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Total Synthesis and Biological Evaluation of (−)-Apicularen A and Its Analogues

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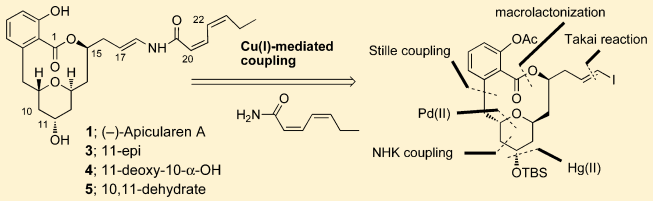
Supporting Information

ABSTRACT: The total synthesis of (−)-apicularen A (**1**), a highly cytostatic 12-membered macrolide, and its analogues is described. The convergent and distinct approach not only provides **1**, but also opens the opportunity to synthesize C10−C11 functional analogues of **1**. The key steps of the total synthesis include assembling of iodoalkene **12** and aldehyde **13** by Nozaki−Hiyama−Kishi (NHK) coupling, stereospecific construction of 2,6-*trans*-disubstituted dihydropyran by Pd(II)-catalyzed 1,3-chirality transfer reaction, and Yamaguchi macrolactonization. The (17*E*,20*Z*,22*Z*)-heptadienoylenamine moiety in the side chain is installed by an efficient Cu(I)-mediated coupling to complete the synthesis. Analogues of C11-epi-, C11-deoxy-C10-α-hydroxy-, and C10−C11 dehydrated apicularen A **3**−**5** were also prepared. Cytostatic activities of (−)-apicularen A and the three analogues for three different cancer cell lines are described.



INTRODUCTION

(−)-Apicularen A (**1**), a highly cytostatic 12-membered macrolide, was first isolated by Kunze et al. from a variety of strains of the myxobacterial genus *Chondromyces* in 1998.[1] Subsequently, Jansen et al. determined the gross structure of **1** by X-ray crystallographic analysis.[2] Compound **1** showed not only the potent cytostatic activity against a wide range of human cancer cell lines, such as ovarian, prostate, lung, kidney, cervix, leukemia, and histiocytic cells, with IC_{50} values in the range of 0.23−6.79 nM,[1] but also antiangiogenesis properties,[3a] induction of apoptosis,[3b,c] production of nitric oxide,[3d] and inhibition of vacuolar (H^+)-ATPase (V-ATPase).[3e−g]

The structures of apicularen A and B and salicylhalamides[4a] possess a unique *N*-(2*Z*,4*Z*)-heptadienoylenamine unit in the branch of the benzomacrolactone ring, and other related members of this benzomacrolactone having the *O*-methyloxime butenamide moiety instead of heptadienoylenamide of apicularen include lobatamides,[4b] oximidines,[4c] CJ-12950, and CJ-13357[4d] (Figure 1). All the members of this macrolide family were found to be potent and selective inhibitors of mammalian V-ATPase.[4−6] Indeed, these naturally occurring V-ATPase inhibitors have received increasing attention[5] and are expected to be promising molecules for the treatment of diseases such as cancer and osteoporosis.[6]

The key structural features of (−)-apicularen A include a 2,6-*trans*-tetrahydropyran (THP) ring and four stereogenic centers embedded in a 12-membered salicylate macrolactone. A highly unsaturated *N*-(2*Z*,4*Z*)-heptadienoylenamine side chain also appears on the macrolactone core. Because of the unique structural features and potent biological activity, **1** has attracted interest from a number of synthetic research groups. To date, five total syntheses[7] including ours have been achieved. In addition, five formal total syntheses[8] and several synthetic efforts[9] as well as analogue syntheses[10] have also been reported.

Although apicularen A displays potent cytostatic activity with an IC_{50} value in the low nanomolar range, its *O*-glycoside apicularen B with *N*-acylglucosamine shows markedly less activity,[1] and its C11 *O*-acetate **2** exhibits 75% less potency.[10a] Nicolaou's group[10a] and Maier's group[10b] have synthesized several analogues of apicularen A by modifying the side chain, and in studying their activity against different cancer cell lines, they found an importance of the *N*-(2*Z*,4*Z*)-heptadienoylenamine unit for the biological activity. It is interesting that the C11 deoxy analogue was less active than **1** against several cancer cell lines but was 2-fold more potent against a few multidrug-resistant cell lines.[10b] These results imply an important role of the functionality around the C11 position as well as the (17*E*,20*Z*,22*Z*)-*N*-dienoylenamine moiety for the cytostatic activities in **1** and these related compounds. However, no synthetic and biological studies for the C10 hydroxy and C10−C11 dehydrated analogues have yet been made. In this paper, we report a full account of the total synthesis of (−)-apicularen A involving more details of C10−C11 functionalization and stereospecific construction of the dienoylenamine unit as well as the synthesis and cytostatic activity of its C10−C11 functional analogues **3**−**5** (Figure 2).

RESULTS AND DISCUSSION

Strategic Consideration. Our interest in the synthesis of (−)-apicularen A and its analogues stemmed from its unique molecular architecture with a bridged 2,6-*trans*-tetrahydropyran located in a 12-membered macrolactone ring and also because

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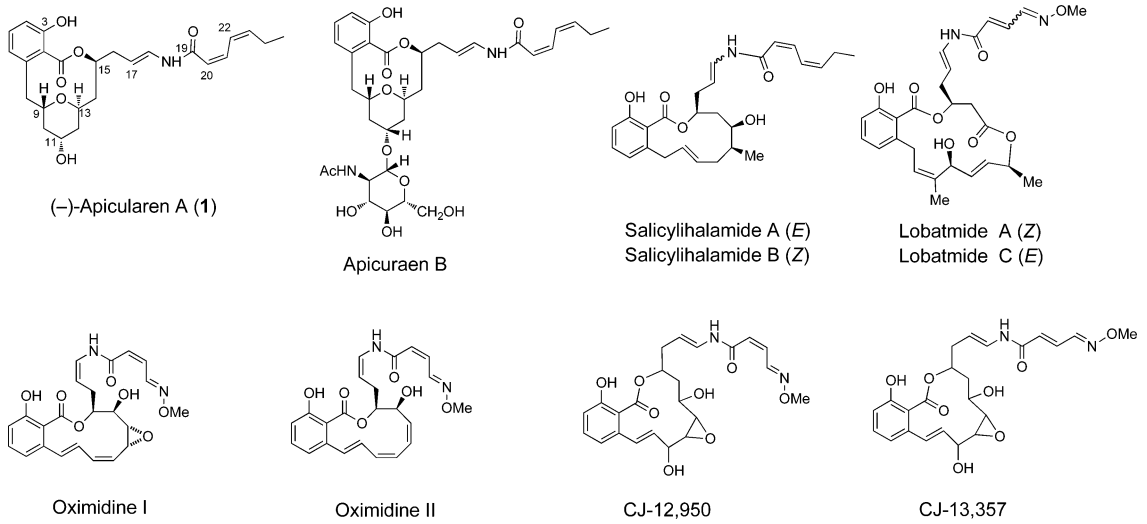


Figure 1. Structures of benzolactone *N*-acylenamide natural products.

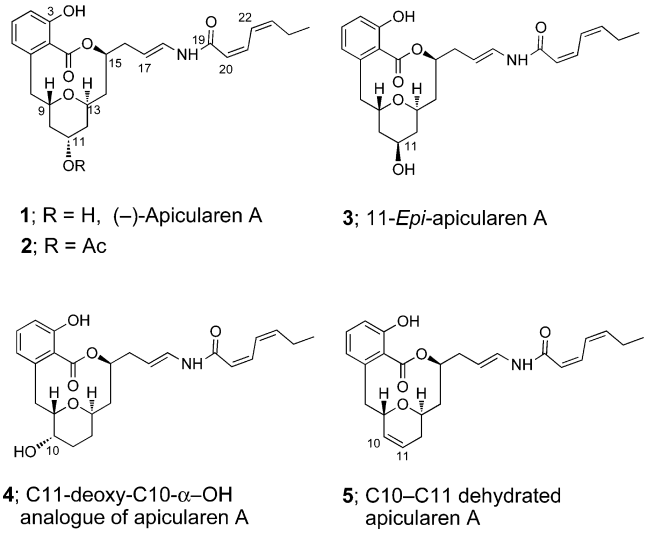
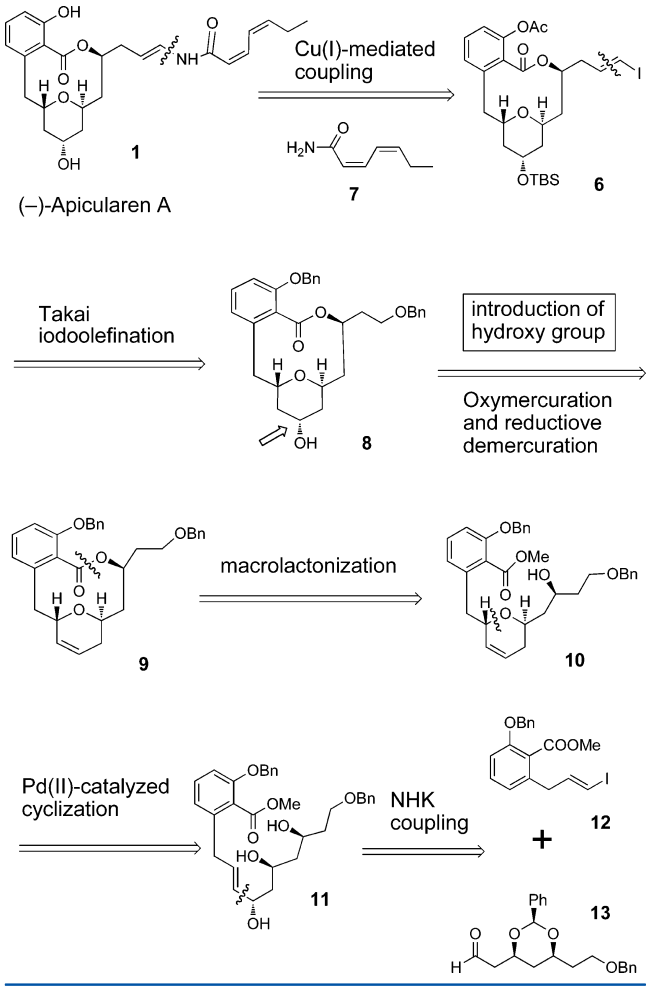


Figure 2. Structure of (−)-apicularen A and its analogues.

of its potent biological activity. Recently in our laboratory, an efficient protocol has been developed for the stereoselective construction of 2,6-*cis*- or 2,6-*trans*-disubstituted dihydropyran and tetrahydropyran rings by using Pd(II)-catalyzed 1,3-chirality transfer reactions.[11,12] This synthetic methodology has been applied for the synthesis of several complex natural products successfully. In continuation, we sought to apply this methodology to the synthesis of **1**, as outlined in our retrosynthetic plan (Scheme 1). In the preceding total syntheses of apicularen A,[7a−d] three different strategies were taken for the construction of the highly sensitive (*Z*,*Z*)-dienoylenamine side chain. De Brabander et al. constructed the side chain from the α,β-unsaturated carboxylic acid via Curtius rearrangement, followed by addition of an organometallic reagent to the isocyanide intermediate to afford the dienoylenamine unit as a mixture of alkenes.[7a] Maier et al. generated the side chain dienoylenamine unit from the *N*-dienoyl hemiaminal by dehydration to provide the unit as a 3:1 mixture of *E*- and *Z*-isomers.[7d] Nicolaou et al. introduced the conjugated (*Z*,*Z*)-dienoylenamine moiety prior to the macrolactonization by Cu(I)-catalyzed coupling of iodoalkene with (2*Z*,4*Z*)-hepta-2,4-dienamide **7** under Shen and Porco's conditions[13] because attempts to construct the side chain

Scheme 1. Retrosynthetic Analysis of 1



(*Z*,*Z*)-dienoylenamine on the macrolactone core gave poor results due to its instability under harsh coupling reaction conditions.[7b] Although Panek et al. successfully attached the (*Z*,*Z*)-dienoylenamine side chain to the macrolactone core,[7c] the coupling product was obtained only in 40% yield.

