Stereochemical Elucidation of the Pentacyclopropane Antifungal Agent FR-900848

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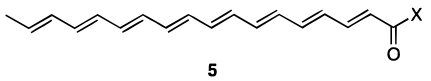
Full structural elucidation of FR-900848, an antifungal pentacyclopropane nucleoside natural product from *Streptoverticillium fervens*, is reported. A series of model compounds were prepared using multiple asymmetric Simmons−Smith cyclopropanation reactions. Comparisons of spectroscopic data of synthetic alkenes **9** and **10**, quatercyclopropanes **11** and **12**, and imidazolidines **13** and **14** with FR-900848 and its degradation products **2**, **3**, and **4** were consistent with the full structural assignment of the natural product as structure **7**.

Introduction

FR-900848 (**1**) is a novel 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. This makes it an attractive lead for novel therapeutic agents against the human pathogen *Aspergillus fumigatus*, which is responsible for significant morbidity and mortality among AIDS and other immunosupressed patients.[2] Structurally FR-900848 (**1**) is remarkable since its aliphatic side chain is endowed with five cyclopropanes, four of which are contiguous. Although the initial degradation studies at Fujisawa determined the constitution of the molecule,[1] there were 11 elements of ambiguity in the structure: the geometry of Δ^{18}, the stereochemistry of the isolated cyclopropane, and the stereochemistry of the quatercyclopropane unit. Tanaka and co-workers, however, did establish[3] that the central quatercyclopropane unit **3** obtained by ozonolysis with a sodium borohydride workup and acetylation was C_2-symmetric (Scheme 1). This partial structural assignment followed from the simplicity of the ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ for diester **3**. On the basis of this fact it is tempting to speculate as to the structure of FR-900848 (**1**). Although when we started our work in the area there was no information on the biosynthesis of FR-900848 (**1**), it was reasonable to speculate as to the origin of the fatty acid side chain in *Streptoverticillium fervens*.[4] We considered that since the carbon count is odd at C_{23}, it is likely that all the cyclopropanes are introduced late from a polyenoic acid precusor. This precusor may be derived via a mixed acetate/propanoate biosynthetic origin and be already C_{23} or, more likely, the precusor may be the C_{18}-polyene **5** in which the five cyclopropanes are introduced from a C_1 source such as *S*-adenosyl methionine. If the C_{18}-polyene **5** is indeed a key biosynthetic intermediate then the



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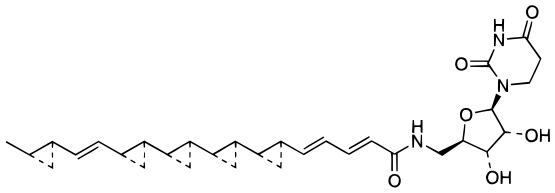
geometry is most likely to be *all-trans* since $\Delta^{2,4}$ are unequivocally *trans*. If these suppositions are true, FR-900848 (**1**) should be represented by either **6** or **7** since each enzymatic cyclopropanation should retain the alkene geometry and show the same absolute stereochemical bias. In addition, the geometry of Δ^{18} should be *trans* following the same biosynthetic speculations.



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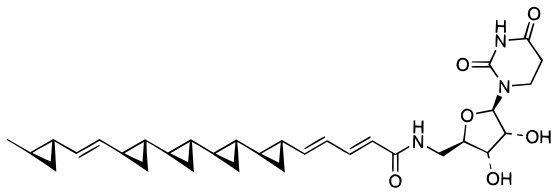

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We have now undertaken a full structural elucidation of FR-900848 (**1**) which unambiguously establishes its absolute stereochemistry as **7** and follows (but of course does not verify) the biosynthetic hypothesis. During the course of this work, ourselves,[5] Armstrong,[6] and Zercher[7] have independently reported stereoselective methods for the preparation of bicyclopropanes, all of which are relevant to the total synthesis of FR-900848 (**1**). Falck[8] has also undertaken the synthesis of polycyclopropanated compounds as precursors to FR-900848 (**1**) and has speculated as to the biosynthetic origin of the natural

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‡ Colorado State University.
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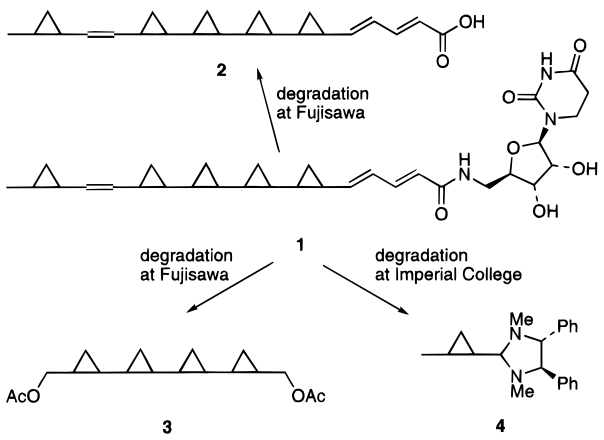
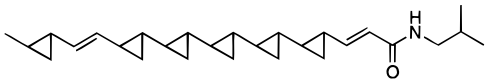
(1) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748.
(2) Kwon-Chung, J. K.; Bennett, J. E. *Medical Mycology;* Lee & Febiger: Philadelphia, 1992.
(3) Tanaka, H. Fujisawa Pharmaceutical Co. Ltd., personal communication, Aug 2, 1991.
(4) Barrett, A. G. M. 6th International Kyoto Conference on New Aspects of Organic Chemistry, Kyoto, Japan, Nov 7−11, 1994.
(5) (a) Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1783. (b) Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc., Chem. Commun.* **1995**, 355.
(6) Armstrong, R. W.; Maurer, K. W. *Tetrahedron Lett.* **1995**, *36*, 357.
(7) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181.
(8) Falck, J. R.; Mekonnen, B.; Yu, J. *Book of Abstracts,* 209th American Chemical Society National Meeting, Anaheim, CA, April 2−6, 1995; American Chemical Society: Washington, DC, 1995; Abstract 057.

S0022-3263(96)00054-0 CCC: $12.00

Scheme 1



product. Buchert and Reissig[9] have reported the synthesis of highly substituted bicyclopropanes. Also, a thorough X-ray crystallographic study of bicyclopropane has been conducted by Nijveldt and Vos.[10] Herein we report full experimental details for the structural elucidation of FR-900848 (**1**) which was previously reported in communication format.[11−14] These studies were an essential prerequisite for our total synthesis of FR-900848 (**1**) also recently reported.[15] After the communications we have published on FR-900848 (**1**)[11−14] and during the drafting of this paper, Kuo *et al.* have reported on the isolation and structural determination of U-106305 (**8**).[16] This natural product is remarkably similar to FR-



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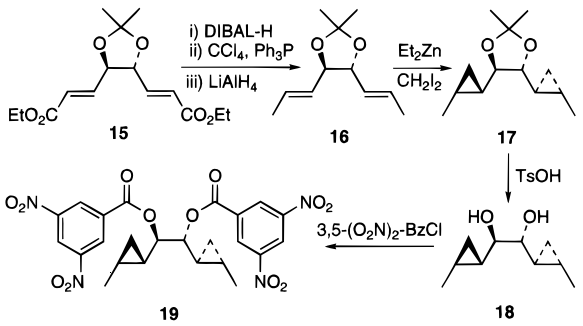
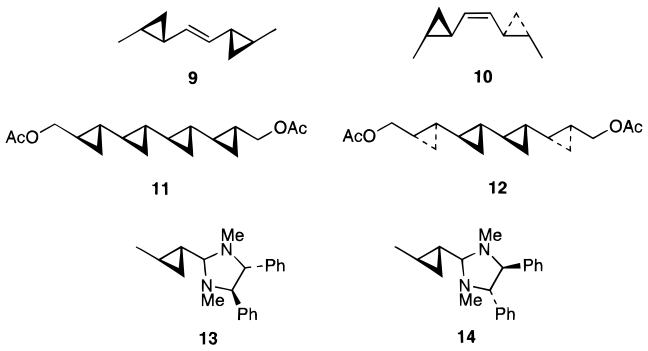
900848 (**1**), and strangely, the authors claim it is of "a structural class of compounds not previously reported". Although only the relative stereochemistry of U-106305 (**8**) was established, we believe that the cyclopropanes of this natural product will have the same absolute stereochemistry as determined for FR-900848 (**1**). The biogenetic studies conducted by the Upjohn group showed that the backbone of U-106305 (**8**) was derived from acetate and that the methylene carbons of the cyclopropanes arose from the methyl group of L-methionine. These findings are consistent with our proposed biosynthesis of FR-900848 (**1**).[4]

We considered that the full structure of FR-900848 (**1**) should be available from comparisons of model systems, prepared via unambiguous syntheses, and fragments of

Scheme 2



the natural product from partial degradation. In particular we sought to establish the geometry of Δ^{18} from the elaboration of the (*E*)-alkene **9** and (*Z*)-alkene **10**, the C_2-symmetric quatercyclopropane core from the preparation of the diacetates **11** and **12**, and the stereochemistry of the isolated cyclopropane from the two imidazolidine derivatives **13** and **14**.



