JOC Article

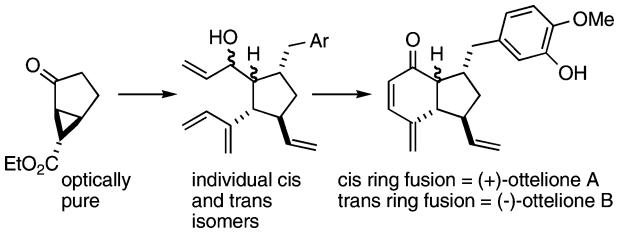
Synthesis of the Potent Anticancer Agents Ottelione A and Ottelione B in Both Racemic and Natural Optically Pure Forms

Derrick L. J. Clive* and Dazhan Liu

Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

derrick.clive@ualberta.ca

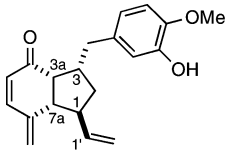
Received December 12, 2007



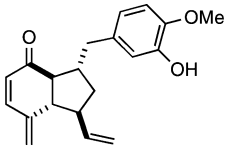
The powerful antitumor agents ottelione A and B were synthesized in racemic form by a method that relies on selective ring closing metathesis. Optically pure natural (+)-ottelione A was then made from D-ribose, via an α-keto cyclopropane. A key feature of the route is that the cyclopropyl group controls the stereochemistry in the attachment of the $ArCH_2$ unit and is then converted by the action of SmI_2 into a vinyl group, so that the substituents on the resulting five-membered ring have the required trans relationship. Epimerization of an intermediate gave access by the same method to the trans ring fused isomer (−)-ottelione B.

Introduction

The otteliones, designated as A (**1**)[1,2] and B (**2**),[1] are exceedingly powerful anticancer agents,[1] as judged by in vitro tests against a large panel of tumor cell lines. Both compounds were isolated from a freshwater plant, *Ottelia alismoides*,[3] collected in Egypt,[1] but the amount of each obtained represented only 0.0009% of the dried weight of the sample. Structural

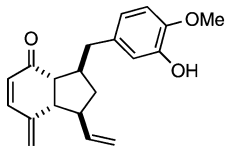


1 (+)-ottelione A)

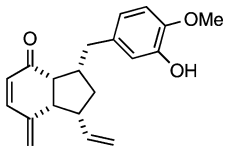


2 (-)-ottelione B)

studies were undertaken in the United States,[1] and extensive NMR investigations served to identify the structure and relative stereochemistry of ottelione B as shown in **2**. In the case of ottelione A, however, these studies suggested the two possibilities, **3** and **4**.



3



4

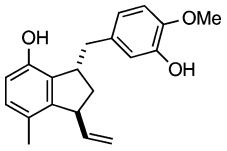
Ottelione A was found to be identical to a compound, also isolated from *O. alismoides*, that had been described without any stereochemistry assignment in a Rhone−Poulenc Rorer patent.[2] A later publication from the Rhone−Poulenc Rorer laboratories[4] assigned the relative stereochemistry shown in **1** to ottelione A, based on NOE measurements, and this conclusion was subsequently confirmed by synthesis of the racemic compound.[5] Both the NMR structural work[1] and the investigations at Rhone−Poulenc Rorer[2,4] were combined with biological evaluations that served to identify the extremely strong anticancer activity. In the case of the evaluation[1] at the National Cancer Institute (U.S.) against a panel of ca. 60 tumor cell lines, the impressive level of activity was quantified, and the compounds were found to have GI_{50} values in the subnanomolar

(1) Ayyad, S.-E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102−8106.
(2) Leboul, J.; Provost, J. WO 96/00205.
(3) Cook, C. D. K.; Symoens, J.-J.; Urmi-König, K. *Aquatic Botany* **1984**, *18*, 263−274.
(4) Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharmacol.* **2000**, *57*, 553−563. This publication identifies what is here called ottelione A as substance PRP112378.
(5) Mehta, G.; Islam, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2396−2398.

10.1021/jo702635t CCC: $40.75
Published on Web 03/15/2008

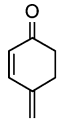
to picomolar range. Ottelione B appears to be less potent than ottelione A. Ottelione A has been shown to inhibit tubulin polymerization and is able to disassemble preformed microtubules.[4] Some of the information available on the anticancer activity of the otteliones appears to have been reported only in a Ph.D. Thesis[6] and in the Abstracts of ACS National Meetings.[7] Ottelione B appears to be more selective toward cancer cell lines than ottelione A.[6] Extracts of *O. alismoides* also have been reported to kill tubercular bacteria.[8]

Examination of the structures of the otteliones raises the possibility that they might be prone to tautomerization to the aromatic compound **5**, and in fact, **5** was isolated along with **1**[2]

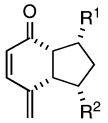


5

and is also cytotoxic; its tubulin activity, however, is only a fifth of that of ottelione A.[4] A few extended dienone systems, such as **6**[9,10] and **7a**,**b**,[9c] have been known for many years; they were prepared under seemingly harsh conditions but do not readily aromatize.

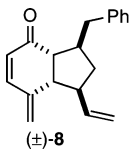


6

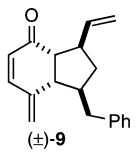


7a,b R^1 = vinyl, R^2 = H; R^1 = H, R^2 = vinyl

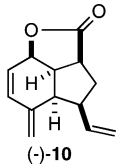
The potent anticancer properties of the otteliones clearly make them important synthetic objectives. As mentioned previously, synthetic studies have played a role in establishing the structure of ottelione A. The majority[11] of the early synthetic work in this area was reported from Mehta's laboratory. Chemists in his group first prepared the model compounds (±)-**8**,[12] (±)-**9**,[12] and (−)-**10**.[13] With the experience thus gained, structure **1**



(±)-**8**

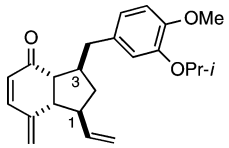


(±)-**9**

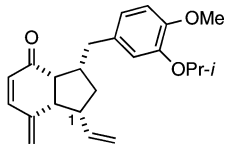


(-)-**10**

was synthesized in a racemic form and was shown to correspond to ottelione A.[5] The remarkable key observation was also made[5] that the treatment of (±)-ottelione A with DBU in hot benzene converted it smoothly (83% yield) into the trans ring fused isomer, ottelione B. During the course of these studies, the racemic *epi*-ottelione derivatives **11** and **12** also were prepared.[14]



11



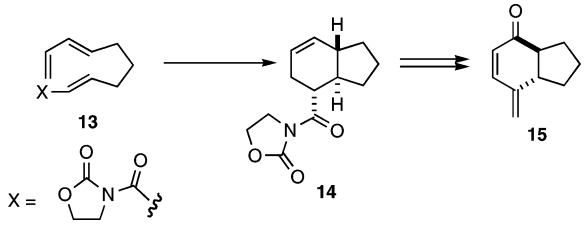
12

Finally, Mehta and Islam described the synthesis of both antipodes of otteliones A and B[15] and established that the natural compounds have the absolute configurations depicted by structures **1** and **2**. Again, the synthesis of ottelione B was by way of a DBU-induced epimerization of the cis isomer (83% yield). At the same time Katoh et al. independently synthesized natural (+)-ottelione A and epimerized it to (−)-ottelione B.[16] However, they reported that epimerization with DBU gave a 1:1 mixture of the two otteliones and found that the epimerization was best performed with *t*-BuOK in *t*-BuOH—conditions that led to a 1:3.3 mixture of the A/B isomers. Separation was difficult but could be achieved by chiral HPLC to give ottelione B (the major isomer of the mixture) in 23% yield. The same group also prepared 3-*epi*-ottelione A in optically pure form.[17] A very recent paper[18] gives full details of the Japanese work including growth inhibition data and inhibitory activity against tubulin polymerization for (+)-ottelione A (**1**), (+)-3-*epi*-ottelione A, and (+)-*O*-acetyl-3-*epi*-ottelione A; all are extremely potent in both respects but may not act by the same mechanism.

Discussion

Preliminary Work. Our own work was begun before any total synthesis had been completed and was initially aimed at **15**, the core structure of ottelione B. This model was eventually reached[19] by way of an intramolecular Diels−Alder reaction mediated by a chiral catalyst (Scheme 1). Just after that model

SCHEME 1. Model Study for Core Structure of Ottelione B



study was completed, the short synthesis of both racemic otteliones was reported by Mehta and Islam,[5] and it did not seem appropriate to continue with our own much longer route. However, about a year later when the syntheses of optically pure otteliones was published from two laboratories—both using

(6) Lewis, H. J. Ph.D. Thesis, University of Minnesota, 2005 (*Diss. Abstr. Int. B* **2005**, *66*, 2073).

(7) (a) Scully, S. L.; Ghose, S.; Marine, S.; Islam, K.; Hoye, T. R.; Mehta, G.; Sreerama, L. *Abstracts of Papers*, 233rd ACS National Meeting, Chicago, IL, March, 25−29, 2007. (b) Dechaine, J. L.; Lewis, H. J.; Ayyad, S.-E. N.; Hoye, T. R.; Sreerama, L. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, March 23−27, 2003.

(8) Li, H.; Li, H.; Qu, X.; Zhao, D.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi* **1995**, *20*, 115−116, 128.

(9) The dienone system of the otteliones is very rare. For examples, see: (a) Birch, A. J. *Proc. R. Soc. N. S. W.* **1949**, *83*, 245−250. (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197−203. (c) Murray, D. F.; Baum, M. W.; Jones, M., Jr. *J. Org. Chem.* **1986**, *51*, 1−7.

(10) Dienone **6** underwent both 1,4- and 1,6-addition with cuprates: Wild, H. *J. Org. Chem.* **1994**, *59*, 2748−2761.