These reported methods for construction of the side chain have been limited by harsh reaction conditions, low yields, and

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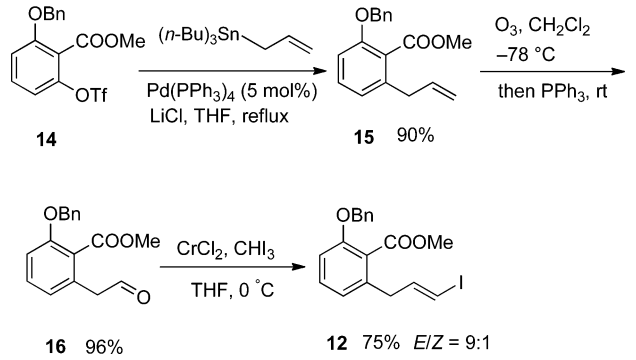
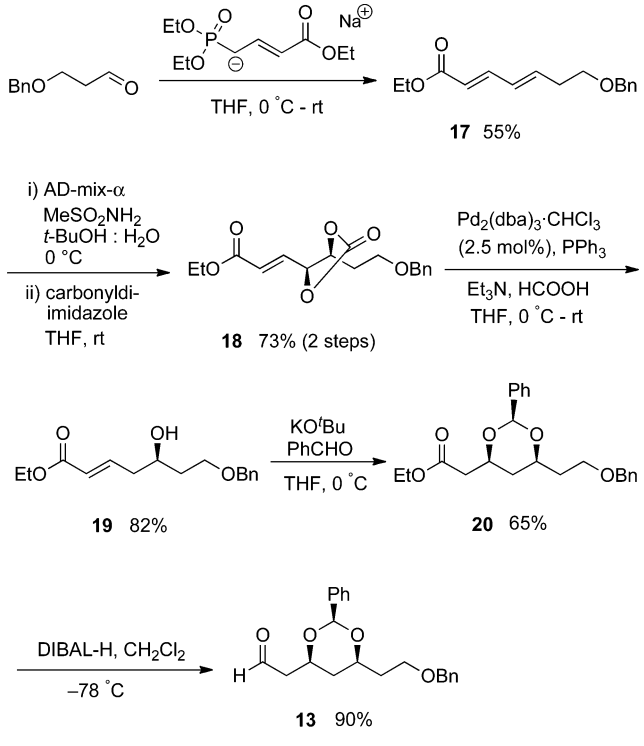
poor selectivities. The development of an efficient and selective method for the construction of the highly sensitive side chain is still required. We have planned an introduction of the *N*-(2*Z*,4*Z*)-hepta-2,4-dienoylenamide side chain by Cu(I)-mediated coupling of the iodoalkene **6** with the dienamide **7** under modified conditions originally developed by Shen and Porco[13] or Buchwald et al.[14] Introduction of an α-hydroxy group at the C11 position would be achieved by oxidation of alkene **9** via epoxidation−reduction, hydroboration−oxidation, or oxymercuration−reduction reaction sequences. The macrolactone **9** could be realized by the Yamaguchi macrolactonization.[15] We envisioned that the Pd(II)-catalyzed cyclization would be useful for regio- and stereospecific construction of the 2,6-*trans*-disubstituted 3,6-dihydro-2*H*-pyran ring system in **10**.[12] The precursor of the cyclization is envisaged as allylic alcohol **11**, which could be assessed by NHK coupling[16] of two advanced fragments, iodoalkene **12** and aldehyde **13** followed by deprotection of benzylidene acetal.

Total Synthesis of (−)-Apicularen A. Syntheses of the fragments **12** and **13** are outlined in Schemes 2 and 3, respectively. The synthesis of **12** began with triflate **14**,[17] which

Scheme 2. Preparation of 12



Scheme 3. Preparation of 13

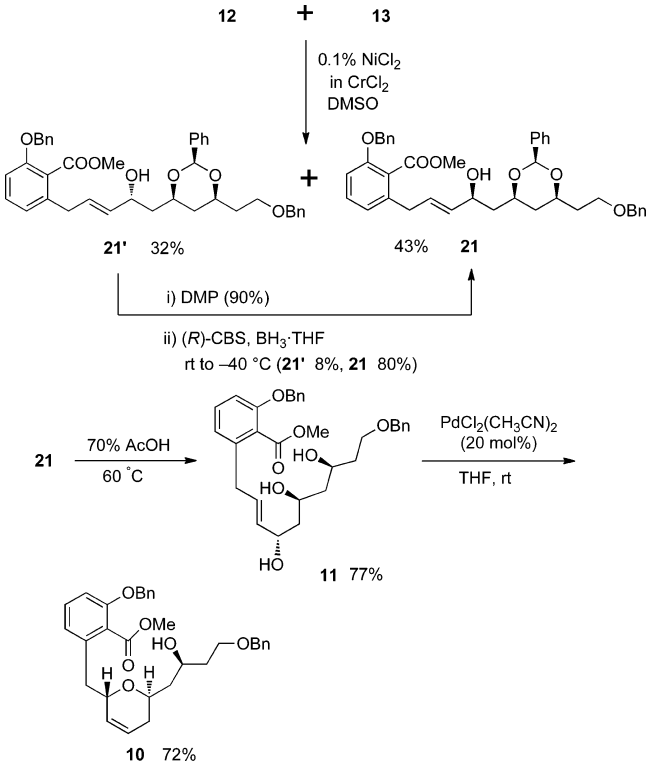


was derived from commercially available methyl 2,6-dihydroxybenzoate. The Stille coupling of **14** with allyltributyltin in the presence of Pd-catalyst gave alkene **15** in 90% yield. Ozonolytic cleavage of the terminal alkene **15** followed by Takai iodoolefination[18] afforded **12** in 72% yield in two steps with excellent selectivity (*E*:*Z* = 9:1).

The synthesis of **13** was performed by the common procedure in the following six steps: (i) Horner−Wadsworth−Emmons condensation of 3-benzyloxypropanal[19] with triethyl phosphonobutenoate[20] (55%), (ii) Sharpless asymmetric dihydroxylation of the alkene (85%, 98% ee), (iii) formation of cyclic carbonate from the resulting diol with carbonyldiimidazole (86%), (iv) Pd-catalyzed reductive ring-opening of the cyclic carbonate (82%), (v) formation of the benzylidene acetal by the Evans protocol[21] (65%), and (vi) DIBAL-H reduction of the ester (90%).

The NHK coupling of the fragments **12** and **13** provided a diastereomeric mixture of allyllic alcohols **21** and **21′** (dr = 1.3:1) in 43 and 32% yields, respectively (Scheme 4). The

Scheme 4. Preparation of C1−C17 Unit



undesired diastereoisomer **21′** was converted into the desired isomer **21** in two steps. Thus, Dess−Martin oxidation[22] of **21′**, followed by diastereoface selective reduction of the resulting ketone using (*R*)-CBS reagent,[23] gave **21** in 72% yield along with **21′** in 7% yield. Deprotection of the benzylidene acetal group of **21** in 70% acetic acid afforded the precursor **11** for the Pd-catalyzed cyclization in 77% yield. The key cyclization of **11** was performed in THF at rt in the presence of $PdCl_2(CH_3CN)_2$ (20 mol %) for 6 h, which smoothly provided the desired 2,6-*trans*-dihydropyran **10** in 72% yield as a single diastereomer, regio- and stereospecifically.

Although we reported the Pd(II)-catalyzed reaction of 6-*exo*- and 6-*endo*-trigonal cyclizations, the mechanism of *endo*-trigonal cyclizations[12] has not been discussed well in comparison with

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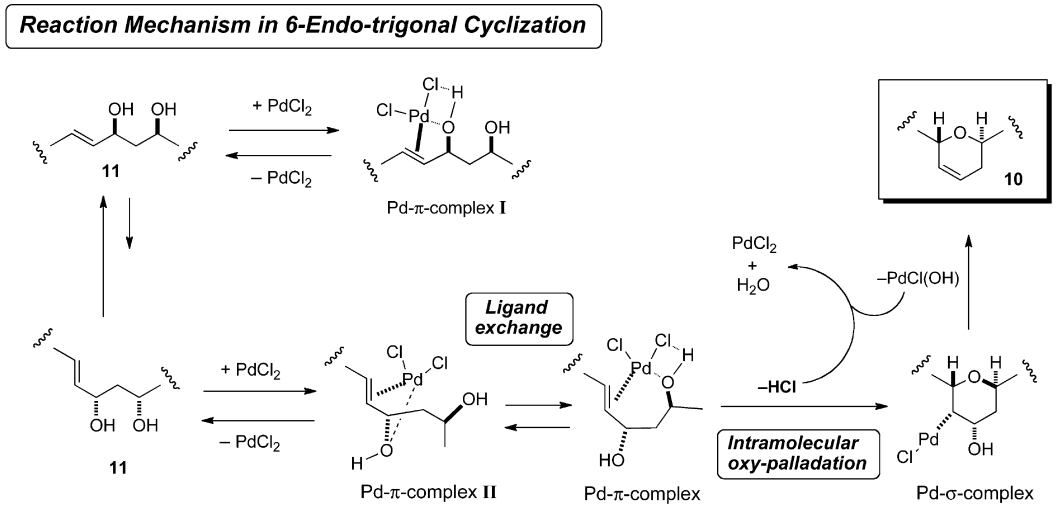
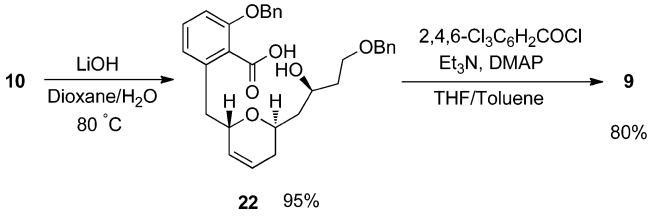
Scheme 5. Reaction Mechanism of 6-*endo*-Trigonal Cyclization



the *exo*-trigonal cyclizations.[11] We considered the formation of **10** via 6-*endo*-trigonal cyclization (Scheme 5). An alkene Pd-π-complex **I** in the extended conformation of **11** would be produced mainly by the hydroxy group directed formation.[11a] However, this complex could not proceed further. On the other hand, the alternative alkene Pd-π-complex **II** generated from the minor conformer in equilibrium afforded *trans*-dihydropyran **10** via the Pd-σ-complex after the ligand exchange and successive intramolecular oxypalladation. Finally, the elimination of PdCl(OH) followed by regeneration of $PdCl_2$ by the reaction with HCl to complete its catalytic cycle.