Results and Discussion

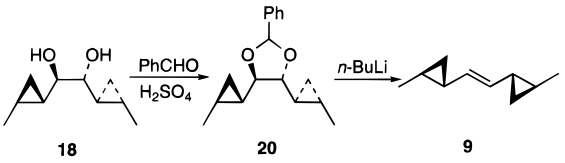
Determination of the Geometry of the Isolated Alkene. Reduction of the known diester **15**[17] (Scheme 2) via the corresponding diol and allylic chloride gave the (*E*,*E*)-diene **16** (56%) as a single geometric isomer. Much to our delight, double Simmons−Smith cyclopropanation proceeded with excellent diastereoselectivity to provide only a single dicyclopropane **17** in high yield (89%). Examination of the ^{1}H NMR and ^{13}C NMR spectra of the product indicated that it was, as expected, C_2-symmetric. In order to determine which of the two possible isomers had been formed, dicyclopropane **17** was subjected to acid-catalyzed acetal hydrolysis to give the vicinal diol **18** (63%). Subsequent esterification using 3,5-dinitrobenzoyl chloride gave the crystalline derivative **19** (84%). The structure of this substance was unequivocally established by a single-crystal X-ray structure determination.[11] This clearly established the relative stereochemistry of all chiral centers present in the molecule. Since diester **15** was originally prepared from 3,4-*O*-isopropylidene-D-mannitol, the crystal structure also allowed for the unambiguous identification of the absolute stereochemistry of dicyclopropanes **17**−**20**, and **9**. Clearly, the stereoselectivity observed in the double cyclopropanation reaction was the result of coordination of the zinc carbenoid reagent by each of the Lewis basic dioxolane

(9) Buchert, M.; Reissig, H. U. *Chem. Ber.* **1992**, *125*, 2723.
(10) (a) Nijveldt, D.; Vos, A. *Acta Crystallogr., Sect. B: Struct. Sci.* **1988**, *B44*, 281. (b) Nijveldt, D.; Vos, A. *Acta Crystallogr., Sect. B: Struct. Sci.* **1988**, *B44*, 289. (c) Nijveldt, D.; Vos, A. *Acta Crystallogr., Sect. B: Struct. Sci.* **1988**, *B44*, 296.
(11) Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1781.
(12) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 407.
(13) Barrett, A. G. M.; Kasdorf, K.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 649.
(14) Barrett, A. G. M.; Kasdorf, K.; Tustin, G. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1143.
(15) Barrett, A. G. M.; Kasdorf, K. *J. Chem. Soc., Chem. Commun.* **1996**, 325.
(16) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629.
(17) Krief *et al.* have dicyclopropanated diester **15** using ylide chemistry to obtain a C_2-symmetrical dicyclopropane with fair selectivity (74% de). Krief, A.; Dumont, W.; Pasau P.; Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039.

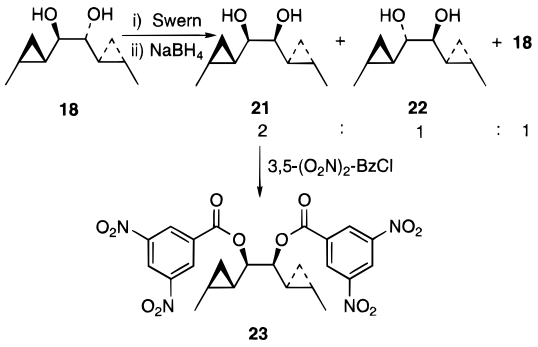
Table 1

	cis-dicyclopropylethene (CCl_4)[21]	(*Z*)-alkene **10** ($CDCl_3$)	*trans*-dicyclopropylethene (CCl_4)[21]	(*E*)-alkene **9** ($CDCl_3$)	side chain acid of FR-900848 (**2**) ($CDCl_3$)	side chain acid of FR-900848 (**2**) (CD_3OD)	FR-900848 (**1**) (DMSO-d_6)
1H NMR δ (ppm)	4.62	4.68	4.97	5.04	5.02	5.00	4.95
1H NMR mult. and *J* (Hz)	m	dd 6.6, 2.2	m	dd 5.3, 2.6	–	dd 5.0, 2.5	dd 5.2, 2.6
13C NMR δ (ppm)	–	131.5	–	130.9	131.1, 130.4	–	130.6, 130.3

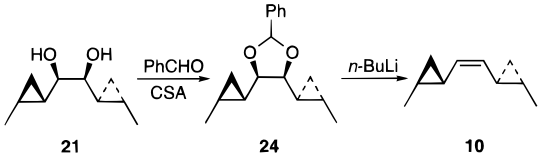
Scheme 3



Scheme 4



Scheme 5



ring oxygens prior to each cyclopropanation event. Taguchi and coworkers[18] have recently reported related facial selectivity in the monocyclopropanation of 1,3-dioxolanylalkenes. Additionally, oxygen ligand coordination to direct the stereochemistry of the Simmons–Smith reaction has been well documented in other systems.[19]

We required a mild and stereospecific method for the reductive elimination of the vicinal diol **18** to provide the corresponding alkene **9**. Clearly harsh reaction conditions have the liability of cyclopropane scission via cyclopropylmethyl carbenium ion rearrangement chemistry. We therefore turned our attention to the *syn*-specific Whitham elimination reaction since this protocol has been shown to respect delicate alkenes such as *trans*-cyclooctene derivatives.[20] Condensation of the diol **18** with benzaldehyde (Scheme 3) gave the benzylidene derivative **20** (64%) which was subsequently lithiated with *n*-butyllithium to provide geometrically pure (*E*)-alkene **9** (60%) on cycloreversion of lithium benzoate. Nishida and co-workers previously reported a geometrically nonselective syntheses of both (*E*)- and (*Z*)-1,2-di-(cyclopropyl)ethene,[21] and comparisons of their spectroscopic data with the corresponding data we observed for alkene **9** are fully consistent with the assignment of *trans*-geometry.

To further substantiate our geometric assignment we sought to also prepare the corresponding (*Z*)-alkene **10**. Oxidation of *syn*-diol **18** using a variation of the Swern reaction[22] (Scheme 4) followed by direct sodium borohydride reduction provided a 2:1:1 mixture of *anti*-diol **21** (36% from **18**) and the two possible *syn*-diols **18** and **22** (36% from **18**). Fortuitously, *anti*-diol **21** was readily separated from the mixture by chromatography, and the mixture of *syn*-diols **18** and **22** could be recycled to provide additional *anti*-diol **21** (33%). The stereochemical assignment of the diol **21** was fully consistent with the appearance of 10 carbons in the ^{13}C NMR spectrum. The inseparable mixture of *syn*-isomers **18** and **22** also showed a total of 10 resonances in the ^{13}C NMR spectrum, five of which coincided with the values obtained for diol **18**. In addition, diol **21** was esterified using 3,5-dinitrobenzoyl chloride to provide the corresponding crystalline derivative **23** in high yield (95%). A single-crystal X-ray structure determination of diester **23** established the relative stereochemistry of all chiral centers present in the molecule.[13] The absolute stereochemistry of the cyclopropane centers of diol **18** were determined from the previous X-ray crystallographic study of diester **19**, which allowed for the identification of the absolute stereochemistry of dicyclopropanes **21**, **23**, **24**, and **10**.

Condensation of the diol **21** with benzaldehyde (Scheme 5) gave a mixture of the two isomers of the benzylidene derivative **24** in excellent yield (96%). Whitham elimination[20] using *n*-butyllithium provided the geometrically pure (*Z*)-alkene **10** (22%) and recovered acetal **24** (49%) (71% total mass recovery). Our assignment of *cis*-geometry for alkene **10** is once again consistent with the spectroscopic assignments made by Nishida and coworkers from their nonselective synthesis of both (*E*)- and (*Z*)-1,2-di(cyclopropyl)ethene.[21] In addition, the assignment of geometry is consistent with the structural assignment of pure (*Z*)-1,2-di(cyclopropyl)ethene prepared by the semihydrogenation of 1,2-di(cyclopropyl)-ethyne.[21] In the infrared spectrum, *trans*-alkene **9** showed *inter alia* 951 cm^{-1} and this diagnostic absorption was absent in the *cis*-alkene **10**. Comparison of the ^1H NMR data reported[21] for *cis*- and *trans*-1,2-dicyclopropylethene also reinforces our assignment of *trans*-geometry for alkene **9** and *cis*-geometry for alkene **10** (Table 1).

Comparison of the spectroscopic data of the *trans*-alkene **9** and *cis*-alkene **10**, with those of both the side chain carboxylic acid of FR-900848 **2** and FR-900848 (**1**) is now possible (Table 1). Of particular note in this analysis is that the coupling constants observed for the vinyl protons in the ^1H NMR spectra of *trans*-alkene **9**

(18) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97.

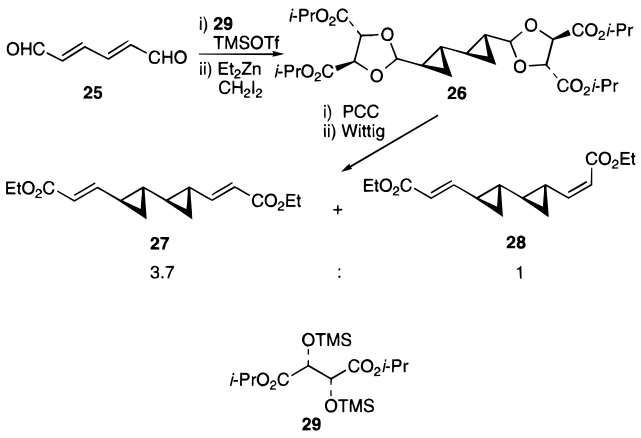
(19) For examples, see: (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254. (b) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447. (c) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61.

(20) Hines, J. N.; Peagram, M. J.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2332.

