# Synthesis and Properties of Oligocyclopropyl-Containing Natural Products and Model Compounds

Jörg Pietruszka*

*Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany*

*Received August 12, 2002*

## *Contents*



Jörg Pietruszka was born 1965 in Hamburg, Germany. He studied chemistry at the universities of Hamburg and Newcastle upon Tyne (England), and obtained his doctorate (Dr. rer. nat.) at the University of Hamburg under the guidance of Prof. Dr. W. A. König in 1993. As part of the degree studies, he also worked for a period of three month under the supervision of Prof. Dr. R. F. W. Jackson (Newcastle upon Tyne). Following two years postdoctoral training under Prof. S. V. Ley at Cambridge University (England), he fulfilled the requirements for his habilitation at the University of Stuttgart in 2001. He was a Liebig Fellow (1995–1997) and held a "Habilitandenstipendium" of the DFG (1998–2000). In 2000/2001, he was a visiting lecturer at the University of Freiburg (Germany), and in 2001/2002, he was a guest professor at the University of Cardiff (Wales). He currently holds a substitute-professorship at the University of Tübingen (Germany). His research interests include the development of new synthetic methods and their application in the synthesis of physiologically active (natural) products. One leading element is the use of enantiomerically pure cyclopropylboronic esters.

## *I. Introduction*

The fascination in total synthesis is as alive as ever: Inspired by nature, endeavors to mimic its efficiency and elegance leads to new advances in chemistry, biology, and medicine. A prominent example in cyclopropane chemistry is the progress achieved after the isolation of the structurally fascinating oligocyclopropanes FR-900848 (**1**)[1] and U-106305 (**2**) (Figure 1).[2] New methods were established on the way toward the elucidation of the relative and absolute configuration of the cyclopropane units (see section II.A.1.), but even after several completed total syntheses, new approaches emerge in the literature. Both will be described in the second part and will be the focus of the review. In the last section the (biological) properties of oligocyclopropanes will be reviewed.

Prior to the isolation of natural oligocyclopropanes, structural and especially conformational issues were primarily investigated (e.g. see refs 3−8). Synthetic approaches to bi- or tercyclopropanes were well-known, but difficulties in separating the sometimes complex diastereomeric mixtures of substituted, racemic products limited their broad applicability. In this introduction these methods are briefly addressed.

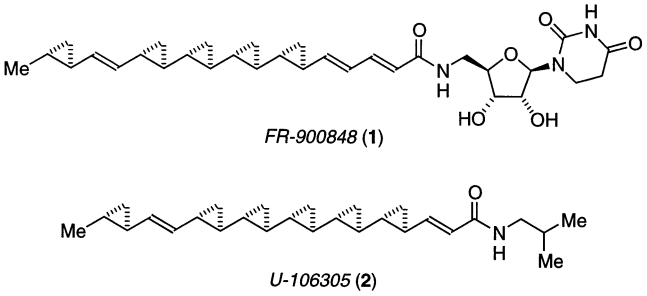



**Figure 1.**

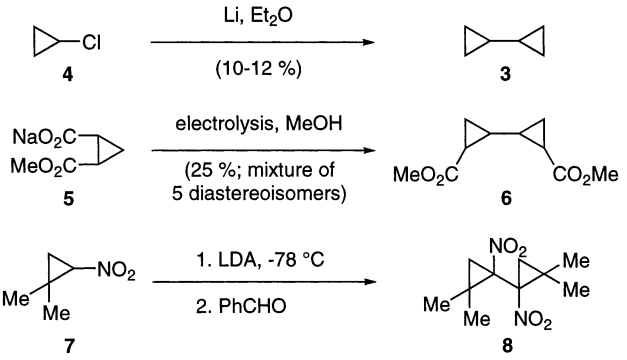
While spontaneous oligomerization of cyclopropenes did not lead to defined, homogeneous prod-

* E-mail: joerg.pietruszka@po.uni-stuttgart.de.

10.1021/cr010027g CCC: $44.00 
Published on Web 02/13/2003

ucts,[9,10] "dimerizations" of suitable precursors were successfully applied (Scheme 1): The parent bicyclo-

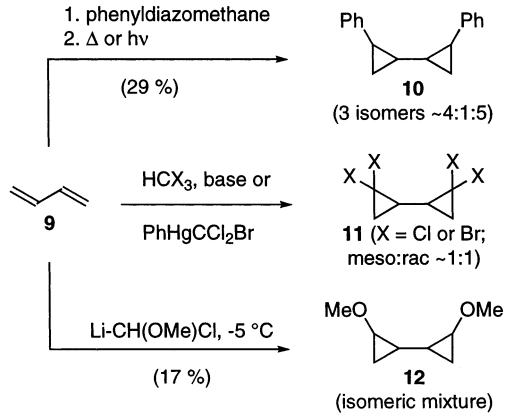
**Scheme 1**




propane (**3**) was first synthesized in 1952 from cyclopropyl chloride (**4**) and lithium by a Wurtz coupling in low yield.[11] Slightly better yields were observed for the electrolysis of carboxylate **5** leading to 2,2′-dicarboxylic esters **6**; however, only a complex mixture containing five diastereoisomers was obtained.[12] It is interesting to note that 1-nitrocyclopropyl anions[13] generated from compound **7** led to, depending on the order of reagent addition, either nitroaldol adducts or the dimers **8**.[14] A general method to bicyclopropanes was not based on the finding.

Several groups started with dienes and especially with 1,3-butadiene (**9**) to synthesize substituted bicyclopropanes (Scheme 2). An inherent problem

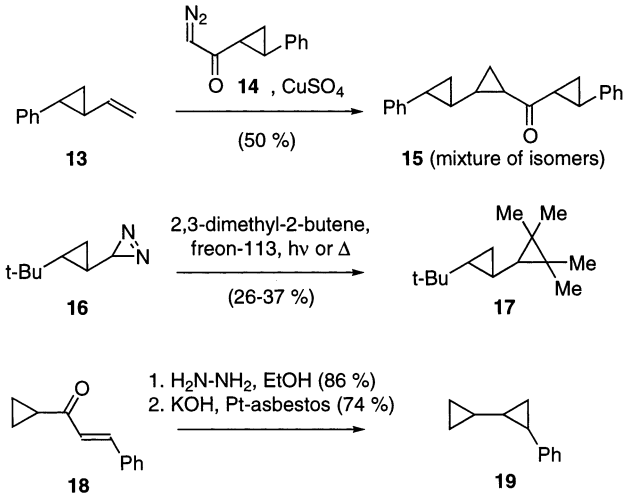
**Scheme 2**




was the control of simple diastereoselectivity, and consequently, only mixtures of isomers were obtained. Different carbene (or carbenoid) sources were utilized: Diazo compounds led after [3 + 2]-cycloaddition followed by thermal of photochemical decomposition of the intermediate to the desired products, e.g. phenyl derivative **10** as a 4:1:5 mixture of isomers.[15] Diazoacetic esters[16,17] and diazomethane (for substituted butadienes)[18,19] were also regularly employed. When 1,3,5-hexatriene was used, a domino reaction involving Cope rearrangements would also give a bicyclopropane, not a tercyclopropane, as one minor component.[20,21] Dihalocarbenes, liberated either from haloform[22−24] or the Seyferth reagent,[25] gave 2,2,2′,2′-tetrahalo-substituted bicyclopropanes **11**. The method was applied several times starting from substituted dienes such as isoprene or 1,3-pentadiene.[24,26] The reduction of the intermediates led either selectively to the 2,2′-dihalo products[22] or to the halogen-free cyclopropanes.[27,28] The latter method was also used to synthesize a tercyclopropane.[29] Finally, the 2,2′-dimethoxy derivative **12** could be obtained as a side product by reacting the corresponding carbene with 1,3-butadiene (**9**).[30] Highly substituted bicyclopropanes bearing methoxy groups were also obtained as a side product when utilizing chromium carbene complexes.[31]

As mentioned before, diazo compounds are convenient reagents to synthesize bicyclopropanes. They were often used especially when unsymmetrical products were desired (Scheme 3): Vinylcyclopropane

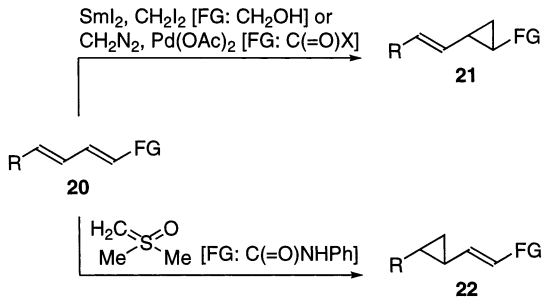
**Scheme 3**




**13** was found to react not only with diazoacetic esters but also with diazo ketones such as the cyclopropane derivative **14**. In a copper-catalyzed reaction, bicyclopropane **15** was obtained as a complex mixture of isomers.[32] But there are also other reagents used for the cyclopropanation that were prone to lose nitrogen: Diazirenes such as the cyclopropane **16**[33,34] and hydrazine[35] were shown to convert suitable olefins to cyclopropanes; e.g. **16** was reacted with 2,3-dimethyl-2-butene to give bicyclopropane **17**, albeit in low yield, and α,β-unsaturated ketone **18** and hydrazine led in two steps to racemic 2-phenylbicyclopropane (**19**).

For practical, selective solutions, not only induced dia- or enantioselective cyclopropanations were essential, but also the question of regioselectivity and simple diastereoselectivity. Whereas methods for retaining the olefin configuration were established, it was more difficult to control the monocyclopropanation of dienes with highly reactive reagents. Nevertheless, in the presence of a functional group, e.g. diene **20**, it was shown that either the vicinal or the remote double-bond reacted, depending on the functional group and on the reagent used (Scheme 4). While standard Simmons−Smith conditions did not allow the isolation of the vinylcyclopropane **21** from a mixture of products, $SmI_2/CH_2I_2$ furnished the product (cyclopropanation of the allylic double bond), albeit in low yield.[36] Electron-deficient dienes yielded preferentially cyclopropane **21** with diazomethane,[37] but sulfur ylides reacted faster with the remote

**Scheme 4**




double bond, and derivative **22** was isolated.[38,39] When an excess of reagent was used, a second, diastereoselective cyclopropanation was achieved.[38−40]

Summarizing, a variety of methods for the synthesis of bi- and tercyclopropanes were available before the isolation of the oligocyclopropanes **1** and **2**. All approaches served their purpose conveniently; however, either the yield or the selectivity of the transformation was not sufficient for an enantioselective natural product synthesis. As reported in a number of reviews,[41−43] this changed dramatically after 1990.

## *II. Synthesis of Natural Oligocyclopropanes*

## A. FR-900848

### *1. Structure Elucidation*

One of the most demanding goals on the way toward the total synthesis of FR-900848 (**1**) was its structure elucidation. After the isolation of the antifungal reagent from the fermentation broth of *Streptoverticillium fervens*, NMR studies allowed for the assignment of the constitution; however, the configuration of the oligocyclopropane was unknown.[1] Before tackling the issue, first the problem of the stereoselective synthesis of bicyclopropanes needed to be solved. The diastereoisomeric phenyl derivatives **23**−**30** (and their enantiomers) were the model compounds of choice (Figure 2). Only after a reliable

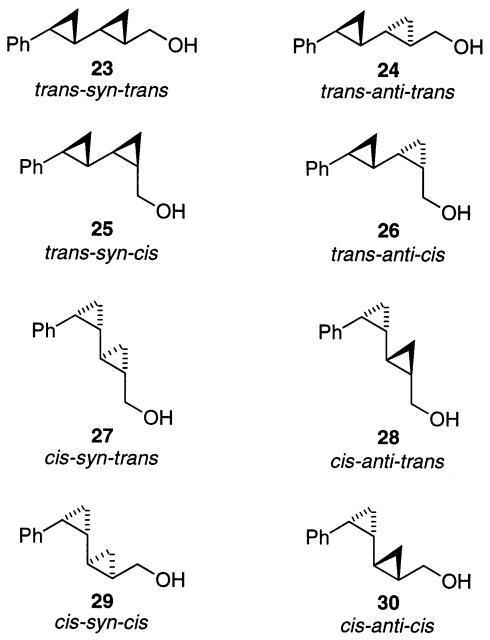
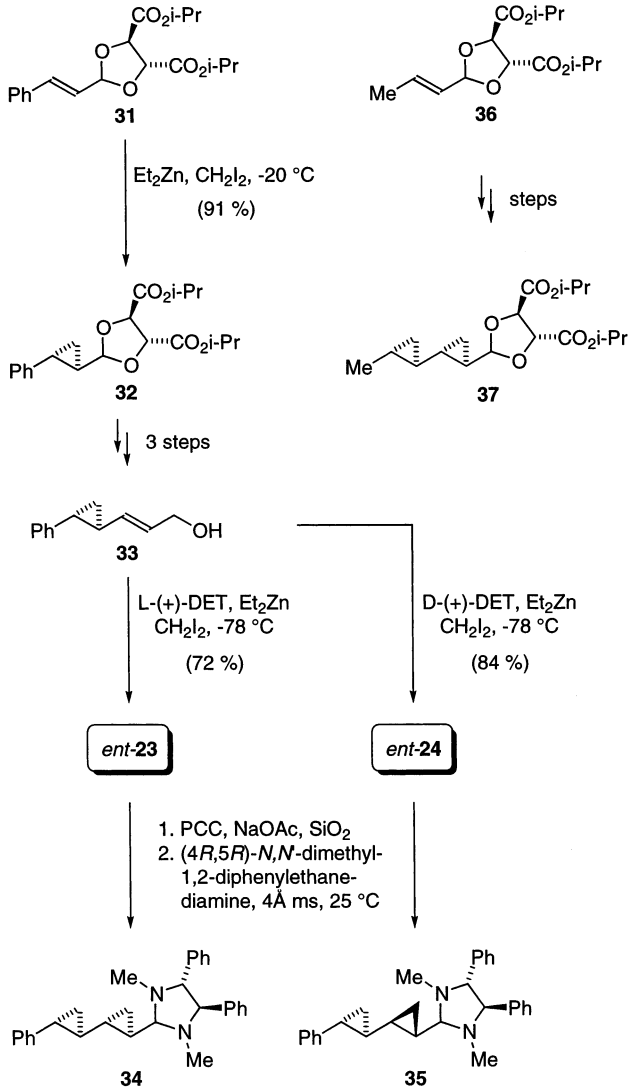



**Figure 2.**

solution for their syntheses would the configuration of the target natural product be investigated.

