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Stereoselective Total Synthesis of Ieodomycins A and B and Revision of the NMR Spectroscopic Data of Ieodomycin B

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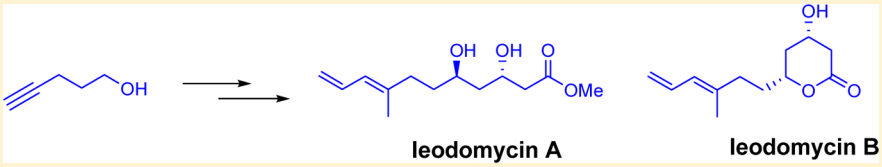
Supporting Information



ABSTRACT: Stereoselective total synthesis of antimicrobial marine metabolites ieodomycin A and B have been accomplished starting from commercially available 4-pentyn-1-ol featuring strategic application of the Negishi reaction, Kumada coupling, and Crimmins acetate aldol. This revises the proton NMR spectra of ieodomycin B.

Marine organisms have long been recognized as a rich source of useful metabolites with applications with human benefits. Isolation, identification, as well as synthesis of those novel metabolites and their active analogues are the subjects of great importance.[1] Marine antimicrobial agents[2] are known to have a major impact to the biopharmaceutical industry because of their broad range of activities against the rapidly growing multidrug resistant bacteria and pathogens which create several life-threatening problems in clinical settings. Ieodomycins A–D (**1**–**4**) (Figure 1), the antimicrobial

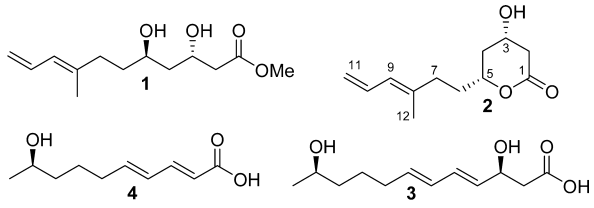
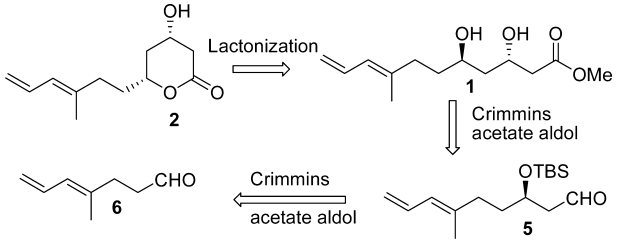


Figure 1. Structures of ieodomycins A–D.

secondary metabolites, were first discovered by Shin and co-workers[3] during their bioassay-guided fractionation studies of the EtOAc extract of 09ID194 strain, a marine microorganism from the Republic of Korea's southern reef, Ieodo. Ieodomycins A–D (**1**–**4**) inhibit the growth of microbial strains such as *Bacillus subtilis*, *Escherichia coli*, and *Saccharomyces cerevisiae* in the submicromolar range. Important bioactivity and interesting structural features of these molecules have rendered them attractive targets for synthetic organic chemists.[4] As a continuation of our[5] endeavor toward asymmetric synthesis of bioactive natural product we have embarked on stereoselective total synthesis of the ieodomycins. In this paper, we describe the total synthesis of ieodomycins A and B which result in the revision of NMR spectroscopic data of ieodomycin B. Structurally, ieodomycin B (**2**) is the *δ*-lactone form of ieodomycin A (**1**), which comprises a *trans*-1,3-diol moiety and a long fatty acid side chain embodied with two conjugated olefins.

Retrosynthetic analysis of ieodomycin A and B is depicted in Scheme 1. The key feature in our synthesis is the application of

Scheme 1. Retrosynthetic Analysis



chiral auxiliary based Crimmins acetate aldol[6] to construct the *trans*-1,3-diol moiety. Ieodomycin B (**2**) could be accomplished from ieodomycin A (**1**) by *δ*-lactonizaton. Ieodomycin A (**1**), in turn, could be synthesized from the protected aldehyde **5** which further could be developed from the aldehyde **6** by two consecutive asymmetric acetate aldol reactions.

Our synthetic endeavor began with commercially available 4–pentyn–1–ol (**7**) which was subjected to Negishi reaction followed by concomitant quenching with I_2 to produce vinyl iodide[7] **8** in 89% yield (Scheme-2). Next, Kumada coupling[7b] with vinylmagnesium bromide and subsequent Swern oxidation[8] furnished moderately volatile aldehyde **6** in good yield over two steps. The aldehyde **6** was then treated with the titanium enolate generated in situ from (*R*)-phenyl alanine derived *N*-acetylthiazolidinethione **9**[9] in presence of $TiCl_4$ and Hunig's base to provide **10** as major and **11** as minor products (dr, **10**:**11** = 4:1) (Scheme 2).

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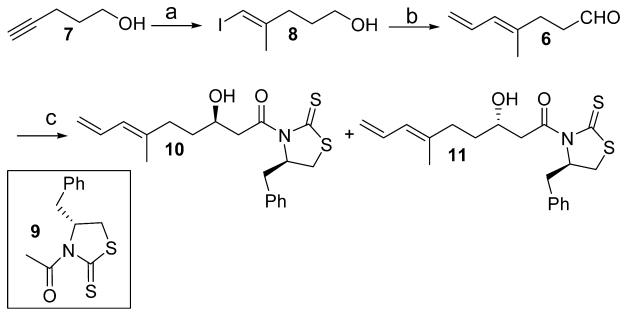
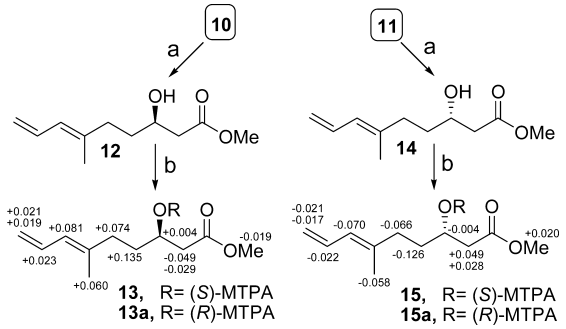
Scheme 2[a]



[a]Reagents and conditions: (a) (i) Me_3Al, Cp_2ZrCl_2, DCE, 0 °C to rt, 24 h then I_2, THF, 0 °C, 30 min, 89%; (b) (i) vinylmagnesium bromide, $(Ph_3P)_4Pd$, toluene, 3 h, 0 °C to rt, 91%, (ii) Swern oxidation, −78 to 0 °C, 2 h, 87%; (c) **9**, $TiCl_4$, DIPEA, CH_2Cl_2, −40 to −78 °C, 3 h, 69%.

