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The Landscape of Lankacidin Biomimetic Synthesis: Structural Revisions and Biogenetic Implications

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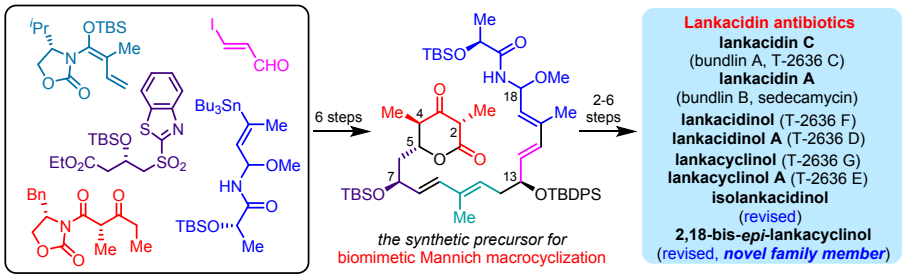
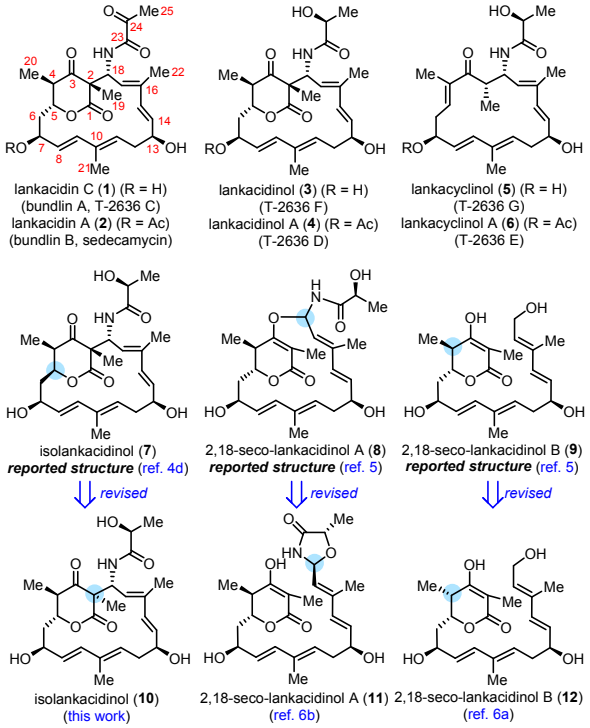


ABSTRACT: In this report, a unified biomimetic approach to all known macrocyclic lankacidins was presented. By taking advantage of the thermolysis of *N*,*O*-acetal to generate the requisite *N*-acyl-1-azahexatriene species, we eventually realized the biomimetic Mannich macrocyclization, from which all of the macrocyclic lankacidins can be conquered by orchestrated desilylation. The reassignments of the reported structures of isolankacidinol (**7** to **10**) and the discovery of a recently isolated "lankacyclinol" found to be in fact 2,18-bis-*epi*-lankacyclinol (**72**), unraveled the previously underappreciated chemical diversity exhibited by the enzymatic macrocyclization. In addition, the facile elimination/decarboxylation/protonation process for the depletion of C1 under basic conditions resembling a physiological environment may implicate more undiscovered natural products with variable C2/C18 stereochemistries (i.e., **62**, **73**, and **75**). The notable aspect provided by a biomimetic strategy is significantly reducing the step count compared with the two previous entries to macrocyclic lankacidins.

INTRODUCTION

The preliminary reports of lankacidin antibiotics from actinomycete strains date back over sixty years ago when the Swiss and Japanese groups independently isolated a nitrogen-containing crystalline lankacidin C (**1**) (**Figure 1**),[1] also referred to as bundlin A or T-2636 C.[2] The complex structure as well as absolute configuration of **1** and its coisolated monoacetate lankacidin A (**2**) were established later by X-ray crystallographic analysis of their hydrazone derivatives.[3] During a period from 1971 to 1975, Harada and coworkers reported several new members (**3**–**7**) from the broth cultures of *Streptomyces rochei* var. *volubilis*,[4] which share the parent 17-membered macrocyclic framework endowed with two pentadienyl alcohols and a bridged, fully substituted β-oxo-δ-lactone with an amide residue adjacent to an all-carbon quaternary center. Isolankacidinol (**7**) was postulated to be a C5-epimer of lankacidinol (**3**) based upon a combination of a 1D NMR experiment and the negative Cotton effect observed in the optical rotatory dispersion (ORD) spectrum of the octahydrotriacetate derivative of **7**.[4d] Lankacyclinol (**5**) and congener **6**, hypothetically derived from the enzymatic eliminative decarboxylation (depleting C1), were also isolated by the same team.[4a,d] In 2018, Wang and coworkers disclosed 2,18-seco-lankacidinol A (**8**) and B (**9**) from *Streptomyces* sp. HS-NF-1178.[5] The *R*-C4 stereochemistry of **9**, the only naturally

Figure 1. Representative Lankacidin Antibiotics.



occurring nonmacrocyclic lankacidin prior to our investigations, was reassigned to *S*-C4 (as shown in **12**) by the Seiple group through total synthesis later in the same year.[6a] Very recently, the structure of **8** was also reassigned by us through a modular approach to rule out the proposed C18–O ether linkage in the original publication.[6b]

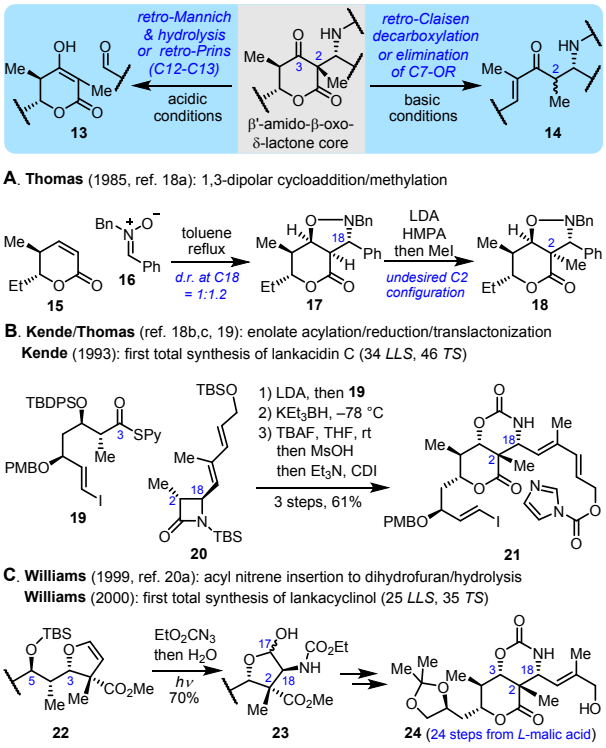
In addition to their structural complexity, lankacidins possess an exceedingly broad array of biological activities. Several congeners have showed strong antibacterial activities against various gram-positive bacteria including multidrug resistant clinical strains such as *Staphylococcus aureus*.[7] The mode of action was recently revealed through the inhibition of protein synthesis by binding at the peptidyl transferase center of the eubacterial large ribosomal subunit.[8] Sedecamycin (the generic name of **2**) exhibited significant growth-inhibitory potency against *Treponema hyodysenteriae*, and it was approved in 1985 as a veterinary drug for the treatment of swine dysentery (SD).[9] Moreover, the same compound displays a promising *in vitro* activity against the *Trypanosoma brucei* parasite with an IC_{50} value of 33 μM, being 66-fold more potent than eflornithine, a clinically used drug for late-stage human African trypanosomiasis.[10] Lankacidin C (**1**) was recently identified as one of the top candidates to combat *Borrelia burgdorferi*, thereby holding great promise for better Lyme disease therapy.[11] Additionally, modest to potent *in vitro* and *in vivo* antitumor activities have been known for decades.[5,12] In 2016, mechanistic studies on the cytotoxic action demonstrated that the lankacidin antibiotic is a novel microtubule-stabilizing agent, which may target the paclitaxel binding site.[13]

Current fermentation to produce lankacidins usually yields a complex mixture of congeners. Moreover, available semisynthetic modifications of the parent macrocycle were severely limited due to its sensitivity to even mildly acidic or basic conditions.[4a,7c,14] Although a couple of analogs have been prepared chemically or enzymatically,[15] a *de novo*, practical synthetic route to lankacidins would arguably enable access to a greater diversity of small-molecule therapeutic leads with improved pharmacological profiles.[16] Herein, we described a full account[17] on the unified synthesis of all known macrocyclic lankacidins in only 8–12 steps, permitting access to a series of C2/C18 diastereomeric congeners as well as revision of the reported structure of isolankacidinol (**7**). We also uncovered that Wang's lankacyclinol, exhibiting cytotoxicity against human adenocarcinoma cells A549 (IC_{50} = 28 μg/mL), is actually a 2,18-bis-epimer of **5**, a new natural product.

RESULTS AND DISCUSSION

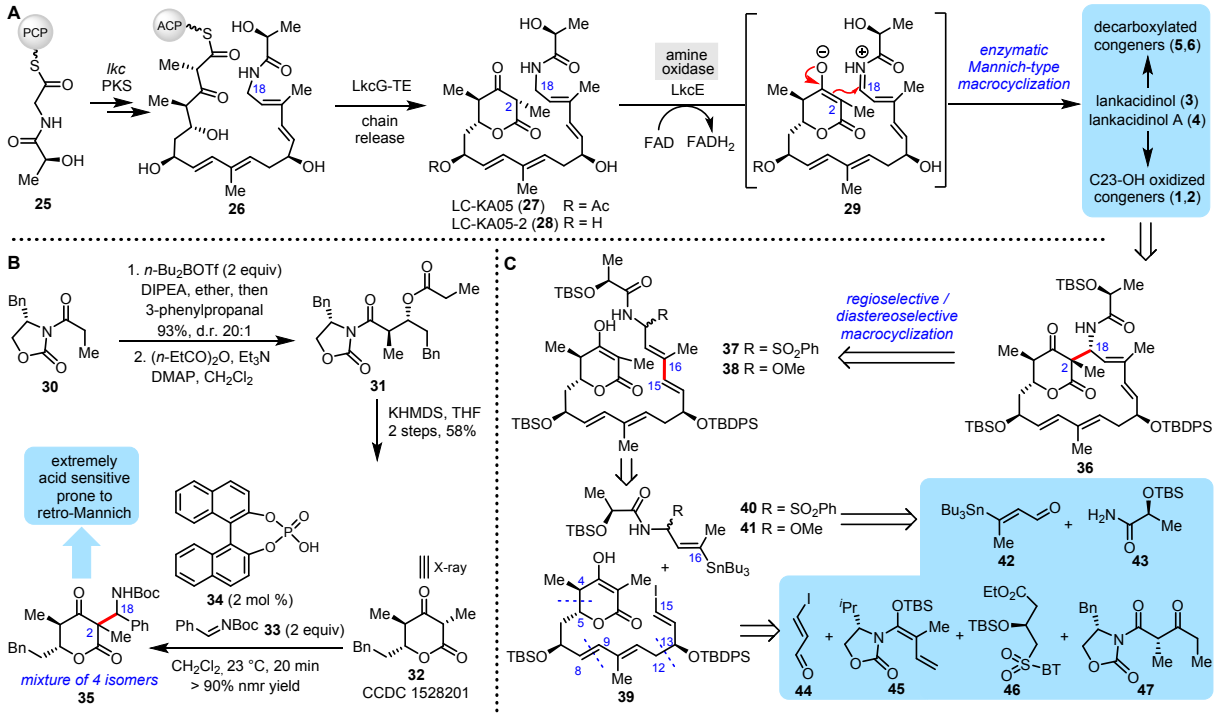
Historical Context and Strategic Considerations. The fascinating biological profile in conjunction with the synthetic challenge has stimulated numerous synthetic efforts for more than three decades.[18-20] Representative approaches to construct the lactone core prior to our own endeavor are summarized in **Scheme 1**. Thomas's early model studies involving 1,3-dipolar cycloaddition followed by methylation provided exclusively undesired C2 stereochemistry.[18a] Later, Thomas and Kende independently devised a translactonization strategy based on similar *L*-aspartic acid-derived β-lactam intermediates where the quaternary stereocenters were established by convergent enolate acylation.[18b,c] By taking advantage of the secured relay transformation of a stable tricyclic carbamate to the natural product, Kende accomplished the first total synthesis of lankacidin C (**1**) in 1993.[19a] This landmark achievement set the stage for the fully synthetic entry to the target antibiotic family. Williams and coworkers also reported their creative studies towards the lactone segment, featuring a regio- and diastereoselective acyl nitrene addition to dihydrofuran **22** to furnish cyclic hemiacetal **23**.[20a] A series of chemical manipulations provided δ-lactone **24** with the C3–OH and the amido appendage protected as carbamate. Although further elaboration of segment **24** to the lankacidins was not fruitful,[20b] the stereocontrolled β-amido ester synthetic methodology developed during the process has been successfully utilized by the same laboratory to synthesize lankacyclinol (**5**), allowing the C2 configuration to be established.[20c]

Scheme 1. Previous Synthetic Approaches to the Lactonic Core of the Lankacidin Antibiotics.



We initially took note from the step-economy issue which plagued all the previous strategies. Each route constructed the β-oxo-δ-lactone core at a relatively early stage and invariably reduced the C3 carbonyl group as a protected alcohol to attenuate the sensitive nature of the intermediate. This not only gives rise to a heteroatom-rich segment containing five contiguous stereocenters, but also maximizes the extraneous protecting-group and redox manipulations needed to access the target, which in turn dramatically attenuated the synthetic efficacy.[21] A fundamentally disparate skeleton-forming strategy employed by the biosynthetic machinery of nature is inspiring.[22] In 2005, Arakawa and coworkers disclosed the

isolation of acyclic δ-lactone LC-KA05 (**27**, **Scheme 2A**) and confirmation of **27** as an essential biosynthetic intermediate.[22c] They



Scheme 2. Biosynthesis Proposal (A), Initial feasibility Studies (B), and Retrosynthetic Analysis of Lankacidins (C).

also identified a multifunctional flavin-dependent amine oxidase (LkcE) responsible for the unusual amide oxidation of **27** at C18, followed by intramolecular C2-enolate trapping of the resultant hypothetical iminium species to complete the lankacidin macrocycle.

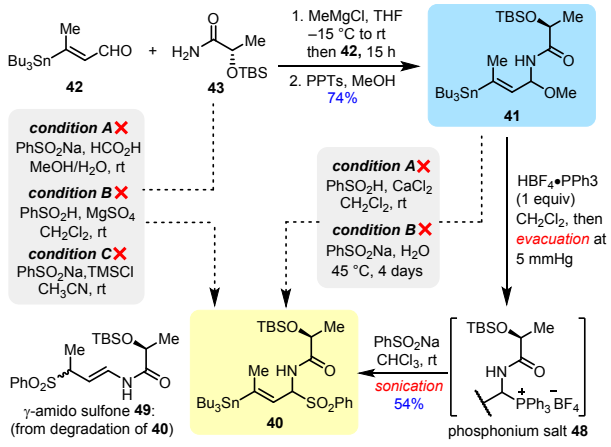
We envisaged a synthetic plan hinging on an unprecedented late-stage stereogenic center-forming Mannich macrocyclization. While the Mannich reaction was well adapted for the construction of five- to seven-membered ring systems,[23] cyclization leading to macrocycles were much less explored.[24] This circumstance was further exacerbated by the elusive nature of critical diastereocontrol.[25] Preliminary feasibility studies were undertaken on truncated β-ketolactone **32**, which wassynthesized from 3-phenylpropanal in a 3-step sequence (**Scheme 2B**).[26] Subjection of **32** to an acid-catalyzed Mannich reaction with *N*-Boc benzaldimine **33**[27] smoothly afforded a diastereomeric mixture of adducts **35** in an 81% yield. Further investigations such as isomer separation and *N*-Boc deprotection under a variety of conditions based on this material proved difficult owing to its propensity to undergo a retro-Mannich reaction.[28] Such a process occurred to neat **35** even during the prolonged storage at temperatures below –20 °C. With these observations in mind, we anticipated that a preinstallation of the *O*-silyl (*S*)-lactoyl group in the macrocyclization precursor might avoid the leverage of late-stage modification to the *N*-protecting group within the strained, energetically unfavorable Mannich adduct.

Retrosynthetic Analysis. The retrosynthetic disconnection began with rupturing the critical C2–C18 bond of our primary target lankacidinol (**3**) to afford a globally protected *N*-acyl azahexatriene surrogate (i.e., **37** or **38**)[29] (Scheme 2C). We anticipate the site-selective desilylations followed by C7-OH acetylation or C24-OH oxidation on **36** after the macrocyclization event will provide access to other macrocyclic members of the family. In turn, formation of the C15–C16 bond via Stille coupling would lead to advanced vinyl iodide **39** and vinyl stannane (i.e., **40** or **41**) with a preinstalled *N*-lactoyl as well as a proper oxidation level at C18. This synthetic design would not only provide a playground for the Mannich macrocylization or intermolecular model studies through facile alteration of different imine surrogates, but also facilitate future synthetic studies toward other acyclic lankacidin-related metabolites. Accordingly, **39** can be prepared from **44** by successive union of three building blocks (**45**–**47**) of similar complexity. The classic carbonyl group-based transformations and bond-forming sequence (i.e., C12–C13, ΔC8–C9, and then C4–C5) to construct **39** was planned to formally emulate the previously proposed chain elongation and termination steps in lankacidin biosynthesis.[22c]

Synthesis of the Truncated Azabutadiene Surrogate Fragments. The preparation of the stannylated amido sulfone **40** from aldehyde **42**[30] and protected chiral lactamide **43**[31], at

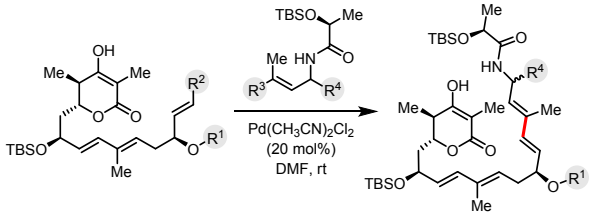
first a seemingly simple transformation, turned out to be a daunting challenge. As outlined in **Scheme 3**, the conventional Brønsted acid[32] and Lewis acid[33] conditions utilizing benzenesulfinic acid or its sodium salt only led to various side products from protodestannylation, double bond isomerization, or desilylation of the starting materials. Explorations based on nucleophilic trapping of the preformed imine obtained via acylation of a *N*-metalloimine species were also fruitless.[34] Thus, an alternative route to initially access *N*,*O*-acetal **41** was evaluated. Using Manolikakes's protocol,[35] **43** was deprotonated with methylmagnesium chloride and subsequently condensated with aldehyde **42** to generate labile hemiaminal intermediate, which underwent acid-catalyzed transacetalization in methanol to provide **41** (74% from **42**) on a decagram-scale. However, arylsulfinate displacement under protonic acid conditions still occurred with extensive destannylation, whereas heating **42** in aqueous sodium arylsulfinate at 45 °C for 4 days only led to recycled starting material. A mild indirect method inspired by Adamek's work was eventually adopted,[36] in which treatment of *N*,*O*-acetal **41** with triphenylphosphonium tetrafluoroborate gave phosphonium salt **48** bearing a polar C_α–P^+ bond after solvent (including the coproduced methanol) removal under high vacuum. Successive exposure of an ethanol-free chloroform solution of this material to powdered sodium arylsulfinate under sonication cleanly furnished α-amido sulfone **40**, which was discovered to exert a pronounced tendency to undergo destannylative sulfonyl migration to afford **49** upon contact with silica gel or even during prolonged storage.[37]

Scheme 3. Various Approaches to Prepare Amido Sulfone **40**.



