Tetrahedron Vol. 43, No. 24, pp. 5775 to 5780, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

Total Synthesis of (±)-Barbatusol

Emil R. Koft, Department of Chemistry
Rensselaer Polytechnic Institute, Troy, NY 12180-3590

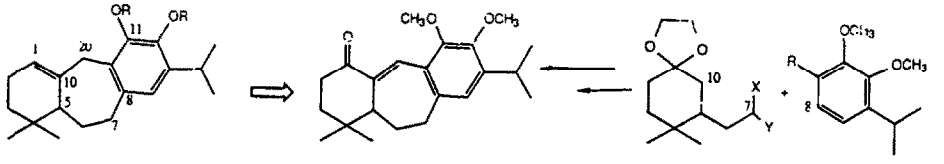
(*Received in USA* 10 *September* 1987)

Abstract - The naturally occurring hypotensive agent barbatusol (**1a**) has been synthesized in racemic form from 3-isopropylveratrole and 4,4-dimethyl-2-cyclohexene-1-one. An improved procedure for deprotection of barbatusol dimethyl ether (**1b**) is described.

Barbatusol (**1a**) is representative of a rare structural type of diterpene thought to arise from rearrangement of the more familiar abietane skeleton.[1] Isolated from the same source as the pharmacologically potent diterpene forskolin,[2] **1a** was found to induce bradycardia and lowering of blood pressure in mice.[1] We report here our successful efforts aimed at the first total synthesis of (±)-barbatusol.

Since Kelecom had shown that the $\Delta^{1,10}$ olefin present in this natural product is easily isomerized to an inseparable mixture enriched in the more stable $\Delta^{5,10}$ and $\Delta^{10,20}$ isomers,[4] a

SCHEME 1



1a R=H
1b R=CH_3

2

4a X,Y= H,I
4b X,Y= O

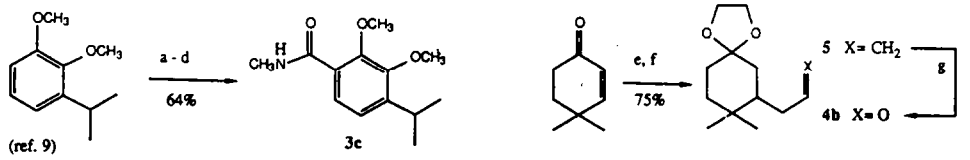
3a R= CHO
3b R= CH_2OH
3c R= $CONHCH_3$

strategy dictating the regiospecific introduction of the desired olefinic linkage at a late stage of the synthesis (i.e. from enone **2**) was formulated. The most direct approach to **2** seemed to be initial C(7)-C(8) bond formation via alkylation of an ortho metalated benzaldehyde synthon (**3**) with iodide **4a**, followed by aldol closure between C(10) and C(20) to form the hexahydrodibenzocycloheptene ring system. Unfortunately, attempted (O,C-8) dimetalation[5] of benzyl alcohol **3b** led to decomposition of the substrate, and while C(8) metalation of amide **3c** proceeded to 100% completion (n-BuLi, THF, -10°, 20 min) as judged by D_2O quench, addition of iodide **4a** to the reaction mixture with or without HMPA gave at best a 30% yield of coupled product. More seriously, all attempts to hydrolize or reduce the resulting hindered benzamide met with failure. In view of the low yield in the alkylation step, prospects for satisfactory results using *in situ* protected ortho metalated benzaldehyde methodology[6] seemed poor.

It is generally appreciated that o-metalated benzamides react with aldehydes much more rapidly and usually in higher yields than with alkyl halides, and that the γ-hydroxyamides so undergo facile cyclization to phthalides with mild acid treatment.[7] Applied to the barbatusol problem, such a strategy would generate unwanted benzylic oxygen functionality[8] at C(7) which could presumably be reductively removed at a later stage.