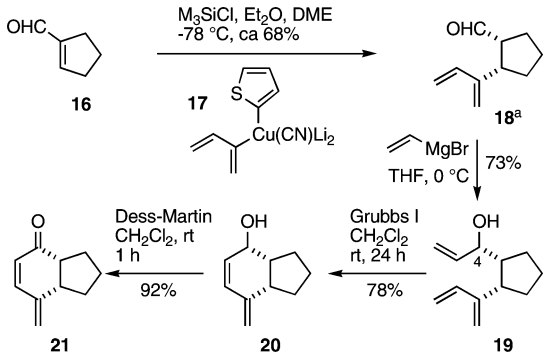
(11) For other synthetic work, see: (a) Hanson, G. H.; Hoye, T. R.; Burke, S. D. *Abstracts of Papers*, 234th ACS National Meeting, Boston, MA, August 19−23, 2007. (b) Kabrhel, J. E. Ph.D. Thesis, University of Minnesota, 2006 (*Diss. Abstr. Int. B* **2007**, *67*, 4425). (c) Ref 7b. (d) Judd, A. S. Ph.D. Thesis, University of Minnesota, 1999 (*Diss. Abstr. Int. B* **2000**, *60*, 5522). (e) Ref 6. (f) Trembleau, L.; Patiny, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 6377−6381. (g) Hoye, T. R.; Lewis, H. J.; Ayyad, S.-E. N.; Hans, J. J. *Abstracts of Papers*, 224th ACS National Meeting, Boston, MA Aug 18−22, 2002.

(12) Mehta, G.; Srinivasa Reddy, D. *Chem. Commun. (Cambridge, U.K.)* **1999**, 2193−2194.

the base-induced isomerization of ottelione A to ottelione B—it became clear that routes involving the A → B isomerization were not straightforward so that further synthetic work on the otteliones was clearly justified, especially in view of their exceptional anticancer potency. Therefore, we took up the project again but with a new plan and, as before, adopted the cautious approach of first making the core structure, although this time we made both core structures,[20] as described next.

Second Generation Route to Core Structures. The readily available unsaturated aldehyde **16**[21] (Scheme 2) was subjected to conjugate addition, using the organocuprate **17**[22,23] in the presence of Me_3SiCl.[24] The conjugate addition[25] gave a mixture of cis and trans isomers that was mainly (ca. 95%) the desired cis compound **18**.

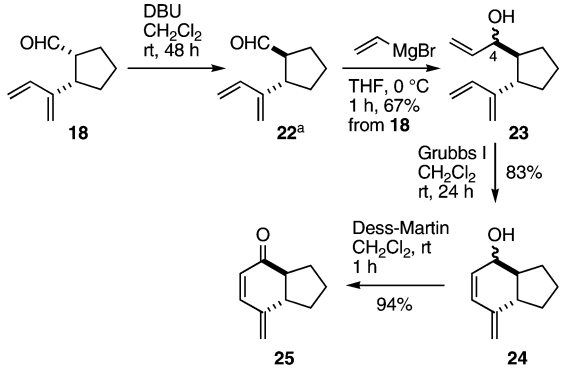
SCHEME 2. Synthesis of Ottelione a Core Structure Based on Ring Closing Metathesis



[a] Material contains ca. 5% of the trans isomer.

Reaction with vinylmagnesium bromide afforded alcohol **19** as a single isomer whose stereochemistry at C(4) (ottelione numbering) was not determined and is, in any case, inconsequential. In the presence of the Grubbs I catalyst (5 mol %), ring closing metathesis occurred to give **20** in 78% yield. This regiochemical outcome was expected, as preferential closure involving the less substituted double bond of a 1,3-diene unit has been observed previously.[26] Finally, Dess—Martin oxidation gave **21**, the core of ottelione A.

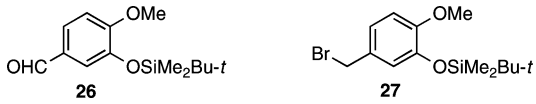
SCHEME 3. Synthesis of Ottelione B Core Structure Based on Ring Closing Metathesis



[a] Material contains ca. 15% of cis isomer.

The trans ring fused core was then made from **18** (Scheme 3). To this end, the aldehyde was exposed to the action of DBU for 48 h at room temperature to produce material that was largely (ca 85%) the trans isomer **22**. Reaction with vinylmagnesium bromide proceeded without incident, and it was possible to isolate **23** (67% yield) as a mixture of C(4) epimers in both of which the side arms on the five-membered ring were trans. Once again, ring closing metathesis with the Grubbs I catalyst was efficient (83%), and the resulting alcohols **24** were oxidized with the Dess—Martin reagent so as to produce **25**, the core of ottelione B. Even though **24** has a trans ring fusion, the ring closing metathesis still involves preferential cyclization via the less substituted double bond of the 1,3-butadiene unit; this preference would appear to be general.

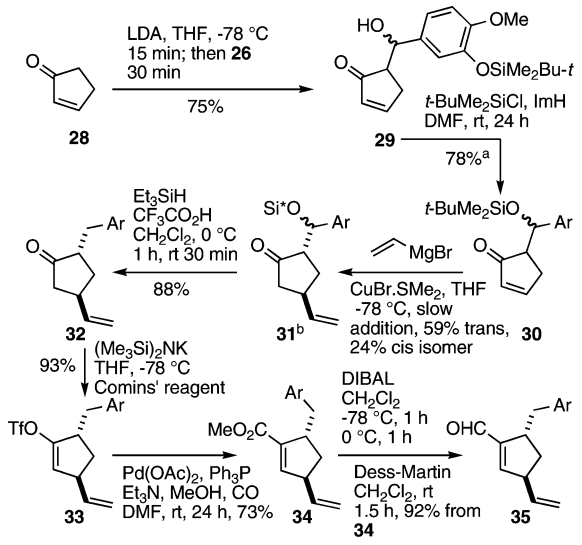
With both the cis and the trans ring fused models in hand, we were able to examine briefly the possibility of epimerizing the cis isomer into the trans isomer, but treatment with DBU in CH_2Cl_2 or in refluxing DME or refluxing PhMe did not effect epimerization to any significant extent.



Synthesis of Racemic Otteliones. At this stage of our studies, the next obvious problem was to introduce substituents on the five-membered ring. Suitable precursors to the aromatic subunit appeared to be the readily available aldehyde **26**[27] and the derived bromide **27**.[28] Attempts to use the bromide for alkylation of 2-cyclopentenone or cyclopentanone were unpromising, but aldol condensation of 2-cyclopentenone[29] with aldehyde **26** worked well (**28** → **29**, 75%). Further experimentation quickly showed that the C(1) vinyl group was best introduced by using the O-silylated aldols **30** (Scheme 4). These were treated with cuprate made from vinylmagnesium bromide and the CuBr·SMe_2 complex. The conjugate addition gave **31** in 59% yield, as well as the corresponding material with cis substituents on the ring (24%). The desired product (**31**) was a 3:1 mixture of epimers differing at the siloxy-bearing carbon. We note that little work has been done on the relative thermodynamic stability

(13) Mehta, G; Islam, K. *Synlett* **2000**, 1473—1475.
(14) Mehta, G.; Islam, K. *Org. Lett.* **2002**, *4*, 2881—2884.
(15) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 6733—6736.
(16) Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903—3906.
(17) Araki, H.; Inoue, M; Katoh, T. *Synlett* **2003**, 2401—2403.
(18) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem.—Eur. J.* **2007**, *13*, 9866—9881.
(19) Clive, D. L. J.; Fletcher, S. P. *J. Chem. Soc., Chem. Commun.* **2002**, 1940—1941.
(20) Preliminary communication: Clive, D. L. J.; Liu, D. *Tetrahedron Lett.* **2005**, *46*, 5305—5307.
(21) Kozikowski, A. P.; Tückmantel, W. *J. Org. Chem.* **1991**, *56*, 2826—2837.
(22) Prepared from lithium 2-thienylcyanocuprate and 2-lithio-1,3-butadiene, which was generated by the literature route: (a) Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans 1* **1986**, 1129—1131. (b) Brown, P. A.; Jenkins, P. R. *Tetrahedron Lett.* **1982**, *23*, 3733—3734. (c) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147—154.
(23) 2-Lithio-1,3-butadiene is also available from 2-(tributylstannyl)-1,3-butadiene: Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1942—1945.
(24) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019—6022. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047—1050.
(25) Kende, A. S.; Jungheim, L. N. *Tetrahedron Lett.* **1980**, *21*, 3849—3852.
(26) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310—7318.
(27) Pettit, G. R.; Singh, S. B.; Cragg, G. M. *J. Org. Chem.* **1985**, *50*, 3404—3406.
(28) Sing, S. B.; Pettit, G. R. *J. Org. Chem.* **1989**, *54*, 4105—4114.
(29) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110—7123.

SCHEME 4. Route to α,β-Unsaturated Aldehyde Needed for Synthesis of Racemic Otteliones

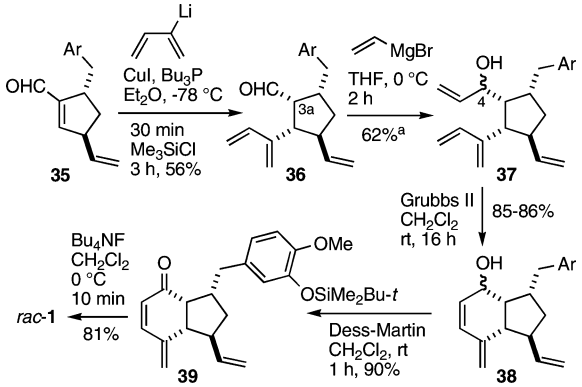


[a] Corrected for recovered **29**. [b] Si* = *t*-BuMe$_2$Si.

of the cis and trans isomers of 2,4-disubstituted cyclopentanones, but the cis isomer appears to be more stable in those few cases examined.[30] At this point, the siloxy group was removed by the action of Et_3SiH[31] in the presence of CF_3CO_2H (**31** → **32**). Various sequences for the last few steps—hydroxyl protection, conjugate addition, and deoxygenation—were examined; that shown in Scheme 4 proved to be the most satisfactory.

