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Total Synthesis of (+)-Cornexistin

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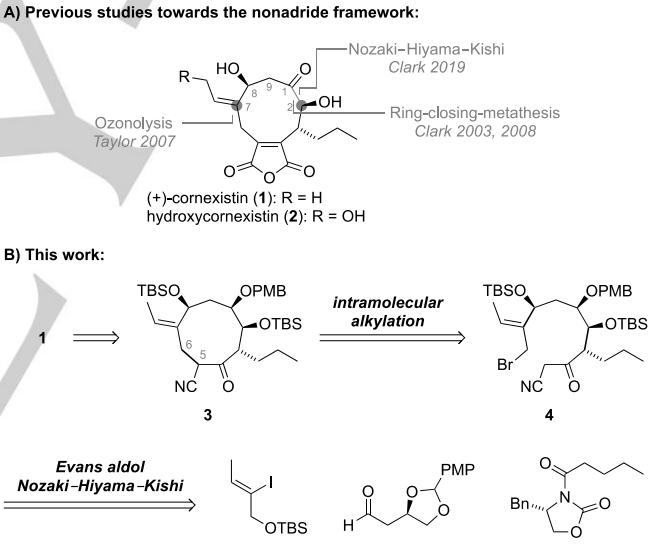
Abstract: Herein, we describe the first total synthesis of (+)-cornexistin as well as its 8-*epi*-isomer starting from malic acid. The robust and scalable route features a Nozaki–Hiyama–Kishi reaction, an auxiliary controlled *syn*-Evans-aldol reaction and a highly efficient intramolecular alkylation to form the nine-membered carbocycle. The delicate maleic anhydride of the nonadride skeleton moiety was accessible via sequential hydrolysis of a β-keto nitrile. The developed route enabled the synthesis of 165 mg (+)-cornexistin.

Due to the rapidly evolving resistance to commercially herbicides, phytotoxic natural products provide a unique opportunity for the development of novel herbicides. Cornexistin (**1**) and hydroxycornexistin (**2**) belong to the unique family of nonadride natural products for which more than 16 members were reported over the last century.[1] The inherent nine-membered carbocycle features a delicate maleic anhydride unit and a β-hydroxy ketone that is linked to a trisubstituted *Z*-alkene. Both functional groups were shown to be acid and base labile leading to ring-opening via hydrolysis of the anhydride or retro-aldol cleavage at C8/C9.[2] In the course of their studies to elucidate the biosynthesis of **1** and **2**, the Cox group determined the absolute stereochemistry by single crystal X-ray diffraction.[3] While nonadrides show various biological activities ranging from cholesterol-lowering, antimicrobial, antitumor, antifungal to antibacterial activity,[1d] **1** and **2** demonstrate outstanding post-emergence herbicidal activity against *monocotyledonous* plants that grow in association with corn.[4] With activity in the range of commercially available herbicides such as glyphosate or bialaphos, whilst exhibiting low toxicity to bacteria, fungi and mammalians,[1a-c] **1** and **2** could represent a unique starting point for the development of novel broad spectrum herbicides. Cornexistin (**1**) was reported to inhibit aspartate amino transferase, however, the exact mode of action remains unclear.[1d] Several research groups have previously investigated the total synthesis of cornexistin (**1**) or hydroxycornexstin (**2**), however all efforts to install the correct substitution pattern failed (Scheme 1A). In seminal work by Clark and Taylor, **1** and **2** were retrosynthetically dissected at C1–C2 (RCM-retron or NHK-retron) or derived by connecting C2–C7 (ozonolysis/ring-expansion retron). The realization of these strategies required a late stage inversion of the C2 stereocenter that turned out to be highly problematic.[5]



Scheme 1. A) Previous studies towards the nonadride framework by Taylor and Clark. B) Retrosynthetic analysis of cornexistin (**1**) and hydroxycornexistin (**2**) based on an intramolecular alkylation strategy. The cyclization precursor **4** arises from a highly convergent three-component coupling strategy.