The absolute configuration of the originated hydroxyl group was further confirmed by modified Mosher's ester method.[10] Our initial attempts to prepare Mosher's esters directly from compounds **10** and **11** following the literature procedure[11] furnished an inseparable complex mixture due to their incomplete derivatization and decomposition. To obtain satisfactory and reliable results in this direction, we followed Scheme-3. Both the compounds **10** and **11** were separately

Scheme 3[a]



[a]Reagents and conditions: (a) MeOH, imidazole, rt, overnight 76−78%; (b) *S*/*R*-Mosher acid, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, toluene, rt, 4 h, 75−83%.

converted to corresponding methyl esters[12] **12** and **14** respectively. Compound **12** was then treated separately with (*S*)-(+)- and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid in presence of 2,4,6-trichlorobenzoyl chloride and Et_3N following the reported procedure[11] to yield (*S*)- and (*R*)-MTPA esters **13** and **13a**, respectively. Similarly, compound **14** was converted to its corresponding (*S*)- and (*R*)-MTPA esters **15** and **15a**, respectively. All of the protons of the pairs of Mosher's esters **13**, **13a** and **15**, **15a** were assigned by ^{1}H NMR. The negative $\Delta\delta$ values [$\Delta\delta = \delta S - \delta R$] (Scheme-3) obtained for H-2 protons from the set of esters **13** and **13a** clearly confirmed the desired (*R*)-configuration of the originated hydroxyl center. In a similar way, the hydroxyl center of compound **11** was established as expected (*S*)-configuration by positive $\Delta\delta$ value acquired for H-2 protons from the esters **15** and **15a**.

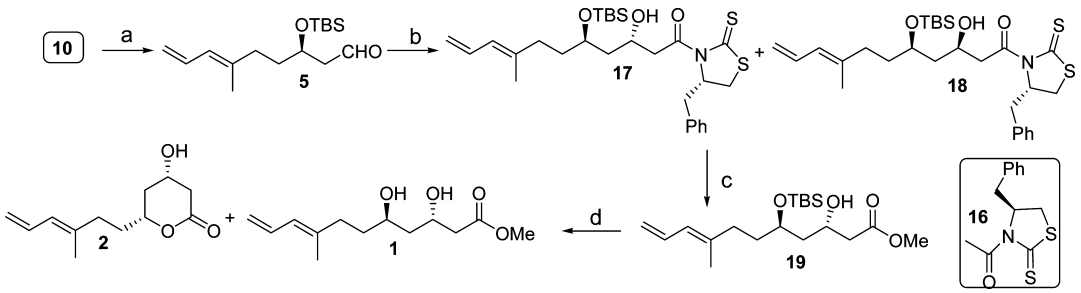
The required amide **10** in our hands was next converted to TBS ether and subsequently reduced by DIBAL-H to afford the aldehyde **5** with 89% yield over two steps (Scheme-4). The aldehyde **5** was reacted quickly to (*S*)-phenylalanine derived *N*-acetylthiazolidinethione[9] **16** to give **17** as major product and **18** as minor product (dr, **17**:**18** = 5:1). The stereochemistry of the 1,3-diol moiety of major compound **17** was confirmed further as the desired one by ^{13}C NMR study[13] of its acetonide **20**,[14] which was prepared in four steps. The required isomer **17** in our hands was transformed next to methyl ester **19** in the presence of MeOH and imidazole.[12] The prefinal compound **19** was set to carry out the crucial TBS cleavage to furnish ieodomycin A (**1**) and ieodomycin B (**2**) in a single step. We have tried a number of reagents (Table-1) with proper

Table 1. Optimization of Conditions for TBS Deprotection by TLC Monitoring and Observed Qualitative Ratio for Compounds 1 and 2

entry	reagent	solvent	temp (°C)	time (h)	ratio (**1**:**2**)
1	CSA	CH_2Cl_2/MeOH (1:1)	0 to rt	1	>9:1
2	TBAF	THF	0	0.5	0:1
3	HF−pyridine	CH_2Cl_2	0	3	1:1
4	AcOH−H_2O (4:1)		0 to rt	5	>9:1

monitoring by thin-layer chromatography (TLC) to optimize the formation of compound **1**. It was observed that both AcOH−H_2O and CSA worked well to cleave the TBS ether to give the compounds **1** as major and compound **2** as minor products. We preferred CSA in the course of our study because

Scheme 4[a]



[a]Reagents and conditions: (a) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, (ii) DIBAL-H, −78 °C, 5 min, 89% over two steps; (b) **16**, $TiCl_4$, DIPEA, CH_2Cl_2, −40 to −78 °C, 3 h, 72% with respect to both compounds **17** and **18**; (c) MeOH, imidazole, rt, overnight, 78%; (d) CSA, CH_2Cl_2/MeOH (1:1), 0 °C, 30 min, 54% with respect to compound **2**.

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of its short reaction time and easier removal under ambient conditions.

Our initial attempts to purify both the compounds **1** and **2** by flash chromatography using silica or silica triturated with Et_3N as stationary phase and variety of solvent systems (EtOAc/hexane, diethyether/hexane, $MeOH/CH_2Cl_2$) as mobile phase failed totally to give compound **1** even in moderate yield due to its rapid conversion into more stable δ-lactone **2** within the column. Finally, use of neutral alumina as stationary phase and EtOAc/hexane as mobile phase served better result in this direction.

During the preparation of this manuscript, a 15-step synthetic route for ieodomycins A and B was published by Koul and his co-workers.[4b] However, there was a mismatch in the chemical shift of the $H\text{-}4_{ax}$ proton of the synthetic compound relative to that reported[3] for the isolated compound.

The ^1H NMR spectra of our acyclic compound **1** recorded immediately after synthesis was comparable to the reported data of ieodomycin A. However, in our hands, unavoidable counter peaks were generated gradually in the purified acyclic compound due to the spontaneous formation of the δ-lactone **2**. This prevented us to take ^{13}C NMR data of compound **1** due to requirement of longer time span for its recording. The optical rotation of the pure acyclic intermediate **1** could not be obtained for the same reason.