Ketone **32** was converted regioselectively into the enol triflate[32] **33**, and this was carbonylated[33] in the presence of MeOH so as to afford ester **34**. Overreduction with DIBAL-H and Dess−Martin oxidation gave the key aldehyde **35**. This compound corresponds to aldehyde **16** used in our model studies on the core skeleton but now carries the required peripheral substituents, and the stage was set for construction of the six-membered ring, which we hoped to accomplish by exactly the same procedure used for the models.

SCHEME 5. Final Steps in Synthesis of Racemic Ottelione A

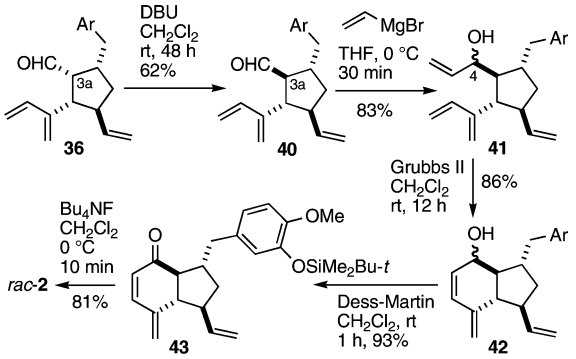


[a] Two isomers obtained in 48 and 14% yields, respectively.

Methyl vinyl ketone was converted into a hydrazone[22a] by reaction with (2,4,6-tri-isopropylbenzene)sulfonylhydrazine[34] and then, by reaction with MeLi, into 2-lithio-1,3-butadiene.[22a] This was converted into the corresponding cuprate by reaction with Bu$_3$P·CuI.[35] The cuprate, in turn, was allowed to react in the presence of Me_3SiCl[24] with enal **35**. The crude product was a mixture of **36** and the corresponding C(3a) epimer, with **36** being the major product (>7:1 to >10:1). The crude material was treated with vinylmagnesium bromide, and a mixture of the allylic alcohols **37** epimeric at C(4) was isolated. The minor isomer (14% yield) and the major isomer (48% yield) were individually subjected to the action of the Grubbs II[36] catalyst in CH_2Cl_2 at room temperature for 16 h. In both cases, ring closing metathesis occurred in the desired fashion. The yield was high (85−86%), and the presence of an additional double bond in the starting material as compared to our model system **19** did not introduce any complications. On the basis of the result of a single experiment with a mixture of epimeric alcohols, the Grubbs I catalyst appeared to work just as well. Dess−Martin oxidation of each alcohol to ketone **39** was likewise uneventful (90%), but the final deprotection of the resulting ketone **39** with Bu_4NF had to be monitored closely, as too long a reaction time caused decomposition of the product. When performed in ice-cold CH_2Cl_2 for 15 min, the desilylation gave racemic ottelione A in 81% yield. Our first experiments were performed in THF, but in this solvent, neither the starting material nor the desired product were obtained.

Aldehyde **36** was then used to produce ottelione B (Scheme 6). Epimerization at C(3a) was again achieved by the action of

SCHEME 6. Final Steps in Synthesis of Racemic Ottelione B



DBU, and aldehyde **40** could be isolated in 62% yield. Reaction with vinylmagnesium bromide gave **41** (83%) as an inseparable mixture of C(4) epimers. Once again, the ring closing metathesis worked well and without any sign of interference from the C(1) vinyl group. Dess−Martin oxidation of alcohols **42** (as a mixture of C(4) epimers) and controlled desilylation now presented no difficulties, and we obtained pure racemic ottelione B. Its NMR spectra are clearly distinguishable from those of ottelione A.

Synthesis of Optically Pure Otteliones.[37] The previous synthesis of the racemic otteliones established that the ring

(30) (a) Harispe, M.; Méa, D.; Horeau, A.; Jacques, J. *Bull. Soc. Chim. Fr*. **1963**, 472−475. (b) Varech, D.; Jacques, J. *Bull. Soc. Chim. Fr*. **1969**, 3505−3515. (c) Sprung, I.; Anhalt, K.; Wahren, U.; Schulze, K. *Monatsh. Chem*. **1999**, *130*, 341−354.

(31) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *47*, 10807−10816.

(32) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

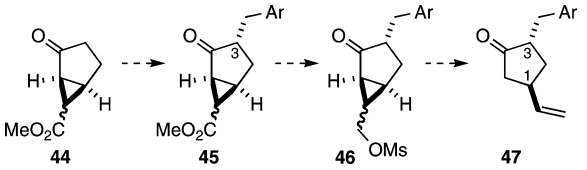
(33) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109−1112.

(34) Cusak, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157−2162.

(35) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1247−1250.

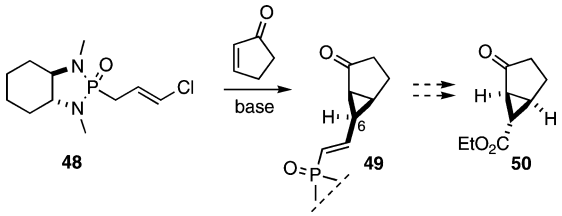
(36) Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV)-dichloride.

SCHEME 7. Planned Approach to Disubstituted Cyclopentanone Needed for Synthesis of Optically Pure Otteliones



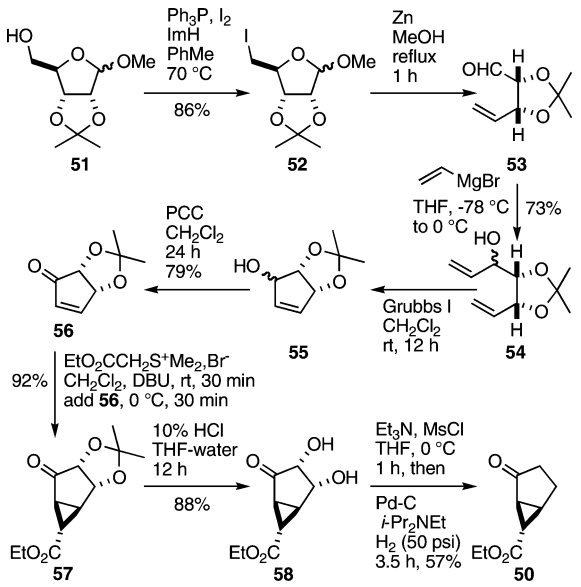
closing metathesis procedure was a reliable method for the tetraenes we had used, but our experiments also had shown that setting up the trans stereochemistry of the C(1) and C(3) substituents by conjugate addition gave an unsatisfactory ratio of epimers. Our experiments also gave no guidance as to how to make optically pure materials. Careful consideration of these two problems—how to improve the trans/cis selectivity and how to obtain optically pure material—suggested that starting materials of type **44** (or synthetically equivalent substances) might satisfy our requirements in all respects: we anticipated that alkylation at C(3) would occur anti to the cyclopropyl group, and if the ester was converted into a leaving group (cf. **45** → **46**), then reduction with SmI_2 might serve to open the cyclopropane and convert it into a vinyl group (cf. **46** → **47**), the overall result being that the cyclopropane would initially serve as a steric shield and then as a vinyl precursor. A very convenient aspect of this plan was that optically pure compounds of type **44** and synthetically equivalent species were already available by literature methods. In particular, the asymmetric cyclopropanation method of Hanessian et al.[38] (Scheme 8) seemed well-suited to our needs, as did routes starting from a carbohydrate. In the case of asymmetric cyclopropanation, we expected that the intermediate **49** would be readily convertible into ester **50**, and in the event, this proved to be the case.[39] Although we used this cyclopropanation in exploratory experiments, most of our work was based on a route from D-ribose because we then avoided the necessity of checking the optical purity of each batch.

SCHEME 8. Route to Optically Pure Cyclopropane by Asymmetric Synthesis



The individual steps of the carbohydrate route were selected from a number of different publications, and we eventually found an acceptable combination of procedures[40] that is summarized in Scheme 9.[41] Methyl 2,3-*O*-ispropylidene-D-ribofuranosides (**51**)[42] were converted into the corresponding iodides **52** using I_2/Ph_3P,[43] and treatment with Zn then generated aldehyde **53** that, without purification, was treated with vinylmagnesium bromide. The resulting epimeric alcohols **54** underwent ring closing metathesis (**54** → **55**) in the presence of the Grubbs I catalyst. PCC oxidation took the route as far as enone **56**, and this was cyclopropanated in near quantitative yield by reaction with (carboethoxymethyl)dimethylsulfonium bromide [$Me_2S^+CH_2CO_2Et\ Br^-$] in the presence of DBU.[44] Acidic hydrolysis then liberated diol **58**, which was converted into the key compound **50** by dimesylation and reduction over Pd−C in the presence of Hünig's base. This last step may involve both hydrogenation and hydrogenolysis or merely two hydrogenation steps.[45]

SCHEME 9. Route to Optically Pure Cyclopropane from Chiral Pool



With the cyclopropane in hand, the next task was to attach the aromatic subunit. Alkylation with bromide **27** gave a poor yield (42%), but aldol condensation with aldehyde **26**, followed by deoxygenation[46] (**50** → **59** → **60**), was satisfactory (79% overall).

Reduction of both carbonyls (**60** → **61**), selective pivaloylation of the primary hydroxyl in **61**, and reoxidation of the remaining secondary hydroxyl produced the cyclopropyl ketone **63**—the substrate for the crucial ring opening that would make the cyclopropyl unit discharge its last function by serving as a precursor to the C(1) vinyl group. On treatment below 0 °C with freshly prepared SmI_2,[47] the desired change (**63** → **47**) occurred in good yield (82%),[48] bringing the work to a point

(37) Preliminary communication: Clive, D. L. J.; Liu, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 3738−3740.

(38) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393−10394.

(39) We prepared the required phosphorus reagent using a Z/E mixture of 1,3-dichloro-1-propenes and obtained a C(6) epimeric mixture of cyclopropanes that, upon ozonolysis, gave an epimeric mixture of acids. The derived ethyl esters were separated to afford ester **50**.