Barrett et al. established a diastereoselective approach to *ent*-**23** and *ent*-**24** (Scheme 5).[44,45] Starting

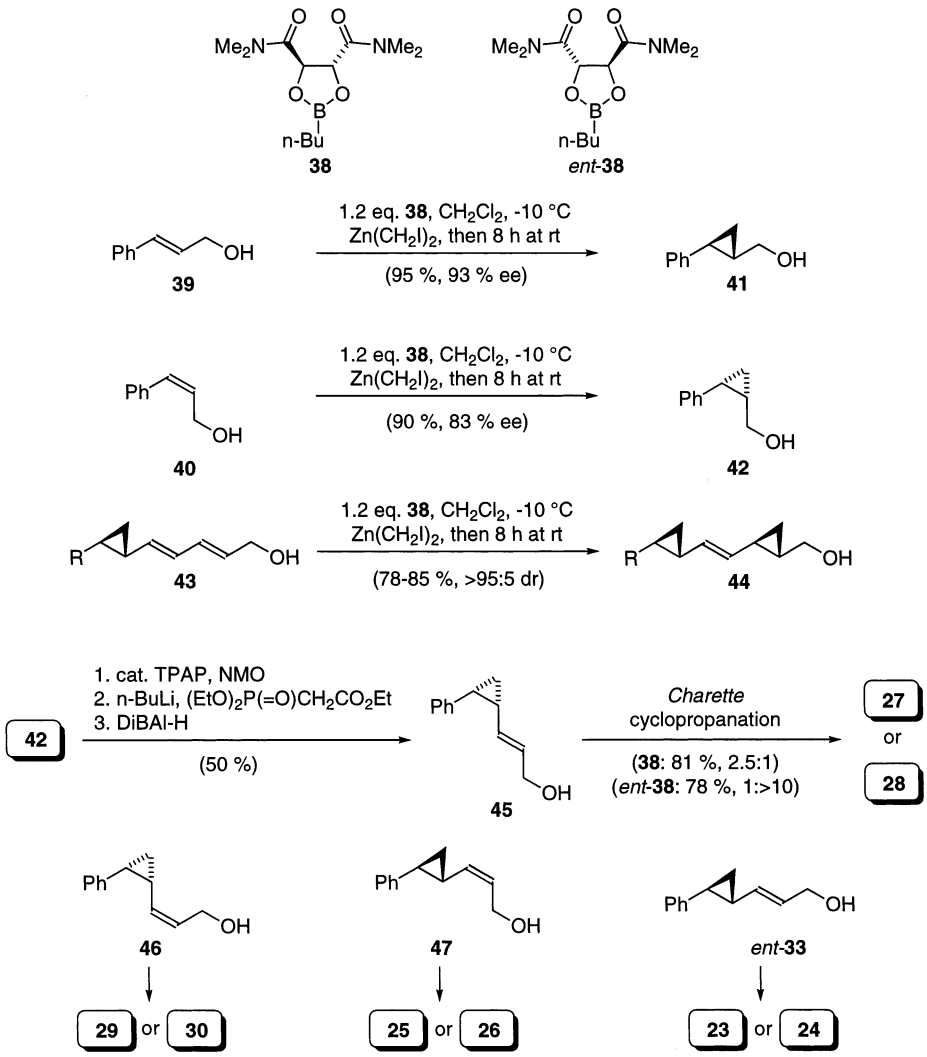
**Scheme 5**




from (*E*)-cinnamaldehyde, the enantiomerically pure acetal **31** was synthesized. By employing Yamamoto's asymmetric Simmons−Smith cyclopropanation protocol,[46,47] cyclopropane **32** was obtained in good yield (91%; dr ∼ 92:8). The diastereoisomers were separated, and the main product was transformed to the allylic alcohol **33** using standard procedures. Reaction with diethylzinc and diiodomethane in the presence of L-(+)-diethyl tartrate [L-(+)-DET][48] led to the bicyclopropanes *ent*-**23** and *ent*-**24** as an inseparable 6:1 mixture. The ratio could be reversed by adding D-(−)-DET. It is important to note that in the absence of the tartrate a 1:1 mixture of the products were obtained. Transformation to the aminals **34** and **35**, respectively, allowed the structural assignment for both diastereoisomers via X-ray analysis of **34**. Similarly, Armstrong and Maurer converted olefin **36** to bicyclopropane **37**.[49]

One of the big achievements in enantioselective cyclopropane formation also takes place at this

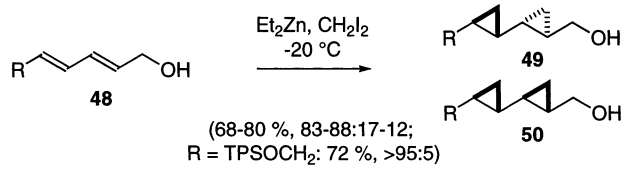
**Scheme 6**




time: the Charette protocol using 1,3,2-dioxaborolanes **38** and *ent*-**38** as chiral modifiers (Scheme 6).[50−54] In high yield and selectivity *E*- and *Z*-cinnamalcohol (**39** and **40**) were cyclopropanated, giving under retention of the olefin configuration the products **41** and **42**, respectively.[53,54] It was established that dienes such as compound **43** react preferentially at the allylic double bond, giving only minor amounts of the tercyclopropane. The diastereomeric ratio was not influenced by the cyclopropane configuration. The reaction was reagent-controlled, and in the presence of **38** dicyclopropylethylene **44** was formed.[53] Zercher et al. used cyclopropanes **41** and **42** for the selective synthesis of all diastereoisomeric bicyclopropanes **23**−**30**.[55−58] The standard sequence contained a Ley oxidation with catalytic amounts of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO),[59] an *E*- or *Z*-selective formation of the corresponding α,β-unsaturated ester, and a reduction with diisobutylaluminum hydride (DiBAl-H), yielding *ent*-**33** and **45**−**47**, respectively. A second Charette cyclopropanation led to the corresponding bicyclopropanes **23**−**30**. It is interesting to note that the reagent-controlled transformation gave excellent selectivities in all but one case: Upon cyclopropanation of **45** in the presence of the chiral modifier, a considerable matched−mismatched interaction was observed and diastereoisomer **27** was obtained in low selectivity. Ylide-mediated cyclopropanation of the intermediate α,β-unsaturated ester[58] or rhodium(II)-catalyzed conversion of the corresponding vinylcyclopropanes in the presence of ethyl diazoacetate[57] showed little facial selectivity.

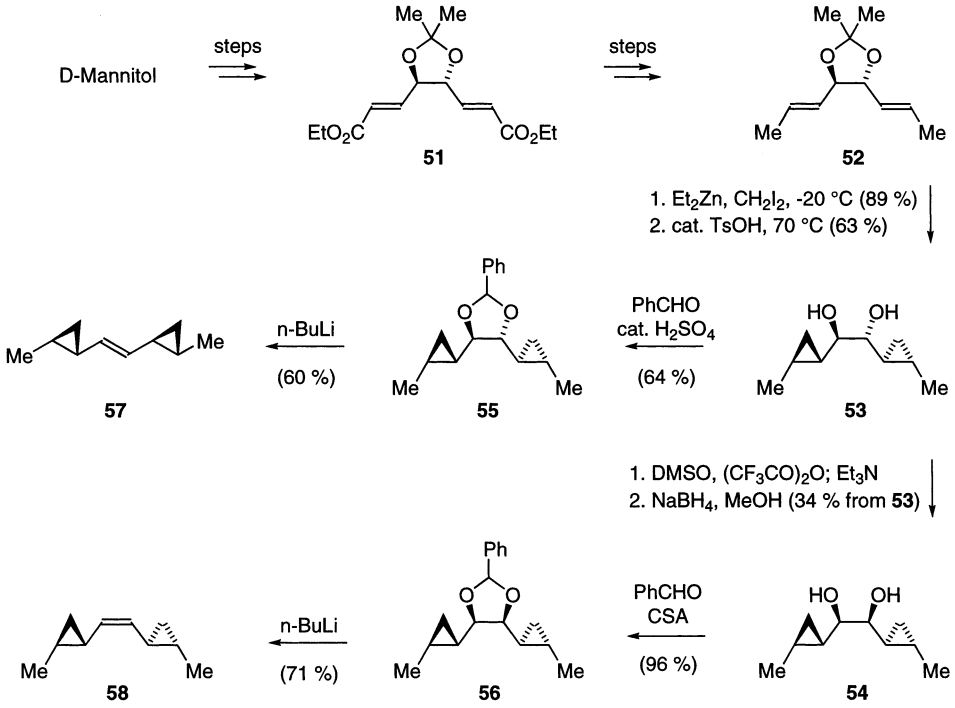
Whereas the cyclopropanation of cyclopropylallyl alcohols gave an ca. 1:1 mixture of diastereoisomers in the absence of an enantiomerically pure reagent, double Simmons−Smith reaction of 2,4-dien-1-ols **48** gave preferentially the *trans*−*anti*−*trans*-bicyclopropanes **49** with minor amounts of the trans−syn−trans product **50** (Scheme 7).[45,60] Best selectivities

**Scheme 7**




were observed for the depicted *tert*-butyldiphenylsilyl (TPS) protected derivative. By starting from diethyl mucoate,[61,62] the enantiomerically enriched (50% ee) intermediate was similarly synthesized using the

**Scheme 8**




Fujisawa protocol[48] (isolation of monocyclopropane) and eventually transformed to the *meso*-bicyclopropane, thus proving the trans−anti−trans configuration.

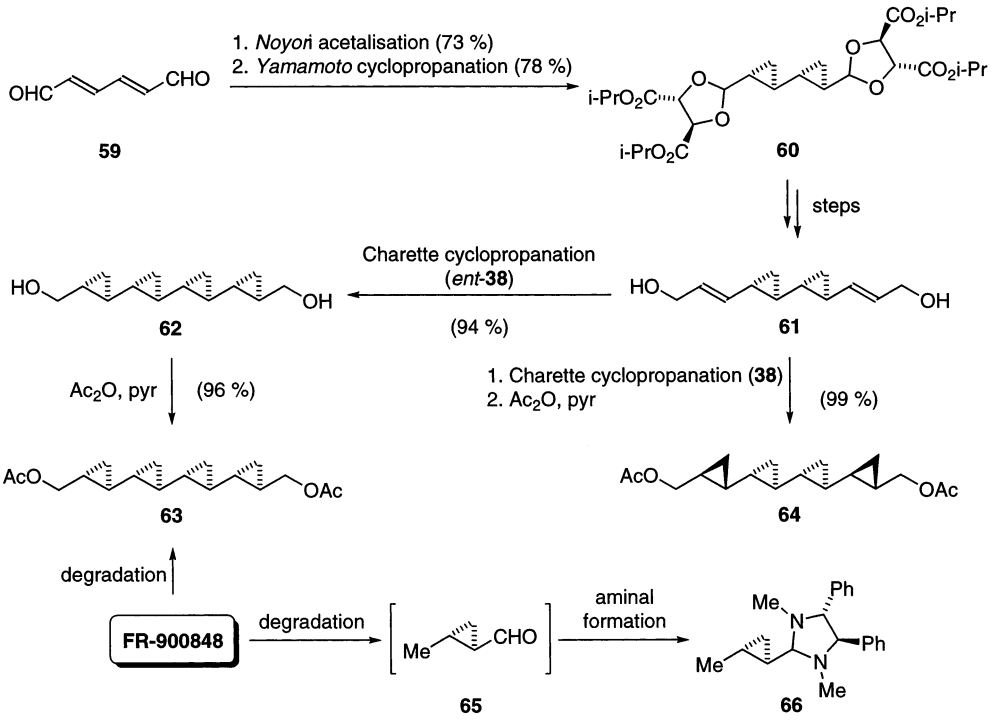
After establishing diastereo- and enantioselective syntheses of bicyclopropane derivatives, the structure elucidation of the natural oligocyclopropane was brought into focus.[63] While initial degradation studies at Fujisawa Pharmaceutical Co. Ltd. determined the constitution of FR-900848 (**1**),[1] there were still a number of ambiguities in the structure. It was speculated that the origin of the fatty acid side chain might be an all-trans $C_{18}$-polyene, especially since the $\Delta^{2,4}$ were unequivocally assigned to be trans. In addition, it was shown that the central quatercyclopropane unit (obtained after ozonolysis, sodium borohydride reduction, and acetylation) was $C_2$-symmetric. First of all, Barrett et al. determined the configuration of the isolated double bond.[64,65] Starting from D-mannitol, the $C_2$-symmetric ester **51** was synthesized (Scheme 8). While Krief et al. used ylide chemistry to obtain a bicyclopropane in fair selectivity (dr 87:13),[66] Barrett et al. first reduced the esters to form **52**, which under Simmons−Smith conditions (followed by deprotection) provided bicyclopropane **53** as a single diastereoisomer.[64] Not only NMR data but also a single crystal X-ray structural determination of the corresponding bis(3,5-dinitrobenzoates) confirmed the assignment. The high selectivity of the step is obviously a result of the coordination of the zinc carbenoid by the Lewis basic dioxolane prior to the cyclopropanation. The diastereoisomeric diol **54** could be obtained after a mono-oxidation/reduction sequence (the *syn*-diols could be separated by chromatography). Again, its structure was unambiguously assigned via X-ray crystallographic studies.[65] Both diols were first converted to the benzylidene acetals **55** and **56**, before a butyllithium-initiated elimination[67] led selectively to the *E*- and *Z*-dicyclopropylethylenes **57** and **58**, respectively. Comparison of the spectroscopic data of both olefins with FR-900848 (**1**), but also with the parent *E*- and *Z*-1,2-dicyclopropylethylene,[68−70] allowed the assignment of the configuration of the isolated double bond in the natural product: The *E*-olefin showed in all cases higher $\delta$ values in $^1$H NMR spectra than the *Z*-olefin (**57**, 5.04 ppm; **58**, 4.68 ppm; FR-900848 (**1**), 5.02 ppm).

The final assignment of the oligocyclopropane array by Barrett et al. was initiated by a Noyori acetalization[71] of muconaldehyde (**59**)[72] followed by a cyclopropanation according to the Yamamoto variation[46,47] of the Simmons−Smith reaction (Scheme 9).[63,73,74] The bicyclopropane **60** was obtained and its structure determined by a single-crystal X-ray structure analysis. Standard transformation led to the bis(allyl alcohol) **61**. Charette cyclopropanation[50,53] in the presence of *ent*-**38** furnished the quartercyclopropane unit **62**.[73] X-ray crystallographic studies of the bis(4-bromobenzoate) confirmed the configuration.[74] After acetylation, reference compound **63** was obtained. Similarly, the second diastereomer **64** was synthesized by using chiral modifier **38**. Comparison of optical rotation and selected spectroscopic data for the two synthetic diacetates **63** and **64** with an authentic sample of the degradation product of FR-900848 (**1**) revealed the configuration of the natural product. In addition, the ozonolysis of FR-900848 (**1**) led to the formation of aldehyde **65**, which was immediately converted to aminal **66**, a compound that was also synthesized by the Barrett group starting from **36** (see Scheme 5). With these results the relative and absolute configuration of the oligocyclopropane was assigned and all that remained was its total synthesis for a final proof.

