chromatographed (15% MeOH/$CHCl_3$) to provide 4.3 mg (57%) of the dehalogenated tetraol **21** as a colorless film; $[\alpha]_D$ = +55.5° (*c* 0.0059, $CHCl_3$); IR (film, cm^{-1}) 3391, 2922; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H_1), 3.94 (dd, $J_{3,2}$ = 8.7 Hz, $J_{3,4}$ = 9.2 Hz, 1 H, H_3), 3.93 (dd, $J_{1',2'eq}$ = 2.6 Hz, $J_{1',2'ax}$ = 10.5 Hz, 1 H, $H_{1'}$), 3.85 (dd, $J_{6',5'}$ = 3.2 Hz, J_{gem} = 11.9 Hz, 1 H, $H_{6'}$), 3.81 (dd, $J_{6,5}$ = 2.0 Hz, J_{gem} = 11.3 Hz, 1 H, H_6), 3.64-3.74 (m, 3 H, $H_{6'}$, H_5, H_6), 3.57-3.63 (m, 2 H, $H_{3'}$, $H_{5'}$), 3.51 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 8.7 Hz, 1 H, H_2), 3.42 (s, 3 H, OCH_3), 3.22 (dd, $J_{4',3'}$ = $J_{4',4'5'}$ = 9.1 Hz, 1 H, $H_{4'}$), 2.08 (ddd, $J_{2'eq,1'}$ = $J_{2'eq,3'}$ = 2.6 Hz, J_{gem} = 11.4 Hz, 1 H, $H_{2'eq}$), 2.07 (dd, $J_{4,3}$ = 9.2 Hz, $J_{4,5}$ = 9.9 Hz, 1 H, H_4), 1.95 (ddd, $J_{2'ax,1'}$ = $J_{2'ax,3'}$ = J_{gem} = 10.4-11.5 Hz, 1 H, $H_{2'ax}$), 1.43 (s, 6 H, isopropylidene CH_3's); ^{13}C NMR (90 MHz, $CDCl_3$) δ 110.8, 99.4, 79.8, 77.9, 76.2, 74.7, 73.9, 70.0, 68.8, 63.1, 62.9, 55.5, 45.4, 33.2, 26.8, 26.7; FAB MS *m/e* 365 (MH^+, 2), 333 (2), 242 (100); HR FAB MS calcd for $C_{16}H_{29}O_9$ 365.1812 (MH^+), found 365.1815. Anal. Calcd for $C_{16}H_{28}O_9$: C, 52.74; H, 7.75. Found: C, 52.45; H, 7.50.

Methyl 4-Deoxy-4-*C*-(1,2-dideoxy-β-D-*gluco*-hexopyranos-1-yl)-α-D-*gluco*-hexopyranoside (22). A solution of disaccharide **21** (5.5 mg, 0.015 mmol) in methanol (2 mL) was treated with *p*-toluenesulfonic acid. After 15 min, the solution was treated with mildly basic ion exchange resin, filtered, and concentrated under reduced pressure. The residue was chromatographed (20% MeOH/$CHCl_3$) to provide 4.3 mg (88%) of the fully deprotected disaccharide **22** as a white film: $[\alpha]_D$ = +73.8° (*c* 0.0037, $CHCl_3$); IR (film, cm^{-1}) 3398, 2923; ^1H NMR (500 MHz, CD_3OD) δ 4.67 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H_1), 3.86 (dm, $J_{1',2'ax}$ = 11.8 Hz, 1 H, $H_{1'}$), 3.83 (dd, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 10.2 Hz, 1 H, H_3), 3.82 (dd, $J_{6',5'}$ = 2.0 Hz, J_{gem} = 11.3 Hz, 1H, $H_{6'}$), 3.79 (dd, $J_{6,5}$ = 2.3 Hz, J_{gem} = 11.5 Hz, 1 H, H_6), 3.74 (ddd, $J_{5,6}$ = 2.3 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,4}$ = 10.5 Hz, 1 H, H_5), 3.66 (dd, $J_{6,5}$ = 5.8 Hz, J_{gem} = 11.5 Hz, 1 H, H_6), 3.65 (dd, $J_{6',5'}$ = 5.3 Hz, J_{gem} = 11.3 Hz, 1 H, $H_{6'}$). 3.52 (ddd, $J_{3',2'eq}$ = 5.0 Hz, $J_{3',4'}$ = 8.7 Hz, $J_{3',2'ax}$ = 11.6 Hz, 1 H, $H_{3'}$), 3.37 (dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 9.5 Hz, 1 H, H_2), 3.37 (s, 3 H, OCH_3), 3.18 (dd, $J_{4',3'}$ = $J_{4',5'}$ = 8.7-9.3 Hz, 1 H, $H_{4'}$), 3.13 (ddd, $J_{5',6'}$ = 2.0 Hz, $J_{5',6'}$ = 5.3 Hz, $J_{5',4'}$ = 9.3 Hz, 1 H, $H_{5'}$), 1.90 (ddd, $J_{2'eq,1'}$ = 1.9 Hz, $J_{2'eq,3'}$ = 5.0 Hz, J_{gem} = 12.6 Hz, 1 H, $H_{2'eq}$), 1.80 (ddd, $J_{4,1'}$ = 2.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.2-10.5 Hz, 1 H, H_4), 1.66 (ddd, $J_{2'ax,1'}$ = $J_{2'ax,3'}$ = 11.6-11.8 Hz, J_{gem} = 12.6 Hz, 1 H, $H_{2'ax}$); ^{13}C NMR (90 MHz, CD_3OD) δ 101.3, 82.3, 75.4, 75.0, 74.2, 73.1, 70.8, 70.7, 64.1, 63.0, 55.5, 47.6, 38.5. Anal. Calcd for $C_{13}H_{24}O_9 \cdot H_2O$: C, 45.61; H, 7.66. Found: C, 45.60; H, 7.40.

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Silicon-Promoted Ring Contractions in the Formation of Carbocyclic Spiro Compounds. Total Synthesis of (-)-Solavetivone

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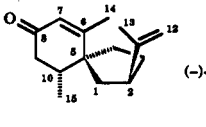
A new method involving silicon-promoted ring contraction was developed for the synthesis of carbocyclic spiro compounds. In the presence of a Lewis acid, (trimethylsilyl)decalinol **12** and (trimethylsilyl)decalin epoxide **11** underwent ring contraction in a highly stereoselective manner to afford spiro[4.5]dec-6-enes **14** and **19**, respectively. The first total synthesis of optically active solavetivone ((-)-**1**) was accomplished in 13 steps by use of this new type of reaction as the key step. Utilization of the silicon-promoted ring contraction solves three problems associated with spiro compound synthesis: (1) efficient generation of the quaternary carbon spiro center, (2) full control of the stereoconfiguration of the spiro center during its formation, and (3) stereospecific establishment of chiral centers on both rings of the spiro unit.

Introduction

Many carbocyclic spiro compounds possess valuable biological or physical properties. Chemical and pharmaceutical industries use some of these compounds extensively. Whereas the spiro moiety exists among alkaloids, steroids, and polycyclic hydrocarbons, the spiro[4.5]decane sesquiterpenes make up the majority of naturally occurring spiro carbocycles.

Several synthetic methods can lead to spiro carbocycles;[1-3] however, few of them give high yields with control of stereochemistry at the spiro center as well as in both rings. Acid-catalyzed rearrangement involving ring contraction can generate spiro compounds stereoselectively,[2] but examples of this method with high yields are rare. We undertook the development of a new synthetic method that can provide good yields of isomerically pure spiro products.