The requisite fragments **3c** and **4b** were prepared as shown in Scheme 2 in 64% (with one purification) and 66% (with two purifications) overall yields, respectively. Metalation of **3c** (Scheme 3) followed by addition of **4b** and then aqueous acid[7] led to the formation of phthalide **7** in 67% yield as a 1:1 mixture of diastereomers inseparable by flash chromatography. It was

SCHEME 2

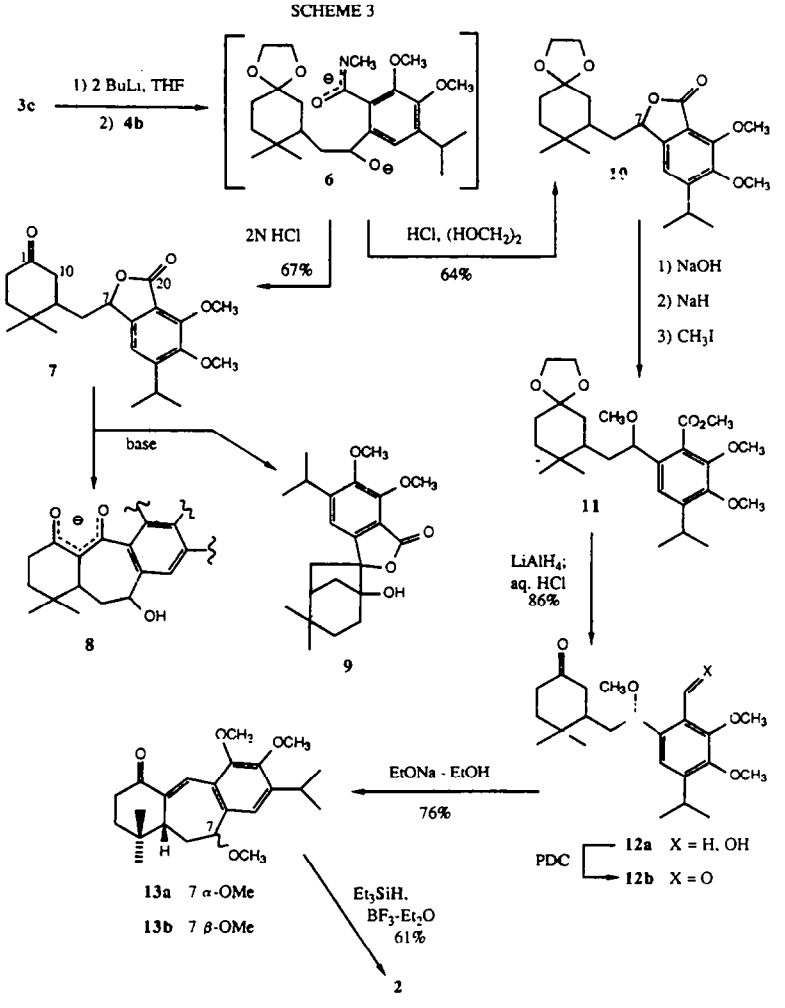


a) BuLi, Et_2O, 25°. b) CO_2. c) $SOCl_2$, CH_2Cl_2. d) $MeNH_2$, THF-H_2O. e) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$ (ref. 10). f) $(CH_2OH)_2$, cat. TsOH, PhH. g) O_3, CH_2Cl_2; Ph_3P.

thought that closure of the seven-membered ring to produce **8** from this intermediate might be possible via condensation between C(10) and C(20). However, treatment of **7** with non-nucleophilic bases under a variety of conditions led only to the bicyclo[3.2.1] octanol **9** in high yield. On the other hand, exposure of crude **6** to acid under nonhydrolytic conditions afforded ketal **10** in 64% yield (94% based on recovered **3c**).