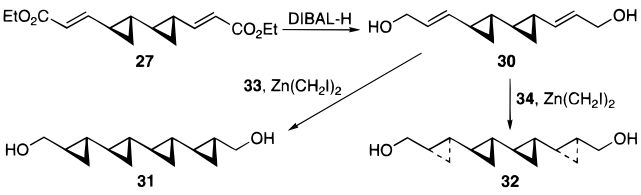
(21) Teraji, T.; Moritani, I.; Tsuda, E.; Nishida, S. *J. Chem Soc. (C)* **1971**, 3252.

(22) Banwell, M. G.; Onrust, R. *Tetrahedron Lett.* **1985**, *26*, 4543.

Scheme 6



Scheme 7



match the values obtained for FR-900848 (**1**) much more closely than those observed for *cis*-alkene **10**. The chemical shift values for the ^{1}H NMR and ^{13}C NMR spectra also show a correlation between the data obtained for *trans*-alkene **9** and the natural product, whereas the *cis*-alkene **10** data shows greater disparity. These findings are consistent with the geometry of the isolated alkene of the side chain of FR-900848 (**1**) being *trans*.

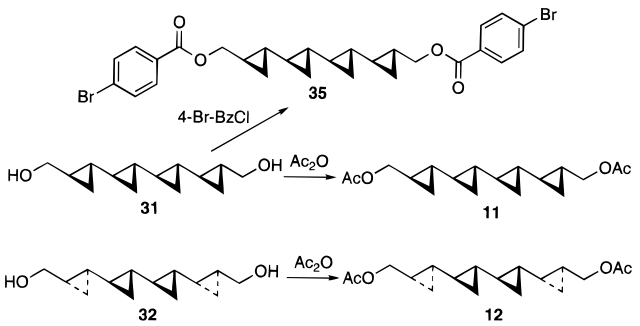
Determination of the Absolute Stereochemistry of the Quatercyclopropane Unit. We sought to prepare diacetates **11** and **12** for comparison with the Fujisawa degradation product **3**. Noyori acetalization[23] of muconaldehyde[24] (**25**) (Scheme 6) followed by cyclopropanation according to the Yamamoto adaptation of the Simmons−Smith reaction[19a,b] provided the bicyclopropane **26** in good yield (56% from **25**). A single-crystal X-ray structure determination of bicyclopropane **26** established the relative stereochemistry of all chiral centers present in the molecule.[12] Since the dioxolane units of the bicyclopropane **26** were derived from (*R*,*R*)-diisopropyl tartrate, the crystal structure also allowed for the unambiguous identification of the absolute stereochemistry of bicyclopropanes **26**−**28** and **30**. Subsequent acid-catalyzed deprotection of the diacetal **26** gave the corresponding dialdehyde which was directly homologated using a double Wittig reaction to provide a separable 3.7:1 mixture of the (*E*,*E*)-diester **27** and the (*E*,*Z*)-diester **28** (61% from diacetal **26**). Unfortunately, attempted isomerization of the unwanted (*E*,*Z*)-diester **28** into more of the desired (*E*,*E*)-diester **27** using photoisomerization in the presence of iodine as catalyst was unsuccessful.

DIBAL-H reduction of diester **27** (Scheme 7) gave the corresponding diol **30** in high yield (91%). Initially we examined the double Fujisawa asymmetric cyclopropanation[19c] of the diene **30** to provide the corresponding quatercyclopropane derivatives. Although such a process proved successful, we have found the recently published

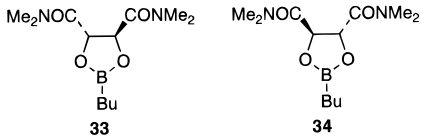
(23) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(24) Davies, S. G.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1346.

Scheme 8



Charette protocol[25] to be far superior. Premixing of diol **30** with dioxaborolane **33** followed by treatment with preformed bis(iodomethyl)zinc[26] gave quatercyclopropane **31** in excellent yield (94%) as predominately one isomer by ^{13}C NMR spectroscopy. Likewise, use of the dioxaborolane **34** gave the quatercyclopropane **32** in quantitative yield. It was apparent from both the ^{1}H and ^{13}C



NMR data that the quatercyclopropanes **31** and **32** were two different C_2-symmetric isomers, and we originally assigned their stereochemistry by analogy with the absolute stereochemistry of monocyclopropanation reactions observed by Charette.[25] However, our structural assignment of these substances was thereby tenuous. Since we planned to use both quatercyclopropanes **31** and **32** to reveal the structure of FR-900848 (**1**), we sought to unambiguously verify that our structural assignments were indeed correct.

Diol **31** was allowed to react with 4-bromobenzoyl chloride (Scheme 8) to provide the corresponding crystalline derivative **35** (87%). A single-crystal X-ray structure determination of diester **35** unambiguously established both the relative and absolute stereochemistry of all chiral centers present in the molecule.[14] Interestingly, the four cyclopropyl units that form the backbone of the molecule are arranged helically. In addition, this assignment allowed us to identify the second C_2-symmetric quatercyclopropane **32** as the *anti*−*syn*−*anti* isomer. Reaction of diols **31** and **32** with acetic anhydride in pyridine respectively provided the diacetates **11** (96%) and **12** (99%).

Comparison of the optical rotation and selected spectroscopic data for the synthetic diacetates **11** and **12** with an authentic sample of the degradation product **3** provided by Dr. H. Tanaka at the Fujisawa Pharmaceutical Company (Scheme 1) was most revealing (Table 2). The ^{13}C NMR chemical shift values established that the natural product had the same relative stereochemistry as the all *syn* quatercyclopropane **11**. Much to our delight, comparison of the magnitudes and signs of the optical rotations showed that diacetates **3** and **11** were indeed identical. Thus the quatercyclopropane unit of

(25) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. Recently a less hazardous procedure has been reported: Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

(26) For a study of the structure of the Simmons−Smith reagent, see: Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723.

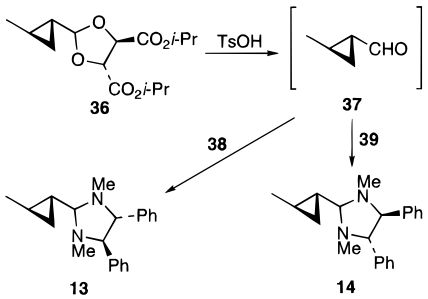
Table 2

	anti−*syn*−*anti* **12**	*all-syn* **11**	FR-900848 degradation unit **3**
^{13}C NMR δ (ppm) ($CDCl_3$)	171.2, 68.4, 21.0, 18.8, 18.2, 18.0, 15.7, 9.0, 8.4	171.2, 68.4, 21.0, 18.7, 18.4, 17.9, 15.8, 8.6, 8.0	171.2, 68.5, 21.0, 18.7, 18.4, 17.9, 15.8, 8.6, 8.0
$[\alpha]_D$ ($CHCl_3$)	−26.0 (*c* 1.01)	−144.7 (*c* 1.07)	−143.8 (*c* 1.04)

Table 3

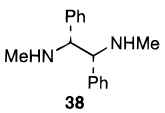
	imidazolidine **14**	imidazolidine **13**	FR-900848 degradation unit **4**
^{1}H NMR δ (ppm) ($CDCl_3$)	7.42−7.24, 3.79, 3.41, 3.21, 2.60, 2.39, 1.30, 0.95−0.87, 0.76−0.74, 0.56−0.53	7.22−7.10, 3.65, 3.27, 3.07, 2.47, 2.25, 1.17, 0.92−0.88, 0.73−0.70, 0.63−0.60	7.22−7.10, 3.65, 3.27, 3.07, 2.47, 2.25, 1.17, 0.92−0.89, 0.78−0.74, 0.61−0.58
^{13}C NMR δ (ppm) ($CDCl_3$)	140.9, 140.1, 128.21, 128.17, 128.1, 127.4, 127.2, 89.5, 78.4, 77.6, 38.6, 36.6, 20.6, 18.4, 11.1, 9.9	140.6, 140.0, 128.2, 128.1, 127.4, 127.3, 90.0, 78.7, 77.2, 39.2, 36.1, 21.3, 18.2, 11.2, 9.4	140.5, 139.9, 128.1, 128.0, 127.3, 127.2, 89.9, 78.6, 77.1, 39.1, 36.0, 21.2, 18.1, 11.1, 9.3
$[\alpha]_D$ ($CHCl_3$)	−17.6 (*c* 1.00)	−20.2 (*c* 1.00)	−20.0 (*c* 0.10)

Scheme 9



the side chain of FR-900848 (**1**) has the same relative and absolute stereochemistry as diacetate **11**.

Determination of the Absolute Stereochemistry of the Terminal Cyclopropane. Finally, we turned our attention to the stereochemistry of the terminal cyclopropane unit of of FR-900848 (**1**). We sought to prepare the two imidazolidine derivatives **13** and **14** for comparison with the imidazolidine **4** obtained from degradation of the natural product **1**. Acetal **36**, which was prepared from the corresponding acetal of crotonaldehyde following the Yamamoto precedent,[19] was purified to diastereoisomeric purity by chromatography. Acid-catalyzed deprotection of acetal **36**[19,27] gave the unstable, volatile aldehyde **37** which was not isolated but directly condensed with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**38**) using the method developed by Alexakis and co-workers[28] to provide the imidazolidine **13** (37% from **36**) (Scheme 9). In a similar fashion, reaction of the crude aldehyde **37** with (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**39**) gave the isomer **14** (33% from **36**). An authentic sample of FR-900848 (**1**) was subject to ozonolysis with a dimethyl sulfide workup. Condensation of the resultant crude mixture of aldehydes with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**38**) and chromatography gave an imidazolidine derivative **4** (92% from **1**) (Scheme 1).