The next important tasks of the synthesis were to install the macrolactone ring and an α-hydroxy group at the C-11 position regio- and stereoselectively. Saponification of the methyl ester **10** with LiOH provided the seco acid **22** in 95% yield (Scheme 6). Yamaguchi macrolactonization of **22** proceeded quite efficiently to give core macrolactone **9** in 80% yield.

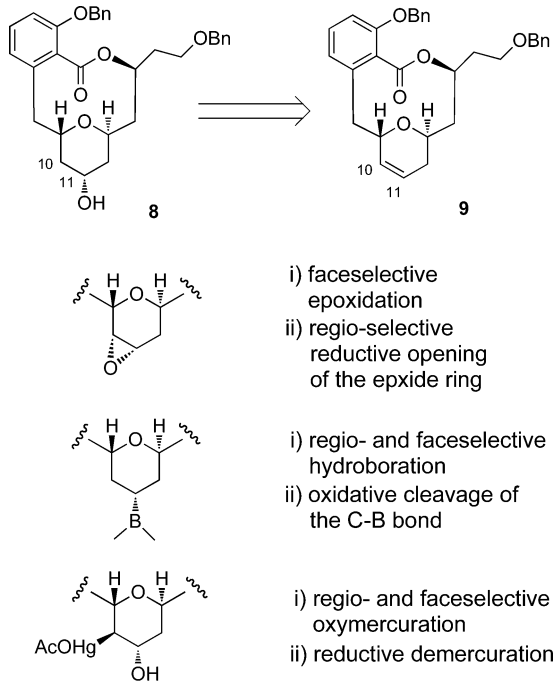
Scheme 6. Synthesis of Macrolactone 9



Face- and regioselective installation of the α-hydroxy group at the C11 position on the C10–C11 double bond is important for the next step. Thus, we explored three different approaches: (a) face- and regioselective hydroboration and oxidative cleavage of the resulting carbon–boron bond; (b) faceselective epoxidation and regioselective reductive opening of the resulting epoxide ring; (c) face- and regioselective oxymercuration and reductive demercuration of the resulted carbon–Hg bond (Scheme 7).

Hydroboration of dihydropyran **9** with BH_3·THF complex and subsequent oxidation with alkaline hydrogen peroxide yielded a C10 secondary alcohol **23** regioselectively in 84% yield with a 1:2 α:β ratio along with the desired C11 alcohol in 12% yield (Scheme 8). Alternatively, epoxidation of **9** with *m*-CPBA followed by DIBAL-H reduction also gave **23** majorly.

Scheme 7. Introduction of the C11 Hydroxy Group



These results indicate that electrophilic reaction occurs from the β-face on the dihydropyran ring of **9**. The diastereoface-selective reaction occurred from the β-side of C10–C11 alkene face in **9**, of which the conformation in Scheme 8 was supported by the calculation study.[24] The regioselective formation of the C–B bond in the hydroboration reaction may take place at the C10 position by a coordinative induction of the ring oxygen atom. If this is correct, electrophilic mercuration might favorably occur at the C10 position from the β-face and install the desired C11 hydroxy group from the α-face. In fact, the treatment of **9** with $Hg(OCOCF_3)_2$ in a mixture of THF and water, followed by reductive demercuration with $NaBH_4$, gave the desired C11 α-hydroxy product **8** preferentially as a mixture with the corresponding β-hydroxy isomer in a 3:1 ratio.

Next, the C11 hydroxy group of **8** was protected with TBSOTf to give **24** and **24′**. At this stage, these C11 diastereomers could be separated, and major α-isomer **24** was obtained in 69% yield

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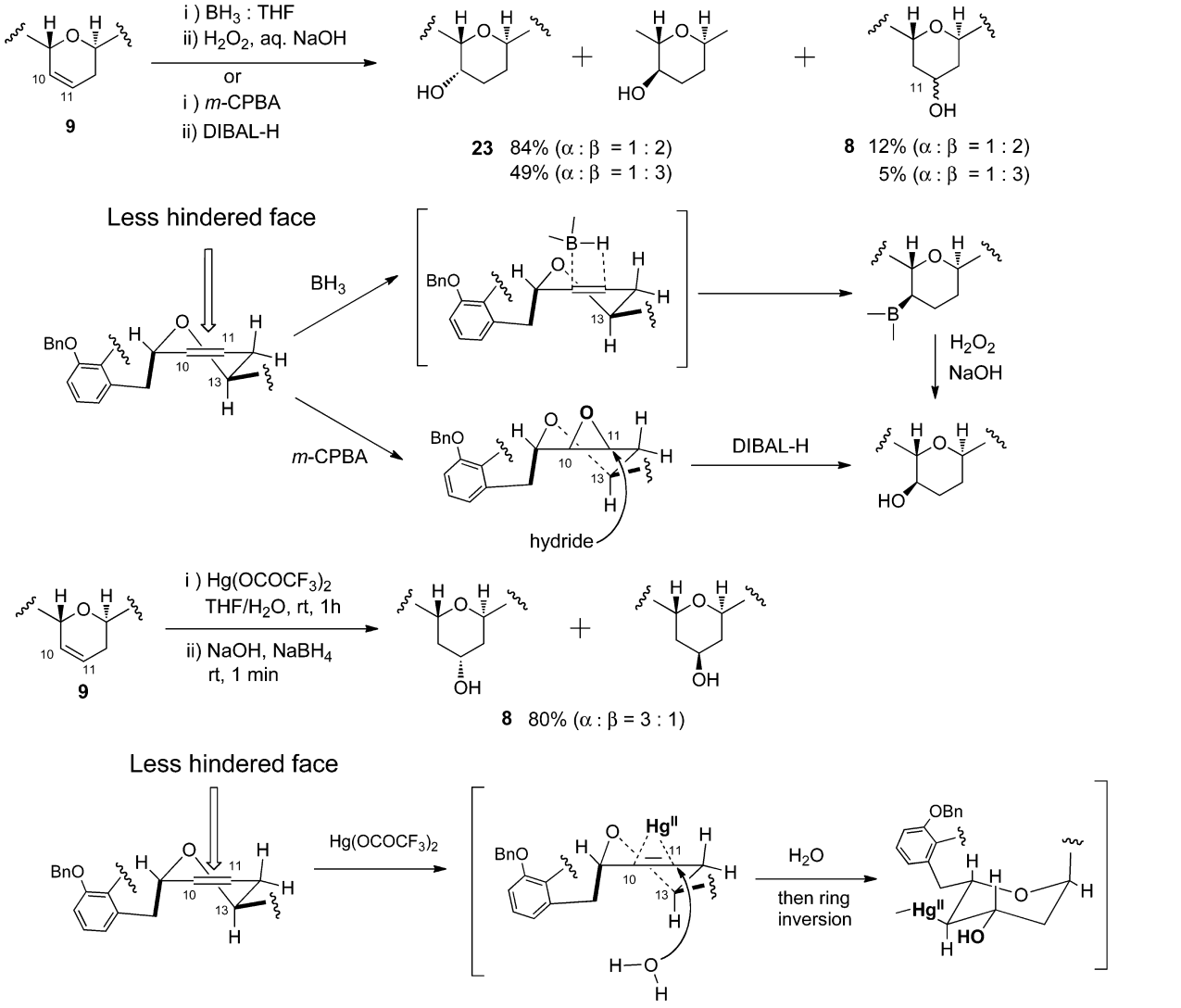
Scheme 8. Faceselective Electrophilic Reaction to 9



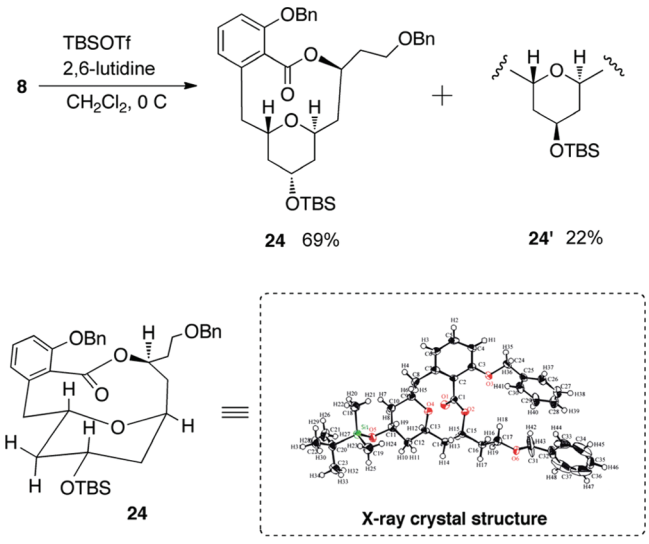
along with undesired minor *β*-isomer **24′** in 22% yield. The stereochemistry of the major diastereomer **24** was confirmed by the single crystal X-ray crystallographic analysis[7e] as shown in Scheme 9.

For completion of the total synthesis, a functionalization of the side chain is remaining, which is outlined in Schemes 10 and 11. Both phenolic and alcoholic *O*-benzyl ethers were removed under the Pd-catalyzed hydrogenolytic conditions to give **25** in quantitative yield. Selective protection of the phenol with acetic anhydride gave acetate **26**, and subsequent oxidation of the primary alcohol at C17 by Dess−Martin periodinane afforded aldehyde **27** in 84% overall yield from **25**. Iodoolefination of **27** by the Takai protocol[18] gave (*E*)-iodoalkene **6** in 65% yield along with the (*Z*)-isomer in 21% yield.

Several formal syntheses[8] have stopped at the stage of **24** or **6**. They probably terminated at this step because of a lack of an efficient coupling method for introducing the conjugated *N*-(*Z*,*Z*)-dienoylenamine unit.