Since hydrogenolysis of the lactone in this substance is disfavored on stereoelectronic grounds, reduction was first attempted with the sodium salt of the hydroxy acid obtained by hydrolysis of **10** with NaOH in methanol. Neither catalytic (H_2/Pd/C, 60 psi) nor dissolving metal (Li/NH_3 or Zn/H_2O/pyridine[11]) conditions were effective in removing the C(7) hydroxyl, so it was

SCHEME 3



decided to carry this oxygen functionality forward with the hope that reduction could be achieved at a later stage. Conversion of the phthalide to ester **11** was accomplished in 76% yield by sequential treatment with NaOH, NaH, and excess methyl iodide. Again, the C(7) methoxy group in this intermediate was resistant to hydrogenolysis. Reduction of **11** with $LiAlH_4$ followed by acidic hydrolysis of the crude product gave keto-alcohol **12a** which was then oxidized with pyridinium dichromate to aldehyde **12b** (82% overall). Aldolization (EtOH/EtONa) then led to a chromatographically separable 1:1 mixture of **13a** and **13b**.

Stereochemical assignments of **13a** (less polar isomer, m.p. 119-122°C) and **13b** (more polar, m.p. 110-112°C) rest on the following observations. First, the signal for the C(7)H in **13a** displayed coupling constants of 13 and 6 Hz, the former value indicating a dihedral angle of approximately 180° between this hydrogen and one borne by C(6). The J values for the C(7) proton in **13b** were 1.5 and 7 Hz, leading to the conclusion that the 7-methoxy group is in approximately equatorial and axial environments in isomers **13a** and **13b**, respectively. Corroborative evidence was found in the behavior of these substances to reduction with triethylsilane in the presence of BF_3 etherate.[12] Separate experiments revealed that **13b**, where the C(7)-O bond is roughly perpendicular to the plane of the aromatic ring, was converted rapidly (0°, 15 min, 90%) to **2**, while reaction of **13a** was much slower and was complicated to some extent by competitive reduction of the enone system after long reaction times. Nevertheless, it was possible to obtain **2** in 61% yield (84% allowing for recovered **13a**) from reduction of a 1:1 mixture of isomers **13**. Unreacted **13a** was then reduced separately (0°, 45 min) to afford additional **2**.

Further reduction of **2** via its tosylhydrazone using Hutchins' procedure[13] led to the formation of (±)-barbatusol methyl ether (**1b**)[1] uncontaminated by olefinic regioisomers. Having produced isomerically pure **1b**, there remained the task of catechol deprotection under conditions which would not isomerize the $\Delta^{1,10}$ olefin. Earlier work by Kelecom[1] and Matsumoto[3b] on barbatusol and pisiferin suggested that acidic regimens would be unsatisfactory, and base catalyzed isomerization to the corresponding styrene was also a clear possibility with various nucleophilic methods.[14]

Compound **14** was chosen as a model and simply prepared by the reaction of lithiated isopropylveratrole[9] with tiglyl bromide. Not surprisingly, treatment of this material with trimethylsilyl chloride/NaI in acetonitrile resulted in rapid olefin isomerization before any demethylation took

14 **15**

place. Attempted oxidation to the o-quinone[15] [$(NH_4)_6Ce(NO_3)_2$ in aqueous MeCN] followed by in situ $NaBH_4$ reduction gave many uncharacterizable products. However, exposure of **14** to 6 equiv. EtSNa in hot DMF[16] resulted in non-regioselective monodemethylation (1 hr at 130°C) followed by slower loss of the second methyl group affording **15** in 60% yield after 3 hrs at 130°C. When applied to **1b**, this method allowed for the successful completion of the total synthesis of racemic **1a** in 4.5% overall yield from 3-isopropylveratrole via a sequence requiring nine purifications.

Acknowledgment. The author thanks the National Institutes of Health for financial support through grant GM36360.

Experimental

IR spectra were recorded in the solvents indicated with a Perkin-Elmer 298 instrument. NMR spectra were obtained in $CDCl_3$ with a Varian XL-200 (200 MHz) or IBM WP-100SY (100 MHz) instruments, with Me_4Si and/or $CHCl_3$ as internal standard. Mass spectral data was obtained at 70 eV with a Hewlett Packard 5987A instrument. Microanalyses were performed by Robertson Laboratory, Madison, NJ. Flash chromatography was performed with the solvents indicated, using Merck silica gel 60, 230-400 mesh, as adsorbent. Reaction mixtures were dried during workup with anhydrous Na_2SO_4. Solvents were reagent grade and used without further purification, except tetrahydrofuran (THF) which was distilled from Na benzophenone ketyl before use.