In the context of our ongoing research program to access xenicin natural products, we recently identified an intramolecular alkylation as the key transformation to form a structurally complex nine-membered carbocycle.[6] For the translation of this strategy to **1**, we first masked the sensitive anhydride unit as the β-keto nitrile **3** (Scheme 1B). Further disconnection at C5/C6 revealed the allylic bromide **4**. As late-stage stereochemical adjustments were considered to be of high risk, we decided to introduce the crucial stereocenters along the northern periphery at an earlier stage.

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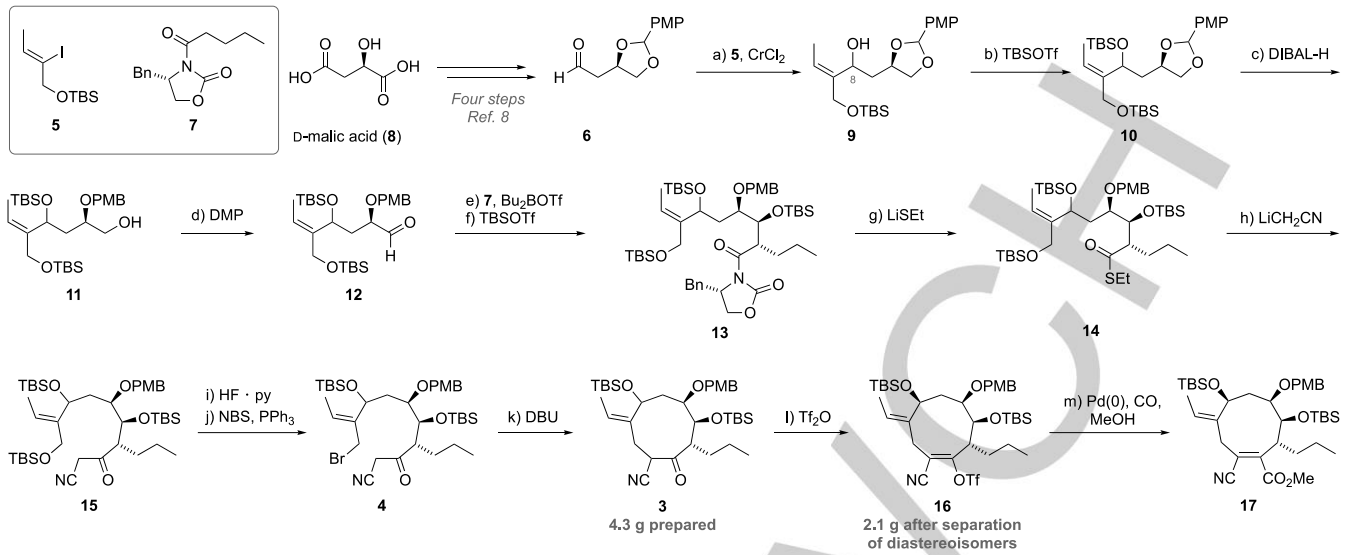

Scheme 2. Synthesis of all carbon precursor **17**. Reagents and conditions: a) **5**, $CrCl_2$, $NiCl_2$, DMF, 0 °C to 23 °C, 58%, d.r. = 1.3:1 at C8; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to 23 °C, 94%; c) DIBAL-H, CH_2Cl_2, –78 °C to –40 °C, 73%; d) DMP, CH_2Cl_2, 23 °C, 86%; e) **7**, Bu_2BOTf, NEt_3, –78 °C to 23 °C; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to 23 °C, 72% over two steps; g) EtSH, *n*-BuLi, THF, 0 °C, 96%; h) MeCN, *n*-BuLi, THF, –78 °C, 78%; i) HF·pyridine, THF/pyridine 2:1, 0 °C, 80%; j) NBS, PPh_3, CH_2Cl_2, –20 °C to –5 °C, 90%; k) DBU, MeCN, 23 °C, 74%; l) Tf_2O, NEt_3, –78 °C, 85% after three cycles; m) $Pd(OAc)_2$, dppf, CO, DIPEA, MeOH, 55 °C, 93%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminiumhydride, DIPEA = *N,N*-diisopropylethylamine, DMF = *N,N*-dimethylformamide, DMP = Dess–Martin periodinane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, NBS = *N*-bromosuccinimide, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, THF = tetrahydrofuran.

