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 byssochlamic acid (**5**),[2b,c,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

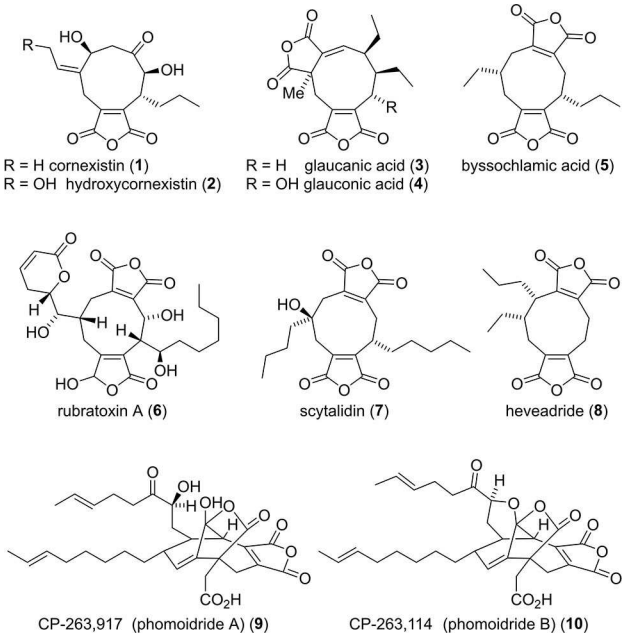

Figure 1. Structures of selected nonadride natural products.

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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.[7] 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[1a–c] 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 **I** or butenolide **II** (Figure 2a).

Contrary to those cyclic components, we opted for the intermolecular merging (**III**) 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).[8] 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.[9] In later studies, they were also able to forge the same carbon-carbon bond by an intramolecular NHK reaction.[10] 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**).[11] 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.[12]

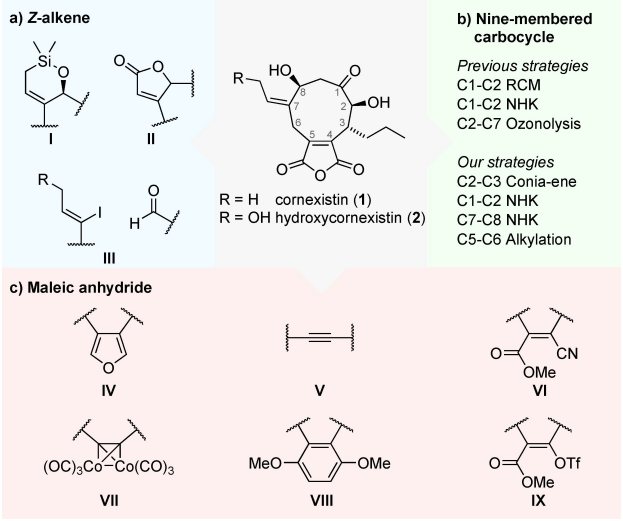

Figure 2. Retrosynthetic analysis of **1** and **2** based on a) the *Z*-alkene, b) the nine-membered carbocycle and c) the maleic anhydride.

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.[13] 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.[14] Ogoshi reported the addition of cyanoformates across alkynes to yield β-cyano acrylates **VI**, which can be sequentially hydrolyzed to maleic anhydrides.[15] In addition, alkynes can be transformed into furans via a cycloaddition/cycloreversion sequence employing oxazoles at high-temperatures.[16] Alternatively, hexacarbonyldicobalt alkyne complexes **VII**[17] were shown to undergo oxidative decomplexation upon treatment with ceric ammonium nitrate to give maleic anhydrides in high yields.[18] Hydroquinones **VIII** were also reported to serve as a useful handle for the introduction of maleic anhydrides, as demonstrated in Stork's synthesis of (±)-byssochlamic acid.[19] Lastly, palladium mediated carbonylation of β-keto ester **IX** derived enol triflates represents a powerful method for the direct access of anhydride moieties.[20] This sequence was successfully applied in Wood's synthesis of phomoidride D.[21]