Preparation of 2,3-dimethoxy-4-isopropyl-N-methylbenzamide (3c). 3-Isopropylveratrole[9] (4 g, 0.022 mol) was dissolved in 40 mL dry Et_2O containing TMEDA (5 mL, 0.033 mol) under an atmosphere of nitrogen. N-butyllithium (0.033 mol, 13.2 mL of 2.5M solution in hexane) was added slowly, and the mixture was allowed to stir 1.5 h at 25°C, after which it was cooled to -60°C and treated with excess solid CO_2. After warming to room temperature, the reaction mixture was washed with 2N HCl to remove the TMEDA, then extracted with 2N NaOH (2 x 50 mL). The basic extract was washed once with Et_2O, then acidified with concentrated HCl and reextracted with ether. The organic phase was dried, filtered and evaporated to yield 4.16 g of crude 2,3-dimethoxy-4-isopropyl benzoic acid as an oil. This material was treated with $SOCl_2$ (0.025 mol, 1.8 mL) and two drops of dimethylformamide in 20 mL of CH_2Cl_2 at 25°C for 2 h protected from moisture by a mineral oil bubbler. After evaporation of solvent and unreacted $SOCl_2$, the residue was taken up in 10 mL dry THF and added dropwise to a stirred solution of $MeNH_2$ (5 mL of 40% solution in H_2O) in 25 mL THF. When the exothermic reaction had subsided, the reaction mixture was partitioned between Et_2O and 2N HCl, dried, filtered and evaporated. Flash chromatography of the residue (EtOAc/hexane, 1:4) afforded 3.32 g (64%) of product as an oil. IR ($CHCl_3$) 3400, 2985, 1640, 1530, 1010 cm^{-1}. NMR (100 MHz) δ 7.93 (br, N-H), 7.67 (d, J=8 Hz, 1H), 7.05 (d, J=8, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.25 (septet, J=7, 1H), 2.95 (d, J=5, 3H), 1.15 (d, J=7, 6H). MS, m/e (rel. intensity): 237 (M^+, 38), 207 (93), 191 (100), 177 (30), 163 (45).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.51; H, 8.34; N, 5.63.

Preparation of 4-allyl-5,5-dimethyl-1,8-dioxaspiro[4.5]decane (5). 3-Allyl-4,4-dimethyl cyclohexanone was prepared via the method of Sakurai[10] from 4,4-dimethyl cyclohexenone (5 g, 0.04 mol), allyltrimethylsilane (5.5 g, 0.048 mol) and $TiCl_4$ (5.5 mL, 0.05 mol) in CH_2Cl_2. The crude product (6.17 g) was sufficiently pure for use in the next step. The ketone was dissolved in 50 mL benzene containing 5 mL ethylene glycol and 50 mg $TsOH \cdot H_2O$, then heated at reflux under a Dean-Stark trap for 5 h. After cooling and washing with saturated $NaHCO_3$ solution, the reaction mixture was dried, filtered, and evaporated. Flash chromatography (ether/hexane, 1:19) gave 6.32 g (75% overall) of **5**. IR (CCl_4): 3060 (w), 2950, 2890, 1095, 940, 910 cm^{-1}. 200 MHz NMR: δ 5.7 (m, 1H), 4.98 (broad d, J=13 Hz, 2H), 3.89 (s, 4H), 2.31 (m, 1H), 1.80-1.20 (m, 8H), 0.94 (s, 3H), 0.89 (s, 3H). MS, m/e (rel. intensity): 210 (M^+, 0.5), 169 (11), 139 (70), 99 (100).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H, 10.25.

