Enantioselective Total Synthesis of (+)-KB343

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ABSTRACT:

A concise total synthesis of the complex guanidinium toxin KB343 is reported traversing through an unusual sequence of chemoselective transformations and strategic skeletal reorganization. The absolute configuration is confirmed through an enantioselective route and the structures of all key intermediates and the natural product itself are unassailably confirmed through X-ray crystallographic analysis.

MAIN TEXT:

KB343 (**1**, Figure 1), is a structurally fascinating pentacyclic guanidinium alkaloid recently isolated by the Sakai group from a tunicate (*Epizoanthus illoricatus*) off the coast of the republic of Palau.[1] It exhibits toxicity in line with other guanidinium toxins such as tetrodotoxin and thus may represent a promising lead to study ion channel biology.[2] A long-held fascination with the synthesis of cyclic guanidine-containing alkaloids such as the pyrrole-imidazoles[3] and indole-imidazoles[4] drew our attention to **1**. Historically such structures present a multitude of challenges stemming from their dense functionality and the high polarity of intermediates. In the present case, **1** harbors three cyclic guanidines (2-aminoimidazoles) expressed as spiro-fused, ring fused, and aromatic variants annealed onto a decalin core. This Communication discloses a concise route

(both racemic and enantioselective) to **1** featuring a number of unconventional tactics and a strategy relying on skeletal reorganization to precisely install the key ring systems (Scheme 1).

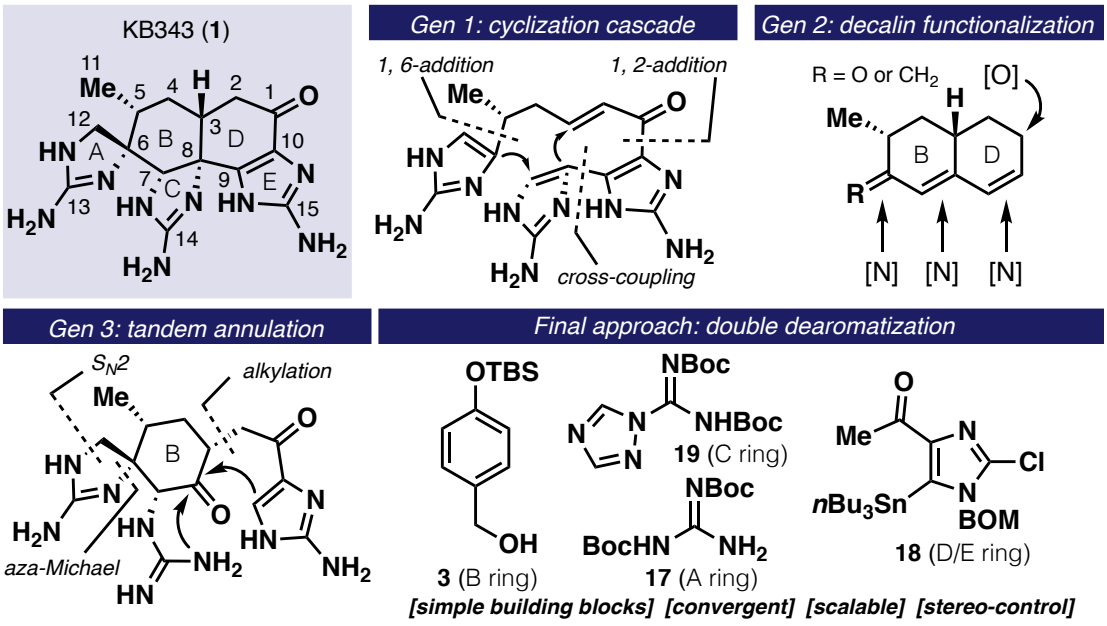


Figure 1. KB343 (**1**): Evolution of synthetic approaches.