Preparation of the Precursor for Mannich Macrocyclization: The Dead-End. With truncated imine equivalent **40** in hand, we went further to construct the linear precursor for the macrocyclization. Toward this end, the Stille coupling of vinyl iodide **39**[38] with stannane **40** was explored in the presence of bis(acetonitrile)dichloropalladium(II) (20 mol%) (**Table 1**, entry 1). However, it only gave rise to partially recycled starting materials together with γ-amido sulfone **49** as the only identifiable product. A number of conditions were examined but all failed to form the long-chain amido sulfone based on these two substrates (for details, see SI, **Figure S1**). Being cognizant of the reluctant transmetalation associated with the sterically congested stannane might be the source of our frustrations,[39a,b] we modified the structures of two Stille coupling partners. Analogous results were observed using a desilylated vinyl iodide **39a** (entry 2). Also noteworthy is the fact that replacement of **40** with **40a** bearing a more reactive trimethylvinyl stannyl moiety[39c] under otherwise identical conditions (cat. $[Pd(CH_3CN)_2Cl_2]$, DMF, 23 °C) resulted in an increase of side product **49** (entry 3). Although by interchanging the tin and iodide substituents of two reaction partners, an unstable product with the desired C15–C16 linkage could be isolated together with the recycled starting materials, further spectroscopic elucidation precluded the existence of an α-amido sulfone structure (entry 4).

Table 1. Attempts of Stille Coupling on Various Substrates.



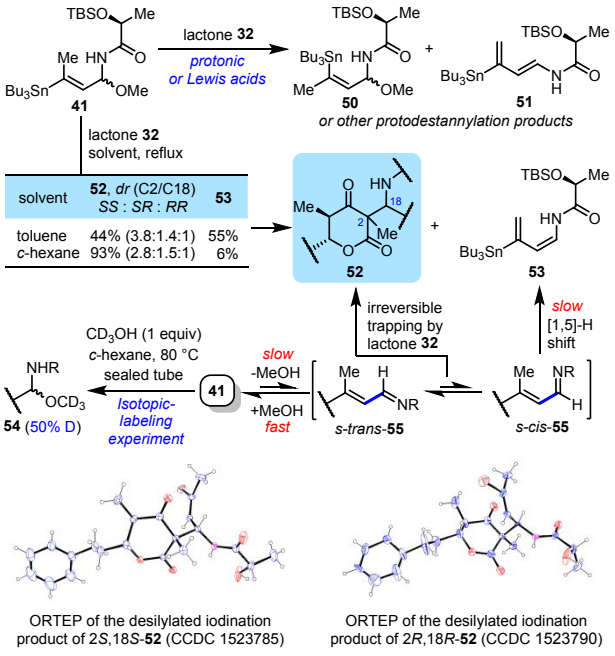
entry[a]	*lactone* fragment			*imine* fragment			*result*[b]
		R^1	R^2		R^3	R^4	
1	**39**	TBDPS	I	**40**	$SnBu_3$	SO_2Ph	---[c]
2	**39a**	H	I	**40**	$SnBu_3$	SO_2Ph	---
3	**39**	TBDPS	I	**40a**	$SnMe_3$	SO_2Ph	---
4	**39b**	TBDPS	$SnMe_3$	**40b**	I	SO_2Ph	---
5	**39**	TBDPS	I	**40c**	$SnBu_3$	SPh	---
6	**39**	TBDPS	I	**40d**	$SnBu_3$	OH	---
7	**39**	TBDPS	I	**48**	$SnBu_3$	PPh_3BF_4	---
8	**39**	TBDPS	I	**41**	$SnBu_3$	OMe	**38**: 45% (57%)[d]
9	**39c**	TBS	I	**41**	$SnBu_3$	OMe	---
10	**39a**	H	I	**41**	$SnBu_3$	OMe	---

[a] Unless otherwise indicated, reactions were performed with a lactone fragment **39** (0.1 mmol) and imine fragment (0.2 mmol) in DMF (0.04 M). [b] Isolated yield. [c] The coupling product not obtained. [d] The reaction was run at a 0.7 mmol scale with $Pd_2(dba)_3$ (20 mol%) and a 64% yield was achieved based on recovered lactonic starting material.

N,O-Acetal-based Mannich Chemistry Revisited: A Thermal Demethoxylation Approach. The enormous, unexpected hurdle in synthesizing **37** via Stille cross-coupling compelled us to abandon amido sulfone as the reaction partner. A systematic evaluation of both reaction partners was thus conducted. Relevant structural moieties including *N*,*S*-acetal, hemiaminal, or phosphonium salt were found to be incompatible with the coupling conditions (entries 5–7). It was pleasing to discover that the coupling between *N*,*O*-acetal **41** and **39** successfully led to **38**, which turned out to be acid-liable but can be obtained in a 45% yield (entry 8).[40] The TBDPS protection of the C13 hydroxyl group proved to be crucial because the coupling products from vinyl iodides bearing TBS protection or no protection on the C13 position were too sensitive to permit purification or characterization (entries 9 and 10). Screening of further coupling conditions

revealed that the use of phosphine ligands had detrimental effects on product formation,[41] presumably due to the facile displacement of the methoxy group in the acetal moiety (for details, see SI of ref. 17). Finally, tris(dibenzylideneacetone)dipalladium (20 mol%) in DMF at 23 °C was selected as the optimal condition for the scale-up preparation of **38** with an improved yield of 57%.[42]

Scheme 4. Thermoregulated Mannich Reaction of the Intramolecular Model Studies.

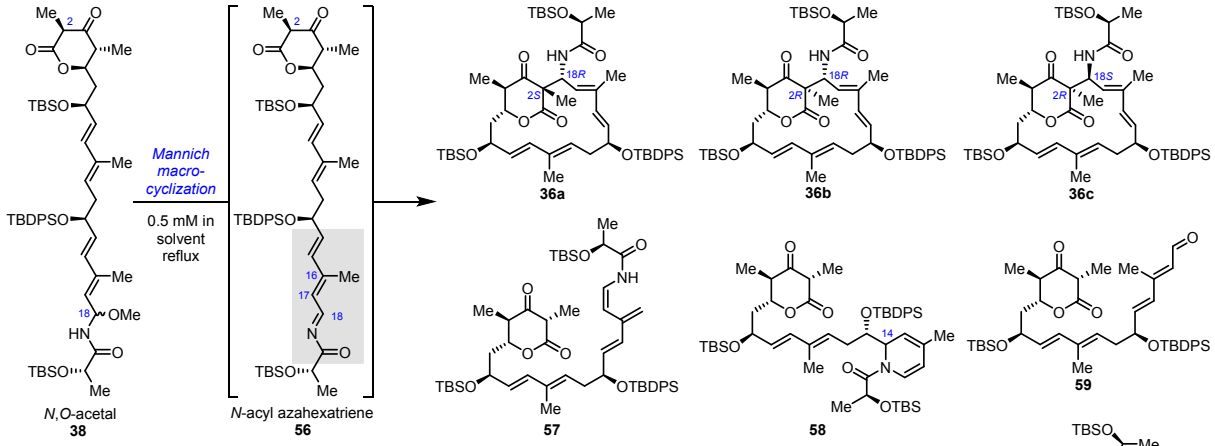


The long-chain *N*,*O*-acetal **38** was the only viable macrocyclization precursor for advancement to the lankacidins. The next focus is to probe suitable *N*,*O*-acetal-based conditions using an intermolecular variant (**Scheme 4**).[43] However, the activated *N*-lactoyl iminium species *in situ* generated from **41** under protonic or Lewis acidic conditions severely suffered from either double bond isomerization followed by recapture by methanol to produce **50** or tautomerization to form *trans*-enamide **51**, and they were found to be reluctant to undergo Mannich addition with the lactonic nucleophile (for details, see SI of ref. 17).[44] To devise a workaround, we became keenly aware of the alcohol exchange phenomenon of *N*,*O*-acetals under pyrolytic conditions reported by Ben-Ishai in 1960s.[45] This thermal demethoxylation of *N*,*O*-acetal has been recently resumed to prepare some bench-stable *C*-phenyl-*N*-acyl imines.[46] However, as a mild method for imine generation, its application in a telescoped C–C bond-forming process has received little attention from the synthetic community.[47] Imine **55** could be formed as a transient species via a thermal depletion of methanol, the conditions of which would not only be strictly neutral and substrate-tolerant, but also facilitate the nucleophilic addition. At the outset, heating a solution of **41** and **32** in toluene resulted in the Mannich adducts **52** in a 44% yield, alongside a substantial amount of *cis*-configured enamide **53**. A survey of solvents revealed that formation of **53** was suppressed by changing the reaction solvent to cyclohexane, allowing **52** to be isolated in a combined yield up to 93% favoring a (2*S*,18*S*)-configured diastereomer (**Scheme 4**).[48] Interestingly, without an external nucleophile, *N*,*O*-acetal **41** was fully recovered (> 90%) even after refluxing in the same solvent overnight. The equilibrative formation of *N*,*O*-acetal *via* a *N*-lactoyl imine was confirmed by an isotopic-labeling experiment preformed with *d*3-methanol. This imine intermediate, albeit at a low concentration, can be irreversibly trapped by lactone **32**.[48] This initial success to assemble an intermolecular model system of the lactonic core via *N*,*O*-acetal-based Mannich chemistry convinced us that the biomimetic macrocyclization strategy would be rewarding if an improved stereofacial control to the imine could be realized. Additionally, decarboxylation of the Mannich adduct under macrocyclic stereocontrol was anticipated to be more stereoselective in installing the C2 stereogenic center present in lankacyclinol.[49,50]

Explorations on Mannich Macrocyclization. The pivotal biomimetic Mannich macrocyclization was thus conducted in refluxing cyclohexane at a concentration of 0.5 mM (**Table 2**, entry 1). Three macrocyclized Mannich adducts **36a-c** were isolated in a combined yield of 46% in a ratio of 6.4:1.0:1.8 (**36a**:**36b**:**36c**). Extensive NMR analysis revealed that these macrocycles were exclusively derived from the α-addition (C2) of the enolate carbon to the imine (C18). As suggested by the presence of a diagnostic NOE interaction between C5-H and C2-Me (for comprehensive presentations of their individual COSY, NOESY and HMBC correlations, see SI, **Figure S3**), only the major diastereomer **36a** has the desired stereochemistry at C2. Additionally, the absolute configurations of newly established stereocenters at C18 in **36a** and **36b** were both inferred to be the (*R*)-configuration based on their successful advancements to lankacyclinol (*vide infra*). The participation of the presumptive *N*-lactoyl azahexatriene species **56** in the Mannich macrocyclization was further ascertained by the coproduction of trienic enamide **57** and dihydropyridine **58**. The former compound, isolated in an 11% yield as an extremely unstable single geometric isomer bearing C17–C18 (*Z*)-alkene, appeared to arise by a 1,5-sigmatropic hydrogen shift involving the C16-Me of the imine *s-cis* conformer (*s* represents the C17–C18 single bond). Moreover, **57** was found to be stable in refluxing cyclohexane for 24 hours, thus supporting an irreversible nature of the *N*-lactoyl imine-enamide tautomerism under experimental conditions. Additionally, byproduct **58** with unassigned stereochemistry at C14 might be derived from the initial *trans*-to-*cis* isomerization of the trisubstituted ΔC16–C17 in the intermediary azatriene system followed by a diastereoselective 6π-azaelectrocyclization[51] (~9:1 *ds*). However, macrocycles (i.e., **60**) generated by intramolecular nucleophilic capture of this ΔC16–C17 isomeric imine were not detected in the reaction mixture. The reactive species **56** can otherwise undergo hydrolysis by reacting with a trace amount of water presented in the reaction system to afford all-*trans* polyenal **59**, the same compound that may already exist as an inseparable contaminant in the starting material **38** (5~15 wt.%).

The crucial thermolytic stereogenic center-generating macrocyclization warrants some additional discussion. High-dilution conditions were found to be necessary to ensure a practical cyclization efficiency. When performed at a higher substrate concentration (5 mM), the reaction was sluggish and only 24% conversion of **38** was observed (**Table 2**, entry 2). Attempts to enhance the diastereoselectivity for **36a** by introducing metal complexation has yet to be effective (entries 3–6). Utilization of nonpolar solvents with lower boiling points such as cyclopentane and *n*-hexane resulted in either no reaction or low conversion accompanied by unidentified side products (entries 7 and 8). Intriguingly, a preference for the formation of cyclization products with *R*-configured quaternary stereocenters was observed when chlorinated aliphatic solvents such as tetrachloromethane and 1,2-dichloroethane (entries 9 and 10), or aromatic solvents were applied (entries 11–15). In particular, upon changing the solvent from cyclohexane to toluene, the cyclization occurred with an increased efficiency, allowing the macrocycles to be isolated in 55% yield in a ratio of 6.9:1.0:6.1 (**36a**:**36b**:**36c**) within 6 hours. At refluxing temperatures higher than 130 °C, the serviceable yields of Mannich adducts (36% for ethylcyclohexane, 45% for *p*-xylene) were achieved, but increased amounts of **57** or **58** were generated. Given the molecular complexity rapidly generated as well as the operational simplicity observed in this biomimetic macrocyclization, the isolated yield of 32% for the desired (2*S*,18*R*)-diastereomer **36a** is remarkable.

Table 2. Optimization of the Thermoregulated Mannich Macrocyclization



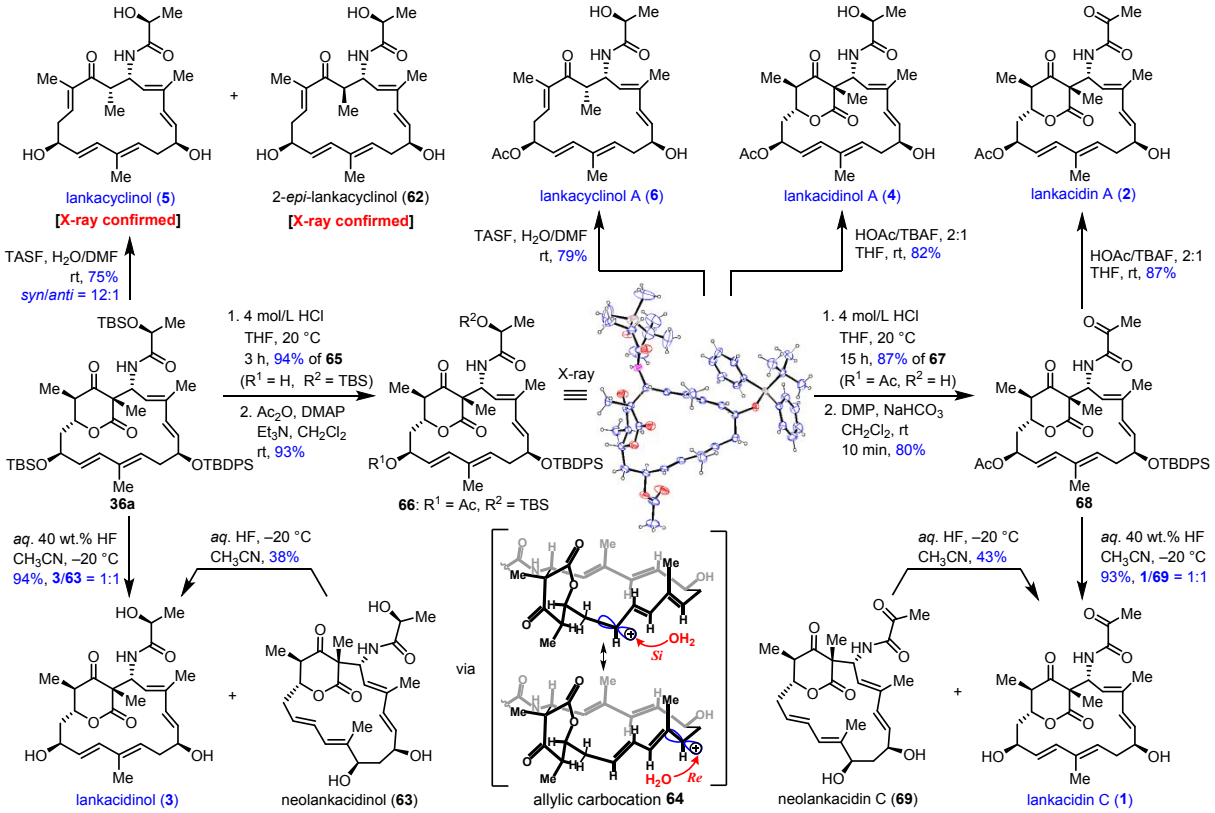
entry[a]	solvent	atmospheric boiling point[d]	additive	Time	conversion[e] of **38**	yield[e] (%) of **36** (*dr* **36a**:**36b**:**36c**)	yield[e] (%) of **57**	yield[e] (%) of **58**
1	cyclohexane[b]	80.7 °C	–	22 h	100%	46 (6.4 : 1.0 : 1.8)	11	4
2	cyclohexane[c]	80.7 °C	–	22 h	24%	14 (7.8 : 1.0 : 4.2)	ND[f]	ND[f]
3	cyclohexane	80.7 °C	$Yb(fod)_3$ (5 mol%)	20 h	100%	31 (3.6 : 1.0 : 2.2)	7	6
4	cyclohexane	80.7 °C	$Pr(fod)_3$ (5 mol%)	25 h	100%	29 (2.9 : 1.0 : 2.3)	9	–
5	cyclohexane	80.7 °C	$Er(fod)_3$ (5 mol%)	22 h	53%	21 (4.4 : 1.0 : 3.0)	10	6
6	cyclohexane	80.7 °C	$Cu(fod)_2$ (5 mol%)	22 h	47%	13 (5.8 : 1.0 : 3.3)	7	–
7	cyclopentane	49.3 °C	–	48 h	< 5%	– [g]	–	–
8	*n*-hexane	69.0 °C	–	60 h	63%	10 (2.7 : 0 : 1.0)	–	–
9	tetrachloromethane	76.8 °C	–	22 h	100%	17 (1.1 : 0 : 1.0)	8	7
10	1,2-dichloroethane	83.5 °C	–	22 h	100%	20 (1.0 : 0 : 1.2)	7	7
11	benzene	80.1 °C	–	24 h	100%	22 (2.1 : 1.0 : 2.9)	12	–
12	hexafluorobenzene	81.0 °C	–	22 h	100%	22 (4.2 : 1.0 : 3.8)	4	3
13	toluene	110.6 °C	–	6 h	100%	55 (6.9 : 1.0 : 6.1)	15	3
14	α,α,α-trifluorotoluene	103.5 °C	–	22 h	100%	30 (2.3 : 1.0 : 2.4)	12	8
15	*p*-xylene	138.5 °C	–	2.5 h	100%	45 (5.4 : 1.0 : 4.7)	25	9
16	ethylcyclohexane	131.8 °C	–	2 h	100%	36 (3.2 : 1.0 : 2.2)	10	18

[a] All reactions were carried out on a 0.03 mmol scale and a concentration of **38** was 0.5 mM unless otherwise noted. [b] Carried out on a 0.3 mmol scale. [c] Carried out on a concentration of 5 mM. [d] From *CRC Handbook of Chemistry and Physics*, 91st ed. Haynes, W. M., Ed.; CRC Press: Boca Raton, FL, 2010. [e] Conversions of **38** and diastereoselectivities of **36** were calculated after isolation. [f] Not determined. [g] Not obtained.