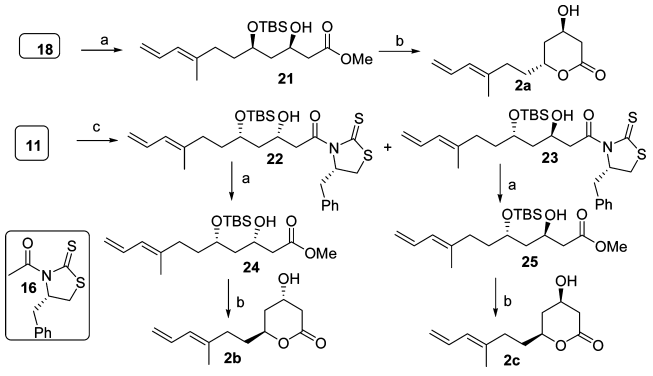
The ^{13}C NMR and optical rotation [reported $[\alpha]^{23}_D$: + 21.0 (c 0.9, $CHCl_3$); observed $[\alpha]^{23}_D$: + 25.8 (c 0.5, $CHCl_3$)] of ieodomycin B although was in close agreement with our synthetic δ-lactone **2** but a considerable difference was observed in proton NMR spectrum. The ^1H NMR spectrum of synthetic δ-lactone **2** exhibited signals for two protons at δ (2.30−2.27) ppm and one proton at δ 1.52 ppm, where as in the isolation paper[3] all those protons appeared at δ (2.30−2.27) ppm and no proton was reported at δ 1.52 ppm. Eventually COSY, HSQC, HMBC correlation spectroscopy of our δ-lactone **2** differed from the originals. This observation prompted us to synthesize all three others possible stereoisomers of ieodomycin B by analogous chemistry as adopted for the δ-lactone **2** (Scheme 5).

Compound **18** (Scheme 4) was converted to methyl ester **21**, and subsequently TBS ether was deprotected by TBAF to furnish lactone **2a** with 70% yield (Scheme 5). Compound **11** was subjected next to a three-step reaction protocol: protection of alcohol as TBS ether followed by reduction with DIBAL-H to get an aldehyde which was subjected further to Crimmins acetate aldol using **16** as an auxiliary to afford the expected compound **22** as the major product and compound **23** as the minor product. Compounds **22** and **23** were next converted separately to methyl ester **24** and **25** by MeOH in presence of imidazole with 76% and 77% yields, respectively. Both the esters **24** and **25** were then transformed individually to lactones **2b** and **2c** in the presence of TBAF with 71% and 83% yields, respectively.

The proton NMR spectra of all stereogenic analogues **2a**, **2b**, and **2c** led us to question the previous assignment. Not a single proton NMR spectrum of those isomers matched perfectly with the reported spectrum. From detailed NMR studies we have seen that the origin of this discrepancy was mainly attributed by the protons attached with C-4 carbon along with some ambiguities in coupling constants. Moreover, the diastereotopic $(H\text{-}4)_{eq}$ and $(H\text{-}4)_{ax}$ protons in that structure[3] were shown to resonate in close proximity at δ 2.27 and δ 2.24 ppm respectively which seemed to be quite contradictory with its architecture.[15] HSQC correlation spectroscopy of our δ lactone **2** clearly exibited that one of the C-4 protons would resonate at δ (2.30−2.25) ppm together with one $(H\text{-}7)_{allylic}$ proton where as other would be at δ 1.52 ppm. The large vicinal coupling (J = 11.5, 8.7 Hz) of H-4 proton resonating at δ1.52 ppm with $(H\text{-}3)_{ax}$ and $(H\text{-}5)_{ax}$ protons unambiguously support their trans diaxial relationship and hence was assigned as $(H\text{-}4)_{ax}$. This new assignment was further confirmed by details NOESY as well as by ROESY correlation spectroscopy which clearly exhibited the anticipated spatial correlations together with very expected 1, 3-*syn* diaxial interaction between $(H\text{-}2)_{ax}$ and $(H\text{-}4)_{ax}$ protons and necessitates the revision (see the personal communication[16]) of the NMR data (Table 2, Supporting Information) of ieodomycin B.

In summary, a short, general, and very flexible strategy has been developed toward the synthesis of reported ieodomycins A and B. This study enabled us to achieve the ieodomycin B in 9 linear steps with an overall yield of 13%. At the same time, an important issue related to the existence of the acyclic ieodomycin A in pure form was also discussed. The adopted strategy paved an easy way for the synthesis of other possible diastereomers of ieodomycin B and simultaneously demonstrated the effect of reagents on δ-lactonization of ieodomycin A to ieodomycin B.

Scheme 5[a]



[a]Reagents and conditions: (a) imidazole, MeOH, rt, overnight, 73−77%; (b) TBAF, THF, 30 min, 0 °C, 70−83%; (c) (i) TBSOTf, 2,6-lutidine, 0 °C, 15 min, quantitative, (ii) DIBAL-H, CH_2Cl_2, −78 °C, 5 min, 88%, (iii) **16**, $TiCl_4$, DIPEA, CH_2Cl_2, −40 to −78 °C, 3 h, 68%.

EXPERIMENTAL SECTION

(*E*)-4-Methylhepta-4,6-dienal (6). To solution of $(COCl)_2$ (1.67 mL, 19.37 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C was added DMSO (2.94 mL, 41.34 mmol) in a dropwise manner with constant stirring under argon atmosphere. After 15 min, the (*E*)-4-methylhepta-4,6-dien-ol[7] (1.63 g, 12.92 mmol in 15 mL of anhydrous CH_2Cl_2) was cannulated to the reaction mixture. After 30 min, Et_3N (9.01 mL, 64.6 mmol) was added and stirred further 30 min at the same temperature. The reaction was allowed to warm slowly to 0 °C and stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated in vacuo at very low temperature. Flash column chromatography (SiO_2, 230−400mesh, 3% Et_2O in hexane) gave moderate volatile aldehyde **6** (1.39 g, 87%) as a colorless oil: R_f = 0.34 (10% Et_2O in hexane) ; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 6.55 (dt, J = 17.0, 10.5 Hz, 1H), 5.87 (d, J = 10.5 Hz, 1H), 5.13 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 10.5 Hz, 1H), 2.58 (t, J = 7.5 Hz, 1H), 2.40 (t, J = 7.5 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1, 137.1, 133.1, 126.4, 115.9, 42.1, 32.0, 16.9.

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(*R*,*E*)/(*S*,*E*)-1-{(*R*)-4-Benzyl-2-thioxothiazolidin-3-yl}-3-hydroxy-6-methylnona-6,8-dien-1-one (10 and 11). To a solution of thiazolidinethione **9** (4.49 g, 17.8 mmol) in anhydrous CH_2Cl_2 (55 mL) at −40 °C was added dropwise freshly distilled $TiCl_4$ (2.07 mL, 18.85 mmol). The yellowish slurry was stirred for 5 min at the same temperature, and DIPEA (3.28 mL, 18.85 mmol) was added dropwise. The deep reddish solution was stirred for another 1 h at −40 °C before being cooled to −78 °C, and aldehyde **6** (1.3g, 10.47 mmol in 15 mL of CH_2Cl_2) was cannulated. Stirring was continued at −78 °C for 20 min and quenched by saturated aqueous NH_4Cl (15 mL). It was extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 15−20% EtOAc in hexane) separated the two diastereomers **10** and **11** with 69% total yield (dr = 4:1).

