# On the Total Synthesis and Determination of the Absolute Configuration of Rishirilide B: Exploitation of Subtle Effects to Control the Sense of Cycloaddition of *o*-Quinodimethides

**Kana Yamamoto,[a] Martin F. Hentemann,[a, b] John G. Allen,[a, c] and Samuel J. Danishefsky*[a, d]**

**Abstract:** The total synthesis of racemic rishirilide B has been accomplished. The synthesis serves to define the relative relationships of its stereogenic centers. Also, starting with readily available chiral pool, *ent*-rishirilide B was synthesized, thereby demonstrating that natural configuration of rishirilide B. The defining step in our total synthesis is the facile cycloreversion of the bis(siloxy)-benzocyclobutane and the intermolecular *o*-quinodimethide Diels–Alder cycloaddition. We believe that the tight regiochemical guidance in this step arises from a meshing of the electron-donating effects of the symmetry-perturbing aromatic OTBS group of the *o*-quinodimethide diene with the reactivity differential of the dienophile (enedione), modulated by the hydroxyl group at the $\alpha$-position. The validity of the hypothesis of hydroxy-directed activation of its vicinal ketone function in the context of the enedione dienophile warrants further study. This type of activation may find broader applications in distinguishing reactivity profiles of key closely related functional groups in organic substrates.

**Keywords:** cycloaddition · fused-ring systems · quinodimethanes · rishirilide · total synthesis

## Introduction

The history of the project to be related herein goes back to a report describing the isolation of two new metabolites from *Streptomyces*, OFR-1056. The structure of the more oxidized A compound (**2**) was arrived at by a crystallographic determination. The formulation of the B compound, as being **1**, arose from spectroscopic data and from the presumption of biogenetic connectivity (**1** → **2**) between the two compounds.[1, 2] This assumption was particularly relied upon to suggest (but not prove) the stereochemistry of **1**.

From a structural standpoint, the rishirilides are of interest in that they present merged aromatic and alicyclic domains. While such arrangements need not be considered, per se, intimidating from the standpoint of modern day synthesis, they did prompt consideration of several issues. First, in the light of the potential sensitivity of the resident functionality, it seemed unlikely that the target systems would be assembled from late-stage, classical ring-forming, electrophilic aromatic substitution reactions. Hence, from the outset, one could discern potentially major advantages in fashioning the aromatic and alicyclic sectors, concurrently, in highly advanced forms. Moreover, the aromatic sectors ("naphtho" or "benzo") of both systems are desymmetrized by the presence of a phenolic function. Provision would be necessary to give appropriate guidance in fashioning the nonsymmetric naphthalene relative to the "cyclohexane" domain of **1**.

These considerations served to stimulate the thought that intermolecular cycloaddition reactions of *o*-quinodimethides might be of considerable value in enabling a convergent and concise total synthesis of the rishirilides. Indeed, as we have described elsewhere,[3] and will briefly summarize below, the cycloaddition chemistry was first proposed with the rishirilides well in mind. Happily, the key premises had been realized in important model demonstrations.[3b] However, application of the method to the rishirilide problem required, in the end, significant improvisations beyond the proposed

[a] Prof. Dr. S. J. Danishefsky, Dr. K. Yamamoto, Dr. M. F. Hentemann, Dr. J. G. Allen
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org

[b] Dr. M. F. Hentemann
Bayer Corporation West Haven, CT 06513 (USA)

[c] Dr. J. G. Allen
Eli Lilly and Company, Lilly Corporate Research Center
Indianapolis, IN 46285 (USA)

[d] Prof. Dr. S. J. Danishefsky
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY 10027 (USA)

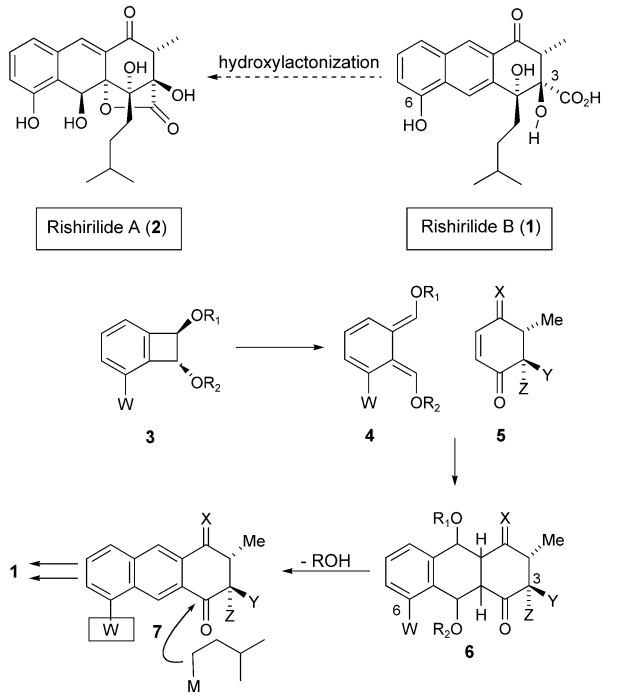


DOI: 10.1002/chem.200304931

cycloaddition reactions. The innovations required to reach these targets may have broader consequences than the successful attainment of the specific goal of providing a total synthesis of rishirilide B (vide infra).

The rishirilides also evoked interest from a biological perspective. Thus, compound **1** is a μM inhibitor of $\alpha$2-macroglobulin.[1] Since this complex protein, in turn, inhibits the action of the fibrinolytic enzyme plasmin,[4] the rishirilides could ultimately enhance plasmin-mediated fibrinolysis for degradation of insoluble fibrin *by suppression of plasmin inhibition*.[5] As such, it occurred to us that rishirilide structures might be of value as functional "small molecule" anti-clotting factors.[5]

Below, we document the first total synthesis of rishirilide B (**1**). We also relate studies wherein target system **1** was synthesized in an enantiomerically homogeneous form from defined precursors. In this way, we are now able to formulate the absolute configuration of rishirilide B. Parenthetically, we enlarge on the concept of providing guidance to intermolecular cycloadditions of *o*-quinodimethides through remote, seemingly subtle, regiocontrol elements.




Scheme 1. Structures of rishirilides and the general synthetic strategy.

## Results and Discussion

While our long-term goals included total syntheses of both **1** and **2**, we started with the former. The hope was that perhaps **2** would be accessible by oxidative cyclization[6] (formally hydroxylactonizaton) of **1** or of intermediates en route to **1**. Furthermore, compound **1**, while chemically less interesting, is actually more active against $\alpha^2$-macroglobulin than is **2**.

In broad terms, the plan for addressing the total synthesis of **1** envisioned cycloaddition of *o*-quinodimethide **4**, generated from the fragmentation of a 1,2-*trans*-disubstituted benzocyclobutene (cf. **3**), with a dienophile of the type **5**.[7] At this early conceptualization stage, we leave unspecified the nature of the R-protecting groups in **3** and **4**, the nature of the aryl-desymmetrizing function W, the optimal $\gamma$-substituents on the dienophile (see **5**) or the Y and Z group at the future C3 atom of the rishirilide. At some point, to be determined on site, the isoamyl group would be introduced at C4 by nucleophilic alkylation of a keto function (Scheme 1).

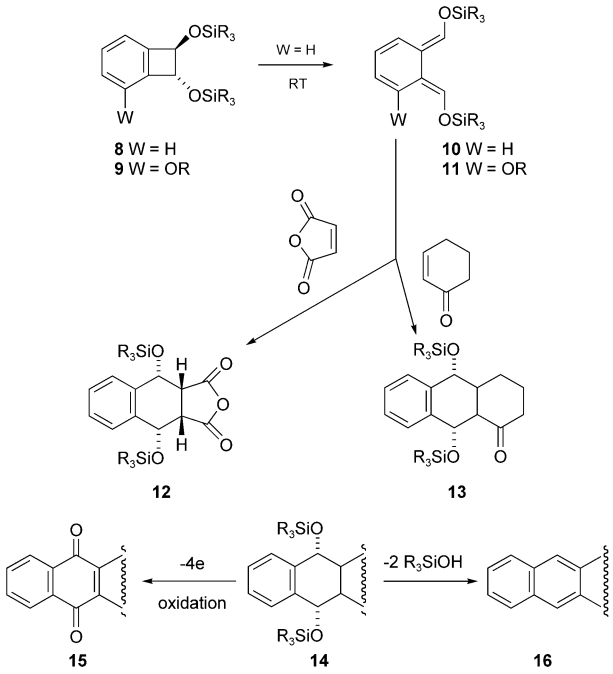
Even casual inspection of this skeletal plan invites significant questions at the level of intermediate **6** as to how the groups, for instance, W and Z destined to emerge in rishirilide B at C6 and C3, respectively, would be mutually coordinated. There was scant knowledge about the way in which preferences exerted by resident functions might be exploited to achieve tight control over the regiochemical sense of cycloaddition.

However, before addressing such relatively subtle matters, it was necessary to validate the central premise of the feasibility of the proposed cycloadditions. While Diels–Alder-like reactions of *o*-quinodimethides with dienophiles are well known, the usefulness of the reaction in the context of syntheses has been confined to intramolecular cases.[8, 9] Seeking substrates for intermolecular cases, we synthesized benzocyclobutenes of the types **8** and **9**. The thought was that the presence of vicinal siloxy functions on the benzocyclobutene would facilitate the cycloreversion step to generate the reactive *o*-quinodimethide valence isomers **10** and **11**, respectively. We have already described our key discoveries concerning this sort of cycloadditon.[3]

We found that benzocyclobutenes of the type **8** exhibit remarkable reactivity with a range of dienophiles. Actually, compounds in the parent series of this type (W = H) are thermochromic. The straw yellow color of these samples at room temperature fades at lower temperature ($\sim 0 \rightarrow 20\,^{\circ}C$). NMR analysis, even of the colored form, fails to detect any species corresponding to *o*-quinodimethides. Nonetheless, **8** reacts with a range of dienophiles at room temperature (cf. maleic anhydride) and upward (cf. cyclohexenone; ca 120 °C). As had been described earlier, the chemistry of the generic type of cycloadduct (cf. **14**) has been developed in several directions.[3a] The most widely studied modalities of progression from type **14** intermediates were 1) oxidation to naphthoquinone substructures and 2) twofold elimination to afford naphthalenes (see **15** and **16**, respectively, Scheme 2).

