Total Synthesis of the Pentacyclopropane Antifungal Agent FR-900848

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Abstract: Quatercyclopropane **31** was oxidized, homologated, reduced, and monocyclopropanated to provide the pentacyclopropane alcohol **35**. Subsequent deoxygenation of alcohol **35** was effected using *N*-(phenylthio)succinimide (**24**) and tributylphosphine followed by Raney nickel desulfurization and deprotection to produce the alcohol **3**. This was oxidized, homologated, and hydrolyzed to provide the fatty acid **2**. BOP-Cl-mediated coupling of acid **2** and the nucleoside amine **40** gave amide **1**, which was spectroscopically identical with an authentic sample of FR-900848 (**1**).

Introduction

FR-900848 (**1**) is a nucleoside isolated from the fermentation broth of *Streptoverticillium fervens*.[1] It shows potent, selective activity against filamentous fungi such as *Aspergillus niger* but is essentially inactive against nonfilamentous fungi such as *Candida albicans* and Gram-positive and -negative bacteria. Structurally this natural product is quite remarkable since it contains five cyclopropane units, four of which are contiguous. In a recent paper[2] and in communication format,[3−6] we have reported degradation and synthetic studies on FR-900848 (**1**) which allowed us to establish its full structure and absolute stereochemistry. During the course of this work ourselves,[7] Armstrong[8] and Zercher[9] have independently reported stereoselective methods for the preparation of bicyclopropanes. Herein we report the total synthesis of FR-900848 (**1**) which was previously reported in communication format.[10] Subsequent to our original publication, Falck and co-workers have reported an alternative total synthesis of FR-900848 (**1**).[11]

Although the condensation of a monocyclopropane derivative and a quatercyclopropane unit is an obvious route to assemble the side chain of FR-900848 (**1**), such a strategy has the disadvantage of poor geometric selectivity in the construction of Δ^{18}. For example, Nishida and co-workers[12] have used a Wittig reaction to prepare 1,2-dicyclopropylethene as a mixture of *cis*- and *trans*-isomers. Julia−Lythgo coupling[13] should be more *trans* selective, but not geometrically specific. In consequence of these considerations, the retrosynthetic approach outlined in Figure 1 was adopted. We envisioned that FR-900848 (**1**) should be available from the acylation of the corresponding nucleoside unit with the side chain acid **2**. In turn, acid **2** should be obtained from the oxidation, homologation, and hydrolysis of alcohol **3**. A key step in our retrosynthetic approach should be the deoxygenation of alcohol **4** to reveal the terminal methyl of pentacyclopropane **3**, followed

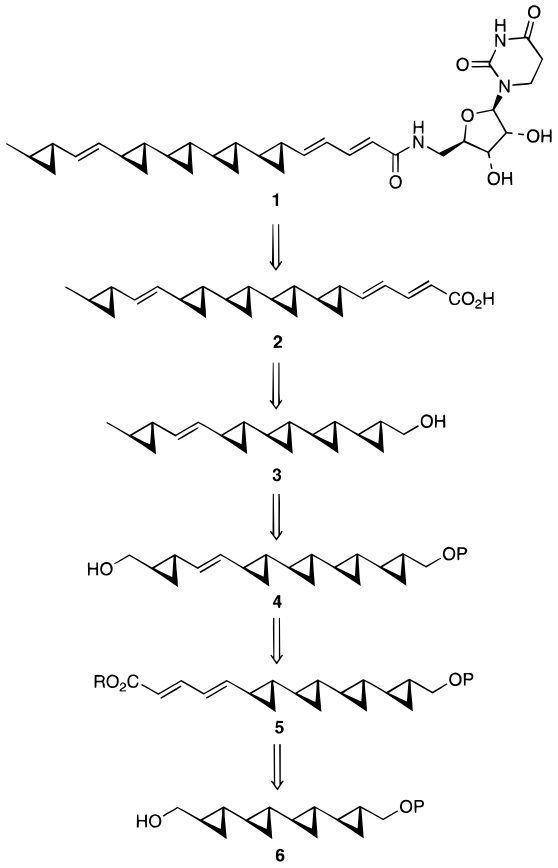

Figure 1.

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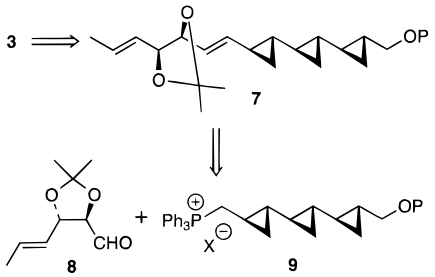
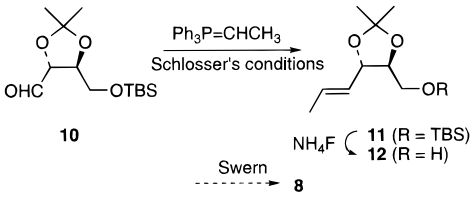


Figure 2.

Scheme 1



by deprotection. In turn, alkene **4** should arise from the stereoselective monocyclopropanation of diene **5**, which should be available from oxidation, homologation, and reduction of alcohol **6**. We have already utilized quatercyclopropane **6** (P = H) in our stereochemical elucidation studies of FR-900848 (**1**).[2,4,6]

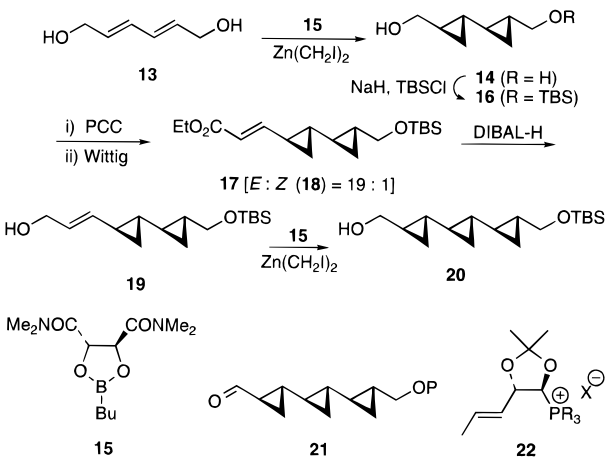
Results and Discussion

Our initial retrosynthetic approach for obtaining alcohol **3** is outlined in Figure 2 utilizing methodology we developed for the synthesis of the structural models of the isolated alkene unit.[2,3,5] It was envisioned that substrate-directed bicyclopropanation of diene **7** followed by Whitham elimination[14] of the vicinal diol unit should give alcohol **3**. Diene **7** is expected to arise from a Wittig reaction between aldehyde **8** and the tercyclopropane **9**.

Marshall and co-workers[15] had recently made use of aldehyde **10** in a synthesis of long-chain polyols. Wittig homologation of aldehyde **10** (Scheme 1) under Schlosser's conditions[16] provided a 6.1:1 mixture of (*E*)-alkene **11** and the corresponding (*Z*)-alkene which was inseparable using normal chromatography techniques (55%). However, chromatotron separation on silver nitrate loaded silica[17] provided geometrically pure (*E*)-alkene **11** (43%) with a minor, yellow impurity. Ammonium fluoride deprotection of (*E*)-alkene **11** gave alcohol **12** (39% from **10**) with none of the purification difficulties encountered when tetrabutylammonium fluoride was used. Swern oxidation[18] of alcohol **12** should provide the desired aldehyde **8**.

We chose to apply the elegant new cyclopropanation methodology recently reported by Charette[19] for the formation of all five cyclopropanes present in FR-900848 (**1**). Therefore, in an improvement of our previous synthesis,[2,4] mucondiol (**13**)[20]

Scheme 2



was bicyclopropanated[19a] (Scheme 2) in the presence of the chiral auxiliary **15** to provide diol **14** in high yield (89%). Monoprotection of C_2-symmetrical diol **14** was effected using the procedure reported by McDougal.[21] Diol **14** was treated with 1 equiv of sodium hydride followed by 1 equiv of *tert*-butyldimethylsilyl chloride to obtain alcohol **16** (49%), recovered diol **14** (20%), and the corresponding diprotected compound (10%). Both diol **14** and the deprotected disilyl ether could be recycled to give more of the desired alcohol **16**. PCC oxidation of alcohol **16** followed by Wittig homologation of the corresponding aldehyde provided a separable 19:1 mixture of (*E*)-ester **17** and (*Z*)-ester **18** (85% from **16**). Unfortunately, there was no applicable isomerization protocol available at this time to convert (*Z*)-ester **18** into more of the desired (*E*)-ester **17**. (*E*)-Ester **17** was reduced using DIBAL-H to provide the alcohol **19**, which was cyclopropanated using Charette's methodology[19a] to give tercyclopropane **20** in high yield (91% from **17**). Although various methods of converting alcohol **20** into the corresponding halides were attempted, all were unsuccessful and resulted in cyclopropane degradation. This precluded synthesis of the Wittig fragment **9**. Indeed, it appears that as soon as the primary alcohol was replaced with any good leaving group, spontaneous ring opening and rearrangement occurred.