For the introduction of the *Z*-alkene linked to the allylic alcohol at C8, we resorted to a Nozaki–Hiyama–Kishi coupling between vinyl iodide **5** and D-malic acid derived aldehyde **6**. Clockwise functional group manipulations were envisioned to enable installation of the C2/C3 stereocenters via reliable *syn*-Evans-aldol chemistry employing **7**.

We commenced our synthesis with the preparation of vinyl iodide **5**, accessible in three steps involving α-iodination (I_2, K_2CO_3, DMAP) of *trans*-crotonaldehyde, reduction ($BH_3{\cdot}Me_2S$, $NaBH_4$) to the allylic alcohol and protection (TBSCl, imH).[7] Aldehyde **6** was available in four steps on large scale (21 g, d.r. = 1.3:1) starting from D-malic acid (**8**) (Scheme 2, see Supporting Information for details).[8] With both building blocks in hand, we investigated the coupling of the two fragments via 1,2-addition. Common procedures involving halogen-metal exchange of **5** (*t*-BuLi, *n*-BuLi, *i*-PrMgCl, Et_2Zn, [*n*-Bu_2(*i*-Pr)Mg]Li) or metal insertion (Mg, Zn, In) were met with failure and only resulted in decomposition of **5** or the undesired 1,2-addition of the metal exchange reagent. Eventually, we found that Nozaki–Hiyama–Kishi conditions ($CrCl_2$, $NiCl_2$) allowed activation of the vinyl iodide **5** and carbon-carbon bond formation to deliver **9** as a mixture of two diastereomers at C8 (58%, d.r. = 1.3:1).[9] To improve the diastereoselectivity, asymmetric versions as reported by Kishi[10] and Berkessel[11] were also investigated, but did not lead to product formation. The mixture was not separated, but directly subjected to TBS-protection and reductive opening of the *para*-methoxybenzylidene acetal to reveal a 1:1 mixture of C8-epimeric primary alcohols **11** in 73% yield.[12] Since the unnatural C8-epimer of **1** represented a valuable substrate for structure-activity-relationship studies and separation turned out to be time-consuming at this stage, we decided to continue the synthesis with the mixture of diastereomers. Oxidation of the primary alcohols **11** utilizing Dess–Martin periodinane gave aldehyde **12** in 86% yield setting the stage for the following *syn*-Evans-aldol reaction. Exposure of **7** to triethylamine in the presence of dibutylboron trifluoromethanesulfonate generated the *Z*-enolate of **7** that underwent a highly-selective *syn*-aldol reaction with **12**.[13] The aldol product was only contaminated with residues of **7** (20%) and did not show any detectable amounts of the undesired *anti*-product. After silylation of the secondary alcohol (TBSOTf, 2,6-lutidine), the protected aldol product **13** was isolated in 72% yield over two steps. Initial attempts to install the required β-keto nitrile moiety by direct cleavage of the auxiliary with $LiCH_2CN$ (CH_3CN, *n*-BuLi, –78 °C) only resulted in ring-opening of the 2-oxazolidinone. Therefore, we first treated **13** with lithium thioethoxide, freshly prepared from *n*-BuLi and thioethanol, to effect clean cleavage of the auxiliary to furnish thioester **14** in almost quantitative yield. Subsequent treatment with $LiCH_2CN$ provided the desired β-keto nitrile moiety in good yield (78%).[14] Selective deprotection of the primary, allylic TBS-group was realized using pyridine hydrofluoride in a 2:1 mixture of tetrahydrofuran and pyridine at 0 °C and delivered the free allylic alcohol in consistent yields of 80%. Subsequent Appel reaction (NBS, PPh_3) completed the synthesis of the highly functionalized cyclization precursor **4**. The robustness of our route allowed for the preparation of 6.9 g of **4** in a single run. For the key-intramolecular alkylation, we first screened a range of carbonate bases in acetonitrile. While lithium carbonate showed no conversion, sodium carbonate, potassium carbonate and cesium carbonate all induced the cyclization of **4** to give the nine-membered carbocycle **3**.[15] Within this series, cesium carbonate showed the highest degree of undesired *O*-alkylation and comparable results were obtained for sodium- and potassium carbonate. The alternative conjugate alkylation was not observed for any of these conditions. The use of

