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Total Synthesis and Bioactivity Profile of (+)-Ieodomycins A and B and their Stereoisomers

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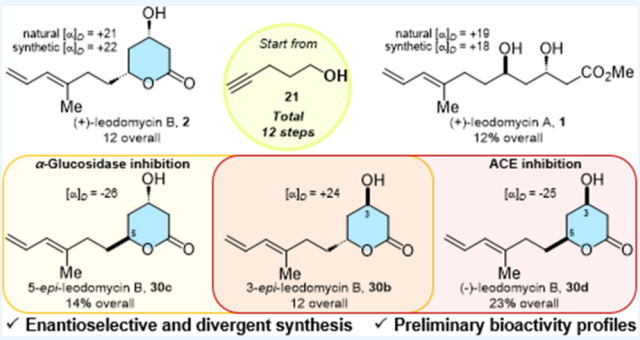
ABSTRACT: Herein, we report the first- and second-generation syntheses of (+)-ieodomycins A and B and their stereoisomers via the late-stage elaboration of their conjugated *E*-diene side chains. Key steps for successful synthesis included Keck asymmetric allylation to introduce a hydroxyl group at the C5 position, consecutive Wipf's carboalumination modification, iodination, Sharpless asymmetric dihydroxylation, one-carbon homologation via cyanation, Mukaiyama lactonization, and Stille cross-coupling to form the conjugated *E*-diene moiety. Further, the preliminary *in vitro* bioactivity profile against various disease-related molecular targets and cell lines was investigated. Results indicated that compounds **30b** and **30c**, diastereoisomers of (+)-ieodomycin B (**2**), serve as α-glucosidase inhibitors, while compounds **30b** and **30d** inhibit the angiotensin-converting enzyme.



INTRODUCTION

Ieodomycins A−D constitute a family of hydroxylated unsaturated fatty acids derived from marine *Bacillus* sp. 091D194, isolated from a sediment sample collected in Ieodo, the southern reef of the Republic of Korea (Figure 1).[1] Ieodomycins C (**3**) and D (**4**) feature an internal conjugated diene, whereas ieodomycins A (**1**) and B (**2**) possess a terminal-conjugated diene. Moreover, ieodomycins A (**1**) and B (**2**) are believed to be interconvertible, with ieodomycins A (**1**) and B (**2**) undergoing lactonization and lactone ring opening, respectively. Similar to other marine natural products, the scarcity of ieodomycins poses a significant challenge for comprehensive biological activity screenings needed to determine their bioactivity profiles.

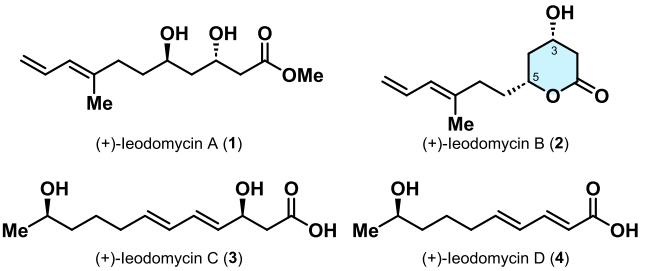


Figure 1. Chemical structures of ieodomycins A−D.

To date, ieodomycins have been recognized for their moderate antimicrobial activities against *Bacillus subtilis* (KCTC 1021, Gram-negative); *Escherichia coli* (KCTC 1923, Gram-positive); and *Saccharomyces cerevisiae* (KCTC 7913, yeast). Several synthetic approaches have been implemented to address this problem.[2] However, the bioactivity profiles of (+)-ieodomycins A (**1**) and B (**2**) have not been elucidated.

In our continued pursuit of exploring marine natural products as sources for the discovery, synthesis, and application of novel pharmaceuticals, we aimed to develop an efficient, divergent synthetic route to (+)-ieodomycins A (**1**) and B (**2**) and their stereoisomers. The objective was to construct their bioactivity profiles and establish a reliable synthesis method for further development. Herein, we report the first- and second-generation total syntheses and bioactivity profiles of (+)-ieodomycins A (**1**) and B (**2**) and their analogues.

RESULTS AND DISCUSSION

Considering the versatility required for the synthesis of natural products for future applications, we designed a divergent approach toward ieodomycin B. This approach involves introducing the terminal-conjugated diene moiety at a late stage through the dehydration of intermediate **I**, which can be

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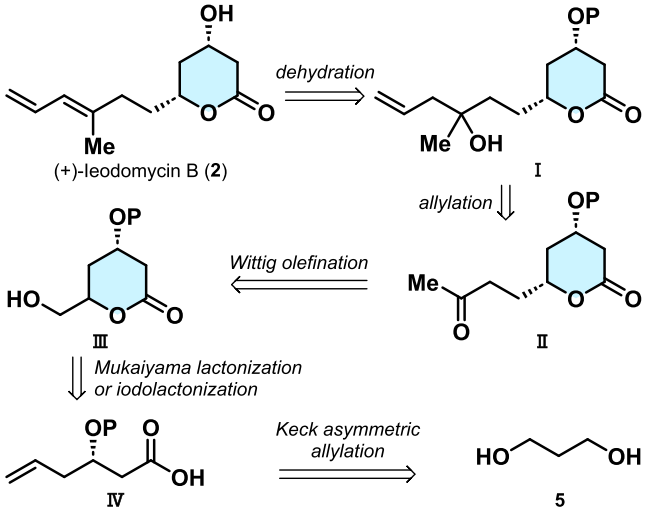
obtained from intermediate **II** by allylation (Scheme 1). Intermediate **II** can be obtained through the oxidation of

Scheme 1. First-Generation Synthetic Strategy of (+)-Ieodomycin B



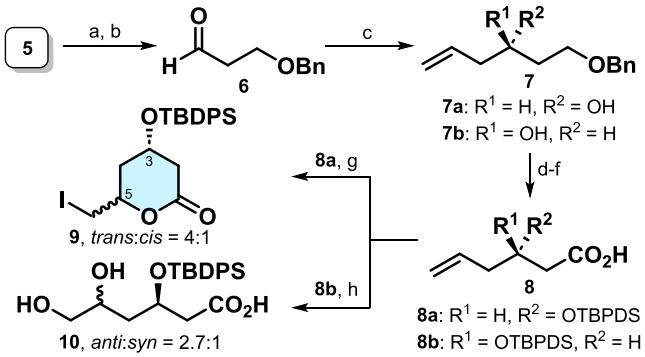
lactone **III** to an aldehyde followed by Wittig olefination and reduction. Lactone **III** can be synthesized through iodolactonization or a two-step process that entails the Sharpless asymmetric dihydroxylation of intermediate **IV** and Mukaiyama lactonization of the resulting diol.

Next, intermediate **IV**, possessing the desired stereochemistry at the C3 position of ieodomycin B, is fabricated using the Keck reaction. The asymmetric allylation of aldehyde **6**, which is derived from 1,3-propanediol **5**, can be achieved via a sequence involving monobenzylation and Swern oxidation reactions.

To demonstrate the feasibility of the synthetic strategy, we initiated the synthesis with the monobenzylation of commercially available 1,3-propanediol **5** to yield primary alcohol,[3] which was subsequently reacted under Swern oxidation conditions to afford aldehyde **6** (Scheme 2).[4] Next, the Keck asymmetric allylation of aldehyde **6** was attempted to furnish homoallylic alcohols **7a** and **7b**,[5] which were treated with TBDPSCl, followed by the DDQ-promoted deprotection of benzyl group and oxidation to carboxylic acids **8a** and **8b** (Scheme 2).[6]

At this stage, two distinct synthetic routes were explored, namely, the iodolactonization of carboxylic acid **8a** and dihydroxylation of carboxylic acid **8b**. Therefore, the iodolactonization of carboxylic acid **8a** furnished the corresponding iodolactone **9** as a diastereomeric mixture (*trans*/*cis* = 4:1),[7] which presumably proceeded predominantly *via* a boat-like transition state, generated by the steric demands of the bulky TBDPS and iodonium substituents (Scheme 2).[8] The treatment of iodolactone **9** with *m*-CPBA yielded *trans*-lactone **11** (Scheme 3).[9] Conversely, the dihydroxylation of carboxylic acid **8b** using $(DHQ)_2PYR$ led to an unexpected reversal of facial selectivity,[10] contrary to predictions based on the Sharpless mnemonic.[11] This resulted in the formation of diol **10** as an inseparable mixture with a diastereoselectivity of 46% *de* (Scheme 2, see the Supporting Information (SI) for details).[12] Identical transformations with other ligands, such as $(DHQ)_2PHAL$ and $(DHQ)_2AQN$, also yielded diol **10** but

Scheme 2. Synthesis of Intermediates 9 and 10[a]



[a]Reaction conditions: (a) Ag_2O, BnBr, CH_2Cl_2, rt, 85%; (b) dimethyl sulfoxide (DMSO), trifluoroacetic acid anhydride (TFAA), triethylamine (TEA), CH_2Cl_2, −78 °C to rt, 82%; (c) (*S*)-BINOL (for **7a**,) or (*R*)-BINOL (for **7b**), $Ti(OiPr)_4$, 4 Å MS, $(n\text{-}Bu)_3Sn(allyl)$, CH_2Cl_2, −78 to −20 °C, **7a**: 91%, **7b**: 89%; (d) TBDPSCl, imidazole, *N*,*N*-dimethylformamide (DMF), 40 °C; (e) DDQ, CH_2Cl_2/pH 7 buffer, 40 °C; (f) PDC, DMF, rt, **8a**: 96%, **8b**: 98% over three steps; (g) $NaHCO_3$, $CHCl_3/H_2O$, rt, then I_2, 0 °C, 91%; and (h) $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4.2H_2O$, *t*-BuOH, H_2O.

with unsatisfactory asymmetric induction (see the SI for details).

Despite the reversed facial selectivity and low diastereomeric ratio, intermediate **10** was subjected to Mukaiyama lactonization, affording an inseparable mixture of lactone **16** (*cis*/*trans* = 2:1).[13] With the key intermediates **11** and **16**,[14] we attempted sequential oxidation using Dess−Martin periodinane, followed by Wittig olefination with acetonyltriphenylphosphonium chloride (**A**) to produce *trans*-*α*,*β*-unsaturated ketones **12** and **17** (Scheme 3).[15] The reduction of **12** under reaction conditions with H_2/Pd−C yielded the expected ketone **13**, whereas applying the same conditions to **17** led to a lactone ring-opened byproduct, likely due to Pd-promoted-double bond migration (not shown, see the SI for detail).[16] As an alternative to H_2/Pd−C, Stryker's reagent ($[(Ph_3P)CuH]_6$) was employed, especially for **17**, to obtain ketone **18**.[17] Allylation with potassium allyltrifluoroborate (H_2C = CH−CH_2BF_3K) provided the desired tertiary alcohols **14** and **19** (Scheme 3).[18] Prior to the dehydration reaction of **14** and **19**, we evaluated the thermal stability of various modified Burgess reagents to select reagent **C** as the optimal reagent (see the SI for details).[19] Consequently, the dehydration reaction of tertiary alcohols **14** and **19** with a modified Burgess reagent **C**, followed by the removal of the TBDPS protection group with TBAF, afforded 5-*epi*-ieodomycin B **15** (*E*/*Z* = 1:1) and (−)-ieodomycin B **20** (*E*/*Z* = 1:1) as inseparable mixtures (Scheme 3). The relatively low stereoselectivity at the C5 position and uncontrolled absolute stereochemistry of the diene moiety at a late stage during the first-generation synthetic strategy demonstrated the necessity for an alternative synthetic route toward the synthesis of ieodomycin B.

To overcome the problems encountered in first-generation syntheses, we designed a second-generation synthetic strategy, focusing on the stereospecific formation of the core lactone ring and the terminal-conjugated diene moiety.

Given their structural similarity, we hypothesized that ieodomycins A (**1**) and B (**2**) could be interconverted through either the lactone ring opening of ieodomycin B (**2**) or lactonization of ieodomycin A (**1**). Next, we postulated that

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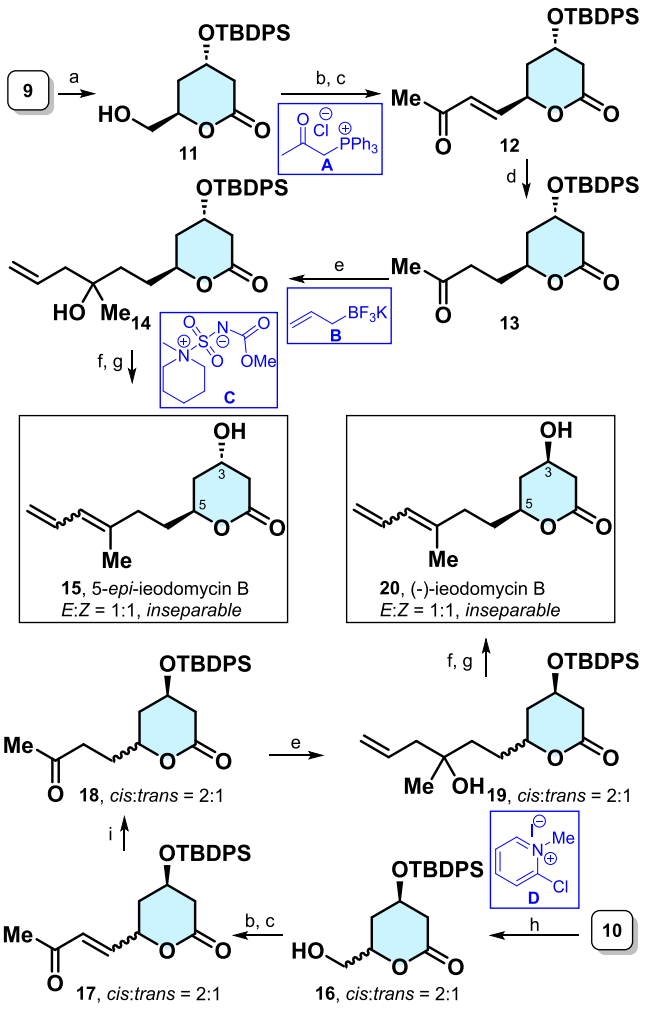
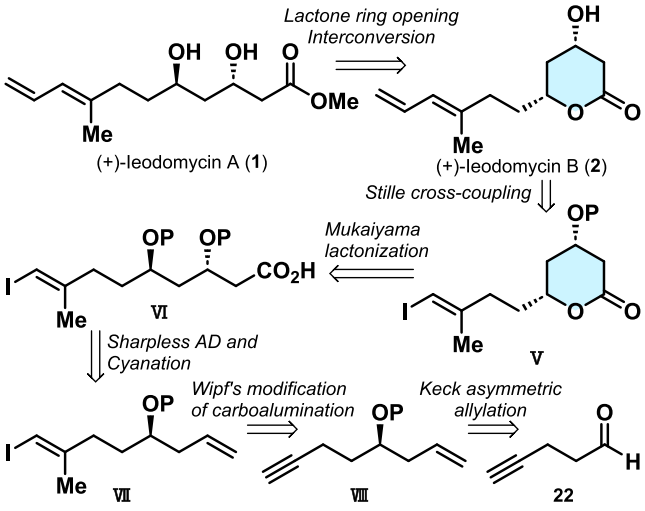
Scheme 3. Synthesis of 5-*epi*- and (−)-Ieodomycin B[a]



[a]Reaction conditions: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 66%; (b) Dess−Martin periodinane, CH_2Cl_2, rt; (c) acetonyltriphenylphosphonium chloride (**A**), *n*-BuLi, tetrahydrofuran (THF), 0 °C; (d) 10% Pd/C, EtOH, H_2, rt, 34% over three steps; (e) potassium allyltrifluoroborate (**B**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, **14**: 89%, **19**: 97%; (f) a modified Burgess reagent (**C**), benzene, reflux; (g) tetra-*n*-butylammonium fluoride (TBAF), AcOH, THF, rt, 79% from **14** and 81% from **19** over two steps; (h) 2-chloro-1-methylpyridinium iodide (**D**), Et_3N, CH_2Cl_2, rt, 58% from **8b** over two steps; (i) Stryker's reagent ($[(Ph_3P)CuH]_6$), poly-(methyl hydrosiloxane), *t*-BuOH, toluene, rt, 59% from **17** over three steps.

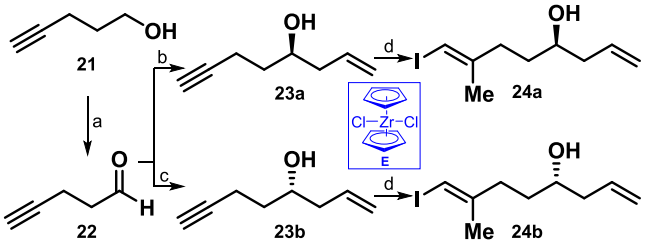
the key intermediate **V** could be obtained with **VI** through a two-step process involving hydrolysis and Mukaiyama lactonization. Intermediate **VI** was derived from vinyl iodide **VII** through Sharpless asymmetric dihydroxylation and one-carbon homologation via cyanation. We anticipated that the issue of controlling the diene moiety configuration in the previous synthetic attempt could be addressed through Wipf's modification of the Zr-catalyzed carboalumination/iodination of homoallylic alcohol **VIII**. This step was expected to yield *E*-vinyl iodide **VII**, which would then serve as a coupling partner for constructing the conjugated diene side chain of the target. As in the first-generation synthesis, the Keck asymmetric allylation reaction of aldehyde **22** was crucial for imparting the desired stereochemistry to homoallylic alcohol **VIII** (Scheme 4).