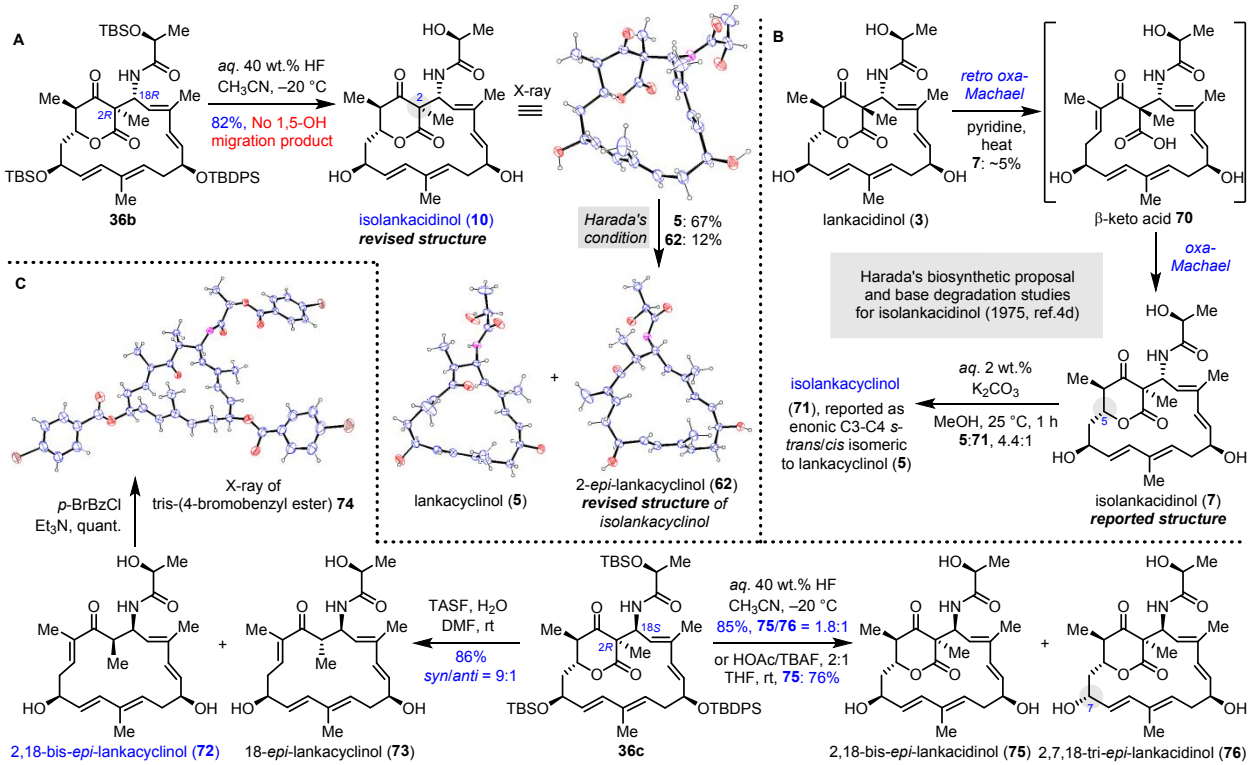
Unified Synthesis of Macrocyclic Lankacidins. By procuring enough quantities of **36a**, we were poised to finalize the synthesis of our preliminary target lankacidinol (**3**). Global deprotection of **36a** was not trivial, as it needed to be executed to tolerate the fragile β-oxo-δ-lactone as well as the dienylic alcohol functionalities. A similar process using bis-TBS-protected lankacidin C as a substrate was declared by the Kende group to be unfruitful with all variants of fluoride-based protocols.[19b] Indeed, exposure of **36a** with either TBAF or tris(dimethylamino)sulfonium difluorotrimethylsilicate

(TASF) both resulted in considerable amounts of side products from elimination of the C7-hydroxyl group. By using excess water as a protic additive in TASF-mediated deprotection,[52] decarboxylation occurred prior to the complete silyl removal, affording lankacyclinol and its C2-epimer in a combined yield of 75% (**Scheme 5**). The synthetic **5** proved to be identical in all respects to natural (–)-lankacyclinol.[4d,21c] The high selectivity for the 2*S*-isomer (**5**/**62**, 12:1) may be attributed to the *Re*-face selective protonation of the intermediary C3-enolate with the stereocontrol imparted from the rigid conformation of the polyene macrocyclic ring.[49] Analysis of the major product by X-ray diffraction unambiguously confirms the configuration at C18 and provided *the first solid state topological structure of the decarboxylated lankacidin macrocycles*. After extensive experimentation (for details, see SI of ref. 17), we uncovered a condition to liberate all of the hydroxyl groups without disturbing the δ-lactone. In this event, prolonged treatment of **36a** with 40 wt.% HF in acetonitrile at –20 °C gave (–)-lankacidinol (**3**) in a 51% yield exhibiting spectroscopic properties in excellent agreement with the literature reports from both Kinashi[53] and Wang[5]. Intriguingly, an isomeric substance **63** (**Scheme 5**, coined as neolankacidinol) was also generated from the same reaction mixture as a single diastereomer (43%), and the detailed NMR studies unveiled a formal C7-hydroxyl

Scheme 5. Diversification of macrocycle **36a** into six natural products of the lankacidin family, In the ORTEP representations of acetate **66**, the thermal ellipsoids are drawn at 20% probability.



Scheme 6. Stereochemical Revision of Isolankacidinol, Isolankacyclinol and a Recently Isolated Lankacyclinol, In the ORTEP representations of **10**, **5**, **62**, and **74**, the thermal ellipsoids are drawn at 20% probability.



shift took place along the diene chain in a highly stereoselective manner (for comprehensive presentations of its COSY, NOESY and HMBC correlations, see SI of ref. 17). It was quickly discovered that **63** could equilibrate with **3** under identical desilylation conditions, thus maximizing the material throughput to access the natural product. This process is assumed to involve a cationic intermediate **64**, which undergoes a nonregioselective reversible hydration reaction under a macrocyclic stereocontrol.[49,54] While numerous reports concerning the degradation chemistry of lankacidin antibiotics exists,[4c,d,7c] to the best of our knowledge, the acid-promoted hydroxyl transportation reaction within the lankacidin skeleton has never been reported in the literature.

Having conquered lankacidinol and lankacyclinol, we continued to synthesize other macrocyclic members of the same family (**Scheme 5**). To this end, removal of the TBS group at the C7 position of **36a** was smoothly realized by aqueous HCl in THF (with the final concentration of HCl in the reaction system to be ~0.3 M) at 20 °C for 3 hours. It is important to note that prolonged reaction time (> 20 h) would lead to a complex mixture of products. Acetylation of the resultant allylic alcohol **65** delivered acetate **66**, the structure and absolute stereochemistry of which were unambiguously determined by single-crystal X-ray diffraction. Upon employing the same condition established for **5**, transformation of **66** into (–)-lankacyclinol A (**6**) proceeded with an equal efficiency (79%). An intended global desilylation of **66** by treatment with aqueous HF in acetonitrile at –20 °C resulted in the complete hydrolysis of the C7-acetate. Another round of experiments identified a 2:1 molar mixture of HOAc/TBAF to be an optimal combination for this desilylation, being capable of delivering (–)-lankacidinol A (**4**) in an 82% yield. To access the last two targets bearing a pyruvoyl substitution at the nitrogen, the C24-hydroxy group was selectively liberated from **66** by prolonged exposure to aqueous HCl, and subsequently oxidized by Dess–Martin periodinane to afford pyruvamide **68** (70% over two steps). Removal of the TBDPS group by utilizing HOAc/TBAF in THF completed the synthesis of (–)-lankacidin A (**2**), while (–)-lankacidin C (**1**)[19] was obtained along with its hydroxyl-migrated congener **69** (referred to as neolankacidin C) by desilylation conducted with aqueous hydrofluoric acid in acetonitrile at –20 °C. The spectral data of the synthetic natural products (**1**,**2** and **4**) were in good agreement with literature values.[53]

Structural Revision of Isolankacidinol and Isolankacyclinol. The NOE correlations of C2-Me with C4-H and lack of the cross peak between C2-Me with C5-H observed in **36b** and **36c** indicated they possessed the same α-Me configuration at the quaternary carbon C2. However, the least predominant isomer **36b** (only 5% isolated yield from **38**) attracted our attention in the process of spectral comparison with the previously identified **36a**, which has β-Me configuration at C2. A large upfield-shift for C5-H proton signal (from δ 4.29 to δ 3.52) and a downfield-shift for C4-H proton signal (from δ 2.34 to δ 2.66) were observed, which are reported by Harada and coworkers to be diagnostically characteristic of isolankacidinol.[4d] For further clarification, **36b** was desilylated by treatment with HF in aqueous acetonitrile at –20 °C for 60 hours and no formal 1,5-hydroxy migration product was observed (**Scheme 6A**). More surprisingly, the NMR spectra and optical rotation (observed $[\alpha]_D^{25} = -189$ (c = 0.13, EtOH); lit: $[\alpha]_D^{25} = -190$ (c = 0.53, EtOH)[4d]) for synthetic macrocycle **10** matched those reported for isolankacidinol,[53,55] which was unfortunately assigned as

the C5-epimer of lankacidinol as shown in **7** (**Scheme 6B**).[4d] The structure and absolute configuration of **10** was further unequivocally established by X-ray crystallographic analysis (Cu Kα), allowing a stereochemical revision of the originally proposed structure of isolankacidinol (**7**) to be C2-epimer of lankacidinol (**10**). This result implies that the documented conversion from lankacidinol to isolankacidinol might initially involve a retro-Mannich reaction to open the 17-membered macrocycle rather than the retro-oxa-Michael cleavage of the lactonic C5–O bond. In fact, the enone carboxylate intermediate **70**, as suggested in the original biogenesis proposal, by the present view might be especially prone to decarboxylation to release lankacyclinol.[56] Moreover, the natural occurrence of 2-*epi*-lankacidinol as a minor congener, as validated by our work, unraveled for the first time the imperfect facial selective nature posed in the enzymatic lankacidin macrocycle-forming process. In addition, the highly stereoselective decarboxylation event realized from either lankacidinol (**3**) or its C2-epimeric skeleton under abiotic conditions also provided valuable insights into the biogenesis of **5**.

In the same publication,[4d] a non-naturally-occurring substance, isolankacyclinol (**71**) was obtained as a minor base degradation product of isolankacidinol (**Scheme 6B**), and its structure was postulated to be *s-trans*/*cis* (s represents enonic single bond C3–C4 in the enone portion) isomeric to lankacyclinol (**5**). To probe this unusual isomerism phenomenon, the synthetic sample of isolankacidinol (**10**) was subjected to the literature-described conditions (aqueous 2 wt.% K_2CO_3 in methanol, 25 °C), two decarboxylated compounds were isolated in excellent combined yield (67%+12%). The major product was readily identified as **5**, which is in accordance with the Harada's result. The minor product was assigned as 2-*epi*-lankacyclinol (**62**). X-ray crystallographic analysis unambiguously confirmed this assignment, and further validated both macrocycles (**5** and **62**) existed as enonic *s-trans* conformers in solid states. Though no NMR spectra were provided by Harada for direct comparison, it is highly probable that isolankacyclinol and 2-*epi*-lankacyclinol might be identical.

2,18-Bis-*epi*-Lankacyclinol: A New Natural Product. During the investigation of the base degradation chemistry of **10**, we keenly noticed that the ^{1}H and ^{13}C NMR spectra of our synthetic lankacyclinol (**5**) collected in CD_3OD differed significantly from those of a recently isolated lankacyclinol sample.[57] This led us to speculate the real structure of the latter might be a diastereoisomer of **5** with the opposite C2/C18-stereochemistry. Thus, the remaining (2*R*,18*S*)-diastereomer **36c** was exposed to TASF in wet DMF, smoothly furnishing two decarboxylated products in excellent yield with a ratio of 9:1 for **72**/**73** (**Scheme 6C**). To our delight, the predominant 2,18-*syn*-isomer bearing a large $^3J_{H,H}$ coupling constant between H-2 and H-18 (10.3 Hz) was found to exhibit spectral properties identical with those reported by Wang.[57] This reassignment was further ascertained by single-crystal X-ray diffraction conducted with its tris-(4-bromobenzyl ester) derivative **74**. The *syn*-selective decarboxylation observed for **36a-c** underscores the powerful stereodirecting influence of the rigid macrocyclic conformation.[49] The elucidation of the existence of **72** in natural environment suggests its non-decarboxylated variant **75** might be an as-yet-undiscovered natural product. Toward this end, **36c** was desilylated under previously established acidic conditions (aq. HF/CH_3CN at –20 °C) to give **75** in 55% yield, along with its C7-epimer **76** in 30% yield (for detailed 2D-NMR analysis of **75** and **76**, see SI, **Figure S4**). This unexpected scenario as compared with those of **36a**/**b** further indicates the sophistication of the chemo- and stereoselectivity profiles stemming from the C2/C18-configuration-dependent conformational change. Upon changing the reagent system to HOAc/TBAF (2:1), global desilylation of **36c** occurred with no C7-epimerization to provide the "missing" natural product 2,18-bis-*epi*-lankacidinol (**75**) in 76% yield.

CONCLUSION

In summary, we have detailed the evolution of a unified biomimetic approach to the capacity of all known macrocyclic lankacidins in the longest linear 7–12 steps from readily available starting materials (such as **44** and **45**). By taking advantage of the thermolysis chemistry of *N*,*O*-acetal to generate the requisite *N*-acyl-1-azahexatriene species, we realized the projected stereoselective Mannich macrocyclization, from the products of which all the macrocyclic lankacidins, including the relatively low-abundant and stereochemically unique isolankacidinol can be conquered by orchestrated desilylative manipulations.

Our work not only constitutes, to our knowledge, the first example of macrocyclic construction (> 14-membered) via a Mannich reaction in the context of complex natural product synthesis but also corroborates, for the first time, the chemical feasibility of the Arakawa-Kinashi's biogenetic hypothesis for the formation of the lankacidin macrocycle. Moreover, the bioinspired strategy-enabled reassignments of the reported structure of isolankacidinol (**7** to **10**), combined with the discovery of a recently isolated lankacyclinol to be in fact its 2,18-bisepimer (**72**), unraveled a previously underappreciated nature of product diversity[58] arising from the late-stage enzymatic oxidative cyclization in lankacidin biosynthesis. In addition, our decarboxylation experiments conducted under mild abiotic conditions with moderate to high selectivities not only shed light upon the dominant occurrence of 2,18-*syn* isomers (**5**, **6** and **72**) in the natural resources, but at the same time strongly implicate that both their precursors (i.e. **75** and as-yet-unisolated **36d**) and minor C1-depleted congeners (i.e. isolankacyclinol **62** and **73**) are potentially undiscovered natural products. Apart from these benefits, the most notable one provided by a biomimetic strategy is the significantly reduced step count compared with two previous entries to macrocyclic lankacidins.[19,20c] Collaborative efforts to explore new analogues for biological mode-of-action investigations as well as to delineate the macrocyclization stereocontrol exerted by the active site of the enzyme are continuing and will be reported in due course.

EXPERIMENTAL SECTION

All non-aqueous reactions were conducted in oven-dried glassware fitted with rubber septa and magnetically stirred under N_2 atmosphere unless otherwise noted. Anhydrous solvents were obtained using standard drying techniques. All commercial grade reagents were used

without further purification unless stated otherwise. Flash chromatography was performed on 230-400 mesh silica gel (Silicycle flash F60) with the indicated solvent systems. Yields refer to chromatographically and spectroscopically homogeneous material. Reactions were monitored by thin layer chromatography (TLC) supplied by Yantai Jiangyou Silicon Material Company (China). NMR spectra were recorded on Varian mercury–400, Bruker AM–400, and Bruker AV–500 spectrometers and chemical shifts are reported in ppm down field from TMS, using residual ^{1}H and ^{13}C signals of the solvent ($CDCl_3$: δ 7.26, 77.16 ppm; CD_3OD: δ 3.31, 49.00 ppm; DMSO-d_6: δ 2.50, 39.52 ppm; acetone-d_6: δ 2.05, 29.84, 206.26) as an internal standard. Data are reported as: (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; J = coupling constant in Hz, integration.). Optical rotations were measured on a Jasco P–1030 digital polarimeter using a 100 mm path-length cell at 589 nm. High-resolution mass spectra (HRMS) were acquired through the National Center for Organic Mass Spectrometry in Shanghai on a Thermo Fisher Scientific LTQ FT Ultra mass spectrometer (mass analyzer type: Fourier transform ion cyclotron resonance (FT-ICR)) with DART (Direct Analysis in Real Time) ionization performed in positive mode. Infrared spectra were recorded as thin films on NaCl plates on a Perkin–Elmer 983 or Digital FT-IR spectrometer and are reported in frequencies of absorption given in reciprocal centimeters (cm^{-1}).

