Iterative Cyclopropanation: A Concise Strategy for the Total Synthesis of the Hexacyclopropane Cholesteryl Ester Transfer Protein Inhibitor U-106305

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Abstract: The first enantioselective total synthesis of the hexacyclopropane natural product U-106305, which is produced by *Streptomyces sp.* UC 11136, is described in full detail. Considerations on the biosynthesis of U-106305 and its close resemblance to the pentacyclopropane bacterial metabolite FR-900848 (**10**) led to the proposal that its previously unknown stereostructure should be represented as **11**. The central C_2-symmetrical quinquecyclopropane unit of **11** was assembled by repeatedly using a three-step cyclopropane "homologation" sequence in an efficient bidirectional approach. Desymmetrized quinquecyclopropane **23** was converted to dienol **13** which was monocyclopropanated stereo- and regioselectively to provide hexacyclopropane **25**. Deoxygenation was achieved by conversion to thioether **29** and desulfurization. The synthesis was completed by a one-pot deprotection−oxidation−Wittig olefination sequence to give **11**. The synthetically derived material was found to be identical in all respects to an authentic sample of U-106305 thus establishing the stereochemical identity of this natural product for the first time. In the course of our studies, several oligocyclopropane derivatives were found to be crystalline compounds and their structures were determined by X-ray crystallography. Among others, X-ray structures of two diastereomeric heptecyclopropanes **27** and **28** are presented. The synthesis of five analogs of U-106305 including the structural hybrid with FR-900848 (**41**) are described. An approach to FR-900848 (**10**) using a late desymmetrization of a C_2-symmetrical quatercyclopropane tetraene **52** is outlined.

Introduction

Cholesteryl ester transfer protein (CETP) catalyzes the redistribution of cholesteryl esters from high-density lipoproteins (HDLs) to low-density lipoproteins (LDLs). High levels of LDLs are the most important risk factor for coronary heart disease, the major cause of death in many industrialized countries.[1] Consequently, the proposal that inhibition of CETP should slow the progression of atheriosclerosis has stimulated the search for inhibitors of this blood protein. U-106305 was isolated as a potent inhibitor of the CETP reaction in the Upjohn Laboratories, and its structure (**1**) was published in 1995 (Figure 1).[2] This astonishing natural product is produced by *Streptomyces sp.* UC 11106. In addition to its interesting biological activity, U-106305 possesses remarkable structural features: six cyclopropane rings, five of which are contiguous. The natural product is the *N*-isobutylamide of the unusual fatty acid that is graced with these six cyclopropane units.

The Upjohn group have shown that the C_{18} backbone of the fatty acid is biosynthetically derived from head-to-tail-linked acetate units, while the cyclopropane methylene carbons stem from methionine.[2] On the basis of these findings, they propose a biosynthetic route where an 8-fold unsaturated carboxylic acid (**2**) is formed *via* the polyketide pathway and subsequently modified by introduction of the six additional carbon atoms to form the cyclopropane rings as shown in Scheme 1a.[2] Such a biocyclopropanation mechanism has been suggested previously for the formation of lactobacillic acid.[3] However, we believe that, with the evidence available at present, a different biosynthetic route cannot be ruled out: incomplete reduction of the growing polyketide chain gives rise to Michael acceptors (**6**). At this stage, cyclopropanation of the polarized double bond of **6** could occur *via* conjugate addition of the (*S*)-adenosylmethionine-derived sulfur ylide **7**, followed by ring closure of enolate intermediate **8** (Scheme 1b). Similar chemistry is well-

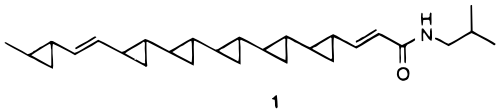

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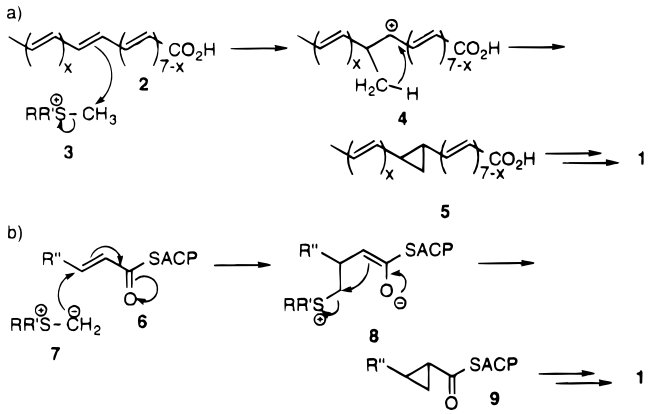
Figure 1.

Scheme 1. Two Plausible Biosynthetic Routes to U-106305[a]



[a] $RR'S^+-CH_3$ = (*S*)-adenosyl methionine; R″ = growing side chain less C_3 unit; ACP = acyl carrier protein.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

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(3) Mann, J. *Secondary Metabolism*, 2nd ed.; Oxford University Press: Oxford, 1992; p 42.

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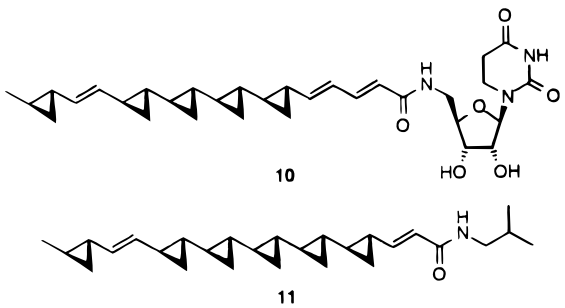


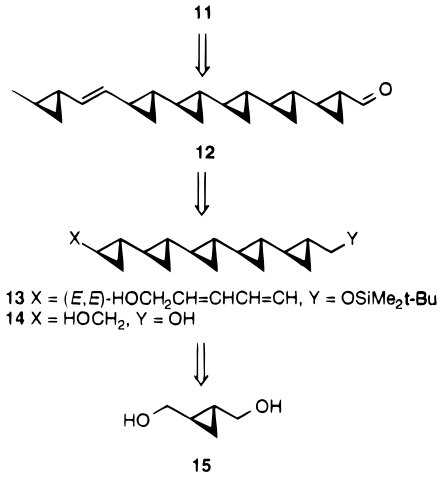
Figure 2.

known *in vitro*, using dimethylsulfoxonium methylide[4] and the involvement of (*S*)-adenosylmethionine-derived sulfur ylides was also suggested to play a role in other biotransformations, e.g., in the biosynthesis of tuberculostearic acid.[3] Cyclopropanation according to Scheme 1b would occur during polyketide synthesis, and in this case, the enzyme responsible for the cyclopropanation would probably be part of the polyketide synthase enzyme complex.

