A New 4C + 2C Annelation Reaction Based on Tandem Michael-Claisen Condensation. 2. Synthesis of Aristolone and Fukinone

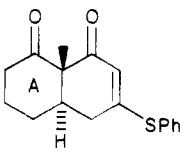
C. V. C. Prasad and Tak Hang Chan*

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

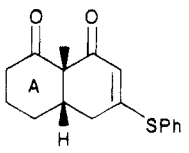
Received May 2, 1986

The utility of the tandem Michael-Claisen annelation sequence in the synthesis of natural products has been demonstrated by the synthesis of aristolone and fukinone.

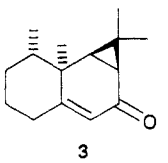
In the preceding paper,[1] we have described an annelation reaction based on the propensity of 3-(phenylthio)-1-(trimethylsiloxy)-1-methoxy-1,3-butadiene (**1**)[2] to undergo Michael reaction with α,β-unsaturated ketones under Lewis acid catalyzed conditions. The Michael adducts in turn were cyclized either with potassium *tert*-butoxide or with lithium thiophenoxide to give a six-membered ring (Scheme I). Furthermore, for the 9-methyldecalin system, it was possible to stereoselectively synthesize the trans or the cis isomers **2a** and **2b** by using this tandem Michael-Claisen condensation.[1] In this paper, we demonstrate the utility of this reaction by the synthesis of two sesquiterpens, (±)-aristolone (**3**) and (±)-fukinone (**4**). In the



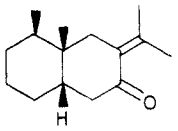
2a



2b



3

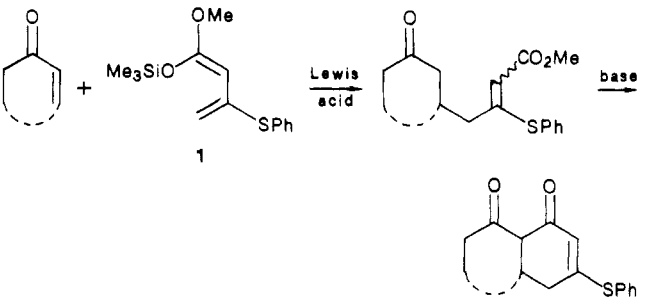


4

conversion of **2** to either **3** or **4**, it is necessary to (1) differentiate between the carbonyl groups in **2**, (2) transform the ring-A carbonyl into a methyl group, preferably with good stereochemical control, and (3) introduce the isopropylidene group regioselectively in **4** and stereoselectively in **3**. Knowledge gained from the study will be useful in the future to elaborate **2** into natural products of greater structural complexity.

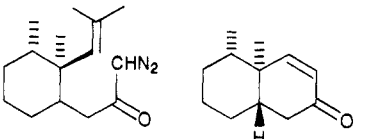
Synthesis of Aristolone. The sesquiterpene (−)-aristolone (**3**) was isolated from *Aristolochia debilis* Sieb. et Zucc.[3] Its structure[4] and absolute configuration[5] have been established. Various syntheses of this sesquiterpene have also been reported.[6,7] In the Piers synthesis,[6] the key step was the cupric sulfate catalyzed intramolecular cyclization of the diazo ketone **5**, which produced a mixture of products, the major component of which was **3**. Ourisson et al.[7] reported the synthesis of **3** in which the isopropylidene moiety was introduced by photolysis of the

Scheme I



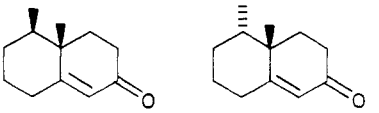
1

pyrazoline derivative prepared by 1,3-dipolar addition of diazo-2-propane to the enone **6**. The enone **6** in turn was



5 **6**

prepared from octalone **7**. Ourisson et al. prepared this compound from 2,3-dimethylcyclohexanone and methyl vinyl ketone by the Robinson's annelation in very poor yield. Furthermore, the octalone **7** consisted of a mixture of two epimers **7a** and **7b** in a ratio of approximately 3:2. Quite recently Huffman et al.[8] have described a silyl enol ether variation of the Robinson's annelation. Although the ratio of **7a** and **7b** improved to 3:1 with good yield, the



