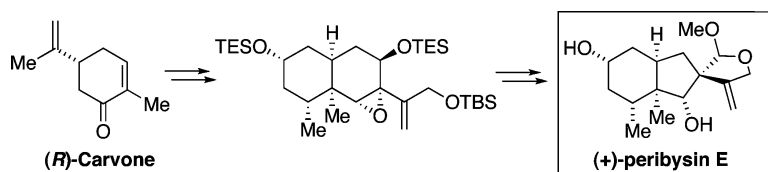


Total Syntheses of (+)- and (#)-Peribysin E

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Total Syntheses of (+)- and (–)-Peribysin E

Angie R. Angeles,[†] Stephen P. Waters,[†] and Samuel J. Danishefsky^{*,†,‡}

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

Received June 24, 2008; E-mail: s-danishefsky@ski.mskcc.org

Abstract: A convergent, stereocontrolled route to either antipode of the cell adhesion inhibitor, peribysin E, has been achieved from carvone. Highlights of the synthesis include a Diels–Alder reaction to generate a *cis*-decalin framework, followed by semipinacol-type ring contraction to secure the stereochemistry of the C₇ quaternary center. Potential mechanistic pathways for the critical ring contraction were studied through deuterium incorporation studies. In addition, an optimized olefin isomerization/Saegusa oxidation protocol is described for the conversion of [4+2] cycloadducts of 2-(trialkylsilyloxy)-1,3-dienes to 1,6(2*H*,7*H*)-naphthalenediones, having stereochemical arrangements not accessible via conventional Robinson annulation protocols. Finally, the ability to independently prepare either enantiomer of peribysin E from the corresponding antipode of carvone led to a reassignment of the absolute configuration of peribysin E.

Introduction

An overarching objective of our laboratory is the synthesis and evaluation of small-molecule natural products (SMNPs) which possess biological profiles that may be of value in the treatment of cancer. High on our list of priorities in these pursuits are viable cancer chemotherapeutic agents which may function through a range of biological mechanisms.¹ In one setting, the drug is designed to attack the diseased cell itself, by targeting a component of the enzymatic or receptor machinery that is critical for the upkeep of neoplasticity.² Drugs which operate under this paradigm are generally termed cytotoxic or antiproliferative agents. Although such agents are widely used to great effect, there is potential benefit to be gained from an alternative approach, wherein the drug is optimized to inhibit some particular element of the support network required for tumor metastasis (i.e., cell adhesion,³ cell migration,⁴ angiogenesis⁵). These antimetastatic agents might be expected to exhibit lower toxicity than traditional cytotoxic agents, although, of course, target selectivity must still be considered. Because these types of agents would primarily serve to inhibit tumor metastasis, the optimal setting for success would be one in which the primary tumor had been resected, through surgery, radiation, or chemotherapy. The antimetastatic agent would be evaluated for its ability to halt progression of the disease, presumably through micrometastasis.

In the context described above, we took note of a newly isolated natural product, termed peribysin E (originally reported as **1**⁶). Isolated by Yamada and co-workers from *Periconia byssoides* OUPS-N133, peribysin E was reported to exhibit potent cell adhesion inhibitory activity.^{7,8} In fact, peribysin E was claimed to be more strongly inhibitory than is herbimycin. In the hopes of gaining more insight into the antimetastatic potential of this particular cell adhesion inhibitor, we initiated a program directed toward the total synthesis of peribysin E. Furthermore, our synthetic route toward peribysin E would oblige us to confront mechanistic and stereochemical issues which are of considerable interest beyond the confines of this particular investigation. Indeed, a total synthesis of the properly configured peribysin E has been accomplished⁹ and is described herein. The synthesis necessitated revision of the assignment of the absolute configuration of peribysin E. Furthermore, the work described below identified some issues of stereochemistry and mechanism not previously considered.

