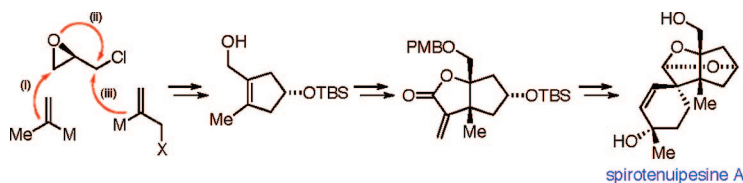# Total Synthesis of Spirotenuipesines A and B

Mingji Dai,[†] Isaac J. Krauss,[‡] and Samuel J. Danishefsky*,[†,‡]

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

s_danishefsky@mskcc.org

Received July 30, 2008

Spirotenuipesines A and B, isolated from the entomopathogenic fungus *Paecilomyces tenuipes* by Oshima and co-workers, have been synthesized. The synthesis features the highly stereoselective construction of two vicinal all-carbon quaternary centers (C_5 and C_6) via an intramolecular cyclopropanation/radical initiated fragmentation sequence and a diastereoselective intermolecular Diels−Alder reaction between α-methylenelactone dienophile **20** and synergistic diene **6a**. Installation of the C_9 tertiary alcohol occurred via nucleophilic methylation. An RCM reaction to produce a tetrasubstituted double bond in the presence of free allylic alcohol and homoallylic oxygenated functional group is also described. This route shortened the synthesis of **11** from 9 steps to 3 steps. We have further developed a strategy to gain access to optically active spirotenuipesines A and B through the synthesis of enantioenriched **10** from commercially available *R*-(−)-epichlorohydrin.

Introduction

Our laboratory has been exploring the therapeutic potential of small molecule, nonpeptidyl, neurotrophically active agents. It is well-known that naturally occurring, polypeptidyl neurotrophic factors (such as NGF, BDNF, and GDNF) play a central role in maintaining critical neurological functions.[1] These neurotrophic factors are responsible for mediating neuronal survival, differentiation, outgrowth, and apoptosis. Diminished neurotrophic support has been linked to the progression of a range of neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. Given their centrality in maintaining proper neurological function, it is not surprising that neurotrophic factors have been the focus of a great amount of interdisciplinary research. Most efforts to date have centered on exposing neurologically compromised subjects to naturally occurring peptidyl neurotrophic factors, in the hopes of promoting neurite outgrowth and survival.[2] However, this approach suffers from some serious drawbacks. Most notably, these polypeptidic agents generally exhibit unfavorable pharmacokinetic properties and require inconvenient drug-delivery techniques, such as direct microinjection to the brain. An alternative approach would be one in which the patient is treated with a small molecule, nonpeptidyl agent that stimulates the production of endogenous neurotrophic factors. Presumably, an appropriately selected small molecule nonpeptidyl agent would be better disposed to cross the blood−brain barrier.

Toward this end, we have taken note of a number of small molecule natural products with demonstrated ability to enhance neurite outgrowth, presumably through the induction of key neurotrophic factors.[3] To date, we have synthesized and evaluated a range of these neurologically active small molecules, including tricycloillicinone,[4] merrilactone A,[5] scabronine G

[†] Columbia University.

[‡] Sloan-Kettering Institute for Cancer Research.

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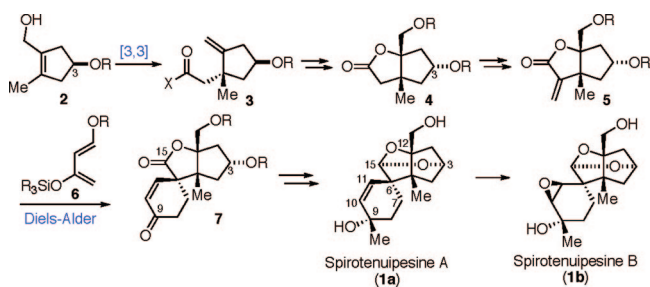
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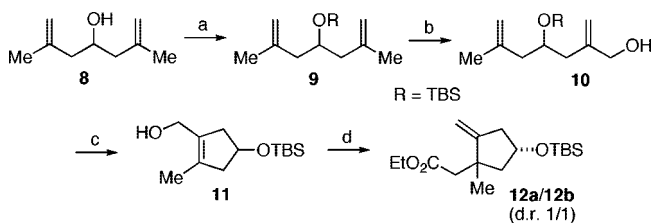**SCHEME 1. Synthetic Strategy toward Spirotenuipesines A and B**

SCHEME 2. Nonstereoselective Claisen Rearrangement[a]

[a] Reagents and conditions: (a) TBSCl (1.0 M in THF, 1.2 equiv), imid. (1.2 equiv), DMF, rt, overnight, 95%; (b) 5% SeO$_2$ on silica gel (0.05 equiv), t-BuOOH (5−6 M in nonane, 2.5 equiv), CH$_2$Cl$_2$, rt, 2 days, 40−50%; (c) Grubbs second-generation catalyst (0.05 equiv), benzene, reflux, 3−4 h, 82%; (d) propionic acid (0.06 equiv), triethyl orthoacetate (7.0 equiv), 180 °C, 2 days, 87%, 1:1 dr.

methyl ester,[6] NGA0187,[7] jiadifenin,[8] 11-*O*-debenzoyltashironin,[9] garsubellin A,[10] and paecilomycine A.[11] Our involvement in this field also led us to pursue the total synthesis of the structurally complex small molecule neurotrophins, spirotenuipesines A and B.[12]

Spirotenuipesines A (**1a**) and B (**1b**) were isolated from the entomopathogenic fungus, *Paecilomyces tenuipes* by Oshima and co-workers in 2004.[13] The researchers found that, upon introduction to 1321N1 human astrocytoma cells, both natural products appeared to facilitate the expression and release of key neurotrophic factors, as evidenced by the ability of the cells to then promote the neuronal differentiation of rat pheochromocytoma cells (PC-12). We recently launched an investigation toward the total synthesis of spirotenuipesines A and B, in the hopes of identifying lead candidates for further biological investigations against neurodegenerative disorders.