### *2. Synthesis by Barrett et al.*

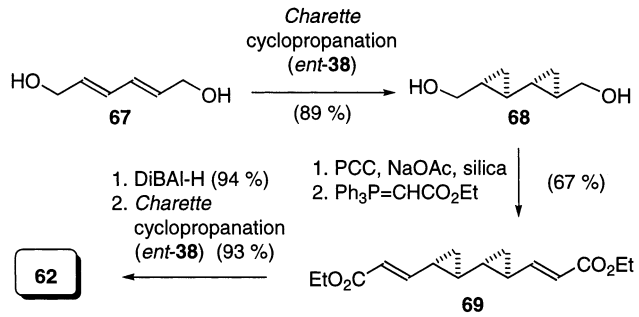
On the basis of the experience of the structure elucidation, the Barrett group went ahead with the

**Scheme 9**




total synthesis of the antifungal agent FR-900848 (**1**).[42] First of all, an improved, bidirectional sequence toward the quartercyclopropane **62** was established (Scheme 10).[75,76] Starting from mucondiol (**67**), readily

**Scheme 10**



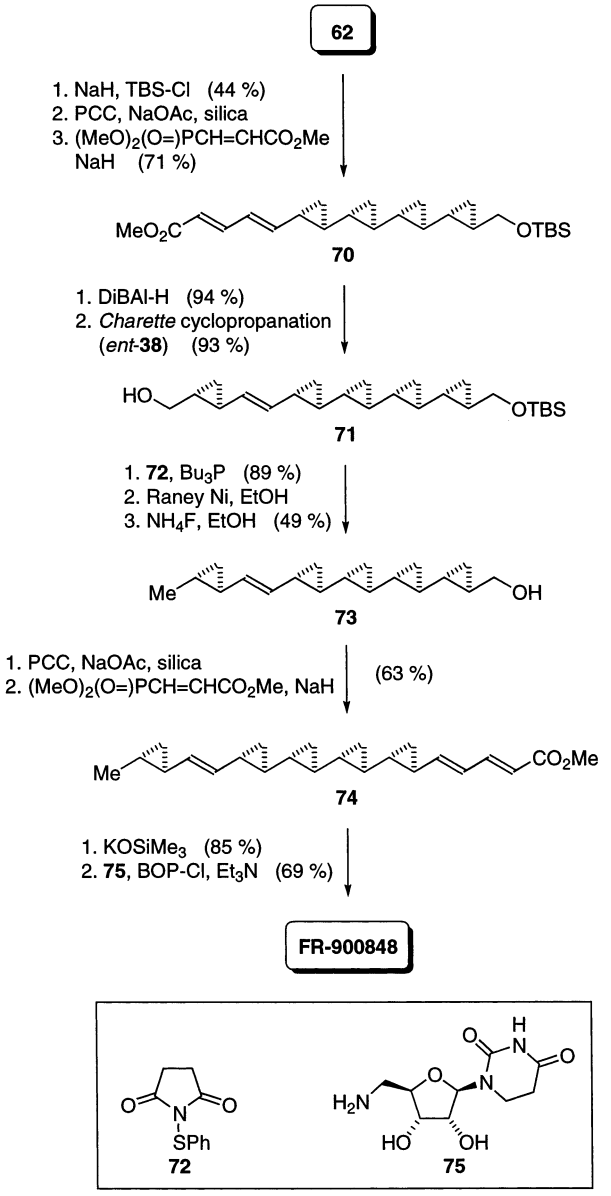

available either from muconic acid[61] or hexa-2,4-diyne-1,6-diol,[62] the power of the Charette cyclopropanation[50,51] was amply demonstrated: Bicyclopropane **68** was predominantly formed in high yield. Oxidation using pyridinium chlorochromate followed by direct homologation provided a separable mixture of *E*,*E*-diester **69** and its *E*,*Z*-isomer (~90:10). The unwanted diester could be partially converted to the desired product by a reagent introduced by Hunter et al. [LiTi(Oi-Pr)$_4$(SPh)].[77] DiBAl-H reduction and consecutive cyclopropanation under Charette conditions led to diol **62**.

Next, quatercyclopropane **62** was converted to dienoate **70** following a standard procedure (Scheme 11; monoprotection, oxidation, and chain elongation). Again, the diester was formed as a mixture (71%; *E*,*E*:*E*,*Z* 84:16), however, the isomerization of the unwanted diene was achieved using Hunter's reagent[77] (63%). Reduction and cyclopropanation in the presence of the chiral modifier *ent*-**38** gave compound **71**, essentially as a single isomer. For the deoxygenation, **71** was treated with the Walker reagent **72**,[78] leading to the corresponding sulfide. Regioselective desulfurization with Raney nickel at −40 °C and subsequent cleavage of the silyl ether provided the oligocyclopropane moiety **73** of FR-900848 (**1**). Oxidation, homologation, and isomerization (in 51% yield) led to the essential precursor **74**. While direct saponification of the ester resulted in decomposition, hydrolysis with potassium trimethylsilanoate[79] gave the acid in good yield. The final step included a BOP-Cl [*N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphoryl chloride][80] activation of the acid, followed by the addition of amine **75**[81] and triethylamine. FR-900848 (**1**) was obtained in good yield for the first time. The synthetic sample was spectroscopically and chromatographically identical with an authentic sample of the natural product. Furthermore, it was established that the optical rotation reported in the original patent[82] was incorrect (the sample was remeasured) and, more important, the absolute configuration of the natural product was confirmed by comparison of the CD spectra.

### *3. Synthesis by Falck et al.*

A little later Falck et al. reported on an elegant alternative synthesis using a reiterative dimerization strategy.[83] The group illustrated a variant of the Horeau principle,[84] leading to material of high enantiomeric enrichment: Charette cyclopropanation of stannane **76**,[85,86] followed by protecting of the primary alcohol, furnished compound **77** in high yield and good selectivity (~88% ee) (Scheme 12). After transmetalation,[87] an oxygen-induced dimerization[88,89] at low temperature provided the *trans*−*syn*−*trans*-bicyclopropane **78** in good yield—using the Horeau amplification principle—with a dramatically improved enantiomeric excess (98% ee). It is noteworthy

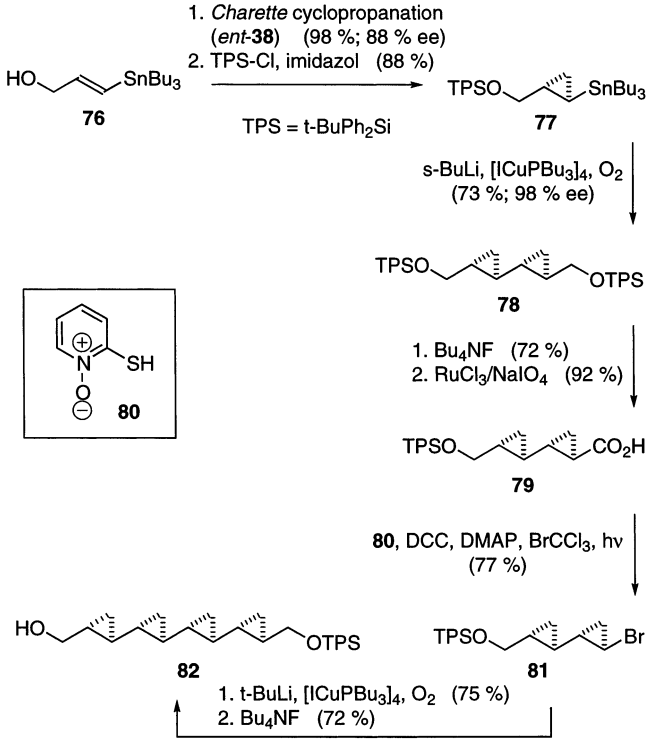
**Scheme 11**



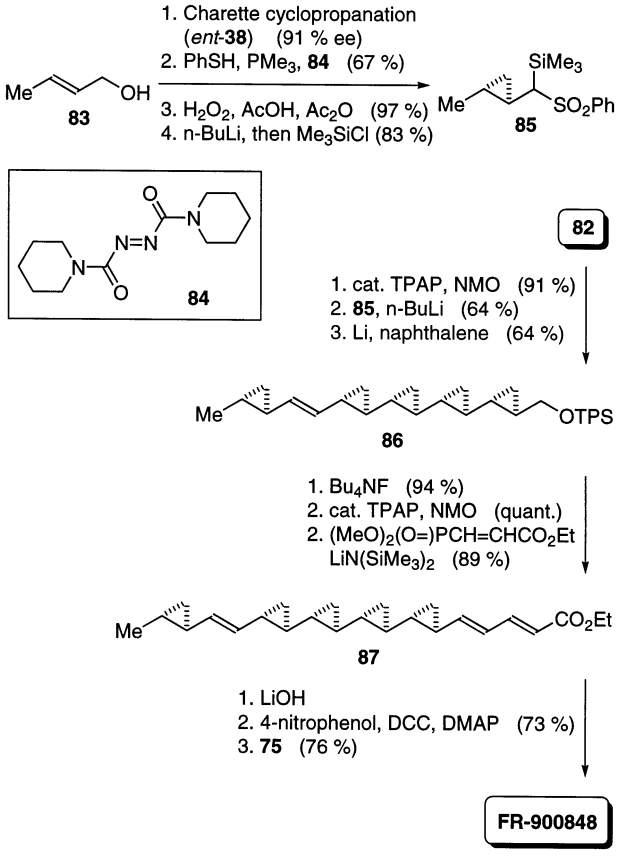

that Itoh et al. also successfully dimerized enantiomerically pure (through kinetic enzymatic resolution[90,91]) tributylstannylcyclopropanes directly.[92] Selective cleavage of one silyl ether and oxidation to carboxylic acid **79** yielded an intermediate for the next level of dimerization and amplification. In a one-pot sequence, acid **79** was first activated with DCC (*N*,*N*′-dicyclohexyl carbodiimide) and coupled with 2-mercaptopyridine *N*-oxide (**80**). Bromide **81** was formed (~94:6 mixture with its cis-isomer) upon photolytic decarboxylation of the Barton thiohydroxamic ester in $BrCCl_3$.[93] Repetition of the dimerization sequence and selective deprotection gave rise to the essentially enantiomerically pure quartercyclopropane **82**.

Whereas for the late-stage couplings toward FR-900848 (**1**) a strategy similar to the Barrett approach was followed, the $\Delta^{14}$ *E*-alkene was formed in a different manner (Scheme 13). Starting from allylic alcohol **83**, the precursor **85** for a Peterson-type olefination was obtained in four steps. After Ley oxidation[59] of **82**, the intermediate aldehyde was

**Scheme 12**




**Scheme 13**



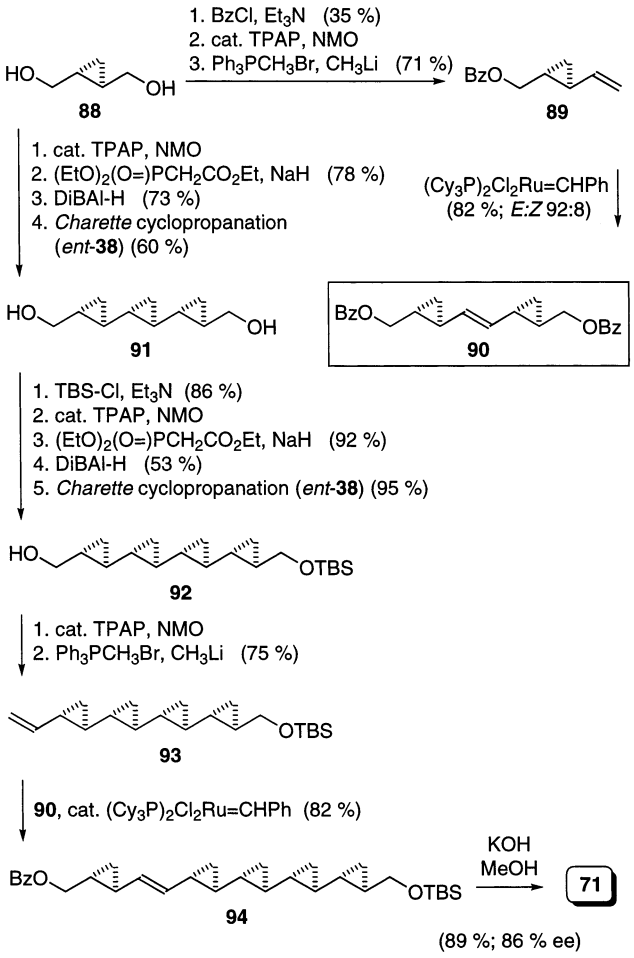

coupled with **85**. The sulfone group was eventually removed using lithium naphthalenide. Variable amounts of the cis-isomer needed to be removed chromatographically beforehand; however, oligocyclopropane **86** could be isolated and the second side chain further elaborated, furnishing the dienoate **87**.

Saponification and condensation with 4-nitrophenol using DCC yielded an active ester. Acylation of 5′-amino-5′-deoxy-5,6-dihydrouridine (**75**) with the reactive intermediate concluded the total synthesis of FR-900848 (**1**).

### *4. Formal Synthesis by Verbicky and Zercher*

Although Barrett et al. and Falck et al. had already given two different solutions for the formation of the $\Delta^{14}$ *E*-alkene, the Zercher group proposed a third alternative for this challenging moiety.[94] Grubbs cross-metathesis[95] was envisaged to be ideal to form the alkene flanked by cyclopropanes. First model couplings were promising, and especially the derivative from **88**, vinylcyclopropane **89**, gave in high yield and good selectivity the "homodimer" **90** (Scheme 14).

**Scheme 14**




Related results with fluorinated vinylcyclopropanes were reported independently by Itoh et al. at about the same time.[96] Using a classical bidirectional approach, Verbicky and Zercher converted **88** to the known tercyclopropane **91**[97−99] also using the Charette protocol.[50,51] After selective monosilylation, chain elongation eventually led to quartercyclopropane **92**. Ley oxidation[59] and olefination with triphenylphosphonium methylide provided vinylcyclopropane **93**. When exposing this intermediate in the presence of **90** to Grubbs' catalyst, the cross-coupling product **94** was formed in good yield as an *E:Z* mixture (>84:16). Removal of the benzoyl protecting group furnished the advanced intermediate **71** in Barrett's total synthesis[75,76] of FR-900848 (**1**).

