A Samarium(II) Iodide Promoted Tandem Radical Cyclization. The Total Synthesis of (±)-Hypnophilin and the Formal Synthesis of (±)-Coriolin

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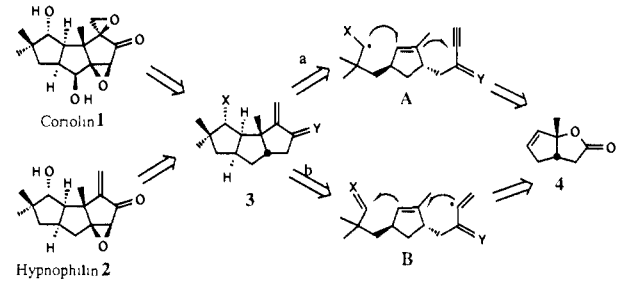
Abstract: Cross-conjugated dienone **18**, a known precursor to (±)-coriolin, is prepared in 13 steps from simple lactone **4**. Selective epoxidation of **18** provides (±)-hypnophilin. Key steps in the synthesis of **18** include a highly efficient S_N2'-anti opening of **4** to give the necessary trans-3,5-disubstituted cyclopentene **11** and the novel SmI_2-induced tandem radical cyclization of aldehyde **14**.

The triquinane sesquiterpenes have been the focus of much synthetic attention because of their unique structural features and biological activities.[2] Over the past several years, we have developed a synthetic strategy based on tandem radical cyclizations which targets the three major classes of triquinanes (linear, angular, and propellane). The ability of radical cyclizations to construct multiple five-membered rings in a controllable fashion has been featured in syntheses of the linear triquinanes hirsutene and capnellene and the angular triquinane silphiperfolene.[3] All three of these natural products are hydrocarbons. Since free-radical reactions tolerate oxygen functionality well, we expected that the same basic strategy could be extended to the preparation of more complex, oxygenated triquinanes. This expectation has been realized in a formal total synthesis of (±)-coriolin (**1**)[4] and in a total synthesis of (±)-hypnophilin (**2**)[5] (Scheme I).

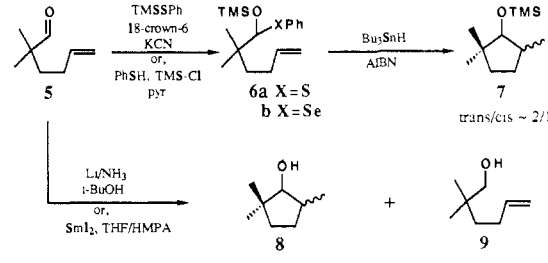
In our synthetic approach, a tandem radical cyclization forms the two outer rings of a triquinane about a central, preformed cyclopentene ring. This strategy is quite flexible in that variations in the nature and disposition of the side chains can lead to different triquinanes. Further, the tandem cyclization can, in principle, by conducted in either of two directions (Scheme I, path a or b). To construct the cis-anti-cis ring fusion of the linear triquinanes, a tandem radical cyclization of a trans-3,5-disubstituted cyclopentene is required. In the case where X = Y = H (Scheme I, path a), such a reaction produces hirsutene.[3a,b] Adaptation of this approach to the highly oxygenated triquinanes coriolin and hypnophilin requires the cyclization of an oxygenated version of A or B, followed by functional group manipulations of the product **3** (Scheme I). The present paper describes our results regarding the generation and cyclization of type A radicals.

Cyclization by path a requires the generation of an α-oxy radical. While a variety of methods are available to produce such radicals,[6] we envisioned that a new (but well precedented[7]) method might best suit our purposes. This method involves the tin hydride mediated reductive cyclization of readily available[8] mixed phe-

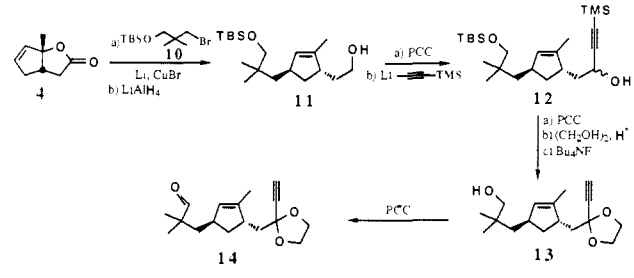
Scheme I



Scheme II



Scheme III



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(2) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1. See also: Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.