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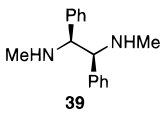

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The spectroscopic data and optical rotations of imidazolidines **13** and **14** were compared to the corresponding data obtained for **4** (Table 3). The ^{1}H and ^{13}C NMR spectra, mp, and the optical rotation value clearly show that derivative **13** is identical with the natural degradation unit **4**, and therefore the absolute stereochemistry of the terminal cyclopropane of the side chain of FR-900848 (**1**) is as shown for the imidazolidine **13**.

Conclusion

It is clear from these results that the structure of FR-900848 (**1**) is depicted by the formula **7**. Comparison of the model alkenes **9** and **10** with the natural product were used to establish the geometry of Δ^{18} as *trans*. The synthetic quatercyclopropanes **11** and **12** were compared with the corresponding FR-900848 degradation product **3** to establish the relative and absolute stereochemistry of the quatercyclopropane core. The synthetic imidazolidines **13** and **14** were compared with the corresponding natural product derivative **4** to establish that the absolute stereochemistry of the terminal cyclopropane. Interestingly and much to our relief, all five cyclopropanes are *trans*-substituted and on the same face of the molecule. The speculations as to the biosynthesis of FR-900848 (**7**) may well be specious, nevertheless they were of some use in prioritization of polycyclopropane targets. Further studies on the total synthesis of FR-900848 (**7**) 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. Column chromatography was carried out on Merck or BDH silica gel 60, 230−400 mesh ASTM using flash chromatography techniques.[29] 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), 1,2-dichloroethane ($ClCH_2CH_2Cl$) (CaH_2, N_2), diethyl ether (Et_2O) (Ph_2CO/Na, N_2), water (H_2O), pentane (CaH_2, N_2), tetrahydrofuran (THF) (Ph_2CO/K, N_2), and toluene (PhMe) (P_2O_5, N_2). The following organic reagents were purified by distillation: acetic anhydride (Ac_2O) (P_2O_5, 12 mmHg), benzaldehyde (PhCHO) (12 mmHg), carbon tetrachloride (CCl_4) (P_2O_5, N_2), diiodomethane (CH_2I_2) (Cu powder, 2 mmHg), dimethyl sulfoxide (DMSO) (CaH_2, 2 mmHg), pyridine (CaH_2, 12 mmHg), triethylamine (Et_3N) (CaH_2, N_2), and trifluoroacetic anhydride (12 mmHg). All other organic solvents and reagents were obtained from commercial sources and used without further purification.

(27) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695.

(28) (a) Manganey, P.; Grojea, F.; Alexakis A.; Normant, J. R. *Tetrahedron Lett.* **1988**, *29*, 2675. (b) Manganey, P.; Grojea, F.; Alexakis A.; Normant, J. R. *Tetrahedron Lett.* **1988**, *29*, 2677.

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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*R*,5*R*)-2,2-Dimethyl-4,5-bis[3-hydroxy-1(*E*)-propen-1-yl]-1,3-dioxolane. DIBAL-H (11 mL, 1.0 M in hexanes, 11 mmol) was added dropwise to a solution of diester **15**[17] (1.13 g, 3.80 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The reaction mixture was allowed to warm slowly to 0 °C over 2 h and quenched by the addition of MeOH (20 mL). The resulting thick slurry was filtered though Celite and the filtrate concentrated. The residue was triturated repeatedly with EtOAc and filtered though Celite, and the filtrate was concentrated. Chromatography on silica (EtOAc) gave the title diol (0.711 g, 87%) as a colorless oil: $[\alpha]^{26}_D = -18.2°$ (*c* 1.00, $CHCl_3$); R_f 0.36 (EtOAc); IR (film) 3391 (broad), 2987, 2934, 2870, 1372, 1235 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.97 (dt, 2H, J = 15.6, 5.0 Hz), 5.70 (ddd, 2H, J = 15.6, 5.0, 1.7 Hz), 4.17−4.12 (m, 6H), 1.73 (broad s, 2H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 126.3, 109.1, 81.4, 62.4, 27.0; MS (CI, NH_3) *m*/*e* 215 $(M + H)^+$, 199, 174, 139; exact mass (CI, NH_3) calcd for $C_{11}H_{19}O_4$ $(M + H)^+$ 215.1283, found 215.1300.

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis[3-chloro-1(*E*)-propen-1-yl]-1,3-dioxolane. CCl_4 (4.8 mL, 50 mmol) was added to a solution of the foregoing diol (2.12 g, 9.92 mmol) and Ph_3P (7.77 g, 29.8 mmol) in THF (60 mL), and the reaction mixture was heated to reflux for 16 h. The reaction mixture was allowed to cool and then concentrated. The residue was triturated repeatedly with pentane and filtered though Celite, and the filtrate was concentrated. Chromatography on silica (10/90 EtOAc/petrol) gave the title dichloride (1.99 g, 80%) as a faint-yellow oil: $[\alpha]^{26}_D = +7.63°$ (*c* 0.93, $CHCl_3$); R_f 0.51 (10/90 EtOAc/petrol); IR (film) 2987, 2872, 1442, 1380, 1231 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.95 (dt, 2H, J = 15.4, 6.6 Hz), 5.81−5.78 (m, 2H), 4.12 (dd, 2H, J = 6.6, 1.2 Hz), 4.06 (dd, 4H, J = 3.3, 1.8 Hz), 1.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.3, 129.9, 109.6, 80.7, 43.8, 26.9; MS (CI, NH_3) *m*/*e* 251 $(M + H)^+$, 235, 228, 210; exact mass (CI, NH_3) calcd for $C_{11}H_{17}{}^{35}Cl_2O_2$ $(M + H)^+$ 251.0606, found 251.0610.

(4*R*,5*R*)-2,2-Dimethyl-4,5-di-1(*E*)-propen-1-yl-1,3-dioxolane (16). A solution of the foregoing dichloride (0.500 g, 1.99 mmol) in Et_2O (15 mL) was added to a suspension of $LiAlH_4$ (1.03 g, 23.9 mmol) in Et_2O (10 mL), and the reaction mixture was heated to reflux for 30 min. The reaction mixture was cooled to 0 °C and quenched by the slow addition of EtOAc (50 mL) followed by concentrated NaOH solution (100 mL). The aqueous layer was extracted with Et_2O (5 × 250 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (2/98 EtOAc/petrol) gave diene **16** (0.290 g, 80%) as a colorless oil: $[\alpha]^{24}_D = -43.6°$ (*c* 1.01, $CHCl_3$); R_f 0.38 (5/95 EtOAc/petrol); IR (film) 2987, 2937, 2876, 1452, 1370, 1235 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.79 (dq, 2H, J = 15.4, 6.6 Hz), 5.54−5.45 (m, 2H), 4.02 (dd, 2H, J = 5.4, 2.0 Hz), 1.72 (dd, 6H, J = 6.6, 1.7 Hz), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.4, 127.1, 108.3, 82.0, 27.1, 17.9; MS (CI, NH_3) *m*/*e* 183 $(M + H)^+$, 176, 167, 142, 125; exact mass (CI, NH_3) calcd for $C_{11}H_{19}O_2$ $(M + H)^+$ 183.1385, found 183.1386.

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,3-dioxolane (17). Et_2Zn (27 mL, 1.0 M in hexanes, 27 mmol) was added to a solution of diene **16** (0.498 g, 2.73 mmol) in $ClCH_2CH_2Cl$ (50 mL) at 0 °C, and the reaction mixture was maintained at 0 °C for 30 min. The reaction mixture was cooled to −20 °C, and CH_2I_2 (4.4 mL, 55 mmol) was added slowly. After 16 h, the mixture was quenched by pouring into saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (5/95 EtOAc/petrol) gave dicyclopropane **17** (0.511 g, 89%) as a colorless oil: $[\alpha]^{26}_D = +63.5°$ (*c* 0.37, $CHCl_3$); R_f 0.28 (5/95 EtOAc/petrol); IR (film) 2986, 2951, 2869, 1454, 1369, 1240 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.07 (dd, 2H, J = 5.9, 2.2 Hz), 1.38 (s, 6H), 1.09 (d, 6H, J = 5.9 Hz), 0.81−0.72 (m, 2H), 0.60−0.50 (m, 4H), 0.42−0.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.4, 85.8, 27.2, 21.0, 18.3, 11.1, 9.8; MS (CI, NH_3) *m*/*e* 211 $(M + H)^+$, 195, 170, 153, 135; exact mass (CI, NH_3) calcd for $C_{11}H_{23}O_2$ $(M + H)^+$ 211.1698, found 211.1675.

(1*R*,2*R*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-dihydroxyethane (18). A solution of acetal **17** (99.6 mg, 0.474 mmol) and $TsOH·H_2O$ (9.0 mg, 0.047 mmol) in THF (5 mL) and H_2O (1 mL) was heated to gentle reflux at 70−75 °C for 14 h. The reaction was quenched by the addition of excess Et_3N (0.5 mL) and concentrated. The residue was azeotroped with EtOH (3 × 10 mL), and chromatography on silica (20/80 to 35/65 to 50/50 EtOAc/petrol) gave diol **18** (51.4 mg, 63%) as a colorless oil: $[\alpha]^{26}_D = +87.0°$ (*c* 1.01, $CHCl_3$); R_f 0.30 (50/50 EtOAc/petrol); IR (film) 3386 (broad), 2999, 2951, 2872, 1455 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.93 (dd, 2H, J = 6.1, 1.7 Hz), 2.18 (broad s, 2H), 1.04 (d, 6H, J = 6.1 Hz), 0.84−0.72 (m, 2H), 0.71−0.58 (m, 2H), 0.55−0.49 (m, 2H), 0.30−0.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.8, 23.3, 18.6, 11.0, 10.5; MS (CI, NH_3) *m*/*e* 188 $(M + NH_4)^+$, 170, 153, 135; exact mass (CI, NH_3) calcd for $C_{10}H_{22}NO_2$ $(M + NH_4)^+$ 188.1651, found 188.1660.