Previous work had shown that polycyclopropane systems such as alcohol **20** were stable to oxidation. Therefore, synthesis of aldehyde **21** should not present any difficulties. One example is present in the literature for the formation and use of a dioxolane ylide related to acetal **22**.[22] However, these ylides are prone to β-elimination, and Schlosser's conditions would definitely induce such decomposition. An alternative method for obtaining (*E*)-alkenes from unstabilized ylides is by variation of the phosphine ligands, and isopropyldiphenylphosphoranes favor the formation of *trans*-alkenes (E:Z = 4.6:1).[23] Unfortunately, we were not successful in attempting to induce reaction between the ylide of dioxolane **22** (R_3 = Ph_2-*i*-Pr) and aldehyde **21**, and this route was abandoned altogether.

We then devised the alternative route described in Figure 1, which makes use of deoxygenation to reveal the terminal methyl as a key step. Alcohol **20** was chosen as an appropriate model system to probe such a deoxygenation. We have been generally frustrated in our attempts to deoxygenate multiple cyclopropanemethanol derivatives. Much of the deoxygenation methodology available in the literature makes use of radical fragmen-

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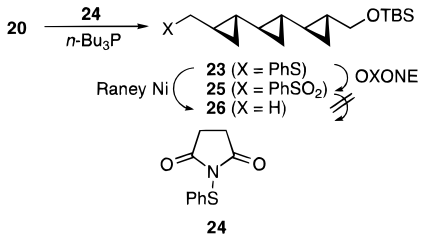
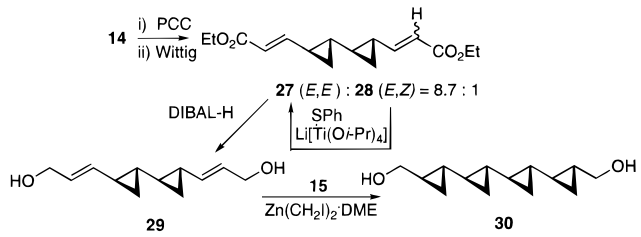
Scheme 3



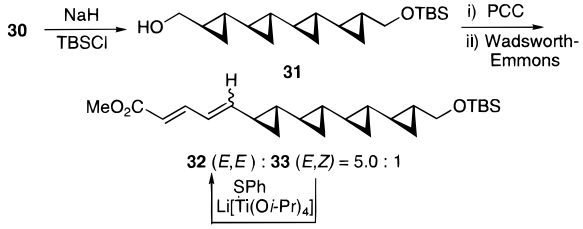
tations,[24] which are clearly unsuitable for cyclopropanated substrates since ring opening occurs rapidly upon α-radical formation.[25] Attempted hydroxyl group activation *via* methanesulfonylation or trifluoromethanesulfonylation and displacement led to extensive ring-opening and degradation. In the same vein, attempted formation of the corresponding halides as mentioned previously resulted in cyclopropane loss. Presumably these failures were the result of (cyclopropylmethyl)carbenium ion rearrangements. Therefore, no direct method of deoxygenation was feasible. However, treatment of alcohol **20** with the Walker reagent[26] (Scheme 3), formed upon mixing *N*-(phenylthio)succinimide (**24**) and tributylphosphine, cleanly gave the sulfide **23** (81%). At that time, reduction of the corresponding sulfone was considered more feasible than desulfurization of sulfide **23** itself. Therefore, oxidation of sulfide **23** using a buffered potassium hydrogen persulfate system[27] gave sulfone **25** in fair yield (56%) and recovered sulfide **23** (32%). Sodium amalgam[28] and various dissolving metal reduction systems[29] were attempted for the desulfurization of sulfone **25**; however, all afforded ring-opening rearrangement products. Reduction of sulfide **23** was then studied. Attempted reductive desulfurization of sulfide **23** *via* a nickel hydridic species formed *in situ* [$NiBr_2$·DME, Ph_3P, $LiAlH_4$][30] or lithium (dimethylamino)naphthalenide[31] also led to cyclopropane obliteration. However, Raney nickel reduction of sulfide **23** fortuitously gave the corresponding terminal methyl compound **26** in good yield (69%). Although Raney nickel reduction of the alkene moiety of the actual substrate was a potential problem, there was literature precedent that the W-2 catalyst might leave the alkene intact.[32] The less well known and less active Raney cobalt[33] was also considered applicable, due to its ability to reduce sulfones in the presence of alkenes.

Attention was then turned to synthesis of the FR-900848 intermediate. PCC oxidation of diol **14** followed by Wittig homologation provided an 8.7:1 separable mixture of (*E*,*E*)-diester **27** and the (*E*,*Z*)-isomer **28** (67% from **14**) as shown in Scheme 4. We had found in related cyclopropane-substituted α,β-unsaturated esters that classical methods to isomerize *Z* to *E* were unsuccessful. Fortunately, a reagent introduced by Hunter[34] for the isomerization of α,β-unsaturated esters had just come to our attention. The unwanted (*E*,*Z*)-diester **28** was

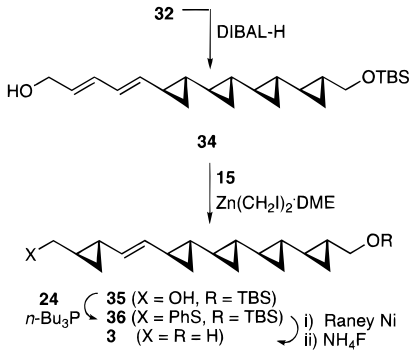
Scheme 4



Scheme 5



Scheme 6



allowed to react with $LiTi(OiPr)_4(SPh)$ and was smoothly converted into diester **27**. This reaction gave additional diester **27** (50%) and recovered (*E*,*Z*)-isomer **28** (40%) which was further isomerized. DIBAL-H reduction of diester **27** proceeded uneventfully to provide diol **29** in high yield (94%). Cyclopropanation of diene **29** under the new Charette conditions[19b] using the chiral auxiliary **15** provided diol **30** (93%) essentially as one isomer by ^{13}C NMR. The spectroscopic and optical rotation data for compounds **27**, **29**, and **30** were comparable with those of authentic samples prepared using an alternate, less concise, route.[2]

Subsequent monoprotection of diol **30** using the McDougal[21] method gave the desired alcohol **31** (44%), recovered diol **30** (44%), and diprotected material (10%) (Scheme 5). Both the starting material **30** and the corresponding disilyl ether were recycled to provide more of the desired alcohol **31**. PCC oxidation of alcohol **31** and subsequent Wadsworth−Emmons homologation gave a separable 5.0:1 mixture of esters **32** and **33** (71% from **31**). Again, Hunter isomerization[34] was utilized to convert the undesired (*E*,*Z*)-isomer **33** into additional (*E*,*E*)-ester **32** (63%).

Treatment of (*E*,*E*)-ester **32** with DIBAL-H provided alcohol **34** in high yield (91%) as shown in Scheme 6. Modification of the Charette asymmetric cyclopropanation protocol[19b] using prolonged reaction at −40 °C was necessary in order to obtain the desired pentacyclopropanealcohol **35** (90%). In contrast, cyclopropanation at −15 °C to room temperature gave predominately the corresponding sextacyclopropane **37** (84%). The

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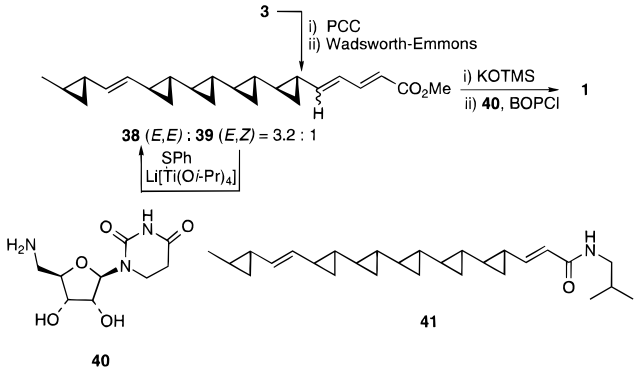
Scheme 7



deoxygenation methodology developed in Scheme 3 was then applied to the real system. Treatment of alcohol **35** with the Walker reagent[26] cleanly gave the sulfide **36** (89%). Fortuitously, when sulfide **36** was allowed to react with Raney nickel at −40 °C in EtOH, regioselective desulfurization took place without concomitant alkene reduction. Subsequent deprotection using ammonium fluoride provided alcohol **3** (49% from **36**).