## B. U-106305

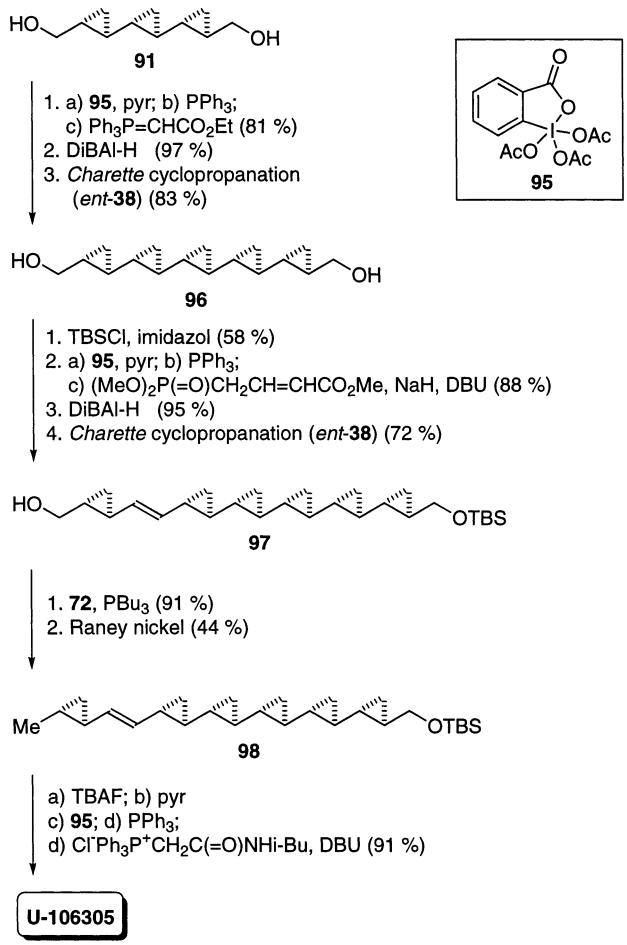
### *1. Structure Elucidation*

U-106305 (**2**) was isolated from the fermentation broth of *Streptomyces* sp. UC-11136 and was shown to be a new cholesteryl ester transfer protein (CETP) inhibitor.[2] Extensive NMR studies and FAB-mass spectrometric investigations allowed the assignment of the constitution of the structurally remarkable inhibitor, bearing six cyclopropane units, five of which are contiguous. It was shown that all alkene units of the fatty amide side chain were *E*-configured and all cyclopropanes were trans-disubstituted. However, none of the absolute configurations of the stereogenic centers were determined. Consequently, there were 64 possible stereoisomeric structures for the natural product. In the end, the final structure (as depicted in Figure 1) was elucidated by two independent total syntheses by Barrett et al.[97] and Charette et al.[98] in 1996.

### *2. Synthesis by Barrett et al.*

The Barrett group reasonably assumed that for the biosynthesis of both natural oligocyclopropanes with an all-trans-configuration the same or at least a similar enzyme is involved in the formation of each cyclopropane entity.[97] In addition, both producing organisms are related and it was consequently hypothesized that the configuration in both compounds would be the same. The predicted structure of U-106305 (**2**) (see Figure 1) made tercyclopropane **91** (Scheme 15)—also used later on by Zercher et al.[94]—the ideal starting point of the total synthesis. It was essential to obtain the material in enantio- and diastereomerically pure form. Especially fractional recrystallization of the intermediates from **88** (81% ee) to **91** allowed an efficient enantiomerical enrichment of the required enantiomer. Moreover, a number of molecular structures (e.g. of **91**) could be unambiguously confirmed by X-ray crystallography.[100] To form the quinquecyclopropane unit, Barrett et al. used a bidirectional approach: Oxidation to the dialdehyde using the Dess−Martin periodinane **95**,[101,102] Horner−Wadsworth−Emmons olefination, DiBAl-H reduction, and double Charette cyclopropanation[50,51] led to the advanced intermediate **96** (X-ray). The one-pot oxidation in the presence of phosphorus ylides was not only a convenient method for the homologation, but also especially efficient:[103] The Wittig reaction proceeded with a very high rate and *E*-selectivity. Obviously, the pyridine−acetic acid buffer from the Dess−Martin reaction (or acetic acid alone) accelerates the second step. Catalysis of the Wittig reaction by carboxylic acids had been observed previously.[104−107] Desymmetrization of the $C_2$-symmetrical diol **96** by formation of the mono-*tert*-butyldimethylsilyl ether proved difficult. The conditions reported by McDougal,[108] previously applied in the synthesis of FR-900848 (**1**) (see Scheme 11), gave just low conversions. A slightly better selectivity was observed when using imidazole (58% product, 22%

**Scheme 15**



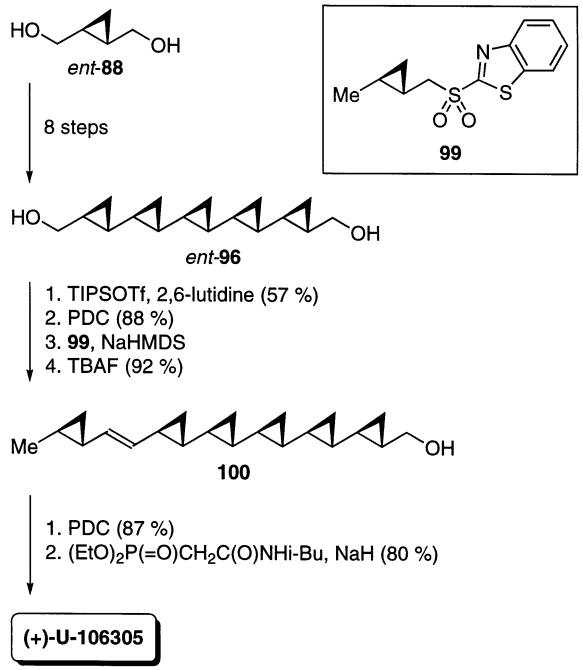

starting material, and 19% disilyl ether). After standard homologation reaction conditions and Charette cyclopropanation, the hexacyclopropane **97** was obtained with excellent stereoselectivity and good regioselectivity. A single septicyclopropane was also formed (27%) as a side product. Its structure was confirmed after deprotection and by an independent synthesis of the second ($C_2$-symmetrical) diastereoisomer. Single-crystal X-ray analyses were obtained for both compounds. A two-step deoxygenation was achieved via thioether formation and reduction with Raney nickel. The yield for this last step (formation of compound **98**) varied depending on the batches of Raney nickel used, and the best results were obtained when some ethylenediamine was added. Some unreacted starting material (14%) was recovered. The synthesis of U-106305 (**2**) was completed by an efficient procedure: Desilylation, oxidation to the aldehyde, and Wittig olefination to introduce the required unsaturated amide were performed in one pot. It was shown that the synthetic sample was identical in all respects with an authentic sample of U-106305 (**2**). Analogues using different amines were also assembled by applying a similar late stage sequence.[100]

It is interesting to note that a related bidirectional approach toward FR-900848 (**1**) using quatercyclopropane **62** (see Scheme 9) failed: Desymmetrization on the tetraene level proved difficult, but especially the late desulfurization did not provide the desired product, and consequently the approach was abandoned.[100]

### *3. Synthesis by Charette et al.*

At about the same time, the Charette group also independently finished their total synthesis of the enantiomeric oligocyclopropane.[98] The group aimed at the same key intermediates as Barrett et al. using the almost identical bidirectional approach. Starting from diol *ent*-**88** the quinquecyclopropane *ent*-**96** (X-ray) was obtained in eight steps (Scheme 16). For the

**Scheme 16**




selective formation of the isolated double bond, Charette and Lebel thought to use a Julia olefination[109−111] between the suitable protected aldehyde (from *ent*-**96** after protection and PDC oxidation) and the benzothiazoyl sulfone **99**. It was found that the nature of the solvent, the counterion, and the temperature influenced the *E:Z* ratio. Best results (81:19) were obtained at −60 °C when a solvent mixture (THF/DMF) and sodium hexamethyldisilazide were used. After deprotection the key intermediate **100** was isolated in high yield. PDC oxidation and chain elongation with diethyl (*N*-isobutylcarbamoyl)methylphosphonate[112] furnished (+)-U-106305 (*ent*-**2**). While all spectroscopic data of the natural and the synthetic compounds were identical, the sign of the optical rotation was opposite. Charette and Lebel did therefore not only confirm the absolute and relative configuration of the natural product, but could also illustrate the power of the reagent-based asymmetric cyclopropanation developed by the Charette group.[50,51,53]

### *4. Synthesis of a Key Intermediate by Zercher et al.*

Zercher and his group were the third group that focused on the assembly of the oligocyclopropane U-106305 (**2**) using a similar strategy at about the same time.[99] Their main concern was the investigation on the substrate and reagent-controlled cyclo-

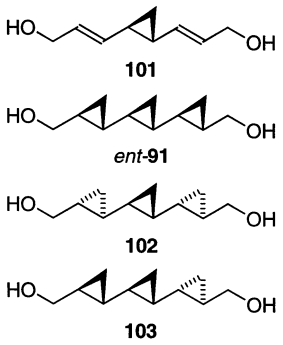



**Figure 3.**

propanation of diol **101** (Figure 3). As anticipated, Simmons−Smith-type[113,114] cyclopropanation led to mixtures (66%) of tercyclopropanes *ent*-**91**, **102**, **103** in the absence of a chiral modifier such as **38** or *ent*-**38**. Although the inseparable mixture gave complex NMR spectra, the structures could be assigned after reagent-controlled Charette cyclopropanations (yield 83% and 65%, respectively).[50,51,53] Although the selectivity was high, minor amounts of other diastereoisomers could not be separated (by chromatography; Barrett et al. and Charette et al. purified the compounds by selective crystallization). This also hampered the following transformation of *ent*-**91** to the quinquicyclopropane *ent*-**96** (similar to the syntheses reported by Barrett et al. and Charette et al.; however, different conditions for the oxidation to the dialdehyde were reported). The key intermediate for the U-106305 (**2**) synthesis was obtained as the major product along with some minor diastereoisomeric impurities.

## C. Model Compounds

### *1. Coronanes*

The *all-syn−trans*-oligocyclopropane arrays of the natural products will undoubtedly restrict the conformational flexibility of their lipophilic domains. Indeed, extensive investigation of the structures in the solid state indicated that regardless of whether the *trans*-1,2-cyclopropane units were syn- or anti-joined, in the preferred conformation the H−C−C−H linkages are all anti, as shown for bicyclopropane (**3**)[4−6] (Figure 4). This is true for all synthetic inter-

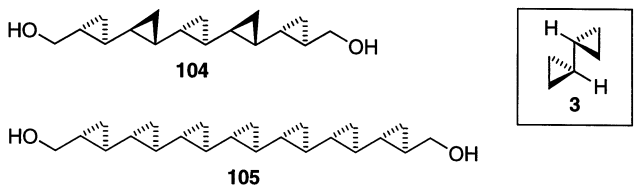
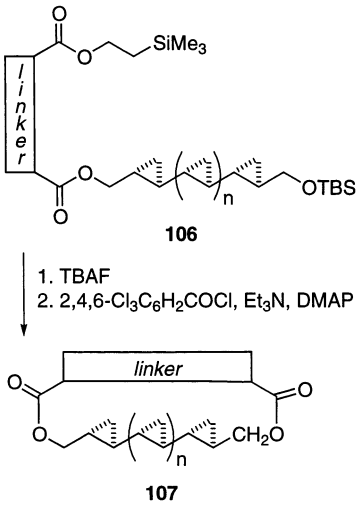


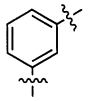
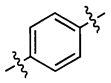
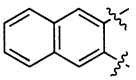
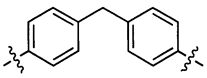
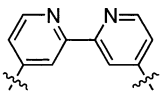
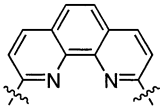

**Figure 4.**

mediates such as ter- (**91**), quarter- (**62**), and quinquecyclopropane (**96**) (vide supra), but also for the all-anti−trans derivative **104** and the septicyclopropane **105**.[115] As a consequence, the *all-anti−trans*-quinquecyclopropane **104** adopts an extended rigid-rod conformation with the methylene portions of the *syn*-cyclopropanes eclipsing, while the all-syn−trans-disubstituted cyclopropane oligomers are helical. By incorporating the oligocyclopropane subunits into a macrocycle, it should not only be possible to form conformationally restricted ring systems, but it might also indicate whether the preference for the extended helical structure, found for the *syn−trans*-oligocyclopropanes, was dictated by crystal packing. A conformationally restricted helix should not allow macrocyclization; however, molecular models clearly indicated considerable conformational mobility for oligocyclopropanes.[116]

On the basis of the experience of their natural product synthesis, first the oligocyclopropanes were incorporated in coronanes. The direct condensation of a diol such as **105** with phthaloyl chloride under high dilution condition gave the corresponding coronane[117] in unsatisfactory yield.[115] A stepwise approach proved to be superior (Scheme 17): Steglich esterification[118,119] of a monoprotected dicarboxylic acid furnished the unsymmetrical diester **106**. Double

**Scheme 17**

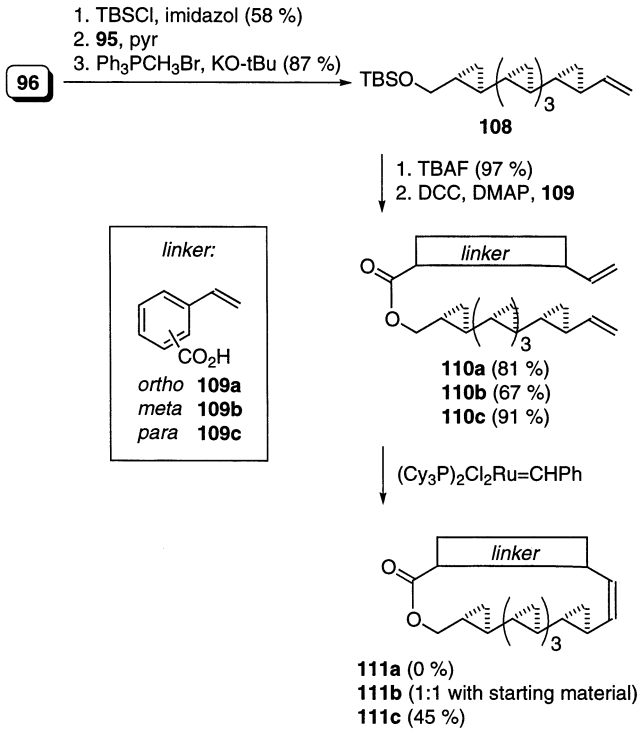



| entry | *linker* | Yield n = 3 | Yield n = 5 |
|---|---|---|---|
| a |  | 74 % | 74 % |
| b |  | 91 % | |
| c |  | 95 % | |
| d |  | | 70 % |
| e |  | 90 % | |
| f |  | 71 % | |
| g |  | 62 % | |

deprotection and macrolactonization under Yamaguchi conditions[120] provided the coronanes **107** in good to excellent yield.[116]

Alternatively, macrocyclization via a ring-closing metathesis (RCM)[121−124] was investigated. Quinquecyclopropane **96** could be conveniently transformed to olefin **108** (Scheme 18).[116] Deprotection and acylation with *o*-, *m*-, or *p*-vinylbenzoic acid (**109a**−**c**) furnished the precursors **110a**−**c**. Attempted RCM of the ortho-derivative, either under standard conditions or using titanium tetraisopropoxide-assisted RCM, were unsuccessful and no **111a** was formed. Cyclization of meta-derivative **110b** via RCM gave an inseparable mixture of **111b** and recovered **110b**. In the case of the para-derivative **110c**, RCM gave macrocycle **111c**, which could be cleanly isolated by recrystallization.