Silicon can direct organic reactions in various ways.[4-6] Recently, Kuwajima[7,8] reported a silicon-directed ring enlargement reaction. Herein, we report a novel silicon-promoted ring contraction reaction and its application as the key step in a total synthesis of a spirocyclic natural product, (-)-solvetivone (**1**).[9]



(-)-Solavetivone (1)

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§ Research fellow of the Alfred P. Sloan Foundation (1986-1990).

(1) Krapcho, A. P. *Synthesis* **1974**, 383 and references cited therein.
(2) Krapcho, A. P. *Synthesis* **1976**, 425 and references cited therein.
(3) Marshall, J. A.; Brady, St. F.; Anderson, B. H. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 283 and references cited therein.
(4) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths; reprinted by Kreiger: Malabar, FL, 1985.
(5) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83.
(6) Negishi, E.-i. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1, Chapter 6.
(7) Tanino, K.; Katoh, T.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 1815.
(8) Katoh, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 1819.

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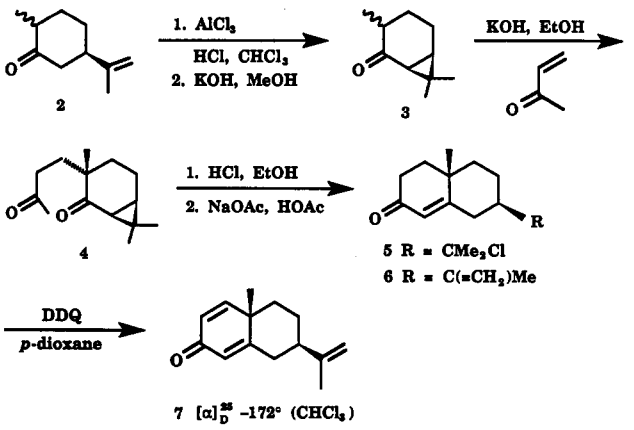
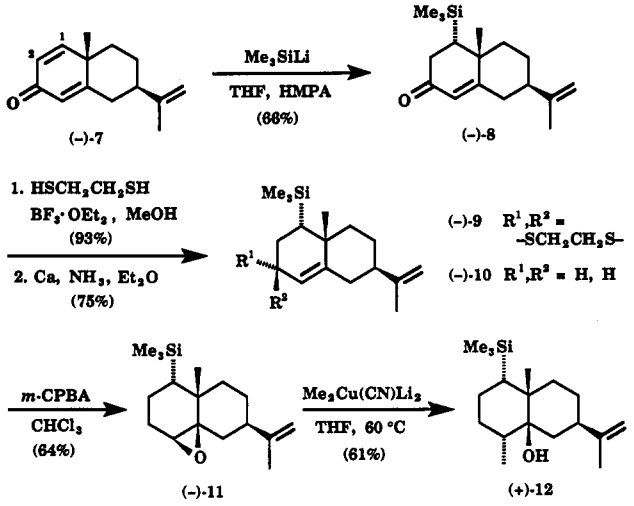
Scheme I



Scheme II



(-)-Solavetivone, a phytoalexin,[10] is a representative of a class of compounds isolated from potato tubers infected with the blight fungus *Phytophthora infestans* or with the soft-rot bacterium *Erwinia carotovora*.[9,11-13] (-)-Solavetivone inhibits germination,[14] germ tube[15] and mycelial growth,[16-18] and essential enzymes[18] of *P. infestans*. It also possesses inhibitory activity against the bacteria *Pseudomonas solanacearum* and *Pseudomonas syringae* pv. *tabaci*.[19] Murai et al. showed that (-)-solavetivone is a biosynthetic precursor of several other phytoalexins,[20-24] including oxylubimin,[20-22] rishitin,[20-22] and phytuberol.[23]

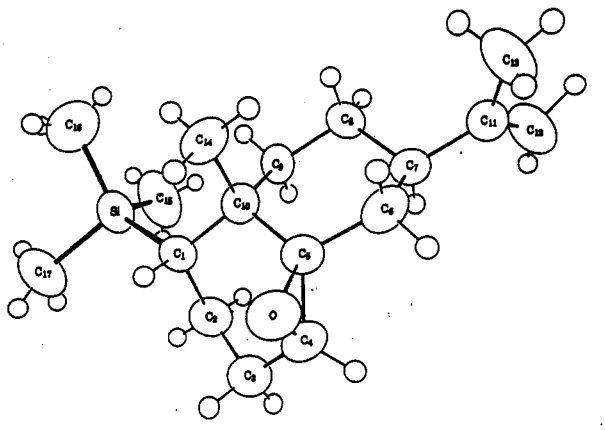


Figure 1. Molecular framework of (-)-11 revealed by single-crystal X-ray diffraction analysis.

Results

The control of the stereocenters of a carbon in decalins is greatly facilitated by the rigidity of the decalin nucleus.[25,26] Ring contraction occurring in a decalin would allow the configuration of some chiral centers to be transferred stereospecifically to the product.[27] Recognizing this advantage, we accomplished a total synthesis of (-)-solavetivone by using a silicon-promoted ring contraction as the key step.

Synthesis of the Precursor, Decalinol (+)-12, for Ring Contraction. We converted (+)-dihydrocarvone (2) to (-)-2-carone[28] (3, Scheme I) by the procedure of Dauben.[29] Then (-)-2-carone (3) was transformed to optically active cross-conjugated trienone (-)-7, via intermediates 4-6, according to the elegant method developed by Caine et al.[30,31]

By reacting trienone (-)-7 with Me_3SiLi,[32,33] we obtained (-)-8 in 66% yield after purification (Scheme II). The GC chromatogram of the crude product mixture showed a small peak (t_R 7.39 min) with retention time close to the major peak corresponding to (-)-8 (t_R 6.82 min). The compound with the small peak was tentatively assigned to the epimer of (-)-8, in which all three ring substituents were cis. The ratio of (-)-8 to this epimer, which was not isolated, was greater than 19:1 by GC.

We reacted (-)-8 with 1,2-ethanedithiol and BF_3·OEt_2 in methanol[34] to give (-)-9 in 93% yield. Relying on our