By contrast, unlike the situation which pertains with unsubstituted system **8**, the compounds bearing a *peri* substituent on the benzo portion of the benzocyclobutene (cf. **9**, W = OMe or $OSiR_3$) are much less reactive. Interestingly, compounds of the type **9** are colorless at room temperature. Although the cycloaddition products produced, and their apparent chemical behavior, are similar to the unsubstituted systems **8**, the much higher temperature required for reaction in the desymmetrizing *peri*-substituted cases (cf. **9**) is certainly disadvantageous. The retarding effect of the donating *peri*-oxy substituent may reflect attenuation of the key cycloreversion reaction arising from abutments in the open *o*-quinodimethide form with the *ortho* OR substituent. Alter-

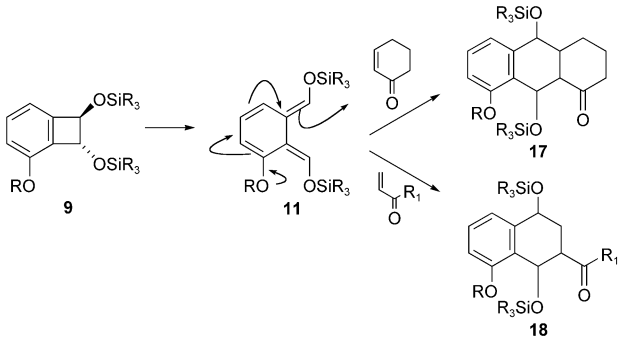
  




Scheme 2. Overview of *o*-quinodimethide Diels–Alder chemistry.

natively, it may reflect incremental steric hindrance in the cycloaddition step.

While the reactivity levels we had come to expect in the unsubstituted series had been badly degraded, the regiochemical patterns in the Diels–Alder reactions of compound **9** were gratifyingly in the predicted direction. Thus, a *peri*-methoxy or -siloxy group tends to direct the orientation in cycloadditions with unsymmetrical dienophiles such that the products arise from "initial" bond formation at the *meta*-, rather than the *ortho*-methide center.[2] Thus, the preferential formation of intermediates **17** and **18** are illustrative of the regiochemical preference governing the case of the *peri*-siloxy function (Scheme 3).



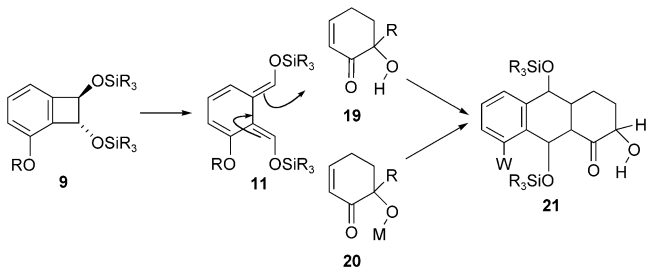

Scheme 3. The directing effect of *peri*-substituent in *o*-quinodimethide Diels–Alder reaction.

As is common in synthesis directed toward provocative natural products, methods initially devised to reach a particular structural type are apt to find application in other pursuits, seemingly unrelated to the initial target that inspired the initial study. So it was here. The concept of the oxygenated *o*-quinodimethides, initially used for the rishirilide problem, found excellent applications in a remarkably efficient total synthesis of idarubicinone and other goal structures.[3a] In this report, however, we return to the initial rishirilide target.

With the background provided above, the central problem in the rishirilide enterprise comes into sharper focus. First, to accommodate the oxygen required eventually at C6, we would necessarily be working with the *peri*-substituted and less reactive class of benzocyclobutenes (cf. **9**). Because of the need to accommodate functionality at C2, C3, and C4, particularly with the last two sites at quarternary carbon atoms, it seemed unlikely that we could incorporate a quinone-centered dienophile into our scheme. Rather, we would have to make do with a less reactive dienophile than a quinone (cf. **5**, $X = H_2$), in the context of diene **11**, for which the diminished reactivity in the required sense was certainly expected.

The issues, delineated above, invited solutions which utilized more maximally activated dienophiles. In principle, one might have supposed that the cycloaddition step could be facilitated by recourse to Lewis acid catalysis, in the tradition of the classical Diels–Alder reaction. However, the case at hand is novel in that a highly labile dienophile is being generated in situ. We started with serious concerns about whether Lewis acid catalysis would work well in such a setting. While the matter was not surveyed exhaustively, early attempts at catalysis in cycloreversion–cycloaddition sequences were not rewarding.

Rather, we came to favor an alternative approach that took in to account the functionality which must ulitmately be required to reach rishrilide. As already alluded to above, it was hoped that the isoamyl group could be introduced at a C4 ketone by "nucleophilic alkylation." We further entertained the possibility that the C3 functionality, present at the point of isoamylation, could direct the nucleophile to the required $\beta$-face of C4. Extending this reasoning one step further, we asked whether this future C3 hydroxy group might not play a pivotal role in *activating* the cyclohexenone carbonyl center and, in so doing, to enhance the directivity of the W function implied in structure **11** (see arrows in Scheme 3). This line of conjecture suggested evaluation of a dienophile of the type **19**, whereby a C3 hydroxyl group, vicinal to ketone, would activate the cyclohexenone, either through hydrogen binding or through targeted catalysis as in **20**. The question is posed implicitly in the proposed alignment, suggested by the ensemble of **11** + **19** (**20**), whereby we leave unresolved the question of whether dienophilic enhancement would arise from a local hydrogen bond or through a suitably interpolated, metal-based catalyst (Scheme 4).

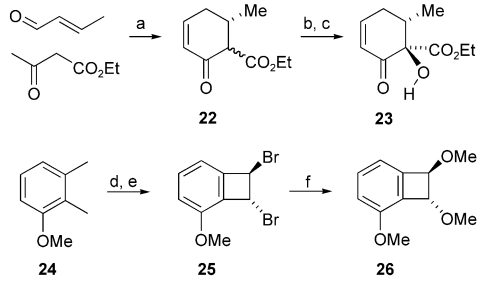



Scheme 4. The hydroxy-directing effect in *o*-quinodimethide Diels–Alder reaction.

We settled upon the specific dienophile **23** to launch the program. This compound contains an ester group at C3, which would correspond to the acid eventually required. The C2 methyl group would also be included, as would the critical C4 hydroxy group for purposes of activation (see discussion above). Missing would be only be the means for implementing the C1 keto group. Several possibilities (vide infra) were entertained to deal with this problem if the basic underlying assumptions of the plan were vindicated.

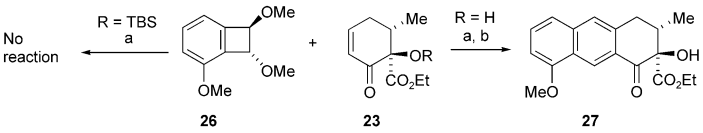
Indeed, compound **22**, a possible precursor of **23** was known, having been previously synthesized from the condensation of ethyl acetoacetate with crotonaldehyde.[10] The conversion of **22** to **23** was accomplished by Rubottom-like oxidation of its readily derived trimethylsilyl enol ether.[11] Seemingly, only one stereoisomer was produced. At this stage it was assumed, but not proven, that the $\alpha$-methyl group had shielded the $\alpha$-face of the molecule, and that the hydroxylation product of **22** was indeed that formulated as **23**.

In selecting our diene precursor for this opening study, we initially favored a situation whereby the W blocking group would be relatively stable, as would the two groups on the cyclobutene moiety ultimately to be eliminated (see prototype step **6** → **7** in Scheme 1). *O*-Methyl protection seemed preferable to *O*-silyl derivatization of the oxygen atoms to be eliminated in the formation of the naphthalene ring. Cleavage of the silyl group in the context of Diels–Alder adduct would expose free hydroxyl groups, which could manifest other forms of chemistry (oxidation, rearrangement) that might compete with the bis-elimination scheme we required (see **6** → **7**). Accordingly, our sequence started with 2,3-dimethylanisole (**24**), which was subjected to tetra side-chain bromination,[12] followed by reductive cyclization[13] with NaI to afford **25**. Subjection of the latter to the action of silver tetrafluoroborate in methanol[14] provided **26**, which was to serve as the precursor for the *o*-quinodimethide system. In this highly exploratory phase, we were willing to accept the fact that the desired **26** was actually the minor product in the synthesis relative to the predominant *cis* isomer (Scheme 5).




Scheme 5. Preparation of dienophile **23** and benzocylobutene **26**. a) NaH, EtOH; HCl(g), 36%; b) TMSCl, NaH, DMF; c) DMDO (0.066 M), 42%, 2 steps; d) NBS, AIBN, *hν*; e) NaI, DMF, 56%, 2 steps; f) $AgBF_4$, MeOH, 71% (*cis*:*trans* = 2.5:1).

In the event, reaction of *trans*-dimethoxybenzocyclobutene **26** and dienophile **23** occurred at 160 °C over 15 hours (Scheme 6). The crude cycloadduct was treated with camphorsulfonic acid in methanol under reflux, providing a compound (65% yield) corresponding to the loss of two

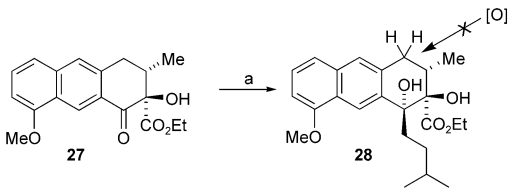



Scheme 6. Attempted Diels–Alder reaction with **26** and dienophile **23**. a) 160 °C, [$D_8$]toluene 15 h; b) CSA, MeOH, 65%, 2 steps.

methanol units from a formal 1:1 adduct. At this stage, the structure of this compound could not be asserted rigorously. However, since only one product appeared to have been produced, we assumed it to be the expected **27**, arising from the alignment contemplated in Scheme 4 (see Scheme 6). A control experiment with TBS-protected **23** supported the notion of the key role of the hydroxyl group in directing this Diels–Alder-like reaction. Benzocyclobutene **26** failed to react with the TBS derivative of **23** (R = TBS) (Scheme 6).

Assuming that the structure assignment is correct, we addressed the next question, that is, the introduction of the isoamyl group by nucleophilic alkylation of the C4 ketone. Given the hindered nature of the ketone in **27**, success could not have been anticipated in advance. We had envisioned a key role for the tertiary hydroxy group not only in directing an isoamyl ogranometallic agent to the otherwise hindered ketone, but also to its $\beta$-face, as required to reach rishirilide B. In the event, reaction of the presumed **27** (i.e., with isoamyl magnesium bromide (3.2 equiv)) afforded a 70% yield of a crystalline product (m.p. 128–129 °C), whose empirical formula corresponds to the addition of $C_5H_{12}$ to **27**. That this structure indeed corresponds to **28** was rigorously established by an X-ray determination.[3a]

It is well to reassert a scientific truism, that is, that the attainment of a desired result following a series of experiments does not necessarily establish the correctness of the underlying rationale that led to the study. This appreciated, it did seem that the strategic C3 alcohol function had seemingly provided activation and directivity in both the critical cycloaddition nucleophilic alkylation steps en route to the bis-protected 1-desoxyrishirilide B (**28**) (Scheme 7).