Preparation of 4-(2-oxoethyl)-5,5-dimethyl-1,8-dioxaspiro[4.5]decane (4b). Ozone was passed through a solution of 5 g (23.8 mmol) of olefin **5** in 100 mL CH_2Cl_2 at -75°C with stirring until the blue color of excess ozone persisted. The reaction mixture was purged with N_2 until colorless, then triphenylphosphine (7.5 g, 28.6 mmol) was added and the mixture allowed to warm to 25°C and stir for 2 h. Evaporation of the solvent followed by chromatography (ethyl acetate/hexane, 1:10) afforded 4.49 g **4b** (89%) as an unstable oil which was stored by freezing in benzene. IR (CCl_4): 2950, 2710, 1720, 1105, 940, 680 cm^{-1}. 200 MHz NMR: δ 9.72 (t, J=1.5 Hz, 1H), 3.90 (s, 4H), 2.49 (dd, J=12, 8, 1H), 2.16-1.95 (m, 2H), 1.64-1.30 (m, 6H), 0.90 (s, 3H), 0.78 (s, 3H). MS, m/e (rel. intensity): 212 (M^+, 0.1), 184 (6), 141 (100), 113 (40).

Preparation of phthalides 7 and 10. Benzamide **3c** (0.968 g, 4.1 mmol) in 15 mL THF was stirred under nitrogen at -10°C while n-butyllithium (8.6 mmol, 3.42 mL of 2.5M solution in hexane) was added dropwise. The deep red mixture was held at -10°C for 0.5 h after which time aldehyde **4b** (1.0 g, 4.5 mmol) in 2 mL THF was added rapidly. Upon warming to room temperature, the mixture was poured into Et_2O-H_2O, the organic phase dried, filtered and evaporated. A sample of this material was purified (SiO_2, ethyl acetate/hexane, 1:1) and displayed the following NMR spectrum (200 MHz): δ 7.10 (s, 0.5H), 7.05 (s, 0.5H), 6.58-6.38 (m, 1H), 4.55 (m, 1H), 3.96-3.66 (m, 10H), 3.25 (septet, J=7 Hz, 1H), 3.14 (apparent t, J=5, 3H), 2.0-0.70 (m, 22H). The crude product was stirred overnight in THF saturated with 10% HCl, submitted to extractive workup and purified by chromatography (hexane/ether, 2:1) to yield 1.02 g (67%) of ketone **7**. IR (CCl_4): 1760, 1710 cm^{-1}. NMR (200 MHz) δ 6.90 (s, 0.5H), 6.88 (s, 0.5H), 5.24 (m, 1H), 4.07 (s, 3H), 3.83 (s, 3H), 3.33 (septet, J=7 Hz, 1H), 2.65-1.30 (m, 9H), 1.18 (d, J=7, 6H), 1.0-0.94 (m, 6H). MS, m/e (rel. intensity): 374 (M^+, 16), 249 (70), 235 (100). The crude hydroxyamide prepared from 2.68 g **3c** and 2.39 g **4b** (11.3 mmol) as described above was stirred for 6 h in 20 mL THF/ethylene glycol (4:1) containing 20 mmol dissolved HCl gas. Neutralization with saturated $NaHCO_3$, extraction with ether followed by chromatography (2:1 hexane/ether) after drying and evaporation gave 3.0 g (64%) of **10** as a semisolid mixture of diastereomers. Further elution with 1:1 ether/hexane gave 0.87 g (32%) of recovered **3c**. IR ($CHCl_3$) C=O 1750 cm^{-1}. NMR (200 MHz) δ 7.0 (s, 0.5H), 6.90 (s, 0.5H), 5.32 (m, 1H), 4.08 (s, 3H), 3.91 (s, 4H), 3.85 (s, 3H), 3.34 (septet, J=7 Hz, 1H), 1.97-1.22 (m, 9H), 1.2 (m, 6H), 0.88-0.74 (m, 6H). MS, m/e (rel. intensity): 418 (M^+, 5.5), 347 (28), 235 (75), 99 (100).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 68.67; H, 8.43.