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 oxasilinane 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 dissected at C5/C6 to provide the allyl bromide **14** and known 3,4-dibromofuran **15**.[22]

The synthesis of **14** commenced with the TBS protection of **16** (TBSCl, imidazole) followed by a Kulinkovich reaction ($Ti(OiPr)_4$, EtMgBr) (Scheme 2).[23] 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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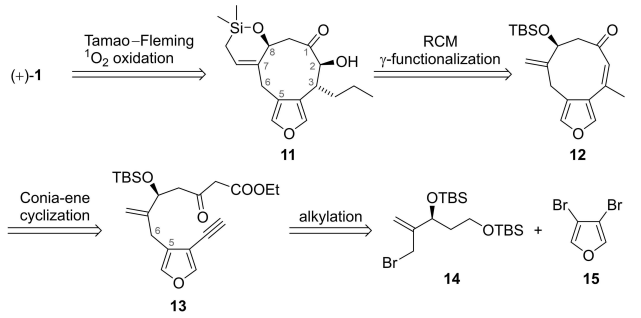
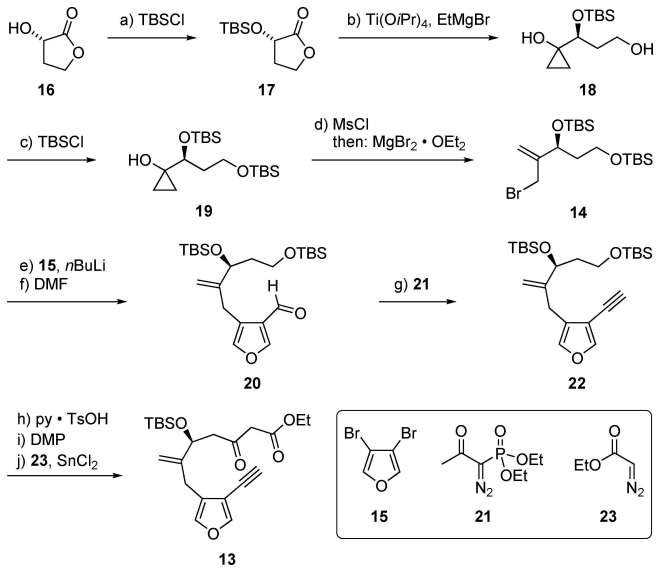


Scheme 1. First generation retrosynthetic analysis of cornexistin.



Scheme 2. a) TBSCl, imidazole, CH_2Cl_2, 72%; b) Ti(O*i*Pr)$_4$, EtMgBr, THF, 10 °C, 55%; c) TBSCl, imidazole, CH_2Cl_2, 95%; d) MsCl, Et_3N, CH_2Cl_2, 0 °C then: $MgBr_2 \cdot OEt_2$, CH_2Cl_2, 40 °C, 61%; e) **15**, *n*BuLi, $MgBr_2 \cdot OEt_2$, CuBr·SMe_2 (20 mol%), THF, −78 to 23 °C then: **14**, 94%; f) *n*BuLi then: DMF, THF, −78 °C, 92%; g) **21**, K_2CO_3, MeOH, 77%; h) py·TsOH, MeOH, 81%; i) DMP, pyridine, CH_2Cl_2, 93%; j) **23**, $SnCl_2$, CH_2Cl_2, 90%. TBSCl: *tert*-butyldimethylsilyl chloride, THF: tetrahydrofuran, MsCl: methanesulfonyl chloride, DMF: *N*,*N*-dimethylformamide, py·TsOH: pyridinium *p*-toluenesulfonate, DMP: Dess–Martin periodinane.