Scheme 7. Directed Grignard addition and unsuccessful oxidation at benzylic position. a) Isoamylmagnesium bromide (1.08 M), THF, 70%.

Clearly, the most efficient route to reach rishirilide B would be to use the synthesis described above to reach an advanced subgoal compound such as **28** and to go on from there to "accomplish functionalization" at C1. While the blocking groups of the starting materials en route to **28** had not been selected with a view to enabling late stage global deprotection, we nevertheless used this C1 desoxy compound as a model for exploring the proposed "end game" functionalizations. Unfortunately, the results of these forays were negative.

A variety of oxidation protocols, including the use of bromosuccinimide and DDQ, as well as chromium- and molybdenum-based oxidizing agents were unsuccessful. The failures either took the form of no reaction, or extensive decomposition leading to a multitude of uncharacterizable products.

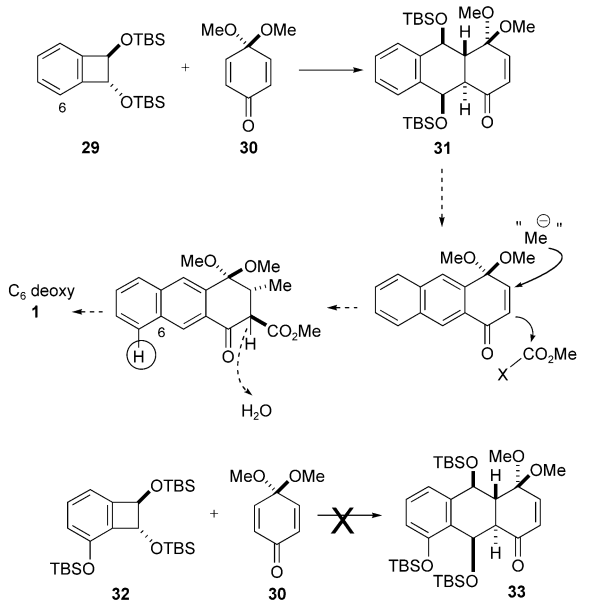
We then launched an exploratory investigation as to the integratability of *p*-quinonemonoketals (cf. **30**) with our *o*-quinodimethide cycloaddition chemistry. In pursuing this approach, we were mindful of the surprisingly poor performances of such quinoneketals in standard Diels–Alder reactions.[15] However, our hope was that systems of the type **9** would be sufficiently reactive to overcome this underemphasized and underappreciated problem. Also, we hoped to build into the *o*-quinodimethide precursor (cf. **9**), a protecting group that would allow for liberation of the eventual phenol.

Two considerations guided our abandonment of the bis-vicinal dimethoxy motif on the four-membered ring. First, as mentioned earlier, our synthetic route to the required dimethyl system gave the required *trans* compound only as the minor product. We had in the interim developed an acceptably stereoselective route to the vicinal *trans*-diol on the four-membered ring (by means of the diketone, as shown below, vide infra). Furthermore, we noted, in related model studies, that bis-siloxy substituents on the cyclobutene are more activating with respect to cycloaddtion chemistry than is the corresponding *trans* vicinal-dimethoxy pattern. Since we were inevitably working with the less reactive *peri*-substituted benzocyclobutene series, it was particularly important to mobilize all of the reactivity potential on the cyclobutene moiety.

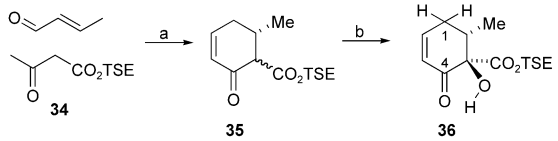
Indeed, it was found that use of the model benzocyclobutene **29** with quinoneketal **30** did seem to provide a 1:1 adduct formulated as **31**. The thought was that the bis-elimination product of an intermediate with useful functionality at "pre C1" might be subject to functionalization at carbons 2 and 3 (starting with conjugate addition at C2) and eventual deprotection at C1. Unfortunately, attempts to extend to the cycloaddition step to encompass a cycloaddition of benzocyclobutene **32** with **30** were unsuccessful (Scheme 8). Once again, we had experienced the retarding effects of a *peri* substituent, this time in the context of a relatively unreactive quinoneketal dienophile such as **30**.

At this stage, we returned to the previously developed hydroxyl-directing effect logic on the dienophile. Having failed to accomplish late stage functionalization after the tricyclic system (cf. **28** derived from **23**) was in place, the hope was to introduce the required handle to properly develop C1 before the cycloaddition. However, we also undertook to build a dienophile from which the eventual acid attached to C3 could in fact be liberated if all else were accomplished. Similar considerations pertained to the C6 phenolic protecting group.

With these considerations in mind, we initially targeted compound **35** as a prospective precursor to reach a dienophile of the required type. This compound was readily synthesized from condensation of $\beta$-trimethylsilylethyl acetoacetate (**34**)[16] with crotonaldehyde, by analogy with the chemistry used to prepare **22** (Scheme 9).

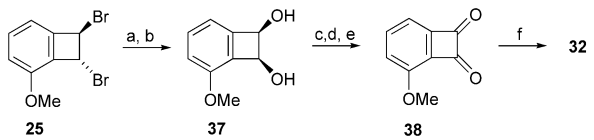



Scheme 8. Quinone-ketal Diels–Alder strategy.




Scheme 9. Preparation of dienophile **36**. Key: TSE = 2-(Trimethylsilyl)-ethyl. a) 1. TSEOH, $Et_2O$, Na; 2. HCl(g), 34%; b) 1. NaH, TBSOTf, DMF; 2. DMDO (0.061M), 76%, 2 steps.

As we focused on a quality total synthesis of our goal system **1**, we needed to work out a much more selective route to our *trans*-disubstituted benzocyclobutene. Earlier (see Scheme 5), we had described a nonselective route to **26** via **25**. We returned to **25**, which was now treated with silver acetate in aqueous acetic acid.[14] The crude product was subjected to the action of sodium methoxide affording diol **37**. This compound was oxidized by a Swern protocol to produce the benzocyclobutene 1,2-dione, **38**.[2, 3b] The *peri*-methoxy group was de-methylated through the action of 48% HBr, and the resultant phenol was silylated, as shown (Scheme 10).



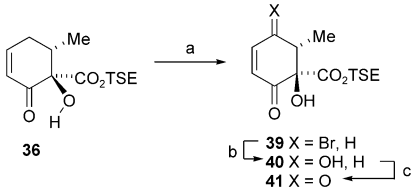

Scheme 10. Efficient synthesis of benzocyclobutane **32**. a) AgOAc, HOAc, $H_2O$, 93%; b) NaOMe, 55%, 2 steps; c) $(COCl)_2$, DMSO, $NEt_3$, 86%; d) 48% HBr, 93%; e) TBSOTf, $NEt_3$, 91%; f) $NaBH_4$ then TBSOTf, $NEt_3$, 83% (*cis*:*trans* = 1:6).

Fortunately, careful reduction of the $\alpha$-diketone with sodium borohydride gave rise primarily to a *trans*-diol with high stereoselection, presumably reflecting the stereochemical guidance provided by the mono-reduced species. Finally, bis-silylation of this diol afforded the silylated system **32**. It was envisioned that such compounds would serve as precur-

sors of the trisilyloxy *o*-quionodimethide entering into cycloaddition.

Given our failure to install C1 functionality at the stage of **28**, we focused on functionalizing **36** at an earlier stage, such that the handle for the eventual C1 ketone would already be present in the dieonophile. Fortunately, it proved possible to achieve $\psi$-functionalization of **36** through the action of *N*-bromosuccinimide (91% yield). Remarkably, neither the bromide **39** nor its derived alcohol **40** (vide infra) underwent cycloaddition with **32**. Surprisingly, these compounds bearing inductively activating groups proved to be less efficacious dienophiles than the C1 unsubstituted counterpart (**23**).

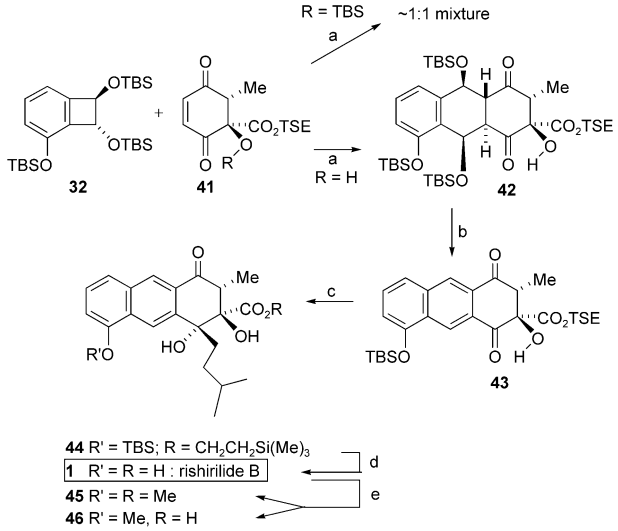
While the reasons for the diminished reactivity exhibited by **39** and **40** are still far from clear, we sought to build a dienophile that was sufficiently activated to undergo cycloaddition with the *peri*-substituted *o*-quinodimethide derived from **32**. The thought was to utilize the enedione **41**. Access to this compound was gained by means of solvolysis of bromide **39**, as shown, providing diol **40**, which upon Dess–Martin oxidation delivered our target dienophile **41** (Scheme 11).




Scheme 11. Allylic oxidation of dienophile **36**. Key: TSE = 2-(trimethylsilyl)ethyl; a) NBS, AIBN, $CCl_4$, 91%; b) $AgCO_3$, acetone, $H_2O$, 63%; c) Dess-Martin periodinane, $CH_2Cl_2$, 92%.

Needless to say, these were grounds for concern as we approached the critical cycloaddition on the basis of using dienophile **40**. It was hoped that the enedione network would manifest greater reactivity than the failed putative dienophiles **39** and **40**. However, even if this would be the case, a significant issue of regiochemistry in distinguishing between the directing effects of the two activating ketone groups would be faced. Our governing rationale was centered around the C3 tertiary alcohol. In earlier studies (see Scheme 6) it appeared that this hydroxyl group was activating the monoactivated dienophile to the point where it underwent cycloaddition with the *peri-o*-quinodimethide, derived from **26**, in a regiospecified manner. *In a similar way, it was hoped that this hydroxyl group would render its vicinal carbonyl group more "directing" than the other (future C1) keto group, lacking hydroxyl-centered incremental activation*. If this line of conjecture were sustained, the preferred orientation would be that required to reach rishirilide B.