(40) Most of the sequence (**51** → **56**) turned out to be the same as that used previously by others: (a) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beuchamp, G. K. *Org. Lett.* **2005**, *7*, 5075−5078. (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993−3996.

(41) See Supporting Information for a summary chart of the two other routes we examined.

(42) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853−3857.

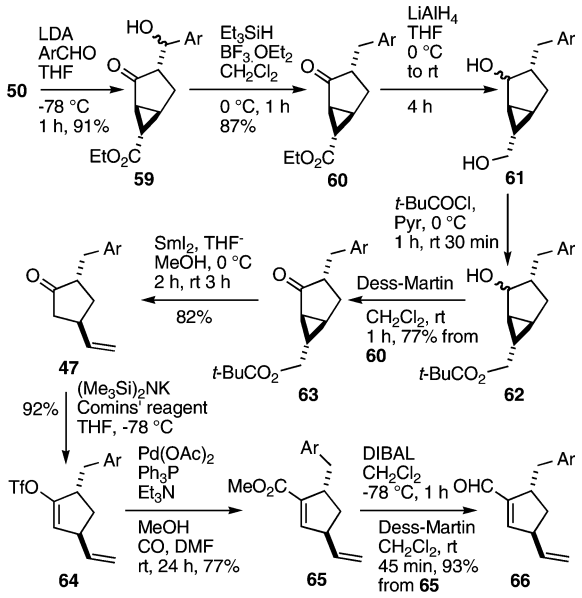
(43) (a) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849−7856. (b) Palmer, A. M.; Jäger, V. *Eur. J. Org. Chem.* **2001**, 1293−1308.

(44) (a) Domínguez, C.; Ezquerra, J.; Prieto, L.; Espada, M.; Pedregal, C. *Tetrahedron: Asymmetry* **1997**, *8*, 511−514. (b) Collado, I.; Domínguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. *Tetrahedron Lett.* **1997**, *38*, 2133−2136.

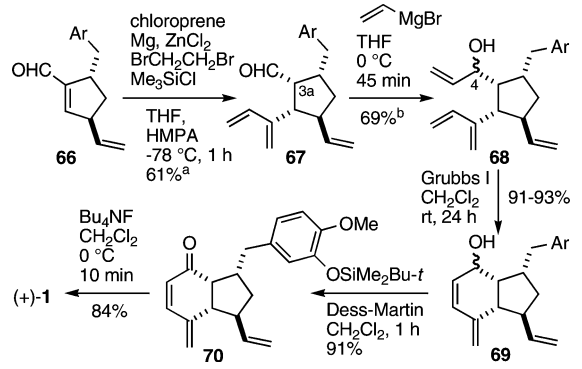
(45) Kalwinch, I.; Metten, K.-H.; Brückner, R. *Heterocycles* **1995**, *40*, 939−952.

(46) Orfanopoulos, M.; Smonou, I. *Synth. Commun.* **1988**, *18*, 833−839.

SCHEME 10. Route to Optically Pure Aldehyde by Ring Opening of Cyclopropane



SCHEME 11. Synthesis of Optically Pure Ottelione A

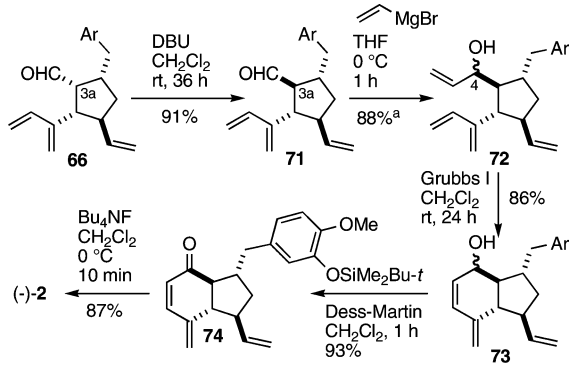


[a] Product **67** is mainly (7:1 to 10:1) the indicated stereoisomer. [b] Two isomers obtained in 50 and 19% yields, respectively.

that overlaps structurally with our route to the racemic otteliones. The choice of a pivaloate for the monoprotection of alcohols **61** was dictated by the greater selectivity in this protection as compared to the use of a benzoate, but the benzoate also underwent the samarium-induced reaction.

Ketone **47** was deprotonated with $(Me_3Si)_2NK$ under kinetic conditions, and the enolate was quenched with Comins' reagent[32] to afford enol triflate **64**. This was carbonylated by a standard method[49] in the presence of MeOH so as to produce ester **65**. Reduction with DIBAL-H and reoxidation gave aldehyde **66**, from which point the procedure used to make racemic otteliones was followed, with minor variations (Schemes 11 and 12), except for the conjugate addition step (Scheme 11, **66** → **67**), which was performed with a magnesium-derived

SCHEME 12. Synthesis of Optically Pure Ottelione B



[a] Compound **72** is a 5:3 mixture of C(4) epimers.

cuprate,[50] in the presence[51] of both Me_3SiCl and HMPA. The conjugate addition occurred exclusively trans to the C(1) vinyl group, and protonation gave mainly (7:1 to 10:1) the indicated stereochemistry (see **67**). The final product, (+)-ottelione A, had a specific rotation very close to the values reported by Mehta and Islam[5] and Katoh et al.[16,18]

As implied previously, diversion of aldehyde **67** to (−)-ottelione B was performed (Scheme 12) by the methods first used with racemic compounds. Our sample of (−)-ottelione B formed crystals suitable for X-ray analysis, but the structure did not provide any obvious evidence that would account for the absence of facile aromatization. The X-ray data (Figure 1) showed that the six-membered ring is in a half-chair conformation with the vinyl group oriented in such a way that the hydrogen atoms at C(1′) and C(7a) are syn and both of the C−H bonds are parallel. The dihedral angle between the carbonyl group and the C(3a)−H bond is about 114°. We were unable to crystallize (+)-ottelione A.

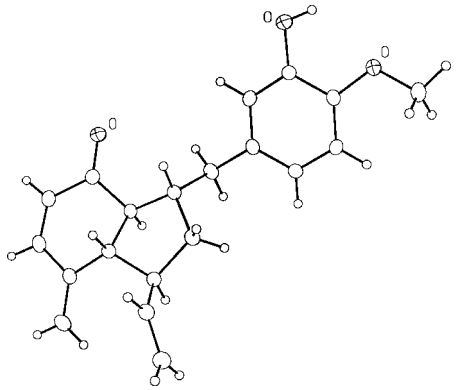


FIGURE 1. ORTEP diagram of (−)-ottelione B.

The specific rotation of our material is close to that reported by Katoh et al.,[16,18] and the compound was easily shown by NMR measurements to be free of contamination by (+)-ottelione A.

Conclusion

The synthetic method described here avoids difficulties encountered in epimerizing ottelione A to ottelione B. Our X-ray

(47) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc*. **1980**, *102*, 2693−2698. (b) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.

(48) For related opening of cyclopropyl ketones, see: (a) Beerli, R.; Brunner, E. J.; Borschberg, H.-J. *Tetrahedron Lett.* **1992**, *33*, 6449−6452. (b) Nivlet, A.; Le Guen, V.; Dechoux, L.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 2115−2118.

(49) Cacchi, S.; Ciatinni, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931−3934.

(50) (a) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc*. **1992**, *114*, 3044−3051. (b) Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003−1006.

(51) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349−362.

structure of ottelione B appears to be the first such measurement for the otteliones, and the route illustrates a very convenient and apparently general level of discrimination between several double bonds in ring closing metathesis. A special feature of the synthesis is the use of a cyclopropane to shield one face of an attached ring and at a later stage to act as a precursor to a vinyl group. It is likely that our approach to the otteliones also could be used to prepare analogues of these very powerful anticancer agents.

Experimental Section

The symbols s, d, t, and q in ^{13}C spectra refer to zero, one, two, or three attached hydrogens, respectively.

(1*S*,3*S*,5*R*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]hydroxymethyl]-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (59). *n*-BuLi (1.6 M in hexane, 2.57 mL, 4.11 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.576 mL, 4.11 mmol) in THF (10 mL). Stirring was continued for 10 min, and the mixture was then cooled to −78 °C. Keto ester **50** (0.574 g, 3.42 mmol) in THF (3 mL plus 0.5 mL as a rinse) was added dropwise, and stirring was continued for 30 min. 3-[(*t*-Butyldimethylsilyl)oxy]-4-methoxybenzaldehyde (**26**[27]) (1.09 g, 4.11 mmol) in THF (3 mL) was added dropwise, and stirring was continued at −78 °C for 60 min. Saturated aqueous NH_4Cl (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 20 cm), using 1:4 EtOAc/hexane, gave **59** (1.35 g, 91%) as a 1:1 mixture (^1H NMR) of two isomers: $[\alpha]_D = 13.4$ (*c* 3.40, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3496, 2954, 2930, 1727, 1511, 1277, 849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, signals for major isomer) δ 0.14−0.15 (m, 6 H), 1.00 (s, 9 H), 1.23−1.27 (m, 3 H), 1.76−1.86 (m, 1.5 H), 1.98 (t, $J = 2.8$ Hz, 0.5 H), 2.11 (t, $J = 3.0$ Hz, 0.5 H), 2.25 (d, $J = 4.0$ Hz, 0.5 H), 2.29−2.37 (m, 2 H), 2.42−2.50 (m, 1.5 H), 3.71 (s, 3 H), 4.11−4.17 (m, 2 H), 4.52 (s, 0.5 H), 4.55 (s, 0.5 H), 5.21 (s, 0.5 H), 6.78−6.84 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, signals for major isomer) δ −4.61 (q), −4.58 (q), 14.1 (q), 18.5 (s), 25.7 (q), 26.8 (q), 27.5 (d), 28.1 (d), 36.0 (d), 48.0 (d), 55.5 (q), 61.3 (t), 75.0 (d), 111.9 (d), 118.2 (d), 119.4 (d), 133.3 (s), 145.0 (s), 150.9 (s), 169.9 (s), 214.74 (s); exact mass *m*/*z* calcd for $C_{23}H_{34}O_6Si$ 434.21246, found 434.21153.