Scheme 4. Second-Generation Synthetic Strategy for Ieodomycins A and B



Second-generation synthesis began with commercially available 4-pentyn-1-ol **21**, which was converted to aldehyde **22** under Swern oxidation conditions (Scheme 5). Aiming to

Scheme 5. Synthesis of Homoallylic Alcohol 24[a]



[a]Reaction conditions: (a) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −78 °C; (b) and (c) (*S*)-BINOL for **23a**, (*R*)- BINOL for **23b**, $Ti(OiPr)_4$, 4 Å MS, (n-Bu)$_3$Sn(allyl), CH_2Cl_2, −78 to −18 °C; (d) zirconocene dichloride (E), Me_3Al, CH_2Cl_2, then I_2, THF, −50 °C, **24a**: 59%, **24b**: 74% over three steps.

introduce the C5 stereocenter of ieodomycin B, we performed the Keck asymmetric allylation of aldehyde **22** to afford homoallylic alcohols **23a** with (*S*)-BINOL and **23b** with (*R*)-BINOL, both achieving excellent enantiomeric purity (Scheme 5).[20] Subsequently, *E*-vinyl iodides **24a** and **24b** were prepared by Wipf's modification of carboalumination using $ZrCl_2Cp_2$ and Me_3Al, followed by iodination. These steps resulted in yields of 59 and 74%, respectively, over three steps from 4-pentyn-1-ol **21** (Scheme 5).[21] These *E*-vinyl iodides remained intact through the final stage of the synthesis, where a conjugated diene moiety was formed by the Stille cross-coupling reaction.

The synthesis of two key intermediates **24a** and **24b** led us to employ the Sharpless asymmetric dihydroxylation reaction for preparing a series of triols **25a−25d**, encompassing all four possible stereochemistries at the C3 and C5 positions in ieodomycin B and its stereoisomers (Table 1).[11] Owing to unsatisfactory efficiency and facial selectivity with standard PHAL-based ligands, various in-house-prepared AD mixtures with different ligands were extensively screened to identify modified cinchona alkaloid ligands including $(DHQ)_2PYR$ and $(DHQD)_2PYR$ suitable for this transformation (see the SI for

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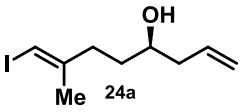
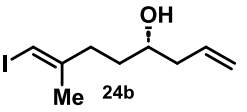
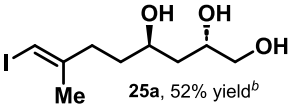
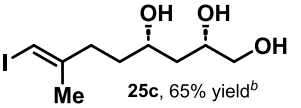
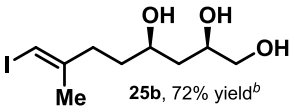
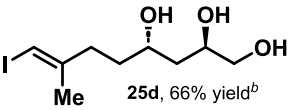
Table 1. Dihydroxylation of Homoallylic Alcohol 24[a]

substrates	 24a	 24b
triols	 **25a**, 52% yield[b] Ligand: $(DHQ)_2PYR$ Ratio[c] **25a**:**25b** = 2.6:1	 **25c**, 65% yield[b] Ligand: $(DHQ)_2PYR$ Ratio[c] **25c**:**25d** = 8.1:1
	 **25b**, 72% yield[b] Ligand: $(DHQD)_2PYR$ Ratio[c] **25a**:**25b** = 1:14.2	 **25d**, 66% yield[b] Ligand: $(DHQD)_2PYR$ Ratio[c] **25c**:**25d** = 1:5.1

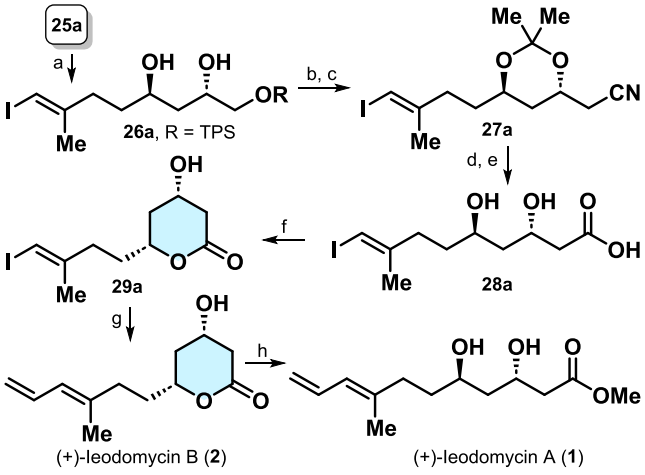
[a]Reaction conditions: Each reaction was carried out with ligand (0.01 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), 0.5 mol % $K_2OsO_4{\cdot}2H_2O$ in *t*-BuOH, and H_2O at 0 °C. [b]Isolated yields. [c]Ratios of isolated products.

details). Consequently, triols **25a** and **25b** were obtained in yields of 52 and 20% (*d.r.* = 2.6:1), respectively, from the reaction of **24a** with an AD mixture containing $(DHQ)_2PYR$. By contrast, the reaction of **24a** under AD reaction conditions with $(DHQD)_2PYR$ furnished **25a** and **25b** in yields of 5 and 71% (*d.r.* = 1:14.2), respectively (Table 1). Triols **25c** and **25d** were obtained in yields of 65 and 8% (*d.r.* = 8.1:1), respectively, from the dihydroxylation of **24b** with $(DHQ)_2PYR$, whereas the same reaction with $(DHQD)_2PYR$ furnished **25c** and **25d** in yields of 13 and 66% (*d.r.* = 1:5.1), respectively (Table 1).

Despite the successful synthesis of triols **25a**−**25d**, challenges remain in establishing the lactone ring and the conjugated *E*-diene side chain. Correspondingly, **25a** was converted to acetonide **27a** through a three-step process involving the sulfonylation of triol **25a** with TPSCl, the protection of the diol moiety in sulfonate **26a** with 2,2-dimethoxypropane,[22] and cyanation with NaCN for one-carbon homologation (Scheme 6). Deprotection of acetonide **27a**, followed by basic hydrolysis, furnished carboxylic acid **28a**,[23] which, without purification, was further treated under Mukaiyama lactonization reaction conditions to produce lactone **29a** in 76% yield over two steps (Scheme 6).[13] The synthesis was completed by the Stille cross-coupling reaction of lactone **29a**, affording ieodomycin B (**2**) in 67% yield.[24] As hypothesized in the synthetic strategy, opening the lactone ring of ieodomycin B (**2**) using K_2CO_3 in MeOH furnished A (**1**) in 93% yield (Scheme 6).

The ^1H and ^{13}C NMR spectra, mass spectra, and optical rotations of synthetic **1** and **2** matched those previously reported (see the SI for details). The successful synthesis of ieodomycins A and B led us to utilize this synthesis for other stereoisomers. Therefore, three stereoisomers of ieodomycin B (**30b**−**30d**) were fabricated via the same route as that of ieodomycin B (**2**) (Scheme 7). Intermediates **28b**−**28d** were obtained from triols **25b**−**25d** via a sequence of reactions, including sulfonylation of triols **25b**−**25d** (77−88% yields), protection of **26b**−**26d** (94−98% yields), cyanation (90−97% yields), deprotection of acetonides **27b**−**27d** (94−99% yields), and basic hydrolysis (Scheme 7).

Scheme 6. Synthesis of (+)-Ieodomycins A and B[a]



[a]Reaction conditions: (a) TPSCl, dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, −78 to −20 °C, 98%; (b) 2,2′-dimethoxypropane, PTSA, acetone, rt, 97%; (c) NaCN, DMSO, 70 °C, 88%; (d) 1 N HCl, THF, 0.5 h, 95%; (e) 7.5 N NaOH, MeOH, 55 °C; (f) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, rt, 76% over two steps; (g) tributyl(vinyl)tin, 10 mol % Pd_2dba_3, *N*,*N*-diisopropylethylamine (DIPEA), NMP, rt, 67%; (h) K_2CO_3, MeOH, rt, 93%. TPSCl: 2,4,6-triisopropyl benzenesulfonyl chloride, PTSA: *p*-toluenesulfonic acid, NMP: *N*-methyl-2-pyrrolidone.

After Mukaiyama lactonization (56−84% yields over two steps), the syntheses of the corresponding ieodomycin B stereoisomers **30b**−**30d** were finalized by the Stille cross-coupling of **29b**−**29d** in 48−93% yields. The syntheses of ieodomycins A and B and the three stereoisomers described herein are summarized in Figure 2.

Our establishment of the synthesis of ieodomycins led us to explore their biological relevance to various disease-related molecular targets and cell lines (Figure 3; see SI for details).

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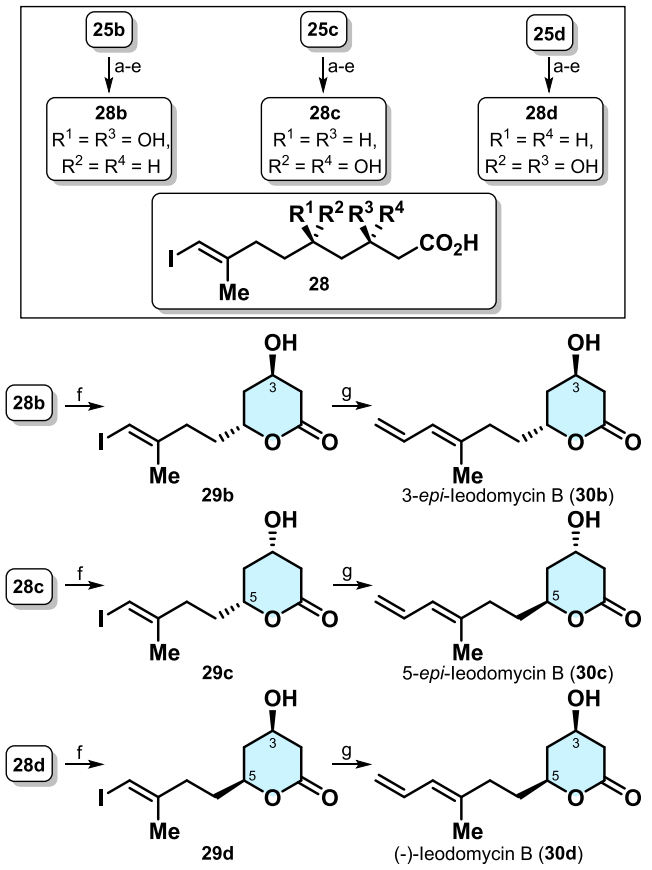
Scheme 7. Synthesis of Stereoisomers of Ieodomycin B[a]



[a]Reaction conditions: (a) TPSCl, DMAP, Et_3N, CH_2Cl_2, −78 to −20 °C, **26b**: 88%, **26c**: 85%, **26d**: 77%; (b) 2,2-dimethoxypropane, PTSA, acetone, rt, **26b-1**: 98%, **26c-1**: 94%, **26d-1**: 98%; (c) NaCN, DMSO, 70 °C, **27b**: 97%, **27c**: 93%, **27d**: 90%; (d) 1 N HCl, THF, rt, **27b-1**: 99%, **27c-1**: 98%, **27d-1**: 94%; (e) 7.5 N NaOH, MeOH, 55 °C; (f) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, rt, **29b**: 65%, **29c**: 56%, **29d**: 84% over two steps; (g) tributyl(vinyl)tin, 10 mol % Pd_2dba_3, DIPEA, NMP, rt, **30b**: 64%, **30c**: 48%, **30d**: 93%.

Compounds **1**, **2**, and **30b**−**30d** were evaluated for their antimicrobial, anticancer, antidiabetic, antihypertensive, anti-inflammatory, antioxidant, whitening, moisturizing, and anti-wrinkle effects (Figure 3; see the SI for details). *In vitro* evaluation of type 2 diabetes-linked enzymes including α-amylase (Figure 4a),[25] DPP4 (dipeptidyl peptidase-4) (Figure 4b),[26] and α-glucosidase[27] identified compounds **30b** and **30c**, diastereoisomers of (+)-ieodomycin B (**2**), as inhibitors, specifically for α-glucosidase (Figure 4c). Notably, 3-*epi*-ieodomycin B (**30b**) exhibited a superior inhibitory effect (IC_{50} = 66.1 μM) against α-glucosidase than did acarbose (IC_{50} = 80.0 μM), a positive control (Figure 4d).

Further, compounds **1**, **2**, and **30b**−**30d** were examined for their effects against ACE, which is linked to hypertension, heart failure, diabetic nephropathy, and type 2 diabetes mellitus.[28] Compounds **30b** and **30d** demonstrated inhibitory effects toward ACE, with IC_{50} values of 1.80 and 1.84 mM, respectively (Figure 4e). In addition to inhibitory effects against α-glucosidase and ACE, the synthesized compounds appeared to exhibit moderate levels of inhibitory effects against tyrosinase (Figure 4f).[29] No effects in other assays for antimicrobial, anticancer, anti-inflammatory, antioxidant, whitening, moisturizing, and antiwrinkle effects (see the SI for details) were observed. Among the five synthesized compounds, the stereoisomers of (+)-ieodomycin B (**2**) such as **30b**, **30c**, and **30d** exhibited significant inhibitory effects against disease-related enzymes such as α-glucosidase, ACE, and tyrosinase.

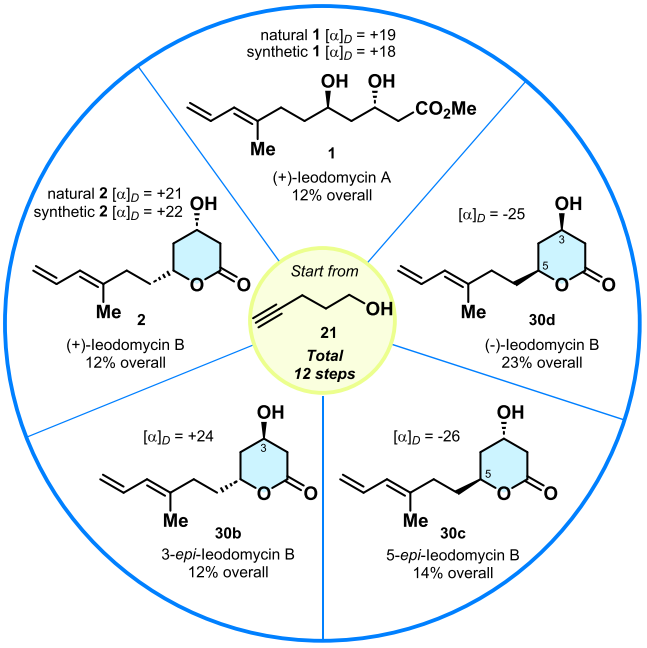


Figure 2. Overview of the prepared ieodomycin stereoisomers.

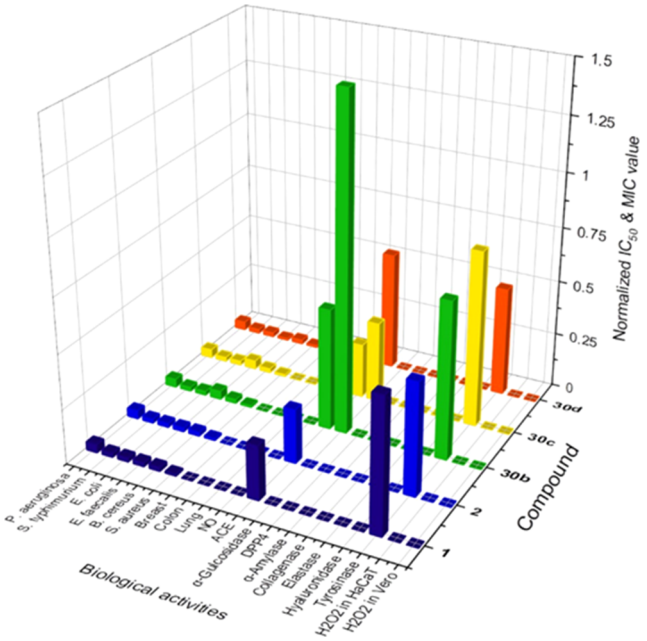


Figure 3. Biological activities of ieodomycins.