Preparation of 9. Keto-lactone **7** (0.27 g, 0.72 mmol) in 1 mL THF was added to a solution of t-BuOK (96 mg, 0.86 mmol) in 0.3 mL t-BuOH and 4 mL THF at 25°C under N_2. After 1 h, TLC (1:1 Et_2O/hexane) showed complete consumption of **7** with concomitant formation of two products in approximately equal amounts. The reaction mixture was poured into 2N HCl/Et_2O; the organic phase was dried, filtered and evaporated. Chromatography of the residue (Et_2O/hexane, 1:4) gave 0.237 g (88%) **9** as a mixture of diastereomers. IR (CCl_4): 3580 (sharp), 3540-3300, 2960, 1760 cm^{-1}. NMR (200 MHz): 7.08 (s, 0.65H), 7.00 (s, 0.35H), 3.98 (s, 3H), 3.81 (s, 3H), 3.30 (septet, 1H), 2.4-1.2 (m, 10H), 1.13 (m, 6H), 1.0 (s, 2H), 0.98 (s, 1H), 0.88 (s, 2H), 0.84 (s, 1H). On standing

the mixture partially solidified; recrystallization from Et_2O/hexane afforded the pure major (aromatic H at δ 7.08) more polar isomer, mp 156-158°C. MS, m/e (rel. intensity): 374 (M^+, 19), 249 (100), 235 (30), 207 (19).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.41; H, 8.01.

Preparation of ester 11. Phthalide **10** (2.9 g, 6.9 mmol) was combined with NaOH (0.8 g, 20 mmol) in 20 mL methanol and heated at reflux for 16 h. After evaporation of solvent the residue was suspended in 40 mL THF and NaH (21 mmol; 0.92 g of 60% oil dispersion) was added, followed by methyl iodide (6.8 g, 0.049 mol). The reaction mixture was stirred and heated at reflux overnight. After the usual workup, chromatography (ethyl acetate/hexane, 1:10) yielded 2.44 g (75%) of **11** as a mixture of diastereomers. IR ($CHCl_3$): 2975, 1720, 1265, 1090, 1030 cm^{-1}. NMR (200 MHz) δ 7.0 (s, 0.5H), 6.98 (s, 0.5H), 4.13-4.0 (m, 1H), 3.92-3.83 (m, 13H), 3.30 (septet, J=7 Hz, 1H), 3.17, 3.12 (singlets, 3H), 1.92-1.00 (m, 9H), 1.18 (d, J=7, 6H), 0.90, 0.78, 0.76, 0.72 (singlets, 6H). MS, m/e (rel. intensity): 464 (M^+, 0.6), 432 (6.4), 281 (100), 213 (5.4), 185 (80).

Preparation of keto-alcohol 12a. Ester **11** (2.44 g, 5.26 mmol) in 5 mL THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.42 g, 10.5 mmol) in 25 mL THF under N_2 at 25°C. After stirring 3 h excess hydride was destroyed by careful addition of H_2O, and the mixture was acidified with 2N HCl. The organic phase was dried and evaporated; the residue was then stirred 20 h with 50 mL 1:10 2N HCl/THF. After neutralization with $NaHCO_3$, the organic phase was dried, evaporated, and the residue chromatographed (ethyl acetate/hexane, 1:3) to give 1.77 g (86%) **12a**. IR ($CHCl_3$): 3610-3200, 2980, 1710, 1450, 1410, 1300, 1100, 1050, 1005 cm^{-1}. NMR (200 MHz): 6.99, 6.92 (singlets, 0.5H each), 4.75-4.58 (m, 2H), 4.33 (broad t, J=8 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.24 (septet, J=7, 1H), 3.12 (s, 3H), 2.60-1.38 (m, 10H), 1.16 (m, 6H), 1.0, 0.90, 0.88, 0.83 (singlets, 1.5H each). MS, m/e (rel. intensity): 392 (M^+, 0.4), 374 (6), 360 (5), 342 (4), 253 (62), 221 (100).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 69.98; H, 9.56.