Data for 10: 55% yield, 2.16 g, yellowish green liquid; R_f = 0.49 (25% EtOAc in hexane); $[\alpha]^{26}_D$ = −44.8 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.34 (m, 2H), 7.29−7.28 (m, 3H), 6.58 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.91 (d, *J* = 10.5 Hz, 1H), 5.40 (m, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 5.0 (d, *J* = 10.5 Hz, 1H), 4.13 (m, 1H), 3.67 (dd, *J* = 17.7, 2 Hz, 1H), 3.41 (dd, *J* = 11.5, 7.4 Hz, 1H), 3.22 (dd, *J* = 13, 3.1 Hz, 1H), 3.15 (dd, *J* = 17.7, 9.4 Hz, 1H), 3.05 (dd, *J* = 13, 10.5 Hz, 1H), 2.91 (d, *J* = 11.5 Hz, 1H), 2.75 (s, 1H), 2.29−2.23 (m, 1H), 2.19−2.14 (m, 1H), 1.79 (s, 3H), 1.74−1.63 (m, 2H); ^{13}CNMR ($CDCl_3$, 125 MHz): 201.6, 173.3, 138.8, 136.6, 133.4, 129.6, 129.1, 127.5, 126.1, 115.2, 68.5, 67.7, 46.0, 37.1, 35.8, 34.5, 32.3, 16.8 ppm; IR (neat) ν_{max} 3427, 2926, 1695 cm^{-1}; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{25}NO_2S_2Na$ $[M + Na]^+$ 398.1224, found 398.1225.

Data for 11: 14% yield, 550 mg, yellowish green liquid; R_f = 0.57 (25% EtOAc in hexane); $[\alpha]_D^{26}$ = −7.3 (*c* 0.8 $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.27 (m, 5H), 6.57 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.41 (m, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.04 (bs, 1H), 3.48 (dd, *J* = 17.5, 9.3 Hz, 1H), 3.40 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.34 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.22 (dd, *J* = 13.0, 3.7 Hz, 1H), 3.16 (bs, 1H), 3.04 (dd, *J* = 13.0, 10.5 Hz, 1H), 2.91 (d, *J* = 11.5 Hz, 1H), 2.28−2.23 (m,1H), 2.18−2.12 (m, 1H), 1.77 (s, 3H), 1.75−1.69 (m, 1H),1.67−1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.6, 173.8, 138.8, 136.5, 133. 4, 129.5, 129.1, 127.4, 125.9, 115.1, 68.3, 68.1, 45.6, 36.9, 35.7, 34.7, 32.2, 16.8; IR (neat) ν_{max} 3441, 2924, 1693 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{25}NO_2S_2Na$ $[M + Na]^+$ 398.1224, found 398.1223.

(*R*,*E*)-Methyl 3-Hydroxy-6-methylnona-6,8-dienoate (12). To a solution of compound **10** (200 mg, 0.53 mmol) in anhydrous methanol (3 mL) at 0 °C was added imidazole (180.4 mg, 2.65 mmol), and the mixture was stirred overnight at rt. The reaction mixture was then quenched with a saturated solution of NH_4Cl (1 mL). Methanol was removed in vacuo and extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 15−20% Et_2O in hexane) afforded pure ester **12** (80 mg, 76%) as a colorless oil: R_f = 0.27 (40% Et_2O in hexane); $[\alpha]^{26}_D$ = −5.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 3.99 (bs, 1H), 3.71 (s, 3H), 2.91 (s, 1H), 2.52 (dd, *J* = 16.5, 3.2 Hz, 1H), 2.44 (dd, *J* = 16.5, 8.9 Hz, 1H), 2.26−2.20 (m, 1H), 2.16−2.10 (m, 1H), 1.76 (s, 3H), 1.70−1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 138.6, 133.2, 125.9, 115.0, 67.6, 51.8, 41.1, 35.6, 34.5, 16.6; IR (neat) ν_{max} 3448, 2925, 1735, 1438 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{18}O_3K$ $[M + K]^+$ 237.0893, found 237.0892.

(*S*,*E*)-Methyl 3-Hydroxy-6-methylnona-6,8-dienoate (14). Same as ester **12**: 78% yield (80 mg) from compound **11** (193 mg); colorless oil; R_f = 0.27 (40% Et_2O in hexane); $[\alpha]^{20}_D$ = +12.8 (*c* 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 16.8 Hz,1H), 4.99 (d, *J* = 10 Hz, 1H), 3.99 (m, 1H), 3.72 (s, 3H), 2.90 (bs, 1H), 2.52 (dd, *J* = 16.4, 3.3 Hz, 1H), 2.43 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.33−2.20 (m, 1H), 2.17−2.10 (m, 1H), 1.77 (s, 3H), 1.68−1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 138.8, 133.4, 126.1, 115.2, 67.8, 51.9, 41.3, 35.8, 34.7, 16.8; IR (neat) ν_{max} 3419, 2925, 1735, 1436 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{18}O_3Na$ $[M + Na]^+$ 221.1154, found 221.1155.

(*R*,*E*)-Methyl-6-methyl-3-[(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]nona-6,8-dienoate (13). To solution of (*S*)-Mosher's acid (35 mg, 0.15 mmol) in anhydrous toluene (1 mL) at room temperature sequentially DMAP (20.8 mg, 0.17 mmol), Et_3N (0.02 mL, 0.17 mmol), and 2,4,6-trichlorobenzoyl chloride (0.02 mL, 0.15 mmol) were added. The white turbid mixture was stirred for 30 min, and a solution of alcohol **12** (10 mg, 0.05 mmol) in dry toluene (0.5 mL) was then cannulated. After being stirred for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.5 mL) and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (silica gel, 100−200mesh, 5% EtOAc in hexane) gave (*S*)-MTPA ester **13** (16 mg, 76%) as a colorless oil: R_f = 0.49 (15% EtOAc in hexane); $[\alpha]^{26}_D$ = −4.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.53 (t, *J* = 3.6 Hz, 2H), 7.41−7.40 (m, 3H), 6.54 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.82 (d, *J* = 10.5 Hz, 1H), 5.45 (m, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1 Hz), 3.60 (s, 3H), 3.53 (s, 3H), 2.67 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.60 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.09 (t, *J* = 7.9 Hz, 2H), 1.93−1.80 (m, 2H),1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 165.9, 137.4, 133.1, 132.2, 129.7, 128.5, 127.6, 126.5, 115.7, 73.3, 55.5, 51.9, 38.5, 35.2, 32.1,16.6; IR (neat) ν_{max} 2953, 2926, 1747 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}F_3O_5Na$ $[M + Na]^+$ 437.1552, found 437.1550.