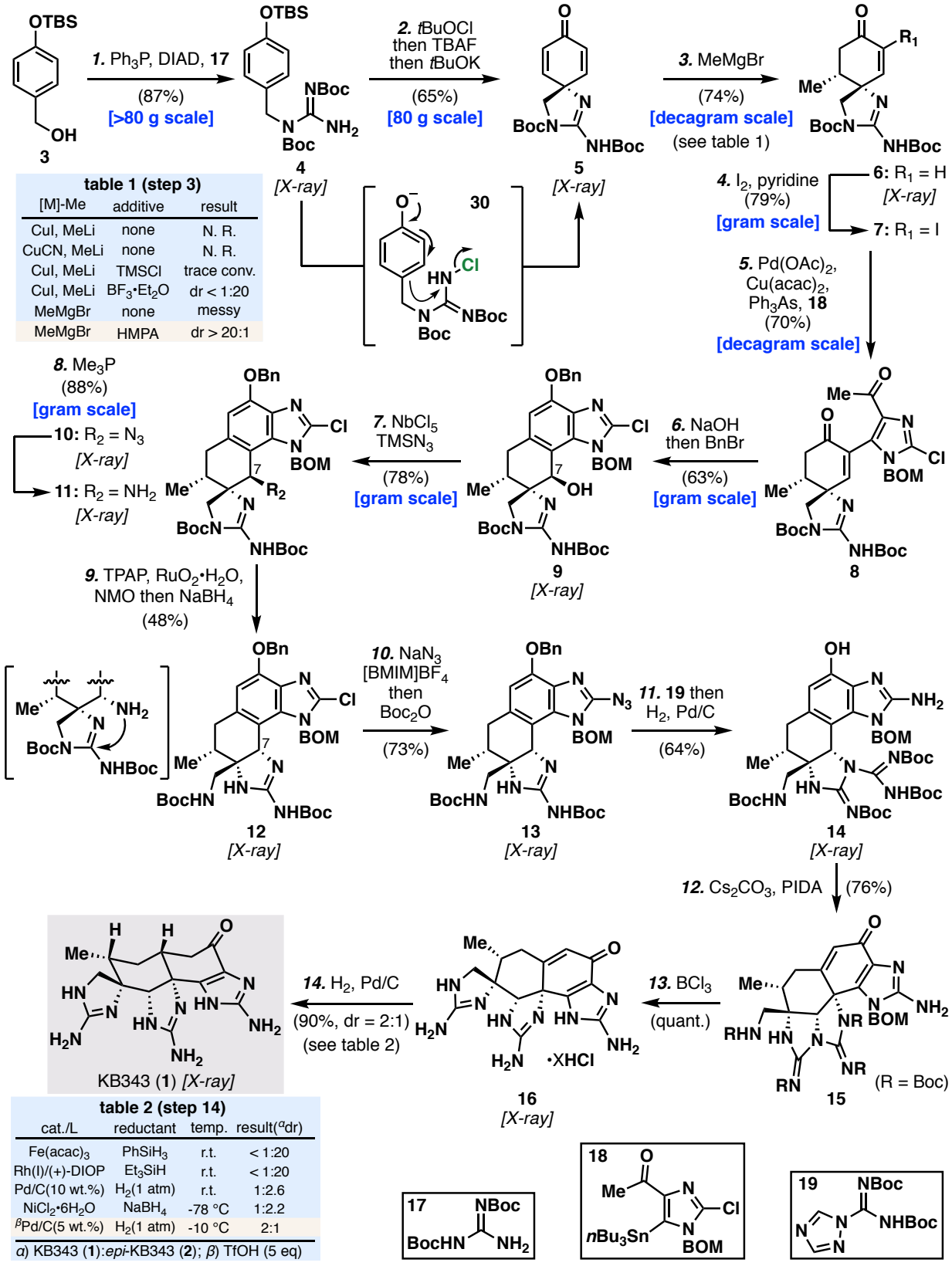
Several generations of retrosynthetic analyses were applied resulting in a successful solution to this puzzle. In the initial design, an ambitious approach wherein a simple linear intermediate would undergo a series of self-condensations controlled by a single methyl-containing stereocenter was pursued (Gen. 1, Figure 1). Unfortunately, the polarity of intermediates and difficulty in controlling the reactivity of such compounds proved unfeasible. Next, a "two-phase" strategy[5] was investigated through the sequential amination of a simple polyunsaturated decalin (Gen. 2). This path, however, resulted in a linear route stymied by functionalization challenges (regio- and stereo-selectivities). The learnings from these two excursions led to a third design plan aiming to annulate multiple rings from a central B-ring precursor (Gen. 3). This plan also faltered due to improper control of stereochemistry and C–N bond forming steps that would not proceed. The final successful route to **1** hinged upon a more convergent design that implemented the lessons of prior approaches and addressed stereochemical and chemoselectivity issues[6] with exquisite control.