7a **7b**

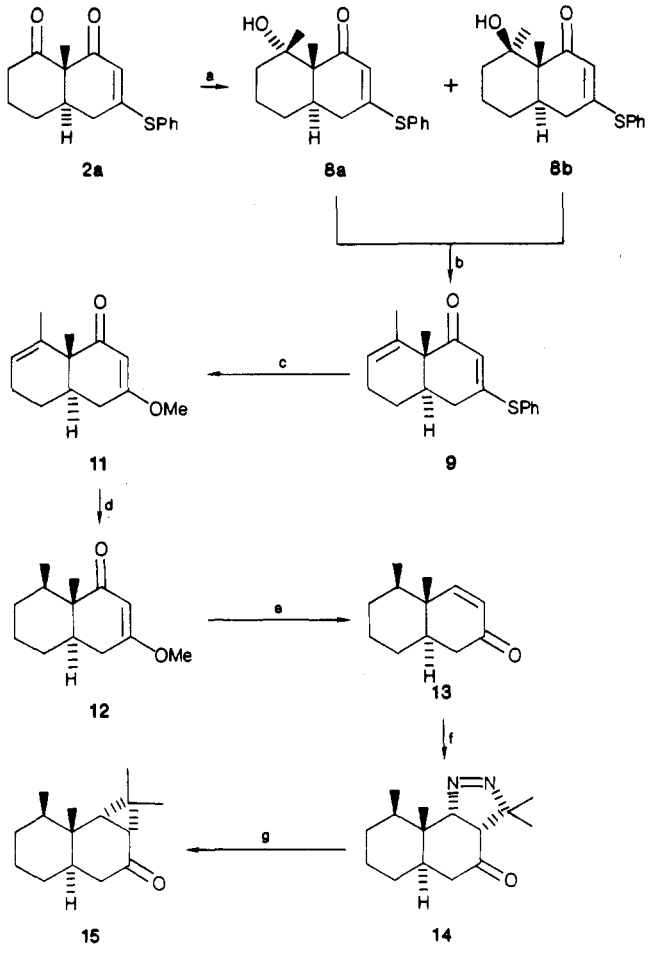
stereocontrol was still not quite satisfactory. We decided to seek a solution to the aforementioned problems with the compound **2a** in our hands.[1]

When compound **2a** was treated with methylmagnesium bromide, the Grignard reagent added smoothly to give the addition product (Scheme II). The ^{1}H NMR spectrum of crude reaction mixture indicated the presence of isomeric alcohols **8a** and **8b** in a ratio of 5:7, which were separated easily. It is noteworthy that the Grignard reagent selectively added to the C(8) carbonyl group instead of the C(1) carbonyl group. When **8a** was treated with 80% H_2SO_4 or with polyphosphoric acid, dehydration proceeded smoothly to give compound **9** and other side products. The side products were presumably due to the hydrolysis of the masked 1,3-dione system. We were very pleased to find that with more concentrated H_2SO_4, dehydration pro-

(1) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.*, preceding paper in this issue.
(2) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1986**, *51*, 3012.
(3) Kariyone, T.; Naito, S. *J. Pharm. Soc. Jpn.* **1955**, *75*, 1511.
(4) (a) Furukawa, S.; Soma, N. *J. Pharm. Soc. Jpn.* **1961**, *81*, 559. (b) Furukawa, S.; Oyamada, K.; Soma, N. *Ibid.* **1961**, *81*, 565. (c) Furukawa, S. *Ibid.* **1961**, *81*, 570.
(5) Buchi, G.; Greuter, F.; Tokoroyama, T. *Tetrahedron Lett.* **1962**, 827.
(6) Piers, E.; Britton, R. W.; De Wall, W. *Can. J. Chem.* **1969**, *47*, 831.
(7) Berger, C.; Frank-Neumann, M.; Ourisson, G. *Tetrahedron Lett.* **1968**, 3451.
(8) Huffman, J. W.; Potnis, S. M.; Satish, A. V. *J. Org. Chem.* **1985**, *50*, 4266.

0022-3263/87/1952-0120$01.50/0

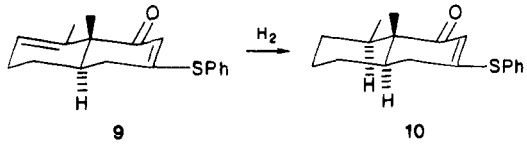
Scheme II[a]



[a] (a) CH_3MgBr; (b) H_2SO_4; (c) $NaOCH_3$–CH_3OH; (d) 5% Pd–$CaCO_3$, H_2; (e) $LiAlH_4$, H^+; (f) $(CH_3)_2CN_2$; (g) $h\nu$.

ceeded readily to give a single compound (**9**) in excellent yield without any apparent hydrolysis. On the other hand, when **8b** was treated with concentrated H_2SO_4, dehydration proceeded but the rate of dehydration was much slower. We thus tentatively assign the stereochemistry of the hydroxyl group in **8a** and **8b** on the basis of the relative ease of dehydration.