(*R*,*E*)-Methyl-6-methyl-3-[(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]nona-6,8-dienoate (13a). Same as ester **13**: 81% yield (22 mg) from ester **12** (13 mg), colorless oil; R_f = 0.52 (15% EtOAc in hexane); $[\alpha]^{26}_D$ = +19.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.53 (m, 2H), 7.41−7.39 (m, 3H), 6.52 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.74 (d, *J* = 10.5 Hz, 1H), 5.45 (m, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 3.66 (s, 3H), 3.55 (s, 3H), 2.72 (dd, *J* = 16.0, 7.9 Hz, 1H), 2.63 (dd, *J* = 16.0, 4.9 Hz, 1H), 1.97−1.94 (m, 2H), 1.81−1.77 (m, 2H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 166.1, 137.5, 133.1, 132.4, 129.7, 128.5, 127.5, 126.4, 115.6, 73.1, 55.6, 52.0, 38.6, 34.8, 31.9, 16.5; IR (neat) ν_{max} 2954, 2925, 1747 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}F_3O_5Na$ $[M + Na]^+$ 437.1552, found 437.1553.

(*S*,*E*)-Methyl-6-methyl-3-[(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]nona-6,8-dienoate (15). Same as **13**: 75% yield (24 mg) from ester **14** (15 mg); colorless oil; R_f = 0.46 (15% EtOAc in hexane); $[\alpha]^{25}_D$ = −9.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (t, *J* = 3.8 Hz, 2H), 7.41−7.40 (m, 3H), 6.52 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.74 (d, *J* = 10.5 Hz, 1H), 5.45 (m, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 2.73 (dd, *J* = 16.0, 7.9 Hz, 1H), 2.63 (dd, *J* = 16.0, 4.9 Hz, 1H), 1.98−1.94 (m, 2H), 1.81−1.77 (m, 2H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 166.1, 137.5, 133.2, 132.4, 129.7, 128.5, 127.5, 126.4, 115.6, 73.1, 55.6, 52.1, 38.6, 34.8, 31.9,16.6; IR (neat) ν_{max} 2952, 2927, 1747 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}F_3O_5Na$ $[M + Na]^+$ 437.1552, found 437.1552.

(*S*,*E*)-Methyl-6-methyl-3-[(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]nona-6,8-dienoate (15a). Same as **13**: 83% yield (21 mg) from ester **14** (12 mg), colorless oil; R_f = 0.5 (15% EtOAc in hexane); $[\alpha]^{26}_D$ = +15.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.54−7.53 (m, 2H), 7.41−7.40 (m, 3H), 6.54 (dt, *J* = 16.8, 10.5 Hz,1H), 5.82 (d, *J* = 10.5 Hz, 1H), 5.45 (m, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 2.68 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.60 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.09 (t, *J* = 7.8 Hz, 2H), 1.93−1.80 (m, 2H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 165.9, 137.3, 133.1, 132.2, 129.7,128.5, 127.6, 126.4, 115.7, 73.2, 55.4, 51.9, 38.4, 35.1, 31.9,16.6; IR (neat)ν_{max} 2952, 2925, 1749 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}F_3O_5Na$ $[M + Na]^+$ 437.1552, found 437.1551.

(*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-6-methylnona-6,8-dienal (5). To an ice-cold solution of compound **10** (1.75 g, 4.63 mmol) in anhydrous CH_2Cl_2 (18 mL) were added sequentially 2,6-lutidine (1.26 mL, 11.58 mmol) and TBSOTf (1.38 mL, 6.02 mmol). The reaction mixture was stirred from 0 °C for 30 min and was quenched by

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saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc. The organic extracts were washed with aqueous $CuSO_4$, water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 1.0−1.5% EtOAc in hexane) furnished the corresponding TBS-protected compound (2.28g, quantitative) as a greenish yellow liquid: R_f = 0.5 (5% EtOAc in hexane); $[\alpha]^{25}_D$ = −87.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.34 (m, 2H), 7.30−7.28 (m, 3H), 6.57 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.28 (m, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.35 (m, 1H), 3.58 (dd, *J* = 17.0, 7.8 Hz, 1H) 3.35 (dd, *J* = 11, 7.1 Hz, 1H), 3.25 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.21 (dd, *J* = 17.0, 4.0 Hz, 1H), 3.04 (dd, *J* = 13.0, 11.0 Hz, 1H), 2.89 (d, *J* = 11.0 Hz, 1H,), 2.12 (t, *J* = 7.8 Hz, 2H),1.77 (s, 3H), 1.67 (m, 2H),0.87 (s, 9H), 0.1 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.3, 172.3, 139.2, 136.7, 133.4, 129.6, 129.1, 127.4, 125.7, 114.9, 69.1, 68.8, 45.9, 36.7, 36.0, 35.2, 32.3, 25.9, 18.2, 16.9, −4.3, −4.5 ppm; IR (neat) ν_{max} 2928, 1697, 1255 cm^{-1}; HRMS (ESI: *m*/*z* calcd for $C_{26}H_{39}NO_2S_2SiNa$ [M + Na]$^+$ 512.2089, found 512.2088.

The solution of the above TBS-protected compound (1.2 g, 2.45 mmol) in anhydrous CH_2Cl_2 (12 mL) was cooled to −78 °C, and DIBAL-H (1.0 M solution in toluene, 4.9 mL, 2.0 equiv) was added dropwise until the green solution became colorless. The reaction was then quenched by a saturated solution of sodium−potassium tartrate (8 mL) and stirred further for 1 h until the two layers separated well. It was then extracted with EtOAc, washed with brine and water, dried (Na_2SO_4), filtered, and concentrated in vacuo. Quick flash column chromatography (SiO_2, 230−400 mesh, 3% EtOAc in hexane) yielded aldehyde **5** (616 mg, 89%) as yellow liquid: R_f = 0.56 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.81 (d, *J* = 2 Hz, 1H), 6.56 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.84 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 16.8 Hz), 4.99 (d, *J* = 10.5 Hz), 4.19 (m, 1H), 2.54 (dd, *J* = 6.0,2.0 Hz, 2H), 2.12−2.05 (m, 2H), 1.76 (s, 3H), 1.69−1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.2, 138.7, 133.3, 125.9, 115.2, 68.0, 50.9, 36.1, 35.4, 25.9, 18.1, 16.8, −4.28, −4.48 ppm.