The general procedure and the synthetic procedures and characterization data of compounds **31**, **32**, **35**, **38**, **39**, **41**, **42**–**47**, **52**, **53**, **59**, **62** and **63**, as well as the natural product NMR spectra comparisons (**5** in acetone-d_6 and **3** in methanol-d_4) have been recorded in our previous work,[17] and are not reproduced here.

Synthesis of α-amido sulfone 40. To a stirred solution of *N*,*O*-acetal **41** (978 mg, 1.7 mmol, 1.0 equiv) in anhydrous CH_2Cl2 (3.4 mL) was added triphenylphosphonium tetrafluoroborate (595 mg, 1.7 mmol, 1.0 equiv, predried *in vacuo* for > 24 hours prior to use to remove H_2O). Stirring was continued for 1 hour at room temperature after which TLC analysis indicated the complete consumption of the starting material. The solvent was evaporated under reduced pressure and the remaining volatiles were completely removed in vacuum to furnish a white, waxy solid. This material was dissolved in anhydrous chloroform (3.4 mL) and treated with anhydrous sodium benzenesulfinate (360 mg, 2.2 mmol, 1.3 equiv). The resultant suspension was sonicated in a bath for 5 min and vigorously stirred for additional 10 min at ambient temperature. The reaction mixture was then concentrated under reduced pressure and rapidly purified by a silica gel column (petroleum ether/EtOAc: 10/1) to afford **40** (626 mg, 54% yield) as a pale-yellow oil and 1.5 : 1 diastereomeric mixture. **TLC** (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.50; $[\alpha]_D^{23}$ = −8.9 (c = 1.11 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.93-7.88 (m, 2H), 7.64-7.61 (m, 1H), 7.54-7.49 (m, 2H), 7.31/7.24* (d, J = 10.2 Hz, 1H), 6.08/6.05* (dd, J = 10.2, 5.6 Hz, 1H), 5.49 (dq, J = 8.8, 1.6 Hz, $^3J_{Sn\text{-}H}$ = 30.4 Hz, 1H), 4.10/4.08* (q, J = 6.6 Hz, 1H), 1.90/1.79* (d, J = 1.6 Hz, $^3J_{Sn\text{-}H}$ = 20.9 Hz, 3H), 1.51-1.44 (m, 6H), 1.37-1.25 (m, 9H), 0.98-0.88 (m, 24H), 0.18 (s, 1.1H), 0.13 (s, 1.1H), 0.09* (s, 1.6H), 0.04* (s, 1.6H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 173.1, 173.0, 155.4, 154.9, 136.9 (2 peaks), 134.0, 133.9, 129.5, 129.4, 129.0, 128.9, 126.2, 125.7, 69.9, 69.6, 65.7, 65.3, 29.0, 27.4 (2 peaks), 25.8, 21.7, 21.4, 20.7, 20.5, 18.0 (2 peaks), 13.8 (2 peaks), 9.4, -4.5 (2 peaks), -5.2, -5.5 ppm; **IR** (thin film): ν_{max} = 3409, 2955, 2929, 2856, 1699, 1493, 1321, 1150, 1118, 832, 781 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{31}H_{58}O_4NSSi^{112}Sn$ [M + H]$^+$: 680.2899, found: 680.2896.

It was discovered that **40** exerted a pronounced tendency to undergo clean conversion to give **49** on contact with silica gel or during prolonged storage at room temperature, and should be kept at −20 °C in a refrigerator. $[\alpha]_D^{26}$ = −20.9 (c = 1.19 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.29/8.27* (d, J = 10.4 Hz, 1H), 7.83-7.80 (m, 2H), 7.65-7.61 (m, 1H), 7.54-7.50 (m, 2H), 6.66/6.63* (dd, J = 14.4, 10.4 Hz, 1H), 5.18/5.16* (dd, J = 14.4, 8.4 Hz, 1H), 4.21/4.29* (q, J = 6.8 Hz, 1H), 3.71/3.70* (dq, J = 8.4, 7.2 Hz, 1H), 1.44/1.43* (d, J = 7.2 Hz, 3H), 1.35/1.34* (d, J = 6.8 Hz, 3H), 0.93 (s, 9H), 0.12/0.11* (s, 3H), 0.10 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 171.9 (2 peaks), 136.9 (2 peaks), 133.9 (2 peaks), 129.3 (2 peaks), 129.0 (2 peaks), 127.8, 127.6, 105.5, 105.2, 69.8, 62.2 (2 peaks), 25.9, 21.8, 18.2, 18.1, 14.0, 13.8, -4.4 (2 peaks), -5.2, -5.3 ppm; **IR** (thin film): ν_{max} = 3405, 3347, 2954, 2930, 2858, 1698, 1664, 1502, 1447, 1306, 1261, 1145, 1123, 1086, 970, 833, 783, 729, 691, 592, 552 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{19}H_{32}O_4NSSi$ [M + H]$^+$: 398.1816, found: 398.1815.

***N*,*O*-acetal 50**. This compound was obtained as a faint yellow oil (32 mg, 23% yield) from the achiral phosphoric acid **34**-catalyzed model Mannich reaction between lactone **32** (0.20 mmol) and *N*,*O*-acetal **41** (0.24 mmol) and exists as a 1.2 : 1 diastereomeric mixture. **TLC** (petroleum ether / ethyl acetate = 20:1 v/v, $KMnO_4$): R_f = 0.36; $[\alpha]_D^{26}$ = −11.8 (c = 1.09 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.96/6.87* (d, J = 10.4 Hz, 1H), 6.00 (m, 1H), 5.40 (m, 1H), 4.19/4.26* (q, J = 6.8 Hz, 1H), 3.30/3.29* (s, 3H), 1.94/1.96* (d, J = 1.2 Hz, $^3J_{Sn\text{-}H}$ = 20.2 Hz, 3H), 1.52-1.44 (m, 6H), 1.41/1.36* (d, J = 6.8 Hz, 3H), 1.33-1.25 (m, 6H), 0.97-0.87 (m, 24H), 0.12 (s, 3.0H), 0.10* (s, 1.5H), 0.07* (s, 1.5H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 174.3, 174.2, 145.8, 145.6, 136.0 (2 peaks), 80.6, 80.3, 70.1, 69.9, 54.9 (2 peaks), 29.2 (2 peaks), 27.4, 27.3, 27.2, 25.8, 25.7, 22.2, 21.8, 18.1, 18.0, 13.7, 10.7, 10.6, -4.6, -4.7, -5.3, -5.4 ppm; **IR** (thin film): ν_{max} = 3416, 2955, 2929, 1695, 1493, 1255, 1118, 1066, 832, 780 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{52}O_2NSi^{112}Sn$ [M − OCH_3]$^+$: 538.2810, found: 538.2807.

Enamide 51. This compound was obtained as a colorless oil (17 mg, 13% yield) from the achiral phosphoric acid **34**-catalyzed model Mannich reaction between lactone **32** (0.20 mmol) and *N*,*O*-acetal **41** (0.24 mmol) **TLC** (petroleum ether / ethyl acetate = 15:1 v/v, $KMnO_4$): R_f = 0.69; $[\alpha]_D^{24}$ = −18.3 (c = 1.04 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 10.8 Hz, 1H), 6.86 (dd, J = 14.4 Hz, 11.2 Hz, 1H), 6.09 (d, J = 14.0 Hz, $^3J_{Sn\text{-}H}$ = 35.6 Hz, 1H), 5.78 (d, J = 2.6 Hz, $^3J_{Sn\text{-}H}$ = 61.6 Hz, 1H), 5.16 (d, J = 2.6 Hz, $^3J_{Sn\text{-}H}$ = 28.8 Hz, 1H), 4.26 (q, J = 6.8 Hz, 1H), 1.56-1.48 (m, 6H), 1.40 (d, J = 6.4 Hz, 3H), 1.35-1.28 (m, 6H), 1.03-1.99 (m, 6H), 0.95 (s, 9H), 0.90-0.86 (m, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 171.5, 148.9, 126.4, 124.4, 121.9, 69.9, 29.2, 27.4, 25.9, 21.8, 18.2, 13.8, 10.0, -4.4, -5.2 ppm; **IR** (thin film): νmax = 3413, 2956, 2929, 2857, 1701, 1643, 1492, 1260, 1118, 960, 897, 832, 781 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{52}O_2NSi^{112}Sn$ [M + H]$^+$: 538.2810, found: 538.2813.

Deuterated *N*,*O*-acetal 54 from isotopic labeling experiment. A 3 mL-pressure vessel equipped with a magnetic stirring bar was charged with a solution of *N*,*O*-acetal **41** (146 mg, 0.25 mmol, 1.0 equiv, as an inseparable 1.4 : 1 diastereomeric mixture) in degassed cyclohexane (2.5 mL). CD_3OH (8.8 mg, 10.1 μL, 1.0 equiv, 99.8 atom % D) was added in one portion. The vial was sealed tightly, immersed into a preheated oil bath at 80 °C with stirring and kept at this temperature for 17 hours. The reaction was cooled to room temperature before all volatiles were removed *in vacuo*. The crude material was subjected to ^{1}H NMR analysis and about 1 : 1 D : H incorporation with respect to methoxyl groups was observed. [Note]: this ratio of deuteration did not change when reaction time was prolonged, thus indicating that an equilibrium state had been reached. When the above mixture was resubjected to the same conditions over several cycles, an analytically-pure sample of **54** (141 mg, 97%) with more than 50 : 1 (D : H) incorporation can be obtained as a colorless oil and as 1.4 : 1 diastereomeric mixture for characterization purposes. **TLC** (petroleum ether / ethyl acetate = 15:1 v/v, $KMnO_4$): R_f = 0.33; $[\alpha]_D^{24}$ = −12.3 (c = 1.29 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.98/6.90* (d, J = 10.0 Hz, 1H), 5.82/5.80* (dd, J = 9.6, 6.4 Hz, 1H), 5.54 (dq, J = 6.8, 2.0 Hz, $^3J_{Sn\text{-}H}$ = 32.4 Hz, 1H), 4.19/4.26* (q, J = 6.8 Hz, 1H), 1.90/1.90* (d, J = 2.0 Hz, $^3J_{Sn\text{-}H}$ = 22.4 Hz, 3H), 1.50-1.43 (m, 6H), 1.41/1.35* (d, J = 6.8 Hz, 3H), 1.33-1.25 (m, 6H), 0.91-0.85 (m, 24H), 0.10 (s, 3.6H), 0.08* (s, 1.2H), 0.04* (s, 1.2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 174.5, 174.4, 146.4 (2 peaks), 136.9,

136.7, 76.3, 75.8, 70.1, 69.9, 54.3 (m), 29.2 (2 peaks), 27.5, 27.4, 25.8, 22.3, 21.9, 20.4, 18.1 (2 peaks), 13.8 (2 peaks), 9.3, 9.2, -4.6 (2 peaks), -5.2, -5.3 ppm; **IR** (thin film): ν_{max} = 3419, 2956, 2929, 2857, 1693, 1494, 1464, 1366, 1339, 1254, 1121, 1073, 1031, 978, 875, 834, 781, 669 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{52}O_2NSi^{112}Sn$ [M − OCD_3]$^+$: 538.2810, found: 538.2812.

Biomimetic Mannich macrocyclization *(Table 2, entry 1)***.** A solution of 1:1 diastereomeric mixture of *N*,*O*-acetal **38** (320 mg, 0.31 mmol, contaminated by 6 wt.% polyenal **59** as indicated by NMR analysis) in cyclohexane (20 mL) was added to a refluxing cyclohexane (600 mL) by cannula transfer. The reaction mixture was stirred at reflux for 22 hours until complete disappearance of 3.31 ppm singlet methoxyl group signal as monitored by NMR analysis. The solution was cooled to ambient temperature and concentrated to give an oily residue, which was purified by preparative TLC (20% EtOAc in petroleum ether) to afford macrocycle **36a** (92 mg, 32% yield), **36b** (13 mg, 5% yield), macrocycle **36c** (26 mg, 9% yield), enamide **57** (32 mg, 11% yield), and dihydropyridine **58** (10 mg, 4% yield), both as colorless oils.

Macrocycle 36a. TLC (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.40; $[\alpha]_D^{25}$ = −79.3 (*c* = 0.76 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 10.4 Hz, 1H, *H*-N), 7.68-7.61 (m, 4H, *H*-Ar), 7.42-7.29 (m, 6H, *H*-Ar), 5.86 (d, *J* = 15.6 Hz, 1H, *H*C_9), 5.64 (dd, *J* = 15.6, 9.4 Hz, 1H, *H*C_8), 5.53 (dd, *J* = 16.0, 8.4 Hz, 1H, *H*C_{14}), 5.47 (t, *J* = 10.8 Hz, 1H, *H*C_{18}), 5.24 (d, *J* = 16.0 Hz, 1H, *H*C_{15}), 4.99 (dd, *J* = 11.2, 5.2 Hz, 1H, *H*C_{11}), 4.50 (d, *J* = 10.8 Hz, 1H, *H*C_{17}), 4.29 (dt, *J* = 12.0, 2.8 Hz, 1H, *H*C_5), 4.24 (m, 1H, *H*C_7), 4.20 (q, *J* = 6.8 Hz, 1H, *H*C_{24}), 3.98 (ddd, *J* = 10.8, 8.4, 4.0 Hz, 1H, *H*C_{13}), 2.47 (m, 1H, H_AC_{12}), 2.34 (dq, *J* = 12.0, 6.8 Hz, 1H, *H*C_4), 2.28-2.21 (m, 2H, H_BC_{12}, H_AC_6), 2.08 (m, 1H, H_BC_6), 1.83 (s, 3H, H_3C_{22}), 1.51 (s, 3H, H_3C_{21}), 1.39 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.35 (s, 3H, H_3C_{19}), 1.17 (d, *J* = 6.8 Hz, 3H, H_3C_{20}), 1.04 (s, 9H, *SiR*), 0.95 (s, 9H, *SiR*), 0.83 (s, 9H, *SiR*), 0.11 (s, 3H, *SiR*), 0.09 (s, 3H, *SiR*), 0.01 (s, 3H, *SiR*), -0.03 (s, 3H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 211.1 (C_3=O), 174.1 (C_{23}=O), 170.3 (C_1=O), 138.9 (C_{16}), 137.1 (C_9H), 136.4 (C_{10}), 136.0 (Ar), 135.9 (Ar), 134.5 (Ar), 134.2 (Ar), 133.7 (C_{15}H), 131.5 (C_{14}H), 130.0 (C_8H), 129.7 (2 peaks, Ar), 128.0 (C_{11}H), 127.7 (Ar), 127.6 (Ar), 124.7 (C_{17}H), 76.3 (C_{13}H), 75.7 (C_5H), 71.0 (C_7H), 70.3 (C_{24}H), 57.1 (C_2), 51.0 (C_{18}H), 46.4 (C_4H), 38.5 (C_6H_2), 37.9 ($C_{12}H_2$), 27.1 (2 peaks, *SiR*), 25.9 (2 peaks, *SiR*), 22.3 ($C_{25}H_3$), 20.9 ($C_{19}H_3$), 19.3 (*SiR*), 18.2 (*SiR*), 12.9 ($C_{22}H_3$), 12.8 ($C_{21}H_3$), 9.7 ($C_{20}H_3$), -3.7 (*SiR*), -4.4 (*SiR*), -4.6 (*SiR*), -5.1 (*SiR*) ppm; **IR** (thin film): ν_{max} = 3415, 2928, 2856, 1753, 1710, 1680, 1501, 1471, 1259, 1062, 963, 834, 802, 702 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{53}H_{82}O_7NSi_3$ [M + H]$^+$: 928.5394, found: 928.5374.

Macrocycle 36b. TLC (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.52; $[\alpha]_D^{24}$ = −83.3 (*c* = 0.80 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.67-7.59 (m, 4H, *H*-Ar), 7.49 (d, *J* = 10.0 Hz, 1H, *H*-N), 7.40-7.29 (m, 6H, *H*-Ar), 6.02 (d, *J* = 15.5 Hz, 1H, *H*C_9), 5.60 (t, *J* = 10.5 Hz, 1H, *H*C_{18}), 5.46 (dd, *J* = 16.0, 7.5 Hz, 1H, *H*C_{14}), 5.38 (d, *J* = 16.0 Hz, 1H, *H*C_{15}), 5.18 (dd, *J* = 15.5, 8.0 Hz, 1H, *H*C_8), 4.99 (m, 1H, *H*C_{11}), 4.76 (d, *J* = 10.0 Hz, 1H, *H*C_{17}), 4.40 (m, 1H, *H*C_7), 4.22 (q, *J* = 6.5 Hz, 1H, *H*C_{24}), 4.11 (m, 1H, *H*C_{13}), 3.52 (t, *J* = 10.5 Hz, 1H, *H*C_5), 2.66 (dq, *J* = 12.0, 6.5 Hz, 1H, *H*C_4), 2.37-2.33 (m, 2H, H_AC_{12}, H_BC_{12}), 2.01-1.95 (m, 1H, H_AC_6), 1.81-1.76 (m, 1H, H_BC_6), 1.70 (s, 3H, H_3C_{22}), 1.48 (s, 3H, H_3C_{21}), 1.41 (d, *J* = 6.5 Hz, 3H, H_3C_{25}), 1.37 (s, 3H, H_3C_{19}), 1.05 (s, 9H, *SiR*), 1.00 (d, *J* = 6.5 Hz, 3H, H_3C_{20}), 0.95 (s, 9H, *SiR*), 0.86 (s, 9H, *SiR*), 0.11 (s, 3H, *SiR*), 0.10 (s, 3H, *SiR*), 0.05 (s, 3H, *SiR*), 0.02 (s, 3H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 204.3 (C_3=O), 173.9 (C_1=O), 173.8 (C_{23}=O), 137.4 (C_{16}), 137.3 (C_9H), 136.0 (*SiR*), 135.9 (*SiR*), 134.4 (C_{15}H), 134.0 (C_{10}), 133.8 (*SiR*), 132.6 (C_{14}H), 129.8 (*SiR*), 129.3 (C_{11}H), 128.3 (C_8H), 127.7 (*SiR*), 127.6 (*SiR*), 126.3 (C_{17}H), 77.1 (C_5H), 76.1 (C_{13}H), 70.7 (C_7H), 70.2 (C_{24}H), 59.3 (C_2), 48.2 (C_{18}H), 44.3 (C_4H), 42.1 (C_6H_2), 36.8 ($C_{12}H_2$), 27.1 (*SiR*), 26.0 (*SiR*), 25.9 (*SiR*), 22.8 ($C_{19}H_3$), 22.3 ($C_{25}H_3$), 19.3 (*SiR*), 18.3 (*SiR*), 18.2 (*SiR*), 13.3 ($C_{21}H_3$), 12.8 ($C_{22}H_3$), 9.7 ($C_{20}H_3$), -4.0 (*SiR*), -4.5 (*SiR*), -4.7 (*SiR*), -5.0 (*SiR*) ppm; **IR** (thin film): ν_{max} = 3407, 2956, 2929, 2890, 2857, 1746, 1718, 1683, 1506, 1472, 1460, 1253, 1111, 1074, 963, 835, 779, 702, 507 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{53}H_{82}O_7NSi_3$ [M + H]$^+$: 928.5394, found: 928.5395.

