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Convergent Total Synthesis of Hikizimycin Enabled by Intermolecular Radical Addition to Aldehyde

Haruka Fujino,† Takumi Fukuda,† Masanori Nagatomo, and Masayuki Inoue*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

ABSTRACT: Hikizimycin (**1**), which exhibits powerful anthelmintic activity, has the most densely functionalized structure among nucleoside antibiotics. A central 4-amino-4-deoxyundecose of **1** possesses 10 contiguous stereocenters on a C1-C11 linear chain and is decorated with a cytosine base at C1 and a 3-amino-3-deoxyglucose at C6-OH. These distinctive structural features of **1** make it an extremely challenging target for de novo construction. Herein, we report a convergent total synthesis of **1** from four known components: 3-azide-3-deoxyglucose derivative **4**, bis-TMS-cytosine **5**, D-mannose **9**, and D-galactose derivative **10**. We first designed and devised a novel radical coupling reaction between multiply hydroxylated aldehydes and α-alkoxyacyl tellurides. The generality and efficiency of this process was demonstrated by the coupling of **7c** and **8**, which were readily accessible from two hexoses, **9** and **10**, respectively. Et_3B and O_2 rapidly induced decarbonylative radical formation from α-alkoxyacyl telluride **8**, and intermolecular addition of the generated α-alkoxy radical to aldehyde **7c** yielded 4-amino-4-deoxyundecose **6-α** with installation of the desired C5,6-stereocenters. Subsequent attachments of the cytosine with **5** and of the 3-azide-3-deoxyglucose with **4** were realized through selective activation of the C1-acetal and selective deprotection of the C6-hydroxy group. Finally, the 3 amino and 10 hydroxy groups were liberated in a single step to deliver the target **1**. Thus, the combination of the newly developed radical-coupling and protective-group strategies minimized the functional group manipulations, and thereby enabled the synthesis of **1** from **10** in only 17 steps. The present total synthesis demonstrates the versatility of intermolecular radical addition to aldehyde for the first time and offers a new strategic design for multi-step target-oriented syntheses of various nucleoside antibiotics and other bioactive natural products.

INTRODUCTION

Nucleosides are endogenous compounds involved in cellular processes essential to all living organisms, such as DNA and RNA synthesis, cell signaling, enzyme regulation, and metabolism. Diverse nucleoside analogues are also found as secondary metabolites of microbial origin, and are collectively designated nucleoside antibiotics.[1] Whereas endogenous nucleosides comprise a nitrogen-containing nucleobase and a furanose, nucleoside antibiotics include various structural modifications on both the nucleobase and sugar moieties, and often possess larger and more intricate architectures. Reflecting the multiple fundamental functions of endogenous nucleosides, these antibiotics perturb a wide variety of cellular metabolic pathways and thereby have a broad range of biological activities, including antibacterial, antifungal, antiviral, antitumor, herbicidal, insecticidal, and immunomodulatory properties. Evolution has optimized the structures of these natural products for their dedicated functions, making them promising scaffolds for the development of new drug leads.[2]

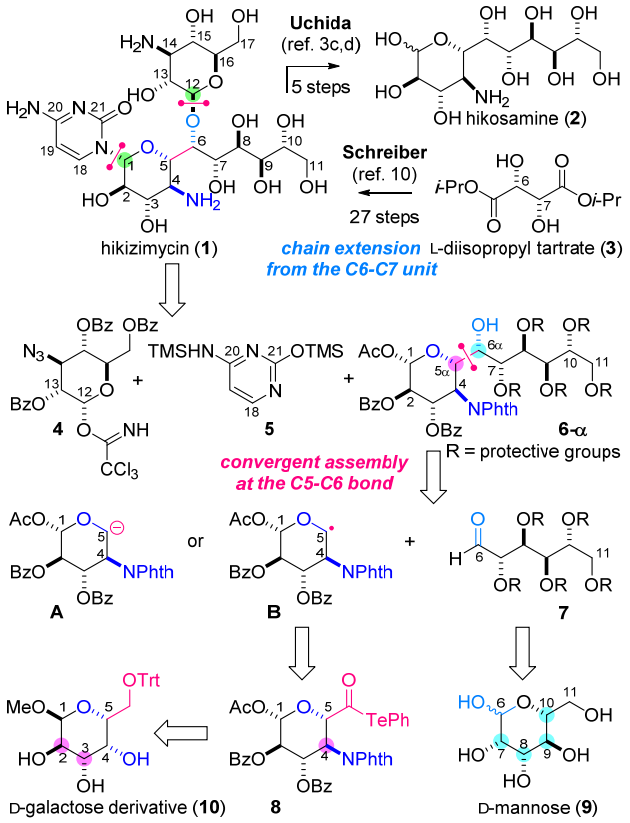
In 1971, hikizimycin (**1**, a.k.a. anthelmycin, Scheme 1) was isolated from the fermentation broth of *Streptomyces* A-5, an organism obtained from a soil sample collected at the Hikizi riverside in Kanagawa, Japan.[3] Degradation studies of **1** having a molecular weight 583 identified the presence of a cytosine base, a 3-amino-3-deoxyglucose sugar (kanosamine), and a complex long-chain 4-amino-4-deoxyundecose sugar with 1 amino and 10 hydroxy groups (**2**, hikosamine). Together, these unique structural features place **1** among the most synthetically challenging of the nucleoside antibiotic natural products. Compound **1** inhibits protein synthesis by preventing peptide-forming reactions[4] and acts as a powerful anthelmintic agent against a variety of common parasites as well as an antibiotic agent.