Structurally, spirotenuipesines A (**1a**) and B (**1b**), are uniquely cyclized trichothecanes[14] containing spirocyclic, tricyclo ring systems. The first-generation total syntheses of spirotenuipesines A and B were completed in 2007.[12] We describe herein the details of the total syntheses of these challenging natural products, and the way in which each stereocenter was installed in an efficient and selective manner. We further disclose an asymmetric strategy by which to gain access to optically active natural product.

Results

A First-Generation Strategy for the Synthesis of Spirotenuipesines A and B. Our general strategy toward spirotenuipesines A (**1a**) and B (**1b**) is outlined in Scheme 1. A key feature of the synthesis would be a Diels−Alder reaction between an α-methylenelactonic dienophile (see **5**) and a synergistic diene[15] (i.e., **6**). Cycloaddition would presumably occur from the convex face of the bicyclic system. Following

unraveling of the primary adduct, enone **7** would be produced. This intermediate would be advanced to spirotenuipesine A (**1a**) through a sequence which includes functionalization of C$_9$, reduction of the C$_{15}$ lactonic carbonyl group, followed by acetal formation between the C$_3$ hydroxyl group and C$_{15}$, disposed on the concave face of the molecule. In contemplating the synthesis of the potential Diels−Alder dienophile, **5**, we anticipated that the lactone functionality (**4**) could be installed through an as-yet unspecified oxidative lactonization protocol (**3** → **4**). From the outset, it was presumed that precursor **3** might be generated through a Claisen-like rearrangement of an allylic alcohol of the type **2**. It was further supposed, with what was ultimately revealed to be unwarranted optimism, that the sigmatropic rearrangement would occur with high stereoselectively *anti* to the resident protected alcohol. Operating under the Claisen rearrangement paradigm, the need for an eventual inversion of configuration at C$_3$ (i.e., **2** → **4**) was anticipated.

Studies Directed toward a Stereoselective Claisen Rearrangement. Our synthesis of the pre-Claisen rearrangement substrate (**11**) commenced with the known dienol **8**,[16] which was protected as the -TBS ether to provide **9** (Scheme 2). Catalytic oxidation with selenium dioxide on silica gel (5%)[17] mediated by *tert*-butylhydrogen peroxide as a co-oxidant afforded the desired allylic alcohol **10**. In an effort to achieve maximum efficiency, we evaluated the feasibility of executing the ring-closing metathesis directly with the *unprotected* allylic alcohol **10**. We were pleased to find that when diene **10** was heated in benzene under reflux, with slow addition of the Grubbs second-generation catalyst,[18] the cycopentenyl adduct **11**, incorporating a tetrasubstituted olefin, was isolated in 82% yield. It should be noted that the RCM route described here constitutes a *major simplification* to the preparation of **11**. Under this protocol, adduct **11** was accessed in 35% overall yield in three steps, while the previously reported literature procedure requires nine steps for the synthesis of this key intermediate.[19] This protocol also represents one of only a few instances in which RCM has been employed to generate a tetrasubstituted olefin.[20]

With **11** in hand, we now turned our attention to the key Claisen rearrangement. To our surprise, the key rearrangement

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SCHEME 3. Hydroxylactonization vs Iodolactonization[a]
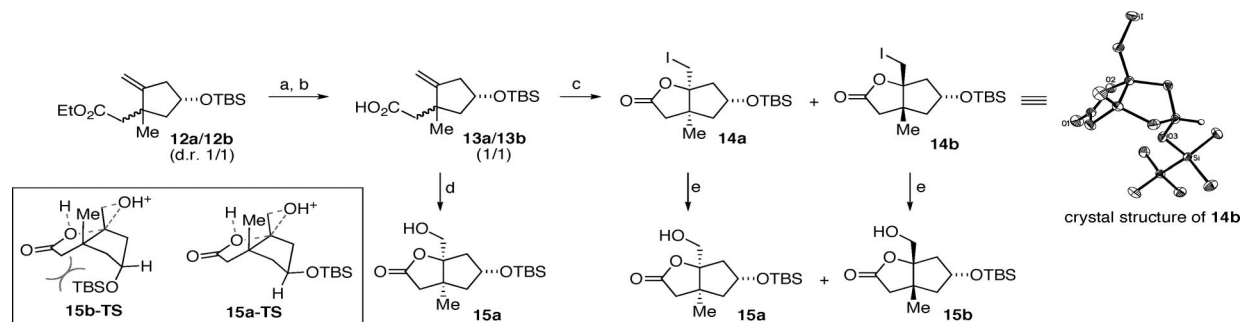
[a] Reagents and conditions: (a) DIBAL-H (1.0 M in toluene, 1.1 equiv), CH$_2$Cl$_2$, −78 °C, 20 min; (b) NaClO$_2$ (6.0 equiv), NaH$_2$PO$_4$−H$_2$O (6.0 equiv), 2-methyl-2-butene (2.0 M in THF, 8.0 equiv), *t*-BuOH, rt, 5 h; (c) NaHCO$_3$ (3.0 equiv), KI (1.3 equiv), I$_2$ (1.3 equiv), THF, rt, overnight, 76% over three steps; (d) *m*CPBA (1.2 equiv), CH$_2$Cl$_2$, 0 °C to rt, 30% for **15a**; 0% for **15b**; (e) AIBN (1.0 equiv), Bu$_3$SnH (3.0 equiv), dry air, toluene, 60 °C, 2 days; then NaBH$_4$ (2.0 equiv), EtOH, 0 °C, 2 h, 75−78%.