Macrocycle 36c. TLC (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.31; $[\alpha]_D^{23}$ = +49.8 (*c* = 1.13 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 10.0 Hz, 1H, *H*-N), 7.70-7.59 (m, 4H, *H*-Ar), 7.42-7.30 (m, 6H, *H*-Ar), 6.22 (d, *J* = 15.5 Hz, 1H, *H*C_9), 6.08 (d, *J* = 16.0 Hz, 1H, *H*C_{15}), 5.47 (dd, *J* = 15.5, 3.5 Hz, 1H, *H*C_{14}), 5.41 (dd, *J* = 15.5, 5.0 Hz, 1H, *H*C_8), 5.39-5.35 (m, 2H, *H*C_{18}, *H*C_{11}), 4.99 (d, *J* = 10.0 Hz, 1H, *H*C_{17}), 4.67 (m, 1H, *H*C_{13}), 4.57 (m, 1H, *H*C_7), 4.27 (q, *J* = 6.8 Hz, 1H, *H*C_{24}), 3.84 (dt, *J* = 11.5, 5.5 Hz, 1H, *H*C_5), 2.73 (dq, *J* = 11.5, 6.5 Hz, 1H, *H*C_4), 2.25-2.19 (m, 1H, H_AC_{12}), 2.13-2.08 (m, 1H, H_BC_{12}), 2.02-2.00 (m, 2H, H_AC_6, H_BC_6), 1.75 (s, 3H, H_3C_{22}), 1.56 (s, 3H, H_3C_{21}), 1.49 (s, 3H, H_3C_{19}), 1.37 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.12 (d, *J* = 6.5 Hz, 3H, H_3C_{20}), 1.10 (s, 9H, *SiR*), 0.97 (s, 9H, *SiR*), 0.92 (s, 9H, *SiR*), 0.13 (s, 3H, *SiR*), 0.11 (s, 3H, *SiR*), 0.06 (s, 3H, *SiR*), 0.06 (s, 3H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 209.6 (C_3=O), 174.0 (C_{23}=O), 172.2 (C_1=O), 139.0 (C_{16}), 136.0 (2 peaks, C_9H, *SiR*), 134.9 (C_{10}), 134.4 (*SiR*), 134.0 (*SiR*), 133.7 (C_{15}H), 130.9 (C_{14}H), 129.9 (*SiR*), 129.7 (*SiR*), 127.9 (C_{11}H), 127.7 (*SiR*), 127.6 (*SiR*), 126.3 (C_8H), 124.3 (C_{17}H), 75.3 (C_5H), 72.1 (C_{13}H), 70.2 (C_{24}H), 70.0 (C_7H), 59.1 (C_2), 52.0 (C_{18}H), 45.5 (C_4H), 42.2 (C_6H_2), 34.5 ($C_{12}H_2$), 27.3 (*SiR*), 26.1 (*SiR*), 25.9 (*SiR*), 23.3 ($C_{19}H_3$), 22.0 ($C_{25}H_3$), 19.5 (*SiR*), 18.4 (*SiR*), 18.2 (*SiR*), 13.2 ($C_{22}H_3$), 13.1 ($C_{21}H_3$), 9.2 ($C_{20}H_3$), -4.5 (*SiR*), -4.6 (*SiR*), -4.7 (*SiR*), -4.9 (*SiR*) ppm; **IR** (thin film): ν_{max} = 3415, 2956, 2930, 2890, 2857, 1750, 1713, 1679, 1498, 1252, 1111, 1077, 969, 833, 779, 702, 504 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{53}H_{82}O_7NSi_3$ [M + H]$^+$: 928.5394, found: 928.5389.

Long-chain enamide 57. TLC (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.33; $[\alpha]_D^{23}$ = −7.5 (*c* = 1.02 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 11.6 Hz, 1H, *H*-N), 7.67-7.60 (m, 4H, *H*-Ar), 7.42-7.26 (m, 6H, *H*-Ar), 6.87 (dd, *J* = 11.6, 9.4 Hz, 1H, *H*C_{18}), 6.16 (d, *J* = 16.0 Hz, 1H, *H*C_9), 5.97 (d, *J* = 15.6 Hz, 1H, *H*C_{15}), 5.70 (dd, *J* = 15.6, 6.4 Hz, 1H, *H*C_{14}), 5.46 (dd, *J* = 15.6, 7.6 Hz, 1H, *H*C_8), 5.42 (t, *J* = 7.6 Hz, 1H, *H*C_{11}), 5.18 (d, *J* = 9.4 Hz, 1H, *H*C_{17}), 5.14 (s, 1H, H_BC_{22}), 5.06 (s, 1H, H_AC_{22}), 4.53 (m, 1H, *H*C_7), 4.35-4.23 (m, 3H, *H*C_5, *H*C_{13}, *H*C_{24}), 3.46 (q, *J* = 6.8 Hz, 1H, *H*C_2), 2.43-2.35 (m, 2H, *H*C_4, H_AC_{12}), 2.30-2.23 (m, 1H, H_BC_{12}), 2.06-1.99 (m, 1H, H_AC_6), 1.96-1.89 (m, 1H, H_BC_6), 1.59 (s, 3H, H_3C_{21}), 1.39 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.32 (d, *J* = 6.4 Hz, 3H, H_3C_{19}), 1.18 (d, *J* = 7.6 Hz, 3H, H_3C_{20}), 1.04 (s, 9H, *SiR*), 0.89 (s, 9H, *SiR*), 0.88 (s, 9H, *SiR*), 0.10 (s, 3H, *SiR*), 0.06 (s, 6H, *SiR*), 0.03 (s, 3H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 204.5 (C_3=O), 172.0 (C_{23}=O), 169.7 (C_1=O), 140.7 (C_{16}), 136.3 (C_9H), 136.1 (*SiR*), 134.8 (C_{14}H), 134.7 (C_{10}), 134.3 (*SiR*), 134.2 (*SiR*), 131.0 (C_{15}H), 129.8 (*SiR*), 129.7 (*SiR*), 128.9 (C_{11}H), 128.7 (C_8H), 127.7 (*SiR*), 127.6 (*SiR*), 122.6 (C_{18}H), 117.2 ($C_{22}H_AH_B$), 108.3 (C_{17}H), 76.8 (C_5H), 73.7 (C_{13}H), 70.6 (C_7H), 70.0 (C_{24}H), 50.3 (C_2H), 46.8 (C_4H), 41.3 (C_6H_2), 37.3 ($C_{12}H_2$), 27.2 (*SiR*), 26.0 (*SiR*), 25.9 (*SiR*), 21.9 ($C_{25}H_3$), 19.5 (*SiR*), 18.3 (*SiR*), 18.1 (*SiR*), 12.8 ($C_{21}H_3$), 12.5 ($C_{20}H_3$), 8.1 ($C_{19}H_3$), -4.0 (*SiR*), -4.6 (2 peaks, *SiR*), -5.0 (*SiR*) ppm; **IR** (thin film): ν_{max} = 3402, 2955, 2929, 2857, 1765, 1725, 1699, 1654, 1489, 1390, 1362, 1255, 1112, 1074, 836, 779, 702 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{53}H_{82}O_7NSi_3$ [M + H]$^+$: 928.5394, found: 928.5397.

Long-chain dihydropyridine 58. TLC (petroleum ether / ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.59; $[\alpha]_D^{24}$ = +152.4 (*c* = 0.99 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4H, *H*-Ar), 7.40-7.32 (m, 6H, *H*-Ar), 6.82 (d, *J* = 7.6 Hz, 1H, *H*C_{18}), 6.04 (d, *J* = 15.6 Hz, 1H, *H*C_9), 5.41 (br d, *J* = 4.4 Hz, 1H, *H*C_{15}), 5.36 (dd, *J* = 15.6, 7.6 Hz, 1H, *H*C_8), 5.27 (t, *J* = 7.2 Hz, 1H, *H*C_{11}), 5.09 (d, *J* = 7.6 Hz, 1H, *H*C_{17}), 4.90 (br t, *J* = 4.4 Hz, 1H, *H*C_{14}), 4.53 (q, *J* = 6.8 Hz, 1H, *H*C_{24}), 4.47 (m, 1H, *H*C_7), 4.30 (t, *J* = 9.8 Hz, 1H, *H*C_5), 4.01 (m, 1H, *H*C_{13}), 3.62 (q, *J* = 6.4 Hz, 1H, *H*C_2), 2.34 (dq, *J* = 10.4, 7.2 Hz, 1H, *H*C_4), 2.23 (m, 1H, H_AC_{12}), 2.03-1.96 (m, 2H, H_AC_6, H_BC_{12}), 1.87 (dd, *J* = 8.8, 2.0 Hz, 1H, H_BC_6), 1.75 (s, 3H, H_3C_{22}), 1.44 (s, 3H, H_3C_{21}), 1.37 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.32 (d, *J* = 6.8 Hz, 3H, H_3C_{19}), 1.14 (d, *J* = 7.2 Hz, 3H, H_3C_{20}), 0.98 (s, 9H, *SiR*), 0.87 (s, 9H,

SiR), 0.86 (s, 9H, *SiR*), 0.05 (s, 3H, *SiR*), 0.04 (s, 3H, *SiR*), 0.02 (s, 3H, *SiR*), 0.02 (s, 3H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 204.8 (C_3=O), 172.4 (C_{23}=O), 169.8 (C_1=O), 136.3 (C_9H), 136.0 (2 peaks, *SiR*), 134.9 (*SiR*), 134.1 (2 peaks, *SiR*, C_{10}), 131.1 (C_{16}), 129.7 (*SiR*), 129.6 (*SiR*), 129.1 (C_{11}H), 128.4 (C_8H), 127.7 (*SiR*), 127.5 (*SiR*), 125.8 (C_{18}H), 116.2 (C_{15}H), 110.4 (C_{17}H), 76.7 (C_5H), 75.9 (C_{13}H), 71.0 (C_{24}H), 70.7 (C_7H), 54.8 (C_{14}H), 50.4 (C_2H), 46.7 (C_4H), 41.4 (C_6H_2), 32.7 ($C_{12}H_2$), 27.0 (*SiR*), 26.0 (*SiR*), 25.9 (*SiR*), 21.2 ($C_{25}H_3$), 20.7 ($C_{22}H_3$), 19.6 (*SiR*), 18.3 (2 peaks, *SiR*), 12.8 ($C_{21}H_3$), 12.5 ($C_{20}H_3$), 8.1 ($C_{19}H_3$), -3.9 (*SiR*), -4.6 (*SiR*), -4.8 (2 peaks, *SiR*) ppm; **IR** (thin film): ν_{max} = 2955, 2930, 2894, 2857, 1764, 1724, 1659, 1590, 1471, 1462, 1428, 1390, 1376, 1361, 1258, 1111, 1089, 1005, 969, 836, 778, 740, 703, 611, 506 cm^{-1}; **HRMS-ESI** (*m/z*): calcd. for $C_{53}H_{81}O_7NNaSi_3$ [M + Na]$^+$: 950.5213, found: 950.5195.

Synthesis of lankacyclinol (5) via desilylation of 36a. Detailed protocols leading to **5** (white solid, 20 mg, 69% yield) have been reported previously.[17] Crystals of lankacyclinol suitable for X-ray analysis were grown by slow evaporation at 5 °C from methanol. In order to make a comparison of our synthetic lankacyclinol with Wang's recently isolated sample,[57] NMR spectroscopic data were recollected on this natural product using methanol-d_4 as a solvent. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.25; $[\alpha]_D^{23}$ = −353.6 (*c* = 0.41 in EtOH); **^{1}H NMR** (400 MHz, CD_3OD): δ = 6.56 (m, 1H, *H*C_5), 6.04 (d, *J* = 15.5 Hz, 1H, *H*C_9), 5.74 (d, *J* = 15.9 Hz, 1H, *H*C_{15}), 5.35 (dd, *J* = 15.3, 8.2 Hz, 1H, *H*C_8), 5.31 (dd, *J* = 15.9, 8.0 Hz, 1H, *H*C_{14}), 5.21 (m, 1H, *H*C_{11}), 5.13 (t, *J* = 10.2 Hz, 1H, *H*C_{17}), 5.08 (t, *J* = 10.1 Hz, 1H, *H*C_{18}), 4.25 (m, 1H, *H*C_7), 4.11-4.04 (m, 2H, *H*C_{24}, *H*C_{13}), 3.64 (dq, *J* = 9.9, 7.0 Hz, 1H, *H*C_2), 2.66-2.56 (m, 2H, H_AC_6, H_BC_6), 2.40 (m, 1H, H_AC_{12}), 2.27 (m, 1H, H_BC_{12}), 1.73 (s, 3H, H_3C_{20}), 1.67 (s, 3H, H_3C_{22}), 1.53 (s, 3H, H_3C_{21}), 1.35 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 0.97 (d, *J* = 6.8 Hz, 3H, H_3C_{19}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, CD_3OD): δ = 205.3 (C_3=O), 177.2 (C_{23}=O), 139.6 (C_4), 139.1 (C_5H), 137.9 (C_9H), 136.7 (C_{15}H), 135.4 (C_{10}), 135.3 (C_{16}), 131.4 (C_{17}H), 131.3 (C_{14}H), 129.8 (C_{11}H), 129.3 (C_8H), 75.2 (C_{13}H), 73.4 (C_7H), 69.3 (C_{24}H), 50.3 (C_{18}H), 44.3 (C_2H), 38.5 (C_6H_2), 37.3 ($C_{12}H_2$), 21.5 ($C_{25}H_3$), 16.3 ($C_{19}H_3$), 13.1 ($C_{21}H_3$), 12.7 (2 peaks, $C_{20}H_3$, $C_{22}H_3$) ppm. **IR** (thin film): ν_{max} = 3327, 2920, 1656, 1639, 1545, 1452, 1370, 1264, 1129, 1017, 959 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{24}H_{36}O_5N$ [M + H]$^+$: 418.2588, found: 418.2582.

Synthesis of lankacidinol (3) via desilylation of 36a. Detailed procedures leading to **3** (white solid, 26 mg, 51% yield) have been reported previously.[17] In order to make a comparison of our synthetic lankacidinol with Wang's recently isolated sample,[5,57] NMR spectroscopic data were recollected on this natural product using DMSO-d_6 as a solvent. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.18; $[\alpha]_D^{23}$ = −215.4 (*c* = 0.06 in DMF); **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 10.2 Hz, 1H, *H*-N), 6.10 (d, *J* = 15.4 Hz, 1H, *H*C_9), 5.86 (d, *J* = 4.7 Hz, 1H, *H*O-C_{24}), 5.55 (d, *J* = 15.7 Hz, 1H, *H*C_{15}), 5.50 (dd, *J* = 15.4, 9.4 Hz, 1H, *H*C_8), 5.36 (dd, *J* = 15.8, 8.1 Hz, 1H, *H*C_{14}), 5.32-5.24 (m, 2H, *H*C_{11}, *H*C_{18}), 5.04 (d, *J* = 4.1 Hz, 1H, *H*O-C_{13}), 4.84 (d, *J* = 4.2 Hz, 1H, *H*O-C_7), 4.73 (d, *J* = 10.7 Hz, 1H, *H*C_{17}), 4.68 (m, 1H, *H*C_5), 4.16 (m, 1H, *H*C_7), 3.95 (m, 1H, *H*C_{24}), 3.88 (m, 1H, *H*C_{13}), 2.40 (m, 1H, *H*C_4), 2.22 (m, 2H, H_AC_{12}, H_BC_{12}), 2.11 (m, 1H, H_AC_6), 1.95 (m, 1H, H_BC_6), 1.70 (s, 3H, H_3C_{22}), 1.41 (s, 3H, H_3C_{21}), 1.26 (s, 3H, H_3C_{19}), 1.24 (d, *J* = 6.7 Hz, 3H, H_3C_{25}), 1.13 (d, *J* = 6.6 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 211.2 (C_3=O), 173.8 (C_{23}=O), 170.5 (C_1=O), 136.9 (C_{16}), 136.0 (C_9H), 135.2 (C_{10}), 132.8 (C_{15}H), 132.1 (C_{14}H), 130.4 (C_8H), 127.7 (C_{11}H), 125.2 (C_{17}H), 75.0 (C_5H), 73.0 (C_{13}H), 68.0 (C_7H), 67.3 (C_{24}H), 56.4 (C_2), 50.0 (C_{18}H), 45.9 (C_4H), 37.3 (2 peaks, C_6H_2, $C_{12}H_2$), 21.2 ($C_{25}H_3$), 20.1 ($C_{19}H_3$), 12.4 ($C_{22}H_3$), 12.3 ($C_{21}H_3$), 9.2 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3438, 3311, 2900, 1733, 1703, 1641, 1440, 1366, 1274, 1120, 1013, 960 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{36}O_7N$ [M + H]$^+$: 462.2486, found: 462.2487.