PCC oxidation of alcohol **3** (Scheme 7), followed by Wadsworth−Emmons homologation provided a separable 3.2:1 mixture of esters **38** and **39** (63% from **3**). Again Hunter isomerization[34] of the unwanted (*E*,*Z*)-ester **39** was used to reclaim additional (*E*,*E*)-ester **38** in fair yield (51%). While saponification of ester **38** resulted in decomposition, hydrolysis using potassium trimethylsilanolate[35] gave the FR-900848 side chain carboxylic acid **2** in good yield (85%). Finally, BOP-Cl[36] activation of acid **2** followed by the addition of amine **40**[37] and triethylamine gave FR-900848 (**1**) in good yield (69%) and recovered acid **2** (10%). The synthetic sample of FR-900848 (**1**) was spectroscopically and chromatographically identical with an authentic sample of the natural product. However, we observed a different specific rotation (−167.0°, *c* 0.40, DMSO-d_6) for synthetic FR-900848 (**1**) from that reported[38] for the natural product (−35°, *c* 0.5, DMSO). As a consequence, we have remeasured the specific rotation of authentic FR-900848 (**1**) under the same conditions as those used for the synthetic amide **1**. Under these conditions, we observed a value of $[\alpha]_D$ −168.1° (*c* 0.42, DMSO-d_6) which is in good agreement with our synthetic material. Clearly, the optical rotation value reported in the patent is therefore incorrect. Finally, the CD spectrum of the synthetic amide **1** correlated well with that from the natural product, confirming the identity of the absolute stereochemistry.

Conclusion

It is clear from these results that Charette[19] triple asymmetric cyclopropanation is appropriate for the elaboration of FR-900848 (**1**) with excellent overall stereochemical control. Alternative strategies involving the condensation of monocyclopropane and quatercyclopropane derivatives to elaborate Δ^{18} have the disadvantages of low geometric control and/or degradation. The methodology outlined in this paper should additionally be relevant for the synthesis of U-106305 (**41**), which has recently been shown to be a CETP inhibitor,[39] and related molecules. Further studies in this area will be reported in due course.[40]

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Experimental Section

All reactions were carried out in an atmosphere of dry nitrogen or argon at room temperature unless otherwise stated. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated. Column chromatography was carried out on Merck or BDH silica gel 60, 230−400 mesh ASTM, using flash chromatography techniques.[41] Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. Petroleum ether (petrol) (40−60 °C) used as a chromatography eluant was distilled; all other chromatography eluants were BDH GPR grade and undistilled. The following reaction solvents were purified by distillation: benzene (PhH) (P_2O_5, N_2), dichloromethane (CH_2Cl_2) (CaH_2, N_2), *N*,*N*-dimethylacetamide (DMA) (BaO, 12 mmHg), diethyl ether (Et_2O) (Ph_2CO/Na, N_2), and tetrahydrofuran (THF) (Ph_2CO/K, N_2). The following organic reagents were purified by distillation: diiodomethane (CH_2I_2) (Cu powder, 2 mmHg), 1,2-dimethoxyethane (DME) (CaH_2, N_2), and triethylamine (Et_3N) (CaH_2, N_2). All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over magnesium sulfate, filtered, and concentrated using a rotary evaporator at ≤40 °C bath temperature. Involatile oils and solids were vacuum dried at <2 mmHg.

(4*S*,5*S*)-2,2-Dimethyl-4-(hydroxymethyl)-5-[1(*E*)-propen-1-yl]-1,3-dioxolane (12). Following the procedure reported by Schlosser and co-workers,[16] PhLi (8.4 mL, 1.2 M in Et_2O, 10 mmol) was added to a stirred suspension of ethyltriphenylphosphonium bromide (3.72 g, 10.1 mmol) in THF (20 mL) and Et_2O (8.0 mL). After 10 min, the mixture was cooled to −70 °C, and a solution of aldehyde **10**[15] (2.77 g, 10.1 mmol) in Et_2O (12 mL) was added. The reaction mixture was warmed to −40 °C over 5 min, PhLi (8.4 mL, 1.2 M in Et_2O, 10 mmol) was added, and the reaction mixture was warmed to −30 °C over 5 min. HCl solution (4.94 mL, 2.25 M in Et_2O, 11.1 mmol) was added followed by 1:1 *t*-BuOK/*t*-BuOH complex (2.87 g, 15.1 mmol). The reaction mixture was allowed to warm to room temperature and, after 16 h, was diluted with Et_2O (100 mL) and filtered though Celite. The filtrate was washed with H_2O (3 × 200 mL), dried, and concentrated. Chromatography on silica (2:98 to 5:95 EtOAc/petrol) provided an inseparable 6.1:1 (*E*)/(*Z*)-alkene mixture (1.60 g, 55%). Chromatotron separation on $AgNO_3$/silica[17] (petrol to 2:98 EtOAc/petrol) provided (*E*)-alkene **11** (1.25 g, 43%) as an oil with a yellow impurity: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.80 (dq, 1H, J = 15.3, 6.5 Hz), 5.48 (ddq, 1H, J = 15.3, 7.8, 1.7 Hz), 4.31−4.25 (m, 1H), 3.78−3.67 (m, 3H), 1.72 (dd, 3H, J = 6.5, 1.7 Hz), 1.42 (s, 3H), 1.40 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

NH_4F (1.44 g, 38.7 mmol) was added to a stirred solution of (*E*)-alkene **11** (1.11 g, 3.87 mmol) in MeOH (45 mL), and the mixture was heated to 60 °C. After 3 h, the reaction mixture was allowed to cool, silica was added, and the mixture was concentrated. Chromatography on silica (20:80 EtOAc/petrol) provided alcohol **12** (0.605 g, 39% from **10**) as a colorless oil: $[\alpha]^{26}_D$ = −5.2° (*c* 1.00, $CHCl_3$); R_f 0.24 (20:80 EtOAc/petrol); IR (film) 3450 (br), 2986, 2935, 2920, 2877, 1676, 1452, 1379, 1371, 1242, 1220 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.85 (dq, 1H, J = 15.3, 6.5 Hz), 5.46 (ddq, 1H, J = 15.3, 8.2, 1.6 Hz), 4.28 (t, 1H, J = 8.2 Hz), 3.86−3.74 (m, 2H), 3.62−3.53 (m, 1H), 1.89−1.84 (m, 1H), 1.73 (dd, 3H, J = 6.4, 1.6 Hz), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 127.8, 108.9, 81.1, 78.2, 60.8, 27.1, 27.0, 17.8; MS (CI, NH_3) *m/e* 173 $(M + H)^+$, 155, 132, 115, 97; exact mass (CI, NH_3) calcd for $C_9H_{17}O_3$ $(M + H)^+$ 173.1178, found 173.1165.

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis(hydroxymethyl)bicyclopropane (14). The following procedure is a modification of that reported by Charette and Juteau.[19a] CH_2I_2 (2.26 mL, 28.5 mmol) was added slowly to a stirred solution of Et_2Zn (58 μL, 0.56 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. After 10 min, a white slurry had formed, and a suspension of mucondiol (**13**)[20] (0.371 g, 3.24 mmol) and dioxaborolane **15** (0.192 g, 7.13 mmol) in CH_2Cl_2 (5.0 mL) was added. The reaction mixture was stirred at room temperature for 20 h, cooled to 0 °C, and quenched by slow addition of saturated NH_4Cl solution (20 mL). The aqueous layer was

(40) For a total synthesis of U-106305 see Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863.
(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

salted (NaCl) and extracted with CH_2Cl_2 (50 mL) using a continuous extractor. Chromatography on silica (EtOAc) provided bicyclopropane **14** (0.408 g, 89%) as a gummy, off-white solid: $[\alpha]^{27}_D = -71.4°$ ($CHCl_3$, $c = 1.00$); R_f 0.25 (EtOAc); IR (film) 3326 (br), 2999, 2869, 2367, 1460, 1419, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.49 (ABXdd, 2H, $J = 11.1$, 6.8 Hz), 3.35 (ABXdd, 2H, $J = 11.1$, 7.4 Hz), 1.89 (s, 2H), 0.92−0.85 (m, 2H), 0.75−0.70 (m, 2H), 0.38−0.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.6, 20.0, 18.8, 8.5; MS (CI, NH_3) *m/e* 160 $(M + NH_4)^+$, 142, 125, 107, 83; exact mass (CI, NH_3) calcd for $C_8H_{18}NO_2$ $(M + NH_4)^+$ 160.1338, found 160.1334. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.27; H, 9.68.