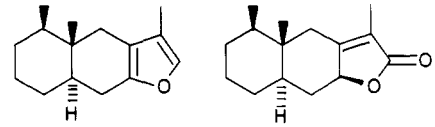
In order to create the vicinal methyl groups, hydrogenation of compound **9** was attempted. In principle, upon



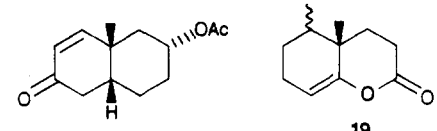
hydrogenation of **9**, the hydrogen delivery should occur selectively from the less hindered side to give compound **10** predominantly. However, attempted hydrogenation of **9** with Pd or with Pt catalysts at different pressures and/or different concentrations gave only the recovered starting material **9**. Presumably our inability to hydrogenate **9** was a result of catalyst poisoning by the sulfur moiety. Accordingly, compound **9** was treated with sodium methoxide in methanol to give **11** in almost quantitative yield. When compound **11** was treated with catalytic amount of 5% Pd–$CaCO_3$ under an atmospheric pressure of hydrogen, hydrogenation proceeded smoothly to give a single compound (**12**) in almost quantitative yield. The ^1H NMR spectrum showed a sharp methyl doublet at 1.20 ppm (J = 6.2 Hz). It is noteworthy that under this condition, the conjugated double bond was unaffected. The next question that remains to be answered is the stereochemistry of the vicinally substituted methyl groups.

Reduction of compound **12** with lithium aluminum hydride gave compound **13** after acidic hydrolysis. The ^1H NMR spectrum of compound **13** showed sharp doublets at 0.94 (J = 6.1 Hz), 5.84 (J = 10.4 Hz), and 7.08 (J = 10.3 Hz) and a sharp singlet at 0.91 ppm. Although compound **13** is known, but, because of the conflicting reports[9,10] on its ^1H NMR data in the literature, we could not establish the stereochemistry of **13** unequivocally at this point. Reaction of compound **13** with diazo-2-propane proceeded smoothly to give the cycloadduct **14** in quantitative yield. Photolysis of compound **14** gave dihydroaristolone **15** in excellent yield. The ^1H NMR spectrum of **15** is identical in all respects with the data reported[10] for dihydroaristolone. The identity of dihydroaristolone clearly suggests that hydrogenation of **11** is highly stereoselective to give cis-substituted vicinal methyl groups. The synthesis of aristolone from dihydroaristolone has already been accomplished by bromination–dehydrobromination.[5] This clearly shows that aristolone can be prepared with a high degree of stereocontrol using our tandem Michael–Claisen annelation sequence.

We note in passing that the intermediate **13** may be a valuable intermediate in the synthesis of other eremophilane sesquiterpenes such as furanoligularone (**16**)[11] and tetrahydroligularenolide (**17**).[12]



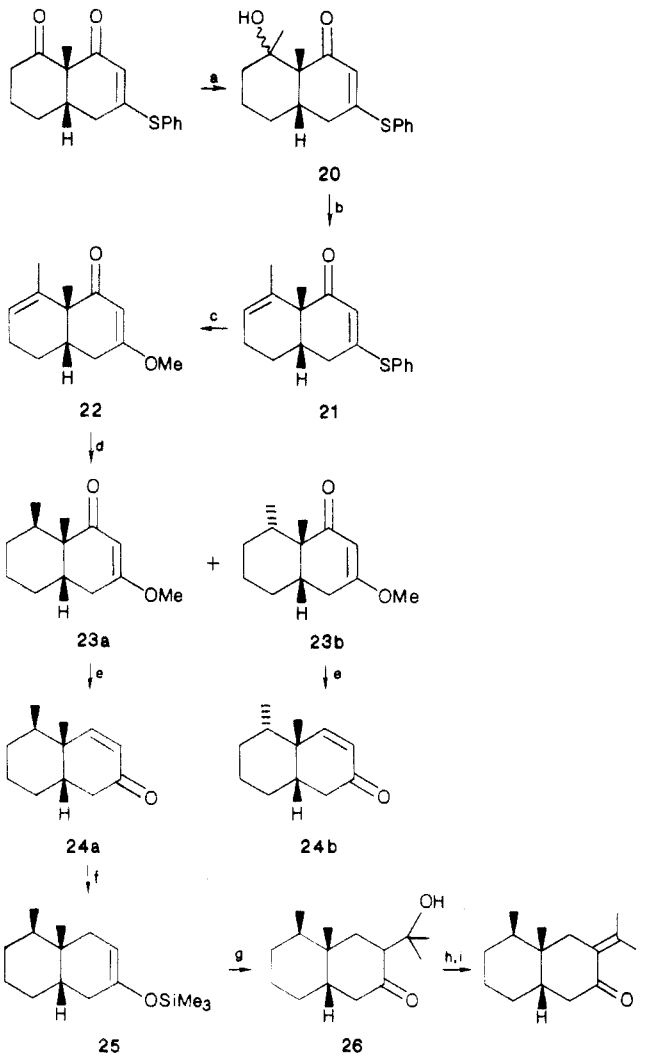
Synthesis of Fukinone. The eremophilane-type sesquiterpene, (+)-fukinone, isolated from *Petasites japonicus* Maxim., has been assigned the structure and absolute stereochemistry as depicted in **4**.[13] Various syntheses of this sesquiterpene have been reported.[14-16] In the Marshall synthesis[14] of fukinone, the key step involves the conjugative methylation of enone **18** with lithium dimethylcuprate. Piers et al.[15] and Pinder et al.[16] also reported the synthesis of fukinone using **19** as the key intermediate.