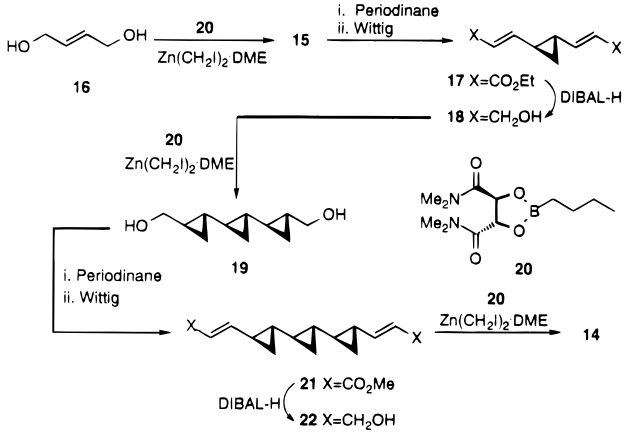
By analyzing the ^{1}H NMR coupling patterns and the 2D NOESY and NMR signal simulation, the Upjohn scientists could assign the two alkene units as *trans* and all of the cyclopropane rings as *trans*-disubstituted.[2] This leaves $2^6 = 64$ possible stereoisomeric structures for this exquisite natural product since the authors did not determine the absolute stereochemistry of any chiral center. However, there is indirect information about the stereostructure of U-106305 from the clear resemblance to the side chain of FR-900848 (**10**, Figure 2). This pentacyclopropane microbial metabolite, a potent and selective antifungal agent, was found in fermentation broths of *Streptoverticillium fervens*.[5] The stereostructure of **10** was recently determined by our group using a combination of degradation studies, partial synthesis, and X-ray crystallography.[6] Subsequently, the first total synthesis of FR-900848 (**10**) was achieved by our group,[7] followed by a total synthesis by Falck and co-workers.[8] The five cyclopropane rings in **10** are located on the same face of an *all-anti* carbon backbone. It is thus likely that similar enzymes are used in the biosynthesis of each of these cyclopropanes. Taking into account the structural similarities between U-106305 and FR-900848 and the producing organisms being related, it is reasonable to speculate that both of these bacterial strains use similar cyclopropanating enzymes. In conclusion, the cyclopropanated fatty acid moieties of FR-900848 and U-106305 should be isostructural, and consequently, we proposed stereostructure **11** for U-106305. Herein, we report the first total synthesis of U-106305 (**11**) which proved our assumptions to be correct. The results were previously reported in preliminary format.[9] Subsequent to our publication, a synthesis of the unnatural enantiomer of U-106305 has been reported.[10]

Retrosynthetic analysis of **11** (Scheme 2) shows that the α,β-unsaturated *N*-isobutylamide moiety should be easily introduced

Scheme 2. Retrosynthetic Analysis of U-106305 (**11**)



Scheme 3. Assembly of Quinquecyclopropane **14**



using a Wittig type olefination of aldehyde **12**. This could be derived from diene **13** by selective cyclopropanation of the double bond that is in proximity to the hydroxyl group, as demonstrated in the synthesis of FR-900848 (**10**).[7] The C_2-symmetrical core quinquecyclopropane **14** might be efficiently produced from the chiral cyclopropanedimethanol (**15**) using a bidirectional approach.

Results and Discussion

Cyclopropanation of the readily available 2(*E*)-butene-1,4-diol (**16**),[11] using preformed $Zn(CH_2I)_2$·DME in the presence of the chiral dioxaborolane **20** according to Charette's protocol,[12] gave **15** in excellent yields. Material of good optical purity (89% enantiomeric excess (ee)) was produced when using 2.1 equiv of **20**, whereas in the presence of 1.1 equiv of **20** only 74% ee was obtained. This synthesis is significantly easier than the literature synthesis of diol **15** *via* the resolution of *trans*-1,2-cyclopropanedicarboxylic acid and subsequent reduction.[13] Oxidation of diol **15** to the corresponding dialdehyde proceeded

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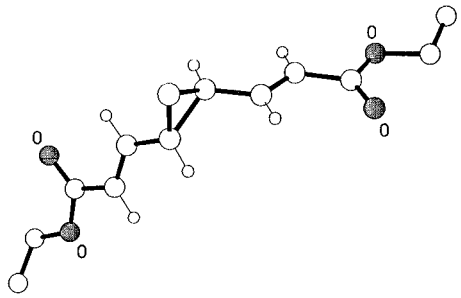


Figure 3. The molecular structure of one of the enantiomers present in the crystals of (*R,R*)(*S,S*)-**17**. The two crystallographically independent molecules in the structure of (*R,R*)-**17** also have essentially this same conformation.

Table 1. Influence of Acetic Acid−Pyridine (py) on the Reactivity of Stabilized Phosphorus Ylides, Formation of Methyl 2-Octadecenoate from Hexadecanal and $Ph_3P{=}CHCO_2Me$[a]

	10 min	1 h	2 h
	52 (34:1)	55 (33:1)	58 (35:1)
1.5 equiv of py	50 (21:1)	55 (27:1)	58 (36:1)
1.5 equiv of HOAc	63 (64:1)	96 (63:1)	99 (57:1)
0.7 equiv of py + 0.7 equiv of HOAc	60 (56:1)	94 (56:1)	99 (58:1)
1.5 equiv of py + 1.5 equiv of HOAc	62 (59:1)	95 (48:1)	99 (52:1)
3 equiv of py + 3 equiv of HOAc	61 (72:1)	95 (71:1)	99 (69:1)

[a] Percent conversion (*E*:*Z* ratio) with or without added pyridine and/or HOAc. Conditions: hexadecanal (1.0 equiv; 0.25 mmol) and $Ph_3P{=}CHCO_2Me$ (1.5 equiv; 0.375 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C; GC-MS detection.

smoothly with Dess−Martin periodinane.[14] In a one-pot procedure, excess oxidant was reduced with PPh_3 and the volatile dialdehyde was directly converted into the diester **17** [96% from **15**, (*E,E*):(*E,Z*) = 28:1] by olefination with $Ph_3P{=}CHCO_2Et$ (Scheme 3). Fractional recrystallization of **17** (81% ee) from Et_2O/hexanes gave first the racemic (17%) and subsequently enantiomerically pure (*E,E*)-diester **17** (75%). The structures for both the enantiomerically pure (*E,E*)-diester **17** and the corresponding racemic modification were confirmed by X-ray crystallography and are shown in Figure 3.

The Wittig reaction leading to **17** proceeded with both extraordinarily high speed and *trans*-selectivity. In order to elucidate the cause for this desirable reactivity, we investigated the influence of additives that are present in the complex reaction mixture during the formation of **17**, using the Wittig reaction between hexadecanal and $Ph_3P{=}CHCO_2Me$ as a model. One such species is acetic acid, generated *in situ* from Dess−Martin periodinane. We found that pyridine−acetic acid buffer or acetic acid alone accelerates the Wittig reaction significantly and leads to increased *trans*-selectivity (Table 1). Catalysis of the Wittig reaction by carboxylic acids has been observed previously.[15] The bis(allylic alcohol) **18** was obtained from diester **17** by diisobutylaluminum hydride (DIBAl-H) reduction in 96% yield (Scheme 3). Previous work by our group has shown that Charette asymmetric cyclopropanation[12] can be applied to the construction of contiguous cyclopropane arrays.[7] Thus, on cyclopropanation of **18**, tercyclopropanedimethanol (**19**) was obtained. Small amounts of unwanted diastereomers were easily removed by recrystallization to give pure stereoisomer **19** (89% yield). The structure of **19** was confirmed by X-ray analysis (Figure 4).

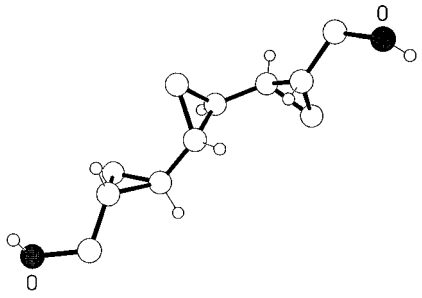
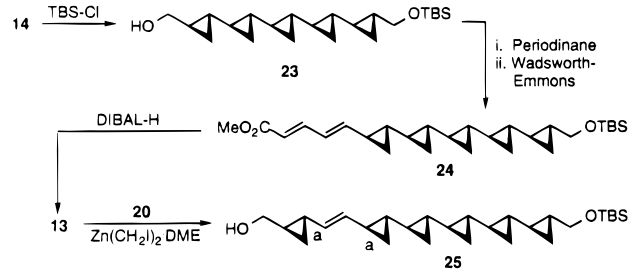


Figure 4. The molecular structure of **19**.