(3) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (c) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991. (d) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106. (e) Curran, D. P.; Kuo, S.-C. *Tetrahedron* **1987**, *43*, 5653.

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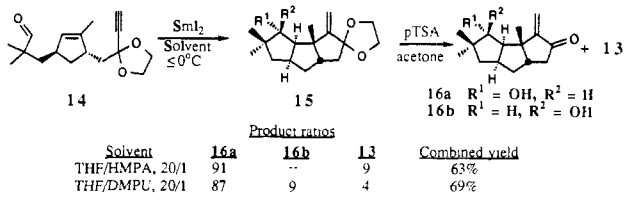
Scheme IV



Product ratios

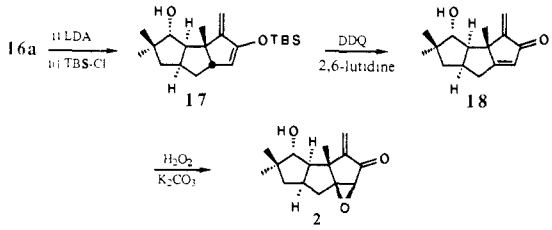
Solvent	16a	16b	13	Combined yield
THF/HMPA, 20/1	91	--	9	63%
THF/DMPU, 20/1	87	9	4	69%

nylthio (trimethylsilyl)oxy acetals. A model study was carried out with the simple aldehyde **5**[9] (Scheme II). Treatment of **5** with thiophenol in the presence of TMS-Cl and pyridine,[8a] or with TMSSPh and KCN–18-crown-6 complex,[8b] provided the hemithioacetal **6a** in 80% purified yield. Standard cyclization of **6** with tri-*n*-butyltin hydride proceeded in 73% yield to give **7**, with modest stereoselectivity in favor of the trans stereoisomer (Scheme II).[10a] This cyclization occurred without recourse to high dilution or syringe pump techniques.[10b] The reaction worked equally well with the more reactive mixed selenoacetal **6b**, though this precursor was less easily handled and purified due to its hydrolytic sensitivity.

The cyclization of aldehyde **5** could also be induced by reduction of the carbonyl with a variety of one electron donors.[6] For example, treatment of **5** with Li/NH_3 gave a 1/1 mixture of alcohols **8** (cyclized) and **9** (reduced). In this case, the cyclized product **8** was formed with greater stereoselectivity (trans/cis ~ 7/1). Reduction of **5** with SmI_2[11] was less encouraging and afforded largely **9** in THF but apparently a mixture of **8** and at least two other unidentified products in THF/HMPA.[11c,d]

With these preliminary results in hand, we began the preparation of suitable cyclization precursors related to A. The known propensity of lactone **4** to undergo S_N2'-anti ring opening upon reaction with organocuprates[12] provided a simple route to the requisite trans-3,5-disubstituted cyclopentenes. Lactone **4** was treated with the cuprate derived from 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropane (**10**),[13] and the resulting carboxylic acid was reduced directly with $LiAlH_4$ to give alcohol **11** in 90% overall yield (Scheme III). A very similar reaction was used in our hirsutene synthesis,[3a,b] but optimization of the reaction conditions (see the Experimental Section) has permitted us to double the previous yield of this key step. From **11**, a series of conventional, elaborative steps (each ≥70% yield) easily furnished **14** in 25–30% overall yield from lactone **4**. A few related aldehydes were also prepared (not shown) by simple manipulations of the oxidation state and protecting groups of the acetylene-bearing side chain.

Scheme V



Unfortunately, the reactions of these aldehydes did not parallel those of the model compound **5**. Despite all attempts, hemithioacetals (or hemiselenoacetals) corresponding to **6** could not be prepared. In general, the starting aldehydes were recovered unchanged, and an appropriate cyclization precursor for the proposed tin hydride cyclization was never generated. Early attempts at reductive cyclization were equally discouraging.[14]