The exceedingly complex chemical structure and significant biological activity of **1** have attracted the interest of the chemical community for many decades.[5] Synthetic chemists have invented creative methods to approach the formidable challenges posed by **1**. Four groups, Secrist,[6] Danishefsky,[7] Fürstner,[8] and Inoue,[9] have reported different solutions for the construction of a protected form of hikosamine (**2**). None of the groups elaborated the prepared hikosamines into **1**, however, highlighting the difficulties in discriminating and activating specific positions of the polyhydroxylated chain for the two glycosylations. Schreiber and Ikemoto disclosed the only total synthesis of **1** in 1990,[10] by taking advantage of a latent C_2-symmetry within the hikosamine structure and utilizing two-directional linear transformations for chain extension and oxidation from L-diisopropyl tartrate (**3**). Selective protection of the polyfunctionalized intermediates allowed for site-selective introduction of the C1-cytosine and C6O-kanosamine moieties to produce **1** in 27 steps.

We envisioned devising a new convergent strategy for the total synthesis of **1** because it is generally more suited for a shorter route than the linear counterpart, which involves stepwise manipulations from a simple starting material.[11] In particular, our continued interest in developing radical-based strategies motivated us to integrate a powerful radical coupling reaction into the synthesis.[12,13] Herein, we detail the development of a novel radical-based route to hikizimycin (**1**) from 4 simple components in 17 steps as the longest linear sequence. The densely functionalized hikosamine structure was convergently built by a newly developed radical coupling reaction between an α-

alkoxy radical and an aldehyde. The protective group pattern of the coupled adduct enabled site- and stereoselective installations of the two appending structures, ultimately yielding **1**. The new strategy and tactics developed here should have further applications for the total syntheses of natural products with polyhydroxylated carbon chains.

Scheme 1. Structure, Reactions, and Synthetic Plan of Hikizimycin (1)[a]



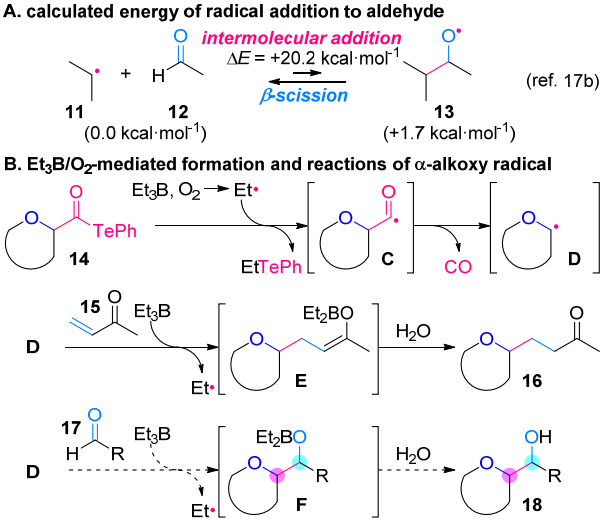
[a]Bz = benzoyl, Trt = trityl, Phth = phthaloyl, TMS = trimethylsilyl.

RESULTS AND DISCUSSION

Synthetic Plan for Hikizimycin. Hikizimycin (**1**) consists of three components: kanosamine, cytosine, and hikosamine (**2**) (Scheme 1). Accordingly, **1** was retrosynthetically dissected into the known compounds **4**[14] and **5**, and the protected hikosamine **6-α**. The C1-anomeric position of **6-α** would be activated as an acetate for introduction of the cytosine, and its C6-alcohol would be discriminated from other hetero functions for O-glycosylation. In the synthetic direction, reactions with **4** and **5** at the C1-acetyl acetal and C6-OH must establish the C1- and C12-stereocenters. To secure the requisite *trans*-relationship of the C1/2- and C12/13-substituents, the proximal C2- and C13-hydroxy groups of **6-α** and **4** were to be protected with the benzoyl groups because of their neighboring-group participation functions. In principle, the differentially protected hikosamine **6-α** would be directly assembled by a polar coupling between anion **A** and aldehyde **7**, or a radical coupling between radical **B** and **7**.[15] The potential for β-elimination of the C4-nitrogen functionality from **A** and for undesired reactions of the multiple acyl protective groups with **A**, however, prevented us from adopting the polar reaction.[16] Hence, we selected a radical reaction instead.