Our initial attempts to couple the key intermediate **6** with **7**[25] under the Porco's conditions[13] involved catalytic use of Liebeskind's catalyst (Cu thiophene-2-carboxylate) with Cs_2CO_3 or Rb_2CO_3 in NMP, DMA, or THF at 70−90 °C or those in the presence of 1,10-phenanthroline. Indeed, these efforts were all fruitless, and only a trace amount of the desired product **28** was obtained.[8a] Next, we examined Buchwald's conditions,[14] using 5 mol % of CuI with Cs_2CO_3 in THF or

Scheme 9. Preparation of 24



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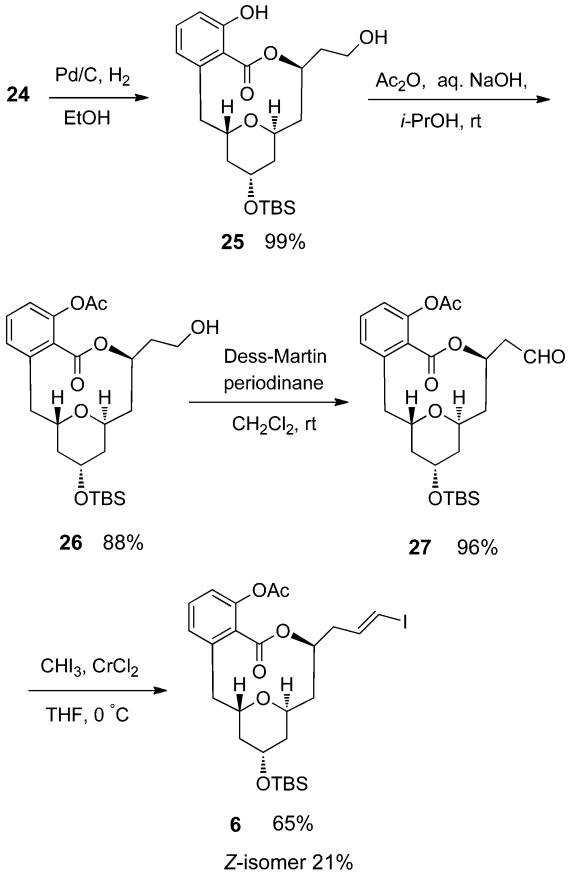
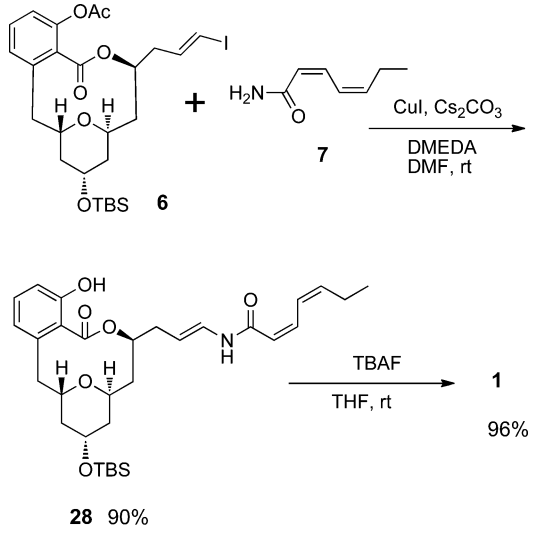
Scheme 10. Preparation of 6



toluene at 60−110 °C in the presence of *N,N′*-dimethylethylenediamine (DMEDA), and this protocol led to a small improvement in the yield of **28**. However, one of the alkenyl bonds was partially isomerized with decomposition of the starting material under the heating conditions, and therefore we employed milder reaction conditions. Gratifyingly, when DMF was used with an excess of CuI (2 equiv), this reaction proceeded at room temperature, and the chemical yield increased dramatically up to 90% without isomerization of the alkenyl bonds (Scheme 11). Fortunately, under the coupling conditions, the phenol acetate was able to be removed at the same time.

Scheme 11. Completion of the Synthesis of 1

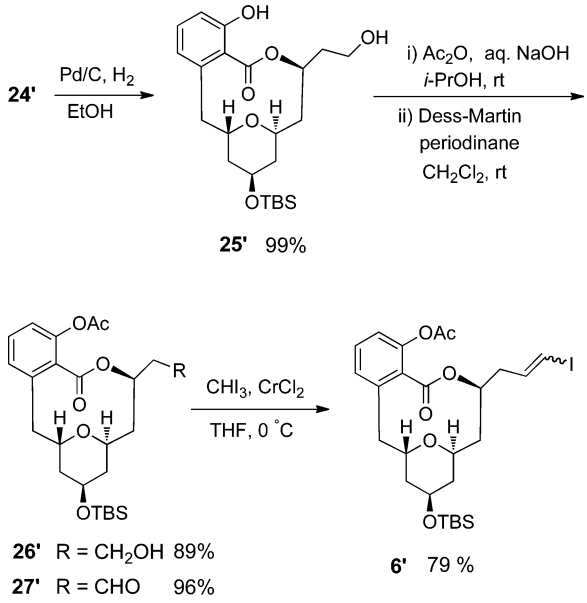


Finally, desilylation of **28** with TBAF afforded (−)-apicularen A (**1**) in 96% yield. The physical and spectroscopic data (^{1}H, ^{13}C, IR, HRMS) as well as specific rotation were fully identical with those reported for the naturally occurring (−)-**1**.[2]

Synthesis and Cytostatic Activity of Analogues of (−)-Apicularen A. In the previous structure and activity investigations of **1** and its analogues in several cancer cell lines, little information was reported regarding the role of the C11 part in cytostatic activity.[10b] Therefore, we planned to synthesize 11-epi-apicularen A (**3**), 11-deoxy-10-α-hydroxyapicularen A (**4**), and C10−C11 dehydrated apicularen A (**5**).

The corresponding precursor, iodoalkene **6′** for the synthesis of **3**, was prepared from **24′** in the same four steps described for the synthesis of **6** (Scheme 12). Hydrogenolysis of **24′** gave debenzylated product **25′** in quantitative yield. Selective acetylation of the phenolic hydroxy group followed by oxidation of the primary hydroxy group gave **27′** in 85% overall yield. The Takai iodoalkenylation provided inseparable *E*- and *Z*-isomers of **6′** in 79% yield with a 3:1 ratio.

Scheme 12. Preparation of 6′



Preparation of iodoalkene **33** was derived from **23** (Scheme 13). The mixture of C10 epimers were silylated with TBSOTf in the presence of 2,6-lutidine to afford the major β-isomer **29** in 65% yield and minor α-isomer **29′** in 32% yield. Hydrogenolysis of **29′** gave **30** in 99% yield. Two steps involving selective acetylation and oxidation provided aldehyde **32** in 83% overall yield from **30**. Iodoalkenylation of **32** gave *E*-idoalkene **33** in 68% yield along with *Z*-isomer in 25% yield.

The remaining precursor **37** was derived from **9** in four steps (Scheme 14). Debenzylation of **9** with BCl_3 in CH_2Cl_2 at −78 °C gave **34** in 96% yield. Selective acetylation and Dess−Martin oxidation gave aldehyde **36** in 80% overall yield from **34**. Finally, iodoalkenylation gave the desired *E*-isomer **37** in 66% yield along with *Z*-isomer in 22% yield.

The final couplings were carried out under the same conditions described for the synthesis of **28**. The reaction of **6′** with dienamide **7** gave the desired C17 *E*-isomer **28′** in 70% yield

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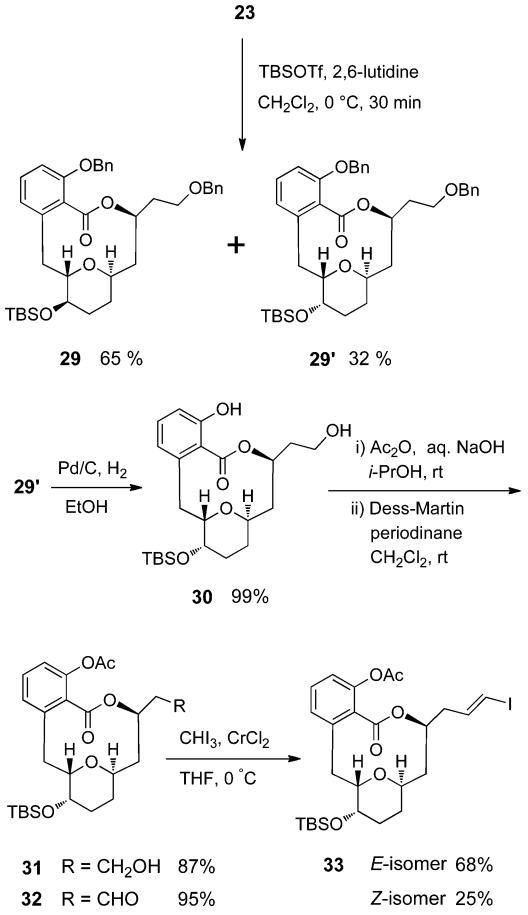
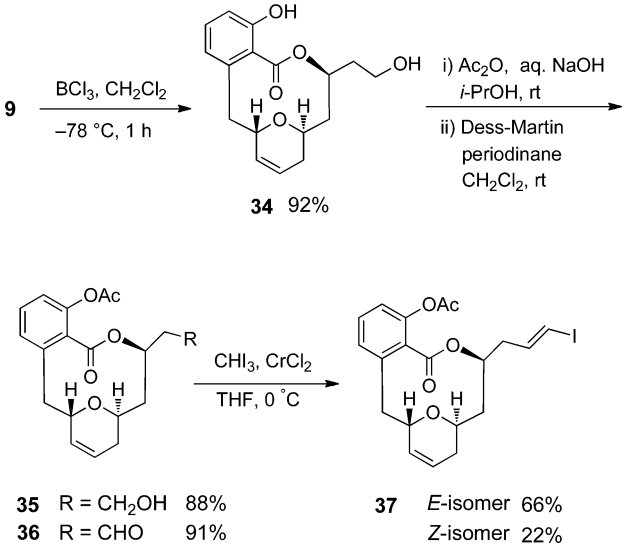
Scheme 13. Preparation of 33

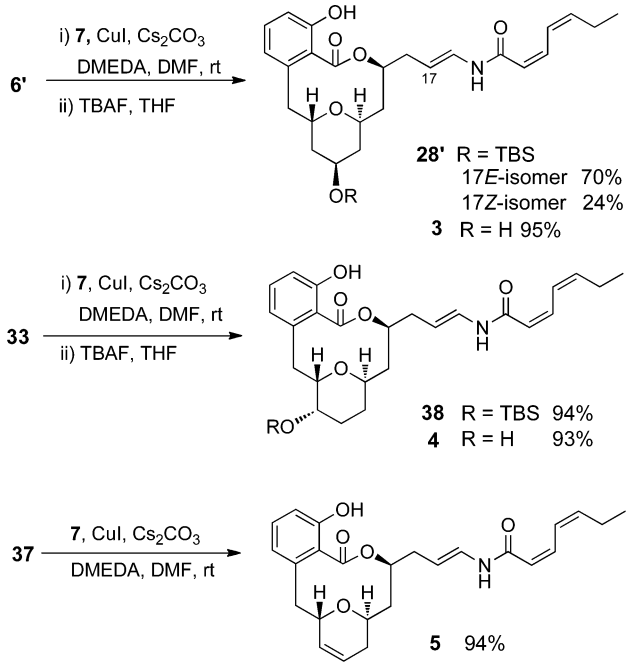


Scheme 14. Preparation of 37



and the corresponding *Z*-isomer in 24% yield. Deprotection of silyl ether of **28′** by TBAF in THF gave C11-epi-apicularen A, **3**, in 95% yield. Similarly, the coupling of **33** with **7** followed by the deprotection of silyl ether furnished the synthesis of C10 α-hydroxy analogue **4** in 84% yield in two steps. Finally, the coupling of **37** with **7** gave compound **5** directly in 94% yield (Scheme 15).

Scheme 15. Synthesis of 3, 4, and 5



Biological Studies. The four synthetic apicularens including (−)-apicularen A were tested for their effects on the proliferation of three tumor cell lines, U-937 (human leukemic monocyte lymphoma cells), HL-60 (human promyelocytic leukemia cells), and PC-3 (human prostate cancer cells) (Table 1). Adriamycin was used as a reference. The C11 epimer

Table 1. Cytostatic Activity (IC_{50} value) of Compounds 1, 3, 4, and 5

		compound			
cell line	adriamycin	**1**	**3**	**4**	**5**
U-937[a]	6.1	27	417	115	27
HL-60[a]	9.2	4.0	449	44	14
PC-3[b]	9.4	3.6	9.5	3.0	1.4

[a] IC_{50} values [nM]. [b] IC_{50} values [μM].