The main difficulty in designing a synthesis of **4** involves the stereocontrol of the vicinally substituted methyl groups

(9) McGuire, H. M.; Odom, H. C.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1879.
(10) Piers, E.; Britton, R. W.; De Wall, W. *Can. J. Chem.* **1969**, *47*, 4307.
(11) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley Sons: New York, 1975; Vol. V.
(12) (a) Piers, E.; Geraghty, M. B. *Can. J. Chem.* **1973**, *51*, 2166. (b) Novotny, L.; Herout, V.; Sorm, F.; Zalkow, L. H.; Hu, S.; Djerassi, C. *Tetrahedron* **1963**, *19*, 1101. (c) Tatee, T.; Takahashi, T. *Chem. Lett.* **1973**, 929. (d) Tatee, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 281.
(13) Naya, K.; Takagi, I.; Kawagushi, Y.; Asada, Y. *Tetrahadron* **1968**, *24*, 5871.
(14) Marshall, J. A.; Cohen, G. M. *J. Org. Chem.* **1971**, *36*, 877.
(15) Piers, E.; Smillie, R. D. *J. Org. Chem.* **1970**, *35*, 3997.
(16) Torrence, A. K.; Pinder, A. R. *Tetrahedron Lett.* **1971**, 745.

Scheme III[a]



[a] (a) CH_3MgBr; (b) H_2SO_4; (c) $NaOCH_3$–CH_3OH; (d) 5% Pd–$CaCO_3$, H_2; (e) $LiAlH_4$, H^+; (f) Li–NH_3, Et_3N–$ClSiMe_3$; (g) $(CH_3)_2CO$, $TiCl_4$; (h) $SOCl_2$, pyridine; (i) Al_2O_3.

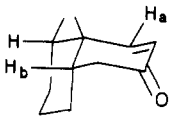
and also in introducing the isopropylidene unit regioselectively. With the compound **2b** in our hands, we decided to seek an entry into the fukinone skeleton with a strategy similar to the synthesis of aristolone.

When compound **2b** was treated with methylmagnesium bromide, the Grignard reagent added smoothly to give the adduct **20** in excellent yield (Scheme III). The ^1H NMR spectrum of the crude reaction mixture indicated the presence of two isomeric alcohols, which were not separable in our hands. The alcohol **20** was dehydrated with concentrated H_2SO_4 to give **21** in excellent yield. The sulfur moiety in **21** was then replaced by a methoxy group with sodium methoxide to give **22**.

When compound **22** was treated with 5% Pd–$CaCO_3$ in ethyl acetate under an atmospheric pressure of hydrogen, hydrogenation took place smoothly. The ^1H NMR spectrum of the crude reaction mixture indicated the presence of two epimers, **23a** and **23b**, in 1:1 ratio. The two epimers were separated easily by column chromatography. Hydrogenation of compound **22** was also tried with other catalysts such as 10% Pd–charcoal or $Rh(PPh_3)_3Cl$, but it did not improve on the stereoselectivity. Chemical reduction of **22** using diborane gave a complicated mixture with little of the reduced products **23**.

In spite of the lack of good stereoselectivity in the hydrogenation of **22**, we decided to push on with the synthesis. The stereochemistries of **23a** and **23b**, cannot be established with certainty with the NMR data. On comparison with known compounds[17] of similar structures, it appeared that **23a** had cis-substituted vicinal methyl groups and **23b** had trans-substituted methyl groups.

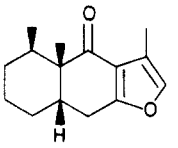
Reduction of compounds **23a** and **23b** with lithium aluminum hydride gave compounds **24a** and **24b**, respectively, after acidic hydrolysis. Compound **24b** showed a double doublet for the vinyl hydrogen H_a at 6.8 ppm (J = 2 Hz and 10 Hz). The smaller coupling constant (J = 2 Hz), which can be explained on the basis of coupling between H_a and H_b protons, indicates that they have the W-conformation as depicted. This is in line with the stereochemistry of trans-substituted vicinal methyl groups.[18]



24b

Compound **24a** on treatment with Li–NH_3 generated the enolate, which upon quenching with chlorotrimethylsilane gave the enol silyl ether **25**. The enol silyl ether **25** on reaction with acetone under titanium tetrachloride catalyzed conditions gave the aldol **26**. Compound **26** was converted to fukinone by the known literature procedure.[14,15] The spectroscopic data of the synthetic material were identical in all respects with those reported for fukinone, thereby establishing the stereochemistry of the methyl groups and the position of the isopropylidene unit. The ease of regiocontrol in the present synthesis is interesting in light of the considerable effort encountered in the previous syntheses on this question.