However, reduction of **14** with SmI_2 in THF at reflux for 3 h produced tricyclic ketal **15** (Scheme IV) and alcohol **13**, albeit in low yields of 11% and 18%, respectively. However, in accordance with literature precedent[11c,d] and the model reaction mentioned previously, addition of HMPA to the reaction medium accelerated the reaction such that it could be performed as a titration at 0 °C (Scheme IV). While the tricyclic ketal **15** could be isolated by using a neutral or slightly acidic workup, it was preferable to deketalize the crude material directly with *p*-toluenesulfonic acid in acetone. The yields indicated in Scheme IV represent isolated yields of the pure products obtained in this way. In the presence of HMPA, the tricyclic alcohol **16a** was now favored over the directly reduced product **13** by a ratio of 91/9. The use of the additive DMPU[15] gave similar results to HMPA with respect to reaction rate and yield, but the product distribution varied in that the formation of alcohol **13** was suppressed while that of stereoisomer **16b** (undetectable with HMPA) was increased (Scheme IV). The two-step procedure involving cyclization and deketalization typically gave pure, crystalline enone **16a** (mp 143–145 °C) in about 60% yield with either cosolvent. The ketal unit of **13** survived the acid treatment, and this compound could be recycled.

Two observations suggest that the cyclization is a one-electron process.[11e] First, the cyclization in THF/HMPA requires less than 2 equiv of SmI_2 (typically ~1.3 equiv are sufficient) to consume the starting aldehyde. When DMPU is used instead of HMPA, a larger excess of SmI_2 is required; however, this reaction mixture is heterogeneous. Second, when the cyclizations (using either cosolvent) were quenched with D_2O, no deuterium was incorporated at the vinyl carbon of **16a** or **16b**. This suggests that the radical that is produced after the tandem cyclization abstracts a hydrogen atom from the solvent more rapidly than it is reduced by SmI_2.

Very recently, Molander and Kenny have reported some related cyclizations of alkenyl β-keto esters using 2 equiv of SmI_2 in THF (no HMPA) in the presence of an added proton source (*tert*-butyl alcohol).[11e] In no case did we deliberately add a proton source until after the consumption of the starting aldehyde. Further research will be required to answer the interesting questions regarding the precise nature and order of the possible intermediate steps in these cyclizations.

To complete the formal synthesis of coriolin, we were obliged only to convert **16a** into cross-conjugated dienone **18**, since this key substance has been taken on to coriolin first by the Danishefsky and Tatsuta groups,[4a–c] and subsequently by several others.[4d–f] Treatment of **16a** with excess LDA and TBS-Cl in THF/DMPU resulted in selective monosilylation to give the silyl dienol ether **17** in 89% yield (Scheme V). The crowded environment about

(8) (a) Chan, T. H.; Ong, B. S *Tetrahedron Lett.* **1976**, 319. (b) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

(9) House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102.

(10) (a) The products were identified by comparison with authentic samples prepared by the reduction of 2,2,5-trimethylcyclopentanone; Rei, M.-H. *J. Org. Chem.* **1978**, *43*, 2173. (b) The cyclization was conducted with 2.0 equiv of Bu_3SnH at 0.02 M (in **6**) in benzene at reflux. In contrast, the acetals lacking the α-*gem*-dimethyl functionality required either high dilution (0.001 M) or syringe pump techniques in order to obtain favorable ratios of cyclized to uncyclized products.

(11) (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (c) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (d) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920; these previous SmI_2-promoted reactions between aldehydes or ketones and olefins have employed activated olefins (α,β-unsaturated esters) in the presence of proton donors. (e) A very recent paper reports SmI_2-promoted additions of ketones to unactivated olefins, also in the presence of proton donors. See: Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367.

(12) Curran, D. P.; Chen, M.-H.; Leszczewski, D.; Elliott, R. L.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612.

(13) This reagent was prepared by a modification of the procedure kindly provided by Professor Hua. See, Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. Bromide **10** was prepared by standard silylation (TBS–Cl, imidazole, DMF) of the corresponding bromo alcohol. See, Searles, S., Jr.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1959**, *24*, 1839.

(14) Irradiation of **14** in HMPA solution (see ref 6c) yielded a complex reaction mixture, whereas treatment with Zn/TMS–Cl (see ref 6b) afforded a bicyclic, tetrasubstituted olefin, which was probably formed by a Lewis acid catalyzed Friedel–Crafts type reaction followed by loss of a proton. Reduction of a related aldehyde with Li/NH_3 gave a complex mixture.