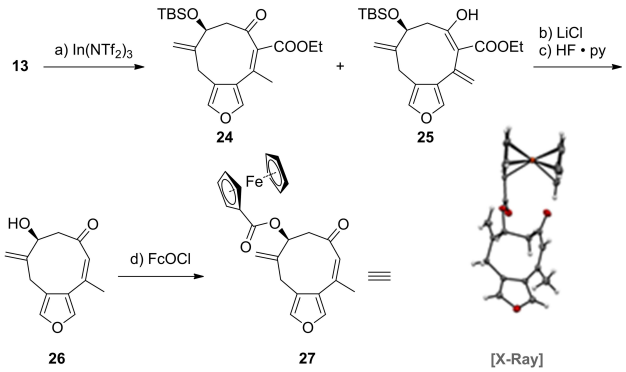
After silylation of the primary alcohol (TBSCl, imidazole), the tertiary alcohol of **19** was mesylated (MsCl, Et_3N) and a magnesium bromide etherate promoted fragmentation then provided the allyl bromide **14** (4.5 g in a single batch). The monometalation of furan **15** (*n*BuLi, $MgBr_2 \cdot OEt_2$) 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**), alkyne **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[25] involving exposure of **13** to tin(II) 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).[26] 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**.[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* = 10:1) employing sodium bis(trimethylsilyl) amide as the base.[28] 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 ($CrCl_2$, $NiCl_2$, DMF)[29] we observed formation of the nine-



Scheme 3. a) Indium(III) tris(trifluoromethanesulfonimide), toluene, 130 °C; b) LiCl, DMSO, 145 °C; c) HF·pyridine, THF (30% over three steps); d) FcOCl, DMAP, CH_2Cl_2, 67%. Thermal ellipsoids are shown at 50% probability.[24] FcOCl: ferrocene carboxylic acid chloride, DMAP: 4-dimethylaminopyridine.

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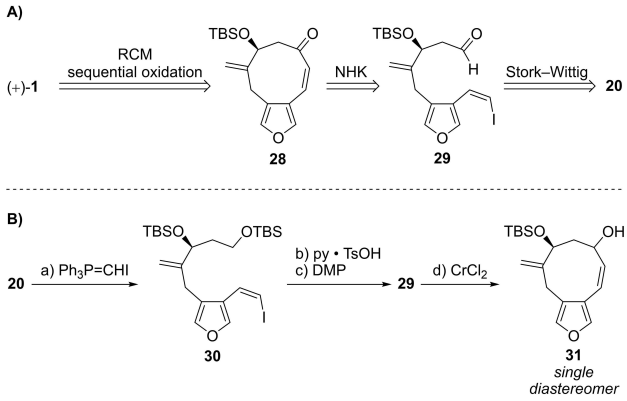
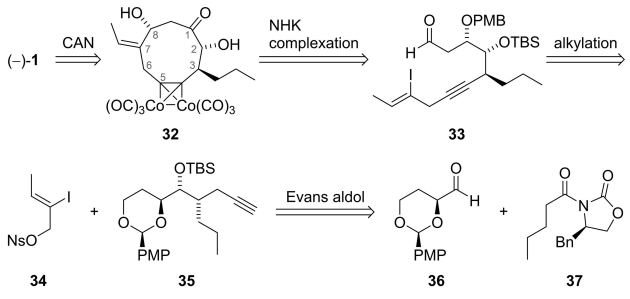


Scheme 4. A) Second-generation retrosynthetic analysis of cornexistin. B) a) $Ph_3P{=}CHI$, THF, HMPA, −78 to 23 °C, 95 %, Z/E 10/1; b) py·TsOH, MeOH, 75 %; c) DMP, CH_2Cl_2, 88 %; d) $CrCl_2$, $NiCl_2$, DMF, 28 %. NaHMDS: sodium bis (trimethylsilyl)amide, HMPA: hexamethyl-phosphoramide.

membered carbocycle **31** in 28 % yield. Unfortunately, all efforts to further improve the yield were met with failure and the scale-up by a factor of four reduced the yield to 17 %, rendering this approach unsuitable. After a series of drawbacks, we evaluated our previous efforts towards **1**. Although both routes allowed for the formation of the nine-membered carbocycle already fused to a maleic anhydride precursor, low yields and a lack of scalability prevented further functionalization of the nine-membered carbocycle. Therefore, we envisaged alternative strategies based on the synthesis of a cyclization precursor already carrying the full decoration along the northern periphery.