Finally, we note that compound **23** can be a valuable intermediate in the synthesis of ligularone (**27**), where the oxo function can be introduced regioselectively.[19]



27

Conclusion

The successful syntheses of aristolone and fukinone suggest that the annelation reaction can be of considerable utility in the synthesis of natural products. Because of the array of functionalities available in **2**, it may serve as a useful entry to the synthesis of the more complicated polyoxygenated diterpenes such as clerodin[20] and forskolin.[21]

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were obtained from films on NaCl plates for liquids and from

(17) Bohlman, F.; Forster, H.-J.; Fischer, C.-H. *Liebigs Ann. Chem.* **1976**, 1487.

(18) For analogous examples, see: Nozoe, T.; Cheng, Y. S.; Toda, T. *Tetrahedron Lett.* **1966**, 3663. (b) Miyashita, M.; Uda, H.; Yoshikoshi, A. *J. Chem. Soc. D* **1969**, 1396. (c) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Chem. Lett.* **1979**, 163.

(19) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Chem. Lett.* **1979**, 163.

(20) Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun.* **1979**, 97, and references therein.

(21) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, *19*, 1669.

solutions in 0.1-mm cells or as a KBr pellet for solids on a Perkin-Elmer 297 spectrophotometer. The ^1H NMR spectra were recorded on Varian XL-200, T-60, and T-60A instruments and are reported in δ units with Me_4Si as internal standard; the abbreviations s = singlet, t = triplet, q = quartet, m = multiplet, and br = broad are used throughout. Mass spectra were obtained on a Dupont 492B machine operating at 70 eV. Column chromatography was performed on silica gel 60 (Merck). Et_3N was dried by distillation from CaH_2. THF was distilled under nitrogen from sodium–benzophenone directly into the reaction vessel. Other solvents were purified by standard procedures.

***trans*-3-(Phenylthio)-8-methyl-4a,5,6,8a-tetrahydronaphthalen-1(4*H*)-one (9).** To a solution of **2a**[1] (1.14 g, 4 mmol) in THF (30 mL) was added under nitrogen 1.29 mL (4 mmol) of 3.1 M methylmagnesium bromide, and the solution was stirred for 90 min. The solvent was evaporated under reduced pressure and the crude reaction mixture was diluted with 100 mL of ether. The reaction mixture was quenched by washing with 5 mL of water and the organic phase was separated. The organic phase was washed twice with two 10-mL portions of water and the washings were added to the aqueous phase. The aqueous phase was washed three times with 20 mL of ether and the washings were added to the organic phase. The combined organic phase was dried (Na_2SO_4) and evaporated. The crude reaction mixture was dissolved in a minimum amount of hexane–ethyl acetate and allowed to stand overnight. The crystallized product **2a** was filtered off and once again the above operation was performed. Then the filtrate was concentrated at reduced pressure and purified by column chromatography (eluant, 15% hexane–ethyl acetate) to give **8a** and **8b** in a ratio of 5:7 with 53% yield. To a stirred solution of **8a** (0.302 g, 1 mmol) in dry ether (2 mL) under nitrogen was added 3.0 g of concentrated H_2SO_4, and the solution was stirred for 2 h at room temperature. Then the reaction mixture was diluted with 25 mL of ether and quenched with 20 g of crushed ice. The organic and aqueous layer were quickly separated and the aqueous phase was washed twice with 25 mL of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (eluant, 10% ethyl acetate–hexane) to give **9** in 87% yield. The above procedure was followed with **8b** also except that stirring was continued for 24 h to give **9** (mp 96–98 °C) in 73% yield: IR (KBr) 2910, 1660, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) 7.43 (s, 5 H), 5.37 (d, J = 2 Hz, 1 H), 5.53–5.33 (m, 1 H), 2.5–1.33 (m, 7 H), 2.02 (d, J = 2 Hz, 3 H), 0.9 (s, 3 H); MS, m/z (relative intensity) 284 (M^+, 40), 176 (37), 175 (47), 147 (50), 115 (20), 108 (100), 67 (68), 39 (78); exact mass calcd for $C_{18}H_{20}OS$ 284.124, obsd 284.127.

***trans*-3-Methoxy-8-methyl-4a,5,6,8a-tetrahydronaphthalen-1(4*H*)-one (11).** To a well-stirred solution of **9** (1.42 g, 5 mmol) in 20 mL of dry methanol under nitrogen was added sodium methoxide (1.35 g, 25 mmol), and the solution was refluxed for 20 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude reaction mixture was diluted with 60 mL of ether. The ether layer was washed twice with 5 mL of water, dried, and evaporated. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **11** in 95% yield: IR (film) 2920, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) 5.52–5.25 (m, 1 H), 5.13 (s, 1 H), 3.65 (s, 3 H), 2.42–1.42 (m, 7 H), 2.05 (d, J = 2 Hz, 3 H), 1.22 (s, 3 H); MS, m/z (relative intensity) 206 (M^+, 41), 139 (12), 108 (100), 93 (46), 68 (22), 28 (42); exact mass calcd for $C_{13}H_{18}O_2$ 206.131, obsd 206.133.