Synthesis of allylic alcohol 65. Hydrochloric acid (approximately 4 M in water, 2.5 mL) was added to a solution of macrocycle **36a** (65 mg, 0.07 mmol) in THF (40 mL) at 20 °C. After stirring for 3 h, the reaction mixture was cooled to −20 °C and quenched by adding saturated $NaHCO_3$ (aq., 40 mL). The resultant slurry was warmed to room temperature and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/EtOAc: 4/1) to afford allylic alcohol **65** (54 mg, 94% yield) as a colorless oil. **TLC** (petroleum ether / ethyl acetate = 1:1 v/v, $KMnO_4$): R_f = 0.36; $[\alpha]_D^{29}$ = −279.6 (*c* = 0.18 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 10.0 Hz, 1H), 7.68-7.60 (m, 4H), 7.41-7.28 (m, 6H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.73 (dd, *J* = 15.6, 9.6 Hz, 1H), 5.53 (dd, *J* = 16.0, 8.4 Hz, 1H), 5.48 (t, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 16.0 Hz, 1H), 5.04 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.36 (dt, *J* = 12.0, 2.8 Hz, 1H), 4.26 (m, 1H), 4.20 (q, *J* = 6.8 Hz, 1H), 3.97 (m, 1H), 2.48 (m, 1H), 2.34-2.17 (m, 4H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.52 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 9H), 0.95 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 210.8, 174.2, 170.3, 139.0, 138.6, 136.2, 136.0, 135.9, 134.4, 134.0, 133.7, 131.5, 129.7 (2 peaks), 129.1, 129.0, 127.7, 127.5, 124.6, 77.4, 76.2, 75.6, 70.3, 70.2, 57.1, 50.9, 46.4, 37.9, 36.8, 27.0, 25.9, 22.3, 20.9, 19.3, 18.2, 12.9, 12.8, 9.7, -4.6, -5.1 ppm; **IR** (thin film): ν_{max} = 3406, 2930, 2857, 1751, 1708, 1669, 1506, 1376, 1257, 1111, 1068, 963, 832, 737, 702 cm^{-1}; **HRMS-DART** (m/z): calcd. for $C_{47}H_{68}O_7NSi_2$ [M + H]$^+$: 814.4529, found: 814.4505.

Synthesis of allylic acetate 66. To a solution of allylic alcohol **65** (30.0 mg, 0.037 mmol, 1.0 equiv) and DMAP (2.3 mg, 0.018 mmol, 0.5 equiv) in CH_2Cl_2 (1.5 mL) was added dropwise in sequence via syringe Et_3N (28.5 mg, 40 μL, 0.276 mmol, 7.5 equiv) and Ac_2O (19.3 mg, 18 μL, 0.185 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 20 min and then quenched by adding saturated $NaHCO_3$ (aq., 15 mL). The biphasic mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (petroleum ether/EtOAc: 5/1) to provide **66** (29.3 mg, 93% yield) as a white solid. A single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of a solution of **66** in CH_2Cl_2/petroleum ether at room temperature. **TLC** (petroleum ether / ethyl acetate = 1:1 v/v, $KMnO_4$): R_f = 0.79; $[\alpha]_D^{29}$ = −138.1 (*c* = 0.97 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 10.4 Hz, 1H), 7.67-7.60 (m, 4H), 7.40-7.28 (m, 6H), 6.13 (d, *J* = 15.6 Hz, 1H), 5.64 (dd, *J* = 15.6, 9.6 Hz, 1H), 5.53 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.48 (t, *J* = 10.4 Hz, 1H), 5.36 (ddd, *J* = 11.0, 10.2, 5.6 Hz, 1H), 5.26 (d, *J* = 15.6 Hz, 1H), 5.07 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.34 (m, 1H), 4.20 (q, *J* = 6.8 Hz, 1H), 3.98 (ddd, *J* = 10.8, 8.6, 4.0 Hz, 1H), 2.46 (m, 1H), 2.33 (m, 1H), 2.28-2.18 (m, 3H), 2.00 (s, 3H), 1.84 (s, 3H), 1.51 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.36 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.95 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 210.4, 174.1, 170.3, 170.2, 141.3, 139.0, 136.0, 135.9 (2 peaks), 134.3, 134.0, 133.6, 131.5, 130.1, 129.7 (2 peaks), 127.7, 127.5, 124.6, 124.2, 76.1, 75.4, 71.8, 70.3, 57.1, 51.0, 46.4, 37.9, 34.4, 27.1, 25.9, 22.3, 21.5, 20.9, 19.3, 18.2, 12.9, 12.6, 9.5, -4.6, -5.1 ppm; **IR** (thin film): ν_{max} = 3412, 2957, 2930, 2898, 2857, 1754, 1734, 1711, 1681, 1506, 1472, 1458, 1364, 1314, 1257, 1240, 1112, 1077, 1015, 963, 859, 796, 703 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{49}H_{70}O_8NSi_2$ [M + H]$^+$: 856.4634, found: 856.4631.

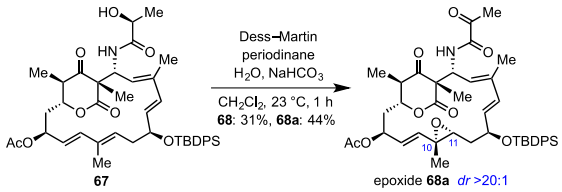
Synthesis of lankacyclinol A (6). A mixture of allylic acetate **66** (8.6 mg, 0.01 mmol, 1.0 equiv) and H_2O (7.2 mg, 0.40 mmol, 40.0 equiv) in DMF (2.5 mL) was treated with TASF (42.2 mg, 0.15 mmol, 15.0 equiv). The resultant solution was stirred for 23 hours at room temperature, diluted with EtOAc (10 mL) and cooled to 0 °C, during which time a mixture of brine (10 mL) and phosphate buffer (aq., pH = 7, 10 mL) was added to quench the reaction. The resultant slurry was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (20 mL) and dried over Na_2SO_4. After filtration and concentration under vacuum, the crude product was

subjected to flash column chromatography on silica ($CHCl_3$/MeOH: 9/1) to afford lankacyclinol A (3.6 mg, 79% yield) as a white solid. **TLC** (dichloromethane / methanol = 9:1 v/v, $KMnO_4$): R_f = 0.46; $[\alpha]_D^{24}$ = −180.0 (*c* = 0.09 in CH_2Cl_2/CH_3OH, 1/3, v/v); **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.62 (d, *J* = 9.6 Hz, 1H, *H*-N), 6.48 (dd, *J* = 10.2, 5.2 Hz, 1H, *H*C_5), 6.05 (dt, *J* = 14.8, 4.2 Hz, 1H, *H*C_8), 5.59 (d, *J* = 4.8 Hz, 1H, *H*O-C_{24}), 5.57 (d, *J* = 16.0 Hz, 1H, *H*C_{15}), 5.34-5.28 (m, 2H, *H*C_7, *H*C_9), 5.25-5.20 (m, 2H, *H*C_{11}, *H*C_{14}), 5.13 (d, *J* = 10.0 Hz, 1H, *H*C_{17}), 4.99 (d, *J* = 4.4 Hz, 1H, *H*O-C_{13}), 4.83 (app q, *J* = 10.0 Hz, 1H, *H*C_{18}), 3.98 (m, 1H, *H*C_{13}), 3.92 (m, 1H, *H*C_{24}), 3.59 (dq, *J* = 10.2, 6.8 Hz, 1H, *H*C_2), 2.68 (m, 1H, H_AC_6), 2.58 (m, 1H, H_BC_6), 2.33 (m, 1H, H_AC_{12}), 2.13 (m, 1H, H_BC_{12}), 2.02 (s, 3H, H_3C_{27}), 1.67 (s, 3H, H_3C_{20}), 1.52 (s, 3H, H_3C_{22}), 1.45 (s, 3H, H_3C_{21}), 1.21 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 0.84 (d, *J* = 6.4 Hz, 3H, H_3C_{19}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 203.3 (C_3=O), 173.7 (C_{23}=O), 169.6 (C_{26}=O), 138.6 (C_8H), 138.5 (C_4), 136.0 (C_{10}), 134.1 (C_{15}H), 132.9 (C_{11}H), 132.3 (C_{16}), 131.0 (C_{14}H), 130.7 (C_{17}H), 130.6 (C_{10}), 123.2 (C_9H), 73.3 (C_7H), 72.5 (C_{13}H), 67.5 (C_{24}H), 48.2 (C_{18}H), 42.3 (C_2H), 36.6 ($C_{12}H_2$), 33.6 (C_6H_2), 21.4 ($C_{25}H_3$), 21.1 ($C_{27}H_3$), 15.6 ($C_{19}H_3$), 12.5 ($C_{21}H_3$), 12.2 (2 peaks, $C_{20}H_3$, $C_{22}H_3$) ppm; **IR** (thin film): ν_{max} = 3333, 2922, 2852, 1725, 1652, 1635, 1552, 1455, 1372, 1306, 1259, 1230, 1129, 1049, 1020, 957, 879, 797 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{26}H_{38}O_6N$ $[M + H]^+$: 460.2694, found: 460.2693.

Synthesis of lankacidinol A (4). To a stirred solution of acetic acid (120 mg, 120 µL, 2.0 mmol) in THF (3.0 mL) at room temperature was added TBAF (1.0 mol/L in THF, 1.0 mL, 1.0 mmol). After stirring for 10 min, 2.4 mL of the reagent prepared as described above was added to a solution of **66** (17.0 mg, 0.02 mmol) in THF (2.0 mL). The resulting reaction mixture was stirred at room temperature for 48 hours and monitored by TLC. Upon complete desilylation, reaction quench was performed by cannulation of the reaction mixture into a vigorously stirred, cold saturated $NaHCO_3$ (aq., 40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The resultant crude residue was purified by preparative TLC (CH_2Cl_2/MeOH, 9/1) to give lankacidinol A (**4**, 8.3 mg, 82% yield) as a white solid. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.38; $[\alpha]_D^{27}$ = −213.1 (*c* = 0.29 in EtOH); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 10.0 Hz, 1H, *H*-N), 6.26 (d, *J* = 15.2 Hz, 1H, *H*C_9), 5.70 (dd, *J* = 15.2, 9.6 Hz, 1H, *H*C_8), 5.59 (d, *J* = 15.6 Hz, 1H, *H*C_{15}), 5.53 (t, *J* = 10.8 Hz, 1H, *H*C_{18}), 5.48 (dd, *J* = 15.6, 8.0 Hz, 1H, *H*C_{14}), 5.43 (dt, *J* = 10.2, 5.2 Hz, 1H, *H*C_7), 5.35 (dd, *J* = 10.0, 6.7 Hz, 1H, *H*C_{11}), 4.67 (d, *J* = 11.0 Hz, 1H, *H*C_{17}), 4.40 (dt, *J* = 12.0, 3.2 Hz, 1H, *H*C_5), 4.23 (qd, *J* = 6.6, 4.0 Hz, 1H, *H*C_{24}), 4.08 (dt, *J* = 8.2, 6.4 Hz, 1H, *H*C_{13}), 2.64 (br d, *J* = 4.4 Hz, 1H, *H*-O), 2.47-2.37 (m, 3H, *H*C_4, H_AC_{12}, H_BC_{12}), 2.35-2.21 (m, 2H, H_AC_6, H_BC_6), 2.03 (s, 3H, H_3C_{27}), 1.89 (d, *J* = 0.8 Hz, 3H, H_3C_{22}), 1.55 (s, 3H, H_3C_{21}), 1.44 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.40 (s, 3H, H_3C_{19}), 1.30 (d, *J* = 6.8 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 211.4 (C_3=O), 173.9 (C_{23}=O), 170.4 (C_{26}=O), 170.0 (C_1=O), 141.2 (C_9H), 139.1 (C_{16}), 136.3 (C_{10}), 134.9 (C_{15}H), 131.1 (C_{14}H), 129.8 (C_{11}H), 125.1 (C_{17}H), 124.6 (C_8H), 75.5 (C_5H), 74.7 (C_{13}H), 71.7 (C_7H), 68.6 (C_{24}H), 57.1 (C_2), 51.4 (C_{18}H), 46.6 (C_4H), 37.0 ($C_{12}H_2$), 34.4 (C_6H_2), 21.6 ($C_{25}H_3$), 21.5 ($C_{27}H_3$), 21.0 ($C_{19}H_3$), 13.0 ($C_{22}H_3$), 12.7 ($C_{21}H_3$), 9.6 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3400, 3341, 2989, 2968, 2923, 2864, 1747, 1719, 1707, 1637, 1553, 1522, 1457, 1434, 1371, 1316, 1241, 1130, 1078, 1023, 958, 799 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{27}H_{38}O_8N$ $[M + H]^+$: 504.2592, found: 504.2590.

Synthesis of desilylation product 67. Hydrochloric acid (approximately 4 M in water, 0.16 mL) was added to a solution of **66** (8.0 mg, 0.009 mmol) in THF (1.4 mL) at room temperature. After stirring for 15 hours, the reaction mixture was carefully quenched by dropwise addition of saturated $NaHCO_3$ (aq., 10 mL). The resultant slurry was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by preparative TLC (petroleum ether/EtOAc: 1/2) to give alcohol **67** (5.8 mg, 87% yield) as a colorless oil. **TLC** (petroleum ether / ethyl acetate = 1:1 v/v, $KMnO_4$): R_f = 0.27; $[\alpha]_D^{23}$ = −245.5 (*c* = 0.21 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.60 (m, 4H), 7.48 (d, *J* = 10.0 Hz, 1H), 7.43-7.31 (m, 6H), 6.14 (d, *J* = 15.2 Hz, 1H), 5.63 (dd, *J* = 15.6, 10.0 Hz, 1H), 5.57 (dd, *J* = 15.6, 8.6 Hz, 1H), 5.51 (t, *J* = 10.4 Hz, 1H), 5.36 (ddd, *J* = 10.8, 10.0, 5.4 Hz, 1H), 5.27 (d, *J* = 15.6 Hz, 1H), 5.07 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.36 (m, 1H), 4.25 (m, 1H), 3.99 (m, 1H), 2.46 (m, 1H), 2.34 (m, 1H), 2.31-2.17 (m, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.51 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 211.4, 173.7, 170.3, 170.0, 141.3, 139.3, 136.0, 135.9 (2 peaks), 134.3, 134.0, 133.4, 131.9, 130.2, 129.8, 129.7, 127.7, 127.6, 124.2, 76.0, 75.4, 71.8, 68.6, 57.1, 51.3, 46.6, 37.9, 34.3, 27.1, 21.7, 21.5, 21.1, 19.3, 13.0, 12.6, 9.5 ppm; **IR** (thin film): ν_{max} = 3395, 2961, 2929, 2857, 1754, 1735, 1710, 1659, 1512, 1454, 1428, 1365, 1313, 1260, 1239, 1111, 1075, 1016, 963, 821, 798, 741, 704, 613, 507 cm^{-1}; **HRMS-ESI** (*m/z*): calcd. for $C_{43}H_{55}O_8NNaSi$ $[M + Na]^+$: 764.3589, found: 764.3590.

Synthesis of pyruvamide 68. A suspension of **67** (16.3 mg, 0.022 mmol, 1.0 equiv, azeotropically dried with benzene) and $NaHCO_3$ (18.9 mg, 0.22 mmol, 10.0 equiv) in dry CH_2Cl_2 (2.0 mL) was added Dess-Martin Periodinane (29.5 mg, 0.066 mmol, 3.0 equiv) in one portion. The mixture was vigorously stirred for 10 min at room temperature until complete consumption of starting material was indicated by TLC. The reaction was quenched with saturated $NaHCO_3$ (aq., 15 mL) and partitioned between CH_2Cl_2 (30 mL) and H_2O (10 mL). The organic layer was collected and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue was purified by preparative TLC (petroleum ether/EtOAc: 3/1) to afford ketoamide **68** (13.1 mg, 80% yield) as a colorless oil. **TLC** (petroleum ether / ethyl acetate = 1:1 v/v, $KMnO_4$): R_f = 0.79; $[\alpha]_D^{24}$ = −178.9 (*c* = 0.69 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 10.0 Hz, 1H), 7.66-7.59 (m, 4H), 7.43-7.30 (m, 6H), 6.14 (d, *J* = 15.4 Hz, 1H), 5.63 (dd, *J* = 15.4, 9.6 Hz, 1H), 5.58 (dd, *J* = 16.0, 8.4 Hz, 1H), 5.42 (t, *J* = 10.4 Hz, 1H), 5.36 (m, 1H), 5.27 (d, *J* = 16.0 Hz, 1H), 5.08 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.37 (m, 1H), 3.99 (m, 1H), 2.48 (s, 3H), 2.46 (m, 1H), 2.34 (m, 1H), 2.31-2.17 (m, 3H), 2.01 (s, 3H), 1.86 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 210.6, 196.6, 170.2, 169.8, 159.7, 141.1, 139.7, 135.8, 135.7, 134.2, 133.9, 133.1, 132.1, 130.1, 129.7, 129.6, 127.6, 127.5, 124.1, 123.4, 75.9, 75.4, 71.6, 56.8, 51.8, 46.4, 37.8, 34.2, 27.0, 24.6, 21.4, 21.0, 19.2, 12.9, 12.5, 9.4 ppm; **IR** (thin film): ν_{max} = 3392, 2965, 2930, 2857, 1753, 1731, 1711, 1689, 1503, 1428, 1360, 1241, 1111, 1070, 1015, 964, 797, 742, 704, 613, 508 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{43}H_{54}O_8NSi$ $[M + H]^+$: 740.3613, found: 740.3610.