SCHEME 4. Synthesis of Dienophile 20[a]
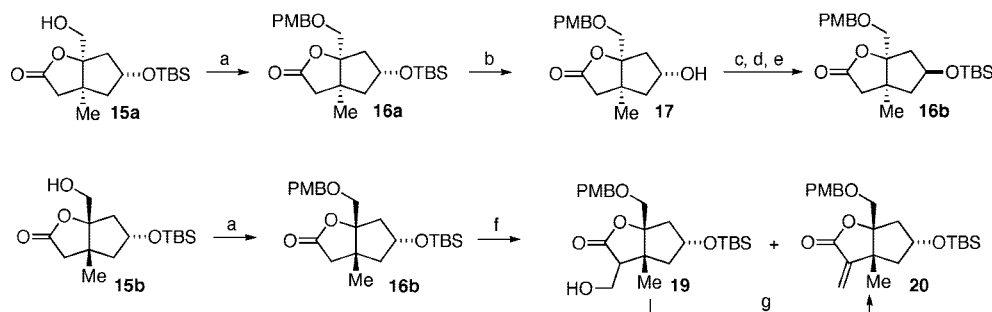
[a] Reagents and conditions: (a) PMB trichloroacetimidate (1.2 equiv), CSA (0.1 equiv), CH$_2$Cl$_2$, rt, overnight, 95%; (b) TBAF (1.0 M in THF, 2.0 equiv), THF, rt, overnight, 87%; (c) PPh$_3$ (1.2 equiv), PhCOOH (1.2 equiv), DIAD (1.2 equiv), toluene, rt, 3 h; (d) K$_2$CO$_3$ (1.0 equiv), MeOH, rt, 7 h, 98%; (e) TBSOTf (2.0 equiv), 2,6-lutidine (20 equiv), CH$_2$Cl$_2$, 0 °C to rt, overnight, 95%; (f) LDA (1.2 equiv), THF, −78 °C, 30 min; then CH$_2$O (gas), 0 °C, 5 min; then rt, overnight, **19**: 65%, **20**: 28%; (g) MsCl (2.0 equiv), TEA (4.0 equiv), CH$_2$Cl$_2$, 0 °C to rt, 4 h; then, DBU (3.0 equiv), CH$_2$Cl$_2$, 3 h, rt, 95%.

proved problematic: all of our efforts to effect an Ireland−Claisen[21] rearrangement of **11** were fruitless. Attempts to employ the Still[22] and Inanaga protocols[23] to introduce the methylene group directly were also unproductive. Fortunately, we were able to achieve rearrangement through the use of the Johnson−Claisen protocol.[24] Surprisingly, at the time, the quaternary carbon center was elaborated with a complete lack of diastereoselectivity (**12a**:**12b** = 1:1). In an attempt to achieve some level of diastereoselectivity, we replaced the silyl protecting group on the secondary alcohol with more electron-deficient functionalities, such as acetate. The hope was that this type of functionality might exhibit some electronic interaction with the electron-rich ketene acetal moiety. However, under all conditions examined, the rearrangement gave 1:1 mixtures of rearranged products.

The diastereomeric mixture of **12a** and **12b** was transformed to carboxylic acids **13a/13b** through a two-step protocol involving DIBAL-H reduction and Pinnick oxidation (Scheme 3).[25] Subsequent iodolactonization afforded a separable mixture of iodides **14a** and **14b** in 76% yield over three steps.[26] The relative stereochemistry of **14b** was confirmed by X-ray

crystallography. Aerobic tin hydride-mediated radical reactions[27] served to convert the iodolactones (**14a** and **14b**) to hydroxy-lactones (**15a** and **15b**, respectively). Interestingly, we also found that when the 1:1 mixture of **13a** and **13b** was treated with *m*-CPBA in CH$_2$Cl$_2$, only **15a** was obtained, in 30% yield. Presumably it is the product of direct hydroxylactonization,[28] without the intermediate formation of epoxide. We speculate that diastereomer **13b**, which does not react under these conditions, most likely would suffer from prohibitive steric interactions in positioning the large -TBS-protected hydroxyl group in the concave face in the transition state (see **15b-TS**). In fact, the observed result supports the notion of a direct hydroxylactonization pathway. A hypothetical intermediate epoxide would have been expected to emerge on the face opposite the resident TBS ether group. Subsequent epoxide ring opening by the intramolecularly appended carboxylate would produce **15b**, rather than the observed product **15a**.

To gain access to sufficient quantities of dienophile **20** to explore the key Diels−Alder reaction, lactones **15a** and **15b** were separately advanced to the same intermediate, **16b**. As outlined in Scheme 4, the free alcohols of **15a** and **15b** were protected as the PMB ethers.[29] Epimer **16a** was then converted to intermediate **16b** through a Mitsunobu reaction,[30] which served to invert the stereocenter at the carbon bearing the

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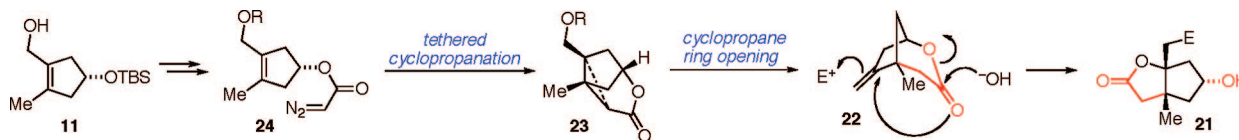
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SCHEME 5.   Intramolecular Cyclopropanation and Ring-Opening Fragmentation

SCHEME 6.   Synthesis of Dienophile 20 via Cyclopropanation and Fragmentation[a]
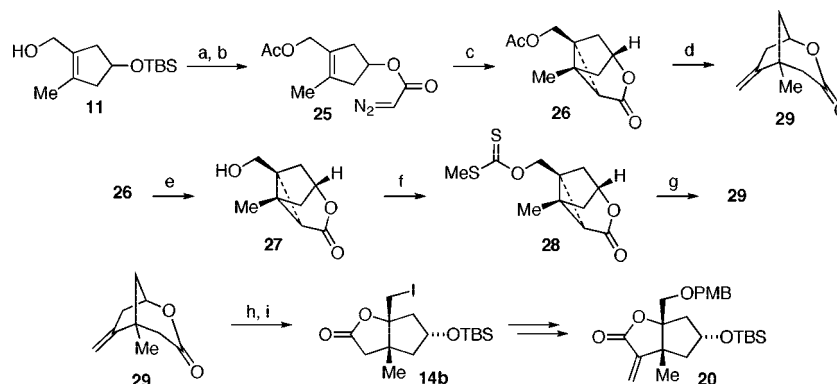
[a] Reagents and conditions: Key: (a) Ac$_2$O, DMAP, TEA, CH$_2$Cl$_2$, rt; TBAF, THF, rt, 84% over two steps; (b) glyoxylic acid chloride tosylhydrazone, *N,N*-dimethylaniline; TEA, CH$_2$Cl$_2$, 0 °C to rt, 88%; (c) bis(*N-tert*-butylsalicylaldiminato)copper(II), tol., reflux, (slow addition of starting material), 91%; (d) Li/NH$_3$, THF, −78 °C to reflux, 1 h, 0−30%; (e) K$_2$CO$_3$, MeOH, rt; (f) KHMDS; CS$_2$; MeI, THF, rt; (g) *n*-Bu$_3$SnH, AIBN, tol., 110 °C, 5 h, 60% over three steps; (h) KOH, MeOH, 60 °C; HCl, then NaHCO$_3$, KI, I$_2$, THF, rt; (i) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C to rt, 77% over three steps.