Radical reactions serve as versatile methods to forge the complex architectures of highly oxygenated natural products because they are compatible with diverse oxygen and nitrogen functionalities, and are applicable to the formation of sterically hindered C–C bonds. Even so, intermolecular radical addition of carbon radical **B** to aldehyde **7** would be highly problematic. As shown in Scheme 2A, the starting carbon radical **11** and aldehyde **12** are energetically favored over the generation of alkoxyl radical **13**.[17] Thus, β-scission of the product **13** readily reverses the reaction.

Scheme 2. (A) Calculated Energy of Radical Addition to Aldehyde (B) Et_3B/O_2-Mediated Formation and Reactions of α-Alkoxy Radical



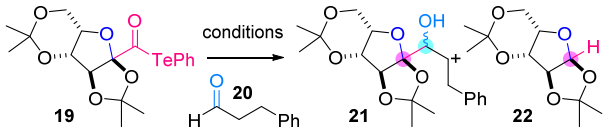
We previously reported an Et_3B/O_2-promoted radical coupling using α-alkoxyacyl telluride **14** and electron-deficient double bonds (Scheme 2B).[18] The first part of this reaction involves the generation of an Et radical from Et_3B and O_2,[19] formation of acyl radical **C** through C–Te homolysis, and decarbonylation to produce α-alkoxy radical **D**.[20] Conjugate addition of **D** to enone **15** and capture of the resultant radical intermediate with Et_3B then gives boron enolate **E** and an Et radical. Protonation of **E** affords the two-component adduct **16**. We decided to exploit this reagent system for aldehyde **17** due to the facile radical initiating and terminating roles of Et_3B. Namely, Et_3B and O_2 would initiate the radical process to produce α-alkoxy radical **D** from **14** and then terminate the process by the formation of borinate ester **F** with ejection of an Et radical. Unlike the corresponding alkoxyl radical, the polar intermediate **F** would not easily undergo the reverse β-scission reaction.[21] Finally, hydrolysis of **F** would give alcohol **18**.

These considerations led us to select α-alkoxyacyl telluride **8** as a precursor of radical **B** (Scheme 1). The sterically cumbersome C4N-phthalimide group of **8** was expected to control the *trans*-relationship of the C4-imide and the C5-carbon chain upon the radical addition.[22] Since we could not predict the C6-stereoselectivity a priori, stereocontrolling effects of the protective groups (R) of **7** had to be investigated during the course of the study (see Scheme 4 below). Compounds **7** and **8** were further traced back to D-mannose (**9**) and D-galactose derivative

(**10**), which together carry the 6 stereocenters of the target **1** (C2, C3, C7, C8, C9, and C10). This utilization of the original chiralities of the two hexoses would greatly contribute to streamline the route to **1**.[23] Hence, our original strategy toward **1** postulated an optimally convergent route, in which three hexoses (**4**, **9**, and **10**) and silylated cytosine **5** were to be coupled and elaborated.

Optimization of Intermolecular Radical Addition Conditions. Our initial effort to devise the key radical coupling was conducted as a model study using the sugar-derived α-alkoxyacyl telluride **19**[18a] and 3-phenylpropanal (**20**) (Table 1). Me_3Al (entry 1),[24] Me_2Zn (entry 2),[25] and Et_3B (entry 3) were selected as representative radical initiators. Consequently, Et_3B was found to be far superior to Me_3Al and Me_2Zn for promoting the radical addition. When **19** and **20** (3 equiv) were treated with Et_3B (5 equiv) in CH_2Cl_2 under air at room temperature, the requisite adduct **21** was obtained in 28% yield along with **22** (39%), which was formed through direct hydrogen-atom abstraction (entry 3).[26] In contrast, the use of Me_3Al and Me_2Zn under air only generated 2% and 4% of **21**, respectively. Lowering the temperature to -30 °C (entry 4) in the presence of Et_3B increased the yield of **21** to 40%. Thus, the presumed scenario illustrated in Scheme 2B was realized using simple and mild reaction conditions.

Table 1. Investigation of Radical Initiators[a]

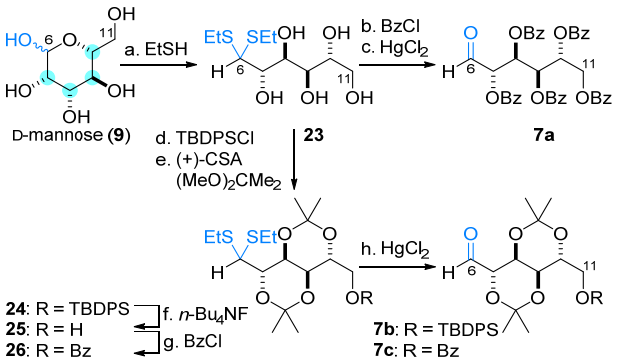


entry	initiator	solvent	yields(%)[b]	
			21	**22**
1	Me_3Al	THF	4	10
2	Me_2Zn	CH_2Cl_2	2	3
3	Et_3B	CH_2Cl_2	28[c]	39
4[d]	Et_3B	CH_2Cl_2	40[c,e]	47

[a]Conditions: **19** (1 equiv), **20** (3 equiv), initiator (5 equiv), solvent (0.1M), open air, 25 °C. [b]Yields were calculated from ^{1}H-NMR analysis. [c]dr = 1.8 : 1 (entry 3) or 2.4 : 1 (entry 4) (The stereochemistries were not determined). [d]Reaction was conducted at -30 °C. [e]Isolated yield.