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 eastern periphery should already

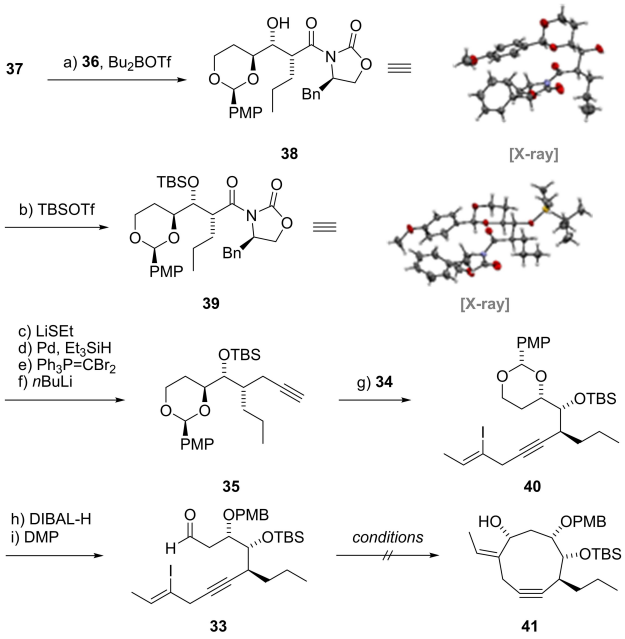


Scheme 5. Retrosynthetic analysis of cornexistin by masking the maleic anhydride as the hexacarbonyldicobalt alkyne complex **32** and formation of the nine-membered carbocycle via intramolecular Nozaki–Hiyama–Kishi reaction.

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 (EtSH, *n*BuLi) which was then reduced to the corresponding aldehyde applying Fukuyama's conditions (Et_3SiH, $NaHCO_3$, 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 (CBr_4, PPh_3 then *n*BuLi) provided **35** in good overall yield.[34]

Next, we turned our attention to the connection of alkyne **35** and allylic nosylate **34** via alkylation.[36] To our delight, the S_N2 pathway was predominantly operative and only traces of the S_N2' 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 6. a) **36**, **37**, Bu_2BOTf, NEt_3, −78 to 23 °C; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 23 °C, 71 % over two steps; c) EtSH, *n*BuLi, THF, 0 °C, 96 %; d) Et_3SiH, Pd/C, $NaHCO_3$, acetone; e) CBr_4, PPh_3, CH_2Cl_2, 0 °C; f) *n*BuLi, THF, −78 to 23 °C, 47 % over three steps; g) **34**, CuI, K_2CO_3, NaI, DMF; h) DIBAL–H, CH_2Cl_2, −78 to 23 °C, 74 % over two steps; i) DMP, CH_2Cl_2, 0 to 23 °C, 86 %. Thermal ellipsoids are shown at 50 % probability.[35] TBSOTf: *tert*-butyldimethylsilyl trifluoromethanesulfonate, DIBAL-H: diisobutylaluminiumhydride.