(15) For the use of DMPU (dimethyltetrahydropyrimidinone), see: Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

the secondary alcohol protected this functionality from silylation. Oxidation of **17** with DDQ/2,6-lutidine[16] in benzene at reflux proceeded without competing hydrolysis of the silyl dienol ether[17] to furnish dienone **18** in 72% yield. The spectra (^{1}H NMR, IR, MS) for this compound agree with those reported previously,[4d] thereby confirming the stereochemical outcome of the SmI_2 cyclization.

Hypnophilin can be prepared in one step from dienone **18** by selective epoxidation of the more strained, trisubstituted olefin.[4c,5c] Treatment of **18** with basic hydrogen peroxide in a two-phase system (K_2CO_3, H_2O, CH_2Cl_2) cleanly, though slowly, afforded **2** (52% yield, 23% recovered **18**). The spectra (^{1}H NMR, ^{13}C NMR, IR, MS) for synthetic (±)-**2** also agree well with those reported.[5b] Very recently, Little has completed a synthesis of hypnophilin with a similar epoxidation of **18**.[5c]

In summary, we have completed a formal total synthesis of (±)-coriolin and a total synthesis of (±)-hypnophilin that further demonstrate the ability of free radical reactions to perform complex chemical transformations in a single step. In addition, while their generality remains open to investigation, the SmI_2 reductive cyclization of unsaturated aldehydes and the tin hydride reduction of hemithio or hemiseleno acetals[18] represent potentially useful methods for the formation of oxygenated cyclopentane rings. Finally, the DDQ oxidation of *tert*-butyl dimethylsilyl enol ethers holds promise as a practical, efficient procedure for the dehydrogenation of ketones.

Experimental Section

General Methods. Reagents and solvents were purchased from the common commercial sources and, with the following exceptions, were used as received or purified by distillation from appropriate drying agents. Diiodoethane was freed of iodine by extraction of a CH_2Cl_2 solution with $Na_2S_2O_3$; CuBr·SMe_2 was prepared by the literature method.[19] Reactions requiring anhydrous conditions were run under an atmosphere of dry argon or nitrogen. Reaction products were purified, when necessary, by flash chromatography[20] over silica gel with the indicated solvents. All NMR spectra were recorded on a FT-Bruker AF-300 spectrometer (300 MHz for ^{1}H; 75 MHz for ^{13}C) with $CHCl_3$ (7.26 ppm, for ^{1}H) or $CDCl_3$ (77.0 ppm, for ^{13}C) as an internal reference, unless stated otherwise. All IR spectra were obtained on an IBM IR/32 FTIR spectrophotometer. Mass spectra were obtained on VG-7000 (low resolution) or Varian MATCH-5DF (high resolution) spectrometers.

***trans*-5-(2-Hydroxyethyl)-3-[3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl]-1-methylcyclopent-1-ene (11).**[3b] Into a dry, three-necked flask were placed dry diethyl ether (20 mL) and lithium wire (123 mg, 17.61 mmol, 0.8% Na content). To the mixture was added 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropane[13] (**10**; 1.65 g, 5.9 mmol), and the lithium metal was then cut into small pieces inside the reaction vessel by using a pair of surgical scissors. A brisk flow of argon through the system was maintained during this operation. The lithiation commenced almost immediately, and the reaction mixture became warm and gray. The mixture was stirred vigorously for 1 h at room temperature and then transferred via syringe to a separate flask under argon and cooled to −78 °C. A solution of CuBr·SMe_2 (602 mg, 2.94 mmol) in Me_2S (5 mL) was added, and the resulting green solution was stirred at −78 °C for 10 min. Lactone **4**[3b] (270 mg, 1.96 mmol) was added in dry THF (5 mL) over ca. 1 min, and the resulting black mixture was stirred at −78 °C for 1 h. The cooling bath was removed, and stirring was continued for 30 min. The reaction was quenched by pouring into 10% aqueous citric acid. The aqueous phase was extracted with ether (three times), and the combined organic layer was washed (2 × H_2O, 1 × brine) and dried (Na_2SO_4). After being allowed to stand overnight, the extract became blue-green and was therefore washed again (1 × 0.1 M HCl, 1 × H_2O, 1 × brine) and dried. After filtration and evaporation of the solvent, the residue was filtered through silica gel (hexane/EtOAc, 2:1) and concentrated to give a pale yellow oil (737 mg). A solution of this material in dry THF (5 mL) was added dropwise to an ice-cold suspension of $LiAlH_4$ (446 mg, 11.74 mmol) in THF (25 mL). The mixture was allowed to reach room temperature and was then stirred for an additional 1 h. The excess hydride was cautiously quenched at 0 °C with 2-propanol. When hydrogen evolution ceased, the mixture was poured into aqueous citric acid and extracted with ethyl acetate (three times). The organic phase was washed (1 × H_2O, 1 × brine), dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc, 4:1) provided **11** as a clear, colorless oil (599 mg, 93.9% from lactone **4**): ^{1}H NMR ($CDCl_3$) δ 5.24 (br s, 1 H), 3.80–3.61 (m, 2 H), 3.22 (s, 2 H), 2.67 (m, 1 H), 2.53 (m, 1 H), 1.82 (m, 2 H), 1.68 (br s, 3 H), 1.72–1.14 (m, 5 H), 0.89 (s, 9 H), 0.84 (s, 6 H), 0.02 (s, 6 H); IR (thin film) 3340, 1100 cm^{-1}; MS, *m/e* 311 (M−CH_3), 269 (M−C_4H_9), 194, 186, 177, 165, 149, 138, 121, 120, 107 (base peak), 93, 81, 75, 73, 69; HRMS calcd for $C_{15}H_{29}O_2Si$ (M−C_4H_9) 269.1937, found 269.1937.