Scheme 4. Synthesis of the Hexacyclopropane **25**



One-pot oxidation−Wittig olefination of **19** gave the diester **21** (81% from **19**) which was reduced with DIBAl-H to give the diene diol **22** in 97% yield. Double Charette cyclopropanation[12] of bis(allylic alcohol) **22** afforded the quinquecyclopropane **14** in quantitative yield (Scheme 3). A single recrystallization gave the desired stereoisomer as a highly crystalline compound (83% from **22**). Its structure was also confirmed by single-crystal X-ray analysis and is shown in the preliminary paper.[9] It should be noted that all of the isolated intermediates in the sequence from **15** to **14** are crystalline compounds. This facilitates the purification processes and the removal of any traces of undesired stereoisomers formed in the cyclopropanation reactions.

The C_2-symmetrical diol **14** was desymmetrized by formation of the mono-*tert*-butyldimethylsilyl (TBS) ether **23**. Monosilylation under the conditions reported by McDougal[16] (NaH, THF) proceeded with selectivity for the formation of the desired monoether **23**; however, conversion was low (45% **23**; 10% di-TBS ether). It was found that use of the standard silylation conditions imidazole in CH_2Cl_2 was more practical, although the reaction showed only a slight selectivity for monosilylation (58% of **23**). Unreacted starting material **14** and the di-TBS ether were isolated in 22 and 19% yields, respectively. The di-TBS ether was easily recycled to the diol **14** in quantitative yield by desilylation with Bu_4NF. Dess−Martin oxidation of **23** and subsequent Wadsworth−Emmons homologation with (*E*)-$(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could be performed in one pot if DMSO was used as the solvent to give an excellent 88% yield of (*E,E*)-ester **24** in addition to 12% of the (*E,Z*)- and (*Z,E*)-isomers (Scheme 4). DIBAl-H reduction of **24** and Charette cyclopropanation of the derived diene **13** (95%) at −25 °C proceeded with excellent stereoselectivity and good regioselectivity to give hexacyclopropane **25** (72%).

Septicyclopropane **26** (27%) was formed as a side product in the Charette cyclopropanation of **13**. Deprotection of **26** gave a nonsymmetrical diol **27** with the undesired additional cyclopropane ring in an *anti*-arrangement to the other cyclopropanes (Scheme 5). Similar stereoselectivity was previously observed for the Simmons−Smith cyclopropanation of simple *trans*-3-

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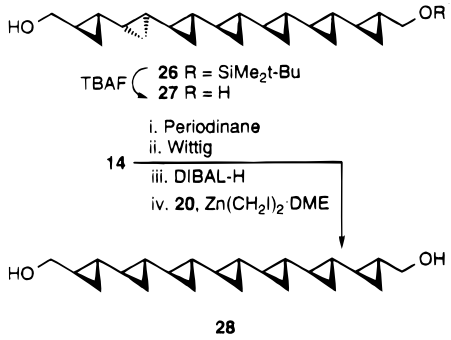
Scheme 5. Formation of the Crystalline septicyclopropane Dimethanols **27** and **28**



28

alkenyl-1-cyclopropanemethanol derivatives which provide *anti*-bicyclopropanes upon Simmons−Smith cyclopropanation.[17] It is probable that the predominant formation of the septicyclopropane **26** with the *anti*-stereochemistry is the result of stereoelectronic effects.[17] Thus, delocalization of the more electron rich σ-bonds (bonds a in structure **25**) should enhance the nucleophilicity of the alkene unit. In consequence, the zinc carbenoid should be preferentially delivered to the opposite face thereby providing the *anti*-isomer **26**. It is possible that the preferential formation of the *anti*-isomer results from steric approach control and the minimization of 1,3-allylic strain. We favor the stereoelectronic argument since 1,2-dicyclopropylalkenes such as **25** are especially reactive toward further cyclopropanation reactions relative to simple alkenes. The structure and stereochemistry of septicyclopropane **27** were confirmed by X-ray crystallography and are shown in Figure 5. This also provides indirect proof for the stereochemistry of the isolated cyclopropane ring in intermediate **25**. In order to study the conformational effect of the *anti*-cyclopropane ring, the *all-syn* septicyclopropane **28** was prepared for comparison by repeating the bidirectional cyclopropane "homologation" sequence (Scheme 5, 56% overall yield). Crystals suitable for single-crystal X-ray analysis were obtained by slow evaporation of a THF solution of **28**, and the X-ray structure is shown in Figure 6. An overlay of the structures of **27** and **28** shows that their *all-syn* quinquecyclopropane units possess identical conformations while the *anti*-cyclopropane in **27** induces a bend in the carbon backbone (Figure 6).

Deoxygenation of alcohol **25** was achieved via phenyl sulfide **29** using a strategy which was employed in our recent synthesis of FR-900848 (**10**).[7] Thus, treatment of alcohol **25** with the reagent[18] derived from *N*-(phenylsulfenyl)succinimide[19] (**31**) and tributylphosphine resulted in smooth formation of thioether **29** (91%, Scheme 6). Much to our relief, desulfurization with Raney nickel proceeded readily to provide **30**. It was found

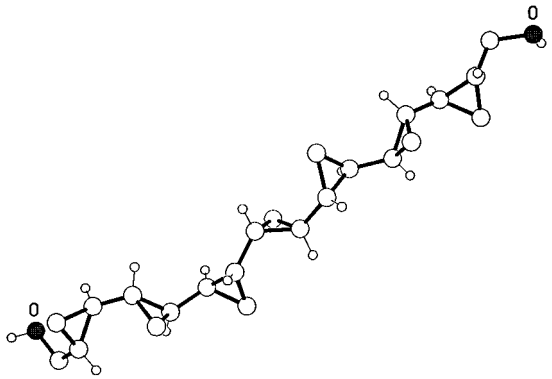


Figure 5. The molecular structure of **27**.

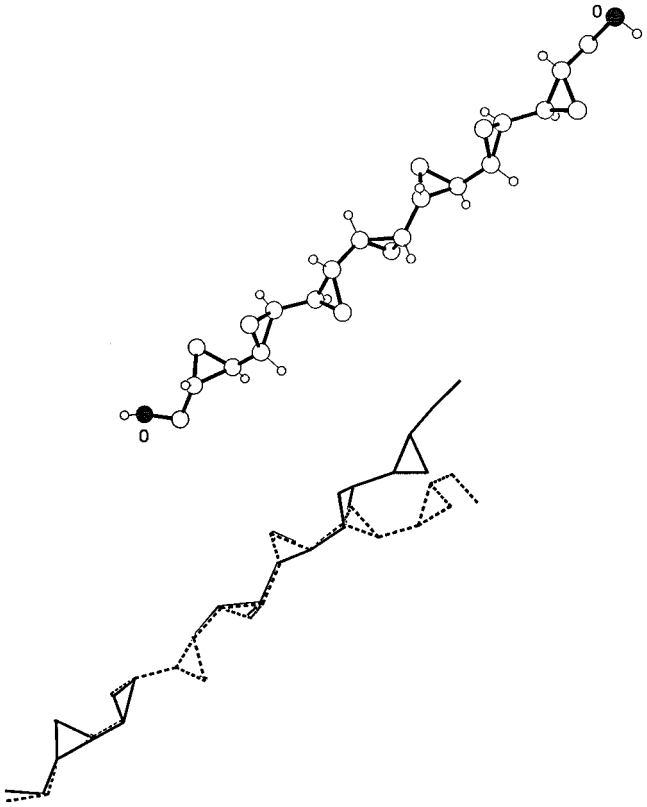


Figure 6. (a) The molecular structure of one of the four crystallographically independent molecules present in the crystals of **28**. All four molecules have very similar conformations. (b) A best fit of the five cochiral cyclopropane rings in **27** (- - -) and **28** (—).

that yields varied when different batches of Raney nickel were used. The best results (58% yield calculated at 86% conversion) were obtained when some ethylenediamine was added and the reaction was stopped on incomplete conversion. Under these conditions, intact unreacted starting material (14%) was recovered. The synthesis of U-106305 (**11**) was completed by desilylation, Dess−Martin oxidation to the aldehyde, and Wittig olefination to introduce the unsaturated isobutylamide. All of these reactions proceeded effectively in a one-pot procedure to give **11** in 91% yield from **30** as a crystalline solid. Both the synthetic material and an authentic sample of U-106305 were compared by ^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, CD, UV, chiral HPLC, melting point, and mixed melting point. They were found to be identical in all respects. Sections of the proton NMR spectra of both compounds are shown in Figure 7. Our results clearly establish the full structure and stereochemistry of U-106305 (**11**).