Dess-Martin oxidation of undried **67** in wet CH_2Cl_2 at room temperature for 1 hour resulted in only 31% yield of **68** and a significant amount of the monoepoxide **68a** was isolated in 44% yield as a colorless oil. $[\alpha]_D^{22}$ = −135.0 (*c* = 0.12 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 10.0 Hz, 1H, *H*-N), 7.64-7.57 (m, 4H, *H*-Ar), 7.41-7.30 (m, 6H, *H*-Ar), 6.02 (dd, *J* = 15.6, 8.8 Hz, 1H, *H*C_8), 5.67 (dd, *J* = 15.6, 8.8 Hz, 1H, *H*C_{14}), 5.47 (d, *J* = 15.6 Hz, 1H, *H*C_{15}), 5.46 (t, *J* = 10.4 Hz, 1H, *H*C_{18}), 5.35 (m, 1H, *H*C_7), 5.28 (d, *J* = 15.6 Hz, 1H, *H*C_9), 4.60 (d, *J* = 11.2 Hz, 1H, *H*C_{17}), 4.34 (m, 1H, *H*C_5), 4.12 (ddd, *J* = 12.0, 8.8, 3.2 Hz, 1H, *H*C_{13}), 2.50 (s, 3H, H_3C_{25}), 2.49 (m, 1H, *H*C_{11}), 2.30-2.21 (m, 3H, *H*C_4, H_AC_6, H_AC_{12}), 2.17 (m, 1H, H_BC_6), 2.01 (s, 3H, H_3C_{27}), 1.88 (s, 3H, H_3C_{22}), 1.60 (m, 1H, H_BC_{12}),

1.38 (s, 3H, H_3C_{19}), 1.25 (d, J = 6.4 Hz, 3H, H_3C_{20}), 1.21 (s, 3H, H_3C_{21}), 1.02 (s, 9H, *SiR*) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 210.3 (C_3=O), 196.6 (C_{24}=O), 170.3 (C_1=O), 170.2 (C_{26}=O), 159.9 (C_{23}=O), 140.9 (C_9H), 139.6 (C_{16}), 136.0 (2 peaks, *SiR*), 135.9 (*SiR*), 133.9 (C_{14}H), 132.5 (C_{15}H), 131.3 (C_8H), 130.0 (*SiR*), 129.9 (*SiR*), 127.8 (2 peaks, *SiR*), 127.7 (*SiR*), 124.4 (C_{17}H), 75.4 (C_5H), 73.1 (C_{13}H), 69.6 (C_7H), 63.3 (C_{11}H), 58.9 (C_{10}), 56.9 (C_2), 52.4 (C_{18}H), 46.8 (C_4H), 37.3 ($C_{12}H_2$), 34.3 (C_6H_2), 27.0 (*SiR*), 24.7 ($C_{25}H_3$), 21.4 ($C_{27}H_3$), 21.0 ($C_{19}H_3$), 13.7 ($C_{21}H_3$), 13.6 ($C_{22}H_3$), 9.4 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3499, 3388, 2960, 2928, 2856, 1743, 1728, 1710, 1690, 1504, 1461, 1428, 1360, 1313, 1260, 1238, 1109, 1079, 1017, 966, 800, 758, 704, 613, 508 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{43}H_{54}O_9NSi$ $[M + H]^+$: 756.3562, found: 756.3548.

Synthesis of lankacidin A (sedecamycin, 2). To a stirred solution of acetic acid (194 mg, 0.18 mL, 3.0 mmol) in THF (4.5 mL) at room temperature was added TBAF (1.0 mol/L in THF, 1.5 mL, 1.5 mmol). After stirring for 10 min, 4.0 mL of the reagent prepared as described above was added to a solution of **68** (25.0 mg, 0.034 mmol) in THF (14.0 mL). The resulting reaction mixture was stirred at room temperature for 56 hours. Upon completion, reaction quench was performed by cannulation of the reaction mixture into a vigorously stirred, cold saturated $NaHCO_3$ (aq., 60 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The resultant crude residue was purified by preparative TLC (petroleum ether/EtOAc: 1/1) to give lankacidin A (**2**, 14.7 mg, 87% yield) as a white solid. **TLC** (petroleum ether / EtOAc = 1:1 v/v, $KMnO_4$): R_f = 0.35; $[\alpha]_D^{25}$ = −243.9 (*c* = 1.14 in EtOH); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.9 Hz, 1H, *H*-N), 6.27 (d, *J* = 15.4 Hz, 1H, *H*C_9), 5.70 (dd, *J* = 15.4, 9.7 Hz, 1H, *H*C_8), 5.60 (d, *J* = 15.8 Hz, 1H, *H*C_{15}), 5.50 (dd, *J* = 15.8, 8.2 Hz, 1H, *H*C_{14}), 5.44 (t, *J* = 10.2 Hz, 1H, *H*C_{18}), 5.43 (m, 1H, *H*C_7), 5.35 (m, 1H, *H*C_{11}), 4.68 (d, *J* = 10.8 Hz, 1H, *H*C_{17}), 4.41 (dt, *J* = 12.1, 3.4 Hz, 1H, *H*C_5), 4.09 (m, 1H, *H*C_{13}), 2.47 (s, 3H, H_3C_{25}), 2.44-2.39 (m, 3H, *H*C_4, H_AC_{12}, H_BC_{12}), 2.35-2.22 (m, 2H, H_AC_6, H_BC_6), 2.03 (s, 3H, H_3C_{27}), 1.91 (s, 3H, H_3C_{22}), 1.55 (s, 3H, H_3C_{21}), 1.39 (s, 3H, H_3C_{19}), 1.31 (d, *J* = 6.7 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ = 210.8 (C_3=O), 196.7 (C_{24}=O), 170.4 (C_{26}=O), 169.9 (C_1=O), 159.8 (C_{23}=O), 141.1 (C_9H), 139.6 (C_{16}), 136.3 (C_{10}), 134.7 (C_{15}H), 131.4 (C_{14}H), 129.7 (C_{11}H), 124.6 (C_8H), 124.3 (C_{17}H), 75.6 (C_5H), 74.7 (C_{13}H), 71.6 (C_7H), 56.9 (C_2), 51.9 (C_{18}H), 46.6 (C_4H), 37.0 ($C_{12}H_2$), 34.3 (C_6H_2), 24.7 ($C_{25}H_3$), 21.6 ($C_{27}H_3$), 21.1 ($C_{19}H_3$), 13.1 ($C_{22}H_3$), 12.7 ($C_{21}H_3$), 9.6 ($C_{20}H_3$) ppm; **IR** (thin film): *ν*max = 3450, 3387, 2927, 2856, 1730, 1709, 1688, 1504, 1453, 1360, 1242, 1161, 1138, 1055, 1014, 965, 866, 825, 811, 799, 738, 675, 626, 583, 547, 534 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{27}H_{36}O_8N$ $[M + H]^+$: 502.2435, found: 502.2434.

Synthesis of lankacidin C (1). A solution of pyruvamide **68** (9.0 mg, 0.012 mmol) in acetonitrile (1.5 mL) was cooled to −20 °C followed by dropwise addition of HF (aq., 40 wt.%, 1.0 mL). The resulting cloudy mixture was vigorously stirred at the same temperature for 65 hours and monitored by TLC. The reaction was quenched by carefully pouring into a vigorously stirred, cold solution of saturated $NaHCO_3$ (aq., 80 mL). The slurry was stirred at room temperature for further 30 min before it was extracted with EtOAc (5 x 20 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated under reduced pressure. Further purification by preparative TLC (CH_2Cl_2/MeOH, 10/1) gave lankacidin C (**1**, 2.4 mg, 44% yield). **TLC** (dichloromethane / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.54; $[\alpha]_D^{20}$ = −195.8 (*c* = 0.08 in EtOH); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 10.0 Hz, 1H, *H*-N), 6.14 (d, *J* = 15.4 Hz, 1H, *H*C_9), 5.80 (dd, *J* = 15.4, 9.5 Hz, 1H, *H*C_8), 5.59 (d, *J* = 15.9 Hz, 1H, *H*C_{15}), 5.50 (dd, *J* = 15.9, 8.1 Hz, 1H, *H*C_{14}), 5.44 (t, *J* = 10.5 Hz, 1H, *H*C_{18}), 5.32 (dd, *J* = 9.7, 7.2 Hz, 1H, *H*C_{11}), 4.67 (d, *J* = 10.9 Hz, 1H, *H*C_{17}), 4.43 (dt, *J* = 9.8, 5.9 Hz, 1H, *H*C_5), 4.33 (dt, *J* = 8.3, 5.5 Hz, 1H, *H*C_7), 2.47 (s, 3H, H_3C_{25}), 2.46 (m, 1H, H_AC_6), 2.44-2.37 (m, 3H, *H*C_4, H_AC_{12}, H_BC_{12}), 2.28 (m, 1H, H_BC_6), 1.91 (s, 3H, H_3C_{22}), 1.56 (s, 3H, H_3C_{21}), 1.39 (s, 3H, H_3C_{19}), 1.26 (d, *J* = 6.8 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 211.0 (C_3=O), 196.7 (C_{24}=O), 170.0 (C_1=O), 159.9 (C_{23}=O), 139.5 (C_{16}), 138.4 (C_9H), 136.5 (C_{10}), 134.9 (C_{15}H), 131.3 (C_{14}H), 129.4 (C_8H), 128.8 (C_{11}H), 124.4 (C_{17}H), 75.8 (C_5H), 74.8 (C_{13}H), 70.1 (C_7H), 56.9 (C_2), 51.9 (C_{18}H), 46.6 (C_4H), 37.0 ($C_{12}H_2$), 36.9 (C_6H_2), 24.7 ($C_{25}H_3$), 21.1($C_{19}H_3$), 13.0 ($C_{22}H_3$), 12.9 ($C_{21}H_3$), 9.8 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3363, 2923, 2853, 1743, 1729, 1706, 1679, 1631, 1512, 1461, 1378, 1260, 1220, 1167, 1134, 1083, 1015, 966, 873, 812 cm^{-1}; **HRMS-DART** (Negative-ion mode) (*m/z*): calcd. for $C_{25}H_{32}O_7N$ $[M - H]^-$: 458.2184, found: 458.2178.

Neolankacidin C (**69**, 2.7 mg, 49% yield) was also isolated as a white waxy solid from the above crude product mixture. **TLC** (dichloromethane / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.45; $[\alpha]_D^{20}$ = +48.7 (*c* = 0.22 in EtOH); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 9.6 Hz, 1H, *H*-N), 6.47 (dd, *J* = 15.4, 11.0 Hz, 1H, *H*C_8), 5.87 (d, *J* = 11.0 Hz, 1H, *H*C_9), 5.80 (d, *J* = 15.4 Hz, 1H, *H*C_{15}), 5.61-5.54 (m, 2H, *H*C_7, *H*C_{14}), 5.35 (dd, *J* = 10.6, 9.7 Hz, 1H, *H*C_{18}), 4.72 (d, *J* = 11.0 Hz, 1H, *H*C_{17}), 4.28 (dt, *J* = 11.5, 3.0 Hz, 1H, *H*C_5), 4.13 (dd, *J* = 11.0, 4.2 Hz, 1H, *H*C_{11}), 3.91 (m, 1H, *H*C_{13}), 2.70 (m, 1H, H_AC_6), 2.51 (m, 1H, *H*C_4), 2.45 (s, 3H, H_3C_{25}), 2.44 (m, 1H, H_BC_6), 2.10 (m, 1H, H_AC_{12}), 2.02 (m, 1H, H_BC_{12}), 1.88 (s, 3H, H_3C_{22}), 1.64 (s, 3H, H_3C_{21}), 1.41 (s, 3H, H_3C_{19}), 1.17 (d, *J* = 6.6 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 209.8 (C_3=O), 196.5 (C_{24}=O), 171.3 (C_1=O), 159.8 (C_{23}=O), 139.2 (C_{16}), 138.5 (C_{10}), 136.5 (C_{15}H), 134.2 (C_8H), 132.9 (C_{14}H), 128.1 (C_9H), 125.8 (C_{17}H), 123.5 (C_7H), 77.9 (C_5H), 77.1 (C_{11}H), 71.9 (C_{13}H), 57.0 (C_2), 53.3 (C_{18}H), 46.2 (C_4H), 40.9 ($C_{12}H_2$), 32.7 (C_6H_2), 24.5 ($C_{25}H_3$), 20.4 ($C_{19}H_3$), 13.0 ($C_{22}H_3$), 11.2 ($C_{21}H_3$), 9.0 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3362, 2923, 2853, 1734, 1702, 1685, 1635, 1521, 1457, 1377, 1333, 1260, 1167, 1138, 1035, 1011, 967, 888, 832, 694, 594 cm^{-1}; **HRMS-DART** (Negative-ion mode) (*m/z*): calcd. for $C_{25}H_{32}O_7N$ $[M - H]^-$: 458.2184, found: 458.2201.

Synthesis of isolankacidinol (10) via desilylation of 36b.. A solution of macrocycle **36b** (18.0 mg, 0.0193 mmol, 1.0 equiv) in acetonitrile (2.0 mL) was cooled to −20 °C and HF (aq., 40 wt.%, 1.6 mL) was slowly added. The resulting cloudy mixture was vigorously stirred at the same temperature for 60 hours. The reaction was then quenched by pouring into a vigorously stirred cold solution of saturated aq. $NaHCO_3$ (80 mL) and stirred at room temperature for further 30 min before it was extracted with EtOAc (3 x 60 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. ([*Note*]: ^{1}H NMR of the crude material indicated formal [1,5]-hydroxy migration product was not formed). The crude desilylation product was subjected to preparative TLC (10% MeOH in $CHCl_3$) to afford isolankacidinol (**10**, 7.3 mg, 82% yield) as a white solid. Recrystallization of the purified material in MeOH/H_2O (8/1, v/v) at 5 °C gave crystals suitable for X-ray diffraction. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.38; $[\alpha]_D^{25}$ = −189.2 (*c* = 0.13 in EtOH); **^{1}H NMR** (400 MHz, CD_3OD): δ = 6.21 (d, *J* = 15.2 Hz, 1H, *H*C_9), 5.82 (d, *J* = 15.6 Hz, 1H, *H*C_{15}), 5.57 (d, *J* = 10.4 Hz, 1H, *H*C_{18}), 5.43 (dd, *J* = 15.6, 7.6 Hz, 1H, *H*C_{14}), 5.32 (m, 1H, *H*C_{11}), 5.29 (m, 1H, *H*C_8), 4.97 (d, *J* = 10.4 Hz, 1H, *H*C_{17}), 4.35 (ddd, *J* = 11.2, 8.4, 4.0 Hz, 1H. *H*C_7), 4.17 (m, 1H, *H*C_{13}), 4.10 (q, *J* = 6.8 Hz, 1H, *H*C_{24}), 3.60 (app t, *J* = 10.8 Hz, 1H, *H*C_5), 3.04 (dq, *J* = 10.8, 6.8 Hz, 1H, *H*C_4), 2.47 (m, 1H, H_AC_{12}), 2.32 (m, 1H, H_BC_{12}), 2.07 (m, 1H, H_AC_6), 1.84 (m, 1H, H_BC_6), 1.73 (s, 3H, H_3C_{22}), 1.63 (s, 3H, H_3C_{21}), 1.38 (s, 3H, H_3C_{19}), 1.37 (d, *J* = 6.8 Hz, 3H, H_3C_{25}), 1.01 (d, *J* = 6.4 Hz, 3H, H_3C_{20}) ppm; **^{13}C{^{1}H} NMR** (100 MHz, CD_3OD): δ = 206.2 (C_3=O), 176.9 (C_{23}=O), 175.0 (C_1=O), 139.2 (C_9H), 138.2 (C_{16}), 136.3 (C_{15}H), 135.0 (C_{10}), 133.4 (C_{14}H), 131.0 (C_{11}H), 128.7 (C_8H), 127.7 (C_{17}H), 78.7 (C_5H), 75.1 (C_{13}H), 70.8 (C_7H), 69.2 (C_{24}H), 60.2 (C_2), 49.6 (C_{18}H), 45.1 (C_4H), 41.6 (C_6H_2), 36.9 ($C_{12}H_2$), 22.8 ($C_{19}H_3$), 21.3 ($C_{25}H_3$), 13.3 ($C_{21}H_3$), 12.9 ($C_{22}H_3$), 9.7 ($C_{20}H_3$) ppm; **IR** (thin film): ν_{max} = 3383, 2929, 1742, 1712, 1659, 1519, 1456, 1376, 1314, 1244, 1123, 1024, 965, 877, 709 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{36}O_7N$ $[M + H]^+$: 462.2486, found: 462.2486.

Decarboxylation of isolankacidinol (10) following Harada's protocol. To a solution of **10** (20.0 mg, 0.044 mmol) in methanol (1.0

mL) was added aq. K_2CO_3 (2 wt.%, 1.0 mL) at room temperature. The reaction mixture was vigorously stirred for 1 hour at the same temperature before acidified to pH = 2 by slow dropwise addition of 1 M HCl (aq.). The mixture was then diluted with EtOAc (30 mL) and brine (30 mL). The layers were separated, the aqueous layer was extracted with additional EtOAc (2 x 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was applied to preparative TLC (CH_2Cl_2/MeOH, 10/1) to give lankacyclinol (**5**, 12.4 mg, 67% yield) and 2-*epi*-lankacyclinol (**62**, 2.2 mg, 12% yield). A crystal of **62** suitable for X-ray analysis were eventually grown by slow evaporation at 5 °C from methanol.