***trans*-5-[2-Hydroxy-4-(trimethylsilyl)but-3-ynyl]-3-[3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl]-1-methylcyclopent-1-ene (12).** Alcohol **11** (1.57 g, 4.8 mmol) was dissolved in dry CH_2Cl_2 (50 mL) in a flask with an argon inlet. Solid NaOAc (1.18 g, 14.4 mmol) and pyridinium chlorochromate (PCC, 3.10 g, 14.4 mmol) were added, and the dark mixture was stirred vigorously at room temperature for 50 min. The reaction mixture was then treated with Florisil, diluted with ether, and filtered through Florisil. The filter cake was rinsed thoroughly with CH_2Cl_2, and the combined filtrate and washings were evaporated. The residue was carefully filtered through silica gel (CH_2Cl_2) to give a pure aldehyde (1.23 g, 79.1%). Into a dry, three-necked flask were placed dry THF (12 mL) and (trimethylsilyl)acetylene (595 mg, 6.07 mmol). The solution was cooled to 0 °C, and *n*-BuLi (1.6 M in hexane, 3.08 mL, 4.94 mmol) was added. After 10 min at 0 °C, the above aldehyde in THF (8 mL) was added to the acetylide solution. The resulting solution was stirred for 30 min at 0 °C, poured into aqueous NH_4Cl, and extracted with CH_2Cl_2 (two times). The organic layer was washed with aqueous $NaHCO_3$ and dried (Na_2SO_4). After filtration and evaporation of the solvent, alcohol **12** was obtained as a pale yellow oil (1.57 g, 97.7%), which required no further purification: ^{1}H NMR ($CDCl_3$) δ 5.25 (br s, 1 H), 4.40 (m, 1 H), 3.22 (s, 2 H), 2.66 (m, 2 H), 1.96–1.08 (m, 10 H), 0.89 (s, 9 H), 0.83 (s, 6 H), 0.171, 0.168 (2 s, 9 H), 0.01 (s, 6 H); IR (thin film) 3360, 2175, 1100 cm^{-1}; MS, *m/e* 365 (M − C_4H_9), 347, 293, 273, 259, 241, 234, 223, 215, 199, 186, 175, 161, 149, 143, 129, 119, 107, 93, 81, 75, 73 (base peak), 69; HRMS calcd for $C_{20}H_{37}O_2Si_2$ (M − C_4H_9) 365.2332, found 365.2332.