3 was found to be 18- or 112-fold less active than **1** against U-937 and HL-60. On the other hand, the C10 isomer **4** indicated 5- to 10-fold less potency than **1**. Compound **5** showed almost the same potency as **1** against U-937 and weaker against HL-60. However, it is interesting to note that compound **4** is a little more effective than **1** against PC-3, and compound **5** is even more active. Although the C11 deoxy analogue possesses weak activity,[10b] our study showed that either C10 α-hydroxy or C10−C11 unsaturated functional groups on the *trans*-THP ring are effective for a very high potency of the cytostatic activity for these cancer cell lines.

CONCLUSION

A concise total synthesis of (−)-apicularen A and novel C10−C11 functionalized analogues **3**, **4**, and **5** has been devised. This convergent and distinct approach involves number of key features. In particular, we could demonstrate efficiency of Pd(II)-catalyzed 1,3-chirality transfer reaction for the stereospecific construction of 2,6-*trans*-disubstituted dihydropyran in this complex natural product synthesis. Oxymercuration and

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reductive demercuration installed the α-hydroxy group at the C11 position regio- and stereoselectively. The Cu(I)-mediated coupling of the iodoalkene with the dienamide has been improved under the mild conditions in DMF without isomerization of alkenyl bonds. Structure−activity relationship studies revealed the importance of C11 α-hydroxy group as well as C10−C11 unsaturated carbon group for high potency of the activity.

EXPERIMENTAL SECTION

Preparation of 23 by Hydroboration and Oxidation. To a stirred solution of **9** (33 mg, 0.081 mmol) in THF (2 mL) was added BH_3·THF (102 μL of 1 M solution in THF, 0.102 mmol) at 0 °C, and the mixture was stirred for 1 h at rt. The reaction was quenched with H_2O_2 (0.5 mL, 30% solution) and NaOH (0.5 mL, 4 N aqueous solution) and stirred further for 3 h at rt. Then, it was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$. Removal of solvent and purification of the crude product by flash column chromatography (silica gel, 60% EtOAc/hexane) afforded **23** (28.7 mg) in 84% yield as a mixture of α and β isomers (1:2) and its regioisomer **8** (4 mg) in 12% yield as a mixture of α and β isomers (1:2). **23**: Colorless oils, R_f (70% EtOAc/hexane) = 0.50; IR ($CHCl_3$ film, cm^{-1}) 3441, 2924, 1715, 1578, 1455, 1265, 1074, 734, 698; ^1H NMR (270 MHz, $CDCl_3$) major isomer δ 7.28 (m, 11H), 6.83 (m, 2H), 5.76 (m, 1H), 5.00 (s, 2H), 4.07 (m, 4H), 3.80 (dd, J = 9.45, 3.78 Hz, 1H), 3.60 (m, 1H), 3.30 (m, 3H), 2.71 (dd, J = 15.1, 1.1 Hz, 1/2H), 2.60 (dd, J = 14.5, 1.1 Hz, 1H), 1.74 (m, 8H); ^{13}C NMR (67.5 MHz, $CDCl_3$) major isomer δ 169.6, 154.8, 138.7, 138.4, 136.5, 130.0, 129.8, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 125.7, 123.2, 123.0, 110.2, 81.1, 72.9, 71.2, 70.5, 69.8, 69.1, 68.8, 68.1, 66.2, 39.1, 37.6, 35.3, 35.0, 34.2, 32.7, 28.3, 27.8, 27.0, 26.6; FAB-MS m/z 503 $(M + H)^+$; FAB-HRMS m/z 503.2427 (Calcd for $C_{31}H_{35}O_6$ 503.2434).

Preparation of 23 by Epoxidation and Reduction. To a stirred solution of **9** (12 mg, 0.029 mmol) in CCl_4 (2 mL) was added *m*CPBA (10.1 mg, 0.0587 mmol), and the mixture was stirred for 48 h at 0 °C. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and condensed under reduced pressure. The crude product was dissolved in dry CH_2Cl_2 (2 mL), and DIBAL-H (1 M toluene solution 42 μL, 0.042 mmol) was dropped into the mixture at −78 °C. The mixture was further stirred at the same temperature for 30 min and quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2 (30 mL), and the extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed, and the residue was purified by flash column chromatography (silica gel, 60% EtOAc/hexane), which afforded **23** (6.1 mg) in 49% yield as a mixture of α and β isomers (1:3) and its regioisomer **8** (0.8 mg) in 5% yield as a mixture of α and β isomers (1:3).

Preparation of 8 by Oxymercuration of 9. To a stirred solution of **9** (48 mg, 0.118 mmol) in THF (3 mL) and water (2.5 mL) was added mercury(II) trifluoroacetate (126 mg, 0.297 mmol), and the mixture was stirred for 1 h at rt. Aq NaOH (3 N, 0.5 mL) solution and $NaBH_4$ (7.4 mg, 0.198 mmol) were added to the mixture for few minutes. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic extract was dried over $MgSO_4$. Removal of solvent and purification of the crude product by flash column chromatography (silica gel, 60% EtOAc/hexane) afforded **8** (40 mg) in 80% yield as an inseparable mixture of α and β diastereomers (3:1). Colorless oil: R_f (70% EtOAc/hexane) = 0.39; IR ($CHCl_3$ film, cm^{-1}) 3434, 2921, 1717, 1578, 1455, 1265, 1091, 751; ^1H NMR (500 MHz, $CDCl_3$) for major isomer δ 7.21 (m, 11H), 6.77 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 5.66 (m, 1H), 4.93 (s, 2H), 4.24 (m, 1H), 3.99 (m, 4H), 3.38 (dd, J = 14.5, 10.0 Hz, 1H), 3.26 (m, 2H), 2.38 (dd, J = 15.5, 1.5 Hz, 3/4 H), 2.27 (dd, J = 14.0, 1.5 Hz, 1/3 H, minor), 1.91 (dt, J = 9.5, 5.0 Hz, 1H) 1.77 (m, 5H), 1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) for major isomer δ 169.1, 154.9, 138.7, 138.5, 136.6, 129.8, 128.4, 128.2, 128.1, 128.0, 127.98, 127.95, 127.8, 127.6, 127.6, 127.5, 127.4, 127.3, 125.8, 127.7, 123.0, 122.9 110.3, 74.9, 72.9, 71.1, 70.9, 70.5, 66.9, 66.3, 65.3, 65.0, 41.0, 39.2, 39.1, 39.0, 38.2, 35.2; EI-MS m/z 502 (M^+), 502, 484, 411, 393, 305, 287, 261, 243, 224, 180, 146, 91, 81, 71, 55, 40; EI-HRMS m/z 502.2361 (Calcd for $C_{31}H_{34}O_6$ 502.2355).

***O*-TBS Protected Compounds 24 and 24′.** To a mixture of **8** (42 mg, 0.083 mmol) and 2,6-lutidine (28 μL, 0.25 mmol) in CH_2Cl_2 (3 mL) at 0 °C was dropped TBSOTf (38 μL, 0.17 mmol). The reaction was stirred at 0 °C for 30 min before being quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, 7−10% EtOAc/hexane) to afford major isomer **24** (36 mg) in 69% yield and minor isomer **24′**(11.5 mg) in 22% yield. Major isomer **24**: mp 122−125 °C; R_f (20% EtOAc/hexane) = 0.45; $[\alpha]_D^{24}$ −4.8 (*c* 0.4 $CHCl_3$); R_f (20% EtOAc/hexane) = 0.45; IR ($CHCl_3$ film, cm^{-1}) 3019, 1715, 1579, 1455, 1215, 755, 668; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 11H), 6.82 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.75 (m, 1H), 5.00 (s, 2H), 4.36 (td, J = 9.3, 3.3 Hz, 1H), 4.11 (q, J = 11.4 Hz, 2H), 3.98 (m, 2H), 3.60 (dd, J = 14.4, 10.8, Hz, 1H), 3.34 (m, 2H), 2.39 (dd, J = 14.7, 1.5 Hz, 1H), 1.86 (m, 4H), 1.60 (m, 4H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 154.8, 139.4, 138.5, 136.7, 129.8, 128.4, 128.2, 127.9, 127.8, 127.7, 127.3, 126.0, 122.9, 110.1, 74.2, 73.0, 71.1, 70.4, 66.4, 65.4, 65.3, 39.9, 39.6, 38.7, 37.9, 35.1, 25.8, 17.9, −4.8; EI-MS m/z 616 (M^+), 559, 525, 419, 393, 359, 321, 307, 287, 261, 235, 224, 199, 181, 163, 145, 131, 107, 91, 83, 73, 57; EI-HRMS m/z 616.3225 (Calcd for $C_{37}H_{48}O_6Si$ 616.3220). Minor isomer **24′**: mp 94−97 °C; R_f (20% EtOAc/hexane) = 0.50; $[\alpha]_D^{24}$ − 11.7 (*c* 0.2 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3015, 1715, 1579, 1458, 1259, 1215, 1091, 755, 667; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 11H), 6.85 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 5.74 (m, 1H), 5.00 (s, 2H), 4.12 (m, 1H), 4.11 (dd, J = 15.6, 12.0 Hz, 2H), 3.95 (m, 2H), 3.41 (dd, J = 13.8, 1.7, Hz, 1H), 3.33 (m, 2H), 2.33 (dd, J = 14.1, 1.5 Hz, 1H), 1.82 (m, 7H), 1.35 (m, 1H), 0.88 (s, 9H), 0.6 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 154.7, 139.3, 138.5, 136.6, 130.0, 128.5, 128.2, 128.0, 127.9, 127.6, 127.3, 125.8, 123.0, 110.2, 74.9, 72.9, 71.3, 70.5, 67.7, 66.3, 66.0, 41.2, 40.5, 39.1, 36.6, 34.8, 25.8, 18.0, −4.5, −4.6; FAB-MS m/z 639 $(M + Na)^+$; FAB-HRMS m/z 639.3112 (Calcd for $C_{37}H_{48}O_6SiNa$ 639.3118).

(2*Z*,4*Z*)-Hepta-2,4-dienamide 7. Amide fragment **7** was prepared according to literature procedure,[25] and ^1H NMR was matched with that reported in the literature: ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 1H), 6.81 (dd, J = 11.7, 10.5 Hz, 1H), 5.85 (m, 1H), 5.65 (d, J = 11.7 Hz, 1H), 5.44 (br, s, 2H), 2.27 (dtd, J = 15, 7.5, 1.5 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H).