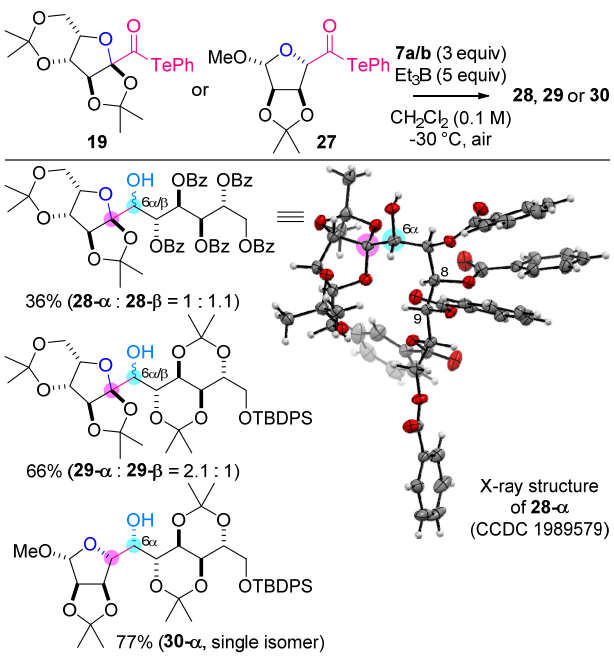
In the next model study, we heightened the challenge by increasing the structural complexity of the acceptor from 3-phenylpropanal (**20**) to the right-half aldehyde **7** of the hikosamine structure. Prior to the coupling, differentially protected tetrabenzoyl **7a** and bis-acetonide **7b**/**c** were prepared as radical acceptors (Scheme 3). The pyranose ring of D-mannose (**9**) was opened using EtSH and HCl to afford dithioacetal **23**. Benzoylation of the four hydroxy groups of **23**, followed by hydrolysis of the dithioacetal with mercury salts, gave rise to **7a**. Alternatively, the primary alcohol of pentaol **23** was selectively capped with the TBDPS group and the remaining secondary alcohols were protected with the two acetonides by treatment with 2,2-dimethoxypropane and (+)-CSA, leading to **24**.[27] The protective group at the primary OH of **24** was transformed from TBDPS to Bz via the standard 2-step procedure to generate **26**. Dithioacetals **24** and **26** were separately converted to **7b** and **7c**, respectively, by $HgCl_2$-mediated hydrolysis.

Scheme 3. Synthesis of Differentially Protected Aldehydes 7a, 7b, and 7c[a]



[a]Reagents and conditions: (a) EtSH, 0.5M HCl in MeOH, 25 °C; (b) benzoyl chloride (BzCl), pyridine, 25 °C, 51% (2 steps); (c) $HgCl_2$, HgO, acetone, MeCN, H_2O, 60 °C, 99%; (d) *tert*-butyldiphenylchlorosilane (TBDPSCl), Et_3N, molecular sieves 4A, *N*,*N*-dimethyl-4-aminopyridine, THF, 50 °C, 79% (2 steps); (e) (+)-10-camphorsulfonic acid ((+)-CSA), $(MeO)_2CMe_2$, 25 °C, 70%; (f) *n*-Bu_4NF, THF, 50 °C; (g) BzCl, pyridine, 50 °C, 100% (2 steps); (h) $HgCl_2$, HgO, CH_2Cl_2, MeCN, H_2O, 25 °C, **7b**: 90% from **24**, **7c**: 97% from **26**. TBDPS = *tert*-butyldiphenylsilyl.

Scheme 4. Intermolecular Radical Addition of α-Alkoxy Carbon Radicals to Aldehydes[a]



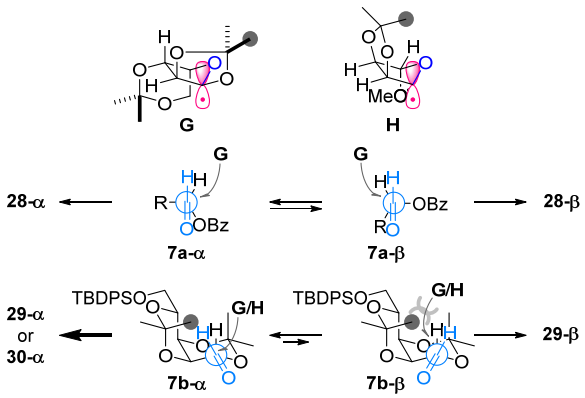
[a]Conditions: acyltellurides **19** or **27** (1 equiv), aldehyde **7a** or **7b** (3 equiv), Et_3B (5 equiv), CH_2Cl_2 (0.1M), open air, –30 °C.