In addition to the total synthesis of U-106305 (**11**), we have examined methods for the synthesis of analogs for biological assay. As examples of this chemistry, we herein report the

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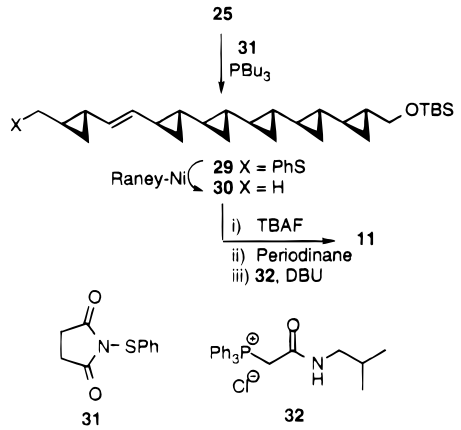
(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(22) SHELXTL PC version 5.03, Siemens Analytical X-Ray Instruments, Inc., Madison, WI, 1994.
(23) Schlosser, M.; Fouquet, G. *Chem. Ber.* **1974**, *107*, 1162−1170.
(24) Bohlmann, F.; Hühn, C. *Chem. Ber.* **1977**, *110*, 1183−1185.
(25) These $[\alpha]^{25}_D$ values were determined by weighing in the synthetic material and dissolving it in 2.00 mL of $CDCl_3$ containing 1.96×10^{-3} mmol L^{-1} MeOAc as a concentration standard (^{1}H NMR integration). The concentration of the authentic material in the same solvent was then determined by ^{1}H NMR.

Scheme 6. Completion of the Synthesis of U-106305 (**11**)



synthesis of representative derivatives **37**−**41** (Scheme 7). The aldehyde **33** was condensed with the keteneylidene $Ph_3P{=}C{=}C{=}O$[26] and benzylamine or morpholine to provide the corresponding α,β-unsaturated amides **37** (20%) and **38** (67%). These reactions presumably take place via nucleophilic addition[26] of the amines and Wittig reaction of the corresponding amide ylides. Since this strategy only proceeded in modest yields, aldehyde **33** was converted into carboxylic acid **34** by Horner−Emmons condensation with trimethylsilyl (dimethoxyphosphono)acetate. In this reaction, aqueous work-up resulted in hydrolysis of the trimethylsilyl ester to provide the carboxylic acid **34** (35%). Alternatively, the same acid **34** was more conveniently prepared from aldehyde **33** by Horner−Emmons condensation with 2-(trimethylsilyl)ethyl (dimethoxyphosphono)acetate to produce ester **35** (98%) and subsequent deprotection using tetrabutylammonium fluoride. The carboxylic acid **34** was converted using EDCI-mediated[27] coupling into the pentachlorophenyl ester **36** which was condensed with tris(hydroxymethyl)methylamine and 5′-amino-5′-deoxy-5,6-dihydrouridine[28] to produce the amides **39** (73%) and **41** (55%). Clearly, amide **41** represents a direct U-106305 (**11**)/FR-900848 (**10**) hybrid. Finally, tetrabutylammonium fluoride mediated deprotection of ester **35** and in-situ coupling of the resultant acid **34** with norephedrine using HBTU[29] gave the amide **40** (93%). These methods have been applied for the assembly of further analogs, and this work will be reported elsewhere in due course.

In our original total synthesis of FR-900848 (**10**), we prepared quatercyclopropane **53** using a bidirectional double Charette cyclopropanation sequence.[7] This diol **53** was desymmetrized by mono-*tert*-butyldimethylsilylation, homologated using chemistry closely following the methods for U-106305 (**11**) (see Schemes 4 and 6), and converted into FR-900848 (**10**). This strategy did not make maximum use of the inherent masked C_2-symmetry of FR-900848 (**10**). We therefore sought to explore a more concise total synthesis of FR-900848 (**10**) as outlined in retrosynthetic format in Scheme 8. FR-900848 (**10**) should be available from tetraenes **48** or **49** via the ester **42**. In turn, tetraenes **48** or **49** should be available from the quatercyclopropane **53** using a bidirectional oxidation and Horner−Emmons sequence. The two potential routes via tetraenes **48** or **49** differ in the methods of desymmetrization and the oxidation level. Herein, we also report our attempts to realize these strategies (also outlined in Scheme 8). Dess−Martin oxidation of diol **53** and Horner−Emmons homologation gave the *all-trans*-tetraene **52** (55%). Other minor geometric isomers were formed in the reaction (22%) but were not characterized. All of our attempts to cleanly monohydrolyze diester **52** were unsuccessful although the use of lithium hydroxide on silica gave acid **51** (22%); this was reduced by formation of the mixed anhydride with ethyl chloroformate and treatment with sodium borohydride to provide alcohol **48** (72%). Alternatively, double reduction of diester **52** with DIBAl-H (97%) and standard desymmetrization (47%) gave the corresponding alcohol **49**. Both alcohols **48** and **49** were converted into the corresponding pentacyclopropanes **46** (67%) and **47** (91%). In turn, both cyclopropanemethanol derivatives **46** and **47** were smoothly

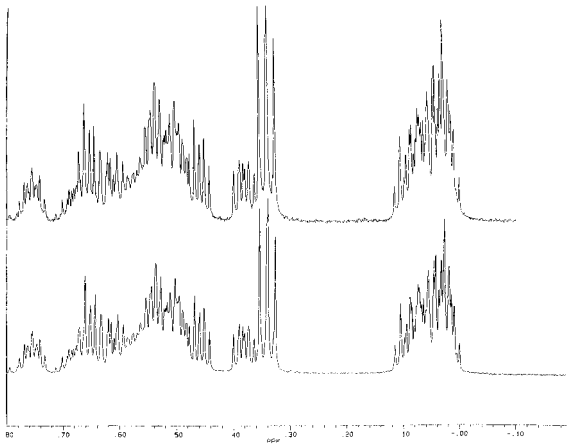
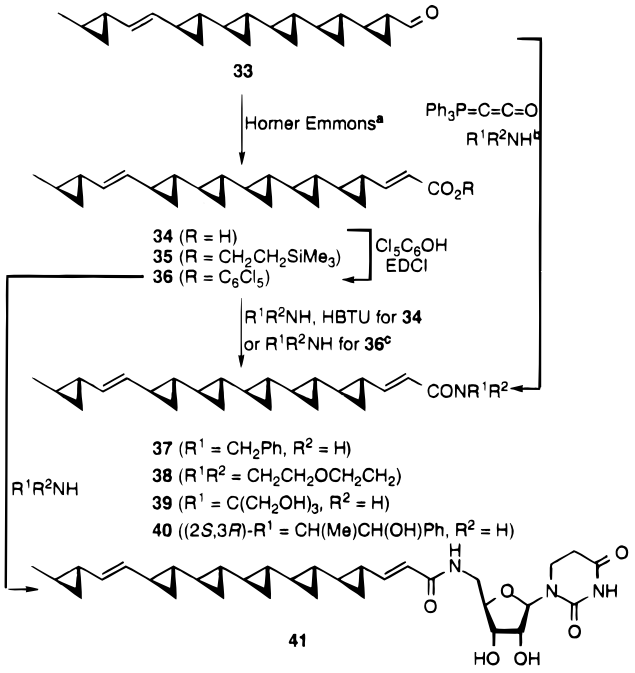


Figure 7. Sections of the ^{1}H NMR spectra (500 MHz, $CDCl_3$) of authentic U-106305 (upper trace) and synthetically derived **11** (lower trace).

