Bestmann reagent led to formation of a complex reaction mixture with only traces of alkyne \(^{35}\) being isolated. Fortunately, following the Corey–Fuchs homologation protocol (CB\(_{11}\), PPh\(_3\), then nBuLi) provided \(^{35}\) in good overall yield.\(^{34}\)

Next, we turned our attention to the connection of alkyne \(^{35}\) and allylic nosylate \(^{34}\) via alkylation.\(^{35}\) To our delight, the S\(_2\)2 pathway was predominantly operative and only traces of the S\(_2\)2’ product were observed. However, this reaction delivered an inseparable mixture of \(^{40}\) contaminated with unreacted alkyne \(^{34}\). After reductive opening of the benzylidene acetal (DIBAL–H), we were able to isolate the pure primary alcohol, which was oxidized to aldehyde \(^{33}\) employing Dess–Martin periodinane. The stage was now set to investigate

**Scheme 4.** A) Second-generation retrosynthetic analysis of cornexistin. B) a) Ph\(_2\)P=CHI, THF, HMPA, –78 to 23°C, 95%, Z/E 10/1; b) py·TsOH, MeOH, 75%; c) DMP, CH\(_2\)Cl\(_2\), 88%; d) CrCl\(_2\), iPr\(_2\)EDI, DMF, 28%, NaNHMDS: sodium bis(trimethylsilyl)amide, HMPA: hexamethyl-phosphoramide.

**Scheme 5.** Retro-synthetic analysis of cornexistin by masking the maleic anhydride as hexacarbonyldicobalt alkyne complex 32 (Scheme 5). Further disconnection of the nine-membered carbocycle at C7/C8 revealed vinyl iodide \(^{34}\). We identified \(^{34}\) as a versatile building block to introduce the Z-configured exocyclic double bond via an alkylation reaction. In contrast to our initial approaches, the C2/C3 stereocenters along the northern periphery should already

**Scheme 6.** a) \(^{36}\), Bu\(_3\)BOTf, NET\(_3\), –78 to 23°C; b) TBSOTf, 2,6-lutidine, CH\(_2\)Cl\(_2\), –78 to 23°C, 71% over two steps; c) EISH, nBuLi, THF, 0°C, 96%; d) E\(_2\)SiH, PPh\(_3\), NaHCO\(_3\), acetone; e) CB\(_{11}\), PPh\(_3\), CH\(_2\)Cl\(_2\), 0°C, f) nBuLi, THF, –78 to 23°C, 47% over three steps; g) \(^{34}\), CuI, K\(_2\)CO\(_3\), NaI, DMF; h) DIBAL–H, CH\(_2\)Cl\(_2\), –78 to 23°C, 74% over two steps; i) DMP, CH\(_2\)Cl\(_2\), 0 to 23°C, 86%. Thermal ellipsoids are shown at 50% probability. TBSOTf: tert-butylimidethylsilyl trifluoromethanesulfonate, DIBAL–H: diisobutylaluminiumhydride.

**Nine-membered ring formation via NHK reaction (Part II)**

For the third strategy, we masked the maleic anhydride as hexacarbonyldicobalt alkyne complex 32 (Scheme 5). Further disconnection of the nine-membered carbocycle at C7/C8 revealed vinyl iodide \(^{33}\). We identified \(^{34}\) as a versatile building block to introduce the Z-configured exocyclic double bond via an alkylation reaction. In contrast to our initial approaches, the C2/C3 stereocenters along the northern periphery should already
the cyclization of 33. Unfortunately, various conditions (CrCl₂, NiCl₂ or Ni(acac)₃, or iBuLi) only resulted in the isolation of dehalogenated starting material. From this observation we concluded that cyclization might be geometrically disfavored for this alkyne. Attempts to modify the substrate geometry by reduction of the alkyne to the alkene (diimide reduction), formation of the furan (4-phenylloxazole, 140 °C) or conversion of the alkyne to its hexacarboxylidicoctol complex (Co₃(CO)₁₀) were unsuccessful. At this stage, we decided to suspend further investigations into this alkyne approach.