Coupling of 6 and 7, Preparation of 28. An oven-dried two-neck 10 mL round-bottom flask was cooled under argon and charged with CuI (8.8 mg, 0.046 mmol), Cs_2CO_3 (37 mg, 0.116 mmol), and **6** (14 mg, 0.023 mmol). The flask was evacuated and backfilled with argon. A mixture of *N*,*N*′-dimethylethylenediamine (12 μL, 0.116 mmol) and **7** (14.5 mg, 0.116 mmol) in dry degassed DMF (2 mL) was added under argon. The resulting dark green mixture was stirred at rt for 1 h. After completion, the reaction mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$. Removal of solvent and purification of the crude product by silica gel flash column chromatography (30% EtOAc/hexane) provided **28** (11.7 mg) in 90% yield as a white solid: mp 152−155 °C (chloroform); R_f (50% EtOAc/hexane) = 0.52; $[\alpha]_D^{24}$ +43.7 (*c* 0.45 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3304, 2927, 1760, 1644, 1463, 1251, 1067, 835, 773; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.93 (dd, J = 14.7, 10.8 Hz, 1H), 6.78 (m, 2H), 6.25 (br, s, 1H), 5.87 (m, 1H), 5.53 (d, J = 11.4 Hz, 1H), 5.46 (m, 1H), 5.18 (dt, J = 14.7, 7.5 Hz, 1H), 4.33 (td, J = 9.9, 4.5 Hz, 1H), 4.03 (m, 1H), 3.85 (m, 1H), 3.57 (dd, J = 14.7, 11.4 Hz, 1H), 2.39 (m, 3H), 2.26 (dtd, J = 15.3, 9.3, 1.5 Hz, 2H), 1.86 (m, 2H), 1.65 (m, 4H), 1.03 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 163.5, 152.7, 142.4, 139.0, 137.0, 130.6, 125.5, 123.8, 123.2, 122.3, 119.1, 114.9, 107.4, 77.4, 73.9, 65.9, 65.4, 39.9, 39.3, 38.7, 37.8, 35.1, 25.7, 20.7, 18.0, 13.9, −4.7; EI-MS m/z 555 (M^+), 540, 526, 498, 480, 446,

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423, 404, 390, 373, 347, 321, 298, 272, 252, 233, 215, 191, 163, 149, 135, 125, 109, 96, 81, 73, 67, 56, 44; EI-HRMS m/z 555.3019 (Calcd for $C_{31}H_{45}NO_6Si$ 555.3016).

(−)-Apicularen A (1). To a solution of **28** (14 mg, 0.025 mmol) in dry THF (1 mL) was added TBAF (75 μL, 1 M solution in THF, 0.075 mmol) at rt, and the reaction was stirred for 5 h. Removal of solvent under reduced pressure and purification by flash column chromatography (silica gel, 40% acetone/hexane) afforded **1** (10.7 mg) in 96% yield as a white solid: mp 136−140 °C (methanol); R_f (50% acetone/hexane) = 0.40; $[\alpha]_D^{24}$ −21.0 (c 0.55, CH_3CN); IR (KBr, cm^{-1}) 3337, 2996, 1717, 1646, 1524, 1462, 1289, 1076, 777; ^1H NMR (500 MHz, acetone-d_6) δ 9.08 (d, J = 10.0 Hz, 1H), 8.37 (s, 1H), 7.51 (t, J = 11 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.91−6.82 (m, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 5.82−5.78 (m, 1H), 5.74 (d, J = 11 Hz, 1H), 5.47−5.41 (m, 1H), 5.27−5.20 (m, 1H), 4.25 (m, 1H), 3.98 (m, 1H), 3.86 (m, 1H), 3.77 (d, J = 3.5 Hz, 1H), 3.34 (dd, J = 14.5, 9.5 Hz, 1H), 2.43 (d, J = 14.5 Hz, 1H), 2.35−2.28 (m, 2H), 2.27−2.24 (m, 2H), 1.94−1.90 (m, 1H), 1.86−1.79 (m, 1H), 1.70−1.65 (m, 1H), 1.59−1.56 (m, 1H), 1.00 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.3, 163.6, 154.2, 141.4, 140.2, 136.7, 130.2, 126.3, 125.4, 122.2, 120.9, 114.4, 108.0, 74.2, 73.7, 68.0, 64.9, 40.3, 39.9, 39.6, 38.9, 36.4, 21.0, 14.3; FAB-MS m/z 464 (M + Na)$^+$; FAB-HRMS m/z 464.2049 (Calcd for $C_{25}H_{31}NO_6Na$ 464.2047).

Synthesis of Analogues. Preparation *O*-TBS Protected Compounds 29 and 29′. To a solution of alcohol **23** (80 mg, 0.158 mmol) and 2,6-lutidine (74 μL, 0.636 mmol) in CH_2Cl_2 (6 mL) was added TBSOTf (110 μL, 0.476 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C for 30 min before being quenched with water. The aqueous layer was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7−10% EtOAc/hexane) to afford the *O*-TBS protected major isomer **29** (64 mg) in 65% yield and minor isomer **29′** (32 mg) in 32% yield as white solids. Major isomer **29**: mp 112−114 °C (20% EtOAc/hexane); R_f (20% EtOAc/hexane) = 0.46; $[\alpha]_D^{24}$ −1.1 (c 0.5 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 2928, 1729, 1579, 1455, 1260, 1106, 836, 755, 697; ^1H NMR (270 MHz, $CDCl_3$) δ 7.31 (m, 11H), 6.81 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.71 (m, 1H), 4.99 (s, 2H), 4.05 (q, J = 11.6 Hz, 2H), 4.02 (m, 1H), 3.71 (t, J = 7.2 Hz, 1H), 3.50 (m, 1H), 3.33 (m, 2H), 3.08 (dd, J = 14.5, 9.1 Hz, 1H), 2.73 (d, J = 14.0 Hz, 1H), 2.08 (m, 1H), 1.83 (m, 3H), 1.58 (m, 4H), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.9, 155.0, 138.7, 138.5, 136.6, 129.7, 128.5, 128.2, 127.9, 127.8, 127.7, 127.3, 125.6, 123.1, 110.1, 79.3, 72.9, 71.1, 70.5, 70.2, 69.8, 66.3, 37.6, 35.8, 35.4, 29.1, 27.9, 25.7, 17.9, −4.1, −4.7; FAB-MS m/z 639 (M + Na)$^+$; FAB-HRMS m/z 639.3115 (Calcd for $C_{37}H_{48}O_6SiNa$ 639.3118). Minor isomer **29′**: mp 115−117 °C (20% EtOAc/hexane); R_f (20% EtOAc/hexane) = 0.53; $[\alpha]_D^{24}$ −4.7 (c 0.25 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 2926, 1722, 1579, 1456, 1259, 1080, 755, 698; ^1H NMR (270 MHz, $CDCl_3$) δ 7.31 (m, 11H), 6.83 (d, J = 7.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.76 (m, 1H), 4.99 (s, 2H), 4.09 (dd, J = 16.2, 11.1 Hz, 2H), 3.90 (m, 3H), 3.29 (m, 3H), 2.68 (d, J = 14.5 Hz, 1H), 1.72 (m, 8H), 0.93 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 154.7, 139.9, 138.5, 136.6, 130.0, 128.4, 128.2, 128.0 127.9, 127.6, 127.3, 126.4, 123.0, 109.9, 80.5, 72.9, 71.3, 70.4, 68.6, 67.8, 66.3, 40.1, 34.9, 30.1, 29.2, 28.7, 25.8, 18.0, −4.6, −4.8; FAB-MS m/z 639 (M + Na)$^+$; FAB-HRMS m/z 639.3115 (Calcd for $C_{37}H_{48}O_6SiNa$ 639.3118).

Preparation of 25′ and 30. A mixture of dibenzyl ether **24′** or **29′** (0.05 mmol) and Pd/C (10 mg, 10% on charcoal) in ethanol (3 mL) was stirred under H_2 at rt for 12 h. The Pd charcoal was removed by filtration through a pad of Celite, and the filtrate was condensed. The crude product was purified by flash column chromatography (silica gel, 60% EtOAc/hexane) to afford diol **25′** or **30** in quantitative yield.

25′, 99% yield. White solid: R_f (40% EtOAc/hexane) = 0.15; $[\alpha]_D^{24}$ +22.3 (c 0.7 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3501, 3019, 1717, 1586, 1466, 1215, 1085, 767, 669; ^1H NMR (270 MHz, $CDCl_3$) δ 8.80 (br, s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.70 (dd, J = 7.5, 0.8 Hz, 1H), 6.66 (dd, J = 8.3, 0.8 Hz, 1H), 5.71 (tt, J = 11.1, 3.5 Hz, 1H), 3.98 (m, 5H), 3.40 (dd, J = 13.8, 12.1 Hz, 1H), 2.28 (dd, J = 13.8, 1.3 Hz, 1H), 1.91 (m, 2H), 1.71 (m, 5H), 1.35 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.9, 152.6, 139.1, 130.5, 123.2, 121.7, 114.0, 74.7, 74.6, 67.3, 65.7, 61.5, 41.3, 41.2, 38.5, 36.6, 36.2, 25.7, 18.0, −4.6; FAB-MS m/z 437 (M + H)$^+$; FAB-HRMS m/z 437.2357 (Calcd for $C_{23}H_{37}O_6Si$ 437.2359).

30, 99% yield. White solid: R_f (40% EtOAc/hexane) = 0.15; $[\alpha]_D^{24}$ +21.8 (c 0.6 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3502, 3476, 2928, 1721, 1586, 1466, 1215, 1076, 772, 668; ^1H NMR (270 MHz, $CDCl_3$) δ 8.63 (br, s, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 5.73 (m, 1H), 4.09 (t, J = 9.9 Hz, 1H), 3.91 (m, 4H), 3.74 (m, 1H), 3.37 (dd, J = 13.7, 11.8 Hz, 1H), 2.51 (dd, J = 14.0, 1.3, Hz, 1H), 1.84 (m, 7H), 1.41 (m, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.6, 152.6, 139.7, 130.5, 123.7, 121.7, 113.9, 80.4, 74.6, 68.5, 67.5, 61.5, 41.1, 36.3, 29.7, 29.4, 28.4, 25.7, 18.0, −4.6, −4.9; FAB-MS m/z 437 (M + H)$^+$; FAB-HRMS m/z 437.2364 (Calcd for $C_{23}H_{37}O_6Si$ 437.2359).

Deprotection of Benzyl Ether for the Synthesis of 34. To a stirred solution of macrolactone **9** (25 mg, 0.051 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added BCl_3 (1 M solution in CH_2Cl_2 0.26 mL, 0.26 mmol). The resulting reaction mixture was stirred at the same temperature for 1 h. The mixture was quenched with methanol (0.1 mL) and saturated solution of $NaHCO_3$ (3 mL) and allowed to warm up to rt. The mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the organic layer was dried over $MgSO_4$. Solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica (60% EtOAc/hexane) to afford **34** (14.5 mg) in 92% yield as a white solid: mp 190−193 °C (CH_2Cl_2); R_f (40% EtOAc/hexane) = 0.17; $[\alpha]_D^{24}$ +47.0 (c 0.75 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3487, 3019, 1723, 1585, 1465, 1215, 769, 668; ^1H NMR (270 MHz, $CDCl_3$) δ 8.91 (br, s, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.75 (dd, J = 7.5, 0.8 Hz, 1H), 6.68 (dd, J = 8.1, 0.8 Hz, 1H), 5.81 (m, 3H), 4.17 (dt, J = 12.1, 2.7 Hz, 1H), 4.00 (m, 4H), 3.37 (dd, J = 13.5, 11.9 Hz, 1H), 2.41 (dd, J = 13.7, 2.1 Hz, 1H), 1.89 (m, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.5, 152.8, 138.8, 130.6, 128.9, 125.5, 123.4, 121.5, 114.3, 76.0, 74.5, 66.3, 61.5, 41.3, 36.5, 36.2, 31.2; FAB-MS m/z 307 (M + H)$^+$; FAB-HRMS m/z 305.1394 (Calcd for $C_{17}H_{21}O_5$ 305.1389).