Scheme 7. Synthesis of Representative Analogs of U-106305 (**11**)



(**a**) $(MeO)_2P(O)CH_2CO_2SiMe_3$, $NaN(SiMe_3)_2$ for **34**; $(MeO)_2P(O)CH_2CO_2CH_2CH_2SiMe_3$, LiCl, DBU for **35**; (**b**) **33** to **37** and **33** to **38** only; (**c**) **39** from **36**, R^1R^2NH; **40** from **34**, HBTU, R^1R^2NH.

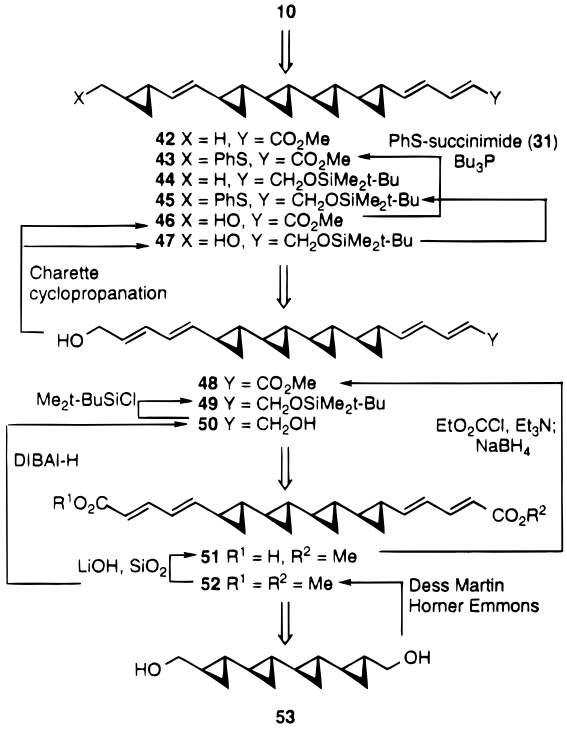
(26) Bestmann, H. J.; Sandmeier, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634.

(27) EDCI [1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride], see: Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. I. *J. Org. Chem.* **1961**, *26*, 2525.

(28) Skaric, V.; Katalenic, D.; Skaric, D.; Salaj, I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2091.

(29) HBTU [*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate], see: Dourtoglou, V.; Ziegler, J. C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269.

Scheme 8. Retrosynthetic Analysis of FR-900848 (**10**) andSynthesis of Pentacyclopropanes **43** and **45**



converted into the corresponding sulfides **43** (52%) and **45** (14%). Unfortunately and notwithstanding this progress, all of our attempts to desulfurize either sulfides **43** or **45** using Raney nickel failed to provide either triene **42** or **44**. This second approach to FR-900848 (**10**) was abandoned.

Conclusion

The isolation of the two microbial metabolites FR-900848 (**10**) and U-106305 (**11**) has stimulated considerable interest in the stereoselective construction of contiguous cyclopropane arrays.[20] The results presented herein demonstrate that iterative bidirectional Charette asymmetric cyclopropanation is a most useful strategy for the assembly of structures such as the central quinquecyclopropane unit of U-106305 (**11**). The finding that many of these cyclopropane derivatives are crystalline compounds has two important implications: rigorous purification of the desired stereoisomer is facilitated and structural aspects of these unique compounds can be studied by means of X-ray crystallography. The methodology is both simple and flexible and amenable for the synthesis of analogs. Further studies on related multiple cyclopropane systems will be reported in due course.

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. Chromatography was carried out on BDH silica 60, 230−400 mesh ASTM, using flash techniques.[21] Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica 60 F_{254} plates (40−60 °C). Petroleum ether (hexanes) used as a chromatography eluant was distilled; all other chromatography eluants were BDH GPR grade and undistilled. The following reaction solvents/reagents were purified by distillation: benzene (PhH) (P_2O_5, N_2), dichloromethane (CH_2Cl_2) (CaH_2, N_2), dimethyl sulfoxide (DMSO) (CaH_2, N_2), 1,2-dimethoxyethane (DME) (CaH_2, N_2), pyridine (CaH_2, N_2), and tetrahydrofuran (THF) (Ph_2CO/K, N_2). All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were concentrated using a rotary evaporator at ≤40 °C bath temperature. Involatile oils and solids were vacuum dried at <2 mmHg.

Crystallographic Data. A summary of the crystal data, data collection, and refinement parameters for **14**, (*R*,*R*)(*S*,*S*)-**17**, (*R*,*R*)-**17**, **19**, **27**, and **28** are given in Table 2. Data for **14**, (*R*,*R*)(*S*,*S*)-**17**, (*R*,*R*)-**17**, **19**, and **27** were collected using ω scans, while for **28** $\omega-2\theta$ scans were employed. All of the structures were solved by direct methods, and all of the non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2. The C−H hydrogen atoms were placed in calculated positions, assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$ [$U(H) = 1.5U_{eq}$(C-Me)], and allowed to ride on their parent atoms. The O−H hydrogen atoms in **14**, **19**, **27**, and **28** were located from ΔF maps and refined subject to a distance constraint (0.90 Å). The absolute chiralities of **14**, (*R*,*R*)-**17**, **19**, **27**, and **28** were all determined by internal reference. Computations were carried out using the SHELXTL PC program system.[22] The crystallographic data (excluding structure factors) for the structures reported in Table 2 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-xxxx-x. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge, CB12 1EZ, U.K. (fax international code +(1223)336-033; e-mail teched@chemcrys.cam.ac.uk).

(*R*,*R*)-1,3-Bis(hydroxymethyl)cyclopropane (15).[23] To diol **16**[11] (3.57 g, 40.5 mmol, 1.00 equiv) in dry CH_2Cl_2 (200 mL) were added dioxaborolane **20** (23.0 g, 85.1 mmol, 2.10 equiv) and 4 Å molecular sieves (3.24 g). The mixture was cooled to −45 °C which resulted in a slurry. According to the literature procedure,[12] a solution of $Zn(CH_2I)_2$·DME (263 mmol, 6.49 equiv) in dry CH_2Cl_2 (250 mL) was added over 30 min *via* canula, which resulted in dissolution of the slurry. The bath temperature was maintained between −30 and −40 °C during the addition. The mixture was allowed to warm to room temperature and left for 16 h. Saturated aqueous NH_4Cl (300 mL) and *i*-PrOH were added with cooling in an ice bath and vigorous stirring. After 1 h, the mixture was filtered and the layers were separated. The aqueous layer was continuously extracted (24 h) with Et_2O. The combined organic extracts were concentrated and chromatographed twice (silica, EtOAc/*i*-PrOH = 6:1 → 3:1 → 2:1) to give **15** (3.75 g, 36.7 mmol, 91%) as a slightly yellow oil: R_f 0.32 (EtOAc/*i*-PrOH = 5:1); bp *ca.* 120 °C (0.4 mbar); IR (film) 3342 (br), 3004, 2875, 1649, 1425, 1066, 1024; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.28 (br s, 2H), 3.87 (dd, J = 11.2, 3.9 Hz, 2H), 3.02 (dd, J = 11.0, 8.8 Hz, 2H), 0.98−1.06 (m, 2H), 0.44 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.14 (2C), 20.01 (2C), 7.23.