(1*S*,3*S*,5*R*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (60). Et_3SiH (3.95 mL, 24.7 mmol), followed by $BF_3{\cdot}Et_2O$ (0.786 mL, 6.20 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **59** (1.35 g, 3.11 mmol) in CH_2Cl_2 (25 mL). Stirring was continued for 1 h. Saturated aqueous $NaHCO_3$ (15 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 30 cm), using 1:6 EtOAc/hexane, gave **60** (1.12 g, 87%) as a colorless oil: $[\alpha]_D = 8.65$ (*c* 1.65, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2931, 2857, 1730, 1512, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 0.99 (s, 9 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.92 (ddd, $J = 5.2, 8.8, 12.8$ Hz, 1 H), 2.04 (t, $J = 2.8$ Hz, 1 H), 2.13−2.29 (m, 2 H), 2.32−2.34 (m, 2 H), 2.39−2.42 (m, 1 H), 3.04 (dd, $J = 3.8, 13.6$ Hz, 1 H), 3.77 (s, 3 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 6.61−6.66 (m, 2 H), 6.74 (d, $J = 8.4$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.64 (q), −4.61 (q), 14.1 (q), 18.4 (s), 25.7 (q), 27.4 (d), 27.6 (d), 29.5 (t), 34.7 (t), 35.8 (d), 43.5 (d), 55.5 (q), 61.2 (t), 112.2 (d), 121.5 (d), 121.8 (d), 131.8 (s), 144.9 (s), 149.5 (s), 170.4 (s), 211.7 (s); exact mass *m*/*z* calcd for $C_{23}H_{34}O_5Si$ 418.21756, found 418.21677.

2,2-Dimethylpropanoic Acid [(1*S*,3*S*,5*S*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-2-oxobicyclo[3.1.0]hex-6-yl]methyl Ester (63). $LiAlH_4$ (0.873 g, 23.0 mmol) was added to a stirred and cooled (0 °C) solution of **60** (3.20 g, 7.66 mmol) in THF (140 mL). The ice bath was removed, and stirring was continued for 4 h. $Na_2SO_4{\cdot}10H_2O$ (24 g) was added, and the solution was diluted with CH_2Cl_2 (50 mL). Stirring was continued for 20 min, and then the mixture was filtered through a pad of Celite (5 cm × 6 cm), using CH_2Cl_2 (30 mL) as a rinse. The filtrate was dried (Na_2SO_4) and evaporated. The residue was dissolved in THF (100 mL), and the solution was cooled to 0 °C. Pyridine (3.72 mL, 46.0 mmol), followed by *t*-BuCOCl (1.89 mL, 15.3 mmol), was added dropwise with stirring. The ice bath was left in place, but not recharged, and stirring was continued for 1.5 h, the mixture having reached room temperature after 1 h. Water (10 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 cm × 15 cm), using 1:3 hexane/EtOAc, gave a colorless oil that was dissolved in CH_2Cl_2(60 mL).

Dess−Martin periodinane (3.25 g, 7.66 mmol) was added to the previous solution, and the mixture was stirred for 1 h. Saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added. The mixture was stirred for 5 min, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 cm × 20 cm), using 1:6 EtOAc/hexane, gave **63** (2.72 g, 77%) as a yellow oil: $[\alpha]_D = -27.7$ (*c* 0.53, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2956, 2858, 1728, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 1.00 (s, 9 H), 1.19 (s, 9 H), 1.67−1.72 (m, 1 H), 1.80−1.86 (m, 2 H), 1.95 (dd, $J = 5.2, 9.2$ Hz, 1 H), 2.09 (dd, $J = 7.2, 13.2$ Hz, 1 H), 2.23−2.30 (m, 2 H), 3.01−3.08 (m, 1 H), 3.76 (s, 3 H), 3.89 (dd, $J = 6.4, 11.6$ Hz, 1 H), 4.03 (dd, $J = 6.4, 11.6$ Hz, 1 H), 6.61−6.66 (m, 2 H), 6.73 (d, $J = 8$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.64 (q), −4.61 (q), 18.4 (s), 24.7 (d), 25.7 (q), 26.1 (d), 27.1 (q), 29.7 (t), 32.5 (d), 34.8 (t), 38.8 (s), 43.8 (d), 55.5 (q), 64.6 (t), 112.1 (d), 121.5 (d), 121.8 (d), 132.3 (s), 144.9 (s), 149.4 (s), 178.3 (s), 212.9 (s); exact mass *m*/*z* calcd for $C_{26}H_{40}O_5Si$ 460.26450, found 460.26488.

(2*S*,4*R*)-2-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-4-ethenylcyclopentanone (47). A SmI_2 solution (80.2 mL, 0.2 M in THF, concentration calculated on the basis of the amount of 1,2-diiodoethane used, assuming 100% yield) was added dropwise to a stirred and cooled (0 °C) solution of **63** (1.94 g, 4.22 mmol) in 10:1 THF−MeOH (5.5 mL). Stirring at 0 °C was continued for 2 h, and another portion of the SmI_2 solution (20 mL) was added. Stirring at 0 °C was continued for 3 h, and water (15 mL) was added. A few drops of 10% HCl were added to dissolve the white precipitate. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 cm × 20 cm), using 1:10 EtOAc/hexane, gave **47** (1.25 g, 82%) as a colorless oil: $[\alpha]_D = -97.0$ (*c* 1.15, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2954, 2930, 1740, 1511, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.88 (dd, $J = 7.0, 7.0$ Hz, 2 H), 2.21 (dd, $J = 6.4, 18.4$ Hz, 1 H), 2.34 (dd, $J = 7.8, 18.4$ Hz, 1 H), 2.46−2.53 (m, 2 H), 2.77−2.82 (m, 1 H), 2.93 (apparent q, $J = 9.0$ Hz, 1 H), 3.78 (s, 3 H), 4.99 (d, $J = 1.5$ Hz, 1 H), 5.02 (ddd, $J = 1.4, 1.4, 6.0$ Hz, 1 H), 5.83 (ddd, $J = 6.3, 10.0, 17.5$ Hz, 1 H), 6.65−6.70 (m, 2 H), 6.76 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.67 (q), −4.65 (q), 18.4 (s), 25.7 (q), 33.8 (t), 35.2 (t), 36.8 (d), 43.9 (t), 48.6 (d), 55.5 (q), 112.1 (d), 114.0 (t), 121.6 (d), 122.0 (d), 132.0 (s), 140.6 (d), 144.9 (s), 149.5 (s), 219.6 (s); exact mass *m*/*z* calcd for $C_{21}H_{32}O_3Si$ 360.21207, found 360.21273.

1,1,1-Trifluoromethanesulfonic Acid (3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-1-cyclopenten-1-yl Ester (64). A solution of **47** (0.986 g, 2.74 mmol) in THF (5 mL plus 1 mL as a rinse) was added dropwise to

a stirred and cooled (−78 °C) solution of $(Me_3Si)_2NK$ (0.5 M in PhMe, 7.12 mL, 3.56 mmol) in THF (10 mL). Stirring was continued for 1 h, and 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-pyridine[32] (1.28 g, 3.57 mmol) in THF (5 mL plus 1 mL as a rinse) was added dropwise. Stirring was continued for 2 h, and the cold bath was then replaced by an ice bath. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 20 cm), using 1:20 EtOAc/hexane, gave **64** (1.25 g, 92%) as a yellow oil: $[\alpha]_D = 59.9$ (*c* 2.60, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2955, 2931, 1213, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.01 (s, 9 H), 1.76−1.83 (m, 1 H), 1.99 (ddd, J = 5.5, 7.5, 13.5 Hz, 1 H), 2.50 (dd, J = 9.0, 13.5 Hz, 1 H), 2.89 (dd, J = 4.1, 13.5 Hz, 1 H), 3.13 (d, J = 6.5 Hz, 2 H), 3.79 (s, 3 H), 4.94−5.01 (m, 2 H), 5.58 (s, 1 H), 5.70 (ddd, J = 8.0, 9.5, 17.0 Hz, 1 H), 6.67−6.72 (m, 2 H), 6.78 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.68 (q), −4.66 (q), 18.4 (s), 25.7 (q), 33.9 (t), 37.0 (t), 43.0 (d), 44.3 (d), 55.5 (q), 112.0 (d), 114.4 (t), 118.6 (apparent q, J = 320 Hz), 119.9 (d), 121.9 (d), 122.2 (d), 130.9 (s), 140.0 (d), 144.9 (s), 149.6 (s), 151.8 (s); exact mass *m*/*z* calcd for $C_{22}H_{31}F_3O_5SSi$ 492.16135, found 492.16030.

(3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-1-cyclopentene-1-carboxylic Acid Methyl Ester (65). $Pd(OAc)_2$ (56.6 mg, 0.252 mmol), followed by Ph_3P (0.132 mg, 0.503 mmol), Et_3N (0.50 mL), and MeOH (3.0 mL) were added to a stirred solution of **64** (1.24 g, 2.52 mmol) in DMF (8 mL). The mixture was purged with CO for 10 min (via a needle below the solvent surface) and stirred under CO (balloon filled with CO) at room temperature for 24 h. Et_2O (40 mL) was added, and the mixture was washed with water (2 × 25 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 25 cm), using 1:20 EtOAc/hexane, gave **65** (0.78 g, 77%) as a yellow oil: $[\alpha]_D = 52.2$ (*c* 1.80, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2955, 2930, 1719, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.150 (s, 3 H), 0.154 (s, 3 H), 1.00 (s, 9 H), 1.73 (td, J = 8.4, 13.2 Hz, 1 H), 2.00 (ddd, J = 2.4, 7.6, 13.2 Hz, 1 H), 2.43 (dd, J = 8.8, 13.6 Hz, 1 H), 2.96 (dd, J = 4.0, 13.6 Hz, 1 H), 3.21−3.27 (m, 2 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.97−5.01 (m, 2 H), 5.68 (ddd, J = 7.2, 10.0, 17.2 Hz, 1 H), 6.62 (s, 1 H), 6.67 (d, J = 2.0 Hz, 1 H), 6.70 (dd, J = 2.0, 8.4 Hz, 1 H), 6.76 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.66 (q), −4.63 (q), 18.4 (s), 25.7 (q), 35.9 (t), 38.4 (t), 45.5 (d), 48.1 (d), 51.4 (q), 55.5 (q), 111.9 (d), 114.4 (t), 122.1 (d), 122.3 (d), 132.9 (s), 139.4 (s), 139.8 (d), 144.6 (s), 146.4 (d), 149.3 (s), 165.5 (s); exact mass *m*/*z* calcd for $C_{23}H_{34}O_4Si$ 402.22263, found 402.22372.