(3*S*,5*R*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dien-1-one (17). To a solution of thiazolidinethione **16** (935 mg, 3.71 mmol) in CH_2Cl_2 (12 mL) at −40 °C was added dropwise freshly distilled $TiCl_4$ (0.43 mL, 3.92 mmol). The yellow slurry was stirred for 5 min. DIPEA (0.68 mL, 3.92 mmol) was added dropwise and stirred for another 2 h at −40 °C. The reaction mixture was cooled to −78 °C, and aldehyde **5** (616 mg, 2.18 mmol, in 10 mL of CH_2Cl_2) was then cannulated. The reaction was continued further at −78 °C for 20 min and quenched by cold saturated aqueous NH_4Cl (10 mL), extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 8−10% EtOAc in hexane) afforded **17** (698 mg, 60%) as a yellow oil: R_f = 0.33 (15% EtOAc in hexane); $[\alpha]^{25}_D$ = +53.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.26 (m, 5H), 6.57 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.87 (d, *J* = 10.5 Hz, 1H), 5.39 (m,1H), 5.11 (d, *J* = 16.8 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.52 (m, 1H), 4.04−4.00 (m, 1H), 3.45 (dd, *J* = 17.5, 2.9 Hz,1H), 3.39 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.29 (dd, *J* = 17.5, 9.0 Hz, 1H), 3.25 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.05 (dd, *J* = 13.0, 10.7 Hz, 1H), 2.89 (d, *J* = 11.5 Hz, 1H), 2.09−2.06 (m, 2H), 1.78 (s, 3H), 1.76−1.71 (m, 3H), 1.64 (ddd, *J* = 14.0, 6.0, 2.2 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.4, 172.5, 139.1, 136.6, 133.4, 129.6, 129.0, 127.4, 125.7, 115.0, 70.6, 68.6, 64.9, 46.8, 41.6, 36.9, 35.7, 34.9, 32.2, 25.9, 18.1, 16.9, −4.4, −4.5; IR (neat) ν_{max} 3502, 2951, 2928, 1697, 1684 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{43}NO_3S_2SiNa$ [M + Na]$^+$ 556.2351, found 556.2350.

***tert*-Butyl (2-[[(4*R*,6*R*)-2,2-dimethyl-6-((*E*)-3-methylhexa-3,5-dienyl)1,3dioxan4-yl]ethoxy]diphenylsilane (20).** Data for compound **20**: R_f = 0.42 (5% EtOAc in hexane); $[\alpha]^{26}_D$ = +23.3 (*c* 0.3, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 500 MHz) δ 7.67−7.65 (m, 4H), 7.43−7.36 (m, 6H), 6.57 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 4.98 (d, *J* = 10.5 Hz, 1H), 4.08 (m, 1H), 3.81−3.65 (m, 3H), 2.18−2.13 (m, 1H), 2.10−2.04 (m, 1H), 1.76 (s, 3H), 1.74−1.62 (m, 3H), 1.58 (m, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 139.0, 135.7, 134.1, 134.0, 133.5, 129.7, 127.8, 125.9, 114.8, 100.4, 66.2, 63.6, 60.2, 39.1, 38.9, 35.7, 34.0, 27.0, 24.9, 19.4, 16.7; IR (neat) ν_{max} 2933, 1110 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{44}O_3SiNa$ [M + Na]$^+$ 515.2957, found 515.2956.

(3*S*,5*R*,*E*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dienoate (19). Same as **12**: 78% (95 mg) from compound **17** (183 mg), colorless oil; R_f = 0.43 (15% EtOAc in hexane); $[\alpha]^{25}_D$ = +7.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (dt, *J* = 16.8, 10.5z, 1H), 5.80 (d, *J* = 10.5 Hz), 5.10 (dd, *J* = 16.8, 1.5 Hz, 1H), 4.98 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.35−4.31 (m, 1H), 4.02−3.98 (m, 1H), 3.71 (s, 3H), 3.60 (d, *J* = 2.3 Hz, 1H), 2.51 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 4.7 Hz, 1H), 2.07−2.04 (m, 2H), 1.76 (s, 3H), 1.73−1.57 (m, 4H), 0.90 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 139.1, 133.4, 125.7, 115.1, 70.6, 65.2, 51.8, 42.2, 41.7, 35.7, 35.1, 26.0, 18.2, 16.9, 0.2, −4.4, −4.5; IR (neat) ν_{max} 3444, 2925, 2854, 1734 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{36}O_4SiNa$ [M + Na]$^+$ 379.2281, found 379.2282.

(3*S*,5*R*,*E*)-Methyl-3,5-dihydroxy-8-methylundeca-8,10-dienoate [leodomycin A (1)] and (4*S*,6*R*,*E*)-4-Hydroxy-6-(3-methylhexa-3,5-dienyl)-tetrahydropyran-2-one [leodomycin B (2)]. A solution of ester **19** (51 mg, 0.14 mmol) in CH_2Cl_2 and MeOH (1:1, 2 mL) was cooled to 0 °C, and CSA (3.3 mg, 0.014 mmol) was added at once. The reaction mixture was then stirred at room temp for 30 min before quenching with Et_3N. The solution was concentrated and purified by column chromatography (neutral alumina, 25−45% EtOAc in hexane) to yield ieodomycin A (**1**) and ieodomycin B (**2**).

Ieodomycin A (1). Eluted with 25% EtOAc in hexane, 35% yield [12 mg together with ieodomycin B (**2**)]; R_f = 0.32 (50% EtOAc in hexane); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.57 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.87 (d, *J* = 10.6 Hz, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 4.94 (d, *J* = 10.6 Hz, 1H), 4.26 (m, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 2.50 (dd, *J* = 15.5, 4.8 Hz, 1H), 2.44 (dd, *J* = 15.0, 8.2 Hz, 1H), 2.19 (m, 2H), 2.11 (m, 1H), 1.76 (s, 3H), 1.59−1.52 (m, 4H); IR (neat) ν_{max} 3409, 2929, 1734, 1438 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}O_4Na$ [M + Na]$^+$ 265.1416, found 265.1417.