***trans*-3-Methoxy-4a,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnaphthalen-1(4*H*)-one (12).** In a 25-mL, three-necked flask were added 30 mg of 5% Pd–$CaCO_3$ and 15 mL of freshly distilled ethyl acetate. The catalyst was saturated with an atmospheric pressure of hydrogen for 30 min followed by addition of **11** (206 mg, 1 mmol) in 1 mL of ethyl acetate. The reaction was followed by measuring the absorption of hydrogen. After the absorption of 22.4 mL of hydrogen, the reaction flask was separated from the hydrogen atmosphere. The catalyst was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **12** in almost quantitative yield: IR (film) 2915, 1670, 1620, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) 5.14 (d, J = 1.4 Hz, 1 H), 3.65 (s, 3 H), 2.31 (ddd, J = 1.4 Hz, 11.6 Hz, 17.7 Hz, 1 H), 2.14 (dd, J = 5.2 Hz, 17.7 Hz, 1 H), 1.94–1.08 (m, 8 H), 1.78 (d, J = 6.2 Hz, 3 H), 0.97 (s, 3 H); MS, m/z (relative intensity) 208 (M^+, 36), 178 (63), 136 (96), 122 (40), 109 (90), 98 (64), 68 (60), 28 (100); exact mass calcd for $C_{13}H_{20}O_2$ 208.146, obsd 208.145.

***trans*-4a,5,6,7,8,8a-Hexahydro-4aβ,5β-dimethylnaphthalen-2(1*H*)-one (13).** To a stirred solution of **12** (416 mg, 2 mmol) in 20 mL of dry ether was added lithium aluminum hyride (38 mg, 4 mmol). After 1 h, once again lithium aluminum hydride (38 mg, 4 mmol) was added and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched with 2 mL of ethyl acetate followed by the addition of 10 mL of 10% aqueous hydrochloric acid. The stirring was continued for another 4 h. The organic phase was separated from the aqueous phase and the aqueous phase was washed three times with 20 mL of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **13** (viscous oil) in 72% yield: IR (film) 2920, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) 7.08 (d, J = 10.2 Hz, 1 H), 5.84 (d, J = 10.2 Hz, 1 H), 2.35 (dd, J = 13.8 Hz, 17 Hz, 1 H), 2.28 (dd, J = 4.8 Hz, 17 Hz, 1 H), 2.00–1.23 (m, 8 H), 0.94 (d, J = 6.1 Hz, 3 H), 0.91 (s, 3 H); MS, m/z (relative intensity) 178 (M^+, 35), 163 (17), 149 (18), 136 (76), 121 (51), 108 (55), 95 (60), 28 (100); exact mass calcd for $C_{12}H_{18}O$ 178.136, obsd 178.139.

1,1aβ,3,3aα,4,5,6,7,7a,7bβ-Decahydro-1,1,7β,7aβ-tetramethyl-2*H*-cyclopropa[*a*]naphthalen-2-one (15). Diazopropane was prepared according to the literature procedure.[22] An etheral solution of diazopropane was added to a solution of **13** (178 mg, 1 mmol) in 10 mL of dry ether at room temperature, until complete reaction occurred, indicated by the persistent color of the diazo compound. Then the solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluant, 20% ethyl acetate–hexane) to give **14** (mp 71–72 °C) in almost quantitative yield. Compound **14** was dissolved in 15 mL of dry benzene and photolyzed (lamp, Hanovia Model no. 608A 36). The reaction was followed by thin layer chromatography. At the end of 8 h, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluant, 10% ethyl acetate–hexane) to give **15** in 95% yield. The spectroscopic properties of **15** are identical in all aspects with those reported earlier.[10]

***cis*-3-(Phenylthio)-8-methyl-4a,5,6,8a-tetrahydronaphthalen-1(4*H*)-one (21).** To a solution of **2b**[1] (1.14 g, 4 mmol) in 100 mL of dry ether under nitrogen was added 1.29 mL of 3.1 M methylmagnesium bromide, and the solution was stirred for 2 h. The reaction mixture was diluted with 50 mL of ether and quenched with 10 mL of water. The organic phase was separated and washed twice with two 15-mL portions of water and the washings were added to the aqueous phase. The aqueous phase was then washed three times with 20 mL of ether and the ether washings were added to the organic phase. The combined organic phase was dried (Na_2SO_4) and was evaporated under reduced pressure. The crude reaction mixture was subjected to dehydration with concentrated H_2SO_4.

To a solution of **20** (302 mg, 1 mmol) in 2 mL of dry ether was added 3.0 g of concentrated H_2SO_4, and the solution was stirred for 2 h. At the end of the reaction, the mixture was diluted with 100 mL of ether and quenched with 15 g of crushed ice. The aqueous and organic layers were quickly separated. The aqueous phase was washed twice with two 50-mL portions of ether and the washings were added to the organic phase. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (eluant, 10% ethyl acetate–hexane) to give **21** (viscous oil) in 89% yield (calculated from **2b**): IR (film) 1665, 1595, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) 7.5–7.30 (m, 5 H), 5.47–5.43 (m, 1 H), 5.4 (d, J = 1.6 Hz, 1 H), 2.65 (ddd, J = 1.6 Hz, 8.6 Hz, 17.7 Hz, 1 H), 2.45 (dd, J = 5.1 Hz, 17.7 Hz, 1 H), 2.21–1.50 (m, 5 H), 1.63 (d, J = 1.7 Hz, 3 H) 1.30 (s, 3 H); MS, m/z (relative intensity) 284 (M^+, 30), 176 (21), 175 (30), 147 (33), 109 (65), 108 (100), 67 (67), 39 (52); exact mass calcd for $C_{18}H_{20}OS$ 284.124, obsd 284.127.