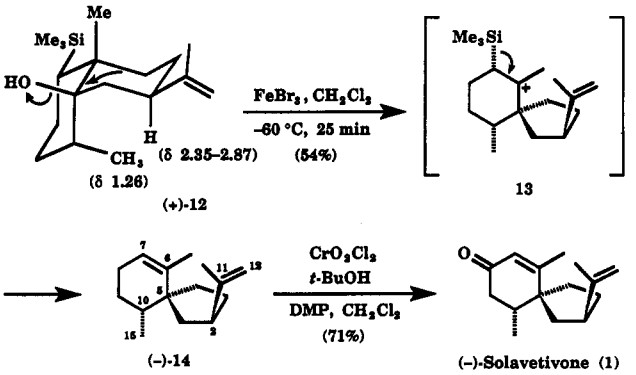
(9) Coxon, D. T.; Price, K. R.; Howard, B.; Osman, S. F.; Kalan, E. B.; Zacharius, R. M. *Tetrahedron Lett.* **1974**, 2921.
(10) Afzal, M.; Al-Oriquat, G. *Heterocycles* **1986**, *24*, 2943 and references cited therein.
(11) Price, K. R.; Howard, B.; Coxon, D. T. *Physiol. Plant Pathol.* **1976**, *9*, 189.
(12) Brindle, P. A.; Kuhn, P. J.; Threlfall, D. R. *Phytochemistry* **1983**, *22*, 2719.
(13) Lyon, G. D. *Phytopathol. Z.* **1984**, *111*, 236.
(14) Harris, J. E.; Dennis, C. *Physiol. Plant Pathol.* **1976**, *9*, 155.
(15) Sato, N.; Yoshizawa, Y.; Miyazaki, H.; Murai, A. *Nippon Shokubutsu Byori Gakkaiho* **1985**, *51*, 494 and references cited therein.
(16) Beczner, J.; Ersek, T. *Acta Phytopathol. Acad. Sci. Hung.* **1976**, *11*, 59.
(17) Stössel, P.; Hohl, H. R. *Mycopathologia* **1981**, *73*, 153.
(18) Hohl, H. R.; Stössel, P.; Hächler, H. *Ann. Phytopathol.* **1980**, *12*, 353.
(19) Tanaka, H.; Uegaki, R.; Fujimori, T.; Kato, K. *Nippon Shokubutsu Byori Gakkaiho* **1983**, *49*, 501.
(20) Murai, A.; Sato, S.; Osada, A.; Katsui, N.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1982**, 32.
(21) Murai, A.; Sato, S.; Osada, A.; Katsui, N.; Masamune, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 24th* **1981**, 521; *Chem. Abstr.* **1982**, *96*, 119085d.
(22) Sato, K.; Ishiguri, Y.; Doke, N.; Tomiyama, K.; Yagihashi, F.; Murai, A.; Katsui, N.; Masamune, T. *Phytochemistry* **1978**, *17*, 1901.
(23) Murai, A.; Yoshizawa, Y.; Miyazaki, H.; Masamune, T.; Sato, S. *Chem. Lett.* **1987**, 1377.
(24) Murai, A.; Yoshizawa, Y.; Katsui, N.; Sato, S.; Masamune, T. *Chem. Lett.* **1986**, 771.
(25) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983, Vol. 5, pp 124-227.
(26) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 2, pp 282-394.
(27) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 190-195.
(28) Caine, D.; Gupton, J. T., III. *J. Org. Chem.* **1974**, *39*, 2654.
(29) Dauben, W. G.; Shaffer, G. W.; Deviny, E. J. *J. Am. Chem. Soc.* **1970**, *92*, 6273.
(30) Caine, D.; Chu, C.-Y.; Graham, S. L. *J. Org. Chem.* **1980**, *45*, 3790.
(31) Caine, D.; Deutsch, H.; Gupton, J. T., III. *J. Org. Chem.* **1978**, *43*, 343.
(32) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063.
(33) Hudrlik, P. F.; Waugh, M. A.; Hudrlik, A. M. *J. Organomet. Chem.* **1984**, *271*, 69.
(34) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.

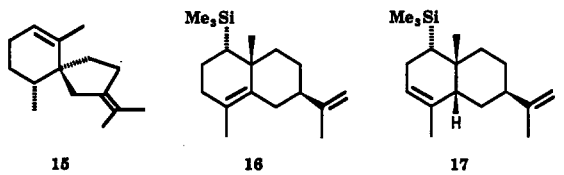
Table I. Reaction Conditions That Provided Spirocyclic Diene (−)-14 from Trimethylsilyl Alcohol (+)-12[a]

entry	acid	equiv	temperature, °C/time, min	products, %[b] (%)[c] 14	15	16	17
1	$FeBr_3$	1.4	−60/25	59 (54)	3	22 (18)	5
2	$FeCl_3$	1.0	−78/75	28		42	8
3[d]	$SnCl_4$	1.0	−95/30	49 (46)		41 (32)	
4[d]	$SnCl_4$	1.0	−78/25	44		56	
5[e]	$AlCl_3$	1.6	−78/60	19	5	30	8
6[e]	$ZnBr_2$	1.2	rt/60	16		76	8

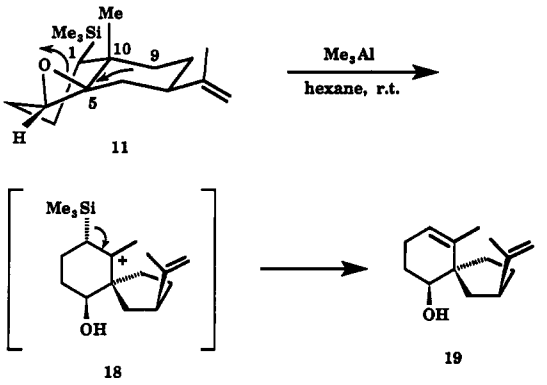
[a] Methylene chloride was the solvent for all reactions. Except where noted, the concentration of (+)-12 was 0.01 M. [b] GC yield. [c] Isolated yield. [d] Concentration of (+)-12 was 0.05 M. [e] Concentration of (+)-12 was 0.03 M.

Scheme III





Scheme IV



experience with the reduction of 1,3-dithiolanes,[35] we used calcium in liquid ammonia with ether as cosolvent to convert the thioacetal moiety of (−)-9 to a methylene unit and thus obtained trimethylsilyl diene (−)-10 in 75% yield.

Using *m*-CPBA, we epoxidized (−)-10 in $CHCl_3$ at −22 °C to give the desired β-4,5-monoepoxide (−)-11 as the only major product in 64% yield (Scheme II). In the GC chromatogram of the crude product mixture, a peak (t_R 8.86 min) with retention time close to that of (−)-11 (t_R 9.17 min) was tentatively assigned to the corresponding α-4,5-monoepoxide. The ratio of (−)-11 to the α-4,5-monoepoxide was greater than 35:1.

We confirmed our structural assignment of epoxide (−)-11, a white crystal, by single-crystal X-ray diffraction analysis.[36] Figure 1 shows the molecular framework of (−)-11, in which the angular methyl group was trans to the Me_3Si group and cis to the epoxy oxygen.

Lipshutz et al.[37] reported that organocuprates $R_2Cu(CN)Li_2$ can add to sterically hindered epoxides to give alkyl-substituted alcohols in excellent yields. Thus we treated (−)-11 with 10 equiv of $Me_2Cu(CN)Li_2$ in THF at 60 °C (Scheme II) and obtained tertiary alcohol (+)-12 in 61% yield.

Proton NMR homonuclear decoupling and nuclear Overhauser effect (NOE) experiments provided evidence to support our stereochemical assignment of (+)-12 (see Scheme III). In the homonuclear decoupling experiment, we simultaneously irradiated the terminal methylene protons at δ 4.69 and 4.70 ppm. We observed peak sharpening of an unresolved multiplet at δ 2.35–2.87 ppm. Conversely, the peaks at δ 4.69 and δ 4.70 ppm were sharpened by irradiation of protons with multiplet at δ 2.35–2.87 ppm. Thus we assigned the multiplet at δ 2.35–2.87 ppm to the allylic methine proton. In an NOE experiment, we irradiated at the frequency of the CH_3CH doublet at δ 1.26 ppm and produced an 18% enhancement of the multiplet at δ 2.35–2.87 ppm. The observed NOE can be explained by the stereoconfiguration and conformation of (+)-12 depicted in Scheme III, in which the CH_3CH methyl and the allylic methine are nearby.

Silicon-Promoted Ring Contraction of Decalinol (+)-12. We optimized the reaction conditions for the silicon-promoted ring contraction of (+)-12 by using various Lewis acids, solvents, and temperatures. Table I lists the results from the most thoroughly examined reactions. In the presence of 1.4 equiv of $FeBr_3$ in CH_2Cl_2 at −60 °C, (+)-12 gave the highest yield (54%) of the desired spiro compound (−)-14 (Scheme III and entry 1 in Table I).

We also isolated three byproducts and assigned them structures 15, 16, and 17. Spiroalkene 15 was formed in 3% yield by a C–C double bond migration in the primary product (−)-14 to a thermodynamically more stable position. Octalin 16 was generated in 18% yield by dehydration of (+)-12. Octalin 17 was produced in 5% yield by sequential ionization of (+)-12, hydride shift, and proton abstraction.