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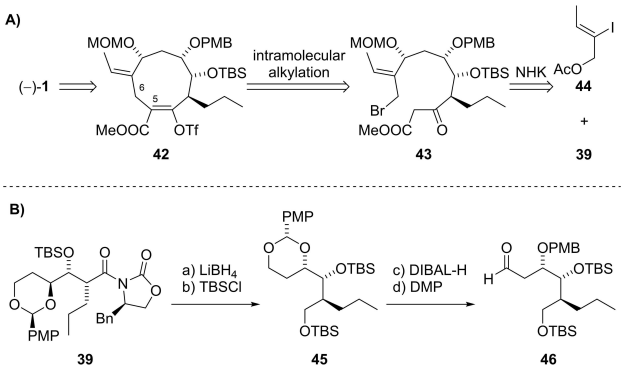
the cyclization of **33**. Unfortunately, various conditions ($CrCl_2$, $NiCl_2$ or $Ni(acac)_2$ or *t*BuLi) only resulted in the isolation of dehalogenated starting material. From this observation we concluded that cyclization might be geometrically disfavored for this alkyne.[37] Attempts to modify the substrate geometry by reduction of the alkyne to the alkene (diimide reduction),[38] formation of the furan (4-phenyloxazole, 140 °C)[16] or conversion of the alkyne to its hexacarbonyldicobalt complex ($Co_2(CO)_8$)[17] were unsuccessful. At this stage, we decided to suspend further investigations into this alkyne approach.

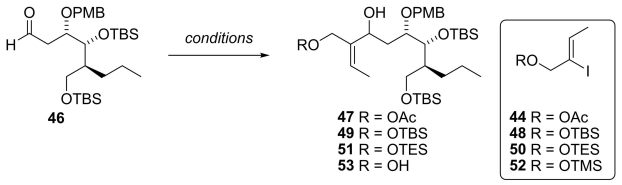
Nine-membered ring formation by intramolecular alkylation

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 7. A) Fourth-generation retrosynthetic analysis of **1**: enol triflate **42** as a precursor for the maleic anhydride and formation of the nine-membered carbocycle through an intramolecular alkylation. B) a) $LiBH_4$, MeOH, Et_2O, THF, 0 °C, 64%; b) TBSCl, imidazole, CH_2Cl_2, 90%; c) DIBAL–H, CH_2Cl_2, −78 to −40 °C, 97%; d) DMP, CH_2Cl_2, 0 to 23 °C, 94%. PMB: *para*-methoxybenzyl, PMP: *para*-methoxyphenyl.

Table 1. Barbier type conditions for the introduction of the Z alkene.



	R	Conditions	Solvent	Yield
1	Ac	$CrCl_2$, $NiCl_2$	DMF	n.r.
2	TBS	Mg	Et_2O	n.r.
3	TBS	*t*BuLi	Et_2O	n.r.
4	TBS	*n*BuLi	THF	n.r.
5	TBS	*i*PrMgCl	THF	n.r.
6	TBS	Et_2Zn	THF	n.r.
7	TBS	[nBu_2(*i*Pr)Mg]Li	THF	n.r.[a]
8	TES	$CrCl_2$, $NiCl_2$	DMF	**51** (64%)[b]
9	TMS	$CrCl_2$, $NiCl_2$ then HCl	DMF	**53** (41%)[c]

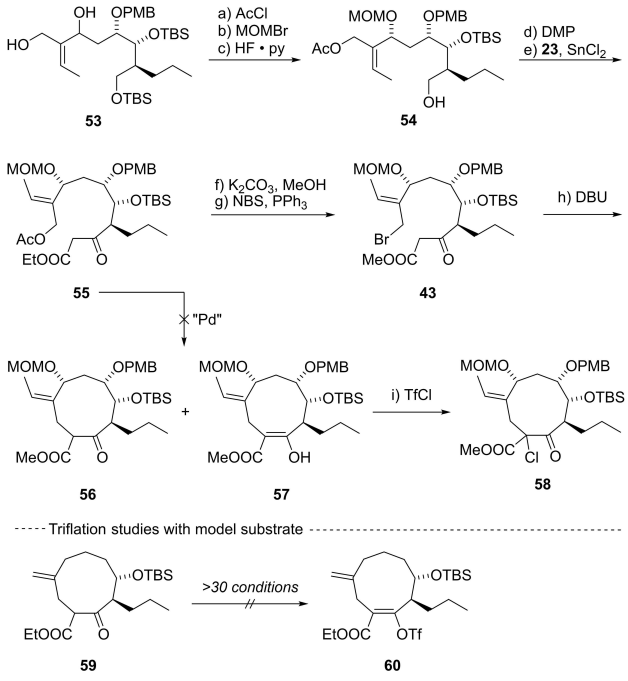
n.r. = no reaction; [a] only 1,2-addition of *n*-butyl was observed; [b] **51** was isolated as a mixture of C8 diastereoisomers **51a** and **51b** (*dr* 2:1); [c] **53** was isolated as a mixture of C8 diastereoisomers **53a** and **53b** (*dr* 2:1).