Two differentially protected **7a** and **7b** were submitted to the radical coupling reactions to evaluate the effects of the protective groups on the reactivity and stereoselectivity (Scheme 4). The Et_3B/O_2-mediated reaction between **19** and **7a** under the optimized conditions in Table 1 indeed furnished the coupling

adduct **28**. The X-ray crystallographic structure of one of the obtained isomers **28-α** accentuated the hindered nature of the newly linked bond between the tetrasubstituted and trisubstituted carbons. Despite the modest yield (36%) and low C6-stereoselectivity (**28-α** : **28-β** = 1 : 1.1), it was noteworthy that the highly oxygenated structure with the nine consecutive asymmetric centers was constructed in a single coupling. The yield and C6-stereoselectivity were further improved by altering the acceptor from **7a** to **7b**. Submission of **19** and **7b** to Et_3B and O_2 at –30 °C produced a 2.1 : 1 mixture of **29-α** and **29-β** in 66% yield.[28] When the D-ribose-derived **27**[18a] was applied to the same conditions, **30-α** was isolated as a sole isomer in 77% yield. The second model study also allowed us to define the structure of the right-half fragment as **7c** for the total synthesis of **1** (Scheme 1). The bis-acetonide moiety of **7c** would control the requisite C6α-stereocenter for **6-α**, while the Bz group at C11-OH of **7c** instead of the TBDPS group of **7b** would be beneficial for its simultaneous removal with other nucleophile-sensitive protective groups (e.g., C2/3O-Bz and C4N-Phth).

The radical addition reactions shown in Scheme 4 introduced the two stereocenters highlighted in pink and cyan circles. The stereochemical outcomes are attributable to the protective groups of both the radical donors (**19**/**27**) and acceptors (**7a**/**b**). Et_3B/O_2 promotes the decarbonylative radical formation of **G** and **H** from tellurides **19** and **27**, respectively (Scheme 5). The bond formation at the α-alkoxy position proceeds from the bottom convex face of the acetonide-protected 5/5-*cis*-fused bicycle of **G** and **H**, establishing the pink-highlighted carbon center. Installation of the cyan-highlighted C6-stereogenic center would be explained by the conformational preferences of the acceptors **7a** and **7b**. Felkin-Ahn-type transition states **7a-α** and **7a-β** are energetically comparable and both accept the radical to generate a comparable amount of **28-α** and **28-β**, respectively. On the other hand, **7b-β** has a severe steric interaction between the radical and the methyl group of the 6/6-*cis*-fused bicycle (highlighted in gray), and thus becomes higher in energy than **7b-α**, which leads to the desired C6α-stereochemistry. Hence, the distinct three-dimensional structure of **7b** fixed by the two acetonides is likely to reflect the selective generation of **29-α** and **30-α**.

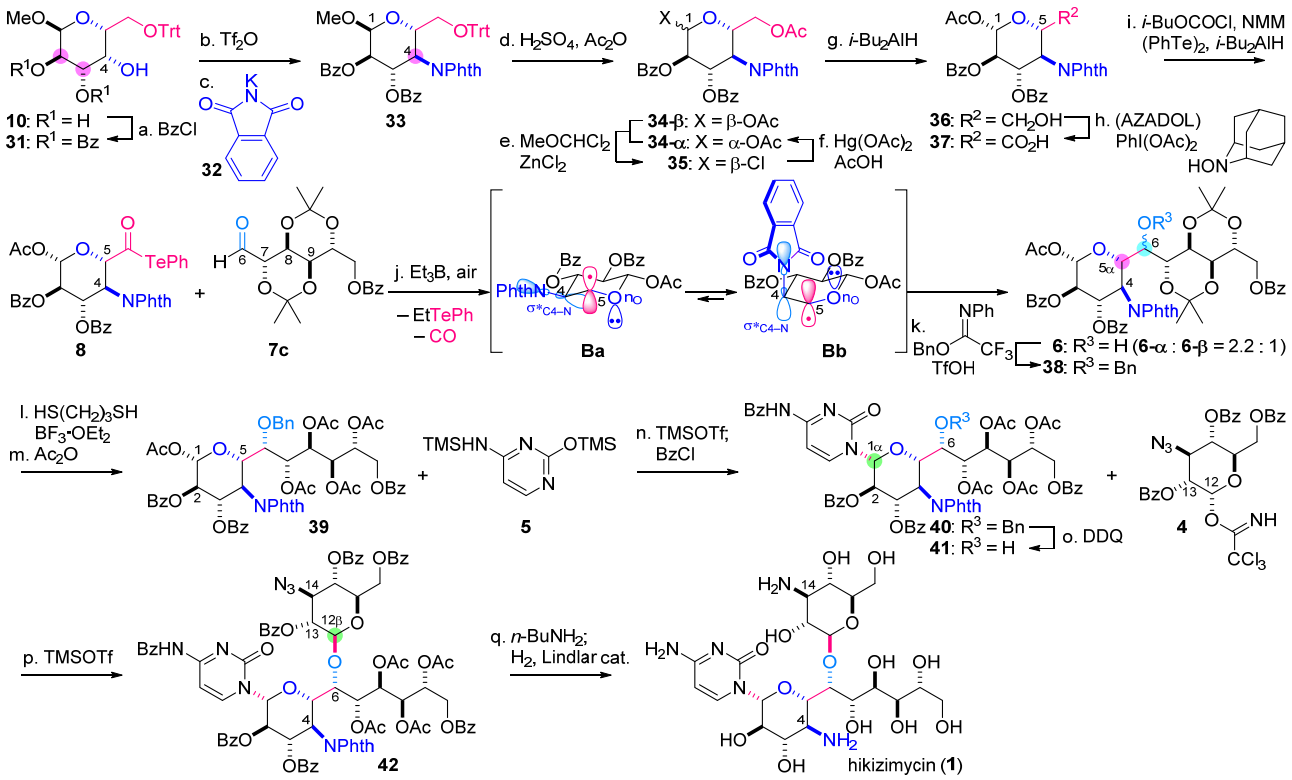
Scheme 5. Rationale for the Stereochemical Outcomes