***trans*-5-(2-Oxo-3-butynyl)-3-(2,2-dimethyl-3-hydroxypropyl)-1-methylcyclopent-1-ene Ethylene Ketal (13).** Alcohol **12** (1.57 g, 3.7 mmol) was oxidized with PCC as described in the previous experiment (reaction time, 4 h) to give the corresponding ketone (1.30 g, 83.5%). A portion of this material (135 mg, 0.32 mmol) was dissolved in dry benzene (15 mL) and treated with ethylene glycol (100 mg, 1.61 mmol), trimethylorthoformate (102 mg, 0.96 mmol), and *p*-toluenesulfonic acid (~3 mg). The mixture was stirred overnight at room temperature and then heated at reflux for 5 h. After being cooled, the mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (two times). The organic phase was washed (2 × H_2O), dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by chromatography (hexane/CH_2Cl_2, 1:1). The ketal (112 mg, 75.2%) was obtained as a clear, colorless oil. The bis silyl compound (272 mg, 0.59 mmol) was treated with *n*-$Bu_4NF·3H_2O$ (555 mg, 1.76 mmol) in THF (15 mL) at room temperature. After 6 h, the reaction mixture was poured into water and extracted three times with CH_2Cl_2 and once with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (hexane/EtOAc, 2:1) to furnish alcohol **13** (139 mg, 85.3%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.25 (m, 1 H), 4.13–3.92 (m, 4 H), 3.30 (s, 2 H), 2.82–2.60 (m, 2 H), 2.52 (s, 1 H), 2.18 (m, 1 H), 2.10 (dd, *J* = 14.2, 2.2 Hz, 1 H), 1.73–1.62 (m, 5 H), 1.58 (br s, 1 H), 1.36 (dd, *J* = 14.0, 6.0 Hz, 1 H), 1.20 (dd, *J* = 14.0, 6.7 Hz, 1 H), 0.88 (s, 6 H); ^{13}C NMR (C_6D_6, 128.0 ppm) δ 141.9, 132.0, 103.5, 82.5, 72.1, 72.0, 64.7, 64.2, 45.5, 44.0, 42.2, 41.3, 39.7, 35.8, 30.1, 24.7, 14.8; IR (thin film) 3430, 3285, 2110, 1040 cm^{-1}; MS, *m/e* 278 (M$^+$), 263 (M − CH_3), 247 (M − CH_2OH), 235, 233, 217, 205, 191, 166, 147, 129, 119, 105, 97, 95, 94 (base peak), 93, 79, 77, 69; HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1882.

***trans*-5-(2-Oxo-3-butynyl)-3-(2,2-dimethyl-3-oxopropyl)-1-methylcyclopent-1-ene Ethylene Ketal (14).** Alcohol **13** (45 mg, 0.16 mmol) was oxidized with PCC as described previously (reaction time, 45 min). Careful filtration through silica gel (CH_2Cl_2) gave the pure aldehyde **14** (38 mg, 84.9%): ^{1}H NMR ($CDCl_3$) δ 9.45 (s, 1 H), 5.17 (m, 1 H), 4.13–3.93 (m, 4 H), 2.78 (m, 1 H), 2.63 (m, 1 H), 2.52 (s, 1 H),

(16) This sequence (silylation/DDQ oxidation) represents a modification of the procedure of Fleming. See: Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

(17) The corresponding TMS dienol ether was highly prone to hydrolysis, and attempted oxidation of this substrate by a variety of methods (Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, 20, 140. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. Reference 16.) invariably gave low yields (15–30%) of dienone accompanied by large amounts (40–60%) of starting enone.

(18) A much more detailed study of this reaction has recently been described by Keck. Keck, G. E. Meeting of the American Chemical Society, New Orleans, LA., Aug 30–Sept 4, 1987. Abstract No. 144 of the Organic Division.

(19) Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*(2), 157.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

2.16–2.07 (m, 2 H), 1.70–1.58 (m, 6 H), 1.47 (dd, J = 14.1, 6.9 Hz, 1 H), 1.06 (s, 3 H), 1.04 (s, 3 H); IR (thin film) 3275, 2695, 2110, 1725 cm^{-1}; MS, m/e 276 (M^+), 261 (M – CH_3), 245, 233, 204, 189, 176, 164, 161, 160, 159, 147, 145, 132, 129, 119, 117, 105, 97, 93 (base peak), 92, 91, 86, 81, 80, 79, 77, 73; HRMS calcd for $C_{17}H_{24}O_3$ 276.1726, found 276.1725.

Preparation of a 0.1 M THF Solution of SmI_2.[11] Samarium metal (powder, 600 mg, 4.00 mmol) was suspended in 20 mL of dry THF in a dry, three-necked flask. Solid 1,2-diiodoethane (564 mg, 2.00 mmol) was added in one portion, and the mixture was stirred vigorously at room temperature. Over the course of ca. 0.5 h, the reaction mixture became green, deposited a yellow precipitate (SmI_3), and evolved heat. Further stirring at room temperature for 1.5 h generated a deep blue solution of SmI_2 (0.1 M) with no visible yellow precipitate.