Silicon-Promoted Ring Contraction of Epoxide (−)-11. Silicon-promoted ring contraction may occur in substrates with an epoxy group as the initiator. In this regard, we considered the unique chemical activity of $AlMe_3$: it can react both as a Lewis acid and as a methyl donor.[38–41] Thus this reagent might catalyze the ring

(35) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E., Jr.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *Org. Chem.* **1986**, *51*, 4731.
(36) Carried out by Professor Raymond J. Butcher at Howard University. The details will be published in the future.
(37) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.
(38) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242.
(39) Kuran, W.; Pasynkiewicz, S.; Serzyko, J. *J. Organomet. Chem.* **1974**, *73*, 187.
(40) Namy, J. L.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* **1970**, 2249.
(41) Lundeen, A. J.; Oehlschlager, A. C. *J. Organomet. Chem.* **1970**, *25*, 337.

contraction of (-)-11 to spirodienol 19 via 18 (Scheme IV). Alternatively, $AlMe_3$ might open the epoxide ring of (-)-11 by S_N2 to give methyl-substituted tertiary alcohol 12 and then to bring about silicon-promoted ring contraction in situ to provide 14.

Alkylation of epoxides with trialkylaluminums generally occurs at the more substituted carbon atom.[39,40] Nevertheless, normal S_N2 at the less hindered carbon atom can compete favorably when the ratio of trialkylaluminum to epoxide is unity or below.[41] The epoxy group of (-)-11 is trisubstituted and in a crowded environment. Methylation at the tertiary carbon of this group might therefore be slow enough to allow substitution at the less hindered secondary carbon to predominate. Consequently, we treated epoxide (-)-11 with 10 equiv of $AlMe_3$ in hexanes at room temperature (Scheme IV). After 4 days, spiro alcohol 19 was obtained in 47% yield.

Completion of the First Total Synthesis of (-)-Solavetivone. We required a method that can efficiently convert (-)-14 to the final target (-)-solavetivone (1) by allylic oxidation of the $C{=}CCH_2$ unit. We were not able to accomplish this transformation with various established reagents.

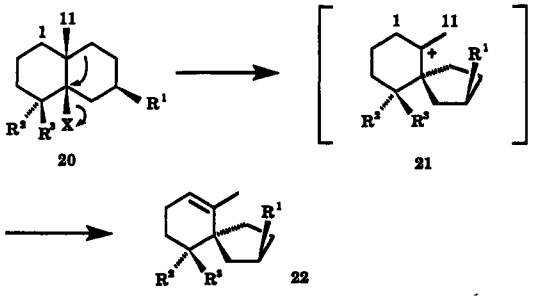
Sharpless and Akashi proposed that the reagent $CrO_2(OCMe_3)_2$ in the presence of pyridine might perform allylic oxidations,[42] but did not provide any working examples. On the basis of the results of Salmond et al. with related reagents,[43] we utilized an excess of $CrO_2(OCMe_3)_2$ in the presence of 3,5-dimethylpyrazole (DMP) for the oxidation of (-)-14. After purification, an oil was obtained in 71% yield, of which the ^1H NMR and broadband decoupled ^{13}C NMR spectra were identical with those of authentic (-)-solavetivone (1). High-resolution mass and IR spectral data also support the assignment of this product as (-)-solavetivone. For the specific rotation, we obtained $[\alpha]^{25}_D$ -135° (*c* 0.2326 g/100 mL, EtOH) for our product. This rotation had a greater absolute value than that (lit.[9] $[\alpha]^{25}_D$ -119° (EtOH)) reported by Coxon et al.

Discussion

Four synthetic routes have been developed to racemic solavetivone,[44-47] but none for the total synthesis of optically active (-)-solavetivone (1). A synthetic entry to (-)-1 would provide the basis for the preparation of its isotopically labeled, homochiral analogues for biosynthetic studies.[48]

We found that 1,4-addition of Me_3SiLi to 7 occurred at the less substituted C–C double bond (i.e., $C_1{=}C_2$) of the cross-conjugated system (Scheme II). Also, Me_3Si^- preferentially added from the α-face of 7. Our findings are consistent with the results of axial 1,4-addition of Me_3SiLi to 2-cyclohexenones.[32] In addition, the stereochemical outcome from our reaction is similar to that obtained by Marshall and Warne.[49] They found that a methyl group of Me_2CuLi adds preferentially from the direction trans to an angular methyl group in dienone substrates.

Scheme V



Epoxidation of 10 with *m*-CPBA took place stereo- and regioselectively to afford 11 as the major product, in which the epoxy group possessed β configuration. The trisubstituted C–C double bond in 10 is more electron-rich than the disubstituted C–C double bond and therefore reacted faster with the peracid.[50] Furthermore, the bulky Me_3Si group blocked the α face of the trisubstituted C–C double bond.[51] In this regard, the Me_3Si group acts as a "bulky proton."[52]

Design of Ring Contractions. For the ring contraction shown in Scheme V, we believed that the yield could be improved if the starting fused-ring compound (20) possessed a special functional group. This group, residing in either C_1 or C_{11} of 20, must be able to stabilize an adjacent positive charge (cf. 21). Moreover, if this functional group eliminated much faster than a proton from 21, a sole spirocyclic alkene would be formed. The location of the C–C double bond in the spiro product would be determined by the position of the cation-stabilizing functional group in 20. Loss of this functional group from the C-1 position in 21 would afford the endocyclic alkene 22. Alternatively, loss of the functional group from the C-11 position in 21 would provide a regioisomer of 22, in which the C–C double bond is exocyclic.

Based upon Fleming's results,[53-56] we considered the Me_3Si group appropriate and, thus, placed it at the C-1 position. To our knowledge, it is unprecedented to use silicon to promote ring contraction for the formation of spiro compounds.

We also studied the silicon-promoted ring contraction using trimethylsilyl epoxide 11 as the substrate (Scheme IV). The epoxy group in 11 can afford a hydroxyl group upon acid-catalyzed ring opening (i.e., 11 → 18). This hydroxyl functionality allows further elaboration of the resultant spiro product 19.

We obtained good yields of spiro products from both (-)-11 and (+)-12. These results indicate that trans coplanar alignment of the C–$SiMe_3$ bond and the migrating C–C bond is not a requirement for silicon-promoted ring contraction. Our findings are also consistent with those reported recently by Lambert et al.:[57] an Me_3Si group can

(42) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5927.
(43) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(44) Murai, A.; Sato, S.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2282.
(45) Iwata, C.; Fusaka, T.; Fujiwara, T.; Tomita, K.; Yamada, M. J. *Chem. Soc., Chem. Commun.* **1981**, 463.
(46) Murai, A.; Sato, S.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2276.
(47) Yamada, K.; Goto, S.; Nagase, H.; Christensen, A. T. *J. Chem. Soc., Chem. Commun.* **1977**, 554.
(48) For examples of the use of isotopically labeled (±)-solavetivone for biosynthetic studies, see refs 20, 23, and 24.
(49) Marshall, J. A.; Warne, T. M., Jr. *J. Org. Chem.* **1971**, *36*, 178.
(50) Knöll, W.; Tamm, C. *Helv. Chim. Acta* **1975**, *58*, 1162.
(51) Chavdarian, C. G.; Heathcock, C. H. *Synth. Commun.* **1976**, *6*, 277.
(52) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946.
(53) Davidson, A. H.; Fleming, I.; Grayson, J. I.; Pearce, A.; Snowden, R. L.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 550.
(54) Fleming, I.; Paterson, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 256.
(55) Fleming, I.; Patel, S. *Tetrahedron Lett.* **1981**, *22*, 2321.
(56) Fleming, I.; Michael, J. P. *J. Chem. Soc., Chem. Commun.* **1978**, 245. See also: Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 1058. Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1981**, *46*, 5045. Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 6343.
(57) Lambert, J. B.; Wang, G.-t.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838.
(58) Hwu, J. R.; Robl, J. A.; Khoudary, K. P. *J. Chromatogr. Sci.* **1987**, *25*, 501.

encourage the formation of a positive charge at a β-carbon even when the C–$SiMe_3$ bond is not trans coplanar to the C–L bond (L = leaving group).