secondary alcohol. Mindful of the sterically hindered environment adjacent to the α-carbon of lactone **16b**, we elected to employ Grieco's protocol[31] to elaborate **16b** to the α-methylene lactone **20**. The expected hydroxymethyl lactone **19** was obtained in 65% yield, along with 28% of α-methylene lactone **20**. Compound **19** was then fully converted to **20** in 95% yield through standard mesylation followed by base induced β-elimination. It is worth mentioning in passing that the hindered α-methylene could not be installed through the use of Eschenmoser's salt[32] or Bredereck's reagent.[33]

Intramolecular Cyclopropanation and Radical-Initiated Fragmentation. Although we could, in practice, reincorporate each of the Claisen adducts (**12a** and **12b**) into our synthesis through a multistep process (Scheme 4), this strategy would force us to compromise in terms of both synthetic efficiency and aesthetic standards. Upon reflection, we began to consider an alternative means by which we might stereoselectively gain access to our target γ,δ-unsaturated esters. As outlined in Scheme 5, we envisioned that bicyclo compound **21** could be obtained from [3.2.1]bicyclolactone **22** due to the *cis*-relationship between the highlighted carboxylate and secondary alcohol moieties. Presumably, **22** could be accessed through a reductive or radical-based ring opening of the cyclopropane ring in compound **23**, operating through cleavage of the Walsh bond.[34] The latter, in turn, would be assembled through an intramolecularly tethered cyclopropanation of **24** (itself derived from **11**). Through such an intramolecular cyclopropanation, we hoped to secure the critical *cis*-relationship between the 2-carbon carboxylate and the secondary hydroxyl group. It was this defined stereochemical relationship which had eluded us under the original Claisen paradigm.

The modified route (see Scheme 6) commenced with the previously synthesized compound **11**. The latter was advanced to **25** through a straightfoward sequence consisting of protection of the primary alcohol, removal of the TBS protecting group, and installation of the diazoacetic ester through the Corey−Myers modified House's procedure.[35] Upon thermal decomposition in the presence of catalytic bis(*N-tert*-butylsalicylaldiminato)copper(II) in toluene, diazoester **25** smoothly underwent intramolecular cyclopropanation to provide the activated cyclopropane **26** in excellent yield.[36] We note that no dimerization or C−H insertion products were observed when copper(II) was used as catalyst, though we did find slow introduction of diazoester **25** into the reaction to be critical. In screening various reaction conditions for reductive ring-opening fragmentation, it seemed to us that Li/NH$_3$ was the most efficient reducing system, though affording only a 30% yield of **29**. Furthermore, the reaction suffered from poor reproducibility. Accordingly, we sought an alternate fragmentation protocol. Upon further investigation, we identified a reliable route from **26** to **29**. Thus, selective K$_2$CO$_3$-mediated deprotection of the acetate in the presence of the strained lactone afforded primary alcohol **27**, which was then readily transformed to xanthate **28**. Finally, Barton−McCombie deoxygenation[37] triggered the tandem radical process, giving rise to [3.2.1]bicyclolactone **29** in over 60% yield for three steps. Hydrolysis of **29** followed by iodolactonization[38] and TBS protection afforded intermediate **14b**, which could be transformed to dienophile **20** using the chemistry described above (Schemes 3 and 4).

It is instructive to reflect on the implications of the interplay between the Claisen and cyclopropanation routes. Consider substrate **11**; under the Claisen protocol, this starting material

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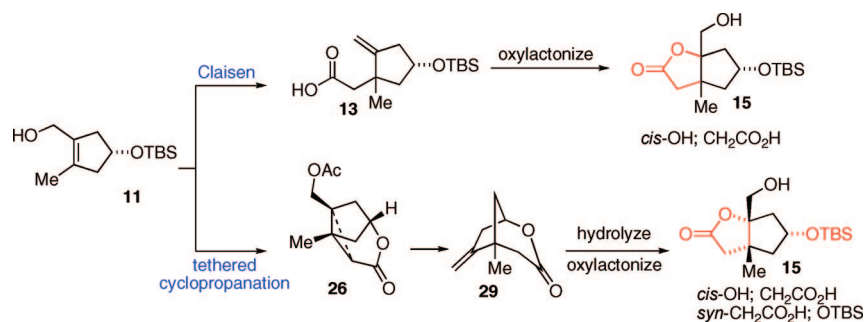(34) Walsh, A. D. *Nature* **1947**, *159*, 165 and 712.

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SCHEME 7. Claisen vs Tethered Cyclopropanation Strategy

**SCHEME 8. Diels−Alder Reaction and Transannular Acetal Formation**[a]
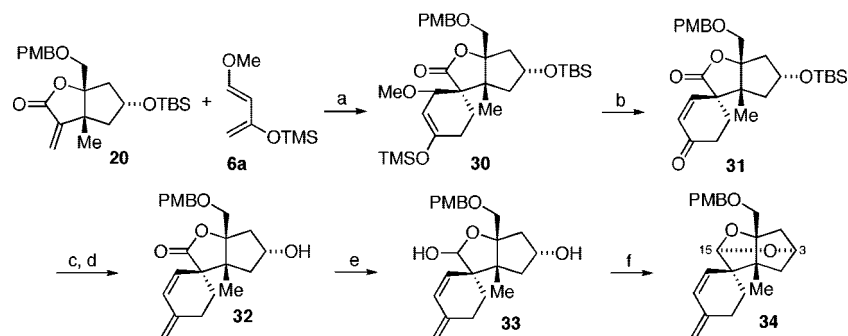
[a] Reagents and conditions: (a) **6a** (10 equiv), methylene blue (0.01 equiv), toluene, 180 °C, 2 days; (b) Amberlite I-120 (acidic), CH$_2$Cl$_2$, rt, 30 min, 90%, 8:1 dr; (c) Ph$_3$P$^+$CH$_3$I$^-$ (6.0 equiv), KHMDS (0.5 M in toluene, 5 equiv), −78 °C; then rt overnight, 96%; (d) TBAF (1.0 M in THF, 2.0 equiv), THF, rt, 1 h, 97%; (e) DIBAL-H (1.0 M in toluene, 2.2 equiv), CH$_2$Cl$_2$, −78 °C, 20 min; (f) CSA (0.36 equiv), 4 Å MS, CH$_2$Cl$_2$, rt, 75 min, 90%.