Results and Discussion

Synthetic Analysis of Peribysin E (1). In designing a synthetic route toward peribysin E (**1**), we envisioned a late-stage intermediate of the type **6**, confident that the final step of the synthesis, i.e., the closure of the C-ring, could be readily accomplished from aldehyde **6** (Figure 1). The defining feature of the proposed route would be a rearrangement step, with ring contraction, of an epoxide, **5**, resulting in the formation of a five-membered ring incorporating the C₇ quaternary center (i.e., **6**). The relative configuration of the newly formed C₇ locus

[†] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research.

[‡] Department of Chemistry, Columbia University.

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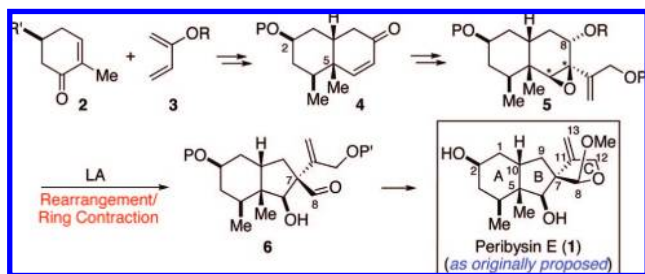


Figure 1. Synthetic strategy toward peribysin E (1).

would be controlled by inversion of the β -oriented epoxide (asterisks, **5**) in the rearrangement step. If the migrating carbon (C_8) were to exist as the free alcohol (**5**, R = H), aldehyde **6** would be obtained directly from the rearrangement. Alternatively, a protected alcohol might emerge from the rearrangement as an acetal. The latter would readily be converted to the target aldehyde. An analysis of the literature revealed a surprising paucity of examples involving comparable ring contractions of fused cyclohexene epoxides bearing internal oxygen nucleophiles, of the type **5**→**6**. Actually, one could envision alternate and better-precedented reaction pathways for an epoxide such as **5**.¹⁰ Sensitive to the possibility of potentially complicating competitive pathways, we sought to design a system in which the desired ring contraction would be favored. Indeed, as will be shown, with considerable effort we were able to suppress nonproductive pathways, thereby achieving the desired rearrangement step with good efficiency.

As outlined in Figure 1, we envisioned preparing the key rearrangement precursor, **5**, through a multistep process commencing with diastereoselective Diels–Alder cycloaddition of a diene of the type **3** and an optically active dienophile such as **2**. It was anticipated that perhaps the R' dienophilic substituent would shield the β -face of the dienophile, thus directing cycloaddition to the desired α -face. In this way, the *cis*-relationship of the C_5 angular methyl group and the C_2 substituent would have been established.

Construction of Enone 10: Unexpected Isomerization of Silyl Enol Ether 9. We originally selected as the dienophilic coupling partner commercially available (*S*)-carvone¹¹ (**7**, Scheme 1). The expectation was that the resident isopropenyl moiety would favorably direct the stereofacial sense of the Diels–Alder cycloaddition. At the appropriate time, this functionality would be readily converted to a hydroxy group with retention of configuration. As hoped, Lewis acid-catalyzed cycloaddition of **7** with diene **8** proceeded to afford intermediate **9**,¹² which was well disposed to undergo subsequent Saegusa oxidation, thereby providing the desired enone **10** in overall 63% yield and high *cis*-selectivity.

It was in the course of optimizing this sequence that we took note of an interesting and unanticipated isomerization event. Though it is not directly relevant to the synthesis of the target structure at hand, we felt it to be worthy of further study, since it charts some new directions for stereoselection. Thus, we had found that when intermediate **9** was heated following workup,

the silyl enol ether had isomerized to compound **11**. Subsequent Saegusa oxidation provided a mixture of enone **12** (20%) and the nonoxidized hydrolysis product, ketone **13** (30%).

We note that Δ 4,3-keto octalone systems of the general type **15** are typically synthesized through Robinson annulation.¹³ However, as is well precedent, this approach tends to result in an octalone bearing a *trans* relationship between the angular substituents and that at C_6 (proto-steroid numbering).¹⁴ Thus, a protocol which would allow access to the *cis*-series related system, as encompassed in octalone **12**, would constitute a new capability for stereocontrol. As such, we sought to investigate the fortuitously discovered isomerization–oxidation sequence in more detail, in the hopes of optimizing conditions to maximize the formation of **12**.