11α-Hydroxy-3-methylene-2β,10,10-trimethyl-1α,6β,8α-tricyclo-[6.3.0.0^{2,6}]undecan-4-one (16a). Aldehyde **14** (55 mg, 0.20 mmol) was dissolved in THF (10 mL) in a dry, three-necked flask. Dry HMPA (0.5 mL) was added, and the mixture was cooled to −78 °C. The SmI_2 solution (2.4 mL, 0.24 mmol) was added dropwise over 5 min to the rapidly stirred solution, each drop producing a transient purple color which dissipated in ~1 s. After the addition, TLC analysis indicated incomplete reaction. Another 1-mL portion of SmI_2 solution was added dropwise (1.7 equiv total), and the resulting purple solution was allowed to warm to 0 °C over 0.5 h. The mixture was then poured into 50 mL of brine containing ~2 g of citric acid, and the mixture was extracted with 1:1 hexane/EtOAc (four times). The organic phase was washed (2 × H_2O, 1 × brine), dried (Na_2SO_4), filtered, and concentrated, and the residue was filtered through silica gel (hexane/EtOAc, 1:1). After removal of the solvent, the crude product (50 mg) was taken up in 20 mL of acetone and treated with p-toluenesulfonic acid (0.5 mg). The mixture was stirred overnight at room temperature, poured into saturated $NaHCO_3$ solution, and extracted with 1:1 hexane/EtOAc (three times). The organic phase was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (hexane/Et_2O/CH_2Cl_2, 2.5:2:1) to give, in order of elution, alcohol **13** (3.0 mg, 5.4%) and enone **16a** (27 mg, 57.9%) as a white, crystalline solid, mp 143–145 °C. Enone **16a**: ^1H NMR ($CDCl_3$) δ 6.03 (s, 1 H), 5.26 (s, 1 H), 3.57 (d, J = 8.7 Hz, 1 H), 2.60–2.30 (m, 4 H), 2.47 (dd, J = 18.2, 6.7 Hz, 1 H), 2.17 (d, J = 18.2 Hz, 1 H), 1.74 (dd, J = 12.8, 8.8 Hz, 1 H), 1.56 (ddd, J = 13.9, 7.3, 2.1 Hz, 1 H), 1.29–1.15 (m, 1 H), 1.24 (s, 3 H), 1.05–0.94 (m, 1 H), 1.02 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.7, 154.1, 117.3, 82.2, 58.2, 53.1, 45.3, 42.9, 40.9, 39.0, 37.2, 26.4, 22.2, 19.5; IR (thin film) 3465, 1720, 1635, 1090 cm^{-1}; MS, m/e 234 (M^+), 192, 166, 163, 159, 147, 135, 123, 121, 120, 111, 110, 109 (base peak), 108, 97, 95, 93, 91, 79, 77, 70, 67; HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1620.

Cyclization of 14 with DMPU as Cosolvent. Aldehyde **14** (70 mg, 0.25 mmol) in 15 mL of dry THF and 0.75 mL of dry DMPU was treated with SmI_2 as described above. In this case, the reaction mixture remained purple and heterogeneous throughout the addition at −78 °C. TLC analysis indicated only about 50% conversion after 1.2 equiv of SmI_2 had been added. The purple mixture was warmed to −10 °C (with no apparent further cyclization) and treated with an additional 1.2 equiv of SmI_2. The crude product mixture was then processed and purified as described above to give, in reverse order of elution, enone **16a** (36 mg, 60.6%), alcohol **13** (2.0 mg, 2.8%), and stereoisomer **16b** (3.5 mg, 5.9%): ^1H NMR for **16b** ($CDCl_3$) δ 6.02 (s, 1 H), 5.24 (s, 1 H), 3.74 (m, 1 H), 2.82–2.65 (m, 2 H), 2.57–2.40 (m, 3 H), 2.16 (d, J = 18.4 Hz, 1 H), 1.84–1.62 (m, 2 H), 1.45–0.80 (m, 2 H), 1.25 (s, 3 H), 1.05 (s, 3 H), 0.94 (s, 3 H).