Total Synthesis of Hikizimycin. Having determined the conditions and stereocontrolling factors for the crucial radical coupling, we set out to prepare the radical donor **8** for the total synthesis of hikizimycin (**1**) (Scheme 6). Benzoylation of the commercially available D-galactose derivative **10** with BzCl and pyridine capped the equatorial C2- and C3-OHs and left the axial C4-OH untouched to afford **31**. The hydroxy group of **31** was transformed to the NPhth group of **33** via Tf_2O/pyridine-promoted triflation and subsequent C4-stereochemical inversion using potassium phthalimide (**32**). Treatment of **33** with Ac_2O in the presence of AcOH and H_2SO_4 exchanged the methyl and trityl groups for acetyl groups, producing a 1 : 8.3 mixture of **34-α** and **34-β**. The following 2 steps were used to synthesize pure **34-α**.[29] The axially-oriented chloride of **35** was installed by subjecting the C1-diastereomers to $MeOCHCl_2$ and $ZnCl_2$,[30] and was replaced with the equatorial C1-acetoxy group of **34-α** by the action of $Hg(OAc)_2$.[31] The primary acetoxy group of **34-α** was then chemoselectively reduced with *i*-Bu_2AlH, and the liberated primary alcohol of **36** was oxidized to the corresponding carboxylic acid of **37** using $PhI(OAc)_2$ and catalytic AZADOL.[32] The requisite radical donor **8** was derivatized from **37** in one pot through formation of the activated ester, followed by attack of an anionic phenyltelluride prepared from $(PhTe)_2$ and *i*-Bu_2AlH.[33]

We next realized the unprecedented intermolecular radical addition of the densely functionalized fragments **8** to **7c**. A mixture of α-alkoxyacyltelluride **8**, aldehyde **7c** (3 equiv), and Et_3B (5 equiv) in CH_2Cl_2 (0.1 M) was exposed to air at -30 °C to deliver **6-α** along with the minor C6-epimer **6-β** in 65% combined yield (**6-α** : **6-β** = 2.2 : 1).[34] Accordingly, the desired **6-α** with its 10 contiguous stereocenters was constructed by stereoselectively forging the hindered C5–C6 bond. As expected from the model experiments in Scheme 4, the desired C6-selectivity was attributable to the bis-acetonide structure of **7c**. On the other hand, the complete C5-stereoselectivity can be rationalized by the three-dimensional arrangement of the C4N-phthalimide group. Et_3B and O_2 induce the elimination of EtTePh and carbon monoxide from telluride **8**, thereby abolishing the C5-stereochemical information upon forming α-alkoxy radical **B**. Pyran **B** can adopt the chair form **Ba** and the boat form **Bb** as representative conformations. Although **Ba** has more sterically preferred equatorial substituents than **Bb**, the C1-radical of **Bb** is more stereoelectronically favorable than **Ba**. Specifically, both **Ba** and **Bb** have secondary orbital interactions between the C1-radical and the pyran oxygen lone pair, yet only **Bb** has a stabilizing interaction between the singly occupied orbital and the co-planar σ*-orbital of the C4–N bond.[35] As a result, **Bb** has a lower energy than **Ba**, which was further corroborated by the DFT calculation of the stable radical conformation at the UM06-2x/6-31+G(d) level of theory (298 K, 1 atm) (Figure 1). The β-oriented bulky C4-NPhth of **Bb** only permits an α-approach by **7c** to install the correct C5α-stereochemistry. Therefore, the strategically selected protective groups contributed to the stereoselective construction of the two tertiary carbons at C5 and C6.