We hoped that a more robust silicon group would tend to suppress nonoxidative hydrolysis of the silyl enol ether, minimizing formation of ketone type **13**. Accordingly, we replaced the trimethylsilyl (TMS) group on the diene with a triethylsilyl (TES) group (**16**, Scheme 2). Cycloaddition with *S*-carvone (**7**) yielded adduct **17** along with a small amount of isomerized silyl enol ether **18** (**17**:**18** = 11:1). Upon silica gel purification, facile olefin isomerization occurred to provide **18** as the major product. Alternatively, simply stirring **17** with silica gel in CH_2Cl_2 afforded 92% of the isomerized adduct **18**, along with 8% of the original silyl enol ether, **17**. Saegusa oxidation of **18** provided the corresponding target enone, **12**, in 81% yield.

The chemistry described above, admittedly in a preliminary setting, points to a new idea for preparing *cis*-substituted decalin systems such as **12** (see asterisks) through recourse to a Diels–Alder isomerization–oxidation sequence. This protocol, discovered by chance, does not have direct implications for the synthesis of peribysin E. However, if generalizable, it should prove to be of great value in the synthesis of certain types of octalones bearing a *cis*-relationship between C_7 and C_{10} (proto-steroid numbering); see asterisks in **12**.

Construction of Intermediate 25. We now return to the synthesis of peribysin E. With an efficient route to enone **10**, the next objective envisioned replacement of the ketonic function at C_4 with a methyl group. First, the conjugated C_8 ketone was temporarily masked as a dithiane, through selective ketalization¹⁵ (**10**→**19**, Scheme 3). Wittig–Levine-type methoxymethenylation¹⁶ of the free C_4 ketone afforded **20**. The latter, following hydrolysis, emerged as **21**. Its aldehyde moiety was converted to a methyl group through a well-established sequence involving reduction, followed by mesylation and a second hydride-mediated reduction.¹⁷ Finally, cleavage of the dithiane function served to restore the C_8 ketone (see intermediate **23**).

With **23** in hand, we directed our attention to the conversion of the C_2 isopropenyl group to the alcohol group ultimately required at C_2 . As shown in Scheme 4, the terminal methylene moiety was converted, by concurrent Johnson–Lemieux oxidation,¹⁸ to a ketone (see **24**). Finally, Baeyer–Villiger oxidation of **24** served to provide an acetate formulated as **25**, given the

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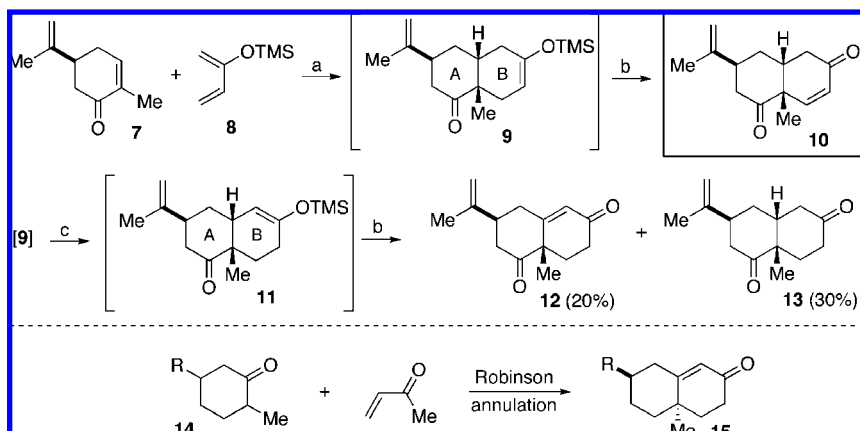
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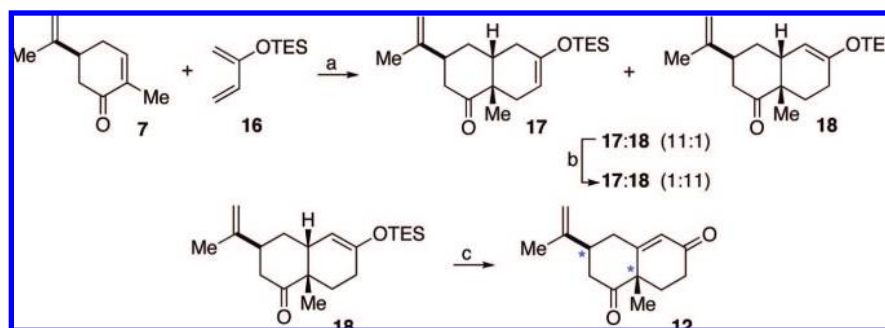
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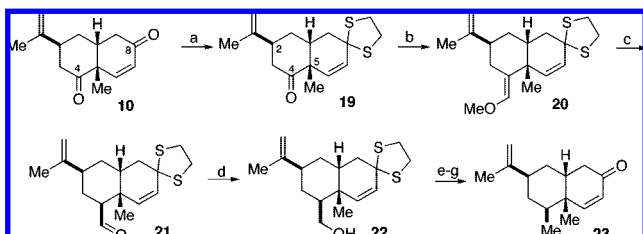
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Scheme 1^a