(1*R*,2*R*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-ethanediyl Bis(3,5-Dinitrobenzoate) (19). 3,5-Dinitrobenzoyl chloride (0.172 g, 0.747 mmol) and Et_3N (0.10 mL, 0.75 mmol) were added to a solution of diol **18** (42.4 mg, 0.249 mmol) in PhH (5.0 mL). The reaction mixture was stirred for 3 days, filtered though Celite, and concentrated. Chromatography on silica (10/90 to 20/80 EtOAc/petrol) gave diester **19** (0.117 g, 84%) as a pale yellow solid. Recrystallization from MeOH/EtOAc gave analytically pure pale yellow crystals: mp 207−208 °C; $[\alpha]^{26}_D = +27.8°$ (*c* 0.97, $CHCl_3$); R_f 0.20 (10/90 EtOAc/petrol); IR ($CHCl_3$) 3102, 3021, 2367, 1734, 1549, 1345 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.23 (t, 2H, J = 2.1 Hz), 9.15 (d, 4H, J = 2.1 Hz), 5.00 (d, 2H, J = 8.7 Hz), 1.13 (d, 6H, J = 5.3 Hz), 1.03−0.90 (m, 4H), 0.76−0.70 (m, 2H), 0.45−0.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 148.8, 133.6, 129.4, 122.6, 81.1, 20.6, 18.2, 12.3, 12.0; MS (CI, NH_3) *m*/*e* 576 $(M + NH_4)^+$, 546, 516, 347; exact mass (CI, NH_3) calcd for $C_{24}H_{26}N_5O_{12}$ $(M + NH_4)^+$ 576.1578, found 576.1624. Anal. calcd for $C_{24}H_{22}N_4O_{12}$: C, 51.61, H, 3.97, N, 10.03, found: C, 51.39, H, 3.73, N, 9.73.

(4*R*,5*R*)-2-Phenyl-4,5-bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,3-dioxolane (20). Concentrated H_2SO_4 (1 drop) was added to a solution of diol **18** (0.104 g, 0.611 mmol), PhCHO (0.13 mL, 1.2 mmol), and 4Å molecular sieves (10 mg) in PhMe (10 mL), and the reaction mixture was heated to reflux for 14 h. The mixture was quenched by the addition of excess Et_3N (0.5 mL), concentrated, dissolved in MeOH (10 mL), and treated with $NaBH_4$ (50 mg, 1.3 mmol) to reduce excess PhCHO. After 1 h, the mixture was quenched by the addition of H_2O (10 mL) and concentrated to remove organic solvents. The resulting aqueous solution was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (5/95 EtOAc/petrol) gave acetal **20** (0.101 g, 64%) as a pale yellow oil: $[\alpha]^{24}_D = +73.0°$ (*c* 1.04, $CHCl_3$); R_f 0.25 (5/95 EtOAc/petrol); IR (film) 3000, 2950, 2868, 1457, 1384 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.40−7.33 (m, 3H), 5.92 (s, 1H), 3.30−3.26 (m, 2H), 1.11 (dd, 6H, J = 5.9, 1.5 Hz), 0.87−0.73 (m, 2H), 0.72−0.60 (m, 4H), 0.46−0.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 129.1, 128.3, 126.7, 102.8, 87.5, 85.8, 21.2, 20.8, 18.3, 11.4, 11.2, 10.0, 9.9; MS (CI, NH_3) *m*/*e* 259 $(M + H)^+$, 235, 170, 153, 135; exact mass (CI, NH_3) calcd for $C_{17}H_{23}O_2$ $(M + H)^+$ 259.1698, found 259.1707.

(*E*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]ethene (9). The following procedure is a modification of that reported by Whitham and co-workers.[20] *n*-BuLi (0.43 mL, 2.0 M in pentane, 0.85 mmol) was added slowly to a solution of acetal **20** (0.100 g, 0.387 mmol) in pentane (2.0 mL) at 0 °C. The solution was allowed to warm slowly for 1 h and maintained at room temperature for 14 h. The mixture was quenched by the addition of H_2O (0.5 mL), and the organic layer was dried. The solution was chromatographed on silica (pentane), and the appropriate fractions were transferred to a volumetric flask and diluted with pentane to 25 mL. A ^1H NMR of the pentane solution (0.500 mL) was run with an internal dioxane reference (0.500 μL) to estimate the yield of (*E*)-alkene **9** (31.4 mg, 60%).

The pentane was removed by atmospheric distillation followed by freeze/thaw under vacuum to provide (*E*)-alkene **9** as a light yellow oil: $[\alpha]^{24}_D = +140.8°$ (*c* 0.13, pentane); R_f 0.74 (pentane); IR (film) 3005, 2998, 2952, 2926, 2867, 1466, 1454, 1384, 1075, 1045, 1023, 951, 871, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (dd, 2H, $J = 5.3, 2.6$ Hz), 1.04 (d, 6H, $J = 6.2$ Hz), 1.02−0.98 (m, 2H), 0.72−0.65 (m, 2H), 0.49−0.46 (m, 2H), 0.41−0.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.9, 22.5, 18.5, 14.9, 14.8; MS (EI) *m/e* 136 [($M^{\bullet+}$), 10], 121 (6), 107 (32), 94 (38), 79 (100); exact mass (EI) calcd for $C_{10}H_{16}$ ($M^{\bullet+}$) 136.1252, found 136.1243.

(1*R*,2*S*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-dihydroxyethane (21). Following the procedure reported by Banwell and Onrust,[22] a solution of trifluoroacetic anhydride (0.76 mL, 5.4 mmol) in CH_2Cl_2 (5.0 mL) was added slowly to a solution of DMSO (0.77 mL, 11 mmol) in CH_2Cl_2 at −78 °C. After 10 min, a solution of diol **18** (0.308 g, 1.81 mol) in CH_2Cl_2 (10 mL) was added slowly. After a further 15 min, the reaction was quenched by the addition of Et_3N (2.3 mL, 16 mmol) and allowed to warm to room temperature. The solution was washed with H_2O (10 mL), 10% HCl acid (10 mL), saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL), and dried. The solution was diluted with MeOH (50 mL) and stirred while $NaBH_4$ (1.03 g, 27.2 mmol) was added slowly to reduce excess PhCHO. After 1 h, the mixture was quenched by the addition of H_2O (20 mL) and concentrated to remove the organic solvents. The aqueous layer was salted (NaCl) and extracted with EtOAc (3 × 150 mL). The combined organic layers were dried and concentrated. Chromatography on silica (20/80 to 35/65 to 50/50 EtOAc/petrol) gave *anti*-diol **21** (0.103 g, 34%) as a gummy white solid and an inseparable 1:1 mixture of *syn*-diols **18** and **22** (0.118 g, 38%) as a gummy white solid. *anti*-Diol **21** showed: $[\alpha]^{29}_D = +54.7°$ (*c* 1.00, $CHCl_3$); R_f 0.22 (50/50 EtOAc/petrol); IR (film) 3343 (broad), 3001, 2953, 2945, 2866, 1455, 1383, 1310 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.98−2.91 (m, 2H), 2.09 (broad s, 1H), 1.97 (broad s, 1H), 1.09 (d, 3H, $J = 5.7$ Hz), 1.03 (d, 3H, $J = 5.9$ Hz), 0.89−0.63 (m, 4H), 0.49−0.36 (m, 2H), 0.34−0.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.1, 78.8, 21.2, 21.0, 18.7, 18.2, 11.3, 11.2, 11.0, 10.8; MS (CI, NH_3) *m/e* 188 $(M + NH_4)^+$, 170, 153, 135; exact mass (CI, NH_3) calcd for $C_{10}H_{22}NO_2$ $(M + NH_4)^+$ 188.1651, found 188.1655. Anal. calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.86; H, 10.46. Mixture of diols **18**/**22**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 78.8, 23.2, 23.0, 18.7, 18.6, 11.6, 11.0, 10.6, 10.5.

(1*R*,2*S*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-ethanediyl Bis(3,5-Dinitrobenzoate) (23). Following the procedure described for the preparation of diester **19**, diol **21** (20.8 mg, 0.122 mmol) was treated with 3,5-dinitrobenzoyl chloride (84.3 mg, 0.366 mmol) and Et_3N (49 μL, 0.37 mmol) to give, after chromatography on silica (10/90 to 20/80 EtOAc/petrol), diester **23** (64.4 mg, 95%) as a pale-yellow solid. Recrystallization from EtOAc/petrol gave analytically pure pale yellow crystals: mp 190−191 °C; $[\alpha]^{29}_D = +8.1°$ (*c* 0.77, $CHCl_3$); R_f 0.22 (10/90 EtOAc/petrol); IR ($CHCl_3$) 3114, 3032, 2962, 1731, 1549, 1345 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.25 (app qn, 2H, $J = 2.2$ Hz), 9.12 (d, 2H, $J = 2.2$ Hz), 9.10 (d, 2H, $J = 2.2$ Hz), 4.88−4.83 (m, 2H), 1.18 (d, 3H, $J = 5.9$ Hz), 1.11 (d, 3H, $J = 5.7$ Hz), 1.08−0.94 (m, 4H), 0.80−0.68 (m, 1H), 0.67−0.60 (m, 2H), 0.53−0.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 148.7, 133.7, 129.5, 122.7, 122.6, 82.0, 81.6, 19.4, 18.9, 18.3, 18.1, 12.5, 12.4, 12.1, 12.0; MS (CI, NH_3) *m/e* 576 $(M + NH_4)^+$, 516, 347, 317, 195; exact mass (CI, NH_3) calcd for $C_{24}H_{26}N_5O_{12}$ $(M + NH_4)^+$ 576.1578, found 576.1624. Anal. calcd for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.37; H, 3.93; N, 9.86.