In order to determine the optical purity, a sample of **15** was distilled in a Kugelrohr apparatus to give a viscous colorless oil of $[\alpha]^{22}_D$ −17.44 (*c* 20.4, EtOH). This material was diacetylated (pyridine, Ac_2O, dry CH_2Cl_2) to give the corresponding diacetate of $[\alpha]^{22}_D$ −15.76 (*c* 2.1, EtOH) corresponding to 89% ee [lit.[13] $[\alpha]^{25}_D$ −17.75 (*c* 2.0, EtOH)].

(*R*,*R*)-1,3-Bis[(*E*)-2-(ethoxycarbonyl)ethenyl]cyclopropane (17). To a solution of cyclopropane **15** of 81% ee (4.14 g, 40.5 mmol, 1.00 equiv) in dry CH_2Cl_2 (250 mL) were added dry pyridine (33 mL) and Dess−Martin periodinane (41.3 g, 97.4 mmol, 2.40 equiv). TLC control after 30 min indicated complete conversion. The reaction mixture was cooled to 0 °C, and PPh_3 (30.0 g, 114 mmol, 2.82 equiv) was added. After 15 min, $Ph_3P{=}CHCO_2Et$ (41.0 g, 118 mmol, 2.90 equiv) was added and the cold bath was removed. TLC control indicated completion of the reaction after 45 min. H_2O was added, the layers were separated, and the aqueous phase was extracted with Et_2O. The organic phases were combined and successively washed with aqueous HCl (2 M), H_2O, saturated aqueous $NaHCO_3$, and brine. The solvent was evaporated, and the residue was dissolved in a minimum amount of CH_2Cl_2 at 40 °C. The mass of Ph_3PO precipitated upon addition of Et_2O (50 mL) and hexanes (250 mL) and was removed. Rotary evaporation and chromatography (silica, EtOAc/hexanes = 1:4 → 1:3) yielded a colorless oil that was fractionally crystallized from Et_2O and hexanes. Almost racemic material (1.65 g, 6.9 mmol, 17%) crystallized first, and then **17** was obtained as colorless crystals. A second crop of **17** was obtained from the mother liquor by chromatography (silica, EtOAc/hexanes = 1:4) in addition to its (*E*,*Z*)-isomer (0.32 g, 1.3 mmol, 3%) to give a total of 7.26 g (30.5 mmol, 75%) of **17**: R_f 0.37 (EtOAc/hexanes = 1:4); mp 42.5−43.5 °C (Et_2O/hexanes); IR (diffuse

Table 2. Crystal Data, Data Collection, and Refinement Parameters[a]

data	**14**	(*R*,*R*)(*S*,*S*)-**17**	(*R*,*R*)-**17**	**19**	**27**	**28**
formula	$C_{17}H_{26}O_2$	$C_{13}H_{18}O_4$	$C_{13}H_{18}O_4$	$C_{11}H_{18}O_2$	$C_{23}H_{34}O_2$	$C_{23}H_{34}O_2$
formula weight	262.4	238.3	238.3	182.3	342.5	342.5
color, habit	clear platy ribbons	clear platy needles	clear plates	clear plates	clear platy needles	clear plates
cryst size (mm)	0.80 × 0.23 × 0.02	0.77 × 0.23 × 0.03	0.67 × 0.60 × 0.17	0.67 × 0.53 × 0.13	0.20 x 0.17 × 0.03	0.77 × 0.63 × 0.03
lattice type	monoclinic	monoclinic	monoclinic	orthorhombic	orthorhombic	monoclinic
space group symbol, number	$P2_1$, 4	$P2_1/c$, 14	$P2_1$, 4	$P2_12_12_1$, 19	$P2_12_12_1$, 19	$P2_1$, 4
cell dimensions						
a (Å)	5.221(1)	17.019(1)	8.460(1)	5.127(1)	5.179(1)	5.181(1)
b (Å)	8.912(1)	9.572(2)	9.789(1)	9.146(1)	8.655(1)	88.825(7)
c (Å)	16.514(1)	8.328(3)	17.089(1)	22.152(1)	42.980(4)	8.573(1)
β (deg)	98.03(1)	94.98(1)	90.83(1)			90.20(1)
V (Å^3)	760.9(1)	1351.6(5)	1415.0(2)	1038.7(1)	1926.5(4)	3944.9(5)
Z	2	4	4[b]	4	4	8[c]
D_c (g cm^{-3})	1.145	1.171	1.118	1.165	1.181	1.153
F(000)	288	512	512	400	752	1504
radiation used	Cu Kα[d]	Cu Kα	Cu Kα	Cu Kα	Cu Kα	Cu Kα[d]
μ (mm^{-1})	0.57	0.71	0.68	0.62	0.56	0.55
θ range (deg)	2.7−62.5	2.6−60.0	2.6−63.0	4.0−62.0	2.1−62.0	2.0−60.0
no. of unique reflns measd	1287	1997	2436	988	1819	5858
obsd, $\lvert F_o\rvert > 4\sigma(\lvert F_o\rvert)$	1231	1452	1958	965	1435	5312
no. of variables	180	163	324	127	235	934
R_1[e]	0.042	0.052	0.053	0.034	0.051	0.050
wR_2[f]	0.112	0.135	0.148	0.093	0.121	0.140
weighting factors *a*, *b*[g]	0.075, 0.072	0.062, 0.428	0.097, 0.111	0.053, 0.106	0.055, 0.384	0.091, 0.579
largest difference peak (hole/eÅ^{-3})	0.14, −0.14	0.23, −0.12	0.20, −0.11	0.12, −0.12	0.22, −0.16	0.16, −0.18

[a] Details in common: graphite-monochromated radiation, Siemens P4 diffractometer, 293 K, refinement based on F^2. [b] There are two crystallographically independent molecules in the asymmetric unit. [c] There are four crystallographically independent molecules in the asymmetric unit. [d] Rotating anode source. [e] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [f] $wR_2 = \sqrt{\{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}}$. [g] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$.

reflectance) 3048, 2984, 1712, 1647, 1368, 1275, 1249, 1151, 1049, 983; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (dd, J = 15.4, 9.5 Hz, 2H), 5.93 (d, J = 15.4 Hz, 2H), 4.19 (q, J = 7.1 Hz, 4H), 1.84 (q, J = 15.5, 8.1 Hz, 2H), 1.28 + 1.30 (t, J = 7.1 Hz + t, J = 7.1 Hz, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.32 (2C), 149.45 (2C), 119.99 (2C), 60.25 (2C), 25.14 (2C), 17.46, 14.27 (2C); λ_{max} 268.0 (ϵ 20 100, EtOH); $[\alpha]^{26}_D$ −333.1 (*c* 1.7, EtOH); MS (CI, NH_3) *m*/*z* 256 $[M + NH_4]^+$, 239 $[M + H]^+$; exact mass (CI, NH_3) calcd for $C_{13}H_{22}NO_4$ $[M + NH_4]^+$ 256.1549, found 256.1551. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.23; H, 7.35.