The synthesis of **1** commenced with commercial benzyl alcohol **3** onto which was appended the first guanidine unit on multi-decagram scale under conventional Mitsunobu conditions to furnish

4 in 87% yield (structure confirmed via X-ray crystallography). The first dearomative cyclization converting **4** to **5** required invention as cyclizations of this type with guanidine nucleophiles either employ expensive transition metals with sulfonamide-protected guanidines[7a] or hypervalent iodine-based oxidants resulting in low-yields of product.[7b] Inspiration was drawn from the scalable synthesis of axinellamine and related alkaloids[3] wherein an electrophilic guanidine species forged a key spirocyclic center onto a pendant olefin. That observation subsequently led to the development of a highly effective electrophilic chlorinating reagent.[8] Thus, guanidine **4** was first treated with *t*BuOCl at room temperature. After 20 minutes TBAF and *t*BuOK were added sequentially to deliver dearomatized spirocycle **5** (structure confirmed via X-ray crystallography) in 65% isolated yield (80 g scale). This reaction presumably proceeds by way of intermediate **30** and it is worth noting that although the initial *N*-chlorinated species is isolable (not very stable) the entire sequence takes place in one reaction vessel. The seemingly simple desymmetrizing installation of the methyl group via conjugate addition proved unusually difficult as canonical conditions all delivered undesired byproducts or the wrong stereochemical outcome (see inset Table 1 and see SI for a more detailed screening table).[9] Eventually it was discovered that when the *in situ* derived magnesiated guanidine was formed it could direct addition to the desired face furnishing **6** (structure confirmed via X-ray crystallography) as a single diastereomer in 74% yield (decagram scale). Following a-iodination[10] of the remaining enone a convergent coupling with the stannane **18** (see SI) was accomplished via Stille coupling. Of note, Stille coupling proved to be the only viable cross-coupling for this pivotal C–C bond forming step and the initial hit (trace product) was optimized to 70% yield on decagram scale through judicious choice of Pd and Cu sources and ligand.[11] Aldol annulation of adduct **8** using aq. NaOH followed by addition of BnBr led to the hydroxylated tetracycle **9** (structure confirmed via X-ray crystallography) as a single diastereomer. Presumably following aldol addition/dehydration the resulting quinone methide species is immediately captured by hydroxide. It was anticipated that either a simple S_N2 reaction of the benzylic alcohol or *in situ* trapping of the putative quinone methide with an amine source would easily deliver the requisite amine stereochemistry at C-7. In the former case, this proved to be impossible as the benzyl alcohol could not be converted to a leaving group of any kind. For the latter case, only attack by hydroxide was observed rather than any N-based nucleophile employed and addition only occurred from the top face due to a rigid conformation blocking attack from the bottom. A rapid detour was therefore undertaken wherein S_N1 substitution using $NbCl_5/TMSN_3$