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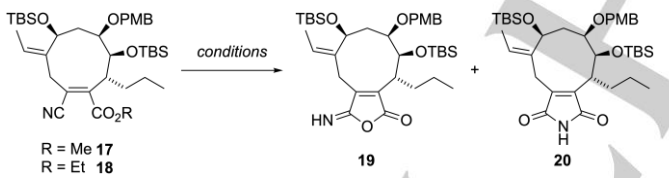
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) further suppressed *O*-alkylation and allowed for the preparation of 4.3 g of **3** in 74% yield. With large quantities of the nine-membered ring in hand, we next focused on the installation of the last missing carbon bond and formation of the delicate maleic anhydride motif. We were pleased to find that treatment of **4** with triflic anhydride and triethylamine successfully delivered the triflate in 65% yield. Unreacted starting material **4** (30%) was recycled to increase the overall yield to 85% after three cycles. Separation of the mixture of C8-epimers by extensive flash column chromatography was also performed at this stage to provide 2.1 g of **16**. Surprisingly, the presence of the nitrile was crucial to enable formation of the triflate. The corresponding keto-ester **27** was resistant to triflation even after an extensive screen of more than 30 reaction conditions (see Supporting Information for details).[16] For the following carbonylation, a combination of $Pd(OAc)_2$ and 1,1'-bis(diphenylphosphino)ferrocene (dppf) in methanol was found to be most effective providing the methyl ester **17** in excellent yields.

With the all carbon precursor **17** in hand, we turned our attention to the challenging hydrolysis of the nitrile (Table 1). Initial efforts to directly form the anhydride under acidic conditions either led to cleavage of the silyl groups and/or formation of complex product mixtures. We therefore investigated a stepwise protocol to generate the anhydride. Treatment of **17** in a 5:1 mixture of tetrahydrofuran and 10% aqueous potassium hydroxide at elevated temperature led to no conversion and only unreacted starting material was recovered (Table 1, entry 1). However, when the hydrolysis was conducted in aqueous methanol, a mixture of imidate **19** and imide **20** was obtained (entry 2).

Table 1. Hydrolysis of nitrile **17**.

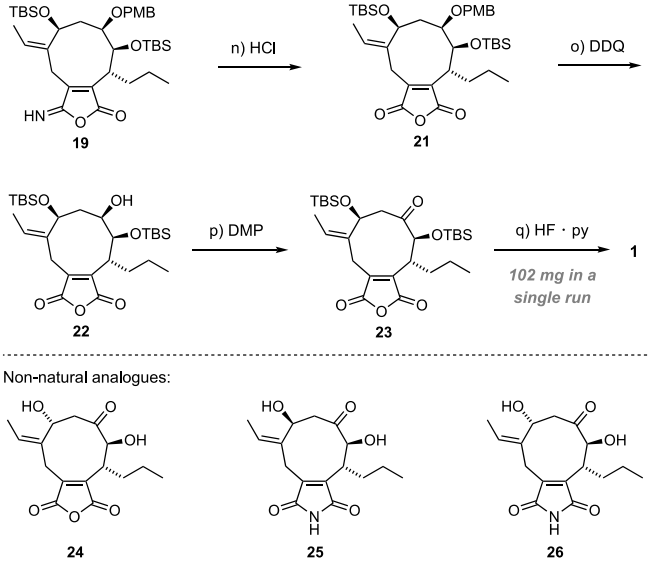


entry	conditions	result
1	10% aq. KOH/THF (5:1), 70 °C, 3 h	no conversion
2	10% aq. KOH/MeOH (5:1), 70 °C, 3 h	**19** (32%), **20** (17%)
3	10% aq. KOH/EtOH (5:1), 70 °C, 3 h	**19** (51%), **20** (9%), **18** (33%)
4	**10% aq. KOH/*i*-PrOH (5:1), 70 °C, 3 h**	**19** (80%), **20** (4%)
5	10% aq. KOH/*t*-BuOH (5:1), 70 °C, 6 h	**19** (75%), **20** (4%)
6	Ghaffar–Parkins catalyst[a], EtOH/H_2O (4:1), 70 °C, 2 d	**20** (84%)

[a] Ghaffar–Parkins catalyst = $[PtH(PMe_2O)_2H(PMe_2OH)]$.