Nine-membered ring formation by intramolecular alkylation

Based on our previous results, we envisioned to use the enoltriflate 42 as a suitable precursor for the maleic anhydride of 1. Retrosynthetic disconnection at C5/C6 revealed allylic bromide 43 which was further disassembled to 39 and 44 (Scheme 7A). The synthesis of the aldehyde began with the reductive cleavage of the Evans-auxiliary (LiBH₄, MeOH, Et₂O, THF, 0 °C) followed by silylation of the primary alcohol (TBSCI, imidazole) to give 45. The PMP acetal was regioselectively opened under reductive conditions (DIBAL-H) yielding the PMB-protected secondary alcohol (Scheme 7B). The primary position was then oxidized to aldehyde 46 employing Dess–Martin periodinane.

Next, merging of (Z)-vinyl-iodide 44 and aldehyde 46 by 1,2-addition chemistry was investigated (Table 1). To our surprise, treatment of a mixture of iodide 44 and aldehyde 46 under NHK conditions (CrCl₂, NiCl₂, DMF) did not show formation of the desired alcohol 47 (entry 1).

Alternative protocols such as halogen/metal exchange (Mg, tBuLi, nBuLi, iPrMgCl, Et₂Zn, [nBu₃(iPr)Mg]Li) with TBSCI-protected iodide 48 did also not show formation of the desired product 49 (entries 2–7). TES-protected iodide 50 reacted under NHK conditions (CrCl₂, NiCl₂) forming a C8-diastereoisomeric mixture (dr 2 : 1) of 51 (entry 8). In order to reduce the overall step count, we turned our attention to using TMS-protected iodide 52 as coupling partner. After NHK coupling (entry 9), an acidic workup enabled cleavage of the TMS-ether to give an inseparable mixture of C8-diastereoisomers 53 (dr 2 : 1). Alcohol 54 was then synthesized from 53 via standard functional group interconversion starting with acetylation of the primary alcohol (AcCl, 2,4,6-collidine), MOM-ether protection of the secondary alcohol (MOMBr, DIPEA) and selective desilylation of the primary alcohol (HF·pyridine) (Scheme 8). At this stage, we
were able to separate the C8-diastereoisomer 54a from 54b by flash column chromatography on silica gel. Formation of the Mosher esters confirmed the desired (R)-configuration for 54a at C8 (see the Supporting Information for details).\[39\] Oxidation of the primary alcohol (Dess–Martin periodinane) gave the corresponding aldehyde which was converted to β-ketoester 55 under Roskamp conditions (SnCl₂, ethyl diazoacetate 23). Attempts to directly close the nine-membered ring employing a previously published protocol using NaH, Pd(PPh₃)₄, 1,2-bis (diphenylphosphino)ethane in THF at 66 °C resulted in complex reaction mixtures.\[40\] Therefore, 55 was converted into bromide 43 by hydrolysis of the acetyl protecting group (K₂CO₃, MeOH) and a subsequent Appel reaction (NBS, PPh₃). The hydrolysis of the acetyl protecting group (MeOH, K₂CO₃) also caused trans-esterification of the ethyl to the methyl ester. To our delight, DBU in acetonitrile cleanly initiates the intramolecular alkylation forming the nine-membered carbocycle in 57% yield as a mixture of keto-enol tautomers (1:1).\[41\] Next, we turned our attention to the formation of the enoltriflate 42. Unfortunately, common triflation agents (Tf₂O, Comins and McMurry reagent) did not show any formation of the desired product while triflic chloride in the presence of KHMS formed a single, new compound within ten minutes. After careful analysis of the obtained spectroscopic data (NMR, HRMS), the formed compound was assigned to chloride 58. This observation was in accordance with the results obtained for the attempted formation of the enol triflate employing model substrate 59. A screen of more than 30 triflation conditions resulted in either recovery of unreacted starting material or decomposition of 59.\[12\] Treatment with TfCl also delivered exclusively the α-chlorinated product.