(Scheme 7A). The synthesis of the aldehyde began with the reductive cleavage of the Evans-auxiliary ($LiBH_4$) followed by silylation of the primary alcohol (TBSCl, 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 ($CrCl_2$, $NiCl_2$, DMF) did not show formation of the desired alcohol **47** (entry 1).

Alternative protocols such as halogen/metal exchange (Mg, *t*BuLi, *n*BuLi, *i*PrMgCl, Et_2Zn, [nBu_2(*i*Pr)Mg]Li) with TBS-protected iodide **48** did also not show formation of the desired product **49** (entries 2–7). TES-protected iodide **50** reacted under NHK conditions ($CrCl_2$, $NiCl_2$) 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



Scheme 8. a) AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 84%; b) MOMBr, DIPEA, DMAP, CH_2Cl_2, 0 to 23 °C, 93%; c) HF·pyridine, THF, 0 to 23 °C, **54a** 51%, **54b** 30%; d) DMP, CH_2Cl_2, 89%; e) **23**, $SnCl_2$, CH_2Cl_2, 67%; f) K_2CO_3, MeOH; g) NBS, PPh_3, CH_2Cl_2, −30 °C, 65% over two steps; h) DBU, MeCN, **56** 25%, **57** 32%, i) KHMDS, TfCl, THF, −78 °C, 62%. MOMBr: bromomethyl methyl ether, DIPEA: *N*,*N*-diisopropylethylamine, NBS: *N*-bromosuccinimide, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, TfCl: trifluoromethanesulfonyl chloride.

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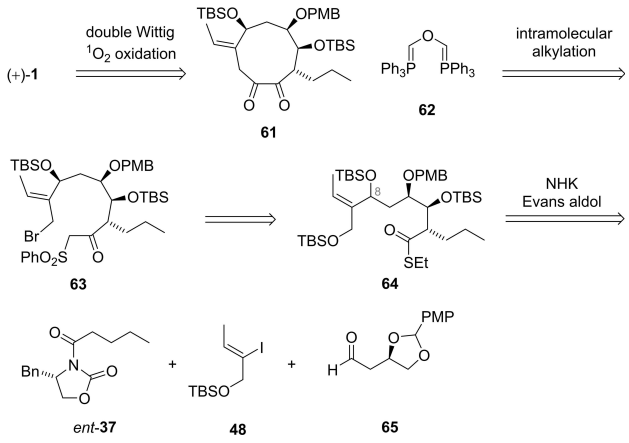
were able to separate the C8-diastereoisomer **54a** from **54b** by flash column chromatography on silica gel. Formation of the Mosher esters confirmed the desired (*R*)-configuration for **54a** at C8 (see the Supporting Information for details).[39] Oxidation of the primary alcohol (Dess–Martin periodinane) gave the corresponding aldehyde which was converted to β-ketoester **55** under Roskamp conditions ($SnCl_2$, ethyl diazoacetate **23**). Attempts to directly close the nine-membered ring employing a previously published protocol using NaH, $Pd(PPh_3)_4$, 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 (K_2CO_3, MeOH) and a subsequent Appel reaction (NBS, PPh_3). The hydrolysis of the acetyl protecting group (MeOH, K_2CO_3) also caused transesterification 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 (Tf_2O, Comins and McMurry reagent) did not show any formation of the desired product while triflic chloride in the presence of KHMDS 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.