A solution of compounds **32** and **41** in toluene was heated at 90° for 12 hours. NMR analysis indicated a relatively clean product. While the spectrum did not rigorously establish the structure of this crude to be **42**, (stereochemistry undetermined), this assignment was certainly not inconsistent, in any way, with the data. Treatment of the presumed **42** with camphorsulfonic acid in pyridine afforded a 72% yield of a compound formulated as **43**. Furthermore, once again a control experiment with TBS derivative of **41** supported the role of hydroxyl-directing in this reaction. Thus Diels–Alder reaction with benzocyclobutene **32** and TBS-protected **41** did occur, but afforded a near 1:1 mixture (Scheme 12).




Scheme 12. Final synthetic sequence to rishirilide B. Key: TSE = 2-(trimethylsilyl)ethyl. a) toluene, 90 °C 12 h; b) CSA, pyiridine, MeOH; 72% 2 steps; c) isoamylmagnesium bromide (0.73 M), THF; d) TAS-F, THF, 65%, 2 steps; e) $CH_2N_2$, $Et_2O$, MeOH, 43% **45**, 15% **46**, 31% **1**.

Following the precedent garnered in the des-oxy series (cf. **27** → **28**), the presumed **43** was subjected to the action of excess isoamyl magnesium bromide. This experiment resulted in mononucleophilic alkylation at C1, with the formation, seemingly, of a single 1:1 addition product formulated as **44**. At this stage, we could take advantage of the removable protecting groups we had installed at the phenolic and carboxylic centers. Indeed, treatment of **44** with TAS-F (TAS-F = tris(dimethylamino)sulfur(trimethylsilyl)difluoride) produced what we assumed to be (±)-rishirilde B (**1**; Scheme 12).

Based solely on our own data, we were not in a position to rigorously assert the stereochemistry at C2–C4 of our synthetic end product. Indeed, there was some temporary concern, since the $^{13}C$ NMR spectrum obtained from our own terminal product, presumed to be **1**, did not fully correspond to the previously published tabulated spectral data for the natural product. No sample of naturally derived **1** was available to allow for a direct material comparison, neither was there a spectrum in chart form for superposition level comparison.

Additionally temporary concern arose from another quarter. Thus, treatment of fully synthetic racemic **1** with diazomethane in diethyl ether/methanol led to the formation of the synthetic methyl ether/methyl ester, presumed to be **45**. Surprisingly, the high-field NMR spectrum (in chart readout) of our fully synthetic compound was drastically different from the spectrum (also in chart form) in studies directed to a total synthesis of rishirilide, ostensibly, the same compound reported by Hauser.[17] Barring a miss assignment, these spectra should have been superimposable. Once again, no reference

material was available for direct comparison with our synthetic product.

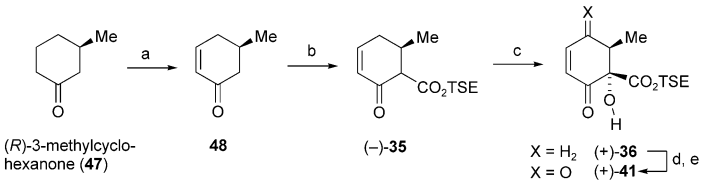
This state of confusion was much relieved, when we were able to obtain a chart spectrum of that corresponding to enantiopure compound prepared some time ago from the bis-methylation of naturally occurring rishirilide B (**1**). The high-field $^1$H NMR spectrum of our synthetic racemic **45** was identical with the spectrum received from Fukuyama. Hence, at this stage, we could be confident that our compound did correspond to naturally occurring rishirilide B, and that the claimed total synthesis product[17] is not rishirilide B methyl ether/methyl ester (i.e., **45**).

Having asserted this, it is important to take note that our total synthesis, per se, to this stage did not rigorously establish the actual relative configurational relationship in synthetic rishirilide B to be that which we supposed. Formally, there still remained the possibility that one or more errors had been incorporated into the structure assignment of **1**. Correspondingly, there could have been one or more faults in our assignments during the unfolding of our synthesis. Put differently, the fact that two compounds are identical does not establish the correctness of their structure assignments.

As it turned out, these concerns could also be laid to rest. Confidence was restored when our fully synthetic racemic **1** had been treated with diazomethane. In addition to the bis-methylation obtained in 33% yield (and assigned as **45**) as discussed above, a mono-methylation product (i.e., **46**), a methyl ester of phenol (m.p. 92–94°), was also obtained. A crystallographic determination of this compound clearly showed it to be **46** thus corroborating our assignments in full (relative) stereochemical detail.[3a] Hence, the structure of rishirilide B does indeed corresponds to **1**, and rishirlide B methyl ether/methyl ester is safely represented as **45**. Remaining to be sorted out is the structure and stereochemistry of the previously claimed total synthesis product,[17] which cannot be **45**.

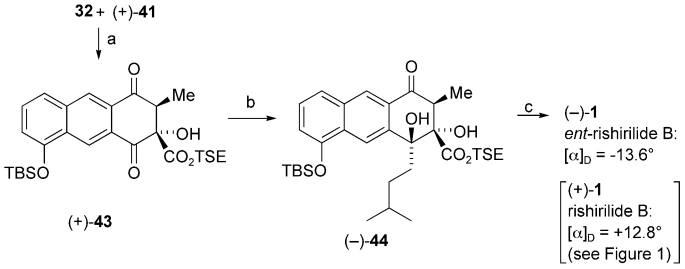
With the gross structure and relative stereochemistry of rishirilide B now secure, we addressed the question as to how chemical synthesis might also serve to establish its absolute configuration. This could be achieved by recourse to a starting material of established absolute stereochemistry and proceeding to reach the end target through steps that are stereochemically unambiguous. Given availability of the natural product, comparison between synthetic and naturally derived material would be optimal. Even in the absence of an actual reference sample, comparisons of the corresponding discerning properties of synthetic and naturally derived material could provide the answer. In the case at hand, there was no naturally derived rishirilide available for direct comparison. Fortunately, however, the measurement of the optical rotation of natural rishirilide B has been recorded.[1]

We focused on synthesizing an enantiomerically defined version of dienophile **41**. In this effort we revisited with modification, its synthesis in an enantio-defined context. Thus, commercially available (*R*)-methylcyclohexanone (**47**), derived in an unambiguous way from pulegone, was converted to the known enone **48** by oxidation with 2-iodoxybenzoic acid (IBX).[18] Subsequently, $\alpha'$C-acylation with 2-(trimethylsilyl)ethoxycarboxy cyanide[19] furnished (−)-**34**, which was carried through the five-step procedure described above to furnish (+)-**41** (Scheme 13).




Scheme 13. Preparation of enantiomerically pure enedione **41**. Key: TSE = 2-(trimetylsilyl)ethyl. a) 2-Iodoxybenzoic acid (IBX), 65 °C, DMSO, PhMe, 36%; b) *i*Pr$_2$NLi, 2-(trimethylsiyl)ethoxycarboxy cyanide, Et$_2$O, 39%; c) 1. NaH, TBSOTf; 2. DMDO, acetone, 28%, 2 steps; d) 1. AIBN, NBS, $CCl_4$; 2. $AgCO_3$, acetone, $H_2O$, 49%, 2 steps; e) Dess-Martin periodinane, $CH_2Cl_2$, 98%.

With dienophile (+)-**41** in hand, the completion of the synthesis was accomplished analogously to that used in (±)-**1**. Cycloadditon of **32** with (+)-**41** was followed by elimination, nucleophilic isoamylation, and deprotection (Scheme 14).




Scheme 14. Completion of the synthesis of *ent*-rishirilide B. Key: TSE = 2-(trimetylsilyl)ethyl a) 1. 90 °C, PhMe; 2. ppts, MeOH, 65%, 2 steps; b) *i*-pentylmagnesium bromide, THF, 73%; c) TAS-F, THF, 43%.

(−)-rishirilide B ($[\alpha]_D^{25} = -13.6$ ($c = 0.320$ in EtOH)) was thus produced in the laboratory. The literature reports pure rishirilide B to have an optical rotation of $[\alpha]_{DE}^{22} = +12.8$ ($c = 0.488$ in EtOH). Based on this enantiospecific synthesis, and assuming the correctness of the literature and polarographic measurement, the natural enantiomer is that shown in structure **1** (Scheme 1). Our fully synthetic optically pure structure is thus (−)-**1** corresponding to *ent*-rishirilide B.

## Conclusion

The total synthesis of racemic rishirilide B has been accomplished. The synthesis serves to define rigorously, for the first time, the relative relationships of its stereogenic centers. Also, starting with (*R*)-3-methylcyclohexanone *ent*-rishirilide B ((−)-**1**) was synthesized, thereby demonstrating that natural rishirilide B is as shown in structure (+)-**1** (Scheme 1).

The defining step in our total synthesis is the cycloreversion of **32** and cycloaddition of its *o*-quinodimethide form with **41**. We believe that the tight regiochemical guidance in this step arises from a meshing of the electron-donating effects of the symmetry-perturbing aromatic OTBS group, with the reactivity differential of the enedione modulated by the hydroxyl group adjacent to the ketone at the future C1. We note that

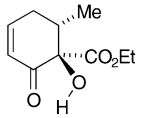
this hydroxy group, at the stage of compound **43**, also directs delivery of the isoamyl Grignard reagent to the required $\beta$-face of the C4 ketone.

The validity of the hypothesis of hydroxy-directed activation of its vicinal ketone function in the context of the enedione dienophile warrants further study. This type of activation may find broader applications in distinguishing reactivity profiles of key closely related functional groups in organic substrates.