(4*R*,5*S*)-2-Phenyl-4,5-bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,3-dioxolane (24). PhCHO (0.31 mL, 3.0 mmol) was added to a stirrred solution of diol **21** (20.5 mg, 0.120 mmol), camphorsulfonic acid (28.1 mg, 0.120 mmol), and 4 Å molecular sieves in PhH (1.0 mL). The mixture was quenched after 4 h by the addition of excess Et_3N (0.5 mL), diluted with Et_2O (20 mL), and washed with basic 5% sodium metabisulfite solution (3 × 25 mL). The organic layer was dried and concentrated. The residue was dissolved in MeOH (20 mL) and treated with excess $NaBH_4$ (0.38 g, 10 mmol). After 1 h, the mixture was quenched by the addition of H_2O (10 mL) and concentrated to remove the organic solvents. The resulting aqueous solution was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (5/95 EtOAc/petrol) gave an inseparable 2:1 mixture of the two isomers of acetal **24** (29.9 mg, 96%) as a pale yellow oil. Major isomer: $[\alpha]^{26}_D = +35.8°$ (*c* 0.57, $CHCl_3$); R_f 0.24 (5/95 EtOAc/petrol); IR (film) 3009, 2952, 2867, 1454, 1396, 1380 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.56−7.52 (m, 2H), 7.41−7.36 (m, 3H), 5.70 (s, 1H), 3.53−3.38 (m, 2H), 1.12 (d, 3H, $J =$ 6.7 Hz), 1.10 (d, 3H, $J = 7.2$ Hz), 0.93−0.85 (m, 3H), 0.66−0.62 (m, 2H), 0.48−0.43 (m, 2H), 0.39−0.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 129.3, 128.3, 127.0, 102.8, 84.2, 83.9, 20.1, 19.6, 18.4, 18.2, 11.9, 11.6, 10.19, 10.17; MS (CI, NH_3) *m/e* 259 $(M + H)^+$, 170, 153, 135, 109; exact mass (CI, NH_3) calcd for $C_{17}H_{23}O_2$ $(M + H)^+$ 259.1698, found 259.1714. Anal. calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found C, 78.75; H, 8.68.

(*Z*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]ethene (10). The following procedure is a modification of that reported by Whitham and co-workers.[20] *n*-BuLi (0.45 mL, 2.0 M in pentane, 0.89 mmol) was added slowly to a solution of acetal **24** (0.105 g, 0.404 mmol) in pentane (2.0 mL) at 0 °C. The reaction mixture was allowed to warm slowly and was maintained at room temperature for 14 h. The reaction mixture was cooled to 0 °C and treated with additional *n*-BuLi (0.22 mL, 2.0 M in pentane, 0.45 mmol) and maintained at room temperature for 9 h. The reaction mixture was cooled to 0 °C and treated with another portion of *n*-BuLi (0.22 mL, 2.0 M in pentane, 0.45 mmol) and maintained at room temperature for 16 h. The reaction was quenched by addition of H_2O (0.5 mL) and the organic layer dried. The solution was chromatographed on silica (pentane) and the appropriate fractions were combined; recovered acetal **24** (51.0 mg, 49%) was also obtained from chromatography on silica (5/95 EtOAc/pentane). The pentane solution containing product was concentrated by atmospheric distillation until ∼10 mL remained. The solution was transferred to a volumetric flask and diluted with pentane to 10 mL. A ^1H NMR of the pentane solution (0.300 mL) was run with an internal dioxane reference (0.500 μL) to estimate the yield of (*Z*)-alkene **10** (12.0 mg, 22%). The pentane was removed by atmospheric distillation followed by freeze/thaw under vacuum to provide (*Z*)-alkene **10** as a light yellow oil: $[\alpha]^{27}_D = +174.2°$ (*c* 0.12, pentane); R_f 0.73 (pentane); IR (film) 2958, 2924, 2904, 1262, 1098, 1029, 916, 807, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (dd, 2H, $J = 6.6, 2.2$ Hz), 1.38−1.33 (m, 2H), 1.08 (d, 6H, $J = 6.0$ Hz), 0.73−0.68 (m, 2H), 0.52−0.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 19.0, 18.6, 15.6, 15.2; MS (EI) *m/e* 136 [($M^{\bullet+}$), 7], 119 (5), 107 (14), 91 (13), 79 (30); exact mass (EI) calcd for $C_{10}H_{16}$ ($M^{\bullet+}$) 136.1252, found 136.1255.

1,3-(*E*,*E*)-1,4-Bis[[(4*R*,5*R*)-4,5-bis[(isopropyloxy)carbonyl]-1,3-dioxolan-2-yl]]butadiene. The following procedure is a modification of that reported by Noyori and co-workers.[23] *N*,*O*-Bis(trimethylsilyl)acetamide (3 drops) and trimethylsilyl trifluoromethanesulfonate (44 μL, 0.22 mmol) were added to a stirred suspension of muconaldehyde (**25**)[24] (0.500 g, 0.454 mmol) and *O*,*O*-bis(trimethylsilyl)diisopropyl-L-tartrate (**29**)[23] (0.515 g, 1.36 mmol) in CH_2Cl_2 (0.50 mL) at −78 °C. The reaction mixture was maintained at −78 °C for 15 min, and at 0 °C for 15 min, during which time the solution turned burgundy. The reaction mixture was maintained at room temperature for 6 h and quenched by addition of pyridine (3 drops). The mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried and concentrated. Chromatography on silica (20/80 EtOAc/petrol) gave diacetal (0.180 g, 73%) as a white solid. Recrystallization from EtOAc/petrol gave analytically pure colorless crystals: mp 88−90 °C; $[\alpha]^{24}_D = -4.1°$ (*c* 1.0, $CHCl_3$); R_f 0.10 (20/80 EtOAc/petrol); IR (film) 2982, 1744, 1464, 1376, 1235, 1202, 1066, 946, 821 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.49 (dd, 2H, $J = 11.6, 3.0$ Hz), 5.90−5.82 (m, 2H), 5.68 (d, 2H, $J = 6.4$ Hz), 5.17−5.06 (m, 4H), 4.74 (d, 2H, $J = 4.0$ Hz), 4.65 (d, 2H, $J = 4.0$ Hz), 1.32−1.28 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.5, 134.1, 130.4, 106.1, 77.5, 69.8, 21.6; MS (CI, NH_3) *m/e* 560 (M +

$NH_4)^+$, 543 $(M + H)^+$. Anal. calcd for $C_{26}H_{38}O_{12}$: C, 57.55; H, 7.06. Found: C, 57.47; H, 7.04.

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis[[(4*R*,5*R*)-4,5-bis[(isopropyloxy)-carbonyl]-1,3-dioxolan-2-yl]]bicyclopropane (26). The following procedure is a modification of that reported by Yamamoto and co-workers.[19a,b] Et_2Zn (173 mL, 1.0 M in hexanes, 173 mmol) was added slowly to a stirred solution of the foregoing diacetal (9.40 g, 17.3 mmol) in $ClCH_2CH_2Cl$ (280 mL) at 0 °C. After 30 min, the reaction mixture was cooled to −20 °C and CH_2I_2 (27.7 mL, 346 mmol) was added slowly. After 20 h, the reaction mixture was quenched by pouring into saturated NH_4Cl solution (2 L). The aqueous layer was extracted with CH_2Cl_2 (5 × 1 L) and the combined organic layers were dried and concentrated. Chromatography on silica (10/90 to 15/85 to 20/80 EtOAc/petrol) gave bicyclopropane **26** (8.17 g, 83%) as an off-white solid. Recrystallization from EtOAc/petrol gave analytically pure colorless crystals: mp 66−67 °C; $[\alpha]^{24}_D = -56°$ (*c* 1.0, $CHCl_3$); R_f 0.20 (25/75 EtOAc/petrol); IR (film) 2989, 2940, 1733, 1374, 1202, 1066, 903 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13−5.06 (m, 4H), 4.85 (d, 2H, J = 6.2 Hz), 4.65 (d, 2H, J = 4.0 Hz), 4.55 (d, 2H, J = 4.0 Hz), 1.33−1.24 (m, 26H), 1.01−0.96 (m, 2H), 0.60−0.57 (m, 2H), 0.42−0.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 168.8, 109.7, 77.4, 69.8, 21.8, 19.0, 15.6, 6.2; MS (CI, NH_3) *m*/*e* 586 $(M + NH_4)^+$, 569 $(M + H)^+$. Anal. calcd for $C_{28}H_{42}O_{12}$: C, 58.94; H, 7.42. Found: C, 58.74; H, 7.14.