SCHEME 9. Nonstereoselective Introduction of C$_9$ Stereocenter[a]
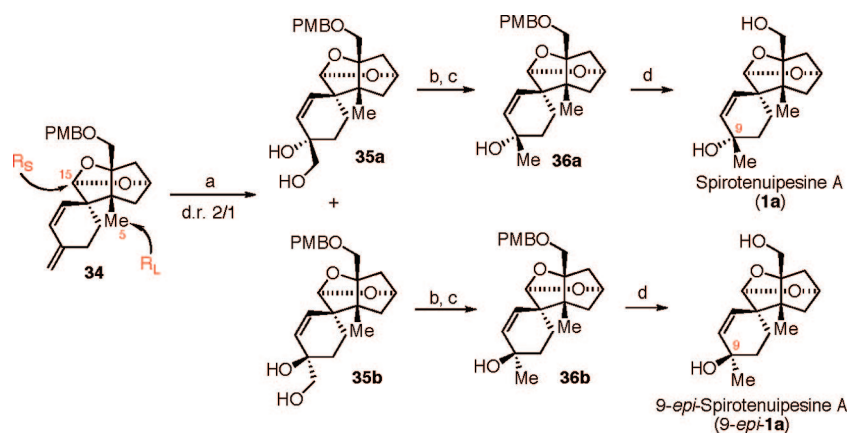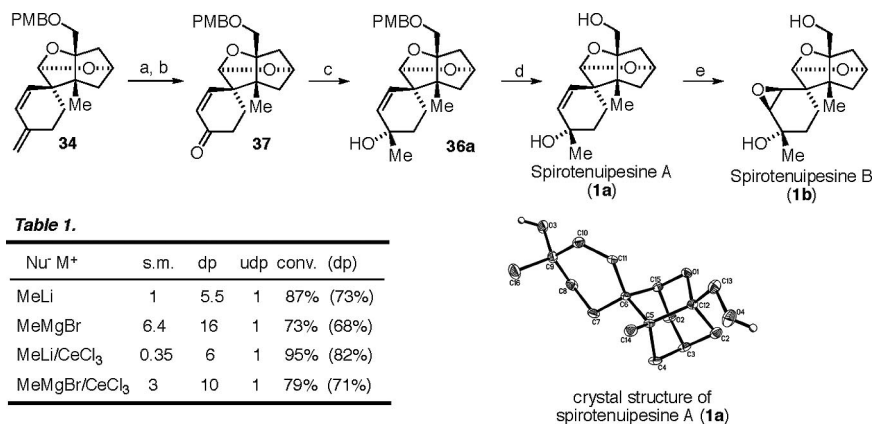

[a] Reagents and conditions: (a) OsO$_4$ (0.05 M in toluene, 1.1 equiv), pyridine, rt, 1.5 h; (b) MsCl (20 equiv), pyridine (40 equiv), CH$_2$Cl$_2$, 15 h, rt, 81%; (c) Super-H (1.0 M in THF, 4.0 equiv), THF, 0 °C, 45 min, 62%; (d) DDQ (2.0 equiv), CH$_2$Cl$_2$/buffer solution pH = 7.00 (18:1), rt, 5 h, 80%.

undergoes what might be viewed as an enelike carboxymethylation (see **13**, Scheme 7). Subsequently, through formal oxylactonization, **15** is produced. In sum, there has been accomplished the equivalent of a *cis*-hydroxycarboxymethylation. However, the relationship between the lactone and the resident OTBS group is not specified. By contrast, the tethered cyclopropanation route leads to **26**. Subsequent site-specific vicinal reductive cleavage again accomplishes overall *cis*-hydroxycarboxymethylation (see **15**) with the important proviso that the cis-bridgehead substituents are now disposed syn to the OTBS group.

Completion of the Total Synthesis of Spirotenuipesines A and B. With an efficient and stereoselective synthesis of dienophile **20** accomplished, we now turned our attention to the critical Diels−Alder reaction. It was anticipated that **20** and

SCHEME 10. Stereochemical Analysis at C$_9$
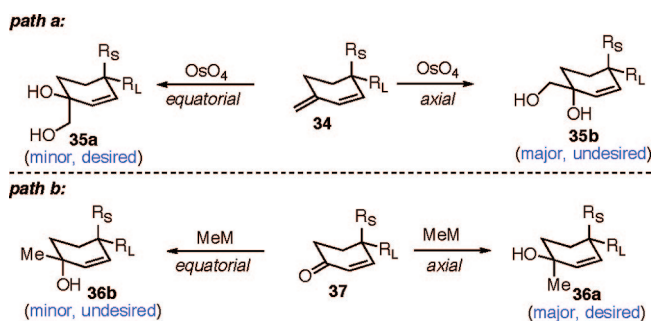
6a would undergo a diastereoselective Diels−Alder cycloaddition, wherein the diene **6a** would approach from the much less hindered convex face of dienophile **20**. The resident TBS

SCHEME 11. Completion of the Total Synthesis of Spirotenuipesine A and B[a]

Table 1.