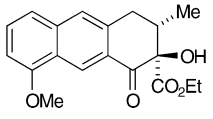
## Experimental Section

**General**: All moisture- or air-sensitive reactions were performed under an $N_2$ or Ar atmosphere in oven-dried glassware. Unless otherwise noted, extracts were dried with anhydrous $MgSO_4$ and concentrated using a rotary evaporator at aspirator pressure. All melting points were determined using an Electrothermal 9100 capillary melting point apparatus and are uncorrected. Solvents used in moisture-sensitive reactions were dried using standard methods. Reagents and starting materials were obtained from commercial suppliers, and used without further purification unless otherwise indicated. Flash chromatography was performed according to the methods of Still, with silica gel (230–400 mesh) obtained from EM science as the stationary phase. The term "deactivated $SiO_2$" refers to silica gel that is pre-treated with 1% $NEt_3$/hexanes for more than 30 min and washed with hexanes prior to use. Purity of isolated compounds was assessed based on examination of the $^1$H NMR spectroscopy and corresponding mass spectral data. IR spectra were recorded on Perkin–Elmer 1600 series FTIR spectrometer from thin films on NaCl plates. $^1$H NMR spectra were obtained with Bruker spectrometers at 400 or 500 MHz. $^{13}$C spectra were obtained with Bruker instruments at 100 or 125 MHz. Spectra chemical shifts were calibrated to the residual protio solvent resonance ($CDCl_3$, $^1$H: $\delta = 7.26$ ppm; $^{13}$C: $\delta = 77.0$ ppm). Low-resolution mass spectra were determined with a PESciex Ap 130 spectrometer. High-resolution mass spectra were determined by the University of California, Riverside MS Facility, Riverside, CA 92521.

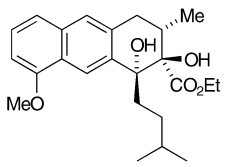
**Cyclohexenone (23)**: NaH (35 mg, 60%, 1.47 mmol) was washed with pentane and taken up in DMF (4 mL). 2-Carboxyethyl-3-methyl-cyclohex-5-en-1-one[11] (0.22 g, 1.23 mmol) was dissolved in DMF (4 mL) and transfered through a cannula at 0 °C into the NaH suspension. After 20 min the mixture was cooled to −78 °C, and TBSCl (0.22 g, 1.47 mmol) was added in DMF (1 mL) through a cannula. After 20 min the mixture was poured into pentane, washed with water and $NaCl_{(aq)}$, dried ($MgSO_4$), and evaporated. The residue was taken up in $CH_2Cl_2$ (10 mL) and cooled to −78 °C and dimethyldioxirane (prepared according to the standard procedure[20] from OXONE™, but without contact with the drying agent: 32 mL, 0.063 M in acetone, 2 mmol) was added dropwise over 20 min. After warming to room temperature over 4 h, most of the solvent was evaporated, and the concentrate was partitioned between $Et_2O$ and $NaCl_{(aq)}$. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (9:1 → 4:1 hexanes/EtOAc) to give pure **23** as a colorless oil (0.22 g, 78%): IR (film): $\tilde{\nu} =$ 3484, 2982, 2934, 1726, 1679, 1461 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.11–7.00 (m, 1H), 6.13 (dd, $J = 2.92$, 10.23 Hz, 1H), 4.26–4.15 (m, 2H), 4.14 (s, 1H), 2.65–2.57 (m, 1H), 2.50–2.40 (m, 1H), 2.36–2.28 (m, 1H), 1.25 (t, $J = 7.02$ Hz, 3H), 1.14 ppm (d, $J = 6.73$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 195.68$, 169.06, 152.91, 126.52, 80.92, 62.01, 38.79, 33.03, 15.26, 14.06 ppm; MS: $m/z$: 221 [$C_{10}H_{14}O_4Na^+$].



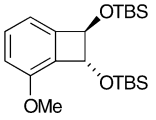

**Diels–Alder reaction and aromatization (27)**: The enone **23** (0.38 g, 1.90 mmol) and benzocyclobutene **26** (0.37 g, 1.90 mmol) were dissolved in [$D_8$]toluene (1 mL) and heated at 160 °C for 15 h in a sealed tube. The solvent was evaporated, the residue was dissolved in MeOH (10 mL), and CSA (10 mg, 43 μmol) was added. After heating the mixture at reflux for 4 h, the solvent was evaporated and the residue was purified by column chromatography (9:1 → 4:1 → 2:1 hexanes/EtOAc) to give pure **27** as a colorless oil (0.41 g, 65%). IR (film): $\nu = 3472$, 2933, 1744, 1682, 1624, 1463, 1240 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.05 (s, 1H), 8.60 (s, 1H), 7.47 (dd, $J = 7.92$ Hz, 1H), 7.33 (d, $J = 8.30$ Hz, 1H), 6.75 (d, $J = 7.65$ Hz, 1H), 4.38 (s, 1H), 4.20–4.05 (m, 2H), 3.99 (s, 3H), 3.30 (dd, $J = 13.67$, 16.92 Hz, 1H), 3.09 (dd, $J = 5.05$, 16.89 Hz, 1H), 2.51 (dt, $J = 5.51$ Hz, 1H), 1.27 (d, $J = 6.68$ Hz, 1H), 1.12 ppm (d, $J = 7.07$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 195.73$, 169.42, 157.15, 138.69, 137.36, 129.80, 127.52, 126.26, 125.25, 124.20, 119.22, 103.70, 81.56, 61.94, 55.54, 39.12, 34.30, 15.90, 14.06 ppm; HRMS (FAB+) calcd for $C_{19}H_{20}O_5$: 328.1311 [$M^+$]; found: 328.1310.




**Isoamyl magnesium bromide addition (28)**: The anthracene **27** (100 mg, 0.305 mmol) was dissolved in THF (3 mL) and isoamyl magnesium bromide (1.08 M $Et_2O$, 0.91 mL, 0.91 mmol) was added dropwise over 2 h. The mixture was partitioned between $Et_2O$ and sat. $NaCl_{(aq)}$, 1N HCl, and sat. $NaHCO_{3(aq)}$, and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (9:1 → 4:1 hexanes/EtOAc) to give the protected core **28** as a white solid (85 mg, 70%). M.p. 128–129 °C (needles from $Et_2O$-hexanes); IR (film): $\nu = 3488$, 2954, 2868, 1715, 1689, 1574, 1462, 1246 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (s, 1H), 7.41 (s, 1H), 7.27–7.23 (m, 2H), 6.90–6.60 (m, 1H), 4.02 (s, 1H), 4.00–3.75 (m, 2H), 3.93 (s, 3H), 3.31 (dd, $J = 8.50$, 17.91 Hz, 1H), 2.82 (dd, $J = 10.22$, 17.89 Hz, 1H), 2.60–2.40 (m, 1H), 2.31 (brs, 1H), 2.08 (dt, $J = 3.80$, 13.70 Hz, 1H), 1.65–1.50 (m, 1H), 1.30–1.20 (m, 2H), 1.02 (d, $J = 6.71$ Hz, 3H), 0.95–0.76 (m, 1H), 0.86 (d, $J = 6.59$ Hz, 3H), 0.74 (d, $J = 6.24$ Hz, 3H), 0.70–0.65 ppm (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 197.37$, 173.47, 151.68, 138.32, 133.30, 129.80, 127.85, 126.57, 122.75, 120.12, 115.39, 83.85, 78.10, 65.13, 48.26, 35.71, 31.16, 28.29, 25.84, 22.74, 22.43, 18.41, 16.67, 10.04, −1.91, −4.12, −4.39; MS: $m/z$: 423 [$C_{24}H_{32}O_5Na^+$].




***trans*-Bis(*tert*-butyldimethlsilyloxy)-3-methoxybenzocyclobutene**: Dimethylanisole tetrabromide[12] (33 g, 60 mmol) and NaI (36 g, 239 mmol) were heated together in DMF (240 mL) at 80 °C for 12 h.[13] The black mixture was diluted with sat. $NaCl_{(aq)}$ (250 mL) and extracted with pentane (3 × 500 mL). The pentane extracts were dried ($MgSO_4$) and evaporated, and the residue was passed through a column of silica gel (95:5 hexanes/EtOAc) to give pure dibromide (8.5 g, 53%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (dd, $J = 7.97$ Hz, 1H), 6.83 (d, $J = 8.46$ Hz, 1H), 6.77 (d, $J =$ 7.42 Hz), 5.49 (s, 1H), 5.41 (s, 1H), 3.56 ppm (s, 3H).



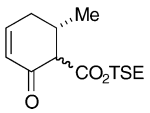

The dibromide (8.5 g, 32 mmol) was dissolved in acetic acid (158 mL) and water (6.3 mL), and silver acetate (11.6 g, 70 mmol) was added. The mixture was then heated (90 °C) 16 h in the dark[14] and then cooled in an ice bath; sat. $NaCl_{(aq)}$ (100 mL) was added then added. The precipitate was removed by filtration through Celite, and the filtrate was partitioned between $CH_2Cl_2$ and sat. $NaCl_{(aq)}$, neutralized ($NaHCO_3$), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (200 mL) and NaOMe (25% in MeOH, 0.5 mL) was added at 0 °C.[14] After 5 h, the mixture was partitioned between $Et_2O$ and 1N $NH_4Cl$, the organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by recrystallization ($CH_2Cl_2$/EtOAc/hexanes) to give *cis*-diol (2.9 g, 55%).

Methyl sulfoxide (5.5 mL, 77.4 mmol) was carefully added to oxalyl chloride (19.4 mL, 38.7 mmol) at −78 °C in $CH_2Cl_2$ (30 mL). The *cis*-diol (2.9 g, 17.6 mmol) was dried by azeotropic distillation with benzene and cannulated into the oxalyl chloride solution in $CH_2Cl_2$ (60 mL), followed by $Et_3N$ (24.5 mL, 176 mmol) added in three portions. The mixture was stirred for 1 h and then washed with 1N HCl (3 × 100 mL) and $NaHCO_3$ (2 × 100 mL), the organic extracts were dried ($MgSO_4$) and evaporated, and the residue recrystallized (EtOAc/hexanes) to give pure 3-methoxybenzocyclobutenedione (2.5 g, 86%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (dd, $J = 7.81$ Hz, 1H), 7.58 (d, $J = 7.28$ Hz, 1H), 7.13 (d, $J = 7.97$ Hz), 4.24 (s, 1H), 5.41 (s, 1H), 3.56 ppm (s, 3H).