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis[3-ethoxy-3-oxo-1(*E*)-propen-1-yl]-bicyclopropane (27) and (1*R*,3*S*,4*S*,6*R*)-1-[3-Ethoxy-3-oxo-1(*E*)-propen-1-yl]-6-[3-ethoxy-3-oxo-1(*Z*)-propen-1-yl]bicyclopropane (28). $TsOH·H_2O$ (5.57 g, 2.93 mmol) was added to a stirred solution of diacetal **26** (7.96 g, 13.9 mmol) in THF (67 mL) and H_2O (13 mL), and the resulting mixture was heated to 55 °C in a preheated oil bath for 18 h. The reaction mixture was poured into saturated $NaHCO_3$ solution (600 mL), salted (NaCl), and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried and concentrated to afford a crude oil. (Carbethoxymethylene)triphenylphosphorane (15.4 g, 44.0 mmol) was added to a stirred solution of the residual crude oil in CH_2Cl_2 (45 mL), and after 16 h, the reaction mixture was concentrated. Chromatography on silica (5/95 to 7.5/92.5 to 10/90 EtOAc/petrol) gave *E*,*E*-diester **27** (1.84 g, 48%) as a yellow oil and *E*,*Z*-diester **28** (0.534 g, 13%) as a yellow oil. *E*,*E*-Diester **27**: $[\alpha]^{30}_D = -246.1°$ (*c* 1.01, $CHCl_3$); R_f 0.21 (10/90 EtOAc/petrol); IR (film) 2981, 2367, 1712, 1643, 1454, 1366, 1301 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.43 (dd, 2H, J = 15.6, 9.9 Hz), 5.83 (d, 2H, J = 15.6 Hz), 4.16 (q, 4H, J = 7.2 Hz), 1.44−1.39 (m, 2H), 1.27 (t, 6H, J = 7.2 Hz), 1.20−1.12 (m, 2H), 0.79−0.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 152.2, 118.4, 60.1, 23.8, 21.3, 14.3, 13.3; MS (CI, NH_3) *m*/*e* 279 $(M + H)^+$, 267, 250, 233, 205; exact mass (CI, NH_3) calcd for $C_{16}H_{23}O_4$ $(M + H)^+$ 279.1596, found 279.1599. Anal. calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.32; H, 7.57. *E*,*Z*-Diester **28**: $[\alpha]^{27}_D = -71.4°$ (*c* 1.01, $CHCl_3$); R_f 0.29 (10/90 EtOAc/petrol); IR (film) 2981, 2938, 1712, 1642, 1446, 1366, 1332, 1301 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.44 (dd, 1H, J = 15.4, 9.9 Hz), 5.82 (d, 1H, J = 15.4 Hz), 5.66 (d, 1H, J = 11.1 Hz), 5.45 (app t, 1H, J = 11.1 Hz), 4.17 (app qn, 4H, J = 6.9 Hz), 2.77−2.70 (m, 1H), 1.45−1.32 (m, 1H), 1.28 (app q, 6H, J = 6.9 Hz), 1.22−1.10 (m, 1H), 0.84−0.72 (m, 4H), 0.68−0.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 166.7, 153.5, 152.5, 118.2, 117.2, 60.0, 59.8, 23.8, 23.5, 21.1, 18.8, 14.3, 13.6, 13.4; MS (CI, NH_3) *m*/*e* 279 $(M + H)^+$, 250, 233, 226, 209, 112; exact mass (CI, NH_3) calcd for $C_{16}H_{23}O_4$ $(M + H)^+$ 279.1596, found 279.1608. Anal. calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.36; H, 7.69.

(1*R*,3*S*,4*S*,6*R*)-1,6-Bis[3-hydroxy-1(*E*)-propen-1-yl]bicyclopropane (30). DIBAL-H (21 mL, 1.5 M in PhMe, 32 mmol) was added to a solution of diester **27** (1.76 g, 6.32 mmol) in CH_2Cl_2 (70 mL) at −78 °C and the solution was maintained at −78 °C for 4 h. The reaction was quenched by slow addition of MeOH (50 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 was concentrated. Chromatography on silica (20/80 to 35/65 to 50/50 EtOAc/petrol) gave diol **30** (1.12 g, 91%) as a gummy white solid: $[\alpha]^{30}_D = -202.7°$ (*c* 1.03, $CHCl_3$); R_f 0.20 (50/50 EtOAc/petrol); IR (film) 3331 (broad), 2999, 2865, 2359, 2342, 1665, 1448 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.66 (dt, 2H, J = 15.3, 6.2 Hz), 5.24 (dd, 2H, J = 15.3, 8.7 Hz), 4.06 (app t, 4H, J = 5.3 Hz), 1.29−1.17 (m, 4H), 0.94−0.87 (m, 2H), 0.55−0.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 126.4, 63.1, 21.8, 20.0, 11.3; MS (CI, NH_3) *m*/*e* 212 $(M + NH_4)^+$, 194, 177, 159, 133; exact mass (CI, NH_3) calcd for $C_{12}H_{22}NO_2$ $(M + NH_4)^+$ 212.1651, found 212.1643. Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.15.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-1,12-Bis(hydroxymethyl)-quatercyclopropane (31). The following procedure is a modification of that reported by Charette and Juteau.[25] CH_2I_2 (89 μL, 1.1 mmol) was added slowly to a stirred solution of Et_2Zn (58 μL, 0.56 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 10 min, a white slurry had formed, and a solution of diol **30** (24.8 mg, 0.128 mmol) and dioxaborolane **33** (75.7 mg, 0.281 mmol) in CH_2Cl_2 (1.5 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 (10 mL). The aqueous layer was salted (NaCl) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried and concentrated. Chromatography on silica (50/50 EtOAc/petrol) gave quatercyclopropane **31** (26.8 mg, 94%) as a gummy off-white solid: $[\alpha]^{26}_D = -182.0°$ (*c* 1.02, $CHCl_3$); R_f 0.19 (50/50 EtOAc/petrol); IR ($CHCl_3$) 3619, 3458 (broad), 3070, 3001, 2928, 2881, 1470, 1414, 1385, 1239, 1219, 1034, 1007 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.39 (dd, 4H, J = 6.9, 2.7 Hz), 1.42 (broad s, 2H), 0.87−0.76 (m, 2H), 0.74−0.66 (m, 2H), 0.59−0.51 (m, 4H), 0.30−0.21 (m, 4H), 0.14−0.06 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9, 19.8, 18.5, 18.4, 18.1, 8.2 (2C); MS (CI, NH_3) *m*/*e* 240 $(M + NH_4)^+$, 222, 187, 161, 145; exact mass (CI, NH_3) calcd for $C_{14}H_{26}NO_2$ $(M + NH_4)^+$ 240.1964, found 240.1960. Anal. calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.34; H, 9.89.

(1*S*,3*R*,4*R*,6*S*,7*S*,9*R*,10*R*,12*S*)-1,12-Bis(hydroxymethyl)-quatercyclopropane (32). Following the procedure described for the preparation of quatercyclopropane **31**, diol **30** (26.2 mg, 0.135 mmol) was treated with a mixture of Et_2Zn (61 μL, 0.594 mmol) and CH_2I_2 (94 μL, 1.2 mmol) in the presence of dioxaborolane **34** (79.9 mg, 0.297 mmol) to give, after chromatography on silica (50/50 EtOAc/petrol), quatercyclopropane **32** (30.4 mg, 100%) as a gummy off-white solid: $[\alpha]^{26}_D = -50.0°$ (*c* 1.03, $CHCl_3$); R_f 0.21 (50/50 EtOAc/petrol); IR ($CHCl_3$) 3615, 3464 (broad), 3079, 3002, 2927, 2881, 1466, 1413, 1384, 1238, 1034, 1006 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.40 (dd, 4H, J = 6.9, 1.5 Hz), 1.29−1.21 (m, 2H), 0.88−0.78 (m, 2H), 0.72−0.64 (m, 2H), 0.58−0.50 (m, 4H), 0.31−0.26 (m, 4H), 0.15−0.08 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9, 19.6, 18.5, 18.3, 18.2, 8.6, 8.5; MS (CI, NH_3) *m*/*e* 240 $(M + NH_4)^+$, 222, 187, 161, 145; exact mass (CI, NH_3) calcd for $C_{14}H_{26}NO_2$ $(M + NH_4)^+$ 240.1964, found 240.1954. Anal. calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.36; H, 9.88.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-Quatercyclopropanediyl-1,12-dimethyl Di-4-bromobenzoate (35). 4-Bromobenzoyl chloride (0.127 g, 0.580 mmol) and Et_3N (72 μL, 0.58 mmol) were added to a stirred solution of diol **31** (25.8 mg, 0.116 mmol) in PhH (5.0 mL). After 20 h, the reaction mixture was diluted with EtOAc (5 mL) and washed with H_2O (2 × 10 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried and concentrated. Chromatography on silica (5/95 EtOAc/petrol) gave diester **35** (59.3 mg, 87%) as a white solid. Recrystallization from EtOAc gave analytically pure clear, colorless crystals: mp 95.0−96.0 °C; $[\alpha]^{25}_D = -74.0°$ (*c* 1.25, $CHCl_3$); R_f 0.23 (5/95 EtOAc/petrol); IR ($CHCl_3$) 3079, 3009, 2962, 2881, 1713, 1591, 1489, 1466, 1402, 1373, 1283, 1272 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.90 (dt, 4H, J = 8.9, 2.1 Hz), 7.58 (dt, 4H, J = 8.9, 2.1 Hz), 4.11 (dd, 4H, J = 7.2, 0.7 Hz), 1.00−0.94 (m, 2H), 0.93−0.80 (m, 2H), 0.60−0.50 (m, 4H), 0.46−0.40 (m, 2H), 0.40−0.31 (m, 2H), 0.14−0.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 131.8, 131.2, 129.5, 128.0, 69.3, 19.0, 18.6, 18.1, 16.0, 8.9, 8.3; MS (CI, NH_3) *m*/*e* 606 $(M + NH_4)^+$, 588, 526, 509, 446, 429, 387; exact mass (CI, NH_3) calcd for $C_{28}H_{32}Br_2NO_4$ $(M + NH_4)^+$ 606.0678, found 606.0687. Anal. calcd for $C_{28}H_{28}Br_2O_4$: C, 57.16; H, 4.80. Found: C, 56.95; H, 4.93.