(1*R*,3*S*,4*S*,6*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(hydroxymethyl)bicyclopropane (16). The following procedure is a modification of that reported by McDougal.[21] Prewashed NaH (0.325 g, 60% dispersion in oil, 8.12 mmol) was suspended in THF (2.0 mL), and a solution of diol **14** (1.15 g, 8.12 mmol) in THF (5.0 mL) was added. A thick slurry formed and was stirred for 45 min before TBSCl (1.22 g, 8.12 mmol) was added. The slurry partially dissolved and was stirred for 45 min. The mixture was quenched by pouring into saturated $NaHCO_3$ solution (100 mL), and the aqueous layer was salted (NaCl) and extracted with CH_2Cl_2 (5 × 200 mL). The combined organic layers were dried and concentrated. Chromatography on silica (20:80 EtOAc/petrol to EtOAc) provided alcohol **16** (1.02 g, 49%) as a faintly yellow oil, recovered diol **14** as a gummy, off-white solid (0.235 g, 20%), and the corresponding diprotected compound (0.304 g, 10%) as a light yellow oil. Alcohol **16**: $[\alpha]^{25}_D = -54.8°$ (c 1.01, $CHCl_3$); R_f 0.27 (20:80 EtOAc/petrol); IR (film) 3347 (br), 2954, 2928, 2885, 2857, 1471, 1255 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.54−3.38 (m, 4H), 1.26 (br s, 1H), 0.89 (s, 9H), 0.87−0.71 (m, 4H), 0.37−0.23 (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9, 66.6, 26.1, 19.9, 19.7, 18.4, 18.2, 17.8, 8.3, 8.1, −5.0; MS (CI, NH_3) *m/e* 274 $(M + NH_4)^+$, 257, 239, 199, 181, 157, 142; exact mass (CI, NH_3) calcd for $C_{14}H_{32}NO_2Si$ $(M + NH_4)^+$ 274.2202, found 274.2216.

(1*R*,3*S*,4*S*,6*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-[3-ethoxy-3-oxo-1(*E*)-propen-1-yl]bicyclopropane (17) and (1*R*,3*S*,4*S*,6*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-[3-ethoxy-3-oxo-1(*Z*)-propen-1-yl]bicyclopropane (18). PCC (0.723 g, 3.35 mmol), NaOAc (0.274 g, 3.35 mmol), and silica (0.8 g) were added to a stirred solution of alcohol **16** (0.572 g, 2.23 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h and at room temperature for 1 h, and filtered though Celite using CH_2Cl_2. The filtrate was concentrated to half-volume, and (carbethoxymethylene)triphenylphosphorane (1.18 g, 3.35 mmol) was added to this stirred solution. After 16 h, silica was added and the mixture concentrated. Chromatography on silica (2:98 to 5:95 EtOAc/petrol) provided (*E*)-ester **17** (0.586 g, 81%) as a colorless oil and (*Z*)-ester **18** (31.3 mg, 4%) as a colorless oil. (*E*)-Ester **17**: $[\alpha]^{25}_D = -119.7°$ (c 1.02, $CHCl_3$); R_f 0.25 (5:95 EtOAc/petrol); IR (film) 2954, 2929, 2869, 1716, 1644, 1472, 1255, 1144 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.45 (dd, 1H, $J = 15.4$, 10.2 Hz), 5.81 (d, 1H, $J = 15.4$ Hz), 4.16 (q, 2H, $J = 7.2$ Hz), 3.54 (ABXdd, 1H, $J = 10.8$, 5.8 Hz), 3.41 (ABXdd, 1H, $J = 10.8$, 6.3 Hz), 1.37−1.32 (m, 1H), 1.30 (t, 3H, $J = 7.2$ Hz), 1.14−1.10 (m, 1H), 0.89 (s, 9H), 0.86−0.78 (m, 2H), 0.78−0.71 (m, 2H), 0.36−0.26 (m, 2H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 153.3, 117.8, 66.2, 60.1, 26.1, 24.4, 21.2, 20.1, 18.4, 17.6, 14.4, 14.0, 7.6, −5.0; MS (CI, NH_3) *m/e* 325 $(M + H)^+$, 267, 221, 210, 193; exact mass (CI, NH_3) calcd for $C_{18}H_{33}O_3Si$ $(M + H)^+$ 325.2199, found 325.2196. Anal. Calcd for $C_{18}H_{32}O_3Si$; C, 66.61; H, 9.94. Found: C, 66.38; H, 9.84. (*Z*)-Ester **18**: $[\alpha]^{25}_D = -14.9°$ (c 0.86, $CHCl_3$); R_f 0.32 (5:95 EtOAc/petrol); IR (film) 2962, 2939, 2857, 1716, 1632, 1472, 1256, 1184 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.64 (d, 1H, $J = 11.2$ Hz), 5.46 (app t, 1H, $J = 11.2$ Hz), 4.18 (q, 2H, $J = 7.2$ Hz), 3.48 (dd, 2H, $J = 5.8$, 2.1 Hz), 2.70−2.63 (m, 1H), 1.30 (t, 3H, $J = 7.2$ Hz), 1.15−1.09 (m, 1H), 0.88 (s, 9H), 0.86−0.74 (m, 2H), 0.65−0.58 (m, 2H), 0.36−0.28 (m, 2H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 154.5, 116.6, 66.3, 59.8, 26.1, 24.5, 19.9, 18.8, 18.5, 17.3, 14.4, 14.2, 7.7, −5.0; MS (CI, NH_3) *m/e* 325 $(M + H)^+$, 267, 210, 193, 182; exact mass (CI, NH_3) calcd for $C_{18}H_{33}O_3Si$ $(M + H)^+$ 325.2199, found 325.2202.

(1*R*,3*S*,4*S*,6*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-[3-hydroxy-1(*E*)-propen-1-yl]bicyclopropane (19). DIBAL-H (8.4 mL, 1.0 M in hexanes, 8.4 mmol) was added to a solution of ester **17** (0.776 g, 2.39 mmol) in CH_2Cl_2 (20 mL) at −78 °C, and the solution was maintained at −78 °C for 4 h. The mixture was quenched by slow addition of MeOH (15 mL) and allowed to warm to room temperature. The resulting thick slurry was filtered though Celite and the filtrate concentrated. The residue was treated with EtOAc and filtered though Celite and the filtrate reconcentrated. Chromatography on silica (20:80 EtOAc/petrol) gave the alcohol **19** (0.663 g, 98%) as a colorless oil: $[\alpha]^{25}_D = -89.6°$ (c 1.00, $CHCl_3$); R_f 0.25 (20:80 EtOAc/petrol); IR (film) 3346 (br), 2954, 2928, 2857, 1670, 1471, 1463, 1255 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.65 (dt, 1H, $J = 15.2$, 6.2 Hz), 5.24 (dd, 1H, $J = 15.2$, 8.8 Hz), 4.05 (app t, 2H, $J = 6.2$ Hz), 3.50 (ABXdd, 1H, $J = 10.8$, 5.8 Hz), 3.42 (ABXdd, 1H, $J = 10.8$, 6.3 Hz), 1.22−1.14 (m, 2H), 0.89 (s, 9H), 0.85−0.70 (m, 3H), 0.54−0.43 (m, 2H), 0.32−0.21 (m, 2H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 126.3, 66.5, 63.6, 26.0, 22.1, 20.0, 19.8, 18.4, 17.8, 11.9, 7.7, −5.0; MS (CI, NH_3) *m/e* 300 $(M + NH_4)^+$, 282, 265, 225, 211; exact mass (CI, NH_3) calcd for $C_{16}H_{34}NO_2Si$ $(M+NH_4)^+$ 300.2359, found 300.2345. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.02; H, 10.70. Found: C, 68.17; H, 10.45.

(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-9-(hydroxymethyl)tercyclopropane (20). Following the procedure described for the preparation of bicyclopropane **14**, alcohol **19** (0.431 g, 1.53 mmol) was treated with a mixture of Et_2Zn (0.359 mL, 3.51 mmol) and CH_2I_2 (0.557 mL, 7.02 mmol) in the presence of dioxaborolane **15** (0.473 mg, 1.76 mmol) to provide, after chromatography on silica (10:90 to 20:80 EtOAc/petrol), tercyclopropane **20** (0.424 mg, 93%) as a colorless oil: $[\alpha]^{26}_D = -91.2°$ (c 1.00, $CHCl_3$); R_f 0.29 (20:80 EtOAc/petrol); IR (film) 3349 (br), 2998, 2954, 2928, 2857, 1471, 1463, 1408, 1255 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.51−3.37 (m, 4H), 1.21 (t, 1H, $J = 5.7$ Hz), 0.89 (s, 9H), 0.86−0.76 (m, 2H), 0.76−0.65 (m, 2H), 0.64−0.55 (m, 2H), 0.32−0.20 (m, 4H), 0.19−0.06 (m, 2H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.0, 66.7, 26.1, 19.8, 19.6, 18.5 (3C), 18.18, 18.15, 8.4, 8.3, 8.1, −5.0; MS (CI, NH_3) *m/e* 314 $(M + NH_4)^+$, 279, 239, 221, 197; exact mass (CI, NH_3) calcd for $C_{17}H_{36}NO_2Si$ $(M + NH_4)^+$ 314.2515, found 314.2538. Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.79; H, 10.85.