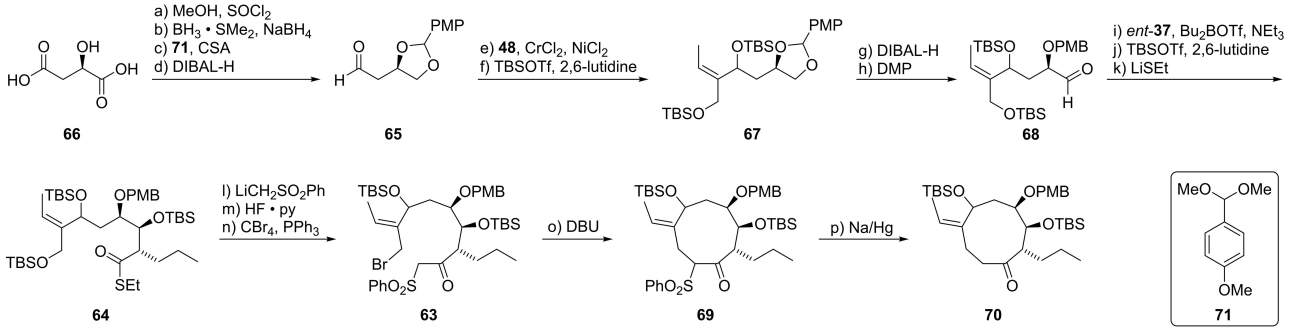
Despite the discouraging results obtained for the triflation of the cyclic β-keto esters, we were confident that the intramolecular alkylation represented a powerful reaction to form the nine-membered carbocycle. We therefore set out to investigate whether exchange of the ester by other electron withdrawing 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



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**.

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 ($SOCl_2$, MeOH), selective reduction of the α-hydroxy ester ($BH_3{\cdot}SMe_2$, cat. $NaBH_4$), acetal protection 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



Scheme 10. a) $SOCl_2$, MeOH, 23 °C, 98%; b) $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, 0 °C, 82%; c) **71**, CSA, CH_2Cl_2, 23 °C, 65%; d) DIBAL–H, CH_2Cl_2/DME, −78 °c; 99%; e) **48**, $CrCl_2$, $NiCl_2$, DMF, 0 °C to 23 °C, 58%, *dr* = 1.3:1 at C8; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 23 °C, 94%; g) DIBAL–H, CH_2Cl_2, −78 to −40 °C, 73%; h) DMP, CH_2Cl_2, 23 °C, 86%; i) *ent*-**37**, Bu_2BOTf, NEt_3, −78 to 23 °C; j) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 23 °C, 72% over two steps; k) EtSH, *n*BuLi, THF, 0 °C, 96%; l) $MeSO_2Ph$, *n*BuLi, THF, −78 °C, 74%; m) HF·pyridine, THF/pyridine 2:1, 0 °C, **S43a** 40%, **S43b** 36%; n) CBr_4, PPh_3, CH_2Cl_2, −20 to −5 °C, **63a** 71%, **63b** 77%; o) DBU, MeCN, 23 °C, **69a** 78%, **69b** 70%; p) Na/Hg, Na_2HPO_4, MeOH, **70a** 69%, **70b** 70%. CSA: camphorsulfonic acid, DME: dimethoxyethane.