**Scheme 18**



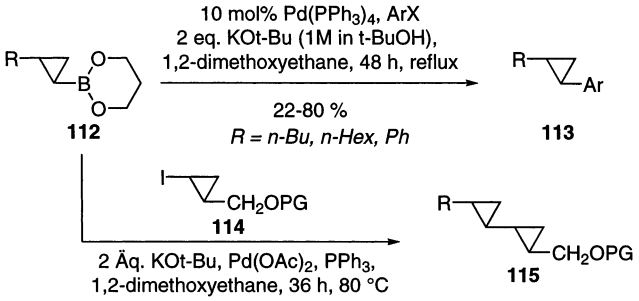

From this investigation it was apparent that the *all-syn*−*trans*-oligocyclopropanes are not fixed in an extended helical structure but showed the expected flexibility. The molecular structure of a number of coronanes (**107a**−**c**,**e**−**f, 111c**) was determined by single-crystal X-ray crystallography. Despite the fact that the anti-conformation in the H−C−C−H linkages remained favorable, if necessary, the oligocyclopropane backbone was twisted to fit the linker. In some cases even two crystallographically independent molecules were present in the asymmetric unit, each with a distinctly different conformation.

### 2. Via Cyclopropylboronic Esters

Falck et al. used cyclopropylstannanes for homocouplings, not only for synthesizing contiguous cyclopropane units but also to enhance the enantiomeric excess of the products (see Scheme 12).[83] As an alternative, Itoh et al. applied the same dimerization, but utilizing lipase-catalyzed reactions to establish essentially enantiomerically pure bicyclopropanes.[90−92] It was not surprising that cross-couplings with boronic esters were next investigated instead of making use of the toxic stannanes. In addition, the sometimes troublesome desymmetrization at a later stage could be avoided. Cyclopropylboronic esters were known for a long time;[125−128] however, only after a more reliable synthetic access was established[129−132] was this class of compounds applied to the synthesis of more advanced target molecules.

The first successful Suzuki couplings[133,134] were reported in 1996 by Hildebrand and Marsden.[135] They established a reliable protocol for the conversion of boronic ester **112** to arylcyclopropanes **113** (Scheme 19). Deng et al. extended the approach, proving that

**Scheme 19**

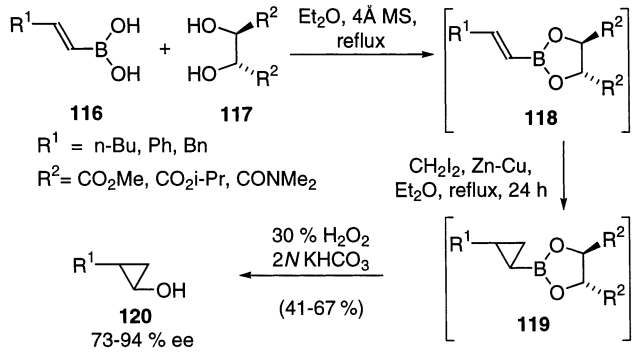



| entry | R | PG | yield |
|---|---|---|---|
| a | n-Bu | Bn | 69 % |
| b | n-Bu | H | 64 % |
| c | $BnOCH_2$ | Bn | 71 % |
| d | Ph | Bn | 60 % |

vinyl-, allyl-, benzyl-, acyl-, and heteroarylcyclopropanes are also accessible by this method.[136−148] More importantly, Charette et al. realized the first cyclopropyl−cyclopropyl cross-coupling between boronic ester **112** and cyclopropyl iodide **114**.[149] It was demonstrated that the nature of the boronic ester also affected the reaction toward the bicyclopropanes **115**: Compared with **112**, the boronic acid or boronic esters of catechol or 1,2-ethanediol decreased the rate and the yield of the transformation.

A drawback was the fact that only a racemic mixture of cyclopropylboronic ester and the corresponding iodide were introduced. Imai et al. were the first to establish a diastereoselective sequence (Scheme 20):[132] Condensation of alkenylboronic acids **116** with tartaric acid derivatives **117** furnished enantiomerically pure alkenylboronic esters **118** that were readily cyclopropanated. The intermediate diastereomeric cyclopropylboronic esters **119** were not separated but directly transformed to the enantiomerically enriched cyclopropanols **120**. The diastereoselective approach was later adopted by others[138,150] and did eventually lead indirectly to enantiomerically pure cyclopropanes.[151] Apart from the auxiliary-controlled access to enantiomerically enriched cyclopropylboronic es-

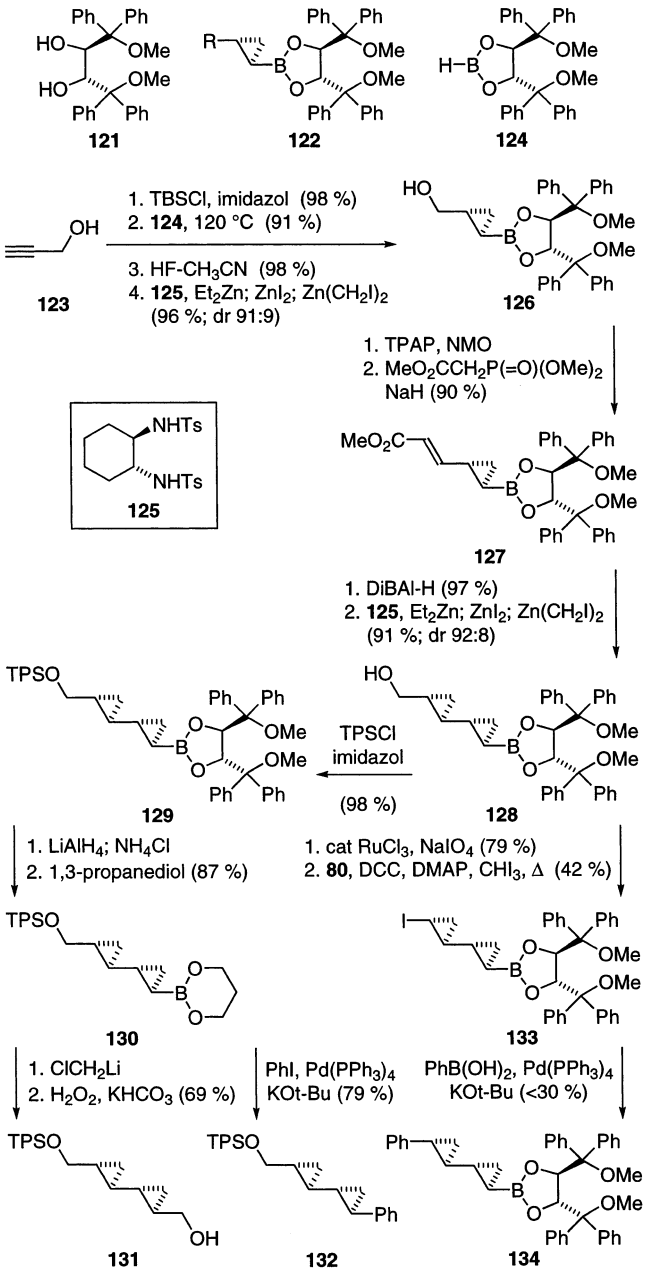
**Scheme 20**




ters, a substrate-controlled reaction to diastereomerically pure derivatives was reported.[152]

A major setback has been the relative lability of this class of compounds: The separation of diastereoisomers was not possible; the advantage of diastereoselective syntheses could not be used. A systematic search for auxiliaries that would yield more stable dioxaborolanes led to diol **121**,[153,154] an efficient auxiliary and protecting group for boronic acids (Scheme 21).[152,154−158] The cyclopropylboronic esters **122** are stable on silica gel, the diastereoisomers can be readily separated and conveniently stored. The intermediates were used for the synthesis of bicyclopropanes:[157,159] Propargyl alcohol (**123**) was protected and subjected to a direct hydroboration with dioxaborolane **124**. The silyl ether was selectively deprotected without effecting the boronic ester moiety. To obtain the desired cyclopropanation product, a reagent-controlled transformation was needed. While in this case the Charette conditions[50,51,53] were not successfully applied—after 72 h the conversion was not complete[154]—Denmark enantioselective cyclopropanation in the presence of substoichiometric amounts of bissulfonamides[160−163] such as **125** gave the cyclopropane **126** in high yield and selectivity.[157] Standard homologation first led to ester **127**, a single-crystal X-ray analysis proving the configuration. Reduction of **127** and a second Denmark cyclopropanation eventually led to bicyclopropane **128**, a key intermediate for a variety of derivatives. The absolute configuration of the second cyclopropane unit was established by chemical correlation. Silyl protection furnished **129**, which was further converted to the more reactive dioxaborinane **130** via an ate-complex. The auxiliary **121** was recovered in near quantitative yield. Matteson homologation[164] of **130** to the known[83] alcohol **131** thus established the configuration of **128**−**130**. Conversion of borinane **130** to the phenyl derivative **132** proved that the enantiomerically pure bicyclopropylboronic esters were also convenient substrates for Suzuki couplings. A further demonstration of the stability of this type of boronic ester was the transformation of the hydroxymethyl derivative **128** to iodide **133**: Oxidation of **128** to the carboxylic acid and Barton decarboxylation[93] led to a ~10:1 mixture of trans:cis-isomers of **133**. The low yield of the last step was not due to a problem during the radical reaction but because of the formation of some unidentified side products during the synthesis of the Barton ester. As shown before by Charette et al.,[149,165] iodocyclopropanes are suitable substrates for

**Scheme 21**

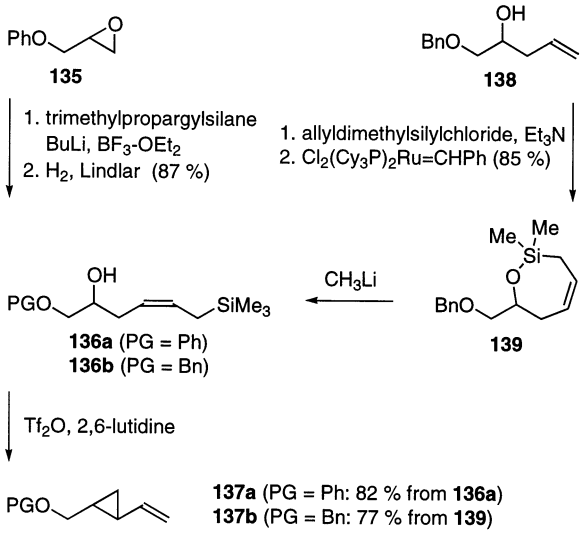



Suzuki couplings, and consequently, **133** gave the phenyl derivative **134** when subjected to the reaction conditions, albeit in low yield. Nevertheless, it was shown that the boronic ester moiety of **133** was not affected during the transformation, but the rate of the conversion was very slow.

### *3. Via Trapping of Homoallyl Cation Intermediates*

A conceptually different approach was followed by Taylor et al.[166,167] On the basis of the postulation that homoallylic cations are reactive intermediates in the biosynthetic pathway of cyclopropane-containing natural products,[168,169] several groups utilized this intermediate to generate cyclopropanes.[170−179] Taylor et al. took advantage of allylsilanes as direct precursors to the cyclopropylcarbinyl cation.[166,167] The intermediate was conveniently synthesized from epoxides **135** by Lewis acid-catalyzed ring-opening with lithiated trimethylpropargylsilane (Scheme 22).[166] Reduc-

**Scheme 22**



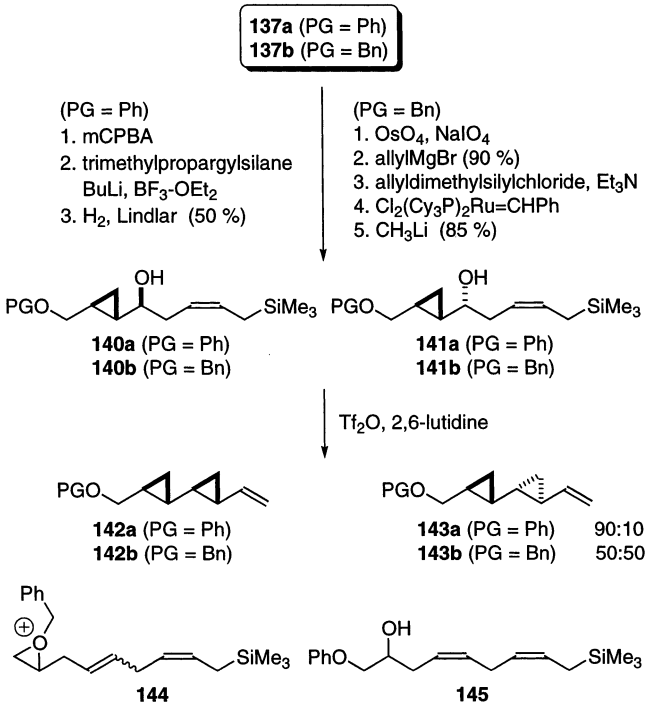

tion of the alkyne was accomplished under an atmosphere of hydrogen in the presence of the Lindlar catalyst. Allylsilane **136a** was isolated in high yield. When exposed to trifluoromethanesulfonic anhydride and 2,6-lutidine, vinylcyclopropane **137a** was obtained. In addition, when enantiomerically pure **136b** was used, only enantiomerically enriched product **137b** was found. A second, alternative sequence to **136b** was also developed, beginning with the easily accessible starting material **138**.[167] After formation of a silyl ether and a consecutive ring-closing metathesis using Grubbs catalyst,[121−124] siloxycycloheptene **139** was isolated. Exposure to methyllithium provided **136b**. Alternatively, HF−pyridine was used to cleave the silyl ether.