(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-9-[(phenylthio)methyl]tercyclopropane (23). The following procedure is a modification of that reported by Walker.[26] *N*-(phenylthio)-succinimide (**24**) (82.5 mg, 0.400 mmol) was added to a stirred solution of *n*-Bu_3P (0.13 mL, 0.40 mmol) in PhH (1.0 mL). After 10 min, a dark purple solution was obtained, and half of the solution was added to a stirred solution of alcohol **20** (54.0 mg, 0.182 mmol) in PhH (2.0 mL). After 30 min, the remaining reagent solution was added to the reaction solution. After 1 h, the reaction mixture was diluted with Et_2O (5 mL) and washed with H_2O (3 × 5 mL). The organic layer was dried and concentrated. Chromatography on silica (petrol to 2:98 EtOAc/petrol) provided sulfide **23** (57.3 mg, 81%) as a light yellow oil: ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.27 (m, 4H), 7.22 (m, 1H), 3.52−3.41 (m, 2H), 2.88 (ABXdd, 1H, $J = 12.8$, 6.6 Hz), 2.78 (ABXdd, 1H, $J = 12.8$, 7.3 Hz), 0.89 (s, 9H), 0.84−0.63 (m, 4H), 0.56−0.50 (m, 2H), 0.35−0.29 (m, 2H), 0.28−0.18 (m, 2H), 0.17−0.05 (m, 2H), 0.04 (s, 6H).

(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-9-[(phenylsulfonyl)methyl]tercyclopropane (25). The following procedure is a modification of that reported by Trost and Curran.[27] Oxone (31.3 mg, 0.102 mmol $KHSO_5$) in pH 5 buffer (1.0 mL) was added to a stirred solution of sulfide **23** (13.2 mg, 0.0340 mmol) in MeOH (1 mL) at 0 °C. The resulting thick slurry was allowed to warm to room temperature and was stirred for 2 h before more Oxone (20.9 mg, 0.0680 mmol $KHSO_5$) was added. After 3.5 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried, and concentrated. Chromatography on silica (10:90 EtOAc/petrol) provided sulfone **25** (8.0 mg, 56%) as a colorless oil and recovered sulfide **23** (4.2 mg, 32%) as a gummy, white solid. Sulfone **25**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.96−7.92 (m, 2H), 7.67−7.55 (m, 3H), 3.52−3.41 (m, 2H), 3.05−2.99 (m, 2H), 0.89 (s, 9H), 0.76−0.42 (m, 6H), 0.29−0.22 (m, 2H), 0.20−0.13 (m, 2H), 0.12−0.05 (m, 2H), 0.04 (s, 6H).

(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-9-methyltercyclopropane (26). W-2 Raney nickel (0.20 g, 50% in H_2O)

was washed with H_2O (3 × 1 mL) and EtOH (3 × 1 mL), suspended in EtOH (1 mL), and added to a vigorously stirred solution of sulfide **23** (13.2 mg, 0.0340 mmol) in EtOH (2 mL). After 2.5 h, the reaction mixture was filtered though Celite using EtOH. Atmospheric distillation removed most of the EtOH, and the residue was dissolved in pentane (2 mL), washed with H_2O (3 × 2 mL), dried, and concentrated. Chromatography on silica (pentane) provided the terminal methyl compound **26** (6.6 mg, 69%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.45−3.41 (m, 2H), 0.96 (d, 3H, J = 5.7 Hz), 0.88 (s, 9H), 0.80−0.63 (m, 2H), 0.57−0.50 (m, 2H), 0.45−0.39 (m, 2H), 0.25−0.18 (m, 2H), 0.16−0.05 (m, 4H), 0.04 (s, 6H).

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis[3-ethoxy-3-oxo-1(*E*)-propen-1-yl]bicyclopropane (27). Following the procedure described for the preparation of esters **17** and **18**, diol **14** (0.926 g, 6.51 mmol) was treated with PCC (4.23 g, 19.5 mmol), NaOAc (1.60 g, 19.5 mmol), and silica (5 g) followed by (carbethoxymethylene)triphenylphosphorane (7.29 g, 19.5 mmol) to provide, after chromatography on silica (5:95 to 10:90 EtOAc/petrol), (*E*,*E*)-diester **27** (1.09 g, 60%) as a gummy, off-white solid and (*E*,*Z*)-diester **28** (0.125 g, 7%) as a colorless oil.

The following procedure is a modification of that reported by Hunter and co-workers.[34] *n*-BuLi (56 μL, 2.0 M in hexanes, 0.11 mmol) was added to a stirred solution of thiophenol (12 μL, 0.11 mmol) in THF (1.0 mL) at 0 °C, and the mixture was maintained at 0 °C for 5 min. A solution of Ti(O-*i*-Pr)$_4$ (31.5 mg, 0.112 mmol) in THF (1.0 mL) was added, and after 5 min, the resulting solution was added to a stirred solution of (*E*,*Z*)-diester **28** (0.125 g, 0.449 mmol) in THF (5.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 72 h, the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated NH_4Cl solution (2 × 50 mL), followed by saturated $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried and concentrated. Chromatography on silica (5:95 to 10:90 EtOAc/petrol) gave (*E*,*E*)-diester **27** (63.1 mg, 50%) as a colorless oil and recovered (*E*,*Z*)-diester **28** (49.3 mg, 40%) as a colorless oil. (*E*,*E*)-Diester **27**: $[\alpha]^{27}_D = -272.5°$ (*c* 0.51, $CHCl_3$) [lit.[2] $[\alpha]^{30}_D = -246°$ (*c* 1.01, $CHCl_3$)]; spectroscopic data were identical with those of diester **27** made using an alternate route.[2]

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis[3-hydroxy-1(*E*)-propen-1-yl]bicyclopropane (29). Following the procedure described for the preparation of alcohol **19**, diester **27** was treated with DIBAL-H (21 mL, 1.0 M in hexanes, 21 mmol) to provide, after chromatography on silica (20:80 to 35:65 to 50:50 EtOAc/petrol), diol **29** (0.759 g, 94%) as a gummy, white solid: $[\alpha]^{27}_D = -196.8°$ (*c* 1.04, $CHCl_3$); [lit.[2] $[\alpha]^{30}_D = -202.7°$ (*c* 1.03, $CHCl_3$)]; spectroscopic data were identical with those of diol **29** made using an alternate route.[2]

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1,12-Bis(hydroxymethyl)quatercyclopropane (30). The following procedure is a modification of that reported by Charette and co-workers.[19b] CH_2I_2 (3.7 mL, 46 mmol) was slowly added to a stirred solution of Et_2Zn (2.3 mL, 23 mmol) and DME (2.4 mL, 23 mmol) in CH_2Cl_2 (45 mL) at −10 °C. After 10 min, the solution was slowly added to a stirred solution of diol **29** (0.738 g, 3.80 mmol) and dioxaborolane **15** (2.26 g, 8.36 mmol) in CH_2Cl_2 (40 mL) at −10 °C. The reaction mixture was allowed to warm slowly to room temperature. After 40 h, the reaction mixture was cooled to 0 °C and quenched by the slow addition of saturated NH_4Cl solution (100 mL). The aqueous layer was salted (NaCl) and extracted with CH_2Cl_2 (5 × 150 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (20:80 to 35:65 to 50:50 EtOAc/petrol) gave quatercyclopropane **30** (0.788 g, 93%) as a colorless oil: $[\alpha]^{27}_D = -181.4°$ (*c* 1.00, $CHCl_3$); [lit.[2] $[\alpha]^{26}_D = -182.0°$ (*c* 1.02, $CHCl_3$)]; spectroscopic data were identical with those of diol **30** made using an alternate route.[2]