(*R*,*R*)-1,3-Bis[(*E*)-3-hydroxy-1-propen-1-yl]cyclopropane (18). To a solution of diester **17** (3.01 g, 12.6 mmol) in dry CH_2Cl_2 (150 mL) at −78 °C was added DIBAl-H in hexanes (1 M, 63 mL) dropwise over 40 min. After 15 min, saturated aqueous NH_4Cl (10 mL), *i*-PrOH (30 mL), some silica, and some Celite were added. The mixture was allowed to warm to room temperature and filtered, and the residues were washed with EtOAc/*i*-PrOH (3:1). Rotary evaporation and chromatography (silica, EtOAc/*i*-PrOH = 19:1 → 10:1) gave an oil that crystallized from EtOAc/hexanes = 1:1 at −20 °C to yield **18**: colorless crystals (1.87 g, 12.1 mmol, 96%); R_f 0.41 (EtOAc); mp 46.5−48 °C (Et_2O/hexanes); IR (diffuse reflectance) 3357, 3285, 3011, 1667, 1451, 998, 977, 958; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (dt, J = 15.3, 6.1 Hz, 2H), 5.29 (dd, J = 15.3, 8.3 Hz, 2H), 4.09 (d, J = 6.0 Hz, 4H), 1.43−1.71 (m, 4H), 0.88 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.76 (2C), 127.38 (2C), 63.45 (2C), 23.27 (2C), 15.10; $[\alpha]^{24}_D$ −139.0 (*c* 1.0, EtOH); MS (CI, NH_3) *m*/*z* 172 $[M + NH_4]^+$, 154 $[M + H]^+$, 137, 119; exact mass (CI, NH_3) calcd for $C_9H_{18}NO_2$ $[M + NH_4]^+$ 172.1338, found 172.1329. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.03; H, 8.80.

(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1,9-Bis(hydroxymethyl)tercyclopropane (19). The bis(allylic alcohol) **18** (1.75 g, 11.3 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (90 mL). Molecular sieves (4 Å, 0.90 g) and dioxaborolane **20** (6.72 g, 24.9 mmol, 2.20 equiv) were added, and the mixture was cooled to −40 °C. A solution of $Zn(CH_2I)_2$·DME (91 mmol) in CH_2Cl_2 (90 mL), prepared according to the literature procedure,[12] was added to the reaction mixture over 30 min. The initially cloudy mixture turned into a clear solution which was allowed to warm and kept at room temperature for 17 h. Saturated aqueous NH_4Cl (150 mL) and *i*-PrOH (30 mL) were added, and the mixture was stirred for 15 min. After filtration, the layers were separated and the aqueous layer was extracted with five portions of CH_2Cl_2/*i*-PrOH (5:1). Rotary evaporation and chromatography (silica, EtOAc/hexanes/*i*-PrOH (5:5:1 → 20:10:6)) gave a viscous oil. Colorless crystals of **19** (1.81 g, 10.1 mmol, 89%) were obtained by crystallization from EtOAc/hexanes (1:3) at 4 °C: R_f 0.32 (EtOAc); mp 67.5−69.5 °C (Et_2O/hexanes); IR (diffuse reflectance) 3285, 1421, 1060, 1016, 730; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.40 (d, J = 6.9 Hz, 4H), 1.64 (s, 2H), 0.80−0.89 (m, 2H), 0.69−0.77 (m, 2H), 0.58−0.64 (m, 2H), 0.25−0.30 (m, 4H), 0.15 (t, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.86 (2C), 19.75 (2C), 18.33 (2C), 18.23 (2C), 8.33, 8.18 (2C); $[\alpha]^{24}_D$ −158.1 (*c* 0.96, EtOH); MS (CI, NH_3) *m*/*z* 200 $[M + NH_4]^+$, 182 $[M + H]^+$; exact mass (CI, NH_3) calcd for $C_{11}H_{22}NO_2$ $[M + NH_4]^+$ 200.1651, found 200.1637. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.25; H, 9.93.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*S*,10*R*,12*R*,13*S*,15*R*)-1-[((*tert*-Butyldimethylsilyl)oxy)methyl]-15-{(*E*)-2-[(1*S*,3*R*)-3-(hydroxymethyl)-1-cyclopropyl]ethenyl}quinquecyclopropane (25). Dienol **13** (602 mg, 1.40 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (10 mL). Molecular sieves (4 Å, 56 mg) and dioxaborolane **20** (397 mg, 1.47 mmol, 1.05 equiv) were added, and the mixture was cooled to −50 °C. A solution of $Zn(CH_2I)_2$·DME (5.56 mmol) in CH_2Cl_2 (15 mL), prepared according to the literature procedure,[12] was added to the reaction mixture over 20 min. The mixture was allowed to warm to −25 °C over 20 min and kept at that temperature for 2 h. TLC control showed that the starting material was essentially consumed and some septicyclopropane material had already been formed. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was vigorously stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). Rotary evaporation and chromatography (silica, EtOAc/hexanes/*i*-PrOH (3:30:1 → 4:16:1)) with repeated chromatography of mixed fractions yielded septicyclopropane **26** (172 mg, 0.38 mmol, 27%) in addition to the desired hexacyclopropane alkene **25** (449 mg, 1.01 mmol, 72%), as a colorless oil: R_f 0.40 (EtOAc/hexanes = 1:2); IR (film) 3340 (br), 3065, 2988, 2954, 2930, 2857, 1087, 1028, 838; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.99−5.09 (m, 2H), 3.37−3.52 (m, 4H), 1.34 (br s, 1H), 1.21−1.28 (m, 1H), 1.00−1.14 (m, 2H), 0.88 (s, 9H), 0.68−0.79 (m, 2H), 0.61−0.68 (m, 1H), 0.44−0.61 (m, 8H), 0.32−0.37 (m, 2H), 0.23 (dt, J = 8.5, 4.8 Hz, 1H), 0.18 (dt, J = 8.3, 4.8 Hz, 1H), 0.01−0.11 +

0.03 + 0.04 (m + s + s, 12H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 131.96, 129.33, 66.73, 66.58, 25.98 (3C), 22.74, 21.90, 20.00, 19.50 (2C), 18.53, 18.43, 18.37, 18.33, 18.27, 18.13 (2C), 18.06, 11.51, 11.37, 8.25, 8.10 (2C), 7.72, −5.09, −5.11; $[\alpha]^{26}_D$ −209.4 (*c* 0.96, EtOH); MS (CI, NH_3) *m*/*z* 460 $[M + NH_4]^+$, 311, 293; exact mass (CI, NH_3) calcd for $C_{28}H_{50}NO_2Si$ $[M + NH_4]^+$ 460.3611, found 460.3658. Anal. Calcd for $C_{28}H_{46}O_2Si$: C, 75.96; H, 10.47. Found: C, 75.99; H, 10.21.