Nu⁻ M⁺	s.m.	dp	udp	conv. (dp)
MeLi	1	5.5	1	87% (73%)
MeMgBr	6.4	16	1	73% (68%)
MeLi/CeCl₃	0.35	6	1	95% (82%)
MeMgBr/CeCl₃	3	10	1	79% (71%)

crystal structure of
spirotenuipesine A (**1a**)

[a] Reagents and conditions: (a) OsO₄ (0.05 M in toluene, 1.1 equiv), pyridine, rt, 1.5 h; (b) NaIO₄, THF/H₂O (1:1), 0 °C to rt, 2 h, 90%; (c) CH₃M (see Table 1 above, 10 equiv), THF, −78 °C, then 0 °C, 3 h; (d) DDQ (2.0 equiv), CH₂Cl₂/buffer solution pH = 7.00 (18:1), rt, 5 h, 80%; (e) Oxone (12.5 equiv), CH₂Cl₂/MeOH/phosphate buffer (pH 9.2)/acetone (1:4:2:0.3), 0 °C, 6 h, 91%.

ether located on the concave face of dienophile **20** would be expected to reinforce the sense of diastereoselectivity. Not surprisingly, the desired cycloadduct **30** was obtained upon heating diene **6a** and dienophile **20** in toluene, with methylene blue as stabilizer (Scheme 8). The cycloadduct **30** formed as a mixture of stereoisomers. Without further purification, both components were hydrolyzed by acidic Amberlite I-120 to afford a separable mixture of enones (dr 8:1), from which the desired epimer, **31**, was isolated in 80% yield.

We hoped next to convert the C₉ ketone function to a terminal olefin group and to install the requisite C₃−C₁₅ transannular acetal functionality. Thus, enone **31** was advanced to **32** through Wittig methenylation followed by removal of the -TBS protecting group. Subsequent lactone reduction afforded hemiacetal **33** as a 2:1 mixture of isomers. Somewhat surprisingly, **33** is apparently quite stable, and only trace amounts of material cyclized spontaneously after 2 days at room temperature. Upon exposure to catalytic amounts of camphorsulfonic acid and molecular sieves for 1 h, transannular acetal **34** was obtained in 90% yield.

The final challenge to be faced was that of installing the tertiary alcohol at C₉ with the required stereochemistry. We first considered a straightforward strategy involving oxidation of the *exo*-methylene group of **34**. However, all efforts to epoxidize the *exo*-methylene group were unsuccessful, and chemoselective dihydroxylation using OsO₄ in pyridine afforded a 2:1 mixture of diastereomers (**35b** and **35a**, Scheme 9). Upon mesylation, followed by superhydride reduction and removal of the PMB ether, we learned that the major epimer (**35b**) was the undesired one, leading to formation of 9-*epi*-spirotenuipesine. It would seem that the *tert*-butyl-like large group (RL) at C₅ locks the conformation of the cyclohexenyl ring, forcing C₁₅ (RS) into a *pseudo*-axial position. Thus, OsO₄ approaches the exomethylene group from its outside axial face, presumably in order to avoid torsional strain. The major product is **35b** (Scheme 10). It seemed that, by reversing the sequence of introduction of the methyl and hydroxyl groups, we would be able to establish the stereochemistry at C₉ in the desired sense. As depicted in Scheme 10, path b, a generic methyl nucleophile (MeM) would be expected to deliver the methyl group through axial attack of ketone **37**, giving the desired **36a** as the major product.

To test this hypothesis, we converted **34** to **37** through dihydroxylation followed by oxidative cleavage (Scheme 11).[39] Diastereoselective nucleophilic methylation was accomplished through the action of methyllithium and ceric chloride,[40] thereby affording **36a** in 82% yield with 6:1 stereoselection in the desired sense. Higher ratios of diastereoselection could be achieved (16:1), though in reduced yield, with methylmagnesium bromide (73%) (Table 1 in Scheme 11). As hoped, it was found that stereoselection does indeed favor attack of the nucleophile from the axial face, wherein the sp³ spiro center serves as an equatorially based conformational lock. The total synthesis of spirotenuipesine A (**1a**) was now completed upon removal of the PMB group, as shown. In addition to the congruencies of the spectral properties with those of natural product, our assignments are secured by a crystallographic determination of fully synthetic **1a**. Parenthetically, we note that we could convert **1a** to **1b** following a reported protocol.[13]

Asymmetric Synthesis of Spirotenuipesines A and B. Upon completion of the syntheses of racemic spirotenuipesine A (**1a**) and B (**1b**), we devised a second-generation asymmetric route. In examining our first-generation synthesis, we focused on reaching dienyl alcohol **10** or cyclopentenyl alcohol **11** in optically active form. With the absolute stereochemistry of the secondary alcohol established at an early stage of the synthesis, we could be confident that our first-generation diastereoselective route would enable the installation of the subsequent stereocenters in the desired sense. Two possible strategies for the synthesis of enantioenriched or enantiopure **11** presented themselves (Scheme 12). Both routes would begin with readily available optically active (*R*)-epichlorohydrin (**38**). The first (path a) envisions sequential openings of **38**, first with isopropenyl cuprate **39** and then with functionalized isopropenyl cuprate **40**, as shown, to ultimately give rise to an intermediate of the type **41**. The unspecified "X" group would be transformed into a hydroxyl group to afford substrate **10**, which is the precursor for the previously discussed RCM reaction. In an alternate route (path b), sequential opening of **38** with isopropenyl cuprate **39** and acetylide **42** would eventually afford an intermediate of the type **43**. Ring-closing enyne metathesis

(39) Garlaschelli, L.; de Tullio, P.; Vidari, G. *Tetrahedron* **1991**, *47*, 6769.
(40) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