(3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-1-cyclopentene-1-carboxaldehyde (66). DIBAL-H (1.0 M in CH_2Cl_2, 1.20 mL, 1.20 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **65** (0.220 g, 0.546 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h. $Na_2SO_4 \cdot 10H_2O$ (2.0 g) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a pad of Celite (3 cm × 5 cm), using CH_2Cl_2 (30 mL) as a rinse. The filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (25 mL). Dess−Martin periodinane (0.278 g, 0.655 mmol) was added, and the mixture was stirred for 45 min. Saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (4 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 cm × 15 cm), using 1:10 EtOAc/hexane, gave **66** (0.189 g, 93%) as a colorless oil: $[\alpha]_D = 72.4$ (*c* 1.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2954, 2857, 1682, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.77 (td, J = 8.4, 13.2 Hz, 1 H), 2.04 (ddd, J = 3.2, 8.0, 13.6 Hz, 1 H), 2.40 (dd, J = 9.2, 13.6 Hz, 1 H), 2.99 (dd, J = 4.0, 13.6 Hz, 1 H), 3.26−3.33 (m, 2 H), 3.77 (s, 3 H), 4.98−5.05 (m, 2 H), 5.70 (ddd, J = 7.2, 10.0, 17.2 Hz, 1 H), 6.64−6.70 (m, 3 H), 6.74 (d, J = 8.0 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.64 (q), −4.61 (q), 18.5 (s), 25.6 (q), 36.0 (t), 37.8 (t), 43.3 (d), 48.4 (d), 55.5 (q), 111.9 (d), 115.0 (t), 122.0 (d), 122.4 (d), 132.6 (s), 139.0 (d), 144.6 (s), 149.3 (s), 149.7 (s), 155.3 (d), 189.9 (s); exact mass *m*/*z* calcd for $C_{22}H_{32}O_3Si$ 372.21207, found 372.21199.

(1*R*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarboxaldehyde (67). The chloroprene solution was prepared by slight modification of a literature procedure.[52] DBU (7.15 mL, 47.8 mmol) was added to a stirred and cooled (0 °C) solution of 3,4-dichloro-1-butene (5.0 g, 40.0 mmol) in PhMe (15 mL). The ice bath was removed, and stirring was continued for 2 h. THF (2 mL) and water (1 mL) were added to dissolve the precipitate, and stirring was continued for 2 h. The organic phase was washed with water, 5% hydrochloric acid, saturated aqueous $NaHCO_3$, and brine and then dried ($MgSO_4$). The drying agent was filtered off, using Et_2O as a rinse, and a small amount of CaH_2 was added to the filtrate. The mixture was kept (no stirring) at room temperature for 30 min, THF (20 mL) and 1,2-dibromoethane (0.5 mL) were added, and, after a few minutes, most of the clear solution (ca. 40 mL) was taken up into a syringe.

1,2-Dibromoethane (0.2 mL) was added to a stirred suspension of Mg (1.65 g) in THF (5 mL). The solution was refluxed for 10 min and cooled to room temperature, and $ZnCl_2$ (1.2 mL, 1 M in THF), followed by the previous chloroprene solution (5 mL), was added. The solution was stirred and heated until initiation occurred. The remaining chloroprene solution was added dropwise at a rate to maintain the reaction mixture at reflux, and refluxing was continued for 1 h after the addition was complete. The concentration of this Grignard solution was approximately 0.4 M as determined (^1H NMR) by reaction with an excess of PhCHO.

The previous chloroprene Grignard solution (0.4 M in THF−PhMe, 1.23 mL, 0.492 mmol) was added to a stirred and cooled (−78 °C) suspension of $CuBr \cdot Me_2S$ (27 mg, 0.131 mmol) in THF (5 mL). The mixture was stirred for 20 min, and HMPA (0.11 mL, 0.632 mmol) was then added.

Me_3SiCl (84 μL, 0.642 mmol) was added to **66** (0.120 g, 0.333 mmol) in THF (4 mL), and the resulting solution was added dropwise to the previous organocopper solution over 10 min by syringe. Stirring at −78 °C was continued for 1 h. Saturated aqueous NH_4Cl (5 mL) was added, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were stirred at 0 °C, and CF_3CO_2H (0.4 mL) was added. Stirring was continued for 1 h, and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O (2 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 cm × 15 cm), using 1:10 Et_2O/hexane, gave **67** [87.1 mg, 61%, containing <10% of the C(3a)/C(7a) trans isomer (^1H NMR)]) as a colorless oil: $[\alpha]_D = -47.4$ (*c* 0.51, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2953, 2856, 1720, 1511, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, signals for C(3a)/C(7a) cis isomer **67** only) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.81 (ddd, J = 6.5, 9.0, 13.5 Hz, 1 H), 2.04 (ddd, J = 9.5, 9.5, 13.5 Hz, 1 H), 2.50−2.59 (m, 2 H), 2.68 (dd, J = 6.0, 12.5 Hz, 1 H), 2.88 (dd, J = 6.5, 11.0 Hz, 1 H), 3.06 (dd, J = 6.0, 11.0 Hz, 1 H), 3.22 (ddd, J = 7.0, 10.5, 17.5 Hz, 1 H), 3.78 (s, 3 H), 4.95−5.01 (m, 2 H), 5.08−5.12 (m, 2 H), 5.23 (d, J = 18.0 Hz, 2 H), 5.71 (ddd, J = 7.4, 10.5, 16.6 Hz, 1 H), 6.35 (dd, J = 11.0, 17.5 Hz, 1 H), 6.65−6.76 (m, 3 H), 9.62 (d, J = 4.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, signals for C(3a)/C(7a) cis isomer **67** only) δ −4.60 (q), 18.5 (s), 25.8 (q), 36.1 (t), 36.8 (t), 43.2 (d), 44.3 (d), 49.0 (d), 55.6 (q), 56.8 (d), 112.2 (d), 113.7 (t), 114.4 (t), 116.4 (t), 121.2 (d), 121.6 (d), 133.6 (s), 139.4 (d), 140.9 (d), 142.3 (s), 144.9 (s),

(52) Cottrell, L.; Golding, B. T.; Munter, T.; Watson, W. P. *Chem. Res. Toxicol.* **2001**, *14*, 1552−1562.

149.2 (s), 204.9 (d); exact mass *m*/*z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.29821.

(1*R*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (68). Vinylmagnesium bromide (1 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **67** (77.0 mg, 0.181 mmol, C(3a)/C(7a) cis isomer/trans isomer = 7:1) in THF (5 mL), and the mixture was stirred for 45 min. Saturated aqueous NH_4Cl (4 mL) and water (3 mL) were added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 15 cm), using 1:5 EtOAc/hexane, gave **68** as a mixture of two isomers epimeric at the hydroxyl-bearing carbon (major isomer, 40.9 mg, 50% and minor isomer, 15.2 mg, 19%). The major isomer had $[\alpha]_D = -70.8$ (*c* 0.40, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3566, 2953, 1512, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.44−1.52 (m, 2 H), 1.90 (ddd, *J* = 8.5, 10.0, 13.0 Hz, 1 H), 2.46−2.60 (m, 3 H), 2.80 (dd, *J* = 7.0, 11.0 Hz, 1 H), 2.96 (dd, *J* = 2.8, 12.5 Hz, 1 H), 3.12 (ddd, *J* = 7.5, 10.5, 17.5 Hz, 1 H), 3.77 (s, 3 H), 4.30 (s, 1 H), 4.85 (d, *J* = 10.0 Hz, 1 H), 4.91 (d, *J* = 17.5 Hz, 1 H), 5.09 (t, *J* = 11.5 Hz, 2 H), 5.20 (d, *J* = 19.5 Hz, 2 H), 5.28−5.32 (m, 2 H), 5.66 (ddd, *J* = 7.5, 10.0, 17.5 Hz, 1 H), 6.04 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1 H), 6.43 (dd, *J* = 11.0, 17.5 Hz, 1 H), 6.69−6.76 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.61 (q), −4.58 (q), 18.5 (s), 25.8 (q), 36.8 (t), 37.7 (t), 44.36 (d), 44.37 (d), 50.1 (d), 50.3 (d), 55.6 (q), 72.8 (d), 112.1 (d), 113.2 (t), 113.5 (t), 113.6 (t), 117.0 (t), 121.4 (d), 121.6 (d), 135.0 (s), 140.2 (d), 142.1 (d), 142.8 (d), 144.7 (s), 145.1 (s), 148.9 (s); exact mass *m*/*z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29092.