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-12-(hydroxymethyl)quatercyclopropane (31). Following the procedure described for the preparation of alcohol **16**, diol **30** (0.640 g, 2.88 mmol) was treated with NaH (0.115 g, 60% dispension in oil, 2.88 mmol) followed by TBSCl (0.434 g, 2.88 mmol) to give, after chromatography on silica (10:90 to 20:80 to 50:50 EtOAc/petrol to EtOAc), alcohol **31** (0.426 g, 44%) as a light yellow oil, recovered diol **30** (0.281 g, 44%) as a white solid, and disilyl ether (0.135 g, 10%) as a light yellow oil. Alcohol **31**: $[\alpha]^{31}_D = -120.7°$ (*c* 1.00, $CHCl_3$); R_f 0.35 (20:80 EtOAc/petrol); IR (film) 3334 (br), 3065, 2997, 2953, 2931, 2887, 2858, 1466, 1410, 1389, 1363 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.47−3.36 (m, 4H), 1.25 (br s, 1H), 0.89 (s, 9H), 0.87−0.79 (m, 2H), 0.73−0.63 (m, 2H), 0.56−0.49 (m, 4H), 0.29−0.16 (m, 4H), 0.14−0.05, (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.0, 66.8, 26.1, 19.8, 19.6, 18.7, 18.6, 18.5 (2C), 18.30, 18.26, 18.1, 8.4 (2C), 8.3, 8.2, −5.0; MS (CI, NH_3) *m/e* 354 $(M + NH_4)^+$, 319, 279, 205, 187; exact mass (CI, NH_3) calcd for $C_{20}H_{40}NO_2Si$ $(M + NH_4)^+$ 354.2828, found 354.2849. Anal. Calcd for $C_{20}H_{36}O_2Si$: C, 71.36; H, 10.78. Found: C, 71.61; H, 10.97.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-12-[5-methoxy-5-oxo-1,3(*E*,*E*)-pentadien-1-yl]quatercyclopropane (32). PCC (0.292 g, 1.36 mmol), NaOAc (0.111 g, 1.36 mmol), and silica (0.3 g) were added to a stirred solution of alcohol **31** (0.305 g, 0.906 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and for 2 h at room temperature and filtered though a silica plug using CH_2Cl_2 and Et_2O, and the filtrate was concentrated to provide a crude oil. Prewashed NaH (72.5 mg, 60% dispension in oil, 1.81 mmol) was suspended in THF (5.0 mL), cooled to 0 °C, and stirred while a solution of (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$ (0.377 g, 1.81 mmol) in THF (5.0 mL) was added slowly. An orange solution developed, and after 30 min, a solution of the residual oil, prepared above, in THF (5.0 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h and quenched by pouring into brine (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried and concentrated. Chromatography on silica (5:95 EtOAc/petrol) provided (*E*,*E*)-ester **32** (0.224 g, 59%) as a colorless oil and (*E*,*Z*)-ester **33** (45.1 mg, 12%) as a light yellow oil. (*E*,*Z*)-Ester **33**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74 (ddd, 1H, J = 15.3, 11.8, 1.0 Hz), 6.01 (app t, 1H, J = 11.2 Hz), 5.86 (d, 1H, J = 15.3 Hz), 5.17 (app t, 1H, J = 10.5 Hz), 3.76 (s, 3H), 3.52−3.42 (m, 2H), 1.66−1.58 (m, 1H), 1.03−0.98 (m, 1H), 0.89 (s, 9H), 0.75−0.52 (m, 8H), 0.27−0.14 (m, 2H), 0.13−0.08, (m, 4H), 0.04 (s, 6H). The (*E*,*Z*)-ester **33** was isomerized directly without further characterization.

Following the procedure described for the isomerization of (*E*,*Z*)-diester **28**, (*E*,*Z*)-ester **33** (45.0 mg, 0.108 mmol) was treated with a mixture of *n*-BuLi (25 μL, 2.2 M in hexanes, 0.054 mmol), thiophenol (5.7 μL, 0.054 mmol), and Ti(O-*i*-Pr)$_4$ (15.2 mg, 0.0540 mmol) to give, after chromatography on silica (5:95 EtOAc/petrol), (*E*,*E*)-ester **32** (28.5 mg, 63%, 67% total from **31**) as a colorless oil: $[\alpha]^{33}_D = -197.0°$ (*c* 1.05, $CHCl_3$); R_f 0.22 (5:95 EtOAc/petrol); IR (film) 3066, 2998, 2952, 2932, 2890, 2957, 1718, 1636, 1464, 1436, 1302 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.21 (ddd, 1H, J = 15.3, 11.1, 0.6 Hz), 6.18 (dd, 1H, J = 14.9, 11.1 Hz), 5.73 (d, 1H, J = 15.3 Hz), 5.63 (dd, 1H, J = 14.9, 9.4 Hz), 3.72 (s, 3H), 3.47 (ABXdd, 1H, J = 10.8, 6.1 Hz), 3.40 (ABXdd, 1H, J = 10.8, 6.3 Hz), 1.28−1.21 (m, 1H), 1.08−0.95 (m, 1H), 0.89 (s, 9H), 0.76−0.51 (m, 8H), 0.28−0.15 (m, 2H), 0.13−0.06, (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 148.4, 145.2, 125.5, 117.4, 66.7, 51.4, 26.1, 24.4, 21.7, 19.7, 19.0, 18.5, 18.4, 18.3, 18.23, 18.18, 13.8, 8.4, 8.2, 7.9, −5.0; MS (CI, NH_3) *m/e* 417 $(M + H)^+$, 391, 359, 302, 285, 253; exact mass (CI, NH_3) calcd for $C_{25}H_{41}O_3Si$ $(M + H)^+$ 417.2825, found 417.2842. Anal. Calcd for $C_{25}H_{40}O_3Si$: C, 72.06; H, 9.68. Found: C, 72.20; H, 9.53.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-12-[5-hydroxy-1,3(*E*,*E*)-pentadien-1-yl]quatercyclopropane (34). Following the procedure described for the preparation of alcohol **19**, (*E*,*E*)-ester **32** (0.255 g, 0.612 mmol) was treated with DIBAL-H (1.5 mL, 1.0 M in hexanes, 1.5 mmol) to give, after chromatography on silica (20:80 EtOAc/petrol), alcohol **34** (0.216 g, 91%) as a colorless oil: $[\alpha]^{33}_D = -184.5°$ (*c* 1.01, $CHCl_3$); R_f 0.29 (20:80 EtOAc/petrol); IR (film) 3341 (br), 3066, 2998, 2953, 2931, 2887, 2858, 1659, 1520, 1254 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.15−6.05 (m, 2H), 5.69 (dt, 1H, J = 14.4, 6.1 Hz), 5.26 (dd, 1H, J = 14.4, 8.7 Hz), 4.15−4.12 (m, 2H), 3.47 (ABXdd, 1H, J = 10.9, 6.1 Hz), 3.40 (ABXdd, 1H, J = 10.9, 6.4 Hz), 1.53 (s, 1H), 1.22−1.11 (m, 2H), 0.89 (s, 9H), 0.76−0.61 (m, 2H), 0.60−0.45 (m, 6H), 0.28−0.12 (m, 2H), 0.12−0.05, (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 132.0, 128.6, 126.7, 66.8, 63.7, 26.1, 23.1, 20.7, 19.6, 18.8, 18.53, 18.46, 18.33, 18.27 (2C), 12.6, 8.4, 8.2, 8.0, −5.00, −5.03; MS (CI, NH_3) *m/e* 406 $(M + NH_4)^+$, 388, 371, 257, 239, 213; exact mass (CI, NH_3) calcd for $C_{24}H_{44}NO_2Si$ $(M + NH_4)^+$ 406.3141, found 406.3126. Anal. Calcd for $C_{24}H_{40}O_2Si$: C, 74.16; H, 10.37%. Found: C, 73.89; H, 10.39.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-12-{2-[(1*S*,2*R*)-2-(hydroxymethyl)cyclopropyl]-1(*E*)-ethen-1-yl}quatercyclopropane (35). The following procedure is a modification of that reported by Charette and co-workers.[19b] CH_2I_2 (0.43 mL, 5.4 mmol) was added dropwise to a stirred solution of Et_2Zn (2.7 mL, 1.0 M in hexanes, 2.7 mmol) and DME (0.28 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) at −15 °C. After 15 min, the solution was added to a stirred solution of (*E*,*E*)-diene **34** (0.210 g, 0.540 mmol) and dioxaborolane **15** (0.354 g, 0.594 mmol) in CH_2Cl_2 (10 mL) at −40 °C. The reaction mixture was maintained at −40 °C for 7 days and quenched by the slow addition of saturated NH_4Cl solution (5 mL). The mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried and concentrated. Chromatography on silica (10:90 to 15:85 to 20:80 EtOAc/petrol) provided alkene **35** (0.197 g, 90%) as a colorless oil: $[\alpha]^{27}_D = -171.5°$ (*c* 1.02, $CHCl_3$); R_f 0.30 (20:80 EtOAc/petrol); IR (film) 3343 (br), 3066, 2998, 2953, 2931, 2887, 2858, 1466, 1254 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (app t, 2H, J = 3.3 Hz), 3.51−3.37 (m, 4H), 1.55 (s, 1H), 1.29−1.21 (m, 2H), 1.12−0.99 (m, 2H), 0.89 (s, 9H), 0.79−0.62 (m, 2H), 0.61−0.49 (m, 6H), 0.39−0.33 (m, 2H), 0.27−0.14, (m, 2H), 0.13−0.05 (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 129.4, 66.8, 66.6, 26.1, 22.8, 22.0, 20.1, 19.60, 19.57, 18.7, 18.52, 18.46, 18.3, 18.2 (2C), 11.6, 11.5, 8.4, 8.2, 7.9, −5.00, −5.03; MS (CI, NH_3) *m/e* 420 $(M + NH_4)^+$, 401, 385, 362, 271, 253; exact mass (CI, NH_3) calcd for $C_{25}H_{46}NO_2Si$ $(M + NH_4)^+$ 420.3298, found 420.3285. Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.56; H, 10.51. Found: C, 74.53; H, 10.81.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*,16*S*,18*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-18-(hydroxymethyl)sextacyclopropane (37). Following the procedure described for the preparation of quatercyclopropane **30**, (*E*,*E*)-diene **34** (25.7 mg, 0.0661 mmol) was treated with a mixture of CH_2I_2 (32 mL, 0.40 mmol), Et_2Zn (20 mL, 0.20 mmol), and DME (21 mL, 0.20 mmol) in the presence of dioxaborolane **15** (43.3 mg, 0.0727 mmol) to give, after chromatography on silica (10:90 to 15:85 to 20:80 EtOAc/petrol), alkene **35** (2.9 mg, 11%) as a colorless oil and sextacyclopropane **37** (23.1 mg, 84%) as a colorless oil: ^1H NMR (270 MHz, $CDCl_3$) δ 3.49−3.36 (m, 4H), 1.57 (br s, 1H), 0.88 (s, 9H), 0.88−0.77 (m, 2H), 0.75−0.60 (m, 2H), 0.54−0.40, (m, 6H), 0.30−0.04 (m, 14H), 0.04 (s, 6H).