CONCLUSIONS

We realized the divergent and enantioselective total synthesis of (+)-ieodomycins A (**1**) and B (**2**) and their stereoisomers (**30b**−**30d**) in 12 steps (13 steps for (+)-ieodomycin A) starting from commercially available 4-pentyn-1-ol **21**. The synthetic approach entails Keck asymmetric allylation and Wipf's modification of carboalumination, followed by iodination, Sharpless asymmetric dihydroxylation, one-carbon

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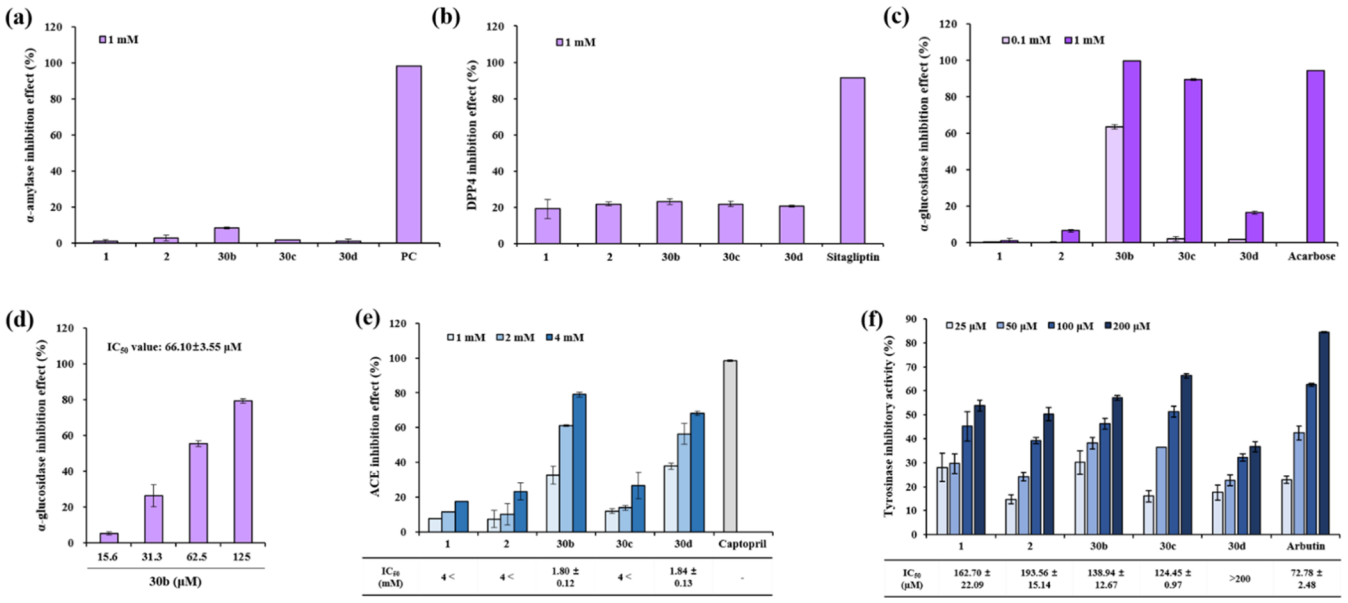

Figure 4. Bioactivity profiles of (+)-ieodomycin A (**1**), (+)-ieodomycin B (**2**), 3-*epi*-ieodomycin B (**30b**), 5-*epi*-ieodomycin B (**30c**), and (−)-ieodomycin B (**30d**) against α-amylase (a), DPP4 (dipeptidyl peptidase-4) (b), α-glucosidase (c, d), angiotensin I converting enzyme (ACE) (e), and tyrosinase (f). PC: positive control.

homologation via cyanation, Mukaiyama lactonization, and Stille cross-coupling. Additionally, it helped us determine the preliminary bioactivity profile of ieodomycins to identify **30b** and **30c** as α-glucosidase inhibitors and **30b** and **30d** as ACE inhibitors. Efforts to derive optimal analogues with pharmaceutical potential are underway.

EXPERIMENTAL SECTION

Synthesis. *General Information.* All chemical reagents and reaction anhydrous were purchased and used from Sigma Aldrich, Alfa Aesar, and TCI without further purification. All reactions were monitored by thin-layer chromatography (TLC, Merck). Silica gel 60 (70−230 mesh, Merck) was used for flash column chromatography. Eluent solvents were purchased and used by distillation from Duksan Chemicals. All glassware instruments were dried at temperatures over 60 °C. All the reactions were carried out under N_2 except using H_2 reaction. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Varian Unity-Inova 500 MHz and a Bruker Avance III 600 MHz spectrometer. ^{1}H NMR was performed at 500 and 600 MHz, and ^{13}C NMR was operated at 125 and 151 MHz. Chemical shifts are reported as δ (ppm) values relative to chloroform-*d* ($CDCl_3$, δ 7.26) and methanol-d_4 (CD_3OD, δ 3.31) coupling constant was noted in Hz units. High-resolution mass spectrometry (HRMS) was performed by liquid chromatography−mass spectroscopy (LC−MS) using a ThermoRiningan and electrospray ionization (ESI-TOF) on a Waters spectrometer from the Korea Basic Science Institute (KBSI). Optical rotation was determined using a Jasco Dip-1000 Digital Polarimeter and a Rudolph Research Analytical Autopol III automatic polarimeter. Melting points were measured on a Fisher−Johns apparatus.

1st Generation Synthesis of (+)-Ieodomycin B. *3-(Benzyloxy)propan-1-o1 (**5-1**).* To a solution of propane-1,3-diol **5** (2 g, 26.28 mmol, 1.0 equiv) in dichloromethane (DCM, 26 mL, 1.0 M), silver oxide(I) (9.13 g, 38.42 mmol, 1.5 equiv) and benzyl bromide (3.43 mL, 28.91 mmol, 1.1 equiv) were added at room temperature. The reaction was stirred for 6 h at room temperature. After completion of the reaction, the mixture was filtered, washed, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 5:1, v/v) to afford product **5-1** (3.67 g, 22.08 mmol, 84%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.27 (m, 5H), 4.52 (s, 2H), 3.78 (dt, *J* = 5.5, 5.5 Hz, 2H), 3.65 (t, *J* = 5.8 Hz, 2H), 2.33 (t, *J* = 5.5 Hz, 1H), 1.86 (tt, *J* = 5.8, 5.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.1, 128.5, 127.8, 127.7, 73.4, 69.5, 62.0, 32.2; HRMS (ESI) for $C_{10}H_{14}O_2Na$ $[M + Na]^+$ calcd 189.0891, found 189.0893. Data are consistent with those reported in the literature.[3]

*3-(Benzyloxy)propanal (**6**).* To a solution of trifluoroacetic anhydride (4.43 mL, 31.88 mmol, 2.0 equiv) in DCM (32 mL), a solution of DMSO (4.53 mL, 63.76 mmol, 4.0 equiv) in DCM (24 mL) was added dropwise at −78 °C. After stirring for 10 min at −78 °C, a solution of **5-1** (2.65 g, 15.94 mmol, 1.0 equiv) in DCM (24 mL) was slowly added. The reaction mixture was stirred for 1 h at −78 °C, and triethylamine (11.1 mL, 79.7 mmol, 5.0 equiv) was added dropwise. The reaction was warmed up to room temperature and stirred for 7 h. For quenching the reaction, water was added and extracted with DCM three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford the product **6** (2.17 g, 13.21 mmol, 82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.8 Hz, 1H), 7.37−7.27 (m, 5H), 4.53 (s, 2H), 3.81 (t, *J* = 6.1 Hz, 2H), 2.70 (dt, *J* = 6.1, 1.8 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 201.3, 137.9, 128.5, 127.9, 127.8, 73.4, 63.9, 44.0; HRMS (ESI) for $C_{10}H_{12}O_2Na$ $[M + Na]^+$ calcd 187.0735, found 187.0733. Data are consistent with those reported in the literature.[30]

*(S)-1-(Benzyloxy)hex-5-en-3-ol (**7a**).* To a solution of (*S*)-BINOL (214.4 mg, 0.749 mmol, 0.1 equiv) in DCM (7.5 mL), 4 Å molecular sieves (3.28 g) were added. After 10 min, a solution of $Ti(OiPr)_4$ (222 μL, 0.749 mmol, 0.1 equiv) in DCM (0.75 mL) was slowly added. The orange-red suspension

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solution was heated to reflux and stirred for 1 h. A solution of **6** (1.23 g, 7.49 mmol, 1.0 equiv) in DCM (1.1 mL) was added at room temperature. Stirring for 5 min, the reaction was cooled down to −78 °C, and allyltributylstannane (2.79 mL, 8.99 mmol, 1.2 equiv) was added. The reaction was kept at −20 °C for 68 h without stirring. For quenching the reaction, saturated aqueous $NaHCO_3$ solution and dichloromethane were added and stirred for 2 h at room temperature. Molecular sieves were removed by using Celite pads. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/acetone = 9:1, v/v) to afford product **7a** (1.40 g, 6.787 mmol, 91%, 99% *ee*) as a colorless oil. $[\alpha]_D^{25}$ = −9.32 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.84 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.13−5.10 (m, 1H), 5.09−5.08 (m, 1H), 4.52 (s, 2H), 3.91−3.84 (m, 1H), 3.72 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 3.65 (ddd, *J* = 8.5, 7.0, 5.5 Hz, 1H), 2.85 (d, *J* = 3.0 Hz, 1H), 2.25 (dd, *J* = 7.0, 7.0 Hz 1H), 1.78−1.74 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.0, 135.0, 128.5, 127.87, 127.80, 117.7, 73.4, 70.5, 69.0, 42.0, 36.0; HRMS (ESI) for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ calcd 229.1204, found 229.1221. Data are consistent with those reported in the literature.[31]

*(R)-1-(Benzyloxy)hex-5-en-3-ol (**7b**).* Compound **7b** (1.99 g, 9.647 mmol, 89%, 95% *ee*) was obtained as a colorless oil from **7** (1.78 g, 10.84 mmol, 1.0 equiv) by the same procedure as **7a** except using (*R*)-BINOL (214.4 mg, 1.84 mmol, 0.1 equiv) instead of (*S*)-BINOL. $[\alpha]_D^{25}$ = +3.33 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5H), 5.82 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.14−5.10 (m, 1H), 5.10−5.08 (m, 1H), 4.51 (s, 2H), 3.91−3.85 (m, 1H), 3.70 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 3.63 (ddd, *J* = 8.5, 7.0, 5.5 Hz, 1H), 2.76 (s, 1H), 2.23 (dd, *J* = 7.0, 7.0 Hz, 2H), 1.81−1.75 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.1, 135.0, 128.6, 127.83, 127.77, 117.7, 73.4, 70.4, 69.0, 42.0, 36.0; HRMS (ESI) for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ calcd 229.1204, found 229.1207. Data are consistent with those reported in the literature.[5]

*(S)-((1-(Benzyloxy)hex-5-en-3-yl)oxy)(tert-butyl)-diphenylsilane (**7a-1**).* To a solution of **7a** (1.0 g, 4.85 mmol, 1.0 equiv) in anhydrous DMF (4.85 mL), imidazole (825 mg, 12.1 mmol, 2.5 equiv) and TBDPSCl (1.6 mL, 6.01 mmol, 1.24 equiv) were added. Then, the reaction was heated to 40 °C and stirred for 18 h. After completion of the reaction, sat. aq. LiCl was added and extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 50:1, v/v) to afford the product **7a-1** (2.07 g, 4.66 mmol, 96%) as a colorless oil. $[\alpha]_D^{25}$ = +2.00 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.0 Hz, 4H), 7.45−7.40 (m, 2H), 7.40−7.30 (m, 6H), 7.30−7.22 (m, 3H), 5.71 (ddt, *J* = 17.4, 10.2, 7.1 Hz, 1H), 4.97 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.91 (dd, *J* = 17.1, 2.1 Hz, 1H), 4.38 (d, *J* = 10.0 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 3.98 (tt, *J* = 5.0, 5.0 Hz, 1H), 3.53−3.44 (m, 2H), 2.24 (ddd, *J* = 11.5, 5.75, 5.75 Hz, 1H), 2.21−2.14 (m, 1H), 1.81−1.77 (m, 2H), 1.05 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 138.6, 136.09, 136.06, 134.7, 134.5, 134.3, 129.69, 129.66, 128.4, 127.7, 127.64, 127.60, 127.5, 117.2, 72.8, 70.4, 67.0, 41.7, 36.2, 27.1, 19.5; HRMS (ESI) for $C_{29}H_{36}O_2NaSi$ $[M + Na]^+$ calcd 467.2382, found 467.2378. Data are consistent with those reported in the literature.[32]

*(R)-((1-(Benzyloxy)hex-5-en-3-yl)oxy)(tert-butyl)-diphenylsilane (**7b-1**).* Compound **7b-1** (2.3 g, 5.17 mmol, 98%) was obtained as a colorless oil from **7b** (1.09 g, 5.28 mmol, 1.0 equiv) by the same procedure as **7a-1**. $[\alpha]_D^{25}$ = −5.99 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.0 Hz, 4H), 7.43−7.41 (m, 2H), 7.40−7.30 (m, 6H), 7.30−7.23 (m, 3H), 5.71 (ddt, *J* = 17.4, 10.2, 7.1 Hz, 1H), 4.98−4.95 (m, 1H), 4.94−4.89 (m, 1H), 4.38 (d, *J* = 10.0 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 3.98 (tt, *J* = 5.5, 5.5 Hz, 1H), 3.53−3.46 (m, 2H), 2.24 (ddd, *J* = 11.5, 5.75, 5.75 Hz, 1H), 2.20−2.13 (m, 1H), 1.85−1.77 (m, 2H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 138.7, 136.09, 136.07, 134.7, 134.5, 134.3, 129.69, 129.66, 128.4, 127.7, 127.64, 127.60, 127.55, 117.2, 72.8, 70.5, 67.0, 41.7, 36.2, 27.1, 19.5; HRMS (ESI) for $C_{29}H_{36}O_2NaSi$ $[M + Na]^+$ calcd 467.2382, found 467.2381. Data are consistent with those reported in the literature.[33]

*(S)-3-((tert-Butyldiphenylsilyl)oxy)hex-5-en-1-ol (**7a-2**).* To a solution of **7a-1** (681 mg, 1.53 mmol, 1.0 equiv) in DCM/pH 7.0 buffer (9:1, v/v, 15.3 mL), DDQ (1.74 g, 7.65 mmol, 5.0 equiv) was added. The reaction was heated to 40 °C and stirred for 22 h. After completion of the reaction, water was added and extracted with diethyl ether three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 9:1, v/v) to afford the product **7a-2** (468 mg, 1.32 mmol, 86%) as a colorless oil. $[\alpha]_D^{25}$ = +39.27 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (t, *J* = 6.8 Hz, 4H), 7.45−7.37 (m, 6H), 5.59 (ddt, *J* = 14.0, 10.0, 7.5, 1H), 4.93 (d, *J* = 10.0 Hz, 1H), 4.87 (dd, *J* = 17.5, 2.0 Hz, 1H), 4.00−3.96 (m, 1H), 3.80−3.73 (m, 1H), 3.66 (ddd, *J* = 11.0, 11.0, 5.5 Hz, 1H), 2.29 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 2.18 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 1.85−1.79 (m, 2H), 1.69−1.62 (m, 1H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.06, 136.01, 134.3, 134.0, 133.7, 129.9, 129.8, 127.8, 127.7, 117.4, 71.8, 59.8, 41.1, 37.6, 27.1, 19.3; HRMS (ESI) for $C_{22}H_{30}O_2NaSi$ $[M + Na]^+$ calcd 377.1913, found 377.1921. Data are consistent with those reported in the literature.[34]

*(R)-3-((tert-Butyldiphenylsilyl)oxy)hex-5-en-1-ol (**7b-2**).* Compound **7b-2** (943 mg, 2.66 mmol, 93%) was obtained as a colorless oil from **7b-1** (1.27 g, 2.86 mmol, 1.0 equiv) by the same procedure as **7a-2**. $[\alpha]_D^{25}$ = −43.92 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 7.69 (m, 4H), 7.43−7.38 (m, 6H), 5.58 (ddt, *J* = 14.0, 10.0, 7.5 Hz, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.86 (dd, *J* = 17.5, 2.0 Hz, 1H), 4.01−3.97 (m, 1H), 3.81−3.74 (m, 1H), 3.65 (ddd, *J* = 11.0, 11.0, 5.5 Hz, 1H), 2.28 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 2.17 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 1.93−1.79 (m, 2H), 1.71−1.64 (m, 1H) 1.06 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.1, 136.0, 134.4, 134.1, 133.8, 130.0, 129.9, 127.8, 127.7, 117.5, 71.8, 59.9, 41.2, 37.6, 27.2, 19.4; HRMS (ESI) for $C_{22}H_{30}O_2NaSi$ $[M + Na]^+$ calcd 377.1913, found 377.1907.