Synthesis of 2,18-bis-*epi*-lankacyclinol (72) via desilylation of **36c**. To a solution of macrocycle **36c** (35.0 mg, 0.038 mmol, 1.0 equiv) and H_2O (27.0 mg, 1.510 mmol, 40.0 equiv) in DMF (9.0 mL) was added TASF (159.0 mg, 0.565 mmol, 15.0 equiv) in one portion. The resulting orange-colored solution was stirred for 24 hours at room temperature, diluted with EtOAc (20 mL) and cooled to 0 °C, during which time a mixture of brine (30 mL) and phosphate buffer (aq., pH = 7, 30 mL) was added to quench the reaction. The resultant slurry was further extracted with additional EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/MeOH, 10/1) to give 2,18-bis-*epi*-lankacyclinol (**72**, 12.1 mg, 77% yield) as a white solid. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.30; $[\alpha]_D^{25}$ = +185.7 (*c* = 0.10 in MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ = 6.66 (m, 1H, *H*C$_5$), 6.07 (d, *J* = 15.6 Hz, 1H, *H*C$_9$), 5.94 (d, *J* = 15.8 Hz, 1H, *H*C$_{15}$), 5.54 (dd, *J* = 15.9, 5.7 Hz, 1H, *H*C$_{14}$), 5.48 (dd, *J* = 15.6, 6.3 Hz, 1H, *H*C$_8$), 5.32 (t, *J* = 7.6 Hz, 1H, *H*C$_{11}$), 5.17 (br d, *J* = 9.6 Hz, 1H, *H*C$_{17}$), 4.97 (t, *J* = 9.9 Hz, 1H, *H*C$_{18}$), 4.41 (m, 1H, *H*C$_7$), 4.36 (m, 1H, *H*C$_{13}$), 4.12 (q, *J* = 6.8 Hz, 1H, *H*C$_{24}$), 3.57 (dq, *J* = 10.3, 6.8 Hz, 1H, *H*C$_2$), 2.74 (ddd, *J* = 13.6, 9.4, 3.9 Hz, 1H, *H*$_A$C$_6$), 2.50-2.36 (m, 3H, *H*$_B$C$_6$, *H*$_A$C$_{12}$, *H*$_B$C$_{12}$), 1.73 (s, 3H, *H*$_3$C$_{20}$), 1.70 (s, 3H, *H*$_3$C$_{22}$), 1.65 (s, 3H, *H*$_3$C$_{21}$), 1.31 (d, *J* = 6.8 Hz, 3H, *H*$_3$C$_{25}$), 0.99 (d, *J* = 6.8 Hz, 3H, *H*$_3$C$_{19}$) ppm; **^{13}C{^{1}H} NMR** (100 MHz, CD_3OD): δ = 206.0 (C$_3$=O), 176.9 (C$_{23}$=O), 140.0 (C$_4$), 139.2 (C$_5$H), 136.8 (C$_{16}$), 136.5 (C$_9$H), 136.2 (C$_{15}$H), 135.2 (C$_{10}$), 130.6 (C$_{14}$H), 129.9 (C$_{17}$H), 129.1 (C$_8$H), 128.5 (C$_{11}$H), 72.0 (C$_7$H), 71.6 (C$_{13}$H), 69.1 (C$_{24}$H), 50.5 (C$_{18}$H), 44.9 (C$_2$H), 37.5 (C$_6$H$_2$), 35.4 (C$_{12}$H$_2$), 21.3 (C$_{25}$H$_3$), 16.2 (C$_{19}$H$_3$), 13.8 (C$_{22}$H$_3$), 13.4 (C$_{21}$H$_3$), 12.4 (C$_{20}$H$_3$) ppm. **IR** (thin film): ν_{max} = 3344, 2922, 2853, 1661, 1631, 1548, 1454, 1370, 1293, 1265, 1126, 1027, 1013, 967, 877 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{24}H_{36}O_5N$ $[M + H]^+$: 418.2588, found: 418.2587.

18-*epi*-lankacyclinol (**73**, 1.4 mg, 9% yield) was also isolated as a white waxy solid from the above crude product mixture. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.40; $[\alpha]_D^{22}$ = +44.2 (*c* = 0.10 in MeOH); **^{1}H NMR** (400 MHz, acetone-d_6): δ = 8.29 (d, *J* = 9.6 Hz, 1H, *H*-N), 6.54 (ddq, *J* = 9.4, 6.0, 1.2 Hz, 1H, *H*C$_5$), 6.16 (d, *J* = 15.6 Hz, 1H, *H*C$_9$), 6.01 (d, *J* = 15.6 Hz, 1H, *H*C$_{15}$), 5.61-5.55 (m, 2H, *H*C$_8$, *H*C$_{14}$), 5.40 (dd, *J* = 8.4, 7.0 Hz, 1H, *H*C$_{11}$), 5.10 (d, *J* = 9.2 Hz, 1H, *H*C$_{17}$), 4.89 (td, *J* = 9.4, 3.4 Hz, 1H, *H*C$_{18}$), 4.74 (d, *J* = 4.8 Hz, 1H, *H*O-C$_{24}$), 4.58-4.52 (m, 2H, *H*C$_{13}$, *H*C$_7$), 4.15 (qd, *J* = 6.8, 5.2 Hz, 1H, *H*C$_{24}$), 3.96 (d, *J* = 4.8 Hz, 1H, *H*O-C$_7$), 3.80 (d, *J* = 4.8 Hz, 1H, *H*O-C$_{13}$), 3.49 (qd, *J* = 7.2, 3.6 Hz, 1H, *H*C$_2$), 2.71 (ddd, *J* = 14.4, 9.4, 6.8 Hz, 1H, *H*$_A$C$_6$), 2.54 (m, 1H, *H*$_B$C$_6$), 2.49-2.36 (m, 2H, *H*$_A$C$_{12}$, *H*$_B$C$_{12}$), 1.80 (s, 3H, *H*$_3$C$_{20}$), 1.79 (s, 3H, *H*$_3$C$_{22}$), 1.62 (s, 3H, *H*$_3$C$_{21}$), 1.29 (d, *J* = 6.8 Hz, 3H, *H*$_3$C$_{25}$), 1.04 (d, *J* = 7.2 Hz, 3H, *H*$_3$C$_{19}$) ppm; **^{13}C{^{1}H} NMR** (100 MHz, acetone-d_6): δ = 208.0 (C$_3$=O), 174.5 (C$_{23}$=O), 139.7 (C$_4$), 139.5 (C$_5$H), 135.1 (C$_{10}$), 135.0 (C$_9$H), 134.7 (C$_{16}$), 133.3 (C$_{15}$H), 131.3 (C$_{14}$H), 130.9 (C$_{17}$H), 128.6 (C$_8$H), 127.9 (C$_{11}$H), 71.1 (C$_7$H), 70.8 (C$_{13}$H), 68.8 (C$_{24}$H), 50.4 (C$_{18}$H), 42.6 (C$_2$H), 37.6 (C$_6$H$_2$), 35.5 (C$_{12}$H$_2$), 21.5 (C$_{25}$H$_3$), 16.4 (C$_{19}$H$_3$), 13.1 (C$_{21}$H$_3$), 12.8 (C$_{22}$H$_3$), 12.3 (C$_{20}$H$_3$) ppm; **IR** (thin film): ν_{max} = 3361, 3201, 2963, 2923, 2853, 1657, 1631, 1519, 1467, 1457, 1377, 1316, 1300, 1261, 1123, 1061, 1028, 967, 871, 806, 722 cm-1; **HRMS-DART** (m/z): calcd. for $C_{24}H_{36}O_5N$ $[M + H]^+$: 418.2588, found: 418.2588.

Synthesis of tris-(4-bromobenzyl ester) derivative 74. A solution of 2,18-bis-*epi*-lankacyclinol **72** (2.2 mg, 5.3 μmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) was treated successively with Et_3N (9.0 μL, 65 μmol, 12.3 equiv), DMAP (0.7 mg, 5.7 μmol, 1.1 equiv) and 4-bromobenzoyl chloride (11.7 mg, 53 μmol, 10.0 equiv). The reaction mixture was stirred at room temperature for 13 hours before partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by preparative TLC (petroleum ether/EtOAc: 2/1) to produce **74** (4.5 mg, quant.) as a white solid. A single crystal suitable for X-ray analysis was obtained by slow evaporation at room temperature from petroleum ether/dichloromethane. $[\alpha]_D^{25}$ = +50.2 (*c* = 0.17 in $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 2H), 7.90 (dd, *J* = 18.6, 7.8 Hz, 4H), 7.62 (d, *J* = 7.8 Hz, 4H), 7.57 (d, *J* = 7.8 Hz, 2H), 6.49 (s, 1H), 6.17 (d, *J* = 15.6 Hz, 1H), 6.06 (s, 1H), 5.99 (d, *J* = 15.0 Hz, 1H), 5.68-5.58 (m, 3H), 5.49 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.45-5.37 (m, 1H), 5.37-5.27 (m, 2H), 4.85-4.74 (m,1H), 3.63 (s, 1H), 2.91-2.84 (m, 1H), 2.76-2.68 (m, 1H), 2.66-2.53 (m, 2H), 1.84 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 5.4 Hz, 3H), ppm. **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ = 203.7, 169.7, 165.1 (2 peaks), 165.0, 140.1, 138.4, 137.3, 136.7, 134.9, 134.4, 132.2, 132.0, 131.9, 131.4, 131.3, 129.4, 128.4, 128.3 (3 peaks), 125.1, 123.4, 74.3, 73.4, 71.6, 51.0, 44.1, 33.5, 31.8, 22.8, 17.9, 16.0, 13.4, 12.7 ppm; **IR** (thin film): ν_{max} = 3300, 2959, 2923, 2853, 1718, 1679, 1660, 1618, 1590, 1540, 1457, 1397, 1263, 1171, 1100, 1012, 972, 847, 800, 756 cm^{-1}; **HRMS-ESI** (m/z): calcd. for $C_{45}H_{44}O_8NBr_3Na$ $[M + Na]^+$: 986.0509, found: 986.0516.

Synthesis of 2,18-bis-*epi*-lankacidinol (75). To a stirred solution of acetic acid (123 mg, 120 μL, 2.0 mmol) in THF (3.0 mL) at room temperature was added TBAF (1.0 mol/L in THF, 1.0 mL, 1.0 mmol). After stirring for 10 min, 1.5 mL of this reagent was added to a solution of **36c** (10.2 mg, 0.011 mmol) in THF (1.5 mL). The resulting reaction mixture was stirred at room temperature for 90 hours and partitioned between saturated $NaHCO_3$ (aq., 40 mL) and EtOAc (20 mL). The separated aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Analysis of the NMR spectra collected on crude residue indicated C7-epimerization was not observed. Purification by preparative TLC (CH_2Cl_2/MeOH: 9/1) gave **75** (3.9 mg, 76% yield) as a white waxy solid. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.38; $[\alpha]_D^{24}$ = +65.7 (*c* = 0.33 in MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ = 8.40 (d, *J* = 10.0 Hz, 1H, *H*-N), 6.20 (d, *J* = 15.6 Hz, 1H, *H*C$_9$), 5.96 (d, *J* = 16.0 Hz, 1H, *H*C$_{15}$), 5.73 (dd, *J* = 16.0, 3.2 Hz, 1H, *H*C$_{14}$), 5.43 (dd, *J* = 15.6, 6.8 Hz, 1H, *H*C$_8$), 5.35-5.30 (m, 2H, *H*C$_{18}$, *H*C$_{11}$), 5.08 (d, *J* = 10.4 Hz, 1H, *H*C$_{17}$), 4.62 (m, 1H, *H*C$_{13}$), 4.47 (td, *J* = 7.7, 4.2 Hz, 1H, *H*C$_7$), 4.15 (q, *J* = 6.8 Hz, 1H, *H*C$_{24}$), 3.84 (ddd, *J* = 11.9, 9.7, 2.4 Hz, 1H, *H*C$_5$), 3.06 (dq, *J* = 12.8, 6.5 Hz, 1H, *H*C$_4$), 2.53 (ddd, *J* = 14.0, 8.5, 3.5 Hz, 1H, *H*$_A$C$_{12}$), 2.38 (ddd, *J* = 13.9, 8.3, 3.8 Hz, 1H, *H*$_B$C$_{12}$), 2.07 (ddd, *J* = 14.1, 9.8, 4.2 Hz, 1H, *H*$_A$C$_6$), 1.96 (ddd, *J* = 14.2, 8.6, 2.5 Hz, 1H, *H*$_B$C$_6$), 1.79 (s, 3H, *H*$_3$C$_{22}$), 1.68 (s, 3H, *H*$_3$C$_{21}$), 1.49 (s, 3H, *H*$_3$C$_{19}$), 1.30 (d, *J* = 6.8 Hz, 3H, *H*$_3$C$_{25}$), 1.09 (d, *J* = 6.5 Hz, 3H, *H*$_3$C$_{20}$) ppm; **^{13}C{^{1}H} NMR** (100 MHz, CD_3OD): δ = 211.2 (C$_3$=O), 177.0 (C$_{23}$=O), 174.4 (C$_1$=O), 139.9 (C$_{16}$), 138.0 (C$_9$H), 136.0 (C$_{10}$), 133.3 (C$_{15}$H), 132.8 (C$_{14}$H), 129.4 (C$_{11}$H), 127.5 (C$_8$H), 125.5 (C$_{17}$H), 77.3 (C$_5$H), 71.5 (C$_{13}$H), 70.4 (C$_7$H), 69.0 (C$_{24}$H), 60.2 (C$_2$), 53.1 (C$_{18}$H), 46.5 (C$_4$H), 41.9 (C$_6$H$_2$), 35.0 (C$_{12}$H$_2$), 23.3 (C$_{19}$H$_3$), 21.0 (C$_{25}$H$_3$), 13.2 (C$_{21}$H$_3$), 13.1 (C$_{22}$H$_3$), 9.0 (C$_{20}$H$_3$) ppm; **IR** (thin film): ν_{max} = 3385, 2978, 2914, 2847, 1735, 1706, 1653, 1517, 1456, 1374, 1252, 1123, 1059, 1023, 967, 877 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{36}O_7N$ $[M + H]^+$: 462.2486, found: 462.2486.

Synthesis of 2,7,18-tri-*epi*-lankacidinol (76) via HF-promoted desilylation of 36c. To a solution of macrocycle **36c** (15.0 mg, 0.0161 mmol, 1.0 equiv) in acetonitrile (1.8 mL) was added HF (*aq*., 40 wt.%, 1.4 mL) at −20 °C. The resulting cloudy mixture was vigorously stirred at the same temperature for 96 hours until complete desilylation of the starting material was achieved as monitored by TLC analysis. The reaction was quenched by pouring into a

vigorously stirred cold solution of saturated $NaHCO_3$ (*aq*., 40 mL). The mixture was stirred for further 30 min and extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was further purified by preparative TLC (5% MeOH in $CHCl_3$, twice development was necessary) to give **75** (4.1 mg, 55% yield) and a slightly polar component 2,7,18-tri-*epi*-lankacidinol (**76**, 2.2 mg, 30% yield) as a colorless oil. **TLC** (chloroform / methanol = 10:1 v/v, $KMnO_4$): R_f = 0.37; $[\alpha]_D^{24}$ = +169.8 (*c* = 0.11 in MeOH); **^{1}H NMR** (500 MHz, CD_3OD): δ = 6.18 (d, *J* = 15.5 Hz, 1H, *H*C$_9$), 5.97 (d, *J* = 16.5 Hz, 1H, *H*C$_{15}$), 5.69 (dd, *J* = 15.5, 3.5 Hz, 1H, *H*C$_{14}$), 5.56 (dd, *J* = 11.5, 5.0 Hz, 1H, *H*C$_{11}$), 5.48 (dd, *J* = 15.5, 9.5 Hz, 1H, *H*C$_8$), 5.30 (d, *J* = 10.5 Hz, 1H, *H*C$_{18}$), 5.07 (d, *J* = 10.5 Hz, 1H, *H*C$_{17}$), 4.62 (m, 1H, *H*C$_{13}$), 4.14 (q, *J* = 7.0 Hz, 1H, *H*C$_{24}$), 4.05 (td, *J* = 10.3, 5.8 Hz, 1H, *H*C$_7$), 3.61 (m, 1H, *H*C$_5$), 3.09 (dq, *J* = 12.8, 6.4 Hz, 1H, *H*C$_4$), 2.48 (ddd, *J* = 13.7, 11.4, 2.5 Hz, 1H, H_AC$_{12}$), 2.43-2.37 (m, 2H, H_BC$_{12}$, H_AC$_6$), 1.83 (ddd, *J* = 16.5, 10.4, 5.0 Hz, 1H, H_BC$_6$), 1.74 (s, 3H, H_3C$_{22}$), 1.58 (s, 3H, H_3C$_{21}$), 1.48 (s, 3H, H_3C$_{19}$), 1.29 (d, *J* = 7.0 Hz, 3H, H_3C$_{25}$), 1.13 (d, *J* = 6.5 Hz, 3H, H_3C$_{20}$) ppm; **^{13}C{^{1}H} NMR** (125 MHz, CD_3OD): δ = 211.1 (C$_3$=O), 177.1 (C$_{23}$=O), 174.1 (C$_1$=O), 139.5 (C$_{16}$), 139.4 (C$_9$H), 136.8 (C$_{10}$), 133.3 (C$_{15}$H), 133.1 (C$_{14}$H), 128.8 (C$_{11}$H), 128.4 (C$_8$H), 125.5 (C$_{17}$H), 77.9 (C$_5$H), 74.0 (C$_7$H), 71.2 (C$_{13}$H), 69.0 (C$_{24}$H), 59.9 (C$_2$), 53.2 (C$_{18}$H), 46.3 (C$_4$H), 42.4 (C$_6$H$_2$), 34.8 (C$_{12}$H$_2$), 23.2 (C$_{19}$H$_3$), 20.9 (C$_{25}$H$_3$), 13.0 (C$_{22}$H$_3$), 12.8 (C$_{21}$H$_3$), 8.9 (C$_{20}$H$_3$) ppm; **IR** (thin film): ν_{max} = 3391, 2915, 2848, 1736, 1708, 1662, 1516, 1456, 1376, 1248, 1120, 1061, 1029, 967, 877 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{25}H_{36}O_7N$ $[M + H]^+$: 462.2486, found: 462.2485.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, as well as spectroscopic and analytical data for all new compounds (PDF)

Crystallographic data for compound **5** (CCDC: 1978830, CIF)

Crystallographic data for compound **62** (CCDC: 1978832, CIF)

Crystallographic data for compound **66** (CCDC: 1978833, CIF)

Crystallographic data for compound **10** (CCDC: 1978835, CIF)

Crystallographic data for compound **74** (CCDC: 1978836, CIF)

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Notes.

The authors declare no competing financial interests.

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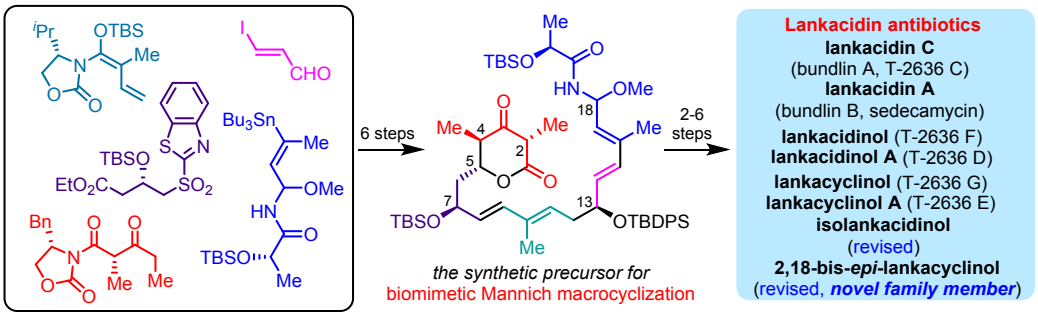

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