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-12-{2-[(1*S*,2*R*)-2-[(phenylthio)methyl]cyclopropyl]-1(*E*)-ethen-1-yl}quatercyclopropane (36). The following procedure is a modification of that reported by Walker.[26] *N*-(Phenylthio)succinimide (**24**) (0.141 g, 0.680 mmol) was added to a stirred solution of *n*-Bu_3P (0.17 mL, 0.68 mmol) in PhH (2.0 mL). After 10 min, a dark purple solution was obtained, and half of the solution was added to a stirred solution of alcohol **35** (54.8 mg, 0.136 mmol) in PhH (3.0 mL). After 30 min, the remaining reagent solution was added to the reaction solution. After 1 h, the reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried and concentrated. Chromatography on silica (petrol to 2:98 EtOAc/petrol) provided sulfide **36** (60.1 mg, 89%) as a faintly yellow oil: $[\alpha]^{30}_D = -131.8°$ (*c* 1.00, $CHCl_3$); R_f 0.16 (2:98 EtOAc/petrol); IR (film) 3065, 2997, 2954, 2929, 2888, 2856, 1471, 1439, 1253 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.30−7.23 (m, 2H), 7.20−7.15 (m, 1H), 5.00−4.98 (m, 2H), 3.46 (ABXdd, 1H, J = 10.8, 6.1 Hz), 3.40 (ABXdd, 1H, J = 10.8, 6.3 Hz), 3.00 (ABXdd, 1H, J = 12.9, 6.4 Hz), 2.76 (ABXdd, 1H, J = 12.9, 7.3 Hz), 1.27−1.20 (m, 2H), 1.05−0.98 (m, 2H), 0.89 (s, 9H), 0.78−0.64 (m, 2H), 0.63−0.48 (m, 6H), 0.37−0.32 (m, 2H), 0.28−0.15, (m, 2H), 0.13−0.05 (m, 4H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 132.0, 129.8, 129.4, 128.9, 126.1, 66.8, 38.9, 26.1, 22.4, 22.0, 20.1 (2C), 19.6, 18.7, 18.53, 18.47, 18.3 (3C), 14.2, 11.6, 8.4, 8.2, 7.9, −5.0; MS (CI, NH_3) *m/e* 512 $(M + NH_4)^+$, 385, 363, 297, 253; exact mass (CI, NH_3) calcd for $C_{31}H_{50}NOSSi$ $(M + NH_4)^+$ 512.3382, found 512.3359. Anal. Calcd for $C_{31}H_{46}OSSi$: C, 75.24; H, 9.37. Found: C, 74.96; H, 9.47.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-(Hydroxymethyl)-12-{2-[(1*R*,2*R*)-2-methylcyclopropyl]-1(*E*)-ethen-1-yl}quatercyclopropane (3). W-2 Raney nickel (9.25 g, 50% in H_2O) was washed with H_2O (3 × 10 mL) and absolute EtOH (3 × 10 mL) and suspended in absolute EtOH (40 mL). The mixture was sonicated for 2 h, and cooled to −60 °C with stirring. A solution of sulfide **36** (0.185 g, 0.374 mmol) in absolute EtOH (10 mL) was added, and the mixture was stirred at −60 °C for 2 days. The reaction mixture was filtered through Celite using absolute EtOH, and the filtrate was concentrated to half-volume. NH_4F (0.278 g, 7.48 mmol) was added to the resulting solution, and the mixture was heated to 65 °C for 26 h. The reaction mixture was allowed to cool, silica was added, and the mixture was concentrated. Chromatography on silica (10:90 to 15:85 to 20:80 EtOAc/petrol) provided alcohol **3** (50.0 mg, 49%) as a light yellow oil: $[\alpha]^{27}_D = -224.3°$ (*c* 1.00, $CHCl_3$); R_f 0.30 (20/80 EtOAc/petrol); IR (film) 3342 (br), 3065, 2998, 2952, 2926, 2868, 1453, 1073, 1025, 954 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (app t, 2H, J = 3.7 Hz), 3.44−3.36 (m, 2H), 1.56 (s, 1H), 1.31−1.19 (m, 1H), 1.03 (d, 3H, J = 6.0 Hz), 1.01−0.96 (m, 1H), 0.89−0.79 (m, 1H), 0.78−0.74 (m, 1H), 0.72−0.65 (m, 2H), 0.59−0.51 (m, 4H), 0.49−0.44 (m, 1 H), 0.40−0.37 (m, 1H), 0.34 (dd, 2H, J = 7.3, 6.6 Hz), 0.29−0.24, (m, 2H), 0.13−0.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.2, 130.6, 67.0, 22.5, 21.9, 20.1, 19.8, 18.61 (2C), 18.55, 18.5, 18.3, 18.1, 14.93, 14.90, 11.6, 8.3 (2C), 7.8; MS (CI, NH_3) *m/e* 290 $(M + NH_4)^+$, 273, 255, 213, 199, 187; exact mass (CI, NH_3) calcd for $C_{19}H_{32}NO$ $(M + NH_4)^+$ 290.2484, found 290.2475. Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.88, H, 10.25.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[5-Methoxy-5-oxo-1,3(*E*,*E*)-pentadien-1-yl]-12-{2-[(1*R*,2*R*)-2-methylcyclopropyl]-1(*E*)-ethen-1-yl}-quatercyclopropane (38). Following the procedure described for the preparation of (*E*,*E*)-ester **32**, alcohol **3** (60.0 mg, 0.220 mmol) was treated with a mixture of PCC (95.2 mg, 0.440 mmol), NaOAc (36.1 mg, 0.440 mmol), and silica (0.1 g), followed by a mixture of NaH (26.4 mg, 60% dispension in oil, 0.660 mmol) and (*E*)-MeO_2-CCH═$CHCH_2P(O)(OMe)_2$ (0.137 g, 0.660 mmol) to provide, after chromatography on silica (1:99 to 2:98 to 3.5:96.5 EtOAc/hexane), (*E*,*E*)-ester **38** (37.3 mg, 48%) as a faintly yellow oil and (*E*,*Z*)-ester **39** (11.6 mg, 15%) as a yellow oil. (*E*,*Z*)-Ester **39**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.76 (ddd, 1H, J = 15.4, 11.7, 1.0 Hz), 6.00 (app t, 1H, J = 11.3 Hz), 5.84 (d, 1H, J = 15.4 Hz), 5.18 (app t, 1H, J = 10.6 Hz), 5.03−4.99 (m, 2H), 3.76 (s, 3H), 2.08−1.90 (m, 1H), 1.72−1.58 (m, 1H), 1.20−1.24 (m, 1H), 1.04 (d, 3H, J = 6.0 Hz), 1.02−0.95 (m, 1H), 0.84−0.78 (m, 2H), 0.68−0.40 (m, 8H), 0.40−0.34 (m, 2H), 0.12−0.04 (m, 4H). The (*E*,*Z*)-ester **39** was isomerized directly without further characterization.