*(S)-3-((tert-Butyldiphenylsilyl)oxy)hex-5-enoic Acid (**8a**).* To a solution of PDC (10.4 g, 27.61 mmol, 11.0 equiv) in anhydrous DMF (11.8 mL), a solution of **7a-2** (890 mg, 2.51 mmol, 1.0 equiv) in DMF (25.1 mL) was slowly added at room temperature. The reaction was stirred for 8 h at room temperature. After completion of the reaction, LiCl (sat. aq.) was added and extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 6:1, v/v) to afford the product **8a** (749 mg, 2.03 mmol, 81%) as a colorless oil. $[\alpha]_D^{25}$

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= +15.31 ($CHCl_3$, c = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.45−7.34 (m, 6H), 5.63 (ddt, J = 17.3, 10.3, 7.3 Hz, 1H), 5.00 (dd, J = 10.0, 2.0 Hz), 4.95 (dd, J = 17.0, 2.0 Hz, 1H), 4.18 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H), 2.50 (ddd, J = 17.0, 15.5, 5.5 Hz, 2H), 2.31−2.18 (m, 2H), 1.04 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 176.2, 136.04, 136.0, 133.7, 133.5, 133.4, 129.96, 129.95, 127.78, 127.75, 118.4, 69.9, 41.4, 40.8, 27.0, 19.3; HRMS (ESI) for $C_{22}H_{28}O_3NaSi$ [M + Na]$^+$ calcd 391.1705, found 391.1698. Data are consistent with those reported in the literature.[7]

*(R)-3-((tert-Butyldiphenylsilyl)oxy)hex-5-enoic Acid (**8b**).* Compound **8b** (823 mg, 2.23 mmol, 89%) was obtained as a colorless oil from **7b-2** (890 mg, 2.51 mmol, 1.0 equiv) by the same procedure as **8a**. $[\alpha]_D^{25}$ = −21.96 ($CHCl_3$, c = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.44−7.33 (m, 6H), 5.61 (ddt, J = 17.3, 10.3, 7.3 Hz, 1H), 4.98 (dd, J = 10.0, 2.0 Hz, 1H), 4.92 (dd, J = 17.0, 2.0 Hz, 1H), 4.16 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H), 2.48 (ddd, J = 17.0, 15.5, 5.5 Hz, 1H), 2.30−2.19 (m, 2H), 1.03 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.2, 136.1, 136.0, 133.9, 133.62, 133.60, 129.9, 127.74, 127.73, 118.4, 69.9, 41.5, 41.1, 27.1, 19.4; HRMS (ESI) for $C_{22}H_{28}O_3NaSi$ [M + Na]$^+$ calcd 391.1705, found 391.1700. Data are consistent with those reported in the literature.[8]

*(4S)-4-((tert-Butyldiphenylsilyl)oxy)-6-(iodomethyl)-tetrahydro-2H-pyran-2-one (**9**).* A solution of **8a** (720 mg, 1.95 mmol, 1.0 equiv) in $NaHCO_3$ (492 mg, 5.86 mmol, 3.0 equiv) in distilled water (12 mL) was stirred at room temperature for 10 min and $CHCl_3$ (12 mL) was added. The reaction was cooled down to 0 °C and stirred for 10 min. And then, I_2 (990 mg, 3.9 mmol, 2.0 equiv) was added in the dark and stirred for 7 h at 0 °C. After completion of the reaction, sat. aq. sodium thiosulfate was added and extracted with DCM three times. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 5:1, v/v) to afford product **9** (878 mg, 1.78 mmol, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) *trans*/*cis* = 4:1, δ 7.64−7.59 (m, 4H), 7.46−7.42 (m, 2H), 7.39−7.36 (m, 4H), 4.74−4.69 (m, 1H), 4.31−4.28 (m, 1H), 4.15−4.10 (m, 0.29H), 4.00−3.95 (m, 0.28H), 3.37−3.31 (m, 2H), 3.29−3.28 (m, 0.5H), 2.65 (ddd, J = 17.4, 5.9, 1.4 Hz, 0.35H), 2.56 (dt, J = 17.5, 2.5 Hz, 1H), 2.51−2.46 (d, J = 17.3 Hz, 1H), 2.43−2.39 (d, J = 4.5 Hz, 1H), 2.23−2.20 (m, 0.36H), 2.03 (dq, J = 14.0, 3.5 Hz, 1H), 1.78−1.71 (m, 0.47H), 1.60−1.55 (m, 2H), 1.05−1.04 (m, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.4, 169.1, 135.77, 135.74, 133.2, 133.06, 133.03, 132.9, 130.32, 130.31, 130.2, 128.1, 128.09, 128.08, 128.07, 128.04, 75.5, 74.4, 64.9, 64.3, 39.5, 38.6, 37.9, 36.1, 27.03, 27.01, 26.98, 26.93, 19.2, 19.1, 8.5, 7.0; HRMS (ESI) for $C_{22}H_{27}O_3INaSi$ [M + Na]$^+$ calcd 517.0672, found 517.0668. Data are consistent with those reported in the literature.[8]

*(4S,6R)-4-((tert-Butyldiphenylsilyl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-2-one (**11**).* To a solution of **9** (810 mg, 1.64 mmol, 1.0 equiv) in anhydrous DCM (20 mL), *m*-CPBA (purity: 70%, 1.2 g, 6.95 mmol, 3.0 equiv) and $NaHCO_3$ (688 mg, 8.19 mmol, 5.0 equiv) were added at 0 °C. The reaction was warmed up to room temperature and stirred for 4 h. After completion of the reaction, sodium thiosulfate (sat. aq.) and $NaHCO_3$ (sat. aq.) were added and extracted with DCM three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford product **11** (416 mg, 1.08 mmol, 66%) as a colorless oil. $[\alpha]_D^{25}$ = −2.66 ($CHCl_3$, c = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.61 (m, 4H), 7.47−7.44 (m, 2H), 7.41−7.37 (m, 4H), 4.93−4.89 (m, 1H), 4.35 (ddd, J = 7.0, 3.5, 3.5 Hz, 1H), 3.86 (dd, J = 12.8, 2.8 Hz, 1H), 3.60 (ddd, J = 12.8, 4.6 Hz and J = 0.9 Hz, 1H), 2.60 (dq, J = 17.5, 1.5 Hz, 1H), 2.42 (dd, J = 17.5, 4.0 Hz, 1H), 1.73 (m, 2H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.0, 135.77, 135.72, 133.2, 133.0, 130.29, 130.28, 128.08, 128.07, 76.99, 64.9, 64.5, 38.9, 31.6, 27.0, 19.2; HRMS (ESI) for $C_{22}H_{28}O_4NaSi$ [M + Na]$^+$ calcd 407.1655, found 407.1649.

*(4S,6R)-4-((tert-Butyldiphenylsilyl)oxy)-6-((E)-3-oxobut-1-en-1-yl)tetrahydro-2H-pyran-2-one (**12**).* To a solution of **11** (40 mg, 0.104 mmol, 1.0 equiv) in anhydrous DCM (1.0 mL, 0.1 M), Dess−Martin periodinane (66.1 mg, 0.156 mmol, 1.5 equiv) was added and stirred for 1.5 h at room temperature. After completion of the reaction, sodium thiosulfate (sat. aq.) and $NaHCO_3$ (sat. aq.) were added. The organic layer was extracted with DCM, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-6-oxotetrahydro-2*H*-pyran-2-carbaldehyde **11-1** was used without further purification. A solution of acetonyltriphenylphosphonium chloride (40.6 mg, 0.114 mmol, 1.1 equiv) in anhydrous THF (1.5 mL) was cooled down to 0 °C. *n*-BuLi (1.24 M in hexanes, 100 μL, 0.125 mmol, 1.2 equiv) was added dropwise into the reaction flask and stirred for 30 min at room temperature. After 30 min, a solution of **11-1** (0.104 mmol, 1.0 equiv) in THF (1 mL) was added at 0 °C and stirred for 4 h. For quenching the reaction, NH_4Cl (sat. aq.) was added and extracted with pentane three times. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 4:1, v/v) to afford product **12** (18 mg, 0.043 mmol, 41%, over 2 steps) as a colorless oil. $[\alpha]_D^{25}$ = +11.98 ($CHCl_3$, c = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 4H), 7.48−7.45 (m, 2H), 7.42−7.39 (m, 4H), 6.66 (dd, J = 15.8, 4.3 Hz, 1H), 6.35 (dd, J = 16.0, 1.5 Hz, 1H), 5.48−5.45 (m, 1H), 4.33−4.30 (m, 1H), 2.64 (dt, J = 17.5, 2.6 Hz, 1H), 2.50 (dd, J = 17.8, 4.3 Hz, 1H), 2.26 (s, 3H), 1.94−1.89 (m, 1H), 1.62−1.59 (m, 1H), 1.07 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.6, 168.9, 142.6, 135.7, 135.6, 133.0, 132.8, 130.39, 130.36, 129.7, 128.13, 128.11, 74.2, 64.2, 39.0, 35.7, 28.2, 26.9, 19.2; HRMS (ESI) for $C_{25}H_{30}O_4NaSi$ [M + Na]$^+$ calcd 445.1811, found 445.1814.

*(4S,6S)-4-((tert-Butyldiphenylsilyl)oxy)-6-(3-oxobutyl)-tetrahydro-2H-pyran-2-one (**13**).* To a solution of **12** (18 mg, 0.0425 mmol, 1.0 equiv) in EtOH (0.43 mL), 10% palladium on carbon (1.4 mg, 0.013 mmol, 0.3 equiv) was added. The reaction was stirred under H_2 at room temperature for 1 h. After completion of the reaction, the catalyst was removed by filtration through a pad of Celite and washed with DCM. The organic layer was evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford product **13** (15 mg, 0.0353 mmol, 83%) as a colorless oil. $[\alpha]_D^{25}$ = −47.97 ($CHCl_3$, c = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (t, J = 7.5 Hz, 4H), 7.46−7.43 (m, 2H), 7.41−7.37 (m, 4H), 4.81−4.76 (m, 1H), 4.27 (quin, J = 7.1 Hz, 1H), 2.75−2.68 (m, 1H), 2.66−2.55 (m, 2H), 2.42 (dd, J = 17.5, 4.5 Hz, 1H), 2.16 (s, 3H), 1.94−1.88 (m, 1H), 1.81−1.73 (m, 2H), 1.52−1.47 (m, 1H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 207.8, 170.2, 135.7, 133.2, 133.1, 130.2, 128.0,

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75.3, 64.5, 39.0, 38.9, 36.2, 30.1, 29.4, 26.9, 19.2; HRMS (ESI) for $C_{25}H_{32}O_4NaSi$ $[M + Na]^+$ calcd 447.1968, found 447.1968.

*(4S,6S)-4-((tert-Butyldiphenylsilyl)oxy)-6-(3-hydroxy-3-methylhex-5-en-1-yl)tetrahydro-2H-pyran-2-one (**14**).* To a solution of **13** (58 mg, 0.137 mmol, 1.0 equiv) in anhydrous DCM (0.78 mL), potassium allyltrifluoroborate (40.4 mg, 0.27 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (0.85 μL, 0.0068 mmol, 0.05 equiv) were added and stirred for 1.5 h at room temperature. After completion of the reaction, $NaHCO_3$ (aq.) was added and extracted with DCM three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford product **14** (57 mg, 0.122 mmol, 89%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 4H), 7.47−7.43 (m, 2H), 7.40−7.37 (m, 4H), 5.88−5.83 (m, 1H), 5.18−5.10 (m, 2H), 4.77 (br s, 1H), 4.28 (s, 1H), 2.58 (d, *J* = 18.5 Hz, 1H), 2.44 (dt, *J* = 17.5, 3.8 Hz, 1H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.83−1.66 (m, 4H), 1.54−1.46 (m, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.45, 170.42, 135.74, 135.72, 133.76, 133.72, 133.3, 133.1, 130.2, 130.1, 128.0, 127.9, 119.2, 119.1, 76.6, 76.5, 71.77, 71.75, 64.5, 46.9, 46.4, 39.0, 36.8, 36.7, 36.2, 36.0, 30.0, 29.9, 26.99, 26.90, 26.5, 19.2; HRMS (ESI) for $C_{28}H_{38}O_4NaSi$ $[M + Na]^+$ calcd 489.2437, found 489.2431.

*(4S,6S)-4-((tert-Butyldiphenylsilyl)oxy)-6-((E)-3-methylhexa-3,5-dien-1-yl)tetrahydro-2H-pyran-2-one (**14-1**).* To a solution of **14** (40 mg, 0.0857 mmol, 1.0 equiv) in benzene (0.86 mL, 0.1M), a modified Burgess reagent (*N*-methyl-*N*-{[(methoxycarbonyl)amino]sulfonyl}piperidinium inner salt, 61 mg, 0.258 mmol, 3.0 equiv) was added at room temperature. The reaction was heated to reflux for 8.5 h. For quenching the reaction, water was added and extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 9:1, v/v) to afford product **14-1** (33 mg, 0.0736 mmol, 86%) as a colorless oil. *E*/*Z* = 1:1, inseparable. ^1H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 4H), 7.47−7.37 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 4H), 6.61−6.52 (m, 1H), 5.86 (d, *J* = 10.0 Hz, 1H), 5.12 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.80−4.75 (m, 1H), 4.29−4.26 (m, 1H), 2.59 (dt, *J* = 17.5 Hz and *J* = 5.5 Hz, 1H), 2.43 (dd, *J* = 17.5, 4.5 Hz, 1H), 2.43−2.30 (m, 1H), 2.26−2.20 (m, 1H), 2.17−2.11 (m, 1H), 1.76 (s, 3H), 1.68−1.63 (m, 1H), 1.59−1.50 (m, 2H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.4, 138.1, 137.9, 135.77, 135.76, 133.4, 133.1, 132.8, 130.23, 130.22, 128.04, 128.034, 128.031, 127.4, 126.3, 115.5, 115.4, 75.6, 75.5, 64.59, 64.55, 39.1, 36.1, 36.0, 34.9, 34.0, 33.7, 29.8, 27.6, 27.0, 23.7, 19.2, 16.7; HRMS (ESI) for $C_{28}H_{36}O_3NaSi$ $[M + Na]^+$ calcd 471.2331, found 471.2331.

*(4S,6S)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one (5-epi-leodomycin B, **15**).* To a solution of **14-1** (32 mg, 0.071 mmol, 1.0 equiv) in THF (2.3 mL), TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol, 3.0 equiv) and AcOH (16 μL, 0.28 mmol, 4.0 equiv) were added at room temperature. The reaction mixture was stirred at room temperature for 5 h. For quenching the reaction, NH_4Cl (sat. aq.) was added and extracted with EtOAc three times. The organic layer was composed of brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford the product 5-*epi*-ieodomycin B, **15** (13.5 mg, 0.0644 mmol, 92%) as a colorless oil. *E*/*Z* = 1:1, inseparable. ^1H NMR (500 MHz, $CDCl_3$) δ 6.58−6.51 (m, 1H), 5.89−5.85 (m, 1H), 5.13−5.08 (m, 1H), 5.04−4.99 (m, 1H), 4.51−4.47 (m, 1H), 3.67−3.65 (m, 1H), 3.58 (d, *J* = 4.0 Hz, 1H), 2.38−2.23 (m, 3H), 2.16−2.13 (m, 1H), 1.91−1.93 (m, 1H), 1.76−1.75 (m, 3H), 1.73−1.66 (m, 1H). HRMS (ESI) for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ calcd 233.1154, found 233.1138. Data are consistent with those reported in the literature.[2m]

*(4R)-4-((tert-Butyldiphenylsilyl)oxy)-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-one (**16**).* $(DHQ)_2PYR$ (13 mg, 0.01 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (1.41 g, 4.26 mmol, 3.0 equiv), K_2CO_3 (591 mg, 4.26 mmol, 3.0 equiv), and $K_2OsO_4{\cdot}2H_2O$ (2.62 mg, 0.007 mmol, 0.005 equiv) were dissolved in *t*-BuOH (18 mL) and H_2O (23 mL). A solution of **8b** (525 mg, 1.42 mmol, 1.0 equiv) in *t*-BuOH (5 mL) was slowly added to the flask at 0 °C and stirred for 18 h at 0 °C. After completion of the reaction, sodium thiosulfate (sat. aq.) was added and stirred for 1 h. For quenching the reaction, water was added and extracted with DCM three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude (3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5,6-dihydroxyhexanoic acid **10** was obtained as a colorless oil and used without further purification. To a solution of crude **10** in anhydrous DCM (36 mL), triethylamine (0.67 mL, 4.82 mmol, 3.4 equiv) and 2-chloro-1-methylpyridinium iodide (725.6 mg, 2.84 mmol, 2.0 equiv) was added and stirred for 4 h at room temperature. After completion of the reaction, water was added and extracted with DCM three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 1:1, v/v) to afford the product **16** (317 mg, 5.33 mmol, 58%, over 2 steps) as a colorless oil. *trans*/*cis* = 2.7:1, ^1H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 8H), 7.44−7.36 (m, 12H), 4.89 (ddd, *J* = 8.8, 8.8, 5.2 Hz, 1H, *cis*), 4.34 (dddd, *J* = 3.3, 3.3, 3.3, 3.3 Hz, 1H, *cis*), 4.12 (m, 2H, *trans*), 3.84 (dd, *J* = 12.3, 2.8 Hz, 1H, *cis*), 3.72 (dd, *J* = 12.8, 2.8 Hz, 1H, *trans*), 3.61 (dd, *J* = 12.8, 5.3 Hz, 1H, *trans*), 3.58 (dd, *J* = 12.8, 5.3 Hz, 1H, *cis*), 2.67 (ddd, *J* = 18.0, 6.5, 1.1 Hz, 1H, *trans*), 2.57 (d, *J* = 18.0 Hz, 1H, *cis*), 2.50 (dd, *J* = 17.0, 7.5 Hz, 1H, *trans*), 2.41 (dd, *J* = 17.8, 4.3 Hz, 1H, *cis*), 1.94 (ddd, *J* = 13.3, 4.2, 4.2 Hz, 1H, *trans*), 1.82 (ddd, *J* = 13.8, 11.5, 9.0 Hz, 1H, *trans*), 1.74−1.71 (m, 2H, *cis*), 1.05 (s, 9H), 1.04 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.3, 170.0, 135.79, 135.77, 135.70, 133.4, 133.2, 133.14, 133.08, 130.3, 130.2, 128.1, 128.0, 77.6, 76.9, 65.2, 64.9, 64.8, 64.6, 39.9, 39.0, 33.9, 31.6, 27.0, 26.9, 19.3, 19.1; HRMS (ESI) for $C_{22}H_{28}O_4NaSi$ $[M + Na]^+$ calcd 407.1655, found 407.1653. Data are consistent with those reported in the literature.[14]

*(R)-4-((tert-Butyldiphenylsilyl)oxy)-6-(3-oxobut-1-en-1-yl)-tetrahydro-2H-pyran-2-one (**17**).* Compound **17** (206 mg, 0.487 mmol, 75%, over 2 steps) was obtained as a colorless oil from **16** (250 mg, 0.65 mmol, 1.0 equiv) by the same procedure as **12**. *trans*/*cis* = 2:1, ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (m, 8H), 7.46−7.37 (m, 12H), 6.64 (m, 2H), 6.33 (dd, *J* = 15.3 Hz and *J* = 1.5 Hz, 1H, *cis*), 6.30 (d, *J* = 15.5 Hz, 1H, *trans*), 5.45 (dt, *J* = 11.0 Hz, 1H, *trans*) 4.66 (ddd, *J* = 2.5 Hz, 1H, *trans*), 4.30 (m, 1H, *cis*), 4.16 (tt, *J* = 8.0, 5.5 Hz, 1H, *trans*), 2.70 (dd, *J* = 17.3, 5.3 Hz, 1H, *trans*), 2.63 (ddd, *J* = 17.5 Hz, 1H, *cis*), 2.53 (dd, *J* = 17.3, 7.8 Hz, 1H, *trans*), 2.48 (dd, *J* = 18.0, 4.0 Hz, 1H, *cis*), 2.24 (s, 3H, *cis*), 2.23 (s, 3H, *trans*), 2.12 (ddd, *J* = 14.0, 4.0, 4.0 Hz, 1H, *trans*), 1.90 (ddd, *J* = 14.5 Hz, 1H, *cis*), 1.75 (ddd, *J* = 13.8, 11.1, 8.8 Hz, 1H,

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trans), 1.58 (ddd, *J* = 12.8, 2.0 Hz, 1H, *cis*), 1.06 (s, 9H), 1.03 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 197.7, 197.6, 169.3, 169.0, 142.6, 141.8, 135.73, 135.70, 135.6, 133.2, 133.0, 132.9, 132.8, 130.38, 130.35, 130.33, 130.26, 129.9, 129.7, 128.12, 128.10, 128.08, 128.0, 75.0, 74.2, 65.2, 64.2, 39.8, 39.1, 37.7, 35.7, 28.23, 28.18, 27.0, 26.9, 19.2, 19.1; HRMS (ESI) for $C_{25}H_{30}O_4NaSi$ $[M + Na]^+$ calcd 445.1811, found 445.1808.