In the $AlMe_3$-induced ring contraction of (–)-11, we obtained only one spirocyclic product (i.e., 19). The absence of other spiroalkenes in this reaction suggests that loss of the Me_3Si group proceeds much more rapidly than loss of a proton from carbocation 18 (Scheme IV). Our result corroborates those reported by Fleming, Warren, and their co-workers[53-56] on fundamental silicon-promoted carbocation rearrangements.

Significance of the New Synthetic Method. Murai, Sato, and Masamune accomplished the shortest total synthesis of racemic solavetivone,[44] which involves 10 steps and provides (±)-solavetivone in 15% overall yield. However, it does not allow control of the stereoconfiguration at C_{10} of the spirovetivane skeleton. Thus a separation of four diastereomers is necessary at an intermediate stage. The other published syntheses of (±)-solavetivone, developed by Iwata,[45] Murai,[46] Yamada[47] and their coworkers, also require the separation of diastereomeric mixtures.

We completed the first total synthesis of (–)-solavetivone. Our route includes 13 steps and provides the target compound in 1.4% overall yield from (+)-dihydrocarvone. Our synthetic strategy affords a high degree of stereocontrol in the formation of each chiral center of (–)-solavetivone.

As a synthetic target, (–)-solavetivone epitomizes carbocyclic spiro compounds. (–)-Solavetivone possesses a chiral center on each ring in addition to the chiral spiro carbon. Our highly stereoselective total synthesis of (–)-solavetivone demonstrates that the silicon-promoted ring contraction method solves the problems associated with spiro compound synthesis. These problems include: (1) generation of the quaternary spiro center, (2) control of the stereoconfiguration of the spiro carbon, and (3) establishment of chiral centers on both rings.

Conclusions

A new method involving silicon-promoted ring contraction was developed for the synthesis of carbocyclic spiro compounds. This method allowed the stereospecific generation of a spiro[4.5]dec-6-ene in good yield from a (trimethylsilyl)decalinol or (trimethylsilyl)decalin epoxide. The first total synthesis of (–)-solavetivone (1) was achieved by application of the silicon-promoted ring contraction as the key step.

In the total synthesis of (–)-solavetivone, the Me_3Si group serves four functions. (1) It afforded stereoselectivity to the epoxidation of trimethylsilyl diene (–)-10 by blocking the α face. (2) The Me_3Si group promoted the acid-catalyzed ring contraction of tertiary alcohol (+)-12 by stabilizing intermediate carbocation 13. (3) The Me_3Si group prevented scrambling of the spiro carbon stereoconfiguration by eliminating rapidly from 13. (4) The Me_3Si group determined the position of the newly formed C–C double bond in the ring-contracted product (–)-14.

Experimental Section

(–)-(6*S*,9*R*)-9-Isopropenyl-6-methylbicyclo[4.4.0]deca-1,4-dien-3-one (7). Method 1. The procedure of Caine et al.[30] was followed. A mixture of 5 (1.13 g, 4.69 mmol, 1.0 equiv) and NaOAc (1.15 g, 14.1 mmol, 3.0 equiv) in AcOH (16 mL) was stirred rapidly and heated at 100 °C for 3 h. The mixture was cooled to room temperature and poured into 20 mL of cold water. The aqueous solution was worked up to afford (+)-6 as a brown oil in 100% yield (0.955 g, 4.67 mmol).

This brown oil was not purified, but was reacted directly with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (98% pure, 1.41 g, 6.10 mmol, 1.3 equiv) in anhydrous *p*-dioxane (120 mL) at reflux with stirring for 44 h. The solution was worked up to give a residue, which was purified by MPLC (1.5 cm × 30 cm column, 18% EtOAc in hexanes as eluant) to afford (–)-7 (0.456 g, 2.25 mmol, 48% overall yield from 5) as a yellow oil. Compound (+)-6 (0.194 g, 0.950 mmol, 20% yield from 5) was also isolated as a yellow oil.

For (+)-6: TLC R_f 0.58 (40% EtOAc in hexanes); $[\alpha]^{25}_D$ +95.0° (*c* 1.0576, CH_2Cl_2); ^1H NMR ($CDCl_3$, 80 MHz) δ 1.24 (s, 3 H, CH_3), 1.3–2.8 (m, 11 H, 5 CH_2 + 1 CH), 1.76 (t, *J* = 1.1 Hz, 3 H, CH_3C=C), 4.76 (br s, 2 H, C=CH_2), 5.75 (br s, 1 H, C=CHC=O); IR (neat) 3075 (w, =CH), 3020 (w, =CH), 1668 (s, conjugated C=O), 1642 (s, C=C), 1616 (s, conjugated C=C), 892 (s, =CH_2) cm^{-1}; exact mass calcd for $C_{14}H_{20}O$ 204.1514, found 204.1517.

For (–)-7: TLC R_f 0.49 (40% EtOAc in hexanes); $[\alpha]^{25}_D$ –172° (*c* 0.6439, $CHCl_3$); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.67–2.52 (m, 7 H, 3 CH_2 + 1 CH), 1.27 (s, 3 H, CH_3), 1.78 (t, *J* = 1.0 Hz, 3 H, CH_3C=C), 4.79 (br s, 2 H, C=CH_2), 6.12 (d, *J* = 1.8 Hz, 1 H, C=CH), 6.20 (dd, *J* = 9.7, 1.8 Hz, 1 H, HC=C*H*C=O), 6.78 (d, *J* = 9.7 Hz, 1 H, HC=CC=O); IR (neat) 3072 (w, =CH), 3032 (w, =CH), 1660 (s, cross-conjugated C=O), 1626 (m, conjugated C=C), 1607 (m, conjugated C=C), 890 (s, =CH_2) cm^{-1}; exact mass calcd for $C_{14}H_{18}O$ 202.1358, found 202.1358.

Method 2. After purification by MPLC, (+)-6 (3.35 g, 16.4 mmol, 1.0 equiv) was dissolved in anhydrous *p*-dioxane (410 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (98% pure, 4.93 g, 21.3 mmol, 1.3 equiv) was added, and the mixture was heated at reflux for 44 h. The solution was worked up, and the resultant residue was chromatographed on silica gel (5.0 cm × 30 cm column, 25% EtOAc in hexanes as eluant) to afford (–)-7 in 74% yield (2.46 g, 12.2 mmol) as an oil.