11α-Hydroxy-3-methylene-2β,10,10-trimethyl-1α,8α-tricyclo-[6.3.0.0^{2,6}]undec-5-en-4-one (18). A dry, three-necked flask was charged with THF (10 mL) and diisopropylamine (52 μL, 0.37 mmol). The solution was cooled to 0 °C and treated with n-BuLi (1.31 M in hexane, 0.24 mL, 0.32 mmol). The mixture was allowed to stir for 15 min at 0 °C, and then enone **16a** (25 mg, 0.11 mmol) in THF (5 mL) was added. Stirring was continued for 45 min at 0 °C, whereupon solid TBS-Cl (32 mg, 0.21 mmol) and DMPU[15] (0.5 mL) were introduced to the reaction mixture. After being stirred for 2 h, the reaction mixture was poured into cold, saturated $NaHCO_3$ solution and extracted with cold hexanes (two times). The organic layers were combined, washed with additional cold $NaHCO_3$ solution, and dried (Na_2SO_4). The product solution was filtered and concentrated to give a yellow oil. This was flushed rapidly through a short column of silica gel by using hexane/EtOAc (8/1). After evaporation of the solvent, the product was obtained as a nearly colorless oil (33 mg, 88.8%). A portion of this crude material (14.5 mg, 0.04 mmol) was dissolved in dry benzene (5 mL) and 2,6-lutidine (15 μL, 0.13 mmol) and treated with DDQ (19 mg, 0.08 mmol). The mixture was then heated at reflux for 20 h, cooled, and poured into $NaHCO_3$ solution. The aqueous phase was extracted with ether (three times), and the extracts were combined and washed successively with saturated $NaHCO_3$ solution, 0.2 M HCl, and saturated $NaHCO_3$ solution. The product solution was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (hexane/EtOAc, 2:1) to afford pure dienone **18** (7.0 mg, 72.4%): ^1H NMR ($CDCl_3$) δ 5.93 (s, 1 H), 5.91 (br s, 1 H), 5.35 (s, 1 H), 3.87 (d, J = 8.4 Hz, 1 H), 2.85–2.60 (m, 2 H), 2.39–2.12 (m, 2 H), 1.91 (dd, J = 12.7, 7.8 Hz, 1 H), 1.69 (br s, 1 H), 1.33–1.18 (m, 1 H), 1.28 (s, 3 H), 1.09 (s, 3 H), 0.92 (s, 3 H); IR (thin film) 3440, 1690, 1650, 1620 cm^{-1}; MS, m/e 232 (M^+), 214, 199, 183, 175, 161, 159, 149, 131, 122, 111 (base peak), 105, 93, 91, 83, 79, 77, 69; HRMS calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1463.

(±)-Hypnophilin (2). Dienone **18** (6.6 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (0.5 mL) in a flask with an argon inlet. Water (5 drops), K_2CO_3 (5.6 mg, 0.04 mmol), and 30% H_2O_2 (3 drops) were added, and the heterogeneous mixture was stirred vigorously at room temperature for 22 h. Additional portions of K_2CO_3 and H_2O_2 (three times the original amounts) were added, and the mixture was stirred for a further 20 h. The reaction mixture was then poured into water and extracted three times with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc, 2:1) provided the pure product as an oil (3.7 mg, 52.4%), along with some starting material (1.5 mg, 22.7%): ^1H NMR ($CDCl_3$) δ 6.13 (s, 1 H), 5.46 (s, 1 H), 3.86 (d, J = 8.8 Hz, 1 H), 3.44 (s, 1 H), 2.73–2.56 (m, 1 H), 2.13 (dd, J = 12.0, 9.0 Hz, 1 H), 1.98–1.86 (m, 3 H), 1.30 (s, 3 H), 1.25 (m, 1 H), 1.20 (dd, J = 12.6, 10.3 Hz, 1 H), 1.07 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.7, 153.7, 121.6, 81.2, 76.0, 61.1, 56.1, 46.1, 45.5, 44.1, 34.5, 30.7, 26.4, 19.6, 17.7; IR (thin film) 3490, 1725, 1635, 1255, 1115 cm^{-1}; MS, m/e 248 (M^+), 233, 230 (M – H_2O), 220, 219, 215, 202, 201, 191, 177, 176, 173, 159, 158, 147, 146, 135, 133, 131, 130, 119, 111, 107, 105 (base peak), 93, 91, 86, 84, 81, 79, 77, 69; HRMS calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1412.

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