^a Reagents and conditions: (a) EtAlCl₂, toluene, 0 °C to rt, 4 h; (b) Pd(OAc)₂, CH₃CN, rt, 4 h, 63% over two steps, 19:1 (*cis:trans*); (c) 100 °C, toluene, 50%, 2:3 (**12:13**).

Scheme 2^a

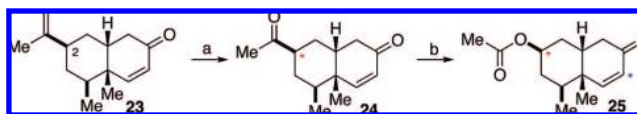
^a Reagents and conditions: (a) EtAlCl₂, toluene, 0 °C to rt, 4 h, 11:1 (**17:18**); (b) silica gel, CH₂Cl₂, rt, 1 h, 70% over two steps, 1:11 (**17:18**); (c) Pd(OAc)₂, DMSO, 0 °C to rt, 12 h, 81%.

Scheme 3^a

^a Reagents and conditions: (a) 1,2-ethanedithiol, MeOH, BF₃·OEt₂, 0 °C, 30 h, 83%; (b) Ph₃PCH₂OCH₃Cl, KN(SiMe₃)₂, THF, -30 to 0 °C to rt, 24 h; (c) 4 N HCl, MeOH, THF, 0 °C to rt, 36 h, 89% over two steps, 13:1 β:α; (d) NaBH₄, MeOH, THF, 0 °C to rt, 2 h, 90%; (e) MsCl, Et₃N, CH₂Cl₂, 0 °C to rt, 1.5 h; (f) LiBHET₃, THF, 0 °C to rt, 24 h, 71% over two steps; (g) (CF₃CO₂)₂IPh, MeOH, H₂O, CH₂Cl₂, rt, 15 min, 87%.

expected retention of configuration in the migration step (see red asterisks at C₂ in **24** and **25**).

Elaboration of the *cis*-Decalin Framework: Iodination and Suzuki Cross-Coupling. We next focused on the installation of a side chain at C₇ (see blue asterisk, **25**, Scheme 4). We hoped to exploit a Suzuki cross-coupling toward that end. Our initial attempts to install a C₇ iodo group following the Johnson protocol (I₂, pyridine)¹⁹ were largely unsuccessful (~20%

Scheme 4^a

^a Reagents and condition: (a) OsO₄, H₂O₂, NaIO₄, 2,6-lutidine, dioxane, rt, 4 h, 85%; (b) *m*CPBA, CH₂Cl₂, 0 °C to rt, 24 h, 45% (80% BORSM).