Scheme 6. Total Synthesis of Hikizimycin[a]



[a]Reagents and conditions: (a) BzCl, pyridine, 25 °C, 58%; (b) trifluoromethanesulfonic anhydride (Tf_2O), pyridine, 0 °C; (c) phthalimide potassium salt (**32**), DMF, 25 °C, 82% (2 steps); (d) H_2SO_4, AcOH, Ac_2O, CH_2Cl_2, 25 °C, 80% (**34-α**: **34-β** = 1 : 8.3); (e) $MeOCHCl_2$, $ZnCl_2$, CH_2Cl_2, reflux; (f) $Hg(OAc)_2$, AcOH, 25 °C, 92% (2 steps); (g) *i*-Bu_2AlH, THF, -78 °C; (h) 2-hydroxy-2-azadamantane (AZADOL), $PhI(OAc)_2$, MeCN, pH 7 buffer, 85% (2 steps); (i) *i*-BuOCOCl, *N*-methylmorpholine (NMM), THF, 0 °C; $(PhTe)_2$, *i*-Bu_2AlH, THF, 25 °C, 88%; (j) Et_3B, air, CH_2Cl_2, -30 °C, 65% (**6-α** : **6-β** = 2.2 : 1); (k) $BnO(=NPh)CF_3$, trifluoromethanesulfonic acid (TfOH), molecular sieves 5A, 1,4-dioxne, reflux; (l) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, MeCN, 25 °C; (m) Ac_2O, pyridine, 50 °C; (n) **5**, trimethylsilyl trifluoromethanesulfonate (TMSOTf), $PhNO_2$, 130 °C; *i*-PrOH, 25 °C; BzCl, pyridine, 25 °C, 19% (4 steps from a 2.2 : 1 mixture of **6-α** and **6-β**); (o) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), CH_2Cl_2, 60 °C, (p) **4**, TMSOTf, CH_2Cl_2, 0 °C, **42**: 39% (2 steps), 12-*epi*-**42**: 22% (2 steps); (q) *n*-$BuNH_2$, MeOH, reflux; H_2, Lindlar catalyst [(5% Pd-$CaCO_3$, $Pb(OAc)_2$, quinoline), 500 wt%], H_2O, 25 °C, 50%. Bn = benzyl.

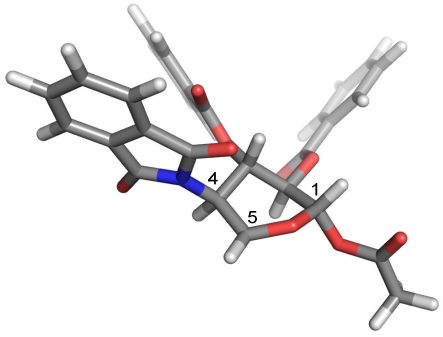


Figure 1. The DFT-optimized structure of radical **B** (UM06-2X/6-31G+(d), 298 K, and 1 atm).

Having prepared the protected hikosamine **6-α**, the final challenging task was the stepwise attachments of the cytosine and kanosamine moieties to this large and complex structure under acidic conditions. To prepare for these two glycosylations, the protective groups were manipulated in the following 3 steps. The C6-alcohol of **6-α** was protected as the acid-resistant benzyl ether of **38** using *N*-phenyl-2,2,2-trifluoroacetimidate and catalytic TfOH.[36] Chemoselective removal of the acid-labile acetonides of **38** was realized by application of the reagent combination of $BF_3{\cdot}OEt_2$ and 1,3-propane dithiol in MeCN without affecting the potentially reactive C1-acetal or benzyl ether.[37] The resultant tetraol was converted to the corresponding pentaacetate **39** using Ac_2O and pyridine. Next, introduction of the cytosine required rather forcing conditions. The freshly prepared bis-TMS-cytosine **5** and **39** were heated to 130 °C in $PhNO_2$ in the presence of TMSOTf to induce the formation of the adduct.[10,38] The C20-amine was benzoylated with BzCl and pyridine in one pot, leading to C1α-benzoylcytosine **40** as a single isomer. Prior to the glycosylation of the kanosamine sugar, C6-alcohol was released from benzyl ether **40** by employing DDQ under anhydrous conditions to produce **41** without removing or transposing the multiple acyl groups. TMSOTf-promoted glycosylation of **41** with the trichloroacetimidate **4**[39,40] in turn proceeded at 0 °C, affording C12β-kanosamine **42** as the major isomer (**42** : 12-*epi*-**42** = 1.8 : 1). Therefore, the requisite C1α–N and C12β–O linkages were stereoselectively formed, presumably because the strategically placed C2O- and C13O-benzoyl groups secured the *trans*-addition of the incoming nucleophiles by neighboring-group participation.