The vinylcyclopropanes **137** were further exploited to synthesize allylsilanes **140/141** by established reactions, taking advantage of the potential of this strategy for an iterative synthetic sequence (Scheme 23).[167] Activation under the usual conditions furnished bicyclopropanes **142** and **143**, respectively. Surprisingly, an identical 1:1 mixture of diastereoisomers **142b** and **143b** was isolated, regardless of whether **140b** or **141b** was used for the transformation. The finding was in contrast to the significant selectivity observed for the phenoxy series (**142a**: **143a**, "∼80% stereospecific"). It was assumed that the benzyl ether assists the ionization of the secondary triflate by stabilizing the homoallylic cation **144**. Sequential cyclization would provide the mixture of diastereoisomers. On the basis of this hypothesis, dienol **145** was synthesized and exposed to the standard activating conditions. Apparently, a similar homoallylic cation was formed, and consequently, the expected 1:1 mixture of diastereoisomers **142a** and **143a** was obtained in 69% yield. This general approach was more recently further exploited for the construction of structurally diverse enantio- and diastereomerically pure vinylcyclopropanes.[180,181]

### *4. Via Bicyclopropylidene*

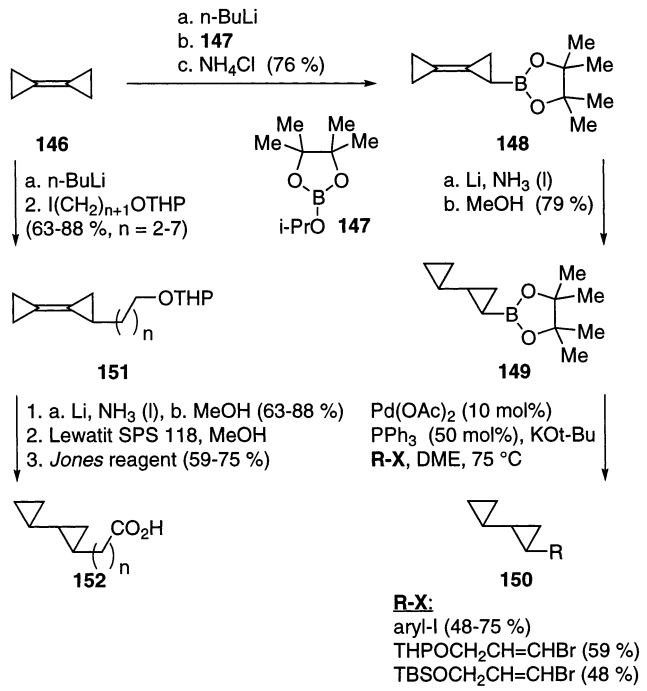
Bicyclopropylidene (**146**) is a broadly applicable synthetic intermediate that is especially versatile for the synthesis of new cyclopropyl-containing com-

**Scheme 23**




pounds:[182−184] A number of new, fascinating cyclopropane architectures could be assembled for the first time.[185−187] The readily available[188,189] $C_6$-building block bicyclopropylidene (**146**) can be easily transformed by deprotonation with *n*-butyllithium followed by electrophilic substitution with appropriate reagents.[190−192] Thus, treatment of the lithiated intermediate with dioxaborolane **147** yielded boronate **148** (Scheme 24).[191,193] Surprisingly, several attempts to

**Scheme 24**

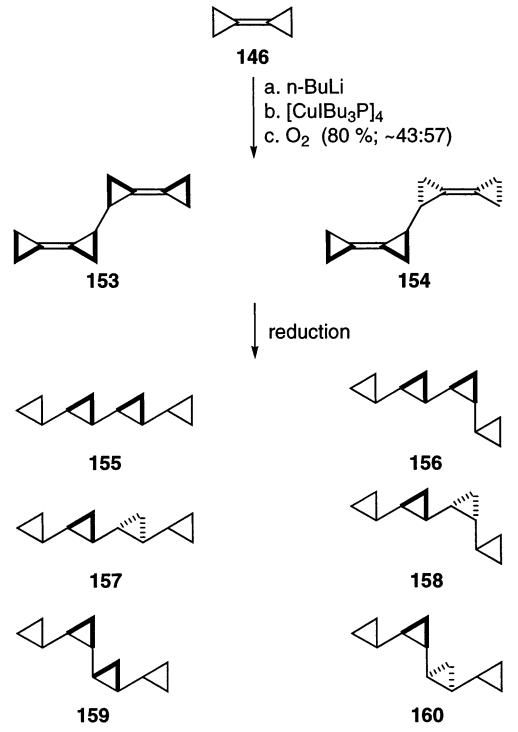



couple boronic ester **148** under typical Suzuki conditions with iodobenzene failed (this is also true for the corresponding stannane). It was reasoned that since

bicyclopropylidene is a particularly good ligand for transition metals, the coupling is prevented. Indeed, after reduction of **148** using Birch conditions, the bicyclopropane **149** could be conveniently coupled under standard conditions (vide supra), furnishing a variety of derivatives **150**. Alternatively, lithiated **146** could be used to synthesize a number of model compounds for biodegradation studies (vide infra) of cyclopropanated fatty acids:[190] With THP-protected $\omega$-iodo alcohols, a suitable precursor **151** was obtained. Reduction, deprotection, and oxidation furnished a number of fatty acids **152**. Furthermore, the same intermediates were used for the synthesis and evaluation of liquid crystalline bicyclopropyl derivatives.[194]

This general approach was extended by an oxidative dimerization of bicyclopropylidene (**146**) (Scheme 25), yielding a mixture of bis(bicyclopropylidenyl) **153**

**Scheme 25**

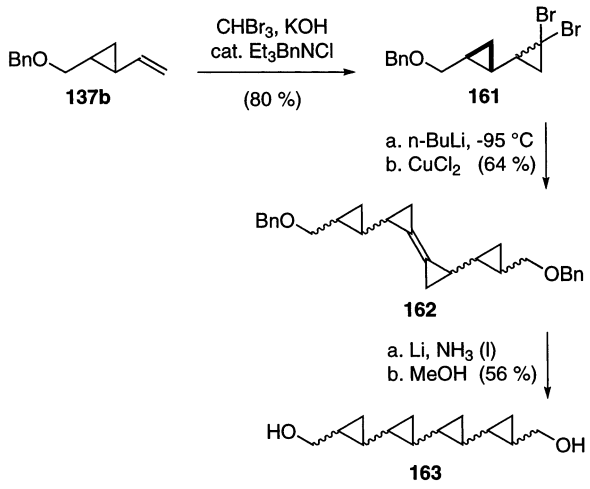



| educt | conditions | product | ratio | yield |
|---|---|---|---|---|
| **153** | $Li/NH_3$ (l); MeOH | **155:156** | 90:10 | 76 % |
| **154** | $Li/NH_3$ (l); MeOH | **157:158** | 90:10 | 97 % |
| **154** | 'diimide', MeOH | **160:158** | 66:34 | 87 % |
| **154** | cat. Pd on $BaSO_4$, $H_2$ | **160** | | 64 % |
| **153** | cat. Pd on $BaSO_4$, $H_2$ | **159** | | 45 % |

(*d*,*l*) and **154** (meso).[195] The diastereoisomers were separated by selective crystallization. The meso-compound **154** was identified by a single-crystal X-ray analysis. Depending on the reaction conditions, reduction furnished the racemic quatercyclopropanes **155**−**160**. While lithium in liquid ammonia gave an inseparable mixture of **155** (trans−syn−trans) and **156** (trans−syn−cis) from **153**, and **157** (trans−anti−trans) and **158** (trans−anti−cis) from **154**, respectively, cis-selective reduction led—after chromatographic separation—to pure products: Reduction of **154** with diimide, generated from 2-nitrobenzenesulfonyl hydrazide, gave *cis*−*anti*−*cis*-**160** as major product; however, considerable amounts of **158** were also formed. Hydrogenation (1 atm $H_2$) in the presence of catalytic amounts of palladium on $BaSO_4$ proved to be highly selective, and *cis*−*syn*−*cis*-**159** (from **153**) and *cis*−*anti*−*cis*-**160** (from **154**) were obtained.

An interesting new perspective for the synthesis of oligocyclopropane[193] was based on the work of Neuenschwander et al.[196−199] Dibromocyclopropane **161**, available by addition of a dibromocarbene to olefin **137b**, was coupled under thermodynamic conditions to yield a mixture of four isomeric bicyclopropylidenes **162** (Scheme 26). Unfortunately, separation of the diastereoisomers was not possible; however, it can be assumed that by starting from nonracemic **137b** and **161**, respectively, the number of isomers could be reduced. This would also be essential for the last step to quatercyclopropanes **163**: In this case, Birch reduction furnished an inseparable mixture.

**Scheme 26**

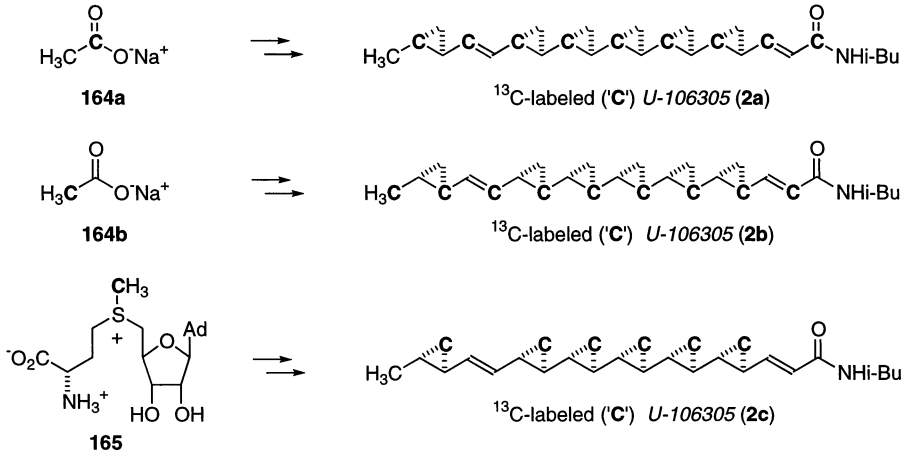



## *III. Properties*

## A. Biosynthesis

Cyclopropane formation in bacterial lipids is well-understood, and the typical source for the methylene unit has been identified in many cases.[200−203] Whereas for the antifungal compound FR-900848 (**1**) no such investigations have been reported, Kuo et al. studied the biosynthesis of the related oligocyclopropane U-106305 (**2**) in detail.[2] It was assumed that acetate was the most likely precursor for the backbone carbons of **2**. To verify this hypothesis, feeding experiments with the $^{13}C$-labeled sodium acetates **164a** or **164b** were carried out (Scheme 27; Ad = adenine). Depending on the position of the label, the $^{13}C$ NMR spectra of the isolated U-106305 (**2**) showed enhancement of different carbon signals (labeled **2a** and **2b**, respectively). This suggested that the backbone of the fatty acid was derived from acetate. Moreover, since a head-to-tail linkage was observed in both cases, a polyketide mechanism is likely. A remaining question was the source of the methylene group. The $C_1$ donor that usually forms the cyclopro-

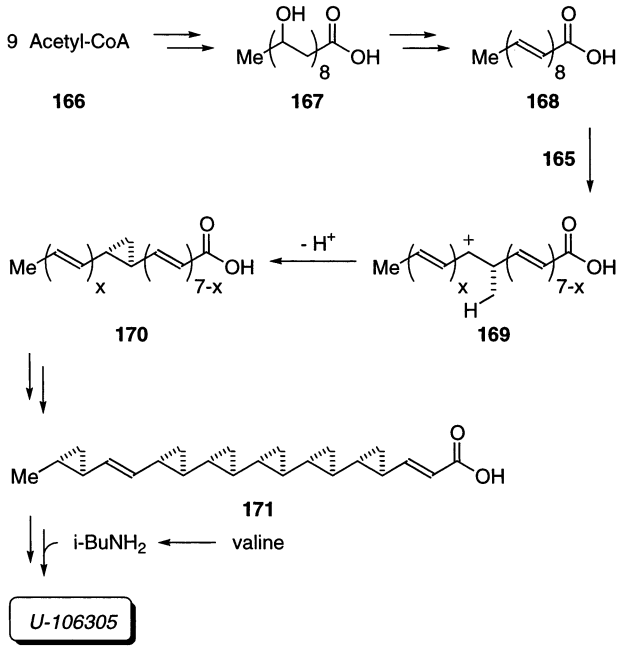
**Scheme 27**




pane ring in cyclopropane containing fatty acids is *S*-adenosylmethionine (**165**). Early studies on the selective blocking of the biogenetic cyclopropanation step clearly demonstrated in vitro and in vivo the absolute requirement of **165**,[204−206] and it was argued that for the oligocyclopropanes the same precursor for the methylene unit was essential. Indeed, feeding experiments with **165** bearing a $^{13}$C label proved that the methylene carbons of all six cyclopropyl groups in **2c** are derived from the methyl group of **165**.

While it was evident that *S*-adenosylmethionine (**165**) was the $C_1$ donor, there are still some questions about the $C_1$ acceptor unit. Kuo et al. assumed a pathway in analogy to cyclopropane fatty acids: In these cases it was conclusively shown that the full-length fatty acid esterified to a phospholipid is essential to obtain cyclopropanated products.[207−209] Methylene addition occurs after completion of the acyl chain. On the basis of this information, the following hypothesis was proposed (Scheme 28):[2]

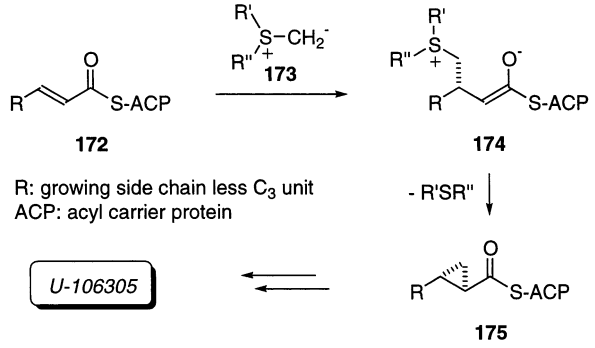
**Scheme 28**




From nine acetyl-CoA **166** units the $C_{18}$ chain was formed. After dehydration of **167**, the unsaturated acid **168** was formed. Next, a methyl group of *S*-adenosylmethionine (**165**) would be slowly transferred, yielding the carbocation intermediate **169**. Like for the formation of the cyclopropane ring from linear monoenes,[210−212] it was assumed that the next step is a fast but partially reversible[213] deprotonation to furnish **170**. Repeated cyclopropanation would eventually lead to the oligocyclopropane **171**. The origin of the isobutyl group and the stage at which the amine is introduced was not proved. However, the fact that no isotopic labeling with acetate (or with **165**) was observed indicated a different carbon source. Possibly isobutylamine was formed by decarboxylation of valine.

Sulfur ylides are well-known to add to α,β-unsaturated carbonyls in vitro to form cyclopropanes.[214] In addition, they were suggested to play a role in biotransformations.[212] On the basis of these facts, an alternative biosynthetic route was proposed by Barrett et al. (Scheme 29):[100] Incomplete reduction of the

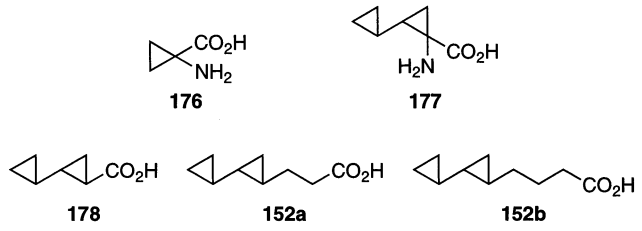
**Scheme 29**




growing polyketide chain could give rise to Michael acceptor **172**. Conjugate addition of the *S*-adenosylmethionine-derived ylide **173** to the polarized double bond of **172** would first give the intermediate **174**. A following ring closure of the enolate could yield the cyclopropane **175**. The enzyme responsible for the cyclopropanation could be part of the polyketide synthase complex.