*(4R)-4-((tert-Butyldiphenylsilyl)oxy)-6-(3-oxobutyl)-tetrahydro-2H-pyran-2-one (**18**).* Stryker's reagent (44 mg, 0.0225 mmol, 5 mol %) was dissolved in *t*-BuOH (129 μL) and anhydrous toluene (4.5 mL) and stirred for 20 min at room temperature. And then, poly(methyl hydorsiloxane) (3.3 mL, 1.35 mmol, 3.0 equiv) was added. After 15 min, **17** (190 mg, 0.45 mmol, 1.0 equiv) was added and stirred for 4 h at room temperature. After the reaction was completed, 1 N KOH (aq.), EtOAc, and 1 N HCl were added in sequence. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by flash column chromatography (*n*-hexane/EtOAc = 3:1, v/v) to afford product **18** (149 mg, 0.351 mmol, 78%) as a colorless oil. *trans/cis* = 2:1, ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (m, 8H), 7.41 (m, 12H), 4.77 (ddt, *J* = 11.5, 9.0, 5.8 Hz, 1H, *cis*), 4.25 (dddd, *J* = 3.0 Hz, 1H, *cis*), 4.08 (ddt, *J* = 8.3, 8.3, 5.5 Hz, 1H, *trans*), 3.98 (ddt, *J* = 12.0, 9.0, 3.0 Hz, 1H, *trans*), 2.64 (m, 6H), 2.46 (dd, *J* = 17.3, 7.8 Hz, 1H, *trans*), 2.41 (dd, *J* = 17.0, 4.0 Hz, 1H, *trans*), 2.15 (s, 3H, *cis*), 2.10 (s, 3H, *trans*), 2.01 (ddd, *J* = 13.5, 3.5, 3.5 Hz, *trans*), 1.89 (m, 2H), 1.75 (m, 3H), 1.62 (m, 1H), 1.48 (ddd, *J* = 13.5, 11.3, 2.5 Hz, 1H, *cis*), 1.04 (s, 9H), 1.03 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.9, 207.8, 170.6, 170.2, 135.8, 135.7, 133.5, 133.3, 133.2, 133.1, 130.2, 130.15, 128.03, 128.00, 127.97, 75.8, 75.3, 65.3, 64.5, 39.8, 39.0, 38.9, 38.57, 38.55, 30.2, 29.4, 29.3, 27.0, 26.9; HRMS (ESI) for $C_{25}H_{32}O_4NaSi$ $[M + Na]^+$ calcd 447.1968, found 445.1966.

*(R,Z)-3-((tert-Butyldiphenylsilyl)oxy)-8-oxonon-5-enoic Acid (**18-1**).* To a solution of **17** (338 mg, 0.799 mmol, 1.0 equiv) in EtOH (8 mL), 10% palladium on carbon (26 mg, 0.3 equiv) was stirred under H_2 at room temperature for 22 h. After this, the catalyst was removed by filtration through a pad of Celite, and the filtrate was washed with DCM. The crude was evaporated *in vacuo* and purified by flash column chromatography (*n*-hexane/EtOAc = 1:10, v/v) to afford product **18-1** (61.2 mg, 0.144 mmol, 18%) as a pale-yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.43−7.32 (m, 6H), 5.51−5.43 (m, 1H), 5.34 (m, 1H), 4.18−4.13 (m, 1H), 3.02 (d, *J* = 7.0 Hz, 2H), 2.47 (d, *J* = 6.0 Hz, 2H), 2.25−2.16 (m, 2H), 2.08 (s, 3H), 1.02 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.2, 176.9, 136.0, 135.9, 133.8, 133.5, 129.9, 129.8, 127.8, 127.6, 125.7, 70.0, 69.9, 47.6, 41.3, 40.3, 29.5, 27.0, 19.3; HRMS (ESI) for $C_{25}H_{32}NaO_4Si$ $[M + Na]^+$ calcd 447.1968, found 447.1962.

*(4R,6S)-4-((tert-Butyldiphenylsilyl)oxy)-6-(3-hydroxy-3-methylhex-5-en-1-yl)tetrahydro-2H-pyran-2-one (**19**).* Compound **19** (34 mg, 0.073 mmol, 97%) was obtained as a colorless oil from **18** (32 mg, 0.075 mmol, 1.0 equiv) by the same procedure as **14**. *cis/trans* = 2:1, ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (m, 8H), 7.45−7.36 (m, 12H), 5.81 (m, 2H), 5.11 (m, 4H), 4.76 (m, 1H, *cis*), 4.26 (m, 1H, *cis*), 4.08 (ddt, *J* = 10.0, 8.3, 6.0 Hz, 1H, *trans*), 3.95 (m, 1H, *trans*), 2.66 (dd, *J* = 17.0, 6.0 Hz, 1H, *trans*), 2.57 (d, *J* = 17.5 Hz, 1H, *cis*), 2.47 (dd, *J* = 17.3, 7.8 Hz, 1H, *trans*), 2.42 (dd, *J* = 17.0, 4.0 Hz, 1H, *cis*), 2.20 (m, 4H), 1.99 (m, 1H), 1.81−1.60 (m, 7H), 1.52−1.36 (m, 4H), 1.15 (s, 3H, *cis*), 1.13 (m, 4H, *trans*), 1.044 (s, 9H), 1.035 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.85, 170.82, 170.5, 170.4, 135.8, 135.7, 133.8, 133.7, 133.65, 133.56, 133.55, 133.4, 133.3, 133.1, 130.22, 130.20, 130.1, 128.03, 128.01, 127.95, 119.3, 119.2, 77.3, 76.6, 76.5, 71.80, 71.77, 71.75, 71.7, 65.43, 65.41, 64.6, 46.97, 46.95, 46.5, 46.4, 39.9, 39.1, 38.5, 38.4, 36.9, 36.84, 36.78, 36.7, 36.3, 36.1, 30.1, 30.03, 29.96, 29.9, 27.0, 26.9; HRMS (ESI) for $C_{28}H_{38}O_4NaSi$ $[M + Na]^+$ calcd 489.2437, found 489.2429.

*(4R,6S)-4-((tert-Butyldiphenylsilyl)oxy)-6-((E)-3-methylhexa-3,5-dien-1-yl)tetrahydro-2H-pyran-2-one (**19-1**).* Compound **19-1** (21 mg, 0.047 mmol, 87%) was obtained as a colorless oil from **19** (25 mg, 0.054 mmol, 1.0 equiv) by the same procedure as **14-1**. *E/Z* = 1:1, inseparable. ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 8H), 7.45−7.36 (m, 12H), 6.51 (ddd, *J* = 13.5, 10.0 Hz, 1H, E), 5.81 (dd, *J* = 10.8 Hz, 1H, E), 5.71 (m, 1H, Z), 5.13−4.93 (m, 4H), 4.72 (d, *J* = 24.0 Hz, 1H, Z), 4.08 (m, 2H), 3.92 (m, 1H), 2.69 (m, 3H), 2.48 (m, 2H), 2.38 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.97 (m, 3H), 1.79 (m, 1H), 1.64 (m, 10H), 1.04 (s, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.83, 170.78, 146.8, 136.6, 135.8, 133.63, 133.60, 133.3, 133.2, 130.22, 130.20, 130.13, 130.11, 128.1, 128.0, 127.96, 127.9, 127.4, 126.3, 119.3, 118.8, 116.6, 116.2, 115.7, 115.54, 115.48, 110.9, 76.5, 76.4, 65.5, 65.4, 39.98, 39.96, 38.3, 37.8, 34.0, 33.8, 27.0, 26.9, 23.7, 23.6, 19.2, 19.1, 16.7, 16.5; HRMS (ESI) for $C_{28}H_{36}O_3NaSi$ $[M + Na]^+$ calcd 471.2331, found 471.2328.

*(4R,6S)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one ((−)-Ieodomycin, **20**).* Compound (−)-ieodomycin, **20** (21.1 mg, 0.100 mmol, 93%) was obtained as a colorless oil from **19-1** (48 mg, 0.107 mmol, 1.0 equiv) by the same procedure as **15**. *E/Z* = 1:1, inseparable. ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (ddd, *J* = 15.0, 10.5, 10.5 Hz, 1H), 5.89 (d, *J* = 10.5 Hz, 1H), 5.07 (dd, *J* = 17.0, 7.5 Hz, 1H), 4.97 (dd, *J* = 10.0 Hz, 1H), 4.26 (m, 1H), 4.20 (m, 1H), 2.86 (dd, *J* = 17.0 Hz, 1H), 2.39 (dd, *J* = 7.0 Hz, 1H), 2.36 (m, 1H), 2.28 (m, 1H), 2.26 (m, 1H), 2.19 (m, 1H), 1.78 (m, 2H), 1.77 (s, 3H); HRMS (ESI) for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ calcd 233.1154, found 233.1152.[2m]

2nd Generation Synthesis of (+)-Ieodomycin B. *(R,E)-8-Iodo-7-methylocta-1,7-dien-4-ol (**24a**).* To a flame-dried round-bottomed flask was added zirconocene dichloride (21.4 g, 148.5 mmol, 2.5 equiv) and CH_2Cl_2 (373 mL), followed by the dropwise addition of $AlMe_3$ (25% w/w in hexane, 130 mL, 297.0 mmol, 5.0 equiv) at 0 °C, while stirring at 0 °C, and homoallylic alcohol **23a** (7.38 g, 59.4 mmol, 98% *ee*) in DCM (25 mL) was added. The mixture was warmed to room temperature and stirred for 23 h at which point carboalumination was complete, as determined by TLC. The mixture was then cooled to −50 °C, a solution of iodine (37.7 g, 297.0 mmol, 5.0 equiv) dissolved in THF (300 mL) was added dropwise, and the reaction mixture was stirred at 0 °C. After 2 h, the reaction mixture was quenched with sat. aq. K_2CO_3 and filtered through a pad of Celite with Et_2O. The aqueous layer was extracted with Et_2O, and then, the combined organic phase was washed with Na_2SO_3 (sat. aq.), brine, and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 10:1, v/v) on silica to afford the product **24a** as a pale-yellow oil (9.3 g, 34.9 mmol, 59% yield over 3 steps). $[\alpha]_D^{25}$ = +11.33 ($CHCl_3$, *c* = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.93 (q, *J* = 1.2 Hz, 1H), 5.81 (dddd, *J* = 16.8, 10.8, 8.0, 6.5 Hz, 1H), 5.16 (s, 1H), 5.15−5.12 (m, 1H), 3.62 (tt, *J* = 8.2, 4.3 Hz, 1H), 2.38 (dddd, *J* = 15.2, 9.8, 5.6, 1.3 Hz, 1H), 2.34−2.26 (m, 2H), 2.15 (dtt, *J* = 13.9, 7.9, 1.1 Hz, 1H),

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1.84 (d, J = 1.1 Hz, 3H), 1.66−1.53 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.80, 134.52, 118.68, 75.07, 69.94, 42.18, 35.87, 34.79, 24.06; HRMS (ESI): m/z calcd for $C_9H_{15}OINa$ $[M + Na]^+$ 289.0065, found 289.0062.

*(S,E)-8-Iodo-7-methylocta-1,7-dien-4-ol (**24b**).* Compound **24b** (11.7 g, 44.1 mmol, 74% yield, over 3 steps) was obtained as a colorless oil from **23b** (7.38 g, 59.4 mmol, 93% *ee*) by the same procedure as **24a**. $[\alpha]_D^{25}$ = −11.33 ($CHCl_3$, c = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.93 (q, J = 1.2 Hz, 1H), 5.81 (dddd, J = 16.8, 10.8, 8.0, 6.5 Hz, 1H), 5.16 (s, 1H), 5.13 (dq, J = 9.1, 1.4 Hz, 1H), 3.62 (tq, J = 7.7, 3.8 Hz, 1H), 2.38 (dddd, J = 15.1, 9.7, 5.5, 1.3 Hz, 1H), 2.33−2.26 (m, 2H), 2.19−2.12 (m, 1H), 1.84 (d, J = 1.1 Hz, 3H), 1.66−1.53 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.81, 134.52, 118.68, 75.07, 69.95, 42.18, 35.87, 34.80, 24.06; HRMS (ESI): m/z calcd for $C_9H_{15}OINa$ $[M + Na]^+$ 289.0065, found 289.0055.

*(2S,4R,E)-8-Iodo-7-methyloct-7-ene-1,2,4-triol (**25a**).* To a solution of $(DHQ)_2PYR$ (8.3 mg, 0.0094 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (930.4 mg, 2.83 mmol, 3.0 equiv), K_2CO_3 (390.6 mg, 2.83 mmol, 3.0 equiv), $K_2OsO_4{\cdot}2H_2O$ (1.7 mg, 4.7 μmol, 0.5 mol %) in *t*-BuOH (19 mL), and H_2O (19 mL) (*t*-BuOH/H_2O = 1:1, v/v) was added **24a** (250.6 mg, 0.94 mmol, 1.0 equiv) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 72 h, at which point hydroxylation was complete, as determined by TLC. Na_2SO_3 was added to the mixture, which was allowed to warm to room temperature. After stirring for 1 h, CH_2Cl_2 was added to the reaction mixture. The organic phase was washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Purification by flash chromatography (CH_2Cl_2/MeOH/acetone = 20:1:1, v/v) provided the product **25a** (146.2 mg, 0.49 mmol, 52%) as a colorless oil and **25b** (56.8 mg, 0.19 mmol, 20%). $[\alpha]_D^{25}$ = +2.00 ($CHCl_3$, c = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.94 (q, J = 1.1 Hz, 1H), 4.03 (ddt, J = 8.6, 7.0, 3.4 Hz, 1H), 3.90 (tdd, J = 8.2, 4.4, 2.8 Hz, 1H), 3.66 (dd, J = 11.0, 3.4 Hz, 1H), 3.54 (dd, J = 11.0, 7.3 Hz, 1H), 2.38 (dddd, J = 15.3, 9.7, 5.5, 1.2 Hz, 1H), 2.29 (dddd, J = 14.2, 9.5, 6.3, 1.1 Hz, 1H), 2.15 (s, 3H), 1.85 (d, J = 0.9 Hz, 3H), 1.71−1.65 (m, 2H), 1.65−1.59 (m, 1H), 1.56 (ddd, J = 14.5, 8.5, 3.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.64, 75.31, 69.53, 68.15, 67.01, 39.41, 35.92, 35.64, 24.12; HRMS (ESI): m/z calcd for $C_9H_{17}O_3INa$ $[M + Na]^+$ 323.0120, found 323.0125.