(1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-Quatercyclopropanediyl-1,12-dimethyl Diacetate (11). Ac_2O (0.11 mL, 1.1 mmol) was added to a stirred solution of diol **31** (50.8 mg, 0.229 mmol) in pyridine (3.0 mL). After 20 h, the reaction mixture was diluted with Et_2O (20 mL) and washed with 10% HCl acid (3 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL), and H_2O (30 mL). The organic layer was dried and concentrated. Chromatography on silica (10/90 EtOAc/petrol) gave diacetate **11** (67.5 mg, 96%) as a gummy white solid: $[\alpha]^{26}_D = -144.7°$ (*c* 1.07, $CHCl_3$); R_f 0.20 (10/90 EtOAc/petrol); IR ($CHCl_3$) 3032, 3009, 1725, 1446, 1378, 1250, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (ABXdd, 2H, *J* = 11.4, 7.2 Hz), 3.80 (ABXdd, 2H, *J* = 11.4, 7.3 Hz), 2.03 (s, 6H), 0.84−0.78 (m, 2H), 0.77−0.71 (m, 2H), 0.56−0.48 (m, 4H), 0.33−0.24 (m, 4H), 0.10−0.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 68.4, 21.0, 18.7, 18.4, 17.9, 15.8, 8.6, 8.0; MS (CI, NH_3) *m*/*e* 324 $(M + NH_4)^+$, 263, 247, 187, 145; exact mass (CI, NH_3) calcd for $C_{18}H_{30}NO_4$ $(M + NH_4)^+$ 324.2175, found 324.2185. Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.67; H, 8.28.

(1*S*,3*R*,4*R*,6*S*,7*S*,9*R*,10*R*,12*S*)-Quatercyclopropanediyl-1,12-dimethyl Diacetate (12). Following the procedure described for the preparation of diacetate **11**, diol **32** (49.8 mg, 0.224 mmol) was treated with Ac_2O (0.11 mL, 1.1 mmol) in pyridine (3.0 mL) to give, after chromatography on silica (10/90 EtOAc/petrol), diacetate **12** (67.7 mg, 99%) as a colorless oil: $[\alpha]^{25}_D = -26.0°$ (*c* 1.01, $CHCl_3$); R_f 0.20 (10/90 EtOAc/petrol); IR ($CHCl_3$) 3031, 3000, 1725, 1460, 1375, 1242, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (ABXdd, 2H, *J* = 11.4, 7.2 Hz), 3.79 (ABXdd, 2H, *J* = 11.4, 7.4 Hz), 2.03 (s, 6H), 0.82−0.78 (m, 2H), 0.73−0.68 (m, 2H), 0.54−0.48 (m, 4H), 0.34−0.28 (m, 4H), 0.08−0.05 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 68.4, 21.0, 18.8, 18.2, 18.0, 15.7, 9.0, 8.4; MS (CI, NH_3) *m*/*e* 324 $(M + NH_4)^+$, 307, 247, 187, 145; exact mass (CI, NH_3) calcd for $C_{18}H_{30}NO_4$ $(M + NH_4)^+$ 324.2175, found 324.2178.

(4*R*,5*R*)-1,3-Dimethyl-2-[(1*R*,2*R*)-2-methylcyclopropyl]-4,5-diphenylimidazolidine (13). A solution of acetal **36**[19] (0.10 g, 0.33 mmol) and $TsOH·H_2O$ (0.62 g, 3.2 mmol) in THF (12.5 mL) and H_2O (2.5 mL) was heated to reflux for 4 h. The mixture was diluted with saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL), and brine (2 × 10 mL), dried, and filtered. The residue was flash vaccuum distilled, and the resulting aldehyde **37** was treated with (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**38**)[28] (0.12 g, 0.50 mmol) and 4 Å molecular sieves at room temperature. After 12 h the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried, and concentrated. Chromatography on silica (10/90 EtOAc/petrol) gave imidazolidine **13** (39 mg, 37%) as a white solid. Recrystallization from Me_2CO/H_2O gave colorless crystals: mp 108−111 °C; $[\alpha]^{24}_D = -20.2°$ (*c* 1.0, $CHCl_3$); R_f 0.25 (5/95 EtOAc/petrol); IR (film) 2900, 2720, 1420, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.10 (m, 10H), 3.65 (d, 1H, *J* = 8.5), 3.27 (d, 1H, *J* = 8.5), 3.07 (d, 1H, *J* = 8.3), 2.47 (s, 3H), 2.25 (s, 3H), 1.17 (d, 3H, *J* = 5.9), 0.92−0.88 (m, 2H), 0.73−0.70 (m, 1H), 0.63−0.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 140.0, 128.2 (2C), 128.1, 127.4, 127.3, 90.0, 78.7, 77.2, 39.2, 36.1, 21.3, 18.2, 11.2, 9.4; MS (CI, NH_3) *m*/*e* 307 $(M + H)^+$, 251, 187, 118; exact mass calcd for $C_{21}H_{27}N_2$ $(M + H)^+$ 307.2174, found 307.2175.

(4*S*,5*S*)-1,3-Dimethyl-2-[(1*R*,2*R*)-2-methylcyclopropyl]-4,5-diphenylimidazolidine (14). Following the procedure described for the preparation of imidazolidine **13**, acetal **36**[19] (0.10 g, 0.33 mmol) was treated with $TsOH·H_2O$ (0.62 g, 3.2 mmol) followed by (4*S*,5*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**39**)[28] (0.12 g, 0.50 mmol) to give, after chromatography on silica (10/90 EtOAc/petrol), imidazolidine **14** (34 mg, 0.11 mmol, 33%) as a colorless oil: $[\alpha]^{24}_D = -17.6°$ (*c* 1.0, $CHCl_3$); R_f 0.25 (5/95 EtOAc/petrol); IR (film) 3028, 2995, 2980, 1610, 1494, 1451, 1282, 1164, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.24 (m, 10H), 3.79 (d, 1H, *J* = 8.5), 3.41 (d, 1H, *J* = 8.5), 3.21 (d, 1H, *J* = 8.3), 2.60 (s, 3H), 2.39 (s, 3H), 1.30 (d, 3H, *J* = 5.9), 0.95−0.87 (m, 2H), 0.76−0.74 (m, 1H), 0.56−0.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 140.1, 128.21, 128.17, 128.1, 127.4, 127.2, 89.5, 78.4, 77.6, 38.6, 36.6, 20.6, 18.4, 11.1, 9.9; MS (CI, NH_3) *m*/*e* 307 $(M + H)^+$, 251, 187, 118; exact mass calcd for $C_{21}H_{27}N_2$ $(M + H)^+$ 307.2174, found 307.2178.

Ozonolysis of FR-900848 (1). Ozone was passed through a solution of FR-900848 (**1**) (5.0 mg, 6.3 μmol) in CH_2Cl_2 (1.5 mL) and isopropyl alcohol (1.5 mL) at −78 °C until the solution turned blue (0.5 min), and after 1 min, the mixture was quenched by the addition of Me_2S (0.1 mL). The resulting solution was allowed to warm for 10 min and added to a mixture of Et_2O (5 mL), 4 Å molecular sieves, and (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (**38**)[28] (16 mg, 0.064 mmol) at room temperature. After 12 h, the reaction mixture was concentrated, and chromatography on silica (10/90 EtOAc/petrol) gave imidazolidine **4** (1.8 mg, 92%) as a white solid. Recrystallization from Me_2CO/H_2O gave colorless crystals: mp 108−111 °C; $[\alpha]^{24}_D = -20.0°$ (*c* 0.10, $CHCl_3$); R_f 0.25 (5/95 EtOAc/petrol); IR (film) 2900, 2720, 1420, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.10 (m, 10H), 3.65 (d, 1H, *J* = 8.5), 3.27 (d, 1H, *J* = 8.5), 3.07 (d, 1H, *J* = 8.3), 2.47 (s, 3H), 2.25 (s, 3H), 1.17 (d, 3H, *J* = 5.9), 0.92−0.89 (m, 2H), 0.78−0.74 (m, 1H), 0.61−0.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 139.9, 128.1 (2C), 128.0, 127.3, 127.2, 89.9, 78.6, 77.1, 39.1, 36.0, 21.2, 18.1, 11.1, 9.3; MS (CI, NH_3) *m*/*e* 307 $(M + H)^+$, 251, 187, 118; exact mass calcd for $C_{21}H_{27}N_2$ $(M + H)^+$ 307.2174, found 307.2184.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of (4*R*,5*R*)-2,2-dimethyl-4,5-bis[3-hydroxy-1(*E*)-propen-1-yl]-1,3-dioxolane, (4*R*,5*R*)-2,2-dimethyl-4,5-bis[3-chloro-1(*E*)-propen-1-yl]-1,3-dioxolane, **16**, **17**, **18**, **20**, **9**, **10**, **12**, **13**, **14**, and **4** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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