Despite the discouraging results obtained for the triflation of the cyclic β-keto esters, we were confident that the intramolecular alkylation represented a powerful reaction to form the nine-membered carbocycle. We therefore set out to investigate whether exchange of the ester by other electron withdrawing groups could serve as a handle for the introduction of the maleic anhydride moiety. In this context, we addressed problematic steps of the previous approach (auxiliary cleavage, NHK) by streamlining the synthesis of the cyclization precursor. We also adjusted the route to access the natural enantiomer of 1, whose absolute configuration was only unambiguously assigned by X-ray single crystal diffraction by the Cox group in 2017.\[42\] We aimed to install the maleic anhydride moiety by late-stage oxidation of a furan, which should be introduced by a double Wittig reaction between 1,2-diketone 61 and Wittig reagent 62 (Scheme 9).\[43\] The nine-membered ring was envisioned to be accessible via intramolecular alkylation of β-keto sulfone 63, which was further disconnected to thioester 64. Carbon–carbon bond cleavage at C2/C3 and C7/C8 then revealed keto-imide ent-37, iodide 48 and aldehyde 65.

Starting from malic acid 66, we accessed aldehyde 65 through esterification (SOCl₂, MeOH), selective reduction of the α-hydroxy ester (BH₃·SMe₂, cat. NaBH₄), acetolysis of the resulting 1,2-diol and subsequent Dibal–H reduction of the methyl ester (Scheme 10).\[44\] The NHK reaction with vinyl iodide 48 then afforded the 1,2-addition product as a mixture of C8-epimers in 58% yield. All efforts to separate the diastereoisomers by flash column chromatography failed and we continued

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**Scheme 9.** Retrosynthetic analysis of 1 based on 1,2-diketone 61 and formation of the nine-membered carbocycle by intramolecular alkylation of β-keto sulfone 63.

**Scheme 10.** a) SOCl₂, MeOH, 23 °C, 98%; b) BH₃·SMe₂, NaBH₄, THF, 0 °C, 82%; c) 71, CSA, CH₂Cl₂, 23 °C, 65%; d) Dibal–H, CH₂Cl₂/DME, –78 °C, 99%; e) 48, CrCl₃, NiCl₂, DMF, 0 °C to 23 °C, 58%, dr = 13:1 at C8; f) TBSOTf, 2,6-lutidine, CH₂Cl₂, –78 to 23 °C, 94%; g) Dibal–H, CH₂Cl₂, –78 to –40 °C, 73%; h) DMP, CH₂Cl₂, 23 °C, 86%; i) ent-37, Bu₂BOT, NEt₃, –78 to 23 °C; j) TBSOTf, 2,6-lutidine, CH₂Cl₂, –78 to 23 °C, 72% over two steps; k) EtSH, nBuLi, THF, 0 °C, 96%; l) MeSO₂Ph, nBuLi, THF, –78 °C, 74%; m) HF·pyridine, THF/pyridine 2:1, 0 °C, 543a 40%, 543b 36%; n) Cbr₄, PPh₃, CH₂Cl₂, –20 to –5 °C, 63a 71%, 63b 77%; o) DIBAL–H, MeCN, 23 °C, 69a 78%, 69b 70%; p) Na/Hg, Na₂HPO₄, MeOH, 70a 69%, 70b 70%; q) CSA: camphorsulfonic acid, DME: dimethoxyethane.
our synthesis with the diastereomeric mixture, which was subjected to TBS protection (TBSOTf, 2,6-lutidine) to give 67. After regioselective reductive opening of the PMB-acetal, the primary alcohol was obtained as a 1:1.3 mixture of C8-diastereomers, which was subsequently oxidized to aldehyde 68 with Dess–Martin periodinane. The subsequent syn-Evans-aldol reaction (Bu₂BOTf, NEt₃) proceeded with an excellent level of stereocontrol. After TBS protection (TBSOTf, 2,6-lutidine), residual amounts of oxazolidinone ent-37 were removed by flash column chromatography and the pure product was isolated in 72% yield over two steps. Cleavage of the auxiliary with LiSEt gave thioester 64 from which installation of the β-keto sulfone moiety was achieved by treatment with freshly prepared LiCH₂SO₂Ph.[46] After selective deprotection of the primary allylic alcohol (HF-pyridine), the C8 epimers were separated by flash column chromatography and the following steps were carried out separately for both epimers. After an Appel reaction, the cyclization precursors 63a and 63b were subjected to our previously established cyclization conditions (DBU, MeCN, 23°C). For both substrates clean conversion to the desired products was observed. However, analysis of the NMR spectra of 69a and 69b was difficult due to signal broadening and the presence of C8-diastereoisomers. Removal of the primary allylic alcohol (HF-pyridine) for the maleic anhydride moiety (Scheme 11). The installation of the β-keto nitrile was achieved by reaction of thioester 64 with LiCH₂CN, analogously to the sulfone approach (Scheme 12).[47] Selective deprotection of the primary allylic alcohol (HF-pyridine) and an Appel reaction (NBS, PPh₃) gave cyclization precursor 73.