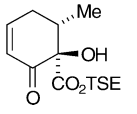
3-Methoxybenzocyclobutenedione (200 mg, 1.23 mmol) was dissolved in methanol (10 mL) and cooled to 0 °C, and $NaBH_4$ (33 mg, 0.87 mmol) was added. After 1 h, the solvent was removed at 0 °C, the residue was passed through a plug of silica with cold EtOAc, and the filtrate was concentrated. The residue was dissolved with $CH_2Cl_2$ (10 mL), the mixture cooled to −78 °C, and TBSOTf (1.13 mL, 4.92 mmol) and $Et_3N$ (0.68 mL, 4.92 mmol) were added. After 2 h, methanol (1 mL) was added. The organic solution was washed with $NH_4Cl_{(aq)}$ and $NaCl_{(aq)}$, dried ($MgSO_4$), and evaporated. Column chromatography (hexanes → hexanes/EtOAc 95:5) gave the pure *trans* compound as a colorless oil (338 mg, 70 %). FTIR (film): $\nu = 2927$, 2855, 1606, 1584, 1482 $cm^{-1}$; $^1H$ NMR (400 MHz, [D$_8$]toluene): $\delta = 7.24$ (dd, $J = 7.70$ Hz, 1H), 6.95 (d, $J = 7.17$ Hz, 1H), 6.87 (d, $J = 8.25$ Hz, 1H), 5.18 (s, 1H), 5.09 (s, 1H), 3.78 (s, 3H), 1.15 (s, 9H), 1.11 (s, 9H), 0.38 (s, 3H), 0.32 (s, 3H), 0.30 (s, 3H), 0.26 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta =$ 155.6, 145.9, 131.0, 127.6, 115.2, 115.1, 79.3, 79.0, 56.9, 25.8, 18.0, −3.9, −4.5, −4.7, −5.1 ppm; HRMS ($NH_3$/CI): calcd for $C_{27}H_{43}O_5Si_2$: 394.2359 [$M^+$]; found: 394.2346.

**Crotonaldehyde condensation (35)**:[11] 2-(Trimethylsilyl)ethyl acetoacetate[16] (5 g, 24.8 mmol), 2-(trimethylsilyl)ethanol (7 mL, 49.6 mmol), crotonaldehyde (2 mL, 24.8 mmol) were dissolved in $Et_2O$ (120 mL) and cooled to 0 °C. Sodium (25 mg) was added and the mixture was stirred for 12 h. Hydrogen chloride was bubbled through the solution for 5 min at 0 °C and left to stir for 4 h. The solvent was evaporated and the residue was purified by column chromatography (9:1 → 4:1 hexanes/EtOAc) to give pure **35** as a colorless oil (2.1 g, 34 %); IR (film): $\nu =$ 2955, 2898, 1738, 1680, 1249, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta =$ 7.00–6.90 (m, 1H), 6.03 (ddd, $J = 0.93$, 2.57, 10.17 Hz, 1H), 4.25 (dd, $J =$ 8.17 Hz, 2H), 3.06 (d, $J = 11.65$ Hz, 1H), 2.50–2.45 (m, 2H), 2.15–2.05 (m, 1H), 1.04 (d, $J = 9.96$ Hz, 3H), 1.05–0.98 (m, 2H), 0.01 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 194.57$, 170.06, 149.68, 128.79, 63.36, 61.75, 33.07, 32.79, 19.77, 17.28, −1.55 ppm; MS: $m/z$: 277 [$C_{13}H_{22}O_3SiNa^+$].



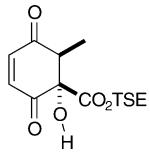

**6-(Trimethylsilylcarbetoxy)-5-(*R*)-methylcyclohexenone ((−)-35)**: This compound was prepared based on the literature procedure.[21] *n*BuLi (21 mL, 31 mmol) was added to a cold (0 °C) solution of *i*$Pr_2NH$ (4.7 mL, 3.4 g, 34 mmol) in $Et_2O$ (110 mL), and the mixture was stirred for 10 min. The resulting pale yellow solution was cooled to −78 °C, and enone **48** (5.2 g, 28 mmol) was added over 10 min, followed by 2-(trimethylsilyl)-ethoxycarboxy cyanide (7.2 g, 80 % purity, 34 mmol) over 30 min with a syringe pump. After 30 min of stirring, water (200 mL) was added, and the aqueous layer was extracted with $Et_2O$ (3 × 80 mL), combined and concentrated. The residue was purified by chromatography with silica gel (1:19 → 1:9 hexanes/EtOAc) to give pure (−)-**35** as a clear oil (2.4 g, 9.5 mmol, 34 %). $[\alpha]_D^{25} = -59.71$ ($c = 2.76$ in $CHCl_3$); MS: $m/z$: 277 [$C_{13}H_{22}O_3SiNa^+$].

**Hydroxy enone (36)**: NaH (0.43 g, 60 %, 10.9 mmol) was washed with pentane and taken up in DMF (20 mL). Enone **35** (2.30 g, 9.06 mmol) was dissolved in DMF (10 mL) and transferred with a cannula at 0 °C into the NaH suspension. After 20 min the mixture was cooled to −78 °C, and TBSOTf (2.50 mL, 10.9 mmol) was added. After 20 min the mixture was poured into pentane; then this mixture was washed with water and $NaCl_{(aq)}$, dried ($MgSO_4$), and evaporated. The residue was taken up in acetone (25 mL) and cooled to −78 °C and dimethyldioxirane (prepared according to the standard procedure,[20] but without contact with drying agent: 148 mL, 0.61 M in acetone, 90 mmol) was added dropwise over 20 min. After warming to room temperature over 4 h, the mixture was concentrated and the residue was partitioned between $Et_2O$ and $NaCl_{(aq)}$, the organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (9:1 → 4:1 hexanes/EtOAc) to give pure **36** as a colorless oil (1.86 g, 76 %). IR (film): $\nu = 3484$, 2955, 2899, 1735, 1684, 1250, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.10–7.00$ (m, 1H), 6.12 (ddd, $J = 2.16$, 9.50 Hz, 1H), 4.23–4.15 (m, 2H), 4.14 (s, 1H), 2.65–2.55 (m, 1H), 2.50–2.40 (m, 1H), 2.36–2.28 (m, 1H), 1.13 (d, $J = 6.71$ Hz, 3H), 1.0–0.94 (m, 2H), 0.00 ppm (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 195.8$, 169.25, 152.98, 126.56, 80.96, 64.57, 38.86, 33.08, 17.52, 15.31, −1.63 ppm; HRMS (DCI/$NH_3$) calcd for $C_{13}H_{26}NO_4Si$: 288.1631 [$M^+$+$NH_3$]; found: 288.1638.




**Hydroxy enone ((+)-36)**: This compound was prepared in a similar manner as (±)-**36**: $[\alpha]_D^{25} = +22.74$ ($c = 0.73$, $CHCl_3$); HRMS (DCI/$NH_3$) calcd for $C_{13}H_{26}NO_4Si$: 288.1631 [$M^+$+$NH_3$]; found: 288.1634.

**Hydroxy enedione (41)**: A solution of **36** (0.54 g, 2.0 mmol), NBS (0.39 g, 2.2 mmol), AIBN (16 mg, 0.1 mmol) in $CCl_4$ (20 mL) was degassed with Ar and then heated at reflux for 1 h. The mixture was cooled, pentane (50 mL) was added and filtered through Celite to remove succinimide. The filtrate was evaporated and the reside was purified by column chromatography (9:1 → 4:1 hexanes/EtOAc) to give pure γ-bromide **39** as a white solid (0.64 g, 91 %). IR (film): $\nu = 3475$, 2953, 2898, 1741, 1725, 1692, 1250, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.11$ (dd, $J =$ 2.35, 10.24 Hz, 1H), 6.02 (dd, $J = 2.10$, 10.14 Hz, 1H), 5.00 (ddd, $J = 2.13$, 9.42 Hz, 1H), 4.22 (s, 1H), 4.20–4.14 (m, 2H), 2.60–2.52 (m, 1H), 1.30 (d, $J = 6.68$ Hz, 3H), 1.0–0.91 (m, 2H), −0.02 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 193.99$, 168.44, 152.06, 125.04, 81.47, 65.19, 50.28, 48.33, 17.35, 13.48, −1.69; HRMS (DCI/$NH_3$) calcd for $C_{13}H_{25}NO_4SiBr$: 366.0736 [$M^+$+$NH_3$]; found: 366.0721.

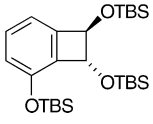



The bromide **39** (0.64 g, 1.82 mmol) was dissolved in acetone/water (8:1, 36 mL), $AgCO_3$ (5 g, 18.2 mmol) was added, and the mixture stirred in the dark for 24 h. The mixture was cooled to 0 °C, $NaCl_{(aq)}$ (20 mL) was added, and the precipitate was removed by filtration through Celite. The filtrate was concentrated to ca. 25 mL and partitioned between $CH_2Cl_2$ and $NaCl_{(aq)}$. The organic layer was dried ($MgSO_4$) and evaporated, and the reside was purified by column chromatography (4:1 hexanes/EtOAc) to give pure γ-alcohol as a white solid (0.33 g, 63 %). M.p. 107.4–107.8 °C (needles from hexanes/EtOAc); IR (film): $\nu = 3484$, 2952, 2906, 1701, 1682, 1254, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.12$ (dd, $J = 4.91$, 10.11 Hz, 1H), 6.13 (d, $J = 10.30$ Hz, 1H), 4.40 (d, $J = 11.82$ Hz, 1H), 4.30–4.18 (m, 2H), 4.16 (s, 1H), 2.37 (dq, $J = 7.03$, 12.99 Hz, 1H), 1.24 (d, $J = 7.08$ Hz, 3H), 1.05–0.95 (m, 2H), 0.02 ppm (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 194.98$, 171.67, 152.00, 124.94, 81.35, 66.15, 40.73, 17.22, 11.20, −1.62 ppm; HRMS (DCI/$NH_3$) calcd for $C_{13}H_{26}NO_5Si$: 304.1580 [$M^+$+$NH_3$]; found: 304.1584.

The alcohol (0.10 g, 0.35 mmol) was dissolved in $CH_2Cl_2$ (10 mL) at 0 °C, Dess–Martin reagent (0.44 g, 1.05 mmol) was added in three portions, and the mixture stirred in the dark for 6 h. The mixture was partitioned between $CH_2Cl_2$ and $Na_2S_2O_3/NaHCO_3$, the organic layer was dried ($MgSO_4$) and evaporated, and the reside was purified by column chromatography (4:1 hexanes/EtOAc) to give pure **29** as a white solid (91 mg, 92 %). M.p. 108.5–108.8 °C (needles from hexanes/EtOAc); IR (film): $\nu = 3464$, 2952, 2896, 1728, 1728, 1690, 1251, 839 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, $J = 10.33$ Hz, 1H), 6.80 (d, $J = 10.35$ Hz, 1H), 4.28 (s, 1H), 4.23–4.12 (m, 2H), 3.01 (q, $J = 6.51$ Hz, 1H), 1.25 (d, $J = 6.49$ Hz, 3H), 1.00–0.85 (m, 2H), −0.02 ppm (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 195.12$, 194.23, 167.84, 144.35, 136.08, 84.38, 66.26, 51.81, 17.34, 8.63, 6.12, −1.69 ppm; HRMS (CDI/$NH_3$) calcd for $C_{13}H_{24}NO_5Si$: 302.1423 [$M^+$+$NH_3$]; found: 302.1414.