The minor isomer had $[\alpha]_D = -59.5$ (*c* 0.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3487, 2953, 1511, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.44−1.55 (m, 1 H), 1.67 (d, *J* = 4.0 Hz, 1 H), 1.86 (ddd, *J* = 7.0, 8.5, 13.0 Hz, 1 H), 2.35−2.40 (m, 1 H), 2.47−2.53 (m, 2 H), 2.83−2.89 (m, 2 H), 3.01 (td, *J* = 8.5, 18.0 Hz, 1 H), 3.78 (s, 3 H), 4.27 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.87 (d, *J* = 10.5, 1 H), 4.91 (d, *J* = 17.0 Hz, 1 H), 5.13 (dd, *J* = 9.5, 10.5 Hz, 2 H), 5.24 (d, *J* = 16.5 Hz, 2 H), 5.34−5.40 (m, 2 H), 5.69 (ddd, *J* = 7.5, 10.5, 17.5 Hz, 1 H), 6.01 (ddd, *J* = 6.5, 10.5, 17.5 Hz, 1 H), 6.47 (dd, *J* = 11.0, 17.5 Hz, 1 H), 6.68−6.77 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.61 (q), −4.58 (q), 18.5 (s), 25.8 (q), 35.7 (t), 36.4 (t), 44.3 (d), 46.3 (d), 48.3 (d), 51.0 (d), 55.6 (q), 72.9 (d), 112.1 (d), 113.3 (t), 113.8 (t), 115.5 (t), 117.1 (t), 121.4 (d), 121.7 (d), 134.3 (s), 140.1 (d), 140.5 (d), 142.2 (d), 144.8 (s), 145.8 (s), 149.1 (s); exact mass *m*/*z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29129.

(1*S*,3*S*,3a*R*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (69). Ar was bubbled for ca. 5 min through a stirred solution of **68** (major isomer, 30.0 mg, 0.0665 mmol) in CH_2Cl_2 (4 mL), and the Grubbs catalyst (first generation, 2.7 mg, 0.0033 mmol) was then added. The mixture was stirred for 24 h and then evaporated. Flash chromatography of the residue over silica gel (1.5 cm × 12 cm), using 1:5 EtOAc/hexane, gave **69** (26.2 mg, 93%) as a colorless oil: $[\alpha]_D = -32.7$ (*c* 0.63, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3403, 2929, 1512, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.00 (s, 9 H), 1.37 (d, *J* = 7.0 Hz, 1 H), 1.64 (ddd, *J* = 5.5, 9.0, 14.5 Hz, 1 H), 1.77 (td, *J* = 10.5, 14.0 Hz, 1 H), 2.05 (td, *J* = 5.5, 8.5 Hz, 1 H), 2.24 (ddd, *J* = 6.0, 10.5, 19.0 Hz, 1 H), 2.39 (dd, *J* = 5.5, 10.5 Hz, 1 H), 2.46 (ddd, *J* = 5.5, 10.0, 19.0 Hz, 1 H), 2.61 (dd, *J* = 9.5, 13.5 Hz, 1 H), 3.03 (dd, *J* = 6.0, 14.0 Hz, 1 H), 3.78 (s, 3 H), 4.32 (broad s, 1 H), 4.72 (s, 1 H), 4.79 (d, *J* = 17.0 Hz, 1 H), 4.89 (dd, *J* = 1.5, 10.0 Hz, 1 H), 4.92 (s, 1 H), 5.62 (ddd, *J* = 8.5, 10.5, 17.0 Hz, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 6.10 (dd, *J* = 2.0, 10.0 Hz, 1 H), 6.74−6.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.59 (q), 18.5 (s), 25.8 (q), 35.6 (t), 37.3 (t), 44.6 (d), 47.2 (d), 50.4 (d), 50.9 (d), 55.6 (q), 65.4 (d), 112.2 (d), 113.6 (t), 114.1 (t), 121.4 (d), 121.5 (d), 128.7 (d), 131.5 (d), 134.5 (s), 141.6 (s), 142.0 (d), 144.8 (s), 149.1 (s); exact mass *m*/*z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25793.

Ar was bubbled for ca. 5 min through a stirred solution of alcohol **68** (minor isomer, 7.0 mg, 0.0154 mmol) in CH_2Cl_2 (2.0 mL), and the Grubbs catalyst (first generation, 0.64 mg, 0.00078 mmol) was then added. The mixture was stirred for 24 h and then evaporated. Flash chromatography of the residue over silica gel (1.5 cm × 10 cm), using 1:10 EtOAc/hexane, gave **69** (6.1 mg, 91%) as a colorless oil: $[\alpha]_D = 37.0$ (*c* 0.20, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3490, 2954, 1511, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.99 (s, 9 H), 1.03 (d, *J* = 6.5 Hz, 1 H), 1.65 (ddd, *J* = 6.0, 10.0, 13.0 Hz, 1 H), 1.98−2.08 (m, 2 H), 2.42−2.51 (m, 2 H), 2.58 (ddd, *J* = 6.5, 10.5, 19.5 Hz, 1 H), 2.85 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.95 (dd, *J* = 8.5, 13.5 Hz, 1 H), 3.78 (s, 3 H), 4.36 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.84−4.91 (m, 3 H), 5.01 (s, 1 H), 5.70 (ddd, *J* = 9.5, 9.5, 17.0 Hz, 1 H), 5.93 (dd, *J* = 6.0, 9.5 Hz, 1 H), 6.19 (d, *J* = 9.5 Hz, 1 H), 6.74−6.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.60 (q), 18.5 (s), 25.8 (q), 36.2 (t), 37.9 (t), 44.6 (d), 45.0 (d), 48.6 (d), 49.9 (d), 55.6 (q), 64.4 (d), 112.1 (d), 113.8 (t), 115.8 (t), 121.4 (d), 121.5 (d), 128.2 (d), 131.5 (d), 135.2 (s), 142.2 (s), 143.7 (d), 144.8 (s), 148.9 (s); exact mass *m*/*z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25904.

(1*S*,3*S*,3a*R*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (70). Dess−Martin periodinane (12.0 mg, 0.0283 mmol) was added to a stirred solution of alcohols **69** (10.0 mg, 0.0235 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$(1 mL), followed by saturated aqueous $NaHCO_3$(1 mL), was added. The mixture was stirred for 5 min, diluted with water (3 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 cm × 10 cm), using 1:10 EtOAc/hexane, gave **70** (9.1 mg, 91%) as an oil: $[\alpha]_D = 14.6$ (*c* 0.35, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2953, 1666, 1510, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.99 (s, 9 H), 1.51−1.56 (m, 1 H), 1.71 (ddd, *J* = 7.1, 9.1, 13.1 Hz, 1 H), 2.43−2.52 (m, 2 H), 2.62 (td, *J* = 8.2, 16.4 Hz, 1 H), 2.79 (t, *J* = 8.2 Hz, 1 H), 2.86 (dd, *J* = 6.1, 8.2 Hz, 1 H), 3.02 (dd, *J* = 4.7, 12.3 Hz, 1 H), 3.77 (s, 3 H), 4.92−4.98 (m, 2 H), 5.33 (s, 2 H), 5.76 (ddd, *J* = 8.1, 10.1, 17.1 Hz, 1 H), 5.94 (d, *J* = 10.1 Hz, 1 H), 6.70−6.75 (m, 3 H), 6.98 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.61 (q), 18.5 (s), 25.8 (q), 35.6 (t), 35.6 (t), 46.4 (d), 48.4 (d), 49.1 (d), 51.4 (d), 55.6 (q), 112.1 (d), 114.4 (t), 119.9 (t), 121.6 (d), 121.8 (d), 128.3 (d), 134.4 (s), 141.9 (d), 143.1 (s), 144.7 (s), 146.0 (d), 149.1 (s), 200.3 (s); exact mass *m*/*z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24383.

(1*S*,3*S*,3a*R*,7a*S*)-1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one [(+)-1]. Bu_4NF (1.0 M in THF, 21.5 μL, 0.0215 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **70** (9.1 mg, 0.0215 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 5 min, and another portion of Bu_4NF (1.0 M in THF, 1.5 μL, 0.0015 mmol) was added. The mixture was stirred at 0 °C for a further 5 min. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 cm × 7 cm), using 1:20 EtOAc−CH_2Cl_2, gave (+)-**1** (5.6 mg, 84%) as a colorless oil: $[\alpha]_D = 19.7$ (*c* 0.28, $CHCl_3$) [lit.[16,18] $[\alpha]_D = 17.3$ (*c* 0.55, $CHCl_3$); lit.[15] $[\alpha]_D = 19.2$ (*c* 0.52, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3417, 2917, 1658, 1510, 1273, 1130, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54−1.59 (m, 1 H), 1.73 (ddd, *J* = 7.1, 9.2, 13.5 Hz, 1 H), 2.48−2.53 (m, 2 H), 2.62 (td, *J* = 8.1, 16.4 Hz, 1 H), 2.79 (t, *J* = 8.2 Hz, 1 H), 2.86 (dd, *J* = 5.8, 8.1 Hz, 1 H), 3.03−3.09 (m, 1 H), 3.86 (s, 3 H), 4.92−4.98 (m, 2 H), 5.32 (d, *J* = 4.1 Hz, 2 H), 5.52 (s, 1 H), 5.76 (ddd, *J* = 8.2, 10.0, 16.8 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 6.68 (dd, *J* = 1.7, 8.2 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.78 (d, *J* = 1.7 Hz, 1 H), 6.98 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

35.7 (t), 35.9 (t), 46.3 (d), 48.6 (d), 49.0 (d), 51.4 (d), 56.0 (q), 110.5 (d), 114.4 (t), 115.0 (d), 119.9 (t), 120.3 (d), 128.3 (d), 135.1 (s), 141.8 (d), 143.0 (s), 144.7 (s), 145.3 (s), 145.9 (d), 200.3 (s); exact mass *m*/*z* calcd for $C_{20}H_{22}O_3$310.15689, found 310.15721. The compound is acid sensitive, and so the solvents for NMR and optical rotation measurements were stored over anhydrous K_2CO_3.