## B. Physiological Properties

Despite the fact that the diverse biological activities of cyclopropane derivatives are well-documented,[215,216]




*Antimicrobal activity:* (MIC: minimum inhibitory concentration)

| entry | test organism | **178**, MIC | **152a**, MIC | **152b**, MIC |
|---|---|---|---|---|
| 1 | *E. coli* | - | - | - |
| 2 | *Pseudomonas sp.* | - | - | - |
| 3 | *Bacillus subtilis* | - | 10 mM | 20 mM |
| 4 | *Rhodococcus ruber* | - | 20 mM | 50 mM |
| 5 | *Schizosaccharomyces pompe* | 50 mM | 20 mM | 20 mM |
| 6 | *Kluyveromyce marxianium* | - | 50 mM | 50 mM |
| 7 | *Hansenula California* | - | 50 mM | 50 mM |
| 8 | *Saccharomyces cervisiae* | - | 20 mM | 50 mM |
| 9 | *Aspergillus nidulans* | - | 20 mM | 10 mM |
| 10 | *Aspergillus niger* | - | 5 mM | 5 mM |

**Figure 5.** (Adapted from ref 190. Copyright 2000 Wiley-VCH.)

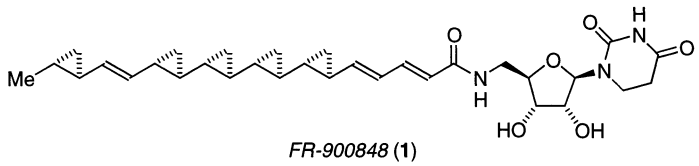
surprisingly little is known about the properties of oligocyclopropanes. An exception is the early interest in 1-amino-1-cyclopropanecarboxylic acid (**176**) and its derivatives (Figure 5). This stems from the fact that the amino acid is present in the tissue of many plants,[217,218] is biosynthesized from *S*-adenosylmethionine (**165**),[219,220] and is the immediate biosynthetic precursor of ethylene, regulating many aspects of plant growth.[221] Nonnatural 1-amino-1-cyclopropanecarboxylic acids were tested for their eventual biological activity, and among those also compound **177** was shown to be a good inhibitor of the ethylene biosynthesis (0.25−16 mM). The steric bulk of the additional cyclopropyl group of **177** accounted for the finding: This group makes it difficult to penetrate the active center of the enzyme. Instead, a 1,4-pentadiene, responsible for the suicide inhibition, is formed.[222−224] More recently, de Meijere et al. tested the antimicrobial spectrum of bicyclopropyl fatty acids **178** and **152a**+**b**.[190,193] Whereas the acid **178** hardly showed any antibiotic activity against any tested organism, bicyclopropanes **152a**+**b** have some activity against Gram-positive bacteria (entries 3 and 4) and showed a slightly increased inhibition of growth of filamentous fungi (entries 9 and 10). No growth inhibitory property was observed against Gram-negative bacteria (entries 1 and 2); the minimum inhibitory concentration for yeasts was high (entries 5−8). In view of the natural oligocyclopropanes **1** and **2**, whose physiological properties are undoubtedly influenced by their peculiar side chain, the investigation of some liquid crystalline derivatives of **178** and **152a**+**b** were very informative. Due to the decreased conformational flexibility of the bicyclopropane moiety, the new compounds have a higher tendency to be crystalline, while the dielectric and optical anisotropies mainly depended on their mesogenic substructures.[194] The findings were in good agreement with the observation that pathogenic mycobacteria (e.g. *Mycobacterium tuberculosis*) appear to have a raised phase transition of their membranes. Having a high proportion of bis-cyclopropanated fatty acids in their cell-wall, the cyclopropanation would seem to be responsible for the effect.[211,225,226]

The physiological properties of the antifungal antibiotic FR-900848 (**1**) were discussed in some detail.[1,82] The neutral substance decomposes at 198−201 °C, is soluble in dimethyl sulfoxide, slightly soluble in methanol, ethyl acetate, and chloroform, but is insoluble in water. The activity against bacteria was determined on nutrient agar and against yeasts and filamentous fungi on potato-glucose agar. The minimum inhibitory concentration was measured after incubation at 37 °C overnight (bacteria) or at 28 °C for 48−72 h (fungi and yeast), respectively. FR-900848 (**1**) shows potent, selective activity against filamentous fungi in concentrations of 0.05−0.5 $\mu$g/mL, suppressing the growth of *Aspergillius niger*, *Mucor rouxianus*, *Penicillium chrysogenum*, *Aureobasidium pullulans*, *Trichophyton* species, *Fusarium oxysporum*, and *Sclerotinia arachidis*. In contrast, it is essentially inactive against nonfilamentous fungi (e.g. *Candida albicans*) and Gram-positive and -negative bacteria (Figure 6). The therapeutic effect is distinct. Activity was not only observed in vitro but also in vivo. Since the 50% lethal dose of FR-900848 (**1**) for mice by intraperitoneal injection to mice was more than 1 g/kg, the compound can be classified as essentially nontoxic. It was proposed that this natural product could represent a significant new lead for the design of nucleoside antifungal agent against the major human pathogen *Aspergillus fumigatus*.[42]

Little is known about the second oligocyclopropyl-containing natural product U-106305 (**2**). The oligocyclopropane was identified and isolated during screening of the fermentation broth (producing culture, U11136) for potent inhibitors of the cholesteryl ester transfer protein (CETP) reaction (in vitro activity $IC_{50} = 25$ $\mu$M).[2] Since the CETP catalyzes the redistribution of cholesteryl esters from high-density lipoproteins to low-density lipoproteins (risk factor for coronary heart disease), an effective and safe CETP inhibitor could potentially be beneficial for patients with atherosclerosis and coronary heart disease.[227−229]

## C. Biodegradation

While detailed studies on the biosynthesis of the cyclopropane ring have been performed, less is known about its further metabolism. Cyclopropane fatty acids are metabolized by mammalian mitochondria, however, it is only the alkyl side chain that is degraded by the usual $\beta$-oxidation pathway. The cyclopropane unit remains unchanged.[200,202,230,231] This is not true for more primitive organisms, e.g. the fungus *Fusarium oxysporum* Schlectendahl, which were shown to cleave the three-membered ring oxidatively: Cyclopropanecarboxylic acid is converted to 4-hydroxybutyric acid.[232,233] Interestingly, more recently it was shown that the development of a tolerance of *Pseudomonas putida* to toluene and related toxic compounds is based on an increasing rigidity of the cell membrane. This short-term re-



*FR-900848* (**1**)

*Antimicrobal activity:*
(MIC: minimum inhibitory concentration)

| Test organism | **1**, MIC [μg/ml] |
|---|---|
| *Aspergillus niger* | 0.05 |
| *Mucor rouxianus* | 0.05 |
| *Aureobasidum pullulans* | 0.05 |
| *Penicillium chrysogenum* | 0.10 |
| *Trichophyton metagrophytes* | 0.20 |
| *Trichophyton asteroides* | 0.50 |
| *Trichophyton rubrum* | 0.50 |
| *Fusarium oxysporum* | 0.10 |
| *Sclerotinia arachidis* | 0.10 |
| *Candida albicans* | 100 |
| *Candida tropicalis* | 100 |
| *Candida guilliermondii* | 0.20 |
| *Cryptococcus albidus* | 100 |
| *Saccharomyces cervisiae* | 100 |
| *Staphylococcus aureus* 209 P | 100 |
| *Escheria coli* NIHJ | 100 |

*Therapeutic effect* on experimentally induced infection of *Trichophyton asteroides* FP594 in guinea pigs (6 skin specimens taken from each of the lesions were cultured on Sabouraud's agar for 7 days at 30 °C to determine viable organisms)

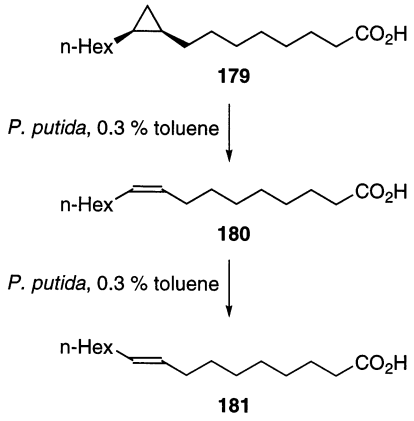
| Drug | Culture results | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| No treatment | | | 4/36 | 32/36 |
| Placebo | | | 4/36 | 32/36 |
| 0.5 % FR-900848 | 6/36 | 4/36 | 19/36 | 7/36 |
| 0.5 % Pyrrolnitrin | 2/36 | 10/36 | 8/36 | 16/36 |

Culture results (numbers of specimen with viable organisms per total numbers of specimen after 7-day culture):
0: no growth
1: growth on skin only
2: growth on the skin and slight on the surrounding agar
3: skin and agar completely covered

**Figure 6.**

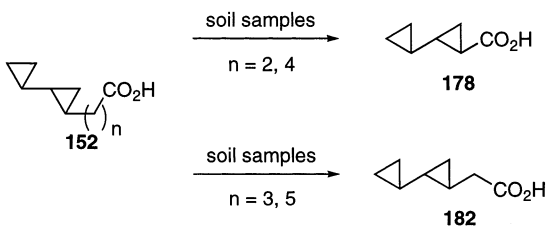
sponse is achieved by a rapid transformation of the cyclopropyl-containing fatty acid **179** to the *Z*-olefin **180** and subsequently to the *E*-isomer **181** (Scheme 30).[234] A similar effect at low concentrations (0.3% toluene) was observed for *p*-xylene and 1-octanol.

**Scheme 30**



Further investigations on the biodegradability of oligocyclopropyl-containing fatty acids revealed that bicyclopropanes **152** were also metabolized by the $\beta$-oxidation pathway (Scheme 31).[190,193] For this project bacterial enrichment cultures from soil samples were grown on media containing **152** as an additional carbon source. It was found that odd-numbered acids led to *trans*-bicyclopropanecarboxylic acid (**178**), whereas even-numbered acids furnished *trans*-bicyclopropaneacetic acid (**182**). Obviously, the bicyclopropyl unit remained untouched in all cases. Next there was an attempt to grow a variety of bacteria strains on media containing **152a** ($n = 2$), **152b** ($n = 3$), or **178** as one or even the sole carbon source.[190,193] While transformations with **152b** and **178** showed an increased growth in eight of 20 strains, only a slight growth was observed in the presence of **152a**. One strain of the genus *Rhodococcus ruber* P-IV-B-11[235] degraded all three compounds completely. In no case could a distinct degradation product be detected. These facts suggested that the *Rhodococcus* species had actually used the acids **152a**, **152b**, and **178** as a carbon source for growth. Reliable information about the metabolic pathway are not yet available.

**Scheme 31**



## IV. Concluding Remarks

The isolation of the two oligocyclopropyl-containg natural products FR-900848 (**1**) and U-106305 (**2**) stimulated a variety of new research projects especially around the selective synthesis of (oligo)cyclopropanes. Some remarkable work toward the elucidation of the relative and absolute configuration was reported that eventually culminated in several total syntheses. New synthetic methods were established. It is important to note that not only organic synthesis gained from these fascinating physiological active natural products, but also considerable progress in biological studies (on cyclopropanes) was achieved.

## V. Acknowledgments

I am especially grateful to a dedicated and enthusiastic group of young chemists: Dr. Joachim E. A.

Luithle, Dipl.-Chem. Andreas Witt, Dipl.-Chem. Thorsten Wilhelm, Dipl.-Chem. Erwin Hohn, and Dipl.-Chem. Niklas Schöne. Our projects have been generously supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Landesgraduierten-Stiftung Baden-Württemberg, and the Institut für Organische Chemie der Universität Stuttgart as well as the Bayer AG, Aventis Pharma Deutschland GmbH, Novartis AG, Boehringer Ingelheim KG, Degussa AG, Clariant GmbH, BASF AG, Roche Diagnostics GmbH, Amano Pharmaceutical Co., Ltd., and Meito Sangyo Co., Ltd. through general gifts of equipment, chemicals, and enzymes. I am indebted to all my academic teachers, in particular Prof. Dr. W. A. König, Prof. Dr. R. F. W. Jackson, and Prof. Dr. S. V. Ley.

## VI. References

(1) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748.
(2) 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.
(3) Bastiansen, O.; de Meijere, A. *Acta Chem. Scand.* **1966**, *20*, 516.
(4) Lüttke, W.; de Meijere, A.; Wolff, H.; Ludwig, H. *Angew. Chem.* **1966**, *78*, 141; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 123.
(5) Bastiansen, O.; de Meijere, A. *Angew. Chem.* **1966**, *78*, 142; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 124.
(6) Eraker, J.; Rømming, C. *Acta Chem. Scand.* **1967**, *21*, 2721.
(7) Stølevik, R.; Bakken, P. *J. Mol. Struct.* **1989**, *197*, 137.
(8) Schrumpf, G.; Süsse, P. *Chem. Ber.* **1972**, *105*, 3041.
(9) Wiberg, K. B.; Bartley, W. J. *J. Am. Chem. Soc.* **1960**, *82*, 6375.
(10) Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1982**, 2244.
(11) Slabey, V. A. *J. Am. Chem. Soc.* **1952**, *74*, 4928.
(12) Binns, T. D.; Brettle, R.; Cox, G. B. *J. Chem. Soc. (C)* **1968**, 584.
(13) Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D.; Kalinowski, H.-O. *Helv. Chim. Acta* **1982**, *65*, 137.
(14) O'Bannon, P. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 9244.
(15) Overberger, C. G.; Zangaro, R. E.; Winter, R. E. K.; Anselme, J.-P. *J. Org. Chem.* **1971**, *36*, 975.
(16) Müller, E.; Roser, O. *J. Prakt. Chem.* **1932**, *133*, 291.
(17) Dolgii, I. E.; Shapiro, E. A.; Nefedov, O. M. *Izv. Akad. Nauk SSSR Ser. Khim.* **1979**, *28*, 1282; *Chem. Abstr.* **1979**, *91*, 157317k.
(18) Armaroli, T.; Dell'Erba, C.; Gabellini, A.; Gasparrini, F.; Mugnoli, A.; Novi, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **2002**, 1284.
(19) Martelli, J.; Carrié, R. *Tetrahedron* **1978**, *34*, 1163.
(20) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715.
(21) Doering, W. v. E.; Roth, W. R. *Angew. Chem.* **1963**, *75*, 27.
(22) Schrumpf, G.; Lüttke, W. *Liebigs Ann. Chem.* **1969**, *730*, 100.
(23) Dehmlow, E. V. *Tetrahedron* **1972**, *28*, 175.
(24) Skattebøl, L. *J. Org. Chem.* **1964**, *29*, 2951.
(25) Seyferth, D.; Burlitch, J. M.; Minasz, R. J.; Mui, J. Y.-P.; Simmons, H. D., Jr.; Treiber, A. J. H.; Dowd, S. R. *J. Am. Chem. Soc.* **1965**, *87*, 4259.
(26) Orchin, M.; Herrick, E. C. *J. Org. Chem.* **1959**, *24*, 139.
(27) Khusid, A. K.; Kryshtal, G. V.; Kucherov, V. F.; Yanovskaya, L. A. *Tetrahedron Lett.* **1977**, 907.
(28) Khusid, A. K.; Kryshtal, G. V.; Kucherov, V. F.; Yanovskaya, L. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1977**, *26*, 2135; *Chem. Abstr.* **1978**, *88*, 22169.
(29) Kazimirchik, I. V.; Lukin, K. A.; Bebikh, G. F.; Zefirov, N. S. *Zh. Org. Khim.* **1983**, *19*, 2523; *Russ. J. Org. Chem.* **1984**, *19*, 2209.
(30) Schöllkopf, U.; Paust, J. *Chem. Ber.* **1965**, *98*, 2221.
(31) Buchert, M.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2723.
(32) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.
(33) Huang, H.; Platz, M. S. *Tetrahedron Lett.* **1996**, *37*, 8337.
(34) Platz, M. S.; Huang, H.; Ford, F.; Toscano, J. *Pure Appl. Chem.* **1997**, *69*, 803.
(35) Smith, L. I.; Rogier, E. R. *J. Am. Chem. Soc.* **1951**, *73*, 3840.
(36) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037.
(37) Marko, I. E.; Giard, T.; Sumida, S.; Gies, A. E. *Tetrahedron Lett.* **2002**, *43*, 2317.
(38) König, H.; Metzger, H.; Seelert, K. *Chem. Ber.* **1965**, *98*, 3712.
(39) Metzger, H.; Seelert, K. *Angew. Chem.* **1963**, *75*, 919.
(40) Horner, J. H.; Tanaka, N.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 10379.
(41) Barrett, A. G. M.; Doubleday, W. W.; Hamprecht, D.; Kasdorf, K.; Tustin, G. J. *Pure Appl. Chem.* **1997**, *69*, 383.
(42) Barrett, A. G. M.; Doubleday, W. W.; Hamprecht, D.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1997**, 1693.
(43) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
(44) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1783.
(45) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. *Tetrahedron* **1996**, *52*, 15325.
(46) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254.
(47) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447.
(48) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61.
(49) Armstrong, R. W.; Maurer, K. W. *Tetrahedron Lett.* **1995**, *36*, 357.
(50) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.
(51) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.
(52) Charette, A. B.; Juteau, H.; Lebel, H.; Deschênes, D. *Tetrahedron Lett.* **1996**, *37*, 7925.
(53) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.
(54) Charette, A. B.; Lebel, H. *Org. Synth.* **1998**, *76*, 86.
(55) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181.
(56) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1995**, *36*, 5495.
(57) Theberge, C. R.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1996**, *61*, 8792.
(58) Cebula, R. E. J.; Hanna, M. R.; Theberge, C. R.; Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **1996**, *37*, 8341.
(59) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(60) Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc., Chem. Commun.* **1995**, 355.
(61) Guha, P. C.; Sankaran, D. K. *Org. Synth. Collect. Vol. III* **1955**, 623.
(62) Naruta, Y.; Nagai, N.; Yokota, T.; Maruyama, K. *Chem. Lett.* **1986**, 1185.
(63) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J. *J. Org. Chem.* **1996**, *61*, 3280.
(64) Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1781.
(65) Barrett, A. G. M.; Kasdorf, K.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 649.
(66) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1989**, *45*, 3039.
(67) Hines, J. N.; Peagram, M. J.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2332.
(68) Teraji, T.; Moritani, I.; Tsuda, E.; Nishida, S. *J. Chem. Soc. (C)* **1971**, 3252.
(69) Lüttke, W.; de Meijere, A. *Angew. Chem.* **1966**, *78*, 544; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 512.
(70) Köbrich, G.; Merkel, D. *Angew. Chem.* **1970**, *82*, 257; *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 243.
(71) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(72) Davies, S. G.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1346.
(73) 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.
(74) Barrett, A. G. M.; Kasdorf, K.; Tustin, G. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1143.
(75) Barrett, A. G. M.; Kasdorf, K. *Chem. Commun.* **1996**, 325.
(76) Barrett, A. G. M.; Kasdorf, K. *J. Am. Chem. Soc.* **1996**, *118*, 11030.
(77) Clauss, R.; Hinz, W.; Hunter, R. *Synlett* **1997**, 57.
(78) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.
(79) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(80) Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413.
(81) Skaric, V.; Katalenic, D.; Sckaric, D.; Salaj, I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2091.
(82) Horikoshi, K.; Yoshida, M. (Fujisawa Pharmaceutical Co., Ltd., Japan), EP 286,330, Oct 12, 1988.
(83) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096.
(84) Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515.
(85) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851.
(86) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045.
(87) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(88) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815.
(89) Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982**, *1*, 667.
(90) Itoh, T.; Takagi, Y.; Tsukube, H. *J. Mol. Catal. B* **1997**, *3*, 259.