conversion). We surmised that the rather low reaction yield could well be attributable to steric interference from the C₅ quaternary center, which might be blocking the pyridine nucleophile from engaging in the required conjugate addition. We hoped to circumvent this problem through the use of TMSN₃, with the expectation that the TMS group would serve as the activator for conjugate addition by the smaller azide (i.e., **26**→**27**, Scheme 5). In the event, we were pleased to observe that addition of TMSN₃, followed by iodine, did provide intermediate **28** which, following azide elimination, suffered conversion to α-iodoenone **29**.²⁰ This reaction proceeded in 71% yield. Intermediate **29** reacted readily with vinyl boronic ester **30**²¹ in a successful Suzuki cross-coupling reaction to afford the fully elaborated *cis*-decalin system, **31**.

“Nucleophilic epoxidation”^{22a} of **31** proceeded with high diastereoselectivity to generate **32**, presumably through axial

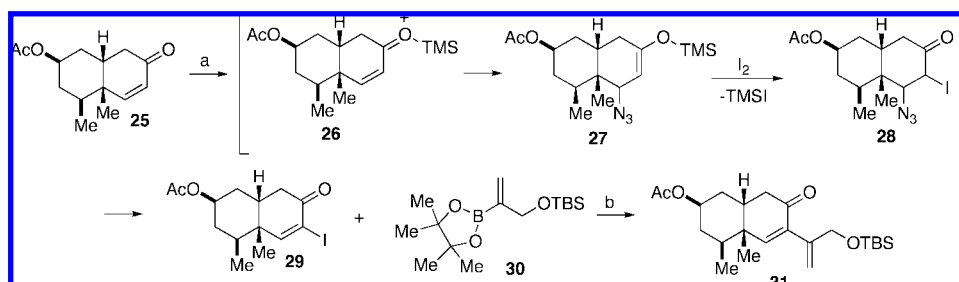
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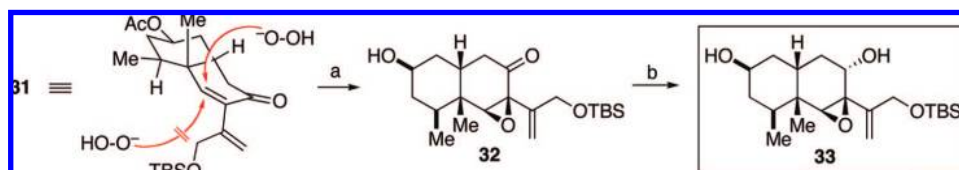
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Scheme 5^a

^a Reagents and conditions: (a) TMS₃N, I₂, pyridine, CH₂Cl₂, 71% (100% BORSM); (b) Pd(PhCN)₂Cl₂, THF:H₂O, Ag₂O, Ph₃As, rt, 4 h, 89%.

Scheme 6^a

^a Reagents and conditions: (a) H₂O₂, NaOH, MeOH, 0 °C, 48 h, (85% BORSM); (b) NaBH₄, MeOH, THF, 0 °C, 45 min, 91%, 7:1.

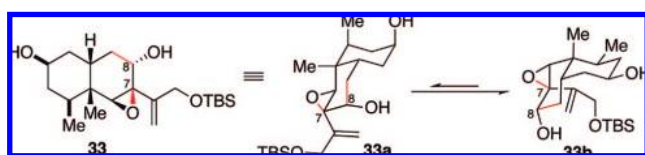


Figure 2. Chair conformations of epoxy diol **36**.

attack of the hydrogen peroxide at the β -carbon of the enone (Scheme 6).²² Subsequent reduction of the ketone was achieved through delivery of the hydride from the convex face of the decalin system, thereby affording epoxy alcohol **33**.²³

Modalities for Accomplishing Ring Contraction: Mechanistic Evaluations. With epoxy alcohol **33** in hand, we were now prepared to evaluate the viability of the critical ring-contracting rearrangement. During the planning stages of the synthesis, some potential complications in the proposed rearrangement had not gone unnoticed. In the conformations of the *cis*-decalin framework (cf. **33a** and **33b**, Figure 2), the epoxide appears to lack the optimal stereoelectronic alignments for concerted base-catalyzed rearrangement. The optimal setting would be one in which the migrating C₈–C₉ bond would be *trans*-anticoplanar to the epoxide C–O bond. Indeed, as shown in Scheme 7, initial attempts to effect ring contraction through base-mediated quasi-Favorski rearrangement²⁴ (**33**→**34**) or through benzylic acid type rearrangement²⁵ (**32**→**36**) were unsuccessful.