**Hydroxy enedione ((+)-41)**: This compound was prepared in a similar manner to the racemate of hydroxy enedione **41**. M.p. 118–118.2 °C (white flakes from hexanes/EtOAc); $[\alpha]_D^{25} = +52.09$ ($c = 0.86$ in $CHCl_3$); MS: $m/z$: 306.9 [$C_{13}H_{24}NO_5Si$+$Na^+$]. (+)-γ-bromide: $[\alpha]_D^{25} = +175.7$ ($c = 1.99$ in $CHCl_3$); MS: $m/z$: 370.9 [$C_{13}H_{25}NO_4SiBr$+$Na^+$]. (−)-γ-alcohol: $[\alpha]_D^{25} =$ −93.40 ($c = 1.03$ in $CHCl_3$); MS: $m/z$: 309.1 [$C_{13}H_{26}NO_5Si$+$Na^+$].

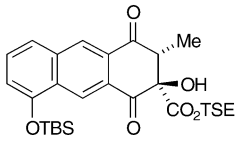
***cis*/*trans*-Tris(*tert*-butyldimethylsilyloxy)benzocyclobutene (32)**: 3-Methoxy benzocyclobutenedione **38** (1 g, 6.17 mmol) was heated at 110–130 °C in 48 % HBr for 7 h. The mixture was cooled, partitioned between sat. $NaCl_{(aq)}$ and EtOAc, the organic layers were dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography (4:1 hexanes/EtOAc) to give pure phenol as a white solid (0.92 g, 93 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (dd, $J =$ 7.66 Hz, 1H), 7.57 (d, $J = 7.35$ Hz, 1H), 7.03 (d, $J = 7.76$ Hz), 1.00 (s, 9H), 0.29 ppm (s, 6H).



The phenol (0.78 g, 5.27 mmol) was suspended in $CH_2Cl_2$ (25 mL) at 0 °C, and $Et_3N$ (0.95 mL, 6.85 mmol) and TBSCl (0.95 g, 6.32 mmol) were added. After stirring for 30 min, the mixture was partitioned between $NaCl_{(aq)}$ and $CH_2Cl_2$, the organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (95:5 hexanes/EtOAc) to give pure (*tert*-butyldimethylsilyloxy)benzocyclobutenedione as a white solid (1.23 g, 91 %). IR (film): $\nu = 2927$, 2858, 1798, 1767, 1309, 1126, 789 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 6.65$ (dd, $J = 7.66$ Hz, 1H), 7.57 (d, $J = 7.35$ Hz, 1H), 7.03 (d, $J = 7.76$ Hz, 1H), 1.00 (s, 9H), 0.28 ppm (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 195.13$, 190.82, 172.38, 163.89, 150.52, 138.20, 126.26, 114.69, 25.35, 18.25, −4.93 ppm; HRMS (DCI/$NH_3$) calcd for $C_{14}H_{18}O_3Si$: 262.1025 [$M^+$]; found 262.1034.

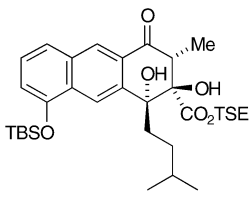
The silyloxydione (0.10 g, 0.38 mmol) was dissolved in MeOH (5 mL) at 0 °C and $NaBH_4$ (10 mg) was added. After 1.5 h, acetone was added, and the mixture was evaporated at 0 °C. The residue was filtered through a plug of silica with EtOAc, and the filtrate was evaporated at 0 °C. The residue was dissolved in $CH_2Cl_2$ (5 mL) and cooled to −78 °C, and $Et_3N$ (0.13 mL, 0.95 mmol) and TBSOTf (0.22 mL, 0.95 mmol) were added. After 1 h, the mixture was evaporated, and the residue was purified by column chromatography (hexanes) to give **32** as a mixture of *trans* and *cis* isomers (colorless oil, 6:1 *trans*:*cis*, 0.15 g, 83 %). The major *trans* isomer was characterized as follows: IR (film): $\nu = 2955$, 2929, 2857, 1601, 1437 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.18$ (dd, $J = 7.81$ Hz, 1H), 6.83 (d, $J = 7.19$ Hz, 1H), 6.70 (d, $J = 8.18$ Hz, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.93 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.01 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta =$ 169.39, 151.30, 146.10, 130.71, 119.84, 116.05, 79.37, 78.65, 25.94, 25.82, 25.71, 18.35, 18.17, 18.04, −2.93, −3.96, −4.04, −4.10, −4.55, −4.65 ppm; HRMS (FAB +) calcd for $C_{26}H_{50}O_3Si_3$ 494.3099 [$M^+$]; found 494.3050. The minor *cis*-isomer was characterized by $^1H$ NMR (400 MHz, $CDCl_3$): $\delta =$ 5.44 (d, $J = 3.75$ Hz, 1H), 5.29 ppm (d, $J = 3.83$ Hz, 1H).

**Diels–Alder cycloadduct (43)**: The enedione **41** (50 mg, 83 %, 85 μmol) and benzocyclobutene **32** (20 mg, 70 μmol) were dissolved in [$D_8$]toluene (1 mL) and heated at 90 °C for 12 h. The solvent was evaporated, the residue was dissolved in MeOH (10 mL), and pyridine (6 μL, 70 μmol) and CSA (16 mg, 70 μmol) were added. After heating the mixture at reflux 4 h, the mixture was evaporated and the reside was purified by column chromatography (95:5 hexanes/EtOAc) to give **43** (9:1 mixture of regioisomers) as a colorless oil (26 mg, 72 %): IR (film): $\nu = 3480$, 2954, 2859, 1747, 1703, 1458, 1255 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 9.03$ (s, 1H), 8.60 (s, 1H), 7.65 (d, $J = 8.17$ Hz, 1H), 7.55 (dd, $J = 8.12$ Hz, 1H), 7.01 (d, $J = 7.49$ Hz, 1H), 4.61 (s, 1H), 4.14–4.00 (m, 2H), 3.23 (q, $J = 6.48$ Hz, 1H), 1.45 (d, $J = 6.51$ Hz, 1H), 1.10 (s, 9H), 0.95–0.76 (m, 2H), 0.30 (s, 3H), −0.09 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 193.55$, 192.99, 168.68, 153.80, 137.21, 132.68, 130.75, 129.46, 127.71, 126.94, 125.82, 122.71, 115.67, 84.18, 65.84, 51.96, 25.78, 18.47, 17.13, 9.04, −1.72, −4.26, −4.35 ppm; HRMS (FAB +) calcd for $C_{27}H_{38}O_6NaSi$: 537.2105 [$M^+$+Na]; found: 537.2092.



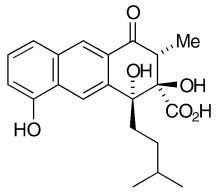

**Diels–Alder cycloadduct ((+)-43)**: This compound was prepared in a similar manner as (±)-**43** (as a 10:1 mixture of regioisomers): $[\alpha]_D^{25} = +5.97$ ($c = 2.68$ in $CHCl_3$).

**Protected (±)-rishirilide B (44)**: The diketoanthracene **43** (107 mg, 0.208 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. Isoamyl magnesium bromide (0.73 M $Et_2O$, 1.43 mL, 1.04 mmol) was added dropwise over 15 min. After 1.5 h additional isoamyl magnesium bromide (0.63 mL, 0.42 mmol) was added to achieve completion as judged by thin-layer chromatography ($R_f$ 0.61, 5 % acetone in toluene). The mixture was partitioned between $Et_2O$ and sat. $NaCl_{(aq)}$, the organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography (95:5 → 9:1 hexanes/EtOAc) to give the protected core as a colorless oil (85 mg, 70 %). IR (film): $\nu = 3484$, 2954, 1719, 1689, 1622, 1573, 1455, 1251 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.51$ (s, 1H), 8.36 (s, 1H), 7.58 (d, $J = 8.23$ Hz, 1H), 7.35 (dd, $J = 7.78$ Hz, 1H), 6.95 (d, $J = 7.12$ Hz, 1H), 4.01 (s, 1H), 3.90–3.75 (m, 2H), 3.10 (q, $J = 6.78$ Hz, 1H), 2.39 (s, 1H), 2.30 (ddd, $J = 3.36$, 12.94 Hz, 1H), 1.68 (ddd, $J = 5.00$, 13.62 Hz, 1H), 1.45–1.28 (m, 2H), 1.29 (d, $J = 6.74$ Hz, 3H), 1.09 (s, 9H), 0.95–0.76 (m, 1H), 0.79 (d, $J = 6.35$ Hz, 3H), 0.67 (d, $J = 6.44$ Hz, 3H), 0.35–0.25 (m, 2H), 0.26, 0.24 (2s, 3H ea.), −0.23 ppm (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 197.37$, 173.47, 151.68, 138.32, 133.30, 129.80, 127.85, 126.57, 122.75, 120.12, 115.39, 83.85, 78.10, 65.13, 48.26, 35.71, 31.16, 28.29, 25.84, 22.74, 22.43, 18.41, 16.67, 10.04, −1.91, −4.12, −4.39 ppm; HRMS (FAB +) calcd for $C_{32}H_{50}O_6Si_2Na$: 609.3038 [$M^+$+Na]; found 609.3013.



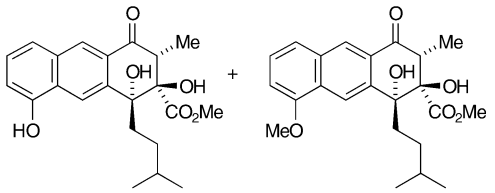

**Protected (−)-rishirilide B ((−)-44)**: This compound was prepared in a similar manner to (±)-**44**: $[\alpha]_D^{25} = -5.22$ ($c = 1.65$ in $CHCl_3$).