Ieodomycin B (2). Eluted with 45% EtOAc in hexane: colorless oil, 54% yield (19 mg); R_f = 0.16 (50% EtOAc in hexane); $[\alpha]^{23}_D$ = +25.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.59 (dt, *J* = 16.7, 10.5 Hz, 1H), 5.89 (d, *J* = 10.5 Hz, 1H), 5.07 (d, *J* = 16.7 Hz, 1H), 4.97 (d, *J* = 10.5 Hz, 1H), 4.26 (m, 1H), 4.19 (m, 1H), 2.86 (dd, *J* = 17.0, 5.6, 1H), 2.36 (dd, *J* = 17.0, 7.1 Hz, 1H), 2.28 (m, 1H), 2.26 (m,1H), 2.18 (m, 1H), 1.80 (m, 2H), 1.78 (s, 3H), 1.52 (ddd, *J* = 13.3,11.5,8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 174.1, 139.1, 134.6, 127.7, 115.7, 78.6, 64.5, 40.3, 38.8, 36.2, 35.0, 16.7; IR (neat) ν_{max} 2922, 1716 cm^{-1} ; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}O_3Na$ [M + Na]$^+$ 233.1154, found 233.1155.

(3*R*,5*R*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dien-1-one (18): yellow oil, 12% (140 mg) from aldehyde **5**(616 mg); R_f = 0.61 (20% EtOAc in hexane); $[\alpha]^{28}_D$ = −52.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.33 (m, 2H), 7.30−7.28 (m, 3H), 6.57 (dt, *J* = 16.9, 10.5 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 5.40 (m, 1H), 5.10 (d, *J* = 16.9 Hz, 1H), 4.99 (d *J* = 10.5 Hz, 1H), 4.33 (m, 1H), 3.97 (m, 1H), 3.56 (dd, *J* = 18, 3.5 Hz, 1H), 3.39 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.30−3.20 (m, 2H), 3.04 (dd, *J* = 13.0, 10.6 Hz, 1H), 2.89 (d, *J* = 11.5 Hz, 1H), 2.09 (m, 2H), 1.77 (s, 3H), 1.74−1.61 (m, 4H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 172.7, 139.3, 136.6, 133.4, 129.6, 129.1, 127.4, 125.7, 115.0, 71.3, 68.5, 66.6, 46.4, 42.9, 36.9, 35.7, 35.1, 32.2, 26.0, 18.2, 16.9, −4.0, −4.3 ppm; IR (neat) ν_{max} 3535, 2927,1693,1255 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{43}NO_3S_2SiNa$ [M + Na] $^+$ 556.2351, found 556.2352.

(3*R*,5*R*,*E*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dienoate (21). Same as compound **19**: 73% yield (63 mg) from **18** (130 mg), colorless oil; R_f = 0.51(20% EtOAc in hexane); $[\alpha]^{27}_D$ = +4.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (dt, *J* = 16.6, 10.6 Hz, 1H), 5.84 (d, *J* = 10.6 Hz, 1H), 5.10 (d, *J* = 16.6 Hz, 1H), 4.99 (d, *J* = 10.6 Hz, 1H), 4.17 (bs, 1H), 3.94 (m, 1H), 3.71 (s,3H), 3.40 (s,1H), 2.49 (d, *J* = 5.8 Hz, 2H), 2.07

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(t, J = 8.1 Hz, 2H), 1.76 (s, 3H), 1.73−1.62 (m, 4H), 0.90 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 139.2, 133.4, 125.7, 115.0, 71.5, 66.9, 51.8, 42.8, 41.8, 35.7, 35.1, 26.0, 18.1, 16.9, −4.0, −4.4 ppm; IR (neat) ν_{max} 3473, 2952, 2929, 1735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{36}O_4SiNa$ [M + Na]$^+$ 379.2281, found 379.2282.

(4*R*,6*R*,*E*)-4-Hydroxy-6-(3-methylhexa-3,5-dienyl)-tetrahydropyran-2-one (2a). To a stirred solution of compound **21** (52 mg, 0.15 mmol) in dry THF (1.5 mL) was added TBAF (1 M solution in THF, 0.22 mL, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature. It was quenched with saturated aqueous NH_4Cl (1 mL), extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 8−10% EtOAc in hexane eluant) afforded pure compound **2a** (22 mg, 70%) as a colorless oil: R_f = 0.41 (60% EtOAc in hexane); $[\alpha]^{23}_D$ = +11.9 (c 0.3, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.59 (dt, J = 16.8, 10.5 Hz, 1H), 5.90 (d, J = 10.5 Hz, 1H), 5.07 (dd, J = 16.8, 1.5 Hz, 1H), 4.99 (dd, J = 10.5, 1.2 Hz, 1H), 4.28−4.24 (m, 1H), 4.22−4.17 (m, 1H), 2.86 (dd, 17, 5.3 Hz, 1H), 2.37 (dd, J = 17, 7.1 Hz, 1H), 2.29−2.24 (m, 2H), 2.21−2.15 (m, 1H), 1.80 (m, 2H), 1.78 (s, 3H), 1.52 (ddd, J = 13.0, 12.0, 8.6 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.8, 139.2, 134.6, 127.7, 115.7, 77.5, 63.5, 39.3, 36.6, 36.1, 35.2, 16.7 ppm; IR (neat) ν_{max} 3427, 2920, 1708,1257 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ [M + Na]$^+$ 233.1154, found. 233.1153.

(3*S*,5*S*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dien-1-one (22): yellow oil; 45.7% (292 mg) overall yield from **11** (450 mg); R_f = 0.59 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +57.8 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.33 (m, 2H), 7.30−7.28 (m, 2H), 6.57 (dt, J = 16.8, 10.5, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.40 (m, 1H), 5.10 (d, J = 16.8 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.33 (m, 1H), 3.97 (m, 1H), 3.56 (dd, J = 17.5, 3.1 Hz, 1H), 3.39 (dd, J = 13, 10.5 Hz, 1H), 3.27−3.21 (m, 2H), 3.04 (dd, J = 13, 10.5 Hz, 1H), 2.89 (d, J = 11.5 Hz, 1H), 2.09 (m, 2H), 1.77 (s, 3H), 1.75−1.64 (m, 4H), 0.9 (s, 9H), 0.11 (s, 3H), 0.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 172.7, 139.3, 136.6, 133.4, 129.6, 129.1, 127.4, 125.7, 114.9, 71.3, 68.5, 66.6, 46.4, 42.9, 36.9, 35.7, 35.2, 32.2, 26.1, 18.2, 16.9, −4.0, −4.3 ppm; IR (neat) ν_{max} 3417, 2927, 1699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{43}NO_3S_2SiNa$ [M + Na] $^+$ 556.2351, found 556.2350.