(–)-(5*S*,6*R*,9*R*)-9-Isopropenyl-6-methyl-5-(trimethylsilyl)bicyclo[4.4.0]dec-1-en-3-one (8). A solution of hexamethyldisilane (95% pure, 804 μL, 3.7 mmol, 2.5 equiv) in hexamethylphosphoramide (1.6 mL) was cooled to –78 °C under argon, whereupon the mixture solidified. Low-halide MeLi (1.3 M in ether, 2.3 mL, 3.0 mmol, 2.0 equiv) and THF (8.0 mL) were added slowly onto the frozen mixture, which was then warmed to 0 °C for 5 min. The resultant orange–red solution was cooled to –78 °C. A solution of trienone (–)-7 (302 mg, 1.49 mmol, 1.0 equiv) in THF (1.5 mL) was injected slowly into the reaction flask. The resultant dark green solution was stirred at –78 °C for 1 h. Water (5 mL) was added into the reaction flask, and the mixture was poured into ether. The ether solution was washed with water and brine, dried over $MgSO_4$(s), filtered, and concentrated. Purification of the residue by MPLC (1.5 cm × 30 cm column, 5% EtOAc in hexanes as eluant) provided (–)-8 in 66% yield (273 mg, 0.988 mmol) as a yellow oil, which was >95% one component by GC. For (–)-8: TLC R_f 0.46 (20% EtOAc in hexanes); GC t_R 6.82 min (column temperature program: initial temperature 170 °C, duration 3.00 min; increment rate 10 °C/min; final temperature 210 °C); $[\alpha]^{25}_D$ –110° (*c* 0.3518, CH_2Cl_2); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.10 (s, 9 H, $Si(CH_3)_3$), 1.14–2.52 (m, 10 H, 4 CH_2 + 2 CH), 1.30 (s, 3 H, CH_3), 1.75 (t, *J* = 1.0 Hz, 3 H, CH_3C=C), 4.75 (br s, 2 H, C=CH_2), 5.78 (br s, 1 H, C=CHC=O); IR (neat) 3076 (w, =CH), 3015 (w, =CH), 1671 (s, conjugated C=O), 1642 (m, =CH_2), 1617 (m, conjugated C=C), 1252 (s, $SiMe_3$), 891 (s, =CH_2), 847 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{17}H_{28}OSi$ 276.1909, found 276.1909.

(–)-(5*S*,6*R*,9*R*)-9-Isopropenyl-6-methyl-5-(trimethylsilyl)bicyclo[4.4.0]dec-1-en-3-one 3-Ethylene Thioacetal (9). Dienone (–)-8 (1.54 g, 5.57 mmol, 1.0 equiv) and 1,2-ethanedithiol (96% pure, 536 μL, 6.13 mmol, 1.1 equiv) were dissolved in MeOH (40 mL) in a flask equipped with a KOH drying tube. Boron trifluoride etherate (754 μL, 870 mg, 6.13 mmol, 1.1 equiv) was added dropwise into the reaction flask, and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was concentrated, and ether was added to the residue. The ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$(s), filtered, and concentrated. The residual cloudy

(59) Stoessl, A.; Stothers, J. B.; Ward, E. W. B. *Can. J. Chem.* 1978, *56*, 645.

yellow oil (1.96 g) was chromatographed on silica gel (19 mm × 95 mm column) with 1% EtOAc in hexanes as eluant to provide (−)-9 in 93% yield (1.84 g, 5.22 mmol) as a colorless oil: TLC R_f 0.58 (5% EtOAc in hexanes); GC t_R 7.05 min (column temperature 220 °C); $[\alpha]^{25}_D$ −155° (c 0.3208, CH_2Cl_2); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.10 (s, 9 H, $Si(CH_3)_3$), 1.14 (s, 3 H, CH_3), 1.15–2.35 (m, 10 H, 4 CH_2 + 2 CH), 1.72 (t, J = 1.0 Hz, 3 H, CH_3C=C), 3.22–3.55 (m, 4 H, SCH_2CH_2S), 4.70 (br s, 2 H, C=CH_2), 5.66 (br s, 1 H, HC=C); IR (CCl_4) 3070 (w, =CH), 1640 (m, C=C), 1252 (s, $SiMe_3$), 890 (s, =CH_2), 840 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{19}H_{32}S_2Si$ 352.1715, found 352.1719.

(−)-(5*S*,6*R*,9*R*)-9-Isopropenyl-6-methyl-5-(trimethylsilyl)bicyclo[4.4.0]dec-1-ene (10). Calcium metal (99.5% pure, 1.04 g, 25.8 mmol, 5.0 equiv) was dissolved in liquid ammonia (130 mL) at −78 °C under an argon atmosphere in a three-necked flask equipped with a dry ice–acetone-cooled Dewar condenser. To this blue solution was added ether (48 mL) and a solution of ethylene thioacetal (−)-9 (1.82 g, 5.16 mmol, 1.0 equiv) in ether (4.0 mL). The cooling bath was removed, and the deep blue solution was kept at reflux for 1.8 h. Solid NH_4Cl was added cautiously to the reaction flask, followed by ether (50 mL), and the ammonia was allowed to evaporate overnight. Saturated aqueous NH_4Cl was added to the residue, and the aqueous phase was extracted with three portions of ether. The combined ether solutions were washed with saturated aqueous NH_4Cl, 10% aqueous NaOH, and brine, dried over $MgSO_4$(s), filtered through Celite, and concentrated. The residue was purified by chromatography on silica gel (19 mm × 95 mm column) with hexanes as eluant to afford (−)-10 as a colorless oil, which was 90% one component by GC (1.13 g, 3.87 mmol, 75% yield). Two unidentified impurities, which have the same R_f as (−)-10 on TLC (hexanes as eluant) were inseparable from (−)-10 by chromatography. For (−)-10: TLC R_f 0.51 (hexanes); GC t_R 3.83 min (column temperature program: initial temperature 170 °C, duration 3.00 min; increment rate 10 °C/min; final temperature 210 °C); $[\alpha]^{25}_D$ −94° (c 0.1425, CH_2Cl_2) (impure sample); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.07 (s, 9 H, $Si(CH_3)_3$), 0.68–2.34 (m, 12 H, 5 CH_2 + 2 CH), 1.15 (s, 3 H, CH_3), 1.73 (t, J = 1.1 Hz, 3 H, CH_3C=C), 4.70 (br s, 2 H, C=CH_2), 5.42 (m, 1 H, HC=C); IR (neat) 3070 (w, =CH), 1644 (m, C=C), 1253 (s, $SiMe_3$), 893 (s, =CH_2), 840 (s, $SiMe_3$), 760 (m, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{17}H_{30}Si$ 262.2117, found 262.2118.

(−)-(1*R*,2*S*,5*S*,6*R*,8*R*)-5,6-Epoxy-8-isopropenyl-1-methyl-2-(trimethylsilyl)bicyclo[4.4.0]decane (11). A solution of *m*-chloroperoxybenzoic acid (80–85% pure, 890 mg, ~4.2 mmol, 1.0 equiv) in $CHCl_3$ (20 mL) was added dropwise to a solution of (−)-10 (1.08 g, 4.13 mmol, 1.0 equiv) in $CHCl_3$ (5.0 mL) at −22 °C (CCl_4/dry ice bath). The resultant white slurry was stirred at the same temperature for 3.5 h. Aqueous NaOH (10%) and ether were added, and the mixture was warmed to room temperature. The organic layer was washed with 5% aqueous Na_2CO_3 and brine, dried over $MgSO_4$(s), and filtered. Removal of the solvents afforded 1.18 g of off-white crystalline solid. Gas chromatographic analysis of the crude product indicated that (−)-11 was the major component (t_R 9.17 min, 75%, column temperature 160 °C). A peak with retention time close to that of (−)-11 was tentatively assigned to the epoxy diastereomer, (1*R*,2*S*,5*R*,6*S*,8*R*)-5,6-epoxy-8-isopropenyl-1-methyl-2-(trimethylsilyl)bicyclo[4.4.0]decane (t_R 8.86 min, 2.1%). The ratio of (−)-11 to the epoxy diastereomer was >35:1. Purification by MPLC (1.5 cm × 45 cm column) with 1% EtOAc in hexanes as eluant provided (−)-11 in 64% yield (735 mg, 2.64 mmol) as a white crystalline solid: mp 76.5–77.0 °C; TLC R_f 0.33 (5% EtOAc in hexanes); $[\alpha]^{25}_D$ −56.2° (c 0.8328, CH_2Cl_2); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.02 (s, 9 H, $Si(CH_3)_3$), 0.60–2.19 (m, 12 H, 5 CH_2 + 2 CH), 1.16 (s, 3 H, CH_3), 1.72 (t, J = 1.1 Hz, 3 H, CH_3C=C), 2.98 (br d, J = 5.0 Hz, 1 H, HCO), 4.70 (br s, 2 H, C=CH_2); IR ($CHCl_3$) 3070 (w, =CH), 1640 (m, C=C), 1248–1205 (s, $SiMe_3$ + epoxide), 938 (m, epoxide), 892 (s, =CH_2), 835 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{17}H_{30}OSi$ 278.2066, found 278.2072.