**(±)-Rishirilide B (1)**: The 2-(trimethylsilyl)ethyl ester (22 mg, 38 μmol) was dissolved in THF (1 mL), TAS-F (70.5 mg, 0.23 mmol) was added under an atmosphere of nitrogen. After 30 min, the mixture was poured onto a column of silica gel. Elution ($CH_2Cl_2 \rightarrow$ 9:1 $CH_2Cl_2$/MeOH → 9:1 $CH_2Cl_2$/MeOH, 0.1 % HOAc) and evaporation gave a residue that was applied in MeOH to a LiChroprep C-18 column that was eluted ($H_2O \rightarrow$ 3:1 $H_2O$/MeOH → 1:1 $H_2O$/MeOH) to give pure **1** as a beige solid (13 mg, 93 %). IR (film): $\nu = 3399$, 2954, 2868, 1677, 1625, 1571, 1451, 1277 $cm^{-1}$; $^1H$ NMR (400 MHz, [$D_4$]MeOH): $\delta =$ 8.41 (s, 1H), 8.38 (s, 1H), 7.43 (d, $J =$ 8.22 Hz, 1H), 7.28 (dd, $J = 7.93$ Hz, 1H), 3.10–3.00 (s, 1H), 2.35 (dd, $J =$ 10.31 Hz, 1H), 1.73 (dd, $J = 8.96$ Hz, 1H), 1.55–1.40 (m, 1H), 1.40–1.20 (m, 5H), 0.83 (d, $J = 6.54$ Hz, 3H), 0.72 ppm (d, $J = 6.55$ Hz, 3H); $^{13}C$ NMR (125 MHz, DMSO): $\delta = 197.68$, 175.69, 152.97, 141.21, 132.34, 130.74, 126.06, 125.97, 125.21, 119.65, 119.36, 109.50, 82.83, 76.66, 48.04, 35.03, 31.19, 28.02, 22.83, 22.54, 10.29 ppm; MS: $m/z$: 395 [$M^+$+Na].




**(−)-Rishirilide B ((−)-1)**: This compound was prepared in a similar manner to (±)-**1**: $[\alpha]_D^{25} = -13.6$ ($c = 0.32$ in EtOH) (lit. $[\alpha]_D^{22} = +12.8$ ($c = 0.448$ in EtOH)).

**(±)-Rishirilide B methyl ester (46) and (±)-dimethyl rishirilide B (45)**: (±)-Rishirilide B (**1**) (13 mg, 35 μmol) was treated with diazomethane (solution in $Et_2O$) in MeOH (4 mL) for 15 min to give a mixture that was evaporated; the residue was purified by chromatography on silica gel (9:1 → 4:1 → 2:1 hexanes/EtOAc → 9:1 $CH_2Cl_2$/MeOH, 0.1 % HOAc) to

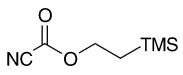



give **45** as a white solid (6 mg, 43 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.52$ (s, 1H), 8.37 (s, 1H), 7.55 (d, $J = 8.25$ Hz, 1H), 7.42 (dd, $J = 7.86$ Hz, 1H), 6.90 (d, $J = 7.68$ Hz, 1H), 4.21 (s, 1H), 4.01 (s, 3H), 3.34 (s, 3H), 3.11 (q, $J =$ 6.85 Hz), 2.50 (s, 1H), 2.30 (dt, $J = 3.84$, 13.47 Hz, 1H), 1.75–1.60 (m, 1H), 1.45–1.30 (m, 2H), 1.27 (d, $J = 6.75$ Hz, 3H), 1.25–1.20 (m, 1H), 0.95–0.80 (m, 2H), 0.79 (d, $J = 6.42$ Hz, 3H), 0.69 ppm (d, $J = 6.40$ Hz, 3H); MS: $m/z$: 423 [$C_{23}H_{28}O_6Na^+$].

Further elution gave **46** as a brown residue (2 mg, 15 %) that on standing in MeOH for 17 d at −20 °C formed brown prisms. M.p. 94–96 °C; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H), 8.30 (s, 1H), 7.57 (d, $J = 8.23$ Hz, 1H), 7.35 (dd, $J = 7.83$ Hz, 1H), 6.94 (d, $J = 7.09$ Hz, 1H), 4.22 (s, 1H), 3.36 (s, 3H), 3.12 (q, $J = 6.81$ Hz), 2.54 (s, 1H), 2.31 (dt, $J = 3.25$, 12.70 Hz, 1H), 1.75–1.60 (m, 1H), 1.45–1.30 (m, 2H), 1.26 (d, $J = 6.55$ Hz, 3H), 1.25–1.20 (m, 1H), 0.95–0.80 (m, 2H), 0.79 (d, $J = 6.32$ Hz, 3H), 0.68 ppm (d, $J =$ 6.48 Hz, 3H); MS: $m/z$: 409 [$C_{22}H_{26}O_6Na^+$]. Further elution recovered the natural product, **1** (4 mg, 31 %).

**Trimethylsilylethylcyanoformate**: This compound was prepared based on the literature procedure.[19] KCN (1.82 g, 28 mmol) and $Bu_3NI$ (111 mg, 0.3 mmol) were added to a solution of trimethylsilylethylchloroformate[22] in $CH_2Cl_2$ (70 mL) and water (70 mL) at RT, and the mixture was stirred



vigorously for 12 h. The two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ ($3 \times 10$ mL). The organic layers were combined, dried, and concentrated to give trimethylsilylethylcyanoformate as a light yellow oil, which was used without further purification (80% purity based on 1H NMR). $^1$H NMR (400 MHz, $CDCl_3$) 4.42 (m, 2H), 1.14 (m, 2H), 0.07 ppm (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 144.4, 109.4, 68.15, 17.23, −1.57 ppm.

**5-(*R*)-Methylcyclohexenone (47)**: This compound was prepared following the literature procedure[18] as a yellow oil. IR (thin film): $\tilde{\nu} = 1680$, 1645 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 6.69$ (ddd, $J = 2.6$, 5.6, 10.1 Hz, 1H), 6.01 (br d, $J = 9.0$ Hz, 1H), 2.48 (dd, $J = 3.3$, 21.2 Hz), 2.42 (dt, $J = 4.4$, 23.0 Hz, 1H), 2.22 (m, 1H), 2.12 (dd, $J = 11.8$, 15.5 Hz, 1H), 2.03 (ddt, $J = 2.6$, 9.7, 18.6 Hz, 1H), 1.07 ppm (d, $J = 6.4$ Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 200.1$, 149.9, 129.8, 65.68, 46.05, 33.84, 30.16, 22.16, 21.01, 15.05, 13.88 ppm.

## Acknowledgement

This work was supported by the National Institutes of Health: AI 16943/CA 28824 (SJD). Postdoctoral Fellowship Support is gratefully acknowledged by KY (Helen Hay Whitney Foundation), MFH (5T32 CA 62948–05) and JGA (NIH-CA-80356). We thank Brian M. Bridgewater and David G. Churchill for providing X-ray data. We thank Dr. George Sukenick for mass spectral analyses.

[1] H. Iwaki, Y. Nakayama, M. Takahashi, S. Uetsuki, M. Kido, Y. Fukuyama, *J. Antibiotics* **1984**, *XXXVII*, 1091.
[2] For a preliminary account on this study see: J. G. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 351.
[3] a) J. G. Allen, M. F. Hentemann, S. J. Danishefsky, *J. Am. Chem. Soc.* **2000**, *122*, 571; b) M. F. Hentemann, J. G. Allen, S. J. Danishefsky, *Angew. Chem.* **2000**, *112*, 2013; *Angew. Chem. Int. Ed.* **2000**, *39*, 1937.
[4] K. N. von Kaula, *Synth. Fibrinolytic Thrombolytic Agents* **1979**, 53.
[5] N. Aoki, *Prog. Cardiovasc. Dis.* **1979**, *21* 267.
[6] For recent review on oxidative cyclization, see; V. Singh, *Acc. Chem. Res.* **1999**, *32*, 324.
[7] a) W. R. Dolibier, H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471; b) S. Niwayama, Y. Wang, K. N. Houk, *Tetrahedron Lett.* **1995**, *36*, 6201.
[8] For selected pioneering studies of intermolecular Diels–Alder reactions, see: a) M. P. Cava, A. A. Deana, K. Muth, **1959**, *81*, 6458; b) Reference [13]; c) L. A. Errede, **1960**, *83*, 949.
[9] a) For reviews on applications of *o*-quinodimethides to natural product synthesis, see: J. L. Charlton, M. M. Alauddin, *Tetrahedron* **1987**, *43*, 2873; J. L. Segura, N. Martín, *Chem. Rev.* **1999**, *99*, 3199; b) For applications in steroid synthesis, see: P.-Y. Michellys, H. Pellissier, M. Santelli. *Org. Prep. Proced. Int.* **1996**, *28*, 545; c) For synthetic applications to other polycyclic natural products, see: T. Kametani, *Pure. Appl. Chem.* **1978**, *51*, 747; W. Oppolzer, *Synthesis* **1978**, 793; W. Oppolzer, *Heterocycles* **1980**, *14*, 1615; P. Magnus, T. Gallagher, P. Brown, P. Pappalardo, *Acc. Chem. Res.* **1984**, *17*, 35.
[10] a) F. M. Hauser, S. A. Pogany, *Synthesis* **1980**, 814; b) B.-D. Chong, Y.-I. Ji, S.-S. Oh, J.-D. Yang, W. Baik, S. Koo, *J. Org. Chem.* **1997**, *62*, 9323.
[11] a) G. M. Rubottom, J. M. Gruber, R. K. Boeckman, Jr., M. Ramaiah, J. B. Medwig, *Tetrahedron Lett.* **1978**, *43*, 4603; b) H. K. Chenault, S. J. Danishefsky, *J. Org. Chem.* **1989**, *54*, 4249.
[12] J. C. Bill, D. S. Tarbell, *O*-Phthalaldehyde, Wiley, **1963**.
[13] a) M. P. Cava, D. R. Napier, *J. Am. Chem. Soc.* **1957**, *79*, 1701; b) M. P. Cava, J. F. Stucker, *J. Am. Chem. Soc.* **1957**, *79*, 1706.
[14] H. Nozaki, R. Noyori, N. Kôzaki, *Tetrahedron* **1964**, *20*, 641.
[15] E. R. Jarvo, S. R. Boothroyd, M. A. Kerr, *Synlett* **1996**, 898.
[16] Y. Ueda, G. Roberge, V. Vinet, *Can. J. Chem.* **1984**, *62*, 2936.
[17] F. M. Hauser, Y.-J. Xu, *Org. Lett.* **1999**, *2*, 335.
[18] K. C. Nicolaou, Y. -L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596.
[19] Prepared based on literature procedure: Y. Nii, K. Okano, S. Kobayashi, M. Ohno, *Tetrahedron Lett.* **1979**, *27*, 2517.
[20] W. Dam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow, M. Schindler, *J. Org. Chem.* **1987**, *52*, 2800.
[21] S. G. Davies, G. Bhalay, *Tetrahedron: Asymmetry* **1996**, *7*, 1595.
[22] R. E. Shute, D. H. Rich, *Synthesis* **1987**, 346.

Received: March 10, 2003 [F4931]