***cis*-3-Methoxy-8-methyl-4a,5,6,8a-tetrahydronaphthalen-1(4*H*)-one (22).** To a well-stirred solution of **21** (1.42 g, 5 mmol) in 20 mL of dry methanol under nitrogen was added sodium

(22) Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Org. Synth.* **1970**, *50*, 27.

methoxide (1.35 g, 25 mmol), and the solution was refluxed for 20 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude reaction mixture was diluted with 60 mL of ether. The etheral layer was washed twice with 5 mL of water, dried, and concentrated. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **22** in 92% yield: IR (film) 2925, 1665, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) 5.46–5.35 (m, 1 H), 5.27 (br, 1 H), 3.68 (s, 3 H), 2.58–1.50 (m, 7 H), 1.68 (d, J = 1.7 Hz, 3 H), 1.32 (s, 3 H); MS, m/z (relative intensity) 206 (M^+, 22), 173 (12), 108 (100), 93 (86), 77 (24), 68 (25); exact mass calcd for $C_{13}H_{18}O_2$ 206.131, obsd 208.132.

***cis*-3-Methoxy-4a,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnaphthalen-1(4*H*)-one (23a).** In a 25-mL, three-necked flask were added 30 mg of 5% Pd–$CaCO_3$ and 15 mL of freshly distilled ethyl acetate. The catalyst was saturated with an atmospheric pressure of hydrogen for 30 min followed by addition of **22** (206 mg, 1 mmol) in 1 mL of ethyl acetate. The reaction was followed by measuring the absorption of hydrogen. After the absorption of 22.4 mL of hydrogen, the reaction flask was separated from the hydrogen atmosphere. The catalyst was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **23a** (oil) and **23b** (mp 72–74 °C) in almost quantitative yield.

23a: IR (film) 2925, 1650, 1620, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) 5.21 (s, 1 H), 3.61 (s, 3 H), 2.45–1.16 (m, 10 H), 1.01 (s, 3 H), 0.77 (d, J = 6.9 Hz, 3 H); MS, m/z (relative intensity) 208 (M^+, 81), 193 (38), 165 (30), 152 (33), 139 (72), 98 (84), 69 (100), 41 (87); exact mass calcd for $C_{13}H_{20}O_2$ 208.146, obsd 208.149.

23b: IR (KBr) 2910, 1655, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) 5.11 (d, J = 1.4 Hz, 1 H), 3.63 (s, 3 H), 2.80 (ddd, J = 1.4 Hz, 6.0 Hz, 18.1 Hz, 1 H), 2.00 (dd, J = 2.4 Hz, 18.1 Hz, 1 H), 1.81–1.28 (m, 8 H), 1.26 (d, J = 2.2 Hz, 3 H), 1.21 (s, 3 H); MS, m/z (relative intensity) 208 (M^+, 35), 178 (46), 139 (70), 136 (65), 109 (90), 98 (65), 79 (66), 68 (65), 28 (100); exact mass calcd for $C_{13}H_{20}O_2$ 208.146, obsd 208.150.

***cis*-4a,5,6,7,8,8a-Hexahydro-4aβ,5β-dimethylnaphthalen-2(1*H*)-one (24a).** To a stirred solution of **23a** (416 mg, 2 mmol) in 20 mL of dry ether was added lithium aluminum hydride (38 mg, 4 mmol). After 1 h, once again lithium aluminum hydride (38 mg, 4 mmol) was added and the mixture refluxed for 2 h. The reaction mixture was quenched with 2 mL of ethyl acetate followed by addition of 10 mL of 10% aqueous hydrochloric acid. The stirring was continued for another 4 h. The organic phase was separated from the aqueous phase and the aqueous phase was washed twice with 20 mL of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant, 10% ethyl acetate–hexane) to give **24a** in 69% yield: IR (film) 2925, 1680, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) 6.8 (d, J = 10 Hz, 1 H), 5.88 (d, J = 10 Hz, 1 H), 2.77–1.23 (m, 10 H), 1.12 (s, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); MS, m/z (relative intensity) 178 (M^+, 41), 163 (29), 150 (15), 136 (78), 122 (37), 108 (82), 94 (36), 80 (42), 28 (100); exact mass calcd for $C_{12}H_{18}O$ 178.136, obsd 178,133.