Septicyclopropane 26: colorless oil; R_f 0.45 (EtOAc/hexanes = 1:2); IR (film) 3346 (br), 3064, 2996, 1463, 1255, 1086, 1026; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.34−3.51 (m, 4H), 1.40 (br s, 1H), 0.90 (s, 9H), 0.78−0.86 (m, 1H), 0.62−0.78 (m, 3H), 0.42−0.57 (m, 10H), 0.16−0.33 (m, 4H), 0.05 (s) + −0.02−0.16 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.96, 66.75, 26.01 (3C), 19.66, 19.54, 18.51 (3C), 18.38 (4C), 18.31 (2C), 18.20 (2C), 17.99, 8.97, 8.46 (2C), 8.32, 8.21, 8.15 (2C), −5.07 (2C), Si*C*$(CH_3)_3$ not detected; MS (CI, NH_3) *m*/*z* 474 $[M + NH_4]^+$, 457 $[M + H]^+$, 439 $[M + H - H_2O]^+$, 399, 381, 360.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*S*,10*R*,12*R*,13*S*,15*R*,16*R*,18*S*,19*S*,21*R*)-1,21-Bis(hydroxymethyl)septicyclopropane (27). TBS ether **26** (62 mg, 0.14 mmol) was dissolved in dry THF (5 mL) and Bu_4NF (1 M in THF, 0.4 mL) was added. After 1 h, rotary evaporation and chromatography (silica, EtOAc/hexanes = 2:1 → EtOAc) gave a slightly yellow solid (42 mg, 0.12 mmol, 90%). Crystals suitable for X-ray analysis were obtained by slow evaporation of an EtOAc solution at 4 °C. Septicyclopropane **27**: colorless crystals; R_f 0.50 (EtOAc); mp 85−87 °C (CH_2Cl_2); IR (film from CH_2Cl_2) 3314 (br), 3069, 1994, 1464, 1405, 1081, 1028; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35−3.45 (m, 4H), 1.43 (br s, 2H), 0.76−0.86 (m, 2H), 0.64−0.73 (m, 2H), 0.40−0.55 (m, 10H), 0.22−0.29 (m, 4H), −0.02−0.13 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 66.96 (2C), 19.73, 19.62, 18.54, 18.47, 18.39 (2C), 18.34 (2C), 18.29, 18.28, 18.26, 18.21, 17.96, 17.93, 8.92, 8.42, 8.37, 8.21, 8.17, 8.11, 8.06; $[\alpha]^{26}_D$ −188.1 (*c* 0.44, EtOH); MS (CI, NH_3) *m*/*z* 360 $[M + NH_4]^+$, 225, 211, 199, 185; exact mass (CI, NH_3) calcd for $C_{23}H_{38}NO_2$ $[M + NH_4]^+$ 360.2903, found 360.2906.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*S*,10*R*,12*S*,13*R*,15*S*)-1-[(*E*)-2-((*N*-Isobutylamino)carbonyl)ethenyl]-15-{(*E*)-2-[(1*R*,3*R*)-3-methyl-1-cyclopropyl]ethenyl}quinquecyclopropane (11). To a solution of the TBS ether **30** (29 mg, 68 μmol, 1.0 equiv) in THF (1.5 mL) was added tetrabutylammonium fluoride (1 M in THF, 0.15 mL, 2.2 equiv). After 15 min, benzene (2 mL) was added, the solvent was removed by rotary evaporation, and DMSO (2.5 mL) and pyridine (0.1 mL, 1.2 mmol, 18 equiv) were added. After 20 min, no TBS ether remained and Dess−Martin periodinane (57 mg, 0.13 mmol, 2.0 equiv) was added. More periodinane (60 mg, 0.14 mmol, 2.1 equiv) was added after 25 min, which led to completion of the oxidation after an additional 12 min. PPh_3 (124 mg, 0.47 mmol, 7.0 equiv) was added with cooling in a cold water bath which was removed after 10 min. Phosphonium chloride **32**[24] (84 mg, 0.20 mmol, 3.0 equiv) and DBU (0.20 mL, 1.3 mmol, 20 equiv) were added, which resulted in a color change to brown. After 90 min, Et_2O and H_2O were added, and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic phases were washed with aqueous HCl (1 M), H_2O, saturated aqueous $NaHCO_3$, and brine. Rotary evaporation and chromatography (silica, EtOAc/hexanes (1:3 → 1:2)) gave essentially pure (NMR) (*E*)-alkene **11** (26 mg) and some of the corresponding (*Z*)-isomer (2 mg, 5 μmol, 7%). Two batches of analytically pure **11** were obtained by crystallization from *t*-BuOMe/hexanes (*ca.* 1:4) at room temperature and then at −20 °C (25 mg, 61 μmol, 91%) as small colorless needles: R_f 0.24 (EtOAc/hexanes = 1:3); HPLC R_f 18.09 min (Chiralpak AD 25 cm × 0.46 cm, 5% EtOH in hexane, flow 1000 μL min^{-1}); mp 111.5−112.5 °C (*t*-BuOMe/hexanes); IR (diffuse reflectance) 3326, 3069, 3004, 2953, 1664, 1625, 1555, 1467, 1261, 1167, 1075, 977, 959, 920; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.32 (dd, J = 15.0, 10.0 Hz, 1H), 5.76 (d, J = 15.0 Hz, 1H), 5.34 (br, 1H), 4.97−5.05 (m, 2H), 3.09−3.18 (m, 2H), 1.78 (septet, J = 6.7 Hz, 1H), 1.22−1.28 (m, 1H), 0.94−1.06 + 1.03 (m + d, J = 6.0 Hz, 5H), 0.85−0.93 + 0.91 (m + d, J = 6.7 Hz, 7H), 0.72−0.80 (m, 1H), 0.44−0.71 (m, 10H), 0.32−0.40 (m, 3H), 0.00−0.12 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.03, 148.50, 131.07, 130.53, 120.23, 46.88, 28.66, 24.16, 22.47, 21.97, 20.70, 20.10 (2C), 20.04, 19.04, 18.63, 18.56, 18.52, 18.37 (2C), 18.16, 14.90, 14.84, 13.52, 11.63, 8.26, 7.99 (2C); λ_{max} 220 (ϵ 24 900, EtOH), 244 (sh); $[\alpha]^{25}_D$ −325.8 (*c* 0.045, $CDCl_3$);[25] MS (CI, NH_3) *m*/*z* 408 $[M + H]^+$; exact mass (CI, NH_3) calcd for $C_{28}H_{42}NO$ $[M + H]^+$ 408.3266, found 408.3322. Anal. Calcd for $C_{28}H_{41}NO$: C, 82.50; H, 10.14; N, 3.44. Found: C, 82.45; H, 9.89; N, 3.29.

U-106305 authentic sample: HPLC R_f 18.07 min (Chiralpak AD 25 cm × 0.46 cm, 5% EtOH in hexane, flow 1000 μL min^{-1}); mp 110−112.5 °C (*t*-BuOMe), mixed melting point with synthetic sample 110−112.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.32 (dd, J = 15.0, 10.0 Hz, 1H), 5.75 (d, J = 15.0 Hz, 1H), 5.34 (br, 1H), 4.97−5.05 (m, 2H), 3.09−3.18 (m, 2H), 1.78 (septet, J = 6.7 Hz, 1H), 1.22−1.28 (m, 1H), 0.96−1.06 + 1.03 (m + d, J = 6.0 Hz, 5H), 0.85−0.93 + 0.92 (m + d, J = 6.7 Hz, 7H), 0.72−0.79 (m, 1H), 0.44−0.71 (m, 10H), 0.31−0.40 (m, 3H), 0.00−0.12 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.04, 148.51, 131.07, 130.54, 120.23, 46.89, 28.67, 24.17, 22.47, 21.98, 20.70, 20.10 (2C), 20.04, 19.05, 18.64, 18.57, 18.52, 18.38 (2C), 18.18, 14.91, 14.85, 13.53, 11.64, 8.27, 8.00 (2C); λ_{max} 220 (ϵ 24 900, EtOH), 244 (sh); $[\alpha]^{25}_D$ −324.4 (*c* 0.037, $CDCl_3$).[25]

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Supporting Information Available: X-ray crystallographic details for (*R*,*R*)(*S*,*S*)-**17**, (*R*,*R*)-**17**, **19**, **27**, and **28** (data for structure **14** has already been deposited at the Cambridge Crystallographic Data Centre[9] and ^{1}H NMR, ^{13}C NMR, CD, and chiral HPLC results for **11** and authentic U-106305 are contained in the Supporting Information of the preliminary paper[9]) and full experimental details for the preparation and characterization of **13**, **14**, **21**−**24**, (1*R*,3*S*,4*R*,6*S*,7*R*,9*R*,10*S*,12*R*,13*S*,15*R*)-1,15-bis[(*E*)-2-methoxycarbonylethenyl]quinquecyclopropane, (1*R*,3*S*,4*R*,6*S*,7*R*,9*R*,10*S*,12*R*,13*S*,15*R*)-1,15-bis[(*E*)-3-hydroxy-1-propen-1-yl]quinquecyclopropane, **28**−**30**, **34**−**41**, **43**, and **45**−**52** (54 pages). See any current masthead page for ordering and Internet access instructions.

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