(3*S*,5*S*,*E*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dienoate (24). Same as compound **19**: 76% yield (106 mg) from compound **22** (210 mg), colorless liquid; R_f = 0.12 (10% EtOAc in hexane); $[\alpha]^{25}_D$ = −12.1 (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (dt, J = 16.7, 10.5 Hz, 1H), 5.84 (d, J = 10.5 Hz. 1H), 5.10 (d, J = 16.7 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.17 (m, 1H), 3.94 (m, 1H), 3.71 (s, 3H), 3.40 (s, 1H), 2.49 (d, J = 5.9 Hz, 2H), 2.07 (t, J = 8.1 Hz, 2H), 1.76 (s, 3H), 1.71−1.58 (m, 4H), 0.90 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 139.2, 133.4, 125.7, 115.0, 71.5, 66.9, 51.8, 42.8, 41.8, 35.7, 35.1, 26.0, 18.1, 16.9, −4.0, −4.4 ppm; IR (neat) ν_{max} 3519, 2953, 2929, 1738 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{36}O_4SiNa$ [M + Na]$^+$ 379.2281, found 379.2281.

(4*S*,6*S*,*E*)-4-Hydroxy-6-(3-methylhexa-3,5-dienyl)-tetrahydropyran-2-one (2b). Same as compound **2a**: 71% yield (40 mg) from compound **24** (95 mg), colorless liquid; R_f = 0.42 (60% EtOAc in hexane); $[\alpha]^{23}_D$ = −9.35 (c 0.3, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.59 (dt, J = 16.8, 10.5 Hz, 1H), 5.89 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 4.26 (m, 1H), 4.20 (m, 1H), 2.87 (dd, J = 17, 5.7 Hz, 1H), 2.37 (dd, J = 17.0, 7.0 Hz, 1H), 2.31−2.25 (m, 2H), 2.21−2.15 (m, 1H), 1.80 (m, 2H), 1.78 (s, 3H), 1.56−1.49 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.5, 139.2, 134.63, 127.7, 115.7, 77.5, 63.5, 39.3, 36.6, 36.1, 35.2, 16.7; IR (neat) ν_{max} 3425,2923, 1708, 1255 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ [M + Na]$^+$ 233.1154, found 233.1155.

(3*R*,5*S*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dien-1-one (23): yellow oil; 14% overall yield (90 mg) from **11** (450 mg); R_f = 0.64 (20% EtOAc in hexane); $[\alpha]^{29}_D$ = −45.2 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.33 (m, 2H), 7.30−7.28 (m, 3H), 6.57 (dt, J = 16.9, 10.5 Hz, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.39 (m, 1H), 5.11 (d, J = 16.9 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 4.52 (m, 1H), 4.04−3.99 (m, 1H), 3.59 (bs, 1H), 3.45 (dd, J = 17.5, 2.9 Hz, 1H), 3.40 (dd, J = 11.5, 7.2 Hz), 3.32−3.23 (m, 2H), 3.05 (dd, J = 13, 10.6 Hz, 1H), 2.89 (d, J = 11.5 Hz, 1H), 2.09−2.06 (m, 2H), 1.78 (s, 3H), 1.76−1.72 (m, 2H), 1.67−1.61 (m, 2H), 0.91 (s, 9H), 0.12 (s, 3H), 0.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ201.5, 172.6, 139.1, 136.7, 133.4, 129.7, 129.1, 127.4, 125.7, 115.0, 70.7, 68.7, 64.9, 46.8, 41.7, 36.9, 35.7, 35.1, 32.2, 26.0, 18.1, 16.9, −4.4, −4.5 ppm; IR (neat) ν_{max} 3485, 2927, 1699, 1257 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{43}NO_3S_2SiNa$ [M + Na]$^+$ 556.2351, found 556.2352.

(3*R*,5*S*,*E*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-8-methylundeca-8,10-dienoate (25). Same as compound **19**: 77% (42 mg) overall yield from **23** (82 mg); colorless liquid; R_f = 0.45 (15% EtOAc in hexane); $[\alpha]^{24}_D$ = −13.2 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (dt, J = 16.8, 10.5 Hz, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 16.8 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.33 (bs, 1H), 3.99 (m, 1H), 3.71 (s, 3H), 3.61 (s, 1H), 2.51 (dd, J = 16, 8 Hz, 1H), 2.44 (dd, J = 16, 4.5 Hz, 1H), 2.06−2.03 (m, 2H), 1.76 (s, 3H), 1.72−1.63 (m, 4H), 0.89 (s, 9H), 0.1 (s, 3H), 0.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ172.9, 139.1, 133.4, 125.7, 115.1, 70.6, 65.2,51.8, 42.2, 41.7, 35.7, 35.0, 26.0, 18.1, 16.9, −4.4, −4.5 ppm; IR (neat) ν_{max} 3435, 2926, 1741, 1585 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{36}O_4SiNa$ [M + Na]$^+$ 379.2281, found 379.2282.

(4*R*,6*S*,*E*)-4-Hydroxy-6-(3-methylhexa-3,5-dienyl)-tetrahydropyran-2-one (2c). Same as compound **2a**: 83% yield (17 mg) from compound **25** (35 mg), colorless oil; R_f = 0.42 (60% EtOAc in hexane); $[\alpha]^{23}_D$ = −18.2 (c 0.3, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.58 (dt, J = 16.8, 10.6 Hz, 1H), 5.88 (d, J = 10.6 Hz, 1H), 5.07 (d, J = 16.8 Hz,1H), 4.97 (d, J = 10.6 Hz, 1H), 4.28−4.22 (m, 1H), 4.19 (m, 1H), 2.86 (dd, J = 17, 5.5 Hz, 1H), 2.36 (dd, J = 17.0, 7.0 Hz, 1H), 2.28−2.24 (m, 2H), 2.20−2.17 (m, 1H), 1.80 (m, 2H), 1.77 (s, 3H), 1.51 (ddd, J = 13.8, 12.0, 8.6 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.2, 139.1, 134.6, 127.7, 115.7, 78.5, 64.4, 40.2, 38.7, 36.2, 35.1, 16.7 ppm; IR (neat) ν_{max} 3417, 1925, 1728, 1249 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ [M + Na]$^+$ 233.1154, found 233.1153.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure, Table 2, copies of NMR (^{1}H, ^{13}C), HRMS of representative compounds, and 2D NMR (COSY, NOESY, ROSEY) of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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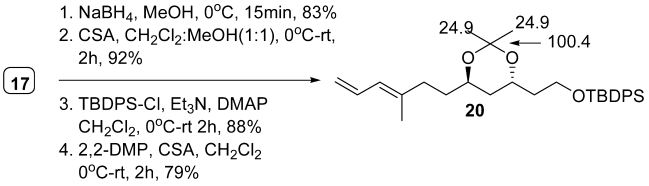
(14) Preparation of compound **20** and characteristic ^{13}C value:



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(16) Personal communications between us and the Koul group indicate that the peak below 1.6 ppm is also present in the NMR spectrum of ieodomycin B and was overlooked in the original report by Shin.