*(2R,4R,E)-8-Iodo-7-methyloct-7-ene-1,2,4-triol (**25b**).* Compound **25a** (302.5 mg, 0.10 mmol, 5%) and **25b** (3.86 g, 12.86 mmol, 71%) were obtained as a colorless oil from **24a** (4.81 g, 18.07 mmol) by the same procedure as **25a** except using $(DHQD)_2PYR$ instead of $(DHQ)_2PYR$. $[\alpha]_D^{25}$ = +8.00 ($CHCl_3$, c = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.94 (q, J = 1.1 Hz, 1H), 3.98 (tt, J = 7.5, 3.6 Hz, 1H), 3.89 (tt, J = 8.0, 4.7 Hz, 1H), 3.68−3.63 (m, 1H), 3.49 (dd, J = 10.3, 7.1 Hz, 1H), 3.26 (s, 1H), 2.90 (s, 1H), 2.39−2.27 (m, 2H), 2.03 (s, 1H), 1.85 (d, J = 1.1 Hz, 3H), 1.64−1.60 (m, 1H), 1.60−1.56 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.64, 75.24, 72.74, 71.53, 66.89, 39.02, 36.07, 35.52, 24.07; HRMS (ESI): m/z calcd for $C_9H_{17}O_3INa$ $[M + Na]^+$ 323.0120, found 323.0127.

*(2S,4S,E)-8-Iodo-7-methyloct-7-ene-1,2,4-triol (**25c**).* Compound **25c** (4.34 g, 14.5 mmol, 65%) and **25d** (505.3 mg, 1.68 mmol, 8%) were obtained as a colorless oil from **24b** (5.91 g, 22.2 mmol) by the same procedure as **25a**. $[\alpha]_D^{25}$ = −6.00 ($CHCl_3$, c = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.94 (s, 1H), 3.96 (tt, J = 7.6, 3.7 Hz, 1H), 3.87 (tt, J = 8.0, 4.5 Hz, 1H), 3.64 (dd, J = 11.1, 3.3 Hz, 1H), 3.47 (dd, J = 11.1, 6.6 Hz, 1H), 2.91 (s, 3H), 2.39−2.25 (m, 2H), 1.84 (s, 3H), 1.65−1.54 (m, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.64, 75.24, 72.74, 71.53, 66.89, 39.02, 36.07, 35.52, 24.07; HRMS (ESI): m/z calcd for $C_9H_{17}O_3INa$ $[M + Na]^+$ 323.0120, found 323.0129.

*(2R,4S,E)-8-Iodo-7-methyloct-7-ene-1,2,4-triol (**25d**).* Compound **25c** (33.0 mg, 0.11 mmol, 13%) and **25d** (163.6 mg, 0.55 mmol, 66%) were obtained as a colorless oil from **24b** (219.8 mg, 0.83 mmol) by the same procedure as **25a** except using $(DHQD)_2PYR$ instead of $(DHQ)_2PYR$. $[\alpha]_D^{25}$ = −2.00 ($CHCl_3$, c = 0.5); ^1H NMR (600 MHz, $CDCl_3$) δ 5.94 (q, J = 1.2 Hz, 1H), 4.03 (tt, J = 7.2, 3.2 Hz, 1H), 3.95−3.87 (m, 1H), 3.66 (dd, J = 11.1, 3.3 Hz, 1H), 3.54 (dd, J = 11.0, 7.2 Hz, 1H), 2.38 (ddd, J = 14.7, 9.8, 5.6 Hz, 1H), 2.29 (ddd, J = 14.6, 9.5 Hz, 6.3 Hz, 1H), 2.22 (s, 3H), 1.85 (d, J = 0.8 Hz, 3H), 1.71−1.64 (m, 2H), 1.64−1.59 (m, 1H), 1.56 (ddd, J = 14.4, 8.6, 3.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.67, 75.26, 69.65, 68.55, 66.99, 39.15, 35.97, 35.56, 24.07; HRMS (ESI): m/z calcd for $C_9H_{17}O_3INa$ $[M + Na]^+$ 323.0120, found 323.0129.

*(2S,4R,E)-2,4-Dihydroxy-8-iodo-7-methyloct-7-en-1-yl 2,4,6-triisopropylbenzenesulfonate (**26a**).* To a flame-dried round-bottom flask was added DMAP (190.6 mg, 1.56 mmol, 0.2 equiv), Et_3N (1.18 g, 11.7 mmol, 1.5 equiv), and **25a** (2.34 g, 7.80 mmol, 1.0 equiv) in CH_2Cl_2 (21 mL). The mixture was subsequently cooled to −78 °C and a solution of 2,4,6-triisopropylsulfonyl chloride (9.45 g, 31.2 mmol, 4.0 equiv) dissolved in CH_2Cl_2 (10 mL) was added dropwise. The reaction was slowly warmed to −20 °C, at which temperature it was stirred over the next 22 h. The reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with CH_2Cl_2, and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 2:1, v/v) on silica to afford the product **26a** (4.32 g, 7.63 mmol, 98%) as a white solid. $[\alpha]_D^{25}$ = +4.00 ($CHCl_3$, c = 0.5); mp: 104−106 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 2H), 5.93 (q, J = 1.2 Hz, 1H), 4.22 (ddt, J = 8.8, 7.1, 3.6 Hz, 1H), 4.11 (quin, J = 6.8 Hz, 2H), 4.07 (dd, J = 10.3, 3.9 Hz, 1H), 3.99 (dd, J = 10.3, 7.1 Hz, 1H), 3.90 (tdd, J = 8.5, 4.5, 2.7 Hz, 1H), 2.91 (quin, J = 6.9 Hz, 1H), 2.39−2.24 (m, 4H), 1.83 (d, J = 1.1 Hz, 3H), 1.69−1.55 (m, 4H), 1.26 (d, J = 6.8 Hz, 12H), 1.26 (d, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.18, 151.00, 147.59, 129.07, 124.03, 75.28, 72.87, 68.25, 67.26, 38.86, 35.90, 35.57, 34.41, 29.82, 24.90, 24.87, 24.03, 23.67; HRMS (ESI): m/z calcd for $C_{24}H_{39}O_5ISNa$ $[M + Na]^+$ 589.1461, found 589.1469.

*(2R,4R,E)-2,4-Dihydroxy-8-iodo-7-methyloct-7-en-1-yl 2,4,6-triisopropylbenzenesulfonate (**26b**).* Compound **26b** (498.2 mg, 0.88 mmol, 88%) was obtained as a white solid from **25b** (299.9 mg, 1.0 mmol) by the same procedure as **26a**. $[\alpha]_D^{25}$ = +0.67 ($CHCl_3$, c = 0.5); mp: 104−106 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 2H), 5.93 (s, 1H), 4.17 (ddq, J = 9.9, 6.8, 4.1, 3.5 Hz, 1H), 4.11 (quin, J = 6.7 Hz, 2H), 4.00 (dt, J = 10.7, 5.4 Hz, 2H), 3.87 (dddd, J = 9.7, 7.3, 4.9, 2.3 Hz, 1H), 2.92 (hept, J = 6.9 Hz, 1H), 2.37−2.25 (m, 2H), 2.19 (s, 2H), 1.84 (s, 3H), 1.68−1.52 (m, 4H), 1.26 (dd, J = 6.8, 2.4 Hz, 18H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.21, 151.02, 147.56, 129.05, 124.04, 75.28, 72.59, 71.37, 70.57, 38.85, 35.93, 35.44, 34.42, 29.84, 24.90, 24.88, 24.05, 23.69; HRMS (ESI): m/z calcd for $C_{24}H_{39}O_5ISNa$ $[M + Na]^+$ 589.1461, found 589.1469.

*(2S,4S,E)-2,4-Dihydroxy-8-iodo-7-methyloct-7-en-1-yl 2,4,6-triisopropylbenzenesulfonate (**26c**).* Compound **26c**

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(392.2 mg, 0.69 mmol, 85%) was obtained as a white solid from **25c** (243.7 mg, 0.81 mmol) by the same procedure as **26a**. $[\alpha]_D^{25}$ = −3.00 ($CHCl_3$, *c* = 0.5); mp: 104−106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.19 (s, 2H), 5.92 (s, 1H), 4.17 (ddt, *J* = 9.9, 6.8, 3.4 Hz, 1H), 4.11 (quin, *J* = 6.7 Hz, 2H), 4.01−3.96 (m, 2H), 3.87 (dddd, *J* = 9.9, 7.4, 4.9, 2.2 Hz, 1H), 3.25 (s, 2H), 2.91 (quin, *J* = 6.9 Hz, 1H), 2.30 (dddd, *J* = 33.7, 14.5, 9.0, 6.2 Hz, 2H), 1.83 (s, 3H), 1.60 (dddd, *J* = 33.4, 14.4, 10.8, 3.6 Hz, 4H), 1.26 (d, *J* = 6.8 Hz, 18H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) *δ* 154.21, 151.01, 147.52, 129.02, 124.04, 75.29, 72.57, 71.41, 70.55, 38.77, 35.88, 35.40, 34.41, 29.83, 24.90, 24.87, 24.04, 23.68; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{39}O_5ISNa$ [M + Na]$^+$ 589.1461, found 589.1459.

*(2R,4S,E)-2,4-Dihydroxy-8-iodo-7-methyloct-7-en-1-yl 2,4,6-triisopropylbenzenesulfonate (**26d**).* Compound **26d** (5.04 g, 8.90 mmol, 77%) was obtained as a white solid from **25d** (3.49 g, 11.6 mmol) by the same procedure as **26a**. $[\alpha]_D^{25}$ = −2.00 ($CHCl_3$, *c* = 0.5); mp: 104−106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.20 (s, 2H), 5.93 (q, *J* = 1.2 Hz, 1H), 4.22 (ddt, *J* = 8.7, 7.1, 3.6 Hz, 1H), 4.12 (quin, *J* = 6.8 Hz, 2H), 4.08 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.00 (dd, *J* = 10.3, 7.0 Hz, 1H), 3.91 (tt, *J* = 7.9, 2.8 Hz, 1H), 2.92 (hept, *J* = 6.8 Hz, 1H), 2.36 (dddd, *J* = 15.2, 9.7, 5.8, 1.2 Hz, 1H), 2.27 (dddd, *J* = 14.1, 9.4, 6.5, 1.2 Hz, 1H), 1.84 (d, *J* = 0.9 Hz, 3H), 1.71−1.54 (m, 6H), 1.27 (d, *J* = 6.8, 2.0 Hz, 12H), 1.26 (d, *J* = 6.9, 2.0 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) *δ* 154.18, 150.99, 147.58, 129.06, 124.03, 75.28, 72.88, 68.23, 67.24, 38.86, 35.89, 35.57, 34.41, 29.82, 24.90, 24.87, 24.03, 23.68; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{39}O_5ISNa$ [M + Na]$^+$ 589.1461, found 589.1464.

*((4S,6R)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl 2,4,6-triisopropylbenzenesulfonate (**26a-1**).* To a stirred solution of sulfonate **26a** (139.0 mg, 0.25 mmol, 1.0 equiv) in acetone (1 mL) was added 2,2-dimethoxypropane (260.4 mg, 2.5 mmol, 10 equiv) and *p*-toluenesulfonic acid (9.5 mg, 0.05 mmol, 0.2 equiv) at room temperature. The resulting colorless solution was stirred at room temperature for 3 h. The reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with CH_2Cl_2 and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 20:1, v/v) on silica to afford **26a-1** (147.0 mg, 0.24 mmol, 97%) as a white solid. $[\alpha]_D^{25}$ = +0.55 (MeOH, *c* = 1.0); mp: 55−57 °C; ^{1}H NMR (600 MHz, CD_3OD) *δ* 7.29 (s, 2H), 5.95 (q, *J* = 1.2 Hz, 1H), 4.15 (hept, *J* = 6.8 Hz, 2H), 4.10−4.05 (m, 2H), 3.98 (dd, *J* = 11.1, 7.5 Hz, 1H), 3.70 (ddt, *J* = 9.6, 7.8, 5.4 Hz, 1H), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.33−2.23 (m, 2H), 1.81 (d, *J* = 0.9 Hz, 3H), 1.63 (ddd, *J* = 13.1, 9.4, 5.9 Hz, 1H), 1.60−1.51 (m, 3H), 1.26 (d, *J* = 6.9 Hz, 18H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) *δ* 155.40, 152.04, 148.63, 131.00, 125.00, 101.80, 75.37, 72.22, 66.79, 66.19, 36.26, 35.51, 34.74, 34.58, 30.80, 25.08, 25.02, 24.96, 23.95, 23.75; HRMS (ESI): *m*/*z* calculated for $C_{27}H_{43}O_5ISNa$ [M + Na]$^+$ 629.1774, found 629.1767.

*((4R,6R)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl 2,4,6-triisopropylbenzenesulfonate (**26b-1**).* Compound **26b-1** (4.673 g, 7.704 mmol, 98%) was obtained as a white solid from **26b** (4.444 g, 7.849 mmol) by the same procedure as **26a-1**. $[\alpha]_D^{25}$ = +2.00 (MeOH, *c* = 0.5); mp: 55−57 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.18 (s, 2H), 5.87 (q, *J* = 1.2 Hz, 1H), 4.16−4.10 (m, 3H), 3.98 (d, *J* = 5.2 Hz, 2H), 3.75 (dddd, *J* = 11.7, 7.9, 4.4, 2.5 Hz, 1H), 2.91 (hept, *J* = 6.9 Hz, 1H), 2.26 (dd, *J* = 8.1, 6.9 Hz, 2H), 1.82 (d, *J* = 1.1 Hz, 3H), 1.62−1.55 (m, 1H), 1.55−1.51 (m, 1H), 1.49 (dt, *J* = 12.7, 2.7 Hz, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 12H), 1.25 (d, *J* = 7.2 Hz, 6H), 1.22−1.16 (q, *J* = 12.0 Hz 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) *δ* 153.83, 150.91, 147.38, 129.59, 123.88, 98.98, 75.14, 71.55, 67.38, 67.19, 34.96, 34.39, 34.16, 33.02, 29.94, 29.75, 24.90, 24.86, 23.91, 23.69, 19.71; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{43}O_5ISNa$ [M + Na]$^+$ 629.1774, found 629.1777.

*((4S,6S)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl 2,4,6-triisopropylbenzenesulfonate (**26c-1**).* Compound **26c-1** (1.054 g, 1.74 mmol, 94%) was obtained as a white solid from **26c** (1.046 g, 1.85 mmol) by the same procedure as **26a-1**. $[\alpha]_D^{25}$ = −5.44 (MeOH, *c* = 0.5); mp: 55−57 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.18 (s, 2H), 5.87 (t, *J* = 1.2 Hz, 1H), 4.13 (quin, *J* = 6.5 Hz, 3H), 3.98 (d, *J* = 5.2 Hz, 2H), 3.78−3.72 (m, 1H), 2.91 (q, *J* = 6.9 Hz, 1H), 2.26 (t, *J* = 7.7 Hz, 2H), 1.82 (s, 3H), 1.62−1.56 (m, 1H), 1.55−1.51 (m, 1H), 1.51−1.47 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.26 (dd, *J* = 6.9, 3.8 Hz, 18H), 1.19 (q, *J* = 11.9 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) *δ* 153.86, 150.94, 147.41, 129.57, 123.91, 99.00, 75.17, 71.57, 67.39, 67.20, 34.98, 34.41, 34.17, 33.04, 29.96, 29.77, 24.92, 24.88, 23.93, 23.71, 19.73; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{43}O_5ISNa$ [M + Na]$^+$ 629.1774, found 629.1776.

*((4R,6S)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl 2,4,6-triisopropylbenzenesulfonate (**26d-1**).* Compound **26d-1** (195.8 mg, 0.32 mmol, 98%) was obtained as a white solid from **26d** (188.9 mg, 0.33 mmol) by the same procedure as **26a-1**. $[\alpha]_D^{25}$ = −0.87 (MeOH, *c* = 1.0); mp: 55−57 °C; ^{1}H NMR (600 MHz, CD_3OD) *δ* 7.28 (s, 2H), 5.94 (q, *J* = 1.3 Hz, 1H), 4.14 (hept, *J* = 6.7 Hz, 2H), 4.09−4.03 (m, 2H), 3.97 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.72−3.66 (m, 1H), 2.94 (hept, *J* = 6.9 Hz, 1H), 2.27 (hept, *J* = 7.4 Hz, 2H), 1.80 (s, 3H), 1.62 (ddd, *J* = 13.0, 9.4, 5.9 Hz, 1H), 1.59−1.49 (m, 3H), 1.25 (d, *J* = 6.7 Hz, 18H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) *δ* 155.41, 152.05, 148.64, 131.01, 125.00, 101.80, 75.35, 72.23, 66.80, 66.20, 36.26, 35.52, 34.74, 34.59, 30.81, 25.07, 25.02, 24.96, 23.94, 23.73; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{43}O_5ISNa$ [M + Na]$^+$ 629.1774, found 629.1769.

*2-((4R,6R)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetonitrile (**27a**).* To a solution of acetonide **26a-1** (30.8 mg, 0.05 mmol, 1.0 equiv) in DMSO (1 mL) was added NaCN (9.8 mg, 0.2 mmol, 4.0 equiv). The reaction mixture was stirred at 70 °C for 6 h. The reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc, and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 20:1, v/v) on silica to afford product **27a** (15.3 mg, 0.044 mmol, 88%) as a colorless oil. $[\alpha]_D^{25}$ = −3.33 (MeOH, *c* = 0.5); ^{1}H NMR (600 MHz, CD_3OD) *δ* 5.98 (q, *J* = 1.2 Hz, 1H), 4.08 (dtd, *J* = 8.6, 6.9, 4.5 Hz, 1H), 3.79 (tdd, *J* = 8.3, 6.9, 4.9 Hz, 1H), 2.67 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.59 (dd, *J* = 16.8, 7.1 Hz, 1H), 2.32 (hept, *J* = 7.3 Hz, 2H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.71 (ddd, *J* = 8.6, 6.7 Hz, *J* = 3.0 Hz, 2H), 1.62 (tdd, *J* = 8.0, 5.5 Hz, *J* = 3.6 Hz, 2H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) *δ* 148.66, 118.84, 102.06, 75.36, 66.86, 64.33, 38.22, 36.28, 34.64, 25.18, 24.92, 24.52, 23.75; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}NO_2INa$ [M + Na]$^+$ 372.0436, found 372.0437.