Preparation of 26′, 31, and 35. To a stirred solution of **25′**, **30**, or **34** (0.06 mmol) in isopropanol (3 mL) was added aq NaOH solution (4 N, 0.5 mL). After the reaction was stirred for 5 min, acetic anhydride (17 μL, 0.18 mmol) was added. The reaction mixture was further stirred for 10 min at rt and diluted with water (5 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layer was dried over $MgSO_4$. Removal of solvent and purification of the crude product by flash column chromatography (silica gel, 50% EtOAc/hexane) afforded **26′**, **31**, or **35** in 89, 87, and 88% yields, respectively.

26′, white solid: R_f (40% EtOAc/hexane) = 0.28; $[\alpha]_D^{24}$ +14.5 (c 0.7 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3501, 2927, 1771, 1718, 1459, 1366, 1256, 1199, 1085, 836, 755; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.3, 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 2H), 5.69 (m, 1H), 4.19 (m, 1H), 3.98 (m, 2H), 3.78 (m, 2H), 3.35 (dd, J = 14.5, 11.0 Hz, 1H), 2.41 (dd, J = 14.5, 1.3 Hz, 1H), 2.28 (s, 3H), 2.15 (m, 1H), 1.87 (m, 2H), 1.74 (m, 3H), 1.61 (m, 1H), 1.37 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168. 8, 168.7, 146.5, 139.3, 129.8, 128.6, 128.0, 120.6, 72.6, 68.5, 65.6, 58.9, 39.9, 39.8, 38.9, 37.8, 37.2, 25.7, 20.8, 18.0, −4.6, −4.7; FAB-MS m/z 479 (M + H)$^+$; FAB-HRMS m/z 479.2460 (Calcd for $C_{25}H_{39}O_7Si$ 479.2465).

31, colorless oil, R_f (50% EtOAc/hexane) = 0.22; $[\alpha]_D^{24}$ +15.8 (c 0.50 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3442, 2929, 1771, 1721, 1608, 1459, 1369, 1269, 1200, 1079, 733; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.3, 7.5 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 5.74 (m, 1H), 4.00 (t, J = 10.2 Hz, 1H), 3.82 (m, 4H), 3.29 (dd, J = 14.5, 11.3 Hz, 1H), 2.65 (dd, J = 14.5, 1.3 Hz, 1H), 2.28 (s, 3H), 1.90 (m, 2H), 1.69 (m, 6H), 1.40 (m, 1H), 0.93 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.8, 168.7, 146.3, 140.1, 129.9, 129.2, 127.9, 120.4, 79.7, 72.7, 68.4, 68.0, 59.0, 39.8, 37.1, 30.2, 29.0, 28.5,

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25.7, 20.9, 18.0, −4.5, −4.9; FAB-MS m/z 479 $(M + H)^+$; FAB-HRMS m/z 479.2469 (Calcd for $C_{25}H_{39}O_7Si$ 479.2465),

35, colorless oil, R_f (50% EtOAc/hexane) = 0.22; $[\alpha]_D^{24}$ +44.5 (c 0.85 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3435, 2927, 1768, 1715, 1608, 1459, 1366, 1204, 1086, 729; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35 (t, J = 7.8 Hz, 1H), 7.13 (dd, J = 7.8, 1.0 Hz, 1H), 7.06 (dd, J = 8.1, 1.0 Hz, 1H), 5.81 (m, 3H), 4.20 (dt, J = 12.1, 2.4 Hz, 1H), 3.97 (td, J = 9.7, 3.2 Hz, 1H), 3.80 (m, 2H), 3.33 (dd, J = 14.0, 12.1 Hz, 1H), 2.50 (dd, J = 14.0, 1.3 Hz, 1H), 2.29 (s, 3H), 1.92 (m, 5H), 1.73 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.8, 146.3, 139.2, 130.1, 129.2, 128.8, 127.6, 125.8, 120.7, 75.9, 72.5, 66.4, 59.0, 40.7, 37.0, 36.6, 31.2, 21.0; FAB-MS m/z 347 $(M + H)^+$; FAB-HRMS m/z 347.1501 (Calcd for $C_{19}H_{23}O_6$ 347.1495).

Preparation of 27′, 32, and 36. To a solution of **26′**, **31**, or **35** (0.05 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (32 mg, 0.75 mmol). The resulting mixture was stirred at rt for 1 h. The reaction was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 10 mL), and dried over $MgSO_4$. Removal of solvent and purification of the crude product by flash column chromatography (silica gel, 30% EtOAc/hexane) afforded aldehyde, **27′**, **32**, or **36** in 96, 95, and 91% yields, respectively.

27′, white solid: R_f (30% EtOAc/hexane) = 0.35; $[\alpha]_D^{24}$ +14.9 (c 0.60 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3019, 2929, 2857, 1769, 1729, 1460, 1371, 1214, 1086, 756, 667; ^1H NMR (270 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.4. 1.1 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.07 (dd, J = 4.3, 0.8 Hz, 1H), 7.07 (dd, J = 4.8, 1.3 Hz, 1H), 6.08 (m, 1H), 4.05 (m, 3H), 3.38 (dd, J = 14.5, 11.8 Hz, 1H), 2.82 (dddd, J = 17.5, 11.0, 8.9, 2.4 Hz, 1H), 2.65 (dddd, J = 17.2, 5.1, 4.0, 1.1 Hz, 1H), 2.39 (dd, J = 14.3, 1.3 Hz, 1H), 2.21 (s, 3H), 2.01 (m, 1H), 1.72 (m, 4H), 1.33 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.7, 168.7, 168.0, 146.5, 139.4, 130.0, 128.4, 127.8, 120.6, 73.3, 68.6, 67.7, 65.6, 48.1, 40.4, 39.9, 38.7, 37.3, 25.7, 20.8, 18.0, −4.7, −4.6; FAB-MS m/z 499 $(M + Na)^+$; FAB-HRMS m/z 499.2131 (Calcd for $C_{25}H_{36}O_7SiNa$ 499.2128).

32, white solid: R_f (30% EtOAc/hexane) = 0.35; $[\alpha]_D^{24}$ +22.8 (c 0.35 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3034, 2914, 1768, 1730, 1460, 1371, 1215, 1078, 757; ^1H NMR (270 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.4. 1.1 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 1.3 Hz, 1H), 7.03 (dd, J = 2.7, 0.8 Hz, 1H), 6.11 (m, 1H), 4.06 (m, 1H), 3.90 (m, 1H), 3.78 (dddd, J = 11.6, 6.7, 5.4, 1.6 Hz, 1H), 3.34 (dd, J = 14.0, 11.6 Hz, 1H), 2.81 (dddd, J = 17.2, 11.3, 8.9, 2.4 Hz, 1H), 2.65 (dddd, J = 17.2, 5.1, 3.2, 0.8 Hz, 1H), 2.62 (dd, J = 14.3, 1.6 Hz, 1H), 2.21 (s, 3H), 1.67 (m, 6H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.7, 168.7, 168.2, 146.4, 140.2, 130.7, 129.0, 127.7, 120.4, 80.0, 68.6, 68.3, 67.4, 48.1, 40.0, 29.8, 29.2, 28.4, 25.7, 20.8, 18.0, −4.6, −4.9; FAB-MS m/z 499 $(M + Na)^+$; FAB-HRMS m/z 499.2124 (Calcd for $C_{25}H_{36}O_7SiNa$ 499.2128).

36, colorless oil, R_f (40% EtOAc/hexane) = 0.25; $[\alpha]_D^{24}$ +47.9 (c 0.65 $CHCl_3$); IR ($CHCl_3$ film, cm^{-1}) 3034, 2914, 1768, 1726, 1459, 1370, 1264, 1202, 1087, 733; ^1H NMR (270 MHz, $CDCl_3$) δ 9.81 (dd, J = 2.4. 1.1 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.12 (dd, J = 7.5, 0.8 Hz, 1H), 7.06 (dd, J = 8.1, 0.8 Hz, 1H), 6.15 (m, 1H), 5.88 (m, 1H), 5.74 (dtd, J = 10.2, 2.4, 1.1 Hz, 1H), 4.18 (dt, J = 12.4, 2.4 1H), 4.02 (m, 1H), 3.36 (dd, J = 14.0, 11.8 Hz, 1H), 2.83 (dddd, J = 17.5, 11.0, 8.9, 2.7 Hz, 1H), 2.68 (dddd, J = 17.2, 5.6, 4.6, 1.1 Hz, 1H), 2.49 (dd, J = 14.3, 2.4 Hz, 1H), 2.21 (s, 3H), 1.92 (m, 2H), 1.80 (td, J = 6.7, 2.7 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.7, 168.7, 168.1, 146.4, 139.3, 130.2, 128.9, 128.8, 127.5, 125.6, 120.7, 75.8, 68.4, 66.1, 48.1, 40.5, 36.6, 31.1, 20.8; FAB-MS m/z 345 $(M + H)^+$; FAB-HRMS m/z 345.1342 (Calcd for $C_{19}H_{20}O_6$ 345.1339).

Preparation of Iodoalkenes 6′, 33, and 37. Slurry of $CrCl_2$ (49 mg, 0.40 mmol) in dry THF (2 mL) was stirred at rt for 15 min. The reaction was cooled to 0 °C. A solution of aldehyde, **27′**, **32**, or **36** (0.06 mmol) and iodoform (53 mg, 0.13 mmol) in THF (1 mL) was added. The resulting reddish-brown mixture was stirred for 6 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with saturated sodium thiosulfate and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification by flash column chromatography (silica gel, 10% EtOAc/hexane) afforded the (E)-iodoalkene **6′**, **33**, or **37** in 79, 68, and 66% yields, respectively.

6′ (E/Z = 3:1). White solid: R_f (20% EtOAc/hexane) = 0.40; IR (film, cm^{-1}) 2927, 1772, 1720, 1459, 1365, 1257, 1199, 1085, 756; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32 (t, J = 8.6 Hz, 1H), 7.06 (m, 2H), 6.55 (m, 3/4H), 6.40 (dt, J = 7.5, 1.3 Hz, 1/3H), 6.32 (m, 1/3H), 6.21 (dt, J = 14.5, 1.6 Hz, 3/4H), 5.62 (m, 1H), 4.10 (m, 1H), 3.97 (m, 2H), 3.37 (dd, J = 14.3, 11.6 Hz, 1H), 2.42 (m, 3H), 2.31 (s, 3/4H), 2.24 (s, 1/3H), 1.95 (m, 1H), 1.76 (m, 3H), 1.58 (m, 2H), 1.35 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.7, 168.5, 146.5, 140.9, 139.5, 136.3, 129.9, 128.6, 127.9, 120.7, 85.4, 77.9, 73.4, 72.7, 67.9, 67.6, 65.6, 40.9, 40.6, 39.9, 39.8, 38.7, 37.2, 25.8, 21.4, 20.9, 18.0, −4.6; FAB-MS m/z 601 $(M + H)^+$; FAB-HRMS m/z 601.1489 (Calcd for $C_{26}H_{38}O_6SiI$ 601.1482).