Treatment with DBU proceeded smoothly to give the cyclized product 74 in 74% yield. To our delight, we were able to isolate the desired enol triflate when a solution of 74 in dichloromethane was treated with triflic anhydride and triethylamine at −78°C. Resubjecting unreacted starting material to the reaction conditions allowed us to obtain the enol triflate in 85% overall yield after two additional cycles. At this stage, separation of the C8 epimers was also achieved by flash column chromatography and the synthesis was continued independently with both epimers. A palladium catalyzed carbylation reaction (Pd(OAc)₃, dpf, Co, MeOH) afforded the all-carbon precursor 72 in excellent yields. Next, we focused on the installation of the delicate maleic anhydride moiety via sequential deprotection and oxidation along the northern periphery were the only missing steps to complete the synthesis of the natural product. Treatment of 75 with DDQ effected clean cleavage of the para-methoxybenzyl ether. The remaining oxidation (Dess–Martin periodinane) and the final deprotection (HF-pyridine) were conducted without purification of the intermediate ketone and gave (+)-cornexistin in 86% over two steps.

**Conclusion**

In conclusion, we have reported the evolution of our strategy for the asymmetric total synthesis of cornexistin. In early strategies, we dissected the nine-membered carbocycle between C2/C3 or C1/C2. Although we were able to successfully re-form this bond either in a Conia-ene or a Nozaki–Hiyama–Kishi reaction, further progress was hampered by low yields and scalability issues. An alternative NHK approach of an alkyne-containing cyclization precursor was also unsuccessful. Finally, we identified an intramolecular alkylation between C5 and C6 as the most efficient strategy to close the nine-membered carbocycle. However, employing a β-keto ester, we ran into unexpected problems during formation of the cyclic enol triflate, and when we resorted to a β-keto sulfone, no additional sulfone moiety (sodium amalgam amalgam) afforded 70a and 70b, and enabled structure validation via 2D NMR. Unfortunately, attempts to convert the β-keto sulfones 69 into 1,2-dicarbonyl 61 (e.g., KHMD, Davis oxaziridine; KHMD, MoO(O)₃) remained unsuccessful and only led to the recovery of unreacted starting material.

In parallel, we investigated nitrile 72 as a suitable precursor for the maleic anhydride moiety of Scheme 11. The installation of the β-keto nitrile was achieved by reaction of thioester 64 with LiCH₂CN, analogously to the sulfone approach (Scheme 12).[47] Selective deprotection of the primary allylic alcohol (HF-pyridine) and an Appel reaction (NBS, PPh₃) gave cyclization precursor 73.

In conclusion, we have reported the evolution of our strategy for the asymmetric total synthesis of cornexistin. In early strategies, we dissected the nine-membered carbocycle between C2/C3 or C1/C2. Although we were able to successfully re-form this bond either in a Conia-ene or a Nozaki–Hiyama–Kishi reaction, further progress was hampered by low yields and scalability issues. An alternative NHK approach of an alkyne-containing cyclization precursor was also unsuccessful. Finally, we identified an intramolecular alkylation between C5 and C6 as the most efficient strategy to close the nine-membered carbocycle. However, employing a β-keto ester, we ran into unexpected problems during formation of the cyclic enol triflate, and when we resorted to a β-keto sulfone, no additional
oxidation was possible. Further investigation revealed a β-keto nitrile as the only substrate that underwent cyclization and postfunctionalization in reproducibly high yields. The successful total synthesis started from β-malic acid and features a NHK reaction (C8 stereocenter), an auxiliary-controlled Evans syn-aldol reaction (C2/C3 stereocenters), a highly efficient intramolecular cyclization to forge the nine-membered carbocycle, and the sequential hydrolysis of a β-cyano acrylate to construct the maleic anhydride. These results should stimulate further interest in this area and might enable the synthesis of currently inaccessible nonadride natural products.

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Conflict of Interest
The authors declare no conflict of interest.

Keywords: herbicides · natural products · nine-membered carbocycles · nonadrides · total synthesis

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