In light of these initial difficulties, we wondered whether a Lewis acid-catalyzed semipinacol rearrangement—operating through the agency of a more reactive allylic cationoid species—would be more suitable for our purposes. In the event, we were pleased to find that exposure of epoxide **33** to YbOTf₃ did give rise to a 2:1 ratio of the desired aldehyde **34** and ketone **37**, respectively (Scheme 8). The ketone **37** was found to be

unstable and underwent ready dehydration, giving rise to the corresponding enone **38** wherein the required aldehyde had been generated via migration of the C₈–C₉ bond. Two distinct mechanistic interpretations could be offered to account for the competitive formation of the undesired **37**. The first (path a, Scheme 8) was of a type previously proposed by Edwards and Maitland²⁶ in the context of the synthesis of cytochalasin N. Applied to the case at hand, it envisions proton elimination from epoxide **33** to afford enol **39**. Following tautomerization, ketone **37** would emerge. In an alternative pathway (path b), the hydride embedded on C₈ would migrate directly, thereby providing the observed ketone byproduct.

The alternate mechanistic pathways suggested above might be distinguishable by suitable deuterium labeling experiments. It is known that there are smaller deuterium isotope effects for hydride migration reactions compared with more common proton transfer steps.²⁷ We thus prepared deuterated epoxy alcohol **40** (Scheme 9). We reasoned that if the reaction proceeded through a proton-transfer pathway (see path a), a considerable isotope effect would be expected.²⁸ By contrast, if the hydride migration pathway (path b) were operative, the isotope effect would be quite small.²⁹ In the event, treatment of **40** with YbOTf₃ gave rise to only a minimal change in the ratio (3:1) of aldehyde **41** and ketone **42**. Given the observed product distribution, one would presume that the undesired ketone side product **37** is primarily generated through a hydride migration pathway (path b).

Armed with this added mechanistic insight, we now returned to the total synthesis of peribysin E. With aldehyde **34** in hand, we had confirmed the viability of the semipinacol rearrangement in effecting the critical ring contraction step. However, for efficiency purposes, we sought a means by which to suppress the undesired hydride migration pathway. In an effort to improve the product distribution of the pinacol rearrangement (**33**→**34**),

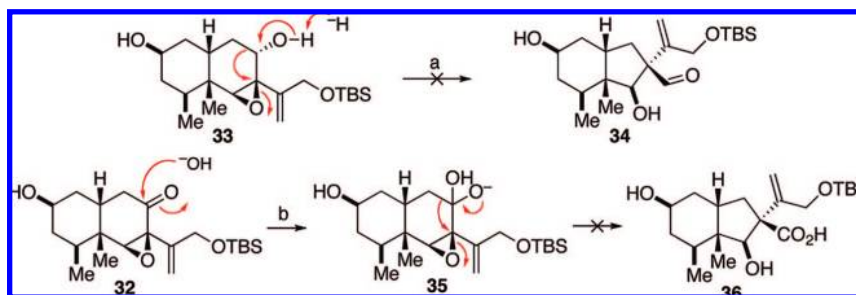
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(23) The relative stereochemistry of **33** was established by crystallographic determination on a derived triol (Supporting Information).