1*S*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarboxaldehyde (71). DBU (1 drop) was added to a stirred solution of **66** (42.0 mg, 0.099 mmol) in CH_2Cl_2 (7 mL). Stirring was continued for 36 h, and then the solvent was evaporated. Flash chromatography of the residue over silica gel (2 cm × 10 cm), using 1:10 EtOAc/hexane, gave **71** (38.2 mg, 91%) as a yellow oil: $[\alpha]_D = -15.3$ (*c* 0.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2930, 2857, 1722, 1511, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.69−1.82 (m, 2 H), 2.57−2.64 (m, 4 H), 2.69 (td, $J = 8.5$, 17.0 Hz, 1 H), 2.84 (t, $J = 9.5$ Hz, 1 H), 3.77 (s, 3 H), 4.93−4.98 (m, 2 H), 5.06 (d, $J = 13.5$ Hz, 2 H), 5.18 (s, 1 H), 5.30 (d, $J = 17.5$ Hz, 1 H), 5.68 (ddd, $J = 7.5$, 10.0, 17.0 Hz, 1 H), 6.31 (dd, $J = 11.0$, 18.0 Hz, 1 H), 6.67−6.77 (m, 3 H), 9.39 (d, $J = 2.0$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.65 (q), 18.5 (s), 25.7 (q), 36.9 (t), 40.7 (t), 40.8 (d), 48.3 (d), 49.0 (d), 55.5 (q), 63.4 (d), 112.1 (d), 114.5 (t), 114.5 (t), 115.0 (t), 121.7 (d), 122.1 (d), 132.5 (s), 137.7 (d), 139.9 (d), 144.9 (s), 146.3 (s), 149.5 (s), 202.1 (d); exact mass *m*/*z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25882.

(1*S*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (72). Vinylmagnesium bromide (1 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **71** (36.3 mg, 0.0852 mmol) in THF (4 mL). Stirring at 0 °C was continued for 1 h, and saturated aqueous NH_4Cl (4 mL), followed by water (1 mL), was added. The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 cm × 15 cm), using 1:10 EtOAc/hexane, gave **72** (34.1 mg, 88%) as a 5:3 mixture (^1H NMR) of two isomers epimeric at the hydroxyl-bearing carbon: $[\alpha]_D = -116.3$ (*c* 0.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3531, 2930, 2857, 1511, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.01 (s, 9 H), 1.46 (broad s, 1 H), 1.53−1.59 (m, 1 H), 1.66−1.67 (m, 1 H), 1.88−1.92 (m, 1 H), 2.16−2.26 (m, 1 H), 2.49−2.56 (m, 3 H), 2.68−2.75 (m, 1 H), 3.78 (s, 3 H), 4.02 (s, 0.5 H), 4.10 (s, 0.5 H), 5.02−5.43 (m, 8 H), 5.61−5.68 (m, 1 H), 5.78−5.86 (m, 1 H), 6.33−6.40 (m, 1 H), 6.68−6.78 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, signals for major isomer) δ −4.61 (q), 18.5 (s), 25.7 (q), 37.0 (t), 39.3 (d), 42.3 (t), 48.9 (d), 51.3 (d), 55.6 (q), 56.5 (d), 73.5 (d), 112.1 (d), 113.9 (t), 114.1 (t), 114.4 (t), 114.8 (t), 121.9 (d), 122.0 (d), 133.9 (s), 138.2 (d), 139.8 (d), 140.5 (d), 144.8 (s), 148.4 (s), 149.2 (s); exact mass *m*/*z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.28975.

(1*S*,3*S*,3a*S*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (73). Ar was bubbled for ca. 10 min through a stirred solution of alcohols **72** (25.0 mg, 0.055 mmol) in CH_2Cl_2 (5 mL), and the Grubbs catalyst (first generation, 4.5 mg, 0.0055 mmol) was added. The mixture was stirred for 20 h and then evaporated. Flash chromatography of the residue over silica gel (2 cm × 10 cm), using 1:6 EtOAc/hexane, gave **73** (20.3 mg, 86%) as a mixture of two epimeric isomers at the hydroxyl-bearing carbon: $[\alpha]_D = -132.3$ (*c* 0.16, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3397, 2929, 1511, 1270, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer signals) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.31 (broad s, 1 H), 1.42−1.51 (m, 1 H), 1.63−1.76 (m, 2 H), 2.09−2.21 (m, 2 H), 2.49 (dd, $J = 8.8$, 13.8 Hz, 1 H), 2.63−2.70 (m, 1 H), 3.01 (dd, $J = 5.8$, 13.8 Hz, 1 H), 3.78 (s, 3 H), 4.28 (s, 1 H), 4.87 (s, 1 H), 4.97 (d, $J = 10.2$ Hz, 1 H), 5.04−5.08 (m, 2 H), 5.64 (d, $J = 9.7$ Hz, 1 H), 5.74−5.83 (m, 1 H), 6.10 (dd, $J = 1.5$, 9.7 Hz, 1 H), 6.71−6.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer signals) δ −4.64 (q), −4.61 (q), 18.5 (s), 25.8 (q), 38.7 (t), 41.4 (t), 43.9 (d), 44.3 (d), 49.5 (d), 55.5 (q), 56.7 (d), 74.6 (d), 110.1 (t), 112.1 (d), 113.8 (t), 121.6 (d), 121.9 (d), 131.4 (d), 133.8 (d), 133.9 (s), 142.9 (d), 144.9 (s), 145.7 (s), 149.3 (s); exact mass *m*/*z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25945.

(1*S*,3*S*,3a*S*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (74). Dess−Martin periodinane (28.7 mg, 0.0676 mmol) was added to a stirred solution of **72** (mixture of two isomers, 24.0 mg, 0.0563 mmol) in CH_2Cl_2 (4 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$ (3 mL), followed by saturated aqueous $NaHCO_3$ (2 mL), was added. The mixture was stirred for 5 min, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 cm × 7 cm), using 1:10 EtOAc/hexane, gave **74** (22.1 mg, 93%) as an oil: $[\alpha]_D = -248.8$ (*c* 0.27, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2952, 2929, 1682, 1511, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.99 (s, 9 H), 1.52−1.62 (m, 1 H), 1.78 (ddd, $J = 6.8$, 9.8, 13.9 Hz, 1 H), 2.27 (dd, $J = 9.8$, 13.9 Hz, 1 H), 2.36 (dd, $J = 9.8$, 13.4 Hz, 1 H), 2.45−2.56 (m, 2 H), 2.70 (td, $J = 9.0$, 18.8 Hz, 1 H), 3.11 (dd, $J = 3.6$, 13.4 Hz, 1 H), 3.78 (s, 3 H), 5.00 (d, $J = 10.3$ Hz, 1 H), 5.08 (d, $J = 17.5$ Hz, 1 H), 5.30 (s, 1 H), 5.44 (s, 1 H), 5.74 (ddd, $J = 8.1$, 10.2, 17.3 Hz, 1 H), 5.94 (d, $J = 9.7$ Hz, 1 H), 6.71−6.75 (m, 3 H), 7.00 (d, $J = 9.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.61 (q), −4.59 (q), 18.5 (s), 25.8 (q), 36.9 (t), 37.9 (d), 40.3 (t), 44.5 (d), 50.5 (d), 55.6 (q), 58.2 (d), 112.0 (d), 114.6 (t), 117.1 (t), 122.0 (d), 122.2 (d), 128.7 (d), 133.3 (s), 141.6 (d), 144.7 (s), 144.8 (s), 147.5 (d), 149.2 (s), 200.6 (s); exact mass *m*/*z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24366.

(1*S*,3*S*,3a*S*,7a*S*)-1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one [(−)-2]. Bu_4NF (1.0 M in THF, 34.0 μL, 0.034 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **74** (12.0 mg, 0.0283 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 10 min, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 cm × 7 cm), using 1:4 EtOAc/hexane, gave (−)-**2** (7.6 mg, 87%) as a colorless solid: mp 141−142 °C [lit.[16,18] 142.2−143.0 °C]; $[\alpha]_D = -331.4$ (*c* 0.18, $CHCl_3$) [lit.[16,18] −333.0 (*c* 0.18, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3431, 2927, 1676, 1511, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (ddd, $J = 8.1$, 10.1, 13.5 Hz, 1 H), 1.79 (ddd, $J = 6.8$, 9.9, 13.8 Hz, 1 H), 2.27 (dd, $J = 9.9$, 13.9 Hz, 1 H), 2.35 (dd, $J = 10.1$, 13.5 Hz, 1 H), 2.48−2.55 (m, 2 H), 2.70−2.77 (m, 1 H), 3.15 (dd, $J = 3.7$, 13.5 Hz, 1 H), 3.86 (s, 3 H), 5.00 (dd, $J = 1.2$, 10.2 Hz, 1 H), 5.09 (d, $J = 17.1$ Hz, 1 H), 5.30 (s, 1 H), 5.45 (s, 1 H), 5.53 (s, 1 H), 5.74 (ddd, $J = 8.1$, 10.2, 17.1 Hz, 1 H), 5.95 (d, $J = 9.7$ Hz, 1 H), 6.69 (dd, $J = 2.0$, 8.2 Hz, 1 H), 6.76 (d, $J = 8.2$ Hz, 1 H), 6.81 (d, $J = 2.0$ Hz, 1 H), 7.00 (d, $J = 9.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0 (t), 37.9 (d), 40.6 (t), 44.5 (d), 50.5 (d), 56.0 (q), 58.3 (d), 110.5 (d), 114.6 (t), 115.4 (d), 117.1 (t), 120.5 (d), 128.7 (d), 134.2 (s), 141.6 (d), 144.8 (s), 144.8 (s), 145.3 (s), 147.6 (d), 200.6 (s); exact mass *m*/*z* calcd for $C_{20}H_{22}O_3$310.15689, found 310.15659.

Acknowledgment. The NSERC is thanked for financial support. D.L. held a Province of Alberta Graduate Fellowship. X-ray data have been deposited in the Cambridge Crystallographic Data Centre and assigned the registry number CCDC 635712.

Supporting Information Available: Experimental procedures for **18**−**25**, **29**−**43**, (±)-**1**, (±)-**2**, benzoate corresponding to **63**, **47**, **50**, **57**−**58**. NMR spectra of (+)-**1**, (−)-**2**, (±)-**1**, (±)-**2**, **19**−**21**, **23**−**25**, **29**−**35**, **37**−**39**, **41**−**43**, **47**, **50**, **57**−**60**, **63**−**74**, and benzoate corresponding to **63**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702635T