afforded azide **10** (structure confirmed via X-ray crystallography) in 78% yield (single diastereomer) followed by Staudinger reduction (88% yield, gram-scale), and an unusual C–N epimerization (48% yield) to deliver **12** (structure confirmed via X-ray crystallography). With regards to the azide installation, $NbCl_5$ was singularly successful amongst all Lewis-acids screened.[12] The amine redox-epimerization strategy, classically employed for alcohols, is rare in natural product synthesis.[13] In this instance, TPAP/NMO was the only successful oxidant of those screened. Finally, during this step an unusual and fortuitous skeletal rearrangement took place wherein the free amine underwent acyl-transfer thereby protecting itself and setting up a favorable geometry for the ensuing steps. The tenth step of the synthesis yet again required an unconventional solution to a simple reaction: S_NAr. Under a variety of known conditions with various nucleophiles only loss of the Boc groups and decomposition was observed, in some cases trace quantities of product could be detected. Ultimately, the use of an ionic liquid ($[BMIM]BF_4$)[14] with NaN_3 at 70 °C delivered azido-imidazole **13** (structure confirmed via X-ray crystallography) in 73% yield (small amount of deprotected product was re-protected in one-pot afterwards). At this juncture the final guanidine unit had to be installed on a preexisting guanidine unit – a challenge with little precedent in the literature.[15] One of the most powerful reagents for installation of this functional group, Turboguan™,[4] was evaluated but proceeded with low conversion. An analog of this reagent bearing a 1,2,4-triazole leaving group[16] proved successful delivering phenol **14** (structure confirmed via X-ray crystallography) in 64% yield after hydrogenolytic benzyl group removal and azide reduction in a one pot process. All that remained was formation of the C-ring, restoration of the spirocyclic A-ring, global deprotection, and a stereoselective reduction on the D-ring. PIDA-mediated dearomatization[17] occurred smoothly to deliver **15** in 76% yield. Subsquent exposure to BCl_3 removed the Boc groups and the BOM group along with concomitant equilibration to the correct connectivity expressed in the pentacyclic ring system thereby affording **16** (structure confirmed via X-ray crystallography) in almost quantitative yield. The selective installation of two hydrogen atoms were all that remained to complete the total synthesis of **1**. Not surprisingly, this required extensive experimentation due to the highly polar nature of **16**, its multiple Lewis-basic sites and its tendency to aromatize via guanidine fragmentation under reductive conditions. Furthermore, the X-ray structure of **16** suggested that the requisite hydrogenation might be favored on the undesired face of the molecule. Indeed, amongst the numerous conditions screened (see inset Table 2 for a small selection and SI for an extensive list),

Scheme 1. Racemic synthetic route toward KB343 (1)[a]