Replacement of methanol with ethanol improved the yield of **19** to 51% and reduced the amount of **20** to 9% (entry 3). The transesterification product **18** (R = Et, 33%) was also isolated and recycled. Switching the solvent to *iso*-propanol, the yield was further improved to 80%, simultaneously decreasing the amount of **20** to 4% (entry 4). Performing the reaction in *tert*-butanol gave comparable results, however the reaction required a significantly longer reaction time (entry 5). Utilizing the Ghaffar–Parkins catalyst resulted in clean hydrolysis of **17** to afford **20** as the only detectable product (entry 6).[17]

To unveil the maleic anhydride moiety, the obtained imidate **19** was further hydrolyzed. Stirring a solution of **19** in a 5:1 mixture of 0.1 M aqueous hydrochloric acid and tetrahydrofuran resulted in rapid consumption of the starting material and clean conversion to **21** in good yields (Scheme 3). For the completion of the synthesis, selective deprotection and oxidation along the northern periphery had to be accomplished. To avoid hydrolysis of the delicate anhydride moiety to the water-soluble diacid, 0.2 M aqueous hydrochloric acid was used in the work-up procedures for all anhydride containing intermediates. Cleavage of the *para*-methoxybenzyl ether was cleanly achieved upon exposure to DDQ and delivered alcohol **22** in 88% yield. The subsequent oxidation also proceeded smoothly, however ketone **23** was found to be sensitive to silica gel, resulting in a substantial loss of material after purification. We assume that this loss might be a result of retro-aldol cleavage or hydrolysis of the sensitive maleic anhydride. Efforts to isolate any byproducts were met with failure. To avoid purification by column chromatography, the reaction mixture was diluted with pentane and the suspension was filtered over a short plug of Celite. The crude ketone was then directly exposed to pyridine hydrofluoride in tetrahydrofuran to give (+)-cornexistin in 86% yield over two steps. The obtained analytical data of synthetic **1** were in full agreement with the data reported by Nakajima[1b] and Cox.[3b] The C8-epimer **24** of the natural product and the corresponding imide analogues **25** and **26** were obtained under identical conditions (see Supporting Information for details). Finally, we also investigated the late-stage oxidation of **1** to **2**. Unfortunately, exposure of **1** to a panel of oxidation conditions (e.g. SeO_2; PIDA, I_2, hv or NBS, AIBN) only led to no reaction or decomposition of **1**.



Scheme 3. n) 0.1 M aqueous HCl/THF 5:1, 23 °C, 90%; o) DDQ, CH_2Cl_2/H_2O 10:1, 0 °C, 88%; p) DMP, CH_2Cl_2, 23 °C; q) HF·pyridine, 0 °C to 23 °C, 86% over two steps. DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane, THF = tetrahydrofuran.

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In conclusion, we accomplished the first total synthesis of the natural herbicide (+)-cornexistin **1**. The robust route features a Nozaki–Hiyama–Kishi reaction and an Evans auxiliary controlled *syn*-aldol reaction to rapidly access multigram quantities of the highly functionalized cyclization precursor **4**. Formation of nine-membered carbocycle was accomplished via a base-mediated intramolecular alkylation reaction in good yield. The installation of the delicate maleic anhydride was achieved from a β-keto-nitrile moiety. The developed synthetic platform allowed for the preparation of 165 mg (102 mg in a single run) and enables access to several fully synthetic derivatives that are inaccessible via semi-synthesis.

Acknowledgements

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Keywords: total synthesis • nonadride • herbicidal natural products • nine-membered carbocycles

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[12] The corresponding secondary alcohols were formed in 23% yield and were recycled via oxidative acetal formation (DDQ) and reductive ring-opening. See Supporting Information for details.

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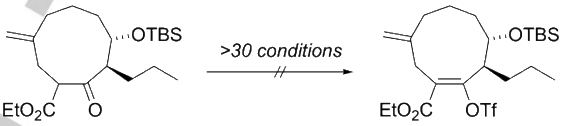
[16] Ketone **27** exists as a mixture of keto-enol tautomers (~2:1).



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