(91) Mitsukura, K.; Korekiyo, S.; Itoh, T. *Tetrahedron Lett.* **1999**, *40*, 5739.
(92) Itoh, T.; Emoto, S.; Kondo, M. *Tetrahedron* **1998**, *54*, 5225.
(93) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(94) Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **2000**, *41*, 8723.
(95) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427.
(96) Itoh, T.; Mitsukura, K.; Ishida, N.; Uneyama, K. *Org. Lett.* **2000**, *2*, 1431.
(97) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863.
(98) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327.
(99) McDonald, W. S.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 1215.
(100) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608.
(101) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(102) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(103) Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376.
(104) Rüchardt, C.; Eichler, S.; Panse, P. *Angew. Chem.* **1963**, *75*, 858.
(105) Bose, A. K.; Manhas, M. S.; Ramer, R. M. *J. Chem. Soc. (C)* **1969**, 2728.
(106) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1.
(107) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1.
(108) McDougal, P. G.; Rico, J. G.; Oh, Y.-L.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
(109) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.
(110) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.
(111) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.
(112) Landor, P. D.; Landor, S. R.; Odyek, O. *J. Chem. Soc., Perkin Trans. 1* **1977**, 93.
(113) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353.
(114) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
(115) Barrett, A. G. M.; Gross, T.; Hamprecht, D.; Ohkubo, M.; White, A. J. P.; Williams, D. J. *Synthesis* **1998**, 490.
(116) Barrett, A. G. M.; Hamprecht, D.; James, R. A.; Ohkubo, M.; Procopiou, P. A.; Toledo, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2001**, *66*, 2187.
(117) Wehle, D.; Fitjer, L. *Angew. Chem.* **1987**, *99*, 135; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 130.
(118) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(119) Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(120) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(121) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(122) Fürstner, A., Ed. *Alkene Metathesis in Organic Synthesis*; Springer-Verlag: Berlin, 1998.
(123) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
(124) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.
(125) Matteson, D. S.; Schaumberg, G. D. *J. Org. Chem.* **1966**, *31*, 726.
(126) Bubnov, Y. N.; Nesmeyanova, O. A.; Rudashevskaya, T. Y.; Mikhailov, B. M.; Kazansky, B. A. *Tetrahedron Lett.* **1971**, 2153.
(127) Bubnov, Y. N.; Grigoryan, M. S.; Mikhailov, B. M. *Zh. Obshch. Khim.* **1972**, *42*, 1738; *Chem. Abstr.* **1973**, *78*, 29869.
(128) Bubnov, Y. N.; Kazanskii, B. A.; Nesmeyanova, O. A.; Rudashevskaya, T. Y.; Mikhailov, B. M. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, *26*, 2545; *Chem. Abstr.* **1978**, *88*, 74419.
(129) Danheiser, R. L.; Savoca, A. C. *J. Org. Chem.* **1985**, *50*, 2401.
(130) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605.
(131) Fontani, P.; Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 4815.
(132) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986.
(133) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(134) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
(135) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893.
(136) Wang, X.-Z.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2663.
(137) Zhou, S.-M.; Yan, Y.-L.; Deng, M.-Z. *Synlett* **1998**, 198.
(138) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem.* **1998**, *110*, 3061; *Angew. Chem., Int. Ed.* **1998**, *37*, 2845.
(139) Ma, H.-r.; Wang, X.-h.; Deng, M.-z. *Synth. Commun.* **1999**, *29*, 2477.
(140) Chen, H.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1609.
(141) Chen, H.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 4444.
(142) Chen, H.; Deng, M.-Z. *Org. Lett.* **2000**, *2*, 1649.
(143) Yao, M.-L.; Deng, M.-Z. *New J. Chem.* **2000**, *24*, 425.
(144) Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 5034.
(145) Yao, M.-L.; Deng, M.-Z. *Heteroat. Chem.* **2000**, *11*, 380.
(146) Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, *41*, 9083.
(147) Yao, M.-L.; Deng, M.-Z. *Synthesis* **2000**, 1095.
(148) Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* **2000**, *41*, 3951.
(149) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809.
(150) Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977.
(151) Pietruszka, J.; Wilhelm, T.; Witt, A. *Synlett* **1999**, 1981.
(152) Pietruszka, J.; Witt, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293.
(153) Nakayama, K.; Rainier, J. D. *Tetrahedron* **1990**, *46*, 4165.
(154) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287.
(155) Luithle, J. E. A.; Pietruszka, J. *Liebigs Ann./Recueil* **1997**, 2297.
(156) Luithle, J. E. A.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651.
(157) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **2000**, *65*, 9194.
(158) Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, 2557.
(159) Luithle, J. E. A., Dissertation, Universität Stuttgart, 2001.
(160) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2215.
(161) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219.
(162) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.
(163) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390.
(164) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.
(165) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718.
(166) Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057.
(167) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257.
(168) Baertschi, S. W.; Brash, A. R.; Harris, T. M. *J. Am. Chem. Soc.* **1951**, *73*, 2509.
(169) Jarstfer, M. B.; Blagg, B. S. J.; Rogers, D. H.; Poulter, C. D. *J. Am. Chem. Soc.* **1996**, *118*, 13089.
(170) Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, *21*, 4835.
(171) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970.
(172) Nagasawa, T.; Onoguchi, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 1023.
(173) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739.
(174) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224.
(175) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31.
(176) White, J. D.; Jensen, M. S. *Synlett* **1996**, 31.
(177) Krief, A.; Provins, L. *Synlett* **1997**, 505.
(178) Hannessian, S.; Reinhold, U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8967.
(179) Hannessian, S.; Ninkovic, S.; Reinhold, U. *Tetrahedron Lett.* **1996**, *37*, 8971.
(180) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601.
(181) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964.
(182) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93.
(183) de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, 3809.
(184) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89.
(185) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem.* **1999**, *111*, 3682; *Angew. Chem., Int. Ed.* **1999**, *38*, 3474.
(186) von Seebach, M.; Kozhushkov, S. I.; Boese, R.; Benet-Buchholz, J.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Angew. Chem.* **2000**, *112*, 2617; *Angew. Chem., Int. Ed.* **2000**, *39*, 2495.
(187) Faust, R. *Angew. Chem.* **2001**, *113*, 2312; *Angew. Chem., Int. Ed.* **2001**, *40*, 2251.
(188) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502.
(189) de Meijere, A.; Kozhushkov, S. I.; Späth, T. *Org. Synth.* **2000**, *78*, 142.
(190) Löhr, S.; Jacobi, C.; Johann, A.; Gottschalk, G.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 2979.
(191) Löhr, S.; de Meijere, A. *Synlett* **2001**, 489.
(192) de Meijere, A.; Kozhushkov, S. I.; Zefirov, N. S. *Synthesis* **1993**, 681.
(193) Löhr, S., Dissertation, Universität Göttingen, 2000.
(194) Miyazawa, K.; Löhr, S.; de Meijere, A. *Mol. Cryst. Liq. Cryst.* **2002**, *373*, 83.
(195) von Seebach, M., Dissertation, Universität Göttingen, 2000.
(196) Borer, M.; Loosli, T.; Neuenschwander, M. *Chimia* **1991**, *45*, 382.
(197) Loosli, T.; Borer, M.; Kulakowska, I.; Minger, A.; Neuenschwander, M.; Engel, P. *Helv. Chim. Acta* **1995**, *78*, 1144.
(198) Borer, M.; Neuenschwander, M. *Helv. Chim. Acta* **1997**, *80*, 2486.
(199) Huwyler, R.; Li, X.; Bönzli, P.; Neuenschwander, M. *Helv. Chim. Acta* **1999**, *82*, 1242.
(200) Christie, W. W. *Top. Lipid Chem.* **1970**, *1*, 1.
(201) Grogan, D. W.; Cronan, J. E., Jr. *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 429.
(202) Thiele, O. W. *Lipide, Isoprenoide mit Steroiden*; Thieme: Stuttgart, 1979.

(203) Rawlings, B. J. *Nat. Prod. Rep.* **1998**, *15*, 275.
(204) Zalkin, H.; Law, J. H.; Goldfine, H. *J. Biol. Chem.* **1963**, *238*, 1242.
(205) Cronan, J. E., Jr.; Reed, R.; Taylor, F. R.; Jackson, M. B. *J. Bacteriol.* **1979**, *138*, 118.
(206) Taylor, F. R.; Cronan, J. E., Jr. *Biochemistry* **1979**, *18*, 3292.
(207) Thomas, P. J.; Law, J. H. *J. Biol. Chem.* **1966**, *241*, 5013.
(208) Cronan, J. E., Jr.; Nunn, W. D.; Batchelor, J. G. *Biochim. Biophys. Acta* **1974**, *348*, 63.
(209) Wang, A.-Y.; Grogan, D. W.; Cronan, J. E., Jr. *Biochemistry* **1992**, *31*, 11020.
(210) Lederer, E. *Quart. Rev.* **1969**, *23*, 453.
(211) Yuan, Y.; Barry, C. E., III. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 12828.
(212) Mann, J. *Secondary Metabolism*, 2nd ed.; Oxford University Press: Oxford, 1992; p 42.
(213) Buist, P. H.; MacLean, D. B. *Can. J. Chem.* **1982**, *60*, 371.
(214) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(215) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511.
(216) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1.
(217) Burroughs, L. F. *Nature (London)* **1957**, *179*, 360.
(218) Vähätalo, M.-L.; Virtanen, A. I. *Acta Chem. Scand.* **1957**, *11*, 741.
(219) Lieberman, M.; Kunishi, A.; Mapson, L. W.; Wardale, D. A. *Plant Physiol.* **1966**, *41*, 376.
(220) Boller, T.; Herner, R.; Kende, H. *Planta* **1979**, *145*, 293.
(221) Lieberman, M. *Annu. Rev. Plant Physiol.* **1979**, *30*, 533.
(222) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103.
(223) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem.* **1985**, *97*, 1074; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1044.
(224) Pirrung, M. C.; McGeehan, G. M. US Patent 4,851,035, 1986.
(225) George, K. M.; Yuan, Y.; Sherman, D. R.; Barry, C. E., III. *J. Biol. Chem.* **1995**, *270*, 27292.
(226) Yuan, Y.; Lee, R. E.; Besra, G. S.; Belisle, J. T.; Barry, C. E., III. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6630.
(227) Yalpani, M. *Chem. Ind.* **1996**, 85.
(228) Sikorski, J. A.; Glenn, K. C. *Annu. Rep. Med. Chem.* **2000**, *35*, 251.
(229) Shinkai, H. *Exp. Opin. Ther. Patents* **2001**, *11*, 739.
(230) Wood, R.; Reiser, R. *J. Am. Oil Chem. Soc.* **1965**, *42*, 315.
(231) Chung, A. E. *Biochim. Biophys. Acta* **1966**, *116*, 205.
(232) Schiller, J.; Chung, A. E. *J. Biol. Chem.* **1970**, *245*, 6553.
(233) Schiller, J. G.; Chung, A. E. *J. Biol. Chem.* **1970**, *245*, 5857.
(234) Ramos, J. L.; Duque, E.; Rodríguez-Hervas, J.-J.; Godoy, P.; Haïdour, A.; Reyes, F.; Fernández-Barrero, A. *J. Biol. Chem.* **1997**, *272*, 3887.
(235) Saeki, H., Dissertation, Universität Göttingen, 1998.

CR010027G