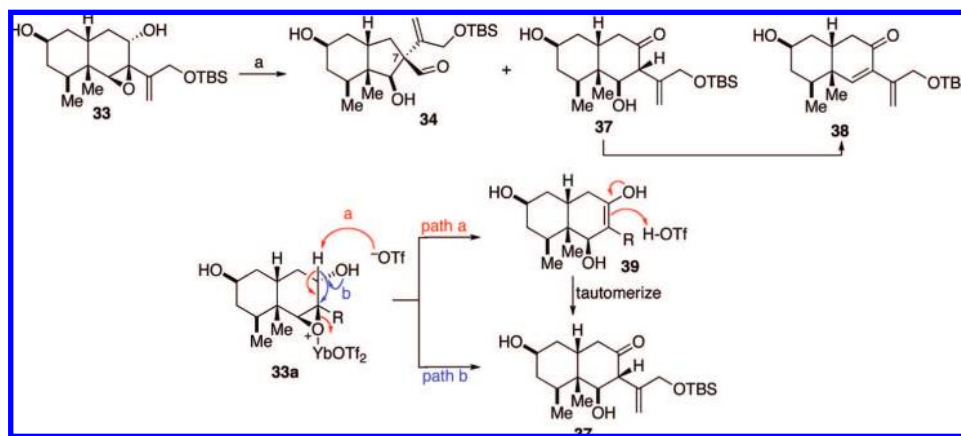
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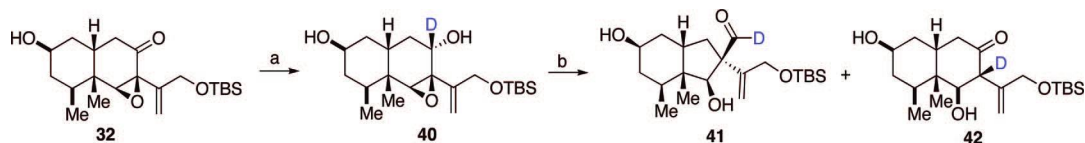
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Scheme 7^a

^a Reagents and conditions: (a) KH, THF, 0 °C to rt, 1 h, decomposition; (b) NaOH, MeOH, 0 °C to rt, 2 h, multiple products.

Scheme 8^a

^a Reagents and conditions: (a) YbOTf₃, THF, 0 °C to rt, 24 h, 50%, 2:1.

Scheme 9^a

^a Reagents and conditions: (a) NaBD₄, MeOH:THF, 0 °C, 30 min, 91%, 6:1; (b) YbOTf₃, THF, 0 °C to rt, 24 h, 39%, 3:1.

we first screened a range of Lewis acids. Unfortunately, all Lewis acids examined led to recovery of starting material or decomposition. Postulating that the resident free hydroxyl groups might be incompatible with mediation by Lewis acids, we prepared modified intermediate **43**, in which both free hydroxyls were protected with TES groups (Scheme 10). Happily, upon exposure of **43** to TiCl₄, the desired ring contracted rearrangement product **34** was formed as the principal product, with the required configuration at the newly formed C₇ quaternary center.³⁰ Only a 5% yield of the β-hydroxyketone (**37**) was observed under optimized conditions.³¹ Treatment of **34** with HCl–methanol afforded the target system, peribysin E. *We think*

that these findings are illustrative of the connectivity between mechanistic thinking and process optimization.

Reassignment of the Absolute Configuration of Peribysin E.

The proton and carbon spectra of fully synthetic peribysin E were identical to the spectra of naturally derived natural product provided by Professor Yamada, though the spectra of the synthetic material were cleaner. We noted, however, a very significant discrepancy in the optical rotation measurements. The synthetic material had a specific rotation of $[\alpha]_D^{25} = -52.17$ ($c = 0.11$, EtOH), while the natural peribysin E is reported to possess a specific rotation of $[\alpha]_D^{25} = -262.2$ ($c = 0.11$, EtOH). Though both samples exhibited the same sign of rotation, the discrepancy in the magnitude of rotation was so large as to raise a serious concern as to the matter of identity. In order to further clarify this unexpected finding, we prepared the diacetate of our synthetic peribysin E and determined the rotation to be $[\alpha]_D^{25} = -34.78$ ($c = 0.069$, EtOH). By contrast, the naturally derived peribysin E diacetate was reported to have a specific rotation of $[\alpha]_D^{25} = +35.00$ ($c = 0.069$, EtOH). On the basis of this information, we could only conclude that the original assignment