*2-((4S,6R)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetonitrile (**27b**).* Compound **27b** (2.314 g, 7.488 mmol, 97%) was obtained as a colorless oil

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from **26b-1** (4.673 g, 7.704 mmol) by the same procedure as **27a**. $[\alpha]_D^{25}$ = +18.67 (MeOH, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 2.0, 1.1 Hz, 1H), 4.14−4.08 (m, 1H), 3.81−3.75 (m, 1H), 2.54 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.47 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.83 (s, 3H), 1.66−1.60 (m, 2H), 1.59−1.55 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.28 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.32, 116.98, 99.45, 75.26, 67.44, 65.33, 36.05, 34.97, 33.99, 29.99, 25.15, 23.92, 19.84; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}NO_2INa$ $[M + Na]^+$ 372.0436, found 372.0438.

*2-((4R,6S)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetonitrile (**27c**).* Compound **27c** (589.2 mg, 1.69 mmol, 93%) was obtained as a colorless oil from **26c-1** (1.11 g, 1.82 mmol) by the same procedure as **27a**. $[\alpha]_D^{25}$ = −22.00 (MeOH, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (q, *J* = 1.1 Hz, 1H), 4.11 (dtd, *J* = 11.8, 6.1, 2.6 Hz, 1H), 3.80−3.75 (m, 1H), 2.53 (dd, *J* = 16.6, 5.9 Hz, 1H), 2.47 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.83 (s, 3H), 1.65−1.60 (m, 2H), 1.56 (ddt, *J* = 13.8, 8.1, 4.3 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.31−1.24 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.30, 116.97, 99.42, 75.25, 67.42, 65.30, 36.03, 34.95, 33.97, 29.97, 25.13, 23.91, 19.83; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}NO_2INa$ $[M + Na]^+$ 372.0436, found 372.0440.

*2-((4S,6S)-6-((E)-4-Iodo-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetonitrile (**27d**).* Compound **27d** (19.5 mg, 0.056 mmol, 90%) was obtained as a colorless oil from **26d-1** (37.5 mg, 0.062 mmol) by the same procedure as **27a**. $[\alpha]_D^{25}$ = +2.00 (MeOH, *c* = 0.5); ^{1}H NMR (600 MHz, CD_3OD) δ 5.98 (q, *J* = 1.2 Hz, 1H), 4.11−4.05 (m, 1H), 3.82−3.76 (m, 1H), 2.67 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.59 (dd, *J* = 16.8, 7.1 Hz, 1H), 2.37−2.27 (m, 2H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.74−1.69 (m, 2H), 1.62 (tdd, *J* = 7.9, 5.5 Hz, 3.4 Hz, 2H), 1.35 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD) δ 148.64, 118.82, 102.04, 75.40, 66.84, 64.30, 38.21, 36.28, 34.63, 25.18, 24.93, 24.52, 23.77; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}NO_2INa$ $[M + Na]^+$ 372.0436, found 372.0434.

*(3R,5R,E)-3,5-Dihydroxy-9-iodo-8-methylnon-8-enenitrile (**27a-1**).* To a stirred solution of **27a** (69.0 mg, 0.20 mmol, 1.0 equiv) in THF (2.0 mL) was added 1 N HCl (1.6 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with $NaHCO_3$ to adjust pH to 7. The aqueous layer was extracted with CH_2Cl_2, and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1.5:1, v/v) on silica to afford the product **27a-1** (58.0 mg, 0.19 mmol, 95%) as a colorless oil. $[\alpha]_D^{25}$ = −4.00 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96 (q, *J* = 1.2 Hz, 1H), 4.28 (dtd, *J* = 8.9, 5.9, 2.9 Hz, 1H), 3.94 (tdd, *J* = 8.2, 4.4, 2.9 Hz, 1H), 2.69−2.52 (m, 2H), 2.60 (s, 2H), 2.36 (ddd, *J* = 14.7, 9.3, 5.8 Hz, 1H), 2.29 (ddd, *J* = 14.7, 8.7, 6.7 Hz, 1H), 1.85 (d, *J* = 0.9 Hz, 3H), 1.81−1.76 (m, 1H), 1.72−1.60 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.35, 117.82, 75.53, 68.49, 65.28, 41.91, 35.86, 35.27, 26.34, 24.01; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}NO_2INa$ $[M + Na]^+$ 332.0123, found 332.0121.

*(3S,5R,E)-3,5-Dihydroxy-9-iodo-8-methylnon-8-enenitrile (**27b-1**).* Compound **27b-1** (2.03 g, 6.566 mmol, 99%) was obtained as a colorless oil from **27b** (2.314 g, 6.627 mmol) by the same procedure as **27a-1**. $[\alpha]_D^{25}$ = +6.00 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.19 (dtd, *J* = 8.7, 5.8, 2.7 Hz, 1H), 3.90 (dtd, *J* = 9.1, 6.2, 2.6 Hz, 1H), 2.85 (s, 2H), 2.55 (d, *J* = 5.8 Hz, 2H), 2.38−2.26 (m, 2H), 1.85 (s, 3H), 1.79−1.68 (m, 2H), 1.68−1.62 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.27, 117.49, 75.57, 72.05, 68.33, 41.76, 36.11, 35.39, 26.40, 24.00; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}NO_2INa$ $[M + Na]^+$ 332.0123, found 332.0123.

*(3R,5S,E)-3,5-Dihydroxy-9-iodo-8-methylnon-8-enenitrile (**27c-1**).* Compound **27c-1** (34.4 mg, 0.45 mmol, 98%) was obtained as a colorless oil from **27c** (39.9 mg, 0.11 mmol) by the same procedure as **27a-1**. $[\alpha]_D^{25}$ = −8.67 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.98 (q, *J* = 1.2 Hz, 1H), 4.19 (dtd, *J* = 9.7, 5.8, 2.6 Hz, 1H), 3.91 (dtd, *J* = 10.0, 6.1, 2.6 Hz, 1H), 2.55 (d, *J* = 5.9 Hz, 2H), 2.32 (tt, *J* = 14.3, 7.4 Hz, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.80−1.74 (m, 1H), 1.74−1.68 (m, 1H), 1.66 (td, *J* = 7.8, 6.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.27, 117.53, 75.55, 71.94, 68.28, 41.74, 36.07, 35.36, 26.40, 24.00; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}NO_2INa$ $[M + Na]^+$ 332.0123, found 332.0126.

*(3S,5S,E)-3,5-Dihydroxy-9-iodo-8-methylnon-8-enenitrile (**27d-1**).* Compound **27d-1** (14.8 mg, 0.048 mmol, 94%) was obtained as a colorless oil from **27d** (17.8 mg, 0.051 mmol) by the same procedure as **27a-1**. $[\alpha]_D^{25}$ = +2.67 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.98 (q, *J* = 1.1 Hz, 1H), 4.29 (dtd, *J* = 8.9, 6.0, 3.0 Hz, 1H), 3.97 (tdd, *J* = 8.1, 4.4, 3.0 Hz, 1H), 2.59 (dd, *J* = 6.0, 2.7 Hz, 2H), 2.37 (dddd, *J* = 14.1, 9.5, 5.9, 1.2 Hz, 1H), 2.30 (dddd, *J* = 14.1, 9.1, 6.5, 1.2 Hz, 1H), 2.04 (s, 2H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.84−1.78 (m, 1H), 1.74−1.62 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.34, 117.75, 75.54, 68.57, 65.34, 41.85, 35.88, 35.26, 26.33, 24.01; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}NO_2INa$ $[M + Na]^+$ 332.0123, found 332.0126.

*(4S,6R)-4-Hydroxy-6-((E)-4-iodo-3-methylbut-3-en-1-yl)-tetrahydro-2H-pyran-2-one (**29a**).* To a solution of **27a-1** (1.13 g, 3.65 mmol, 1.0 equiv) in MeOH (73 mL) was added 7.5 N NaOH (4.87 mL). The reaction mixture was stirred at 55 °C for 38 h. Carboxylic acid was complete as determined by TLC. The reaction was quenched with 1 N HCl to adjust pH to 7, and evaporated *in vacuo*. Crude **28a** was used without further purification. A solution of 2-chloro-1-methylpyridinium iodide (4.66 g, 18.25 mmol, 5.0 equiv) in CH_2Cl_2 (11 mL) was added dropwise to a solution of crude **28a** and Et_3N (1.33 g, 13.14 mmol, 3.6 equiv) in CH_2Cl_2 (80 mL). After the reaction was stirred at room temperature for 13 h. The organic phase was washed with brine and dried over Na_2SO_4. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1:2, v/v) on silica to afford the product **29a** (863.3 mg, 2.78 mmol, 76% yield, over 2 steps) as a white oil. $[\alpha]_D^{23}$ = +37.41 ($CHCl_3$, *c* = 0.9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97 (q, *J* = 1.1 Hz, 1H), 4.26 (ddt, *J* = 9.2, 7.9, 5.7 Hz, 1H), 4.19−4.13 (m, 1H), 2.91 (ddd, *J* = 17.1, 5.9, 1.4 Hz, 1H), 2.50−2.41 (m, 1H), 2.47 (dd, *J* = 17.0, 7.9 Hz, 1H), 2.39−2.33 (m, 1H), 2.24 (dddd, *J* = 13.6, 5.5, 3.0, 1.4 Hz, 1H), 1.90−1.83 (m, 4H), 1.77 (dddd, *J* = 13.8, 9.6, 6.6, 4.2 Hz, 1H), 1.61 (ddd, *J* = 13.7, 11.7, 9.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.32, 146.55, 76.09, 76.00, 63.99, 39.65, 37.95, 34.84, 33.70, 23.98; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{15}O_3INa$ $[M + Na]^+$ 332.9964, found 332.9968.

*(4R,6R)-4-Hydroxy-6-((E)-4-iodo-3-methylbut-3-en-1-yl)-tetrahydro-2H-pyran-2-one (**29b**).* Compound **29b** (54.5 mg, 0.18 mmol, 65% yield, over 2 steps) was obtained as a white oil from **27b-1** (82.6 mg, 0.27 mmol) by the same procedure as **29a**. $[\alpha]_D^{23}$ = +39.63 ($CHCl_3$, *c* = 0.9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97 (q, *J* = 1.2 Hz, 1H), 4.67 (ddt, *J* = 11.6, 7.8, 3.6 Hz, 1H), 4.42−4.38 (m, 1H), 2.73 (dd, *J* = 17.7, 4.9 Hz, 1H),

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2.63 (ddd, J = 17.7, 3.6, 1.8 Hz, 1H), 2.51−2.44 (m, 1H), 2.39−2.32 (m, 1H), 1.95 (dtd, J = 14.3, 3.3, 1.8 Hz, 1H), 1.85 (s, 3H), 1.81 (ddd, J = 9.9, 8.4, 5.1 Hz, 1H), 1.78−1.71 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.19, 146.77, 75.86, 74.89, 62.88, 38.76, 36.09, 34.91, 33.78, 24.05; HRMS (ESI): m/z calcd for $C_{10}H_{15}O_3INa$ $[M + Na]^+$ 332.9964, found 332.9967.

*(4S,6S)-4-Hydroxy-6-((E)-4-iodo-3-methylbut-3-en-1-yl)-tetrahydro-2H-pyran-2-one (**29c**).* Compound **29c** (77.8 mg, 0.25 mmol, 56% yield, over 2 steps) was obtained as a white oil from **27c-1** (138.1 mg, 0.45 mmol) by the same procedure as **29a**. $[\alpha]_D^{23}$ = −40.74 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, $CDCl_3$) δ 5.97 (q, J = 1.2 Hz, 1H), 4.67 (ddt, J = 11.6, 7.8, 3.6 Hz, 1H), 4.39 (dq, J = 7.0, 3.6 Hz, 1H), 2.73 (dd, J = 17.7, 4.9 Hz, 1H), 2.63 (ddd, J = 17.6, 3.5, 1.8 Hz, 1H), 2.50−2.44 (m, 1H), 2.38−2.32 (m, 1H), 1.95 (dtd, J = 14.3, 3.3, 1.8 Hz, 1H), 1.85 (s, 3H), 1.81 (ddd, J = 9.8, 8.4, 5.3 Hz, 1H), 1.78−1.71 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.26, 146.76, 75.86, 74.92, 62.84, 38.75, 36.06, 34.90, 33.77, 24.05; HRMS (ESI): m/z calcd for $C_{10}H_{15}O_3INa$ $[M + Na]^+$ 332.9964, found 332.9970.

*(4R,6S)-4-Hydroxy-6-((E)-4-iodo-3-methylbut-3-en-1-yl)-tetrahydro-2H-pyran-2-one (**29d**).* Compound **29d** (23.8 mg, 0.077 mmol, 84% yield, over 2 steps) was obtained as a white oil from **27d-1** (69.2 mg, 0.22 mmol) by the same procedure as **29a**. $[\alpha]_D^{23}$ = −39.26 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, $CDCl_3$) δ 5.97 (q, J = 1.1 Hz, 1H), 4.27 (ddt, J = 9.2, 7.9, 5.7 Hz, 1H), 4.19−4.13 (m, 1H), 2.92 (ddd, J = 17.2, 5.9, 1.4 Hz, 1H), 2.50−2.42 (m, 2H), 2.36 (dddd, J = 14.3, 9.4, 6.6, 1.1 Hz, 1H), 2.24 (dddd, J = 13.6, 5.4, 3.0, 1.4 Hz, 1H), 1.91−1.82 (m, 4H), 1.80−1.74 (m, 1H), 1.61 (ddd, J = 13.6, 11.7, 9.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.29, 146.55, 76.08, 76.00, 64.00, 39.65, 37.96, 34.85, 33.71, 23.99; HRMS (ESI): m/z calcd for $C_{10}H_{15}O_3INa$ $[M + Na]^+$ 332.9964, found 332.9967.

*(4S,6R)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one ((+)-Ieodomycin B, **2**).* A solution of **29a** (34.9 mg, 0.11 mmol, 1.0 equiv) and tributyl(vinyl)tin (69.8 mg, 0.22 mmol, 2.0 equiv) in NMP (1.1 mL) was treated with DIPEA (71.1 mg, 0.55 mmol, 5.0 equiv) and Pd_2dba_3 (10.1 mg, 0.011 mmol, 10 mol %) at room temperature under N_2. The flask was covered with aluminum foil. The reaction mixture was stirred for 5 h. The reaction was quenched with aq. NH_4Cl. The aqueous layer was extracted with Et_2O. The combined organic phase was washed with 1 N KF solution and brine, and dried over Na_2SO_4. The residue was purified by flash column chromatography (n-hexane/EtOAc = 1:1, v/v) on silica to afford ieodomycin B, **2** (15.6 mg, 0.074 mmol, 67%) as a colorless oil. $[\alpha]_D^{23}$ = +22.22 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, CD_3OD) δ 6.59 (dt, J = 16.8, 10.5 Hz, 1H), 5.89 (dd, J = 10.8, 0.5 Hz, 1H), 5.08 (dd, J = 16.8, 2.1 Hz, 1H), 4.97 (dd, J = 10.2, 2.1 Hz, 1H), 4.26 (dddd, J = 12.1, 7.7, 4.9, 3.1 Hz, 1H), 4.20 (ddt, J = 8.6, 7.2, 5.8 Hz, 1H), 2.86 (ddd, J = 16.9, 5.8, 1.1 Hz, 1H), 2.37 (dd, J = 16.9, 7.1 Hz, 1H), 2.30−2.24 (m, 2H), 2.18 (ddd, J = 14.5, 8.9, 6.6 Hz, 1H), 1.85−1.76 (m, 2H), 1.78 (s, 3H), 1.52 (ddd, J = 13.7, 11.7, 8.5 Hz, 1H); 13C{1H} NMR (151 MHz, CD_3OD) δ 173.93, 138.93, 134.40, 127.50, 115.47, 78.40, 64.26, 40.07, 38.60, 36.01, 34.83, 16.51; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1154, found 233.1161.

*(4R,6R)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one (3-epi-Ieodomycin B, **30b**).* Compound 3-*epi*-ieodomycin B, **30b** (2.3 mg, 0.011 mmol, 64%) was obtained as a colorless oil from **29b** (5.2 mg, 0.017 mmol) by the same procedure as ieodomycin B, **2**. $[\alpha]_D^{23}$ = +24.44 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, CD_3OD) δ 6.59 (dt, J = 16.8, 10.5 Hz, 1H), 5.90 (ddd, J = 10.9, 2.3, 1.1 Hz, 1H), 5.08 (dd, J = 16.8, 2.2 Hz, 1H), 4.97 (dd, J = 10.2, 2.2 Hz, 1H), 4.68 (dddd, J = 11.2, 7.9, 4.8, 3.2 Hz, 1H), 4.28−4.24 (m, 1H), 2.72 (dd, J = 17.7, 4.7 Hz, 1H), 2.54 (ddd, J = 17.7, 3.3, 1.9 Hz, 1H), 2.28 (ddd, J = 14.8, 9.7, 5.5 Hz, 1H), 2.19 (ddd, J = 14.2, 9.2, 6.8 Hz, 1H), 1.96 (dddd, J = 14.3, 4.0, 3.2, 2.0 Hz, 1H), 1.85−1.73 (m, 3H). 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD) δ 173.53, 138.96, 134.41, 127.52, 115.44, 77.28, 63.32, 39.14, 36.36, 35.96, 34.98, 16.54; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1154, found 233.1157.