***cis*-4a,5,6,7,8,8a-Hexahydro-4aβ,5α-dimethylnaphthalen-2(1*H*)-one (24b)** was prepared according to the above procedure using **23b** (416 mg, 2 mmol) in 71% yield: IR (film) 2905, 1675, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) 6.79 (dd, J = 2.2 Hz, 10.2 Hz, 1 H), 5.92 (d, J = 10.2 Hz, 1 H), 2.88 (dd, J = 5.0 Hz, 17.5 Hz, 1 H), 2.17–1.24 (m, 9 H), 1.22 (s, 3 H), 1.04 (d, J = 7 Hz, 3 H); MS, m/z (relative intensity) 178 (M^+, 36), 163 (19), 150 (17), 136 (100), 121 (54), 108 (73), 94 (58), 80 (64), 28 (88); exact mass calcd for $C_{12}H_{18}O$ 178.136, obsd 178.134.

Trimethylsilyl Enol Ether 25. A solution of **24a** (140 mg, 0.79 mmol) in THF (4 mL) containing *tert*-butyl alcohol (47 mg, 0.63 mmol) was added dropwise over 10 min to a solution of lithium (16 mg, 2.2 mmol) in ammonia (20 mL). The solution was stirred for 15 min, and the excess lithium was destroyed by addition of a few drops of isoprene. The ammonia was evaporated under a stream of argon at 0 °C and finally at room temperature (1 h). THF (5 mL) was then added and the reaction was cooled to 0 °C followed by rapid addition of a quenching solution of chlorotrimethylsilane (2.2 mmol) and triethylamine (2.2 mmol) in 3 mL of THF (previously centrifuged to remove the ammonium salt). The reaction was stirred for 15 min and the solvent was evaporated. Then 100 mL of cold, dry hexane was added and the precipitated salts were removed by filtration. The filtrate was concentrated under reduced pressure to give **25** as a colorless oil in almost quantitative yield. NMR analysis indicated a single compound that was used without further purification: IR (film) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) 4.7–4.5 (m, 1 H), 2.6–1.17 (m, 12 H), 0.83 (s, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.13 (s, 9 H).

Keto Alcohol 26. To a solution of **25** (112 mg, 0.5 mmol) and acetone (35 mg, 0.6 mmol) in 10 mL of dry CH_2Cl_2 under nitrogen at −78 °C was added titanium tetrachloride (0.06 mL, 0.5 mmol) and stirring was continued for 4 h. At the end of 4 h, the reaction was quenched with aqueous $NaHCO_3$ followed by extraction with ether. The ether extract was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **26** (viscous oil) in 68% yield: IR (film) 3480, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 4.02 (s, 1 H), 1.26 (s, 6 H), 0.96 (s, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); MS, m/z (realtive intensity) 223 (3), 180 (42), 124 (29), 109 (92), 55 (63), 43 (100).

(±)-Fukinone (4). To a solution of the keto alcohol **26** (80 mg) in 5 mL of dry pyridine at 0 °C was added 50 μL of thionyl chloride, and the resulting solution was stirred for 15 min. The solvent was removed under reduced pressure at 0 °C. Then the crude product was eluted from 10 g of Merck alumina with 30% ethyl acetate–hexane. Finally, the compound was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **4** in 81% yield: IR (film) 1685, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 1.93 (s, 3 H), 1.77 (s, 3 H), 0.95 (s, 3 H), 0.88 (d, J = 7.0 Hz, 3 H); MS, m/z (relative intensity) 220 (M^+, 37), 149 (32), 135 (19), 123 (34), 111 (32), 109 (66), 95 (53), 91 (43), 68 (81), 41 (100); exact mass calcd for $C_{15}H_{24}O$ 220.183, obsd 220.184. These spectral data were in complete agreement with the spectral data reported for the natural product (+)-fukinone.[13]

Acknowledgment. Financial support from Merck Frosst Canada, NSERC, and FCAC are gratefully acknowledged. C.V.C.P. thanks McGill University for the award of the Bindra fellowship.

Registry No. (±)-**2a**, 105229-79-6; (±)-**2b**, 105229-80-9; (±)-**3**, 20536-71-4; (±)-**4**, 25828-19-7; (±)-**8a**, 105229-81-0; (±)-**8b**, 105229-82-1; (±)-**9**, 105229-83-2; (±)-**11**, 105229-84-3; (±)-**12**, 105229-85-4; (±)-**13**, 25249-81-4; (±)-**14**, 105307-88-8; (±)-**15**, 20536-76-9; (±)-**20** (isomer 1), 105229-86-5; (±)-**20** (isomer 2), 105229-87-6; (±)-**21**, 105229-88-7; (±)-**22**, 105229-89-8; (±)-**23a**, 105229-90-1; (±)-**23b**, 105229-91-2; (±)-**24a**, 105229-92-3; (±)-**24b**, 105229-93-4; (±)-**25**, 105229-94-5; (±)-**26**, 105307-89-9; 2-diazopropane, 2684-60-8; acetone, 67-64-1.