SCHEME 12.   Synthetic Plan for the Asymmetric Synthesis of Spirotenuipesines A and B
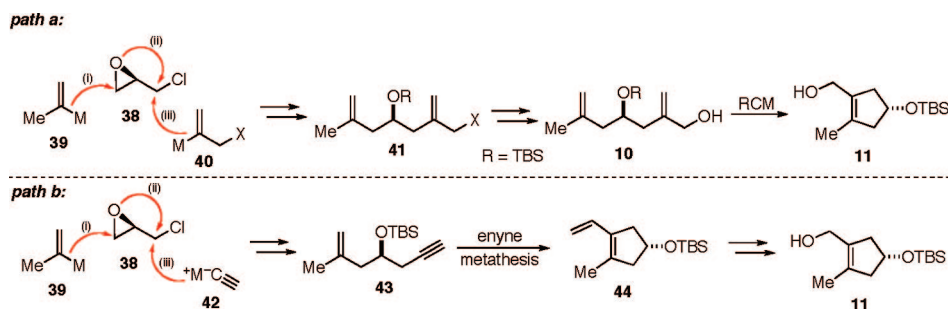
SCHEME 13.   Asymmetric Synthesis of 10^a
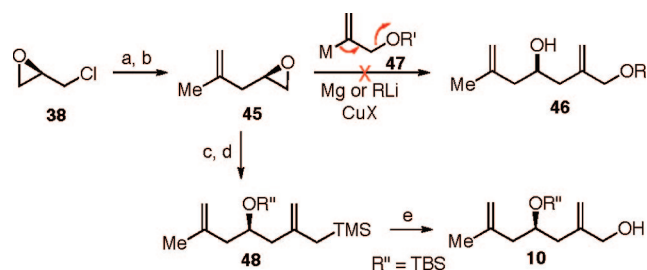
^a Reagents and conditions: (a) CuI cat., 2-propenylmagnesium bromide, Et$_2$O −78 to −30 °C, 15 min; then R-(−)-epichlorohydrin, −30 to −20 °C; (b) NaOH, CH$_2$Cl$_2$, 24 h, 58% for two steps; (c) Mg (0), 1,2-dibromoethane, 1-bromo-1-trimethylsilylmethylethene, reflux, THF; epoxide 45, CuI, THF, −60 °C, 2 h, 98%; (d) TBSCl, imidazole, DMF, 0 °C to rt, 24 h, 93%; (e) PhSeCl, SnCl$_2$ cat., CH$_2$Cl$_2$, −78 to 0 °C, 23 min; then 30% (wt) H$_2$O$_2$, pyridine, CH$_2$Cl$_2$, 20 min, 73%.

would then give rise to **44**, which, following suitable degradation of the terminal olefin, would provide **11**.

As shown in Scheme 13, the viability of path a was investigated. Following treatment with isopropenyl cuprate, R-(−)-epichlorohydrin underwent the desired epoxide ring opening/ring closure sequence to afford **45**. Our preliminary efforts to attack the newly generated epoxide of **45** with cuprate reagents derived from 2-bromoprop-2-en-1-ol[41] or its ethers (cf. **47**) were unsuccessful, presumably due to low reactivity or to 1,2-elimination of the cuprate, which would lead to unproductive formation of allene.[42,43] An alternate cuprate reagent, derived from 1-bromo-1-trimethylsilylmethylethene,[44] was chosen to avoid the problem of 1,2-elimination. The expectation was that the TMS group could be subsequently transformed into the requisite hydroxyl group.[45] As shown in Scheme 13, under these conditions compound **48** was formed in excellent yield from **45** through a two-step sequence of cuprate addition and

(41) Cousseau, J. *Synthesis* **1980**, 805.
(42) (a) Corey, E. J.; Widiger, G. N. *J. Org. Chem.* **1975**, *40*, 2975. (b) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016.
(43) We also made enyne intermediate A by the following sequential epoxide ring openings with following deprotection and protection procedures. However, enyne metathesis of A gave diene B as a minor product as well as triene C as major product. The difficulties encountered by selective oxidative cleavage of B and C discouraged us from further pursuing this route.
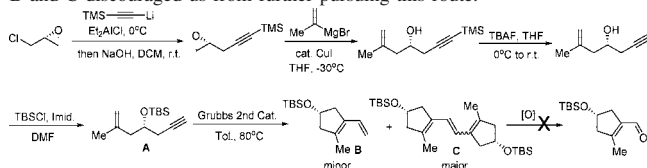
(44) (a) O'Brien, M.; Taylor, N. H.; Thomas, E. R. *Tetrahedron Lett.* **2002**, *43*, 5491. (b) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12058.
(45) Nishiyama, H.; Itagaki, K.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5285.

protection of the resultant secondary alcohol. Upon exposure to PhSeCl and subsequent H$_2$O$_2$ oxidation, the optically active alcohol **10** was generated. We noted that this two-step sequence provided a general solution to the problem of 1,2-elimination of metallo-reagents bearing oxygenated leaving groups. With an efficient route to enantioenriched **10** in hand, we are confident that we now have means by which to gain entry into the optically active series of spirotenuipesines A and B.

Conclusion

In summary, the syntheses of spirotenuipesines A (**1a**) and B (**1b**) have been accomplished. Key features of the synthesis include (1) the development of an improved RCM route to the tetrasubstituted cyclopentenyl system, **11**, (2) the diastereoselective synthesis of the key bicyclic lactone **21** through recourse to a tethered cyclopropanation strategy, and (3) the stereoselective assembly of the spirocyclic system through Diels−Alder reaction between α-methylenelactone dienophile **20** and synergistic diene **6a**.[46] We have further developed a strategy by which to access optically active spirotenuipesines A and B through the synthesis of enantioenriched **10**.

At a biological level, the concise stereocontrolled total syntheses have allowed us access to sufficient quantities of material to begin to study the biological activity of these compounds. Biological studies are underway and will be reported in due course.

Experimental Section

(R)-2-(2-Methylallyl)oxirane (45). To a suspension of CuI (1.73 g, 9.08 mmol) in Et$_2$O (90 mL) was added 2-propenylmagnesium bromide (0.5 M in THF, 100 mL, 50 mmol) at −78 °C. The resulting mixture was placed in a −30 °C bath for 15 min, and then R-(−)-epichlorohydrin (3.56 mL, 45.4 mmol) was added dropwise. The mixture was stirred for 30 min at −30 to −20 °C, by which time the initial yellow-orange color had turned to black. The reaction was quenched with saturated aqueous NH$_4$Cl and washed with 4 × 20 mL of H$_2$O to give 6.2 g chlorohydrin as a colorless oil, which by ^{1}H NMR contained a small amount of THF but was otherwise pure. ^{1}H NMR (500 MHz, CDCl$_3$): 4.91 (s, 1H), 4.83 (s, 1H), 3.98 (m, 1H), 3.63 (dd, J = 11.1, 3.8 Hz, 1H), 3.53 (dd, J = 11.1, 6.4 Hz, 1H), 2.30 (m, 2H), 2.18 (d, J = 3.9 Hz, 1H), 1.78 (s, 3H).