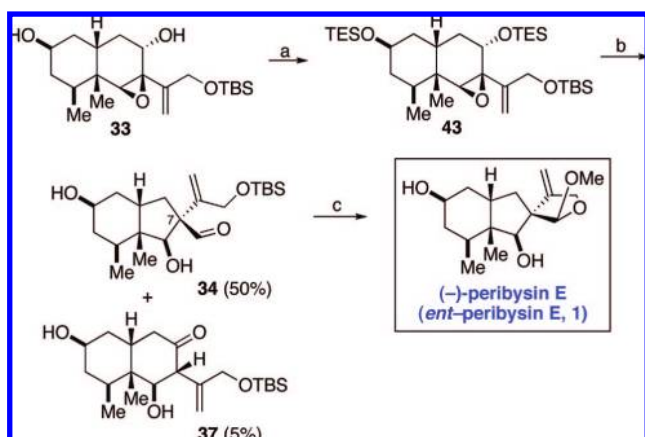
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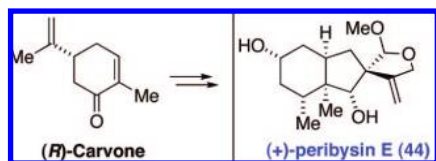
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Scheme 10^a

^a Reagents and conditions: (a) TESCl, imidazole, DMF, rt, 12 h, 93%; (b) TiCl₄, CH₂Cl₂, -78 °C, 5 min, 50%, 10:1 (34:37); (c) HCl, MeOH, 0 °C, 1 h, 80%.

Scheme 11. Synthesis of (+)-Peribysin E (44)



of absolute configuration for peribysin E had, in fact, been incorrect. We had thus synthesized *ent*-peribysin E (1, Scheme 10).

Finally, in order to provide full clarity to the situation, we repeated all of the steps of the synthesis, starting from (*R*)-carvone. We ultimately reached peribysin E, with the absolute configuration **44** (Scheme 11). Indeed, the optical rotation of the fully synthetic diacetate of **44**, [α]_D²⁵ = +37.49 (*c* = 0.069, EtOH), was found to be consistent with that reported for the naturally derived material. In light of the validity of the assignments of absolute configurations of carvone enantiomers,¹¹ and our full confidence in the stereochemical logic of the syntheses, we now conclude that peribysin E is properly depicted as **44**, and that our original target structure (**1**) corresponds to *ent*-peribysin E.

Preliminary *in vitro* biological evaluations were conducted with synthetic peribysin E (**44**) and *ent*-peribysin E (**1**). In an adhesion assay of human leukemia HL60 cells to human umbilical vein endothelial cells (HUVECs), a dose-dependent effect was observed for peribysin E (**44**), first detectable at 4 μ M and reaching a maximum at 100 μ M. At concentrations above 100 μ M, the HUVECs began to detach from the bottom of the well in response to the drug treatment, thus rendering specific HL60 adhesive evaluation unfeasible. In contrast, *ent*-peribysin E (**1**) exhibited minor effects on HL60 adhesion at concentrations above 50 μ M. We are thus able to conclude that the anti-adhesive property of peribysin E is apparently enantiospecific.

Summary

In conclusion, we have achieved the enantioselective total syntheses of both (+)- and (-)-peribysin E, commencing with the corresponding enantiomers of carvone. A chance observation as to the isomerization of **17**→**18** opens up new possibilities for stereocontrol in octalone synthesis. A critical semipinacol type ring contraction allowed for the stereocontrolled generation of a 5,6-spiro system from a Diels–Alder-derived *cis*-decalin. It is expected that the quantities of peribysin E now available through total synthesis will enable a more thorough evaluation of its promising cell-adhesion inhibitory properties. Such investigations are currently being pursued as part of our long-standing program in the area of oncologically relevant SMNPs through biomechanistically relevant pathways.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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