Ring Contraction of (−)-(1*R*,2*S*,5*S*,6*R*,8*R*)-5,6-Epoxy-8-isopropenyl-1-methyl-2-(trimethylsilyl)bicyclo[4.4.0]decane (11). Trimethylaluminum (2.0 M solution in hexanes, 381 μL, 0.761 mmol, 1.0 equiv) was added in one portion to neat epoxide (−)-11 (21.2 mg, 0.0761 mmol, 1.0 equiv) at −5 °C under Ar. The mixture was warmed to room temperature and stirred for 4 days. Hexanes (2 mL) was then injected into the reaction flask, and the mixture was cooled to −5 °C. Aqueous KOH (3 M) was added cautiously to the mixture, which was then poured into hexanes. The organic layer was washed with 3 M aqueous KOH and brine, dried over $MgSO_4$(s), filtered, and concentrated to give a colorless oil (16.5 mg). This colorless oil was purified by chromatography on silica gel (1.0 cm × 23.0 cm column, 5% ether in hexanes as eluant) to afford 19 in 47% yield (7.5 mg, 0.036 mmol) as a white solid. A second product was isolated in 24% yield (5.3 mg, 0.018 mmol) as a colorless oil, but was not identifiable.

For 19: mp 43.0–45.0 °C; TLC R_f 0.24 (20% ether in hexanes); GC t_R 4.30 min (column temperature program: initial temperature 150 °C, duration 5.00 min; increment rate 10 °C/min; final temperature 170 °C); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.65–2.80 (m, 11 H, 5 CH_2 + 1 CH), 1.73 (m, 6 H, 2 CH_3C=C), 3.63 (m, 1 H, HCO), 4.72 (br s, 2 H, C=CH_2), 5.31 (m, 1 H, HC=C); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.565 (q), 21.376 (q), 22.960 (t), 27.598 (t), 32.425 (t), 35.725 (t), 36.810 (t), 47.478 (d, C_2), 50.620 (s, C_5), 74.239 (d, C_{10}), 108.199 (t, C_{12}), 120.969 (d, C_7), 138.758 (s, C_8), 148.329 (s, C_{11}); IR (melt) 3540–3120 (m, OH), 3076 (w, =CH), 1642 (m, C=C), 1048 (m, CO), 888 (m, =CH_2), 801 (w) cm^{-1}; exact mass calcd for $C_{14}H_{22}O$ 206.1671, found 206.1672.

(+)-(1*R*,2*S*,5*R*,6*S*,8*R*)-8-Isopropenyl-1,5-dimethyl-2-(trimethylsilyl)bicyclo[4.4.0]decan-6-ol (12). A solution of MeLi (1.3 M in ether, 8.20 mL, 10.7 mmol, 19.5 equiv) was added dropwise to a suspension of CuCN (491 mg, 5.48 mmol, 10.0 equiv) in THF (5.5 mL) at −78 °C under argon. The mixture was warmed to room temperature, and the resultant tan solution was stirred for 5 min. This solution was cooled to −78 °C, and a solution of epoxide (−)-11 (152 mg, 0.547 mmol, 1.0 equiv) in THF (1.4 mL) was added dropwise into the reaction flask. The mixture was heated at 55–60 °C for 144 h. The excess $(CH_3)_2Cu(CN)Li_2$ was destroyed cautiously at room temperature with a buffer solution made from one volume of concentrated NH_4OH and nine volumes of saturated aqueous NH_4Cl. The mixture was poured into ether, and the organic layer was washed with fresh buffer solution and brine, dried over anhydrous $MgSO_4$(s), filtered, and concentrated. The residue was purified by chromatotron (1-mm plate, 5% EtOAc in hexanes as eluant) to afford (+)-12 in 61% yield (98.1 mg, 0.333 mmol) as a colorless oil: TLC R_f 0.34 (10% EtOAc in hexanes); GC t_R 6.71 min (column temperature program: initial temperature 170 °C, duration 3.00 min; increment rate 10 °C/min; final temperature 210 °C); $[\alpha]^{25}_D$ +36.5° (c 0.8283, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 9 H, $Si(CH_3)_3$), 1.06 (m, 1 H, SiCH), 1.07 (s, 3 H, CH_3), 1.26 (d, J = 7.6 Hz, 3 H, CH_3CH), 1.33 (s, 1 H, OH), 1.36–1.98 (m, 11 H, 5 CH_2 + 1 CH), 1.73 (br s, 3 H, CH_3C=C), 2.35–2.87 (m, 1 H, HCC=C), 4.69 (br s, 1 H, HC=C), 4.70 (br s, 1 H, HC=C); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 0.749 (q, SiC_3), 19.245 (t), 20.428 (q), 20.678 (q), 25.737 (t), 26.059 (q), 32.631 (t), 33.844 (t), 35.355 (d), 41.273 (s, $C(C)_4$), 41.388 (t), 41.898 (d), 42.626 (d), 75.326 (s, CO), 108.365 (t, C=CH_2), 149.722 (s, C=CH_2); IR (neat), 3645–3255 (m, OH), 3080 (m, =CH), 1643 (m, C=C), 1253 (s, $SiMe_3$), 1071 (m, CO), 893 (s, =CH_2), 838 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{18}H_{34}OSi$ 294.2379, found 294.2379.

(−)-(2*R*,5*S*,10*R*)-2-Isopropenyl-6,10-dimethylspiro[4.5]-dec-6-ene (14). A solution of trimethylsilyl alcohol (+)-12 (33.9 mg, 0.115 mmol, 1.0 equiv) in CH_2Cl_2 (1.3 mL) was added dropwise to a suspension of anhydrous $FeBr_3$ (47.2 mg, 0.160 mmol, 1.4 equiv) in CH_2Cl_2 (10.2 mL) at −60 °C. After the mixture was stirred for 22 min at the same temperature, pyridine (78 μL, 76 mg, 0.96 mmol, 8.3 equiv) was injected, and stirring was continued for 15 min. The mixture was warmed to room temperature and filtered through basic alumina (Woelm, activity grade I, 1 cm × 6 cm column, CH_2Cl_2 as eluant). By GC analysis of the filtrate, (−)-14 was found to be the major product (59%). The byproducts that were detected included 15 (3%), 16 (22%), and 17 (5%). The solvents were removed by distillation through a 3-cm vigreux column. Purification of the residue by chromatotron (1-mm plate, silica gel containing 4% $AgNO_3$ on silica gel, 1% EtOAc in pentane as eluant) and removal of solvents under reduced pressure at −20 °C afforded (−)-14 in 54% yield (12.8 mg, 0.0626 mmol) and 16 in 18% yield (5.6 mg, 0.020 mmol) as colorless oils.