The above crude chlorohydrin (6.2 g, ~45 mmol) was dissolved in 50 mL of CH$_2$Cl$_2$, crushed NaOH pellets (3.6 g, 90 mmol) were added, and the resulting suspension was stirred at room temperature for 24 h (reaction was monitored by ^{1}H NMR of aliquots). MgSO$_4$ was then added, and the reaction mixture was filtered and

(46) For earlier precedents: (a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (b) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.

concentrated at 30 °C/450 mmHg to remove almost all solvent. The remaining small amount of THF was removed by a short column of SiO_2, eluting with 5:1 pentane/Et_2O. Fractions were concentrated to remove almost all solvent at 30 °C/450 mmHg. The final 2−3 mL solvent was removed by evaporation under N_2 stream to give pure, solvent-free epoxide **45**, 2.6 g (58% over two steps) as a colorless volatile oil. $[\alpha]^{22.8}_D$ +2.7 (*c* 1.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 4.83 (app s, 2H), 3.03 (m, 1H), 2.79 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.50 (dd, *J* = 2.8, 5.2 Hz, 1H), 2.28 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.19 (dd, *J* = 15.2, 5.2 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 141.2, 112.1, 51.1, 46.9, 40.8, 23.0. MS (APCI+): calcd for $C_6H_{11}O$ (M + H) 99.07, found 99.23.

(R)-2-Methyl-6-((trimethylsilyl)methyl)hepta-1,6-dien-4-ol. Magnesium turnings (1.24 g, 51.8 mmol) were flame-dried under an argon atmosphere. After the mixture was cooled to room temperature, THF (5 mL) was added. To this mixture was added 1,2-dibromoethane (50 μL) to activate the magnesium turnings. Neat 1-bromo-1-trimethylsilylmethylethene (1.0 g, 5.18 mmol) was added slowly (15 min). Reflux was maintained for another 30 min.

To a cold (−60 °C) solution of epoxide **45** (270 mg, 2.75 mmol) in THF (5 mL) was added copper(I) iodide (74.5 mg, 0.39 mmol). The above Grignard solution in THF was added quickly to the suspension. A THF rinse (3 mL) of the Grignard solution was also added to the suspension. After the reaction was warmed from −60 °C to room temperature over 2 h, the mixture was quenched with aqueous saturated NH_4Cl. The mixture was diluted with ether, washed with aqueous saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate: 12/1) to give the desired product (573 mg, 98%). $[\alpha]^{21.8}_D$ +13.5 (*c* 0.53, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 4.87 (s, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 3.89 (m, 1H), 2.06−2.21 (m, 4H), 1.99 (s, 1H), 1.79 (s, 3H), 1.61 (d, *J* = 13.2 Hz, 1H), 1.55 (d, *J* = 13.2 Hz, 1H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.5, 142.7, 113.0, 110.1, 66.5, 46.0, 45.5, 26.7, 22.5, −1.5. MS (APCI+): calcd for $C_{12}H_{23}OSi$ (M − H) 211.16, found 211.23.

(R)-tert-Butyldimethyl(2-methyl-6-((trimethylsilyl)methyl)hepta-1,6-dien-4-yloxy)silane (48). To a solution of the above material (124 mg, 0.585 mmol) in 3 mL of DMF were added imidazole (80 mg, 1.17 mmol) and TBSCl (106 mg, 0.70 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 20 mL of water and extracted with ether (3 × 20 mL). The combined organic phases were washed with water and brine, respectively, dried over $MgSO_4$, and concentrated to give **48** (178 mg, 93%) without further purification. $[\alpha]^{21.3}_D$ +1.84 (*c* 1.24, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 4.78 (s, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 4.58 (s, 1H), 3.93 (m, 1H), 2.08−2.24 (m, 4H), 1.74 (s, 3H), 1.55 (d, *J* = 13.6 Hz,

1H), 1.51 (d, *J* = 13.6 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.4, 142.9, 113.0, 109.9, 70.0, 46.1, 27.1, 25.9, 23.0, 18.1, −1.1, −1.4, −4.4, −4.5. MS (APCI+): calcd for $C_{18}H_{39}OSi_2$ (M + H) 327.2, found 327.4.

(R)-4-(tert-Butyldimethylsilyloxy)-6-methyl-2-methylenehept-6-en-1-ol (10). To a solution of **48** (56 mg, 0.17 mmol) in 3 mL of CH_2Cl_2 were added PhSeCl (28 mg, 0.143 mmol) and a catalytic amount of $SnCl_2$ at −78 °C. The reaction was stirred at −78 °C for 17 min, warmed to 0 °C, and stirred for another 23 min. After the solvent was removed, the residue was put on a Florisil column for 15 min. The selenide was washed off the column with hexane/ethyl acetate (10/1). After concentration, the selenide was subsequently treated with 30% (wt) H_2O_2 (162 mg, 1.43 mmol) and pyridine (23 μL) in CH_2Cl_2 (3 mL) at 0 °C for 20 min. The reaction mixture was quenched with aqueous 20% $Na_2S_2O_3$, diluted with ether, washed with 20% $Na_2S_2O_3$, 1 N HCl, aqueous saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (hexane/ethyl acetate: 8/1) to give desired product **10** (34 mg, 88% based on PhSeCl or 73% based on **48**). $[\alpha]^{23.3}_D$ +22.3 (*c* 0.93, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 5.11 (s, 1H), 4.90 (s, 1H), 4.80 (s, 1H), 4.73 (s, 1H), 4.05 (d, *J* = 6.40 Hz, 2H), 3.98 (m, 1H), 2.81 (t, *J* = 6.40 Hz, 1H), 2.26 (m, 4H), 1.73 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 145.6, 142.2, 114.0, 113.3, 70.4, 66.4, 45.2, 41.1, 25.8, 22.8, 18.0, −4.66, −4.71. HRMS (FAB+): calcd for $C_{15}H_{31}O_2Si$ 271.2093, found 271.2079.

Supporting Information Available: Experimental procedures and characterization for new compounds and crystallographic data for compounds **14b** and **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8016814