33 (E)-isomer. White solid: R_f (20% EtOAc/hexane) = 0.44 (0.48 for Z-isomer); IR (film, cm^{-1}) 2928, 1772, 1721, 1459, 1367, 1267, 1199, 1078, 757; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 6.40 (dt, J = 14.0, 7.02 Hz, 1H), 6.21 (dt, J = 14.3, 1.3 Hz, 1H), 5.62 (m, 1H), 4.02 (m, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 3.32 (dd, J = 14.3, 11.6 Hz, 1H), 2.62 (dd, J = 14.3, 1.3 Hz, 1H), 2.40 (m, 2H), 2.30 (s, 3H), 1.64 (m, 6H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.7, 168.6, 146.4, 141.0, 140.2, 129.9, 129.2, 127.8, 120.4, 79.9, 72.6, 68.4, 67.4, 40.8, 39.9, 29.8, 29.4, 28.5, 25.7, 21.4, 18.0, −4.6, −4.9; FAB-MS m/z 601 $(M + H)^+$; FAB-HRMS m/z 601.1486 (Calcd for $C_{26}H_{38}O_6SiI$ 601.1482).

37 (E)-isomer. Colorless oil: R_f (30% EtOAc/hexane) = 0.60 (0.65 for Z-isomer); $[\alpha]_D^{24}$ +6.7 (c 0.4 $CHCl_3$); IR (film, cm^{-1}) 2927, 1770, 1717, 1457, 1365, 1263, 1198, 1088; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35 (t, J = 8.1 Hz, 1H), 7.12 (dd, J = 8.1, 0.8 Hz, 1H), 7.07 (dd, J = 7.5, 0.8 Hz, 1H), 6.56 (dt, J = 14.3, 7.0 Hz, 1H), 6.22 (dt, J = 14.5, 1.3 Hz, 1H), 5.88 (m, 1H), 5.73 (dtd, J = 12.9, 2.4, 0.8 Hz, 1H), 5.65 (m, 1H), 4.17 (dt, J = 11.6, 2.4 Hz, 1H), 3.97 (m, 1H), 3.35 (dd, J = 14.0, 11.8 Hz, 1H), 2.43 (m, 3H), 2.30 (s, 3H), 2.24 (s, 1H), 1.81 (m, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.7, 168.6, 146.4, 140.9, 139.3, 130.1, 129.1, 128.8, 127.6, 125.7, 120.7, 78.0, 75.8, 72.4, 66.1, 40.7, 40.4, 36.6, 31.2, 21.4; FAB-MS m/z 469 $(M + H)^+$; FAB-HRMS m/z 469.0515 (Calcd for $C_{20}H_{22}O_5I$ 469.0512).

Coupling of Iodoalkenes 6′ with 7, Synthesis of 28′. The reaction of **6′** (10 mg, 0.016 mmol) and **7** (10.5 mg, 0.083 mmol) was performed by the same procedure described for the synthesis of **28**. After the work up, purification of the crude product by flash column chromatography (silica gel, 30% EtOAc/hexane) provided **28′** (6.5 mg) in 70% yield and the corresponding Z-isomer (2.2 mg) in 24% yield. Data for major E-isomer **28′**, white solid: R_f (30% EtOAc/hexane) = 0.41 (0.50 for Z-isomer); $[\alpha]_D^{24}$ +41.9 (c 0.25 $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.27 (m, 3H), 7.16 (t, J = 7.5 Hz, 1H), 6.93 (dd, J = 14.3, 10.8 Hz, 1H), 6.77 (m, 3H), 6.37 (br, s, 1H), 5.85 (m, 1H), 5.54 (d, J = 11.6 Hz, 1H), 5.47 (m, 1H), 5.19 (dt, J = 13.5, 7.5 Hz, 1H), 4.03 (m, 3H), 3.39 (dd, J = 13.7, 11.8 Hz, 1H), 2.37 (m, 2H), 2.25 (dtd, J = 15.1, 7.8, 1.8 Hz, 2H), 1.94 (m, 1H), 1.72 (m, 4H), 1.33 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.4, 163.4, 152.3, 142.6, 139.0, 137.1, 130.6, 125.7, 123.8, 123.4, 122.4, 119.0, 115.1, 107.2, 77.4, 73.7, 67.6, 65.6, 40.8, 40.2, 38.4, 37.1, 34.7, 25.8, 20.7, 18.0, 13.9, −4.7, −4.6; FAB-MS m/z 556 $(M + H)^+$; FAB-HRMS m/z 556.3097 (Calcd for $C_{31}H_{46}NO_6Si$ 556.3094).

Coupling of Iodoalkenes 33 and 37 with 7. The coupling reaction of **33** and **37** with **7** was performed by the same manner described for the synthesis of **28** to give **38** and **5**, both in 94% yield, respectively. **38**, 94% yield. White solid: R_f (30% EtOAc/hexane) = 0.40; $[\alpha]_D^{24}$ +42.9 (c 0.25 $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.16 (t, J = 8.3 Hz, 1H), 6.93 (m, 2H), 6.74 (m, 2H), 6.33 (br, s, 1H), 5.86 (m, 1H), 5.53 (d, J = 11.1 Hz, 1H), 5.46 (m, 1H), 5.18 (dt, J = 14.5, 7.3 Hz, 1H), 4.08 (m, 1H), 3.91 (m, 1H), 3.73 (m, 1H), 3.42 (dd, J = 14.0, 11.8 Hz, 1H), 2.48 (dd, J = 14.0, 1.3 Hz, 1H), 2.38 (t, J = 7.0 Hz, 2H), 2.25 (dtd, J = 15.1, 7.5, 1.3 Hz, 2H), 1.65 (m, 6H), 1.02 (t, J = 7.3 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.3, 163.4, 152.4, 142.5, 139.8, 137.1, 130.7, 125.7, 123.8, 122.4, 119.0, 114.9, 107.2, 80.0, 74.1,

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68.4, 67.6, 40.0, 34.9, 30.6, 28.8, 28.1, 25.7, 20.7, 18.0, 13.9, −4.6, −4.9; FAB-MS m/z 556 (M + H) $^+$; FAB-HRMS m/z 556.3085 (Calcd for $C_{31}H_{46}NO_6Si$ 556.3094). **5**, white solid: mp 149−151 °C (methanol); R_f (40% EtOAc/hexane) = 0.25; $[\alpha]_D^{24}$ +3.5 (c 0.25 $CHCl_3$); ^{1}H NMR (270 MHz, acetone-d_6) δ 9.10 (d, J = 10.0 Hz, 1H), 8.43 (s, 1H), 7.51 (t, J = 10.8 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.89 (m, 2H), 6.79 (d, J = 7.0 Hz, 1H), 5.81 (m, 3H), 5.51 (m, 1H), 5.26 (dt, J = 14.5, 7.2 Hz, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.22 (dd, J = 13.7, 11.8 Hz, 1H), 3.46 (dd, J = 13.5, 1.8 Hz, 1H), 2.35 (m, 1H), 2.27 (dtd, J = 15, 7.5, 1.6 Hz, 2H), 1.89 (m, 2H), 1.69 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (67.5 MHz, acetone-d_6) δ 171.6, 164.7, 155.0, 142.5, 141.3, 137.9, 131.6, 131.5, 127.6, 127.4, 127.1, 126.4, 123.0, 121.9, 115.7, 109.1, 78.1, 75.5, 68.2, 42.1, 38.0, 37.0, 33.1, 22.1, 15.4; FAB-MS m/z 556 (M + H)$^+$; FAB-HRMS m/z 424.2129 (Calcd for $C_{25}H_{30}NO_5$ 424.2124).

Synthesis of 3 and 4. Compounds **3** and **4** were prepared by the same manner described for the synthesis of **1**.

3, 95% yield. White solid: mp 117−120 °C (methanol); R_f (70% EtOAc/hexane) = 0.20; $[\alpha]_D^{24}$ −10.9 (c 0.20, CH_3CN); ^{1}H NMR (270 MHz, acetone-d_6) δ 9.10 (d, J = 11.3 Hz, 1H), 8.48 (s, 1H), 7.51 (m, 1H), 7.13 (t, J = 8.3 Hz, 1H), 6.89 (m, 2H), 6.77 (m, 2H), 6.69 (d, J = 7.5 Hz, 1H), 5.76 (m, 2H), 5.45 (m, 1H), 5.24 (dt, J = 14.8, 7.8 Hz, 1H), 3.92 (m, 3H), 3.78 (d, J = 4.6 Hz, 1H), 3.31 (dd, J = 13.2, 10.8 Hz, 1H), 2.30 (m, 5H), 1.70 (m, 6H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.6, 164.5, 154.8, 142.4, 141.7, 137.7, 137.6, 131.3, 127.2, 126.3, 123.1, 121.8, 115.3, 108.9, 76.6, 75.4, 69.1, 66.3, 42.8, 41.8, 40.3, 37.9, 36.8, 21.9, 15.2; FAB-MS m/z 442 (M + H)$^+$; FAB-HRMS m/z 442.2224 (Calcd for $C_{25}H_{31}NO_6$ 442.2230).

4, 93% yield. White solid: mp 107−110 °C (methanol); $[\alpha]_D^{24}$ −85.0 (c 0.20, CH_3CN); R_f (70% EtOAc/hexane) = 0.31; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.10 (d, J = 11.0 Hz, 1H), 8.45 (s, 1H), 7.51 (t, J = 11 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.89 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 5.79 (q, J = 7.5 Hz, 1H), 5.74 (d, J = 11 Hz, 1H), 5.45 (m, 1H), 5.24 (dt, J = 14.5, 7.5 Hz, 1H), 3.97 (m, 2H), 3.80 (d, J = 7.5 Hz, 1H), 3.16 (dd, J = 15.0, 11.0 Hz, 1H), 2.63 (t, J = 13.5 Hz, 1H), 2.30 (m, 4H), 1.71 (m, 6H), 1.00 (t, J = 7.0 Hz, 3H); ^{13}C NMR (67.5 MHz, acetone-d_6) δ 170.9, 164.4, 154.7, 142.3, 141.7, 137.6, 131.1, 127.2, 126.2, 123.0, 121.7, 115.0, 108.8, 80.6, 75.2, 70.0, 69.0, 36.9, 33.0, 32.0, 24.1, 21.8, 15.1; FAB-MS m/z 442 (M + H)$^+$; FAB-HRMS m/z 442.2227 (Calcd for $C_{25}H_{32}NO_6$ 442.2230),

Experiment for the Cytostatic Activity. Cell lines (U-937 (human leukemic monocyte lymphoma cell line) and HL-60 (human promyelocytic leukemia cells)) were provided by the RIKEN BRC through the National Bio-Resource Project of the MEXT, Japan. These cells were cultured in RPMI-1640 supplemented with 10% fetal bovine serum (FBS). PC-3 cells (human prostate cancer cell line) were cultured in DMEM supplemented with 10% FBS.

MTT Assay. Growth inhibition of various cell lines was determined 4 days after the addition of compounds by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay according to the manufacturer's directions (Nacalai Tesque Cat. 23506). Briefly, 5 × 10^3 cells were placed in a 96 well plate with 100 μL of RPMI or DMEM containing 10% FBS and incubated for 24 h. The cultured cells were treated with various concentrations of compounds for 4 days. Then, the treated cells were incubated with MTT reagents at 37 °C for 4 h. After dissolving the resulting crystals in DMSO, plates were read in a microplate reader (model 680, Bio lad) at 570 nm. Control contained the same concentration of DMSO as the compound treated cells.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and crystal data for **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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