For (−)-14: TLC R_f 0.60 (hexanes); GC t_R 5.77 min (column temperature program: initial temperature 130 °C, duration 8.00 min; increment rate 10 °C/min; final temperature 160 °C); $[\alpha]^{25}_D$

−87.8° (c 0.3928, CH_2Cl_2); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.90 (d, J = 6.6 Hz, 3 H, CH_3CH), 1.10–2.79 (m, 12 H, 5 CH_2 + 2 CH), 1.68 (br s, 3 H, CH_3C=CH), 1.74 (br s, 3 H, CH_3C=CH_2), 4.70 (br s, 2 H, C=CH_2), 5.28 (m, HC=C); ^{13}C NMR (CD_2Cl_2, 101 MHz) δ 14.948 (q, C_{15}), 20.236 (q), 21.275 (q), 22.352 (t), 27.458 (t), 33.185 (t), 34.365 (t), 38.146 (d, C_{10}), 44.190 (t), 47.155 (d, C_2), 48.856 (s, C_5), 108.193 (t, C_{12}), 121.148 (d, C_7), 139.565 (s, C_6), 149.048 (s, C_{11}); IR (neat) 3080 (w, =CH), 3035 (w, =CH), 1646 (w, C=C), 891 (m, =CH_2) cm^{-1}; exact mass calcd for $C_{15}H_{24}$ 204.1878, found 204.1878.

For 15: TLC R_f 0.60 (hexanes); GC t_R 6.29 min (column temperature program: initial temperature 130 °C, duration 8.00 min; increment rate 10 °C/min; final temperature 160 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.20–1.76 (m, 5 H), 1.61 (m, 6 H, $(CH_3)_2C$=C), 1.63 (m, 3 H, CH_3C=CH), 1.82–2.36 (m, 6 H, 3 CH_2C=C), 5.36 (m, 1 H, HC=C); exact mass calcd for $C_{15}H_{24}$ 204.1878, found 204.1879.

For 16: TLC R_f 0.60 (hexanes); GC t_R 13.27 min (column temperature program: initial temperature 130 °C, duration 8.00 min; increment rate 10 °C/min; final temperature 160 °C); ^1H NMR ($CDCl_3$, 80 MHz) δ 0.06 (s, 9 H, $Si(CH_3)_3$), 0.62–2.63 (m, 12 H, 5 CH_2 + 2 CH), 1.13 (s, 3 H, CH_3), 1.62 (br s, 3 H, CH_3C=C), 1.75 (t, J = 1.0 Hz, 3 H, CH_3C=CH_2), 4.72 (br s, 2 H, C=CH_2); IR (neat) 3070 (w, =CH), 1643 (m, C=C), 1252 (s, $SiMe_3$), 890 (s, =CH_2), 838 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{18}H_{32}Si$ 276.2273, found 276.2277.

For 17: TLC R_f 0.60 (hexanes); GC t_R 14.98 min (column temperature program: initial temperature 130 °C, duration 8.00 min; increment rate 10 °C/min; final temperature 160 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 9 H, $Si(CH_3)_3$), 0.85 (m, 1 H, HCSi), 1.14 (s, 3 H, CH_3), 1.36–1.82 (m, 6 H, 3 CH_2), 1.65 (m, 3 H, CH_3C=CH), 1.72 (br s, 3 H, CH_3C=CH_2), 1.89–2.08 (m, 4 H, 1 CH_2C=C and 2 HCC=C), 4.67 (br s, 2 H, C=CH_2), 5.54 (br s, 1 H, HC=C); IR (CCl_4) 3060 (w, =C–H), 1640 (w, C=C), 1250 (s, $SiMe_3$), 890 (s, =CH_2), 838 (s, $SiMe_3$) cm^{-1}; exact mass calcd for $C_{18}H_{32}Si$ 276.2273, found 276.2275.

(−)-Solavetivone ((−)-(2*R*,5*S*,10*R*)-2-Isopropenyl-6,10-dimethylspiro[4.5]dec-6-en-8-one, 1).[9,21,59] A solution of 3,5-dimethylpyrazole (209 mg, 2.17 mmol, 30 equiv) and *t*-BuOH (137 μL, 107 mg, 1.45 mmol, 20 equiv) in CH_2Cl_2 (2.7 mL) was cooled to −78 °C, whereupon a precipitate formed. Chromyl chloride (58.7 μL, 112 mg, 0.724 mmol, 10 equiv) was added to this suspension over 5 min. The mixture was stirred for 5 min at −78 °C and then warmed to room temperature. A solution of spiro diene (−)-14 (14.8 mg, 0.0724 mmol, 1.0 equiv) in CH_2Cl_2 (0.20 mL) was added rapidly into the reaction flask. The resultant clear, dark brown solution was stirred at room temperature for 38 h. Dimethyl sulfide (53 μL, 45 mg, 0.72 mmol, 10 equiv) was added to quench the excess oxidant. The solution was concentrated under a stream of nitrogen to a volume of 1.5 mL. Then ether (3 mL) was added dropwise, and the mixture was stirred for 10 min to complete the precipitation of chromium salts. The mixture was filtered through a column of Celite (1.0 cm × 10 cm) with ether as eluant. The filtrate was washed with 5% aqueous NaOH, 5% aqueous HCl, and brine, dried over anhydrous $MgSO_4$(s), filtered, and concentrated. The residue was purified by chromatography on silica gel (9.5 mm × 150 mm column) with 10% Et_2O in pentane as eluant to afford (−)-solavetivone (1) in 71% yield (11.2 mg, 0.0514 mmol) as a colorless oil.

For (−)-1: TLC R_f 0.34 (20% EtOAc in hexanes); GC t_R 6.32 min (column temperature 160 °C); $[\alpha]^{25}_D$ −135° (c 0.2326, EtOH) (lit.[9] −119° (EtOH)); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (d, J = 7.2 Hz, 3 H, CH_3CH), 1.53–1.73 (m, 3 H), 1.76 (br s, 3 H, CH_3C=CH_2), 1.90–1.98 (m, 2 H), 1.95 (br s, 3 H, CH_3C=CC=O), 2.07–2.17 (m, 2 H), 2.22 (dd, J = 16.5, 4.3 Hz, 1 H, HCC=O), 2.50–2.60 (m, 1 H, HCC=C), 2.66 (dd, J = 16.5, 4.7 Hz, 1 H, HCC=O), 4.74 (br s, 2 H, C=CH_2), 5.75 (br s, 1 H, C=CHC=O); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.035 (C_{15}), 21.040 (C_{14}), 21.432 (C_{13}), 32.877 (C_3), 34.498 (C_4), 39.535 (C_{10}), 40.897 (C_1), 43.058 (C_9), 46.626 (C_2), 50.154 (C_5), 108.946 (C_{12}), 125.386 (C_7), 146.981 (C_{11}), 166.372 (C_6), 198.784 (C_8); FT-IR (neat) 3080.2 (w, =CH), 1668.4 (s, conjugated C=O), 1614.1 (m, conjugated C=C), 888.7 (m, =CH_2), 832.2 (w) cm^{-1}; MS *m/e* (relative intensity) 218 (M^+, 60), 203 (20), 190 (20), 176 (20), 161 (20), 137 (60), 121 (22), 108 (60), 84 (100), 68 (59), 55 (10); exact mass calcd for $C_{15}H_{22}O$ 218.1671, found 218.1672.

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Supplementary Material Available: Results of elemental analyses for compounds (+)-6, (−)-7, (−)-8, (−)-9, (−)-10, (−)-11, (+)-12, (−)-14, 15, 16, 17, 19, and (−)-1 (1 page). Ordering information is given on any current masthead page.