*(4S,6S)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one (5-epi-Ieodomycin B, **30c**).* Compound 5-*epi*-ieodomycin B, **30c** (25.3 mg, 0.12 mmol, 48%) was obtained as a colorless oil from **29c** (77.8 mg, 0.25 mmol) by the same procedure as ieodomycin B, **2**. $[\alpha]_D^{23}$ = −25.93 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, CD_3OD) δ 6.59 (dt, J = 16.8, 10.4 Hz, 1H), 5.90 (dd, J = 10.9, 1.2 Hz, 1H), 5.08 (dd, J = 16.8, 2.1 Hz, 1H), 4.97 (dd, J = 10.2, 2.1 Hz, 1H), 4.71−4.65 (m, 1H), 4.26 (m, 1H), 2.72 (dd, J = 17.7, 4.7 Hz, 1H), 2.57−2.51 (m, 1H), 2.28 (ddd, J = 14.8, 9.6, 5.6 Hz, 1H), 2.19 (ddd, J = 14.6, 9.2, 6.8 Hz, 1H), 1.96 (dddd, J = 14.3, 4.0, 3.2, 1.9 Hz, 1H), 1.85−1.73 (m, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD) δ 173.54, 138.96, 134.42, 127.52, 115.44, 77.28, 63.32, 39.14, 36.36, 35.96, 34.98, 16.54; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1154, found 233.1156.

*(4R,6S)-4-Hydroxy-6-((E)-3-methylhexa-3,5-dien-1-yl)-tetrahydro-2H-pyran-2-one ((−)-Ieodomycin B, **30d**).* Compound (−)-ieodomycin B, **30d** (16.0 mg, 0.076 mmol, 93%) was obtained as a colorless oil from **29d** (25.4 mg, 0.082 mmol) by the same procedure as ieodomycin B, **2**. $[\alpha]_D^{23}$ = −24.81 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, CD_3OD) δ 6.59 (dt, J = 16.8, 10.5 Hz, 1H), 5.89 (ddt, J = 10.8, 2.4, 1.2 Hz, 1H), 5.08 (dd, J = 16.8, 2.1 Hz, 1H), 4.98 (dd, J = 10.3, 2.1 Hz, 1H), 4.26 (dddd, J = 12.0, 7.7, 4.9, 3.1 Hz, 1H), 4.20 (ddt, J = 8.5, 6.9, 5.8 Hz, 1H), 2.86 (ddd, J = 16.9, 5.8, 1.2 Hz, 1H), 2.37 (dd, J = 16.9, 7.1 Hz, 1H), 2.32−2.23 (m, 2H), 2.18 (ddd, J = 14.4, 9.1, 6.7 Hz, 1H), 1.87−1.72 (m, 2H), 1.78 (s, 3H), 1.52 (ddd, J = 13.6, 11.7, 8.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD) δ 173.93, 138.93, 134.40, 127.50, 115.47, 78.39, 64.26, 40.07, 38.59, 36.00, 34.83, 16.51; HRMS (ESI): m/z calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1154, found 233.1160.

*Methyl (3S,5R,E)-3,5-Dihydroxy-8-methylundeca-8,10-dienoate ((+)-Ieodomycin A, **1**).* To a solution of ieodomycin B, **2** (1.6 mg, 0.008 mmol) in MeOH (0.27 mL) was added K_2CO_3 (2.8 mg, 0.02 mmol, 2.5 equiv). After stirring at room temperature for 3 h, the reaction was diluted with EtOAc. The combined organic phase was washed with NH_4Cl (sat. aq.), brine, and dried over Na_2SO_4. The residue was purified by flash column chromatography (n-hexane/EtOAc = 2:1, v/v) on silica to afford ieodomycin A, **1** (1.8 mg, 0.0074 mmol, 93%) as a colorless oil. $[\alpha]_D^{23}$ = +17.78 ($CHCl_3$, c = 0.9); ^1H NMR (600 MHz, CD_3OD) δ 6.58 (dt, J = 16.8, 10.5 Hz, 1H), 5.88 (d, J = 10.8 Hz, 1H), 5.05 (dd, J = 16.8, 2.2 Hz, 1H), 4.95 (dd, J = 10.2, 2.2 Hz, 1H), 4.26 (tdd, J = 8.5, 4.7, 3.2 Hz, 1H), 3.78 (dddt, J = 9.9, 7.8, 5.2, 2.2 Hz, 1H), 3.68 (s, 3H), 2.50 (dd, J = 15.1, 4.7 Hz, 1H), 2.45 (dd, J = 15.1, 8.3 Hz, 1H), 2.21 (ddd, J = 15.0, 9.4, 6.6 Hz, 1H), 2.11 (ddd, J = 14.3, 9.1,

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6.7 Hz, 1H), 1.77 (s, 3H), 1.57 (m, 3H), 1.51 (ddd, J = 14.2, 9.4, 3.3 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, CD_3OD) δ 173.85, 139.98, 134.58, 126.94, 114.96, 68.72, 66.49, 52.03, 45.25, 43.81, 37.42, 36.89, 16.66; HRMS (ESI): m/z calcd for $C_{13}H_{22}O_4Na$ $[M + Na]^+$ 265.1416, found 256.1414.

Biological Activity Tests. *Antimicrobial Activity.* Minimal inhibitory concentration (MIC) determination was performed following the Clinical and Laboratory Standards Institute (CLSI) guidelines. The strain *Staphylococcus aureus* ATCC 6538p, *Bacillus cereus* ATCC 10876, *Enterococcus faecalis* KCTC 3511, *E. coli* KCTC 2571, *Salmonella typhimurium* ATCC 14028, and *Pseudomonas aeruginosa* KCCM 11321 were tested. The strains were activated by TSB (Tryptic Soy broth) for 24 h at 37 °C and cultured in Tryptic Soy agar (TSA). The inoculum concentration was 5 × 107 CFU/mL and MHB (Muller−Hillton broth) was used. Compounds **1**, **2**, and **30b−30d** were screened at concentrations ranging from 256 to 0.5 μg/mL. MIC values were obtained after incubating for 18 h for Gram-positive bacteria and 16 h for Gram-negative bacteria at 37 °C. All assays were conducted in triplicate.

Cell Lines and Management. The cell lines used in this study including Vero, RAW264.7, H1299, A549, H460, HCT116, CT26, SW620, SKBR3, HCC38, and 1419 were purchased from the Korean Cell Line Bank (Seoul, Korea). Human keratinocyte cell line (HaCaT) was purchased from the American Type Culture Collection (VA). Vero, HaCaT, and RAW264.7 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with a 10% fetal bovine serum (FBS) and 1% streptomycin (100 μg/mL) and penicillin (100 unit/mL) mixture. H1299, A549, H460, HCT116, CT26, SW620, SKBR3, HCC38, and 1419 cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% FBS and 1% streptomycin (100 μg/mL) and penicillin (100 unit/mL) mixture. These cells were maintained in a controlled environment and incubated at 37 °C under a 5% CO_2 humidified atmosphere.

Determination of Antioxidant Activities. DPPH Radical Scavenging Activity. 20 μL of ieodomycin derivatives and 180 μL of 0.15 mM DPPH solution were mixed in a 96-well plate, and then incubated at room temperature (RT) for 30 min. The absorbance at 515 nm was measured using a Synergy HT microplate reader (BioTek, VT).

H_2O_2 Scavenging Activity. 100 μL of 0.1 M phosphate buffer (pH 5.0) and 20 μL of ieodomycin derivatives were mixed in a 96-well plate. Then, 20 μL of H_2O_2 solution was added to the mixture and then incubated at 37 °C for 5 min. After incubation, 30 μL of 1.25 mM ABTS and 30 μL of peroxidase (1 unit/mL) were added to the mixture and then incubated at 37 °C for 10 min. The absorbance at 405 nm was read using a Synergy HT microplate reader.

Antioxidant Activity in H_2O_2-Treated Vero and HaCaT Cells. The cytotoxicity of ieodomycin derivatives was assessed by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide (MTT) and/or lactate dehydrogenase (LDH) assay. Both Vero cells (1 × 105 cells/mL) and HaCaT cells (6 × 104 cells/mL) were plated in 96-well plates and incubated for 16 h. The cells were treated with ieodomycin derivatives for 1 h. For the MTT assay, MTT solution was added to each well for 3 h. After, culture supernatants were removed and dimethyl sulfoxide (DMSO) was added to dissolve the formazan crystals. The absorbance was measured at 490 nm using a Synergy HT microplate reader. LDH assay was performed according to the manufacturer's protocol (Dogen, Seoul, Korea). 96-well plates were centrifuged at 600g for 5 min and 10 μL of each supernatant was transferred to new 96-well plates. Then, 100 μL of the LDH reaction mixture was added to the wells and incubated at RT for 30 min in the dark. The absorbance was measured at 450 nm using a Synergy HT microplate reader.

The cell viability of ieodomycin derivatives was assessed using MTT and LDH assays. Vero cells were plated in 96-well plates at a concentration of 1 × 105 cells/mL and incubated for 16 h. The cells were treated with ieodomycin derivatives for 1 h. Then, 0.85 mM H_2O_2 solution was treated for another 24 h of incubation. Then, MTT and LDH assays were performed following the procedure shown before. HaCaT cells were seeded in 96-well plates at a cell concentration of 6 × 104 cells/mL, and incubated for 16 h. Ieodomycin derivatives were treated in the cells for 1 h. Then, H_2O_2 solution (1 mM) was added for cotreatment for another 24 h of incubation. Then, the MTT assay was performed following the procedure shown before.

ROS generation of ieodomycin derivatives was assessed using the DCF-DA assay. Both Vero cells (1 × 105 cells/mL) and HaCaT cells (6 × 104 cells/mL) were plated in 96-well plates and incubated for 16 h. The cells were treated with ieodomycin derivatives for 1 h. H_2O_2 solution was added for cotreatment for another 30 min of incubation. Then, DCF-DA solution was added to the cells and incubated for 5 min. The fluorescence at excitation 485 nm/emission 528 nm was measured using a Synergy HT microplate reader.

Determination of Cosmeceutical Activities. Tyrosinase Inhibitory Assay. 110 μL of potassium phosphate buffer (0.1 M, pH 6.5) and 10 μL of tyrosinase (2000 units/mL) in potassium phosphate buffer were mixed with 10 μL of ieodomycin derivatives in a 96-well plate. Then, 20 μL of L-tyrosine (1.5 mM) was added to the mixture and incubated at 37 °C for 15 min. After incubation, the absorbance was measured at 490 nm using a Synergy HT microplate reader.

Hyaluronidase Inhibitory Assay. The solution of hyaluronidase (8 mg/mL) and hyaluronic acid (2.4 mg/mL) in 0.1 M of acetate buffer (pH 3.6) was prepared. 12.5 μL of ieodomycin derivatives and hyaluronidase solution were mixed in an e-tube at 37 °C for 20 min. 25 μL of calcium chloride (12.5 mM) was added and incubated again at 37 °C for 20 min. Afterward, 62.5 μL of hyaluronic acid was added to the mixture and incubated at 37 °C for 40 min. After incubation, the reaction was stopped by adding 2.5 μL of sodium hydroxide (0.4 N) and 25 μL of potassium tetraborate (0.4 N) and incubated at 100 °C for 3 min. Finally, the mixture solution was cooled down at RT and 750 μL of DMAB solution (4 g of DMAB in 35 mL of acetic acid and 5 mL of hydrochloric acid) was treated and then incubated at 37 °C for 20 min. Each mixture was transferred to 96-well plates and the absorbance was measured at 585 nm using a Synergy HT microplate reader.

Elastase Inhibitory Assay. A mixture of *N*-succinyl-Ala-Ala-Ala-*p*-nitroanilide as elastase substrate (1.015 mM) in 0.12 M Tris-HCl buffer (pH 8) was prepared. 130 μL of the substrate solution was mixed with 10 μL of ieodomycin derivatives in the 96-well plates, and preincubated at 25 °C for 10 min. Then, a 10 μL of elastase from the porcine pancrease (0.5 units/mL) in Tris-HCl buffer was mixed with the preincubated mixtures to

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imitate the reaction. After incubation, the absorbance was measured at 410 nm using a Synergy HT microplate reader.

Collagenase Inhibitory Assay. Collagenase inhibition was measured using an assay specific for gelatinase/collagenase (Molecular Probes, OR) following the manufacturer's instructions. Briefly, 80 μL of ieodomycin derivatives were mixed with 20 μL DQ gelatin and 100 μL of Clostridium collagenase (0.2 units/mL) in 96-well plates. After 2 h of incubation, light-protected at RT, the fluorescence intensity was measured with excitation, and emission wavelengths of 485 and 538 nm using a Synergy HT microplate reader.

UVB-Protection on HaCaT Cells. HaCaT cells were seeded in 96-well plates at a cell concentration of 1 × 105 cells/mL, and incubated for 16 h. After pretreatment of ieodomycin derivatives for 2 h, the culture medium was replaced, and the cells were irradiated with UVB (20 mJ/cm^2). Then, ieodomycin derivatives were treated for another 24 h of incubation. The cell viability was assessed using the MTT assay following the process shown before.

Determination of Antidiabetic Activities. α-Amylase Inhibitory Assay. α-Amylase inhibition was measured using an α-amylase inhibitor screening kit (Abcam, Cambridge, U.K.) following the manufacturer's instructions. Briefly, 50 μL of ieodomycin derivatives was mixed with 50 μL of α-amylase solution in 96-well plates. After 10 min of incubation at RT in the dark, 50 μL of the substrate solution was added to the wells. The absorbance at 405 nm was measured in kinetic mode for 25 min using a Synergy HT microplate reader.

α-Glucosidase Inhibitory Assay. α-Glucosidase inhibition was measured using an α-glucosidase inhibitor screening kit (Abcam, Cambridge, U.K.) following the manufacturer's instructions. Briefly, 10 μL of ieodomycin derivatives were mixed with a 10 μL of α-glucosidase solution, and a 60 μL of assay buffer in 96-well plates. After 20 min of incubation at RT in the dark, 20 μL of substrate solution was added to the wells. The absorbance at 410 nm was measured in the kinetic mode for 60 min using a Synergy HT microplate reader.

DPP4 Inhibitory Assay. DPP4 inhibition was measured using a DPP4 inhibitor screening kit (Abcam, Cambridge, U.K.) following the manufacturer's instructions. Briefly, 25 μL of ieodomycin derivatives were mixed with 50 μL of DPP4 solution in 96-well plates. After 10 min of incubation at RT in the dark, 25 μL of substrate solution was added to the wells. The fluorescence intensity was measured at excitation and emission wavelengths of 360 and 460 nm in kinetic mode for 30 min at 37 °C using a Synergy HT microplate reader.

Determination of Angiotensin I Converting Enzyme (ACE) Inhibition Effect. ACE inhibition was measured by a colorimetric method using an ACE kit-WST (DoJindo Laboratories, Kumamoto, Japan), which determines the amount of 3-hyroxybutyric acid generated from 3-hydroxybutyryl-Gly-Gly-Gly by the enzyme. In brief, substrate buffer was prepared with or without ieodomycin derivatives in a 96-well plate and the enzyme solution was added to the wells. After incubation, the indicator solution was added to all the wells. The amount of 3-hyroxybutyric acid was evaluated by measuring the absorbance at 450 nm using a Synergy HT microplate reader.

Measurement of Cell Viability and Nitric Oxide (NO) Production. RAW264.7 cells were seeded into 96-well plates at a density of 2.5 × 105 cells/mL. After incubation for 16 h, the cells were pretreated with ieodomycin derivatives for 1 h, and subsequently 1 μg/mL lipopolysaccharide (LPS; Sigma Aldrich, MO) and incubated for 24 h. Cell viability was measured by the MTT assay according to the procedure shown before. NO production was measured by the Griess assay. Griess reagent (Sigma Aldrich, MO) and culture supernatants were mixed for 10 min in the dark. The absorbance at 540 nm was measured using a Synergy HT microplate reader.

Measurement of Cell Viability in Cancer Cell Lines. Cancer cell lines were selected as follows: three kinds of lung cancer cell lines (H1299, A549, and H460), three kinds of colon cancer cell lines (HCT116, CT26, and SW620), and three kinds of breast cancer cell lines (SKBR3, HCC38, and 1419). Each cell was seeded on 96-well plates at a concentration of 1.5 × 105 cells/mL. After 24 h, the cells were treated with ieodomycin derivatives, and incubated for 48 h. Then, the cell viabilities were measured by MTT assay following the method shown before.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03241.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra, in-detail results of dihydroxylation of **8** and **24**, absolute configuration determination of **10**, stability test of various modified Burgess reagents, and bioactivity screening data (PDF)

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Notes

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