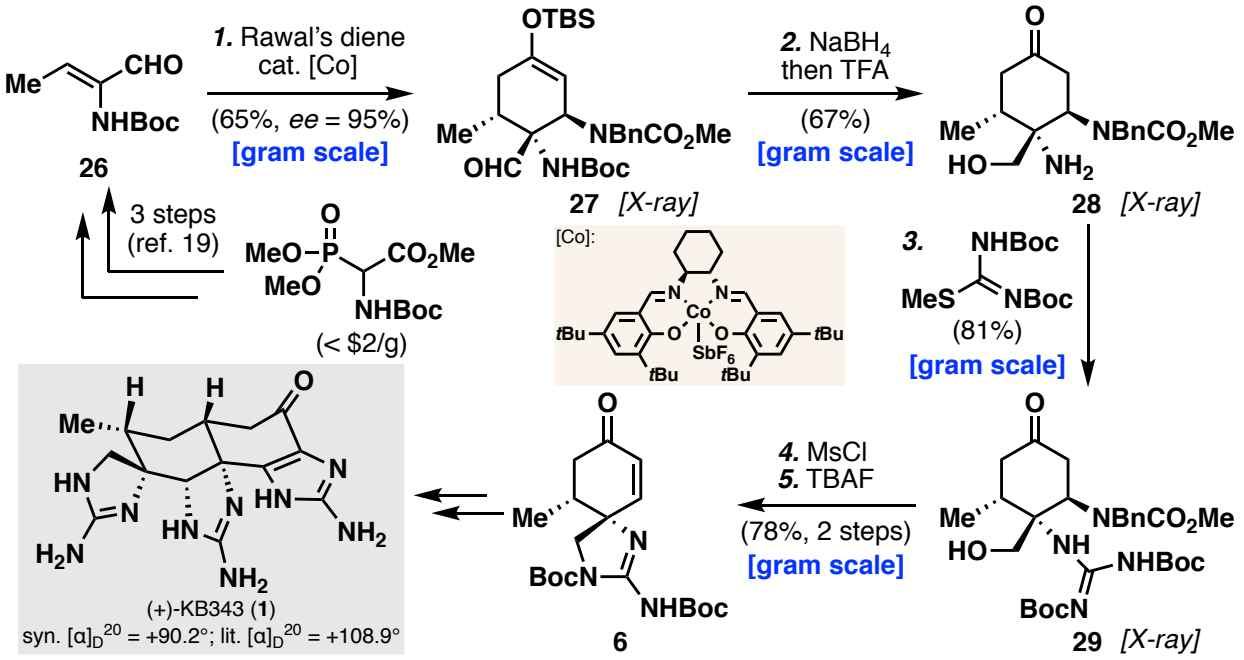


[a]For detailed reagents and conditions, see SI.

aromatization products and epi-KB343 (**2**) predominated. Even under radical-based reduction

conditions, the undesired diastereomer was formed exclusively. The first glimmer of hope emerged from standard Pd/C-based hydrogenation in MeOH solvent. Whereas screening of chiral ligands had only a detrimental effect on selectivity, careful selection of guanidinium counterions showed some promise. Ultimately, by employing a trifluoromethanesulfonic acid counterion, a 2:1 dr favoring **1** (*ca.* total 90% yield) was achieved. The spectra of synthetic **1** matched that of the isolation report[1] and its structure was unequivocally confirmed via X-ray crystallography.

Scheme 2. Enantioselective synthesis of intermediate 6[b]



[b]For detailed reagents and conditions, see SI.

To assign the absolute stereochemistry of **1**, an enantioselective total synthesis was pursued. Initial attempts to render the conjugate addition (Step 3, Scheme 1) asymmetric were met with failure. Thus, a de novo route to enantiopure **6** was developed hinging upon an asymmetric Diels-Alder (DA) reaction as shown in Scheme 2. While a-heteroatom containing dienophiles are known to react with Rawal's diene[18], there are no examples employing enamide-based systems such as aldehyde **26**.[19] Fortunately, assisted by Co-Salen based catalyst[20], the enantioselective DA proceeded in 65% yield with 95% ee (structure of **27** confirmed via X-ray crystallography). Subsequent functional group manipulations, installation of the guanidine, and cyclization intercepted intermediate **6**. The guanidinylation step of hindered amine **28** (structure confirmed via X-ray crystallography) must be done on the free base otherwise only a urea product was isolated. The b-carbamate substituent was strategically kept in place to avoid aza-Michael addition

to afford the fused rather than the spiro-ring system. Processing **6** through the route outlined in Scheme 1 led to enantiopure **1**, enabling the assignment of absolute configuration as depicted in Scheme 2 (by comparison of both optical rotation and CD).

The synthesis of (+)-**1** represents another interesting addition to the field of guanidinium-containing natural product total synthesis. It features a number of unusual maneuvers that might find use in other settings such as N-assisted dienone synthesis and desymmetrization, Nb-catalyzed S_N1 substitution, hindered amine epimerization, ionic-liquid enabled S_NAr, and counterion-assisted diastereoselective late-stage hydrogenation from a tactical standpoint. Strategically, a convergent assembly/annulation approach coupled to temporary skeletal reorganization via acyl transfers effectively simplified an otherwise complex problem.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, and CIF files.

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ACKNOWLEDGMENT

We are grateful to NIH (GM-118176) for financial support; Prof. Sakai for providing authentic sample; Dr. D.-H. Huang and Dr. L. Pasternack (Scripps Research) for NMR spectroscopic assistance; Prof. A. L. Rheingold, Dr. M. Gembicky, and Dr. J. B. Bailey (UCSD) for X-ray crystallographic analysis; Dr. J. Chen, Ms. B. Sanchez and Ms. Q. N. Wong (Scripps Research ASF) for analytical assis-tance; Mrs. T. E.-H. Ewing and Dr. N. J. Truax (Scripps Re-search) for HPLC purification assistance; Dr. M. Jaeger (Scripps Research) for CD spectrum assistance; Sinocompound Co for Pd/C sample; Dr. S. J. Harwood and Ms. S. J. Hill for intellectually stimulating discussions.

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