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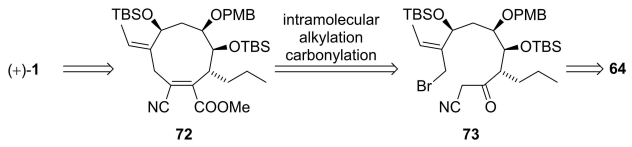
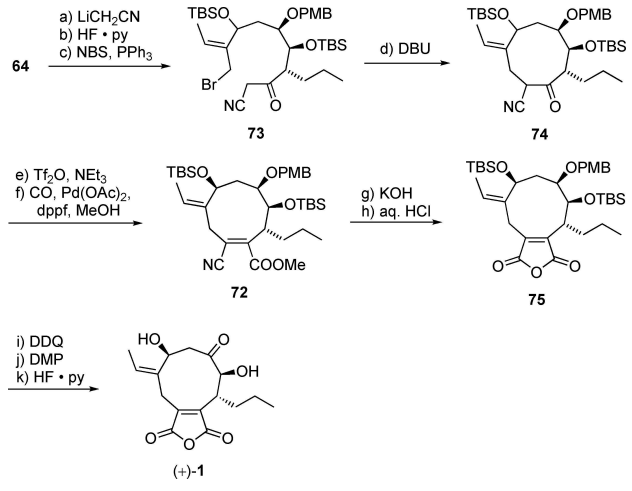
our synthesis with the diastereomeric mixture, which was subjected to TBS protection (TBSOTf, 2,6-lutidine) to give **67**. After regioselective reductive opening of the PMB-acetal, the primary alcohol was obtained as a 1:1.3 mixture of C8-diastereomers, which was subsequently oxidized to aldehyde **68** with Dess–Martin periodinane. The subsequent *syn*-Evans-aldol reaction (Bu_2BOTf, NEt_3) 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 $LiCH_2SO_2Ph$.[45] 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 sulfone moiety (sodium mercury 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., KHMDS, Davis oxaziridine; KHMDS, MoOPh)[46] remained unsuccessful and only led to the recovery of unreacted starting material.



Scheme 11. Retrosynthetic analysis of **1** leading to β-cyano acrylate **72** and formation of the nine-membered carbocycle via an intramolecular alkylation of **73**.



Scheme 12. a) MeCN, *n*BuLi, THF, −78 °C, 78%; b) HF·pyridine, THF/pyridine (2:1), 0 °C, 80%; c) NBS, PPh_3, CH_2Cl_2, −20 to −5 °C, 90%; d) DBU, MeCN, 23 °C, 74%; e) Tf_2O, NEt_3, −78 °C, 85% after three cycles; f) $Pd(OAc)_2$, dppf, CO, DIPEA, MeOH, 55 °C, 93%, g) 10% aq. KOH, *i*PrOH, 70 °C, 80% h) THF/0.1 M aqueous HCl 10:1, 23 °C, 90%; i) DDQ, CH_2Cl_2/H_2O (10:1), 0 °C, 88%; j) DMP, CH_2Cl_2, 23 °C; k) HF·pyridine, 0 to 23 °C, 86% over two steps. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dppf: 1,1′-bis(diphenylphosphino) ferrocene.

In parallel, we investigated nitrile **72** as a suitable precursor for the maleic anhydride moiety (Scheme 11). The installation of the β-keto nitrile was achieved by reaction of thioester **64** with $LiCH_2CN$, analogously to the sulfone approach (Scheme 12).[47] Selective deprotection of the primary allylic alcohol (HF·pyridine) and an Appel reaction (NBS, PPh_3) 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 carbonylation reaction ($Pd(OAc)_2$, dppf, 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 hydrolysis of the nitrile. During our studies we found, that treating **72** with 10% aqueous KOH in *iso*-propanol was the most effective method to provide the hydrolyzed imidate, which could be readily converted into the desired maleic anhydride moiety **75** upon treatment with 0.1 M aqueous hydrochloric acid. Having accomplished this milestone, the 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

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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 D-malic acid and features a NHK reaction (C8 stereocenter), an auxiliary-controlled Evans *syn*-aldol reaction (C2/C3 stereocenters), a highly efficient intramolecular alkylation 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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