The last mission of the total synthesis of **1** from the protected hikizimycin **42** necessitated detachment of the seven Bz, four acetyl, and one phthaloyl groups, and reduction of the C14-azide functionality. We developed an efficient one-pot procedure

to attain these multiple reactions. All 12 acyl groups were simultaneously removed by applying *n*-$BuNH_2$ in refluxing MeOH to deprotect the 10 hydroxy and 2 amino groups.[41] In the same flask, reduction of the C14-azide substituent was accomplished chemoselectively over the unsaturated cytosine ring by hydrogenolysis using the Lindlar catalyst in H_2O.[10] This protocol gave rise to the targeted hikizimycin (**1**) from **42** in 50% yield. The structural integrity of the fully synthetic **1** with its 15 stereocenters was confirmed by comparing the analytical data, including ^1H, ^{13}C NMR, IR, and $[\alpha]_D$, with those of the natural and reported **1**.[10]

CONCLUSION

In summary, we achieved a convergent total synthesis of hikizimycin (**1**) from the three hexose and cytosine structures (**4**, **5**, **9**, and **10**). Remarkably, the exceptionally complex structure of **1** was assembled in 17 steps from **10** without any extra carbon extension or oxygen atom introduction. The synthetic route was realized by devising a novel radical coupling strategy and applying a judicious protective group strategy. First, we established the conditions for the radical coupling between α-alkoxyacyl tellurides and aldehydes. Although intermolecular radical addition to an aldehyde is energetically disfavored, the reagent combination of Et_3B and O_2 uniquely promoted the reaction due to its radical initiating and terminating properties. Thus, the highly oxygenated radical acceptor **7c** and donor **8** were derivatized from **9** and **10**, respectively, and coupled by the action of Et_3B and air. This mild, yet powerful reaction linked the hindered tertiary carbons and installed the desired C5,6-stereocenters, thereby constructing the hikosamine structure **6-α** with its 10 contiguous stereocenters. The cytosine and hikosamine moieties were then attached by two TMSOTf-promoted glycosylations in a C1,12-stereoselective fashion. Importantly, the strategically introduced protective groups of the polyfunctionalized intermediates controlled the stereochemical outcomes. While the bis-acetonide and C4-NPhth structures favorably affected the C5α- and C6α-stereoselectivity of the radical addition, the proximal benzoyl groups secured the C1β- and C12β-glycosidic linkages. Lastly, transformation of the protected hikizimycin **42** into **1** were attained in one pot by detachment of the 12 protective groups and hydrogenation of the one azide function.

Because of its excellent functional group compatibilities, radical addition to aldehydes is particularly advantageous for expeditious construction of densely functionalized molecules. We hope that the described radical chemistry will provide new insights for retrosynthetic analyses in the field of organic chemistry and have broad applications for the total synthesis of other bioactive nucleoside antibiotics and natural products.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.XXXXXX.

Experimental procedures, characterization data, and NMR spectra of all newly synthesized compounds (PDF)
Crystallographic structure for **28-α** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: inoue@mol.f.u-tokyo.ac.jp

ORCID

Haruka Fujino: 0000-0002-5710-0737
Masanori Nagatomo: 0000-0001-9204-194X
Masayuki Inoue: 0000-0003-3274-551X

Author Contributions

†H.F. and T.F. contributed equally.

Notes

The authors declare no competing financial interests.

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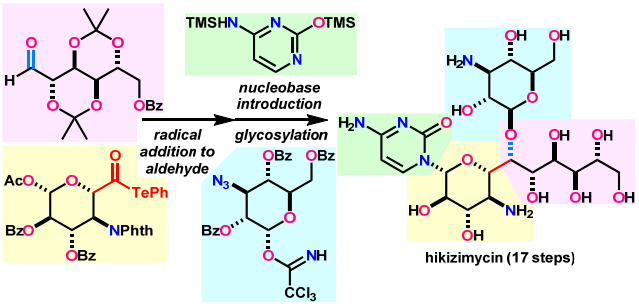

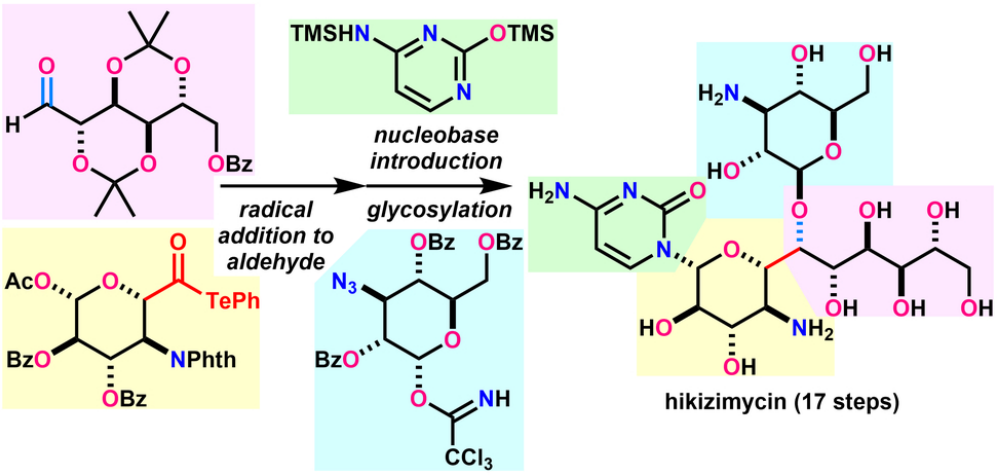

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