Following the procedure described for the isomerization of (*E*,*Z*)-diester **28**, (*E*,*Z*)-ester **39** (11.6 mg, 0.0329 mmol) was treated with a mixture of *n*-BuLi (13 μL, 1.8 M in hexanes, 0.024 mmol), thiophenol (2.1 μL, 0.024 mmol), and Ti(O-*i*-Pr)$_4$ (5.5 mg, 0.024 mmol) to give, after chromatography on silica (1:99 to 2:98 to 3.5:96.5 EtOAc/hexane), (*E*,*E*)-ester **38** (5.9 mg, 51%, 56% total from **3**) as a faintly yellow oil: $[\alpha]^{24}_D = -339.2°$ (*c* 0.84, $CHCl_3$); R_f 0.26 (5:95 EtOAc/petrol); IR (film) 3066, 2997, 2951, 2928, 2867, 1718, 1634, 1434, 1302, 1262, 1239, 1146, 952 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (ddd, 1H, J = 15.3, 11.2, 0.5 Hz), 6.18 (dd, 1H, J = 15.0, 11.2 Hz), 5.73 (d, 1H, J = 15.3 Hz), 5.62 (dd, 1H, J = 15.0, 9.5 Hz), 5.01 (app t, 2H, J = 3.7 Hz), 3.72 (s, 3H), 1.26−1.23 (m, 2H), 1.03 (d, 3H, J = 6.0 Hz), 1.01−0.97 (m, 2H), 0.78−0.75 (m, 1H), 0.69−0.66 (m, 1H), 0.64−0.53 (m, 6H), 0.48−0.44 (m, 1 H), 0.40−0.37 (m, 1H), 0.36−0.33 (m, 2H), 0.12−0.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 148.5, 145.3, 131.2, 130.6, 125.5, 117.4, 51.4, 24.3, 22.5, 21.9, 21.8, 20.1, 19.0, 18.6, 18.5, 18.3, 18.1, 14.93, 14.90, 13.7, 11.6, 7.8 (2C); MS (CI, NH_3) *m/e* 353 $(M + H)^+$, 321, 293, 259, 237, 199; exact mass (CI, NH_3) calcd for $C_{24}H_{33}O_2$ $(M + H)^+$ 353.2481, found 353.2508. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.89; H, 9.25.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[5-Hydroxy-5-oxo-1,3(*E*,*E*)-pentadien-1-yl]-12-{2-[(1*R*,2*R*)-2-methylcyclopropyl]-1(*E*)-ethen-1-yl}-quatercyclopropane (2). The following procedure is a modification of that reported by Laganis and Chenard.[35] Potassium trimethylsilanolate (0.117 g, 0.908 mmol) was added to a stirred solution of (*E*,*E*)-ester **38** (16.0 mg, 0.0454 mmol) in CH_2Cl_2 (5.0 mL), and the reaction mixture was evaporated to dryness by flushing with N_2. CH_2Cl_2 (5.0 mL) was added, and the reaction mixture was again evaporated to dryness. The reaction mixture was dissolved in H_2O (20 mL), treated with 10% HCl (5 mL), and extracted with EtOAc (5 × 30 mL). The combined organic layers were dried and concentrated. Chromatography on silica (20:80 to 35:65 to 50:50 EtOAc/petrol) provided acid **2** (13.0

mg, 85%) as a gummy, off-white solid: $[\alpha]^{24}_D = -352.7°$ (*c* 0.45, $CHCl_3$); R_f 0.30 (50:50 EtOAc/petrol); IR (film) 3065, 2998, 2953, 2927, 2866, 2656 (br), 2565 (br), 1684, 1628, 1417, 1304, 1276, 1160, 999, 950, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, 1H, J = 15.2, 11.2 Hz), 6.22 (dd, 1H, J = 14.9, 11.2 Hz), 5.73 (d, 1H, J = 15.2 Hz), 5.67 (dd, 1H, J = 14.9, 9.6 Hz), 5.01 (app t, 2H, J = 3.7 Hz), 1.31−1.27 (m, 2H), 1.03 (d, 3H, J = 6.0 Hz), 1.01−0.96 (m, 2H), 0.89−0.86 (m, 1H), 0.78−0.74 (m, 1H), 0.69−0.53 (m, 6H), 0.48−0.44 (m, 1 H), 0.40−0.38 (m, 1H), 0.36−0.33 (m, 2H), 0.13−0.03 (m, 4H); ^1H NMR (500 MHz, CD_3OD) δ 4.98 (dd, 2H, J = 5.1, 2.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 149.9, 147.4, 131.2, 130.6, 125.4, 116.8, 24.6, 22.6, 21.96, 21.92, 20.2, 19.0, 18.6, 18.5, 18.4, 18.1, 14.9 (2C), 13.9, 11.6, 7.8 (2C); MS (CI, NH_3) *m/e* 356 $(M + NH_4)^+$, 339, 321, 293, 283, 262, 245; exact mass (CI, NH_3) calcd for $C_{23}H_{31}O_2$ $(M + H)^+$ 339.2324, found 339.2326.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1-[5-[(5′-deoxy-5,6-dihydrouridin-5′-yl)amino]-5-oxo-1,3(*E*,*E*)-pentadien-1-yl]-12-{2-[(1*R*,2*R*)-2-methylcyclopropyl]-1(*E*)-ethen-1-yl}quatercyclopropane (1). The following procedure is a modification of that reported by Cabre and Palomo.[36] Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (8.4 mg, 0.033 mmol) was added to a stirred solution of acid **2** (10 mg, 0.030 mmol) and Et_3N (4.7 μL, 0.033 mmol) in DMA (0.20 mL). After 3 h, Et_3N (6.4 μL, 0.044 mmol) and amine **40**[37] (11 mg, 0.044 mmol) were added. Additional Et_3N (11 μL, 0.075 mmol) and amine **40** (7.3 mg, 0.030 mmol) were added after 18 h. After 24 h, the reaction mixture was diluted with H_2O (5 mL), 10% HCl was added until pH 1 was reached, and the aqueous layer was extracted with EtOAc (10 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), dried, and concentrated. The residue was triturated with EtOAc, and the triturant was concentrated and further triturated with Et_2O. The process was repeated using 70:30 Et_2O/hexane, 50:50 Et_2O/hexane, 30:70 Et_2O/hexane, and hexane. The solution obtained was concentrated, and chromatography on silica (20:80 to 35:65 to 50:50 EtOAc/petrol) provided recovered acid **2** (1.0 mg, 10%) as a gummy, off-white solid. The residues from each trituration were combined, and the resulting semipure amide **1** was chromatographed on octadecyl-functionalized silica (40:60 to 35:65 to 30:70 to 25:75 to 20:80 H_2O/MeOH) and triturated with hexane to provide amide **1** (10 mg, 69%) as an off-white solid: $[\alpha]^{20}_D = -167.0°$ (*c* 0.40, DMSO-d_6); R_f 0.21 (10:90 MeOH/$CHCl_3$); HPLC retention time 6.36 min (15:85 10% acetic acid/MeOH); IR ($CHCl_3$) 3339 (br), 3268 (br), 3068, 3020, 2951, 2927, 2870, 2850, 1718, 1685, 1657, 1621, 1547, 1485, 1452, 1425, 1375, 1352, 1336, 1315, 1275, 1167, 1128, 1097, 1072, 1032, 993, 957, 930, 887, 864, 854 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 281 nm (4.49); ^1H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.03 (t, 1H, J = 5.9 Hz), 6.92 (dd, 1H, J = 15.0, 11.2 Hz), 6.19 (dd, 1H, J = 15.0, 11.2 Hz), 5.87 (d, 1H, J = 15.0 Hz), 5.64 (d, 1H, J = 5.9 Hz), 5.65 - 5.60 (m, 1H), 5.16 (d, 1H, J = 4.8 Hz), 5.06 (d, 1H, J = 4.1 Hz), 4.95 (dd, 2H, J = 5.3, 2.6 Hz), 3.93−3.91 (m, 1H), 3.74−3.73 (m, 1H), 3.68−3.65 (m, 1H), 3.50−3.28 (m, 3H), 3.21−3.18 (m, 1H), 2.49 (m, 2H), 1.25−1.22 (m, 2H), 0.98 (d, 3H, J = 6.0 Hz), 1.00−0.94 (m, 1H), 0.84−0.83 (m, 1H), 0.73−0.70 (m, 1H), 0.65−0.61 (m, 1H), 0.60−0.48 (m, 6H), 0.43−0.39 (m, 1 H), 0.36−0.30 (m, 3H), 0.11−0.09 (m, 2H), 0.08−0.02 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3, 165.6, 153.1, 145.7, 139.4, 130.6, 130.3, 125.5, 121.5, 87.6, 81.2, 71.2, 70.0, 41.0, 36.0, 30.8, 23.3, 22.0, 21.2, 21.0, 19.6, 18.3 (2C), 18.0, 17.8, 17.6, 14.4, 14.1, 12.9, 11.1, 7.63, 7.61; MS (FAB) *m/e* 566 $(M + H)^+$, 506, 484, 452, 437, 413; exact mass (FAB) calcd for $C_{32}H_{44}N_3O_6$ $(M + H)^+$ 566.3230, found 566.3222.

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