Preparation of keto-aldehyde 12b. Alcohol **12a** (1.12 g, 2.86 mmol) was added to 1.6 g (4.25 mmol) pyridinium dichromate in 20 mL dry CH_2Cl_2 and the mixture was stirred at 25°C for 5 h. Dilution with ether, filtration through Celite, evaporation of the solvents and chromatography of the residue (ether/ hexane, 1:5) gave 1.05 g (94%) of aldehyde **12b**. IR (CCl_4): 2960, 1715, 1685, 1450, 1295, 1100, 1040 cm^{-1}. MS, m/e (rel. intensity): 390 (M^+, 10), 358 (81), 326 (11), 251 (100). 200 MHz NMR: δ 10.3 (s, 1H), 7.28, 7.24 (singlets, 1H), 4.95 (broad d, J=10, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 3.32 (septet, J=7, 1H), 3.11, 3.09 (singlets, 3H), 2.76-1.40 (m, 9H), 1.18 (d, J=7, 1H), 0.93, 0.90, 0.88, 0.87 (singlets, 6H).

Preparation of 13a and 13b. Keto-aldehyde **12b** (0.509 g, 1.3 mmol) in 1 mL absolute ethanol was added dropwise to a stirred solution of sodium ethoxide prepared by dissolving 46 mg (2 mmol) Na in 8 mL absolute EtOH under N_2 at 25°C. After 15 min the mixture was neutralized with 2N HCl, most of the solvent was removed in vacuo, and the mixture partitioned between H_2O and ether. The organic phase was dried and evaporated, and the residue chromatographed (ethyl acetate/hexane, 1:15) to give, in order of elution, 0.172 g **13a** (m.p. 119-122°) and 0.178 g **13b** (m.p. 110-112°) in a combined yield of 72%. IR ($CHCl_3$, as a mixture): 2960, 1670, 1585, 1450, 1405, 1310, 1105, 1040 cm^{-1}. NMR (200 MHz), **13a**: 7.79 (s, 1H), 7.09 (s, 1H), 3.94 (dd, J=6, 13 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.33 (septet, J=7, 1H), 3.29 (s, 3H), 2.48 (dd, J=6, 10, 2H), 2.42-1.76 (m, 4H), 1.57-1.42 (m, 1H), 1.23 (d, J=7, 3H), 1.21 (d, J=7, 3H), 0.93 (s, 3H), 0.91 (s, 3H). **13b**: 7.63 (d, J=2 Hz, 1H), 7.02 (s, 1H), 4.14 (dd, J=1.5, 7, 1H), 3.80 (s, 6H), 3.32 (s, 3H), 3.30 (septet, J=7, 1H), 2.72-2.30 (m, 4H), 1.97-1.80 (m, 3H), 1.18 (2d, J=7, 6H), 1.04 (s, 3H), 0.93 (s, 3H). MS, m/e (rel. intensity): 372 (M^+, 93), 341 (39), 340 (32), 326 (21), 325 (23), 243 (100).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.97; H, 8.62.

Preparation of enone 2. A stirred solution of enones **13a** and **b** (1:1, 0.422 g, 1.13 mmol) in 8 mL dry CH_2Cl_2 at 0° under N_2 was treated in rapid succession with $BF_3{\cdot}Et_2O$ (0.2 mL, 1.72 mmol) and Et_3SiH (0.55 mL, 3.42 mmol). After 30 min the mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. Chromatography (EtOAc/hexane, 1:20) of the residue obtained after drying and evaporation of the organic phase yielded 0.236 g (61%) of **2**, followed by 0.119 g (28%) recovered **13a**. IR (CCl_4): 2960, 1675, 1450, 1410, 1100, 1050 cm^{-1}. NMR (200 MHz): δ 7.83 (s, 1H), 6.80 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.31 (septet, J=7 Hz, 1H), 2.65-2.46 (m, 3H), 2.40-2.16 (m, 2H), 1.97-1.80 (m, 2H), 1.66-1.46 (m, 2H), 1.23 (d, J=7, 3H), 1.19 (d, J=7, 3H), 0.99 (s, 3H), 0.90 (s, 3H). MS, m/e (rel. intensity): 342 (M^+, 100), 314 (12), 299 (45), 273 (28), 245 (20), 229 (10).

Preparation of barbatusol dimethyl ether (1b). Enone **2** (0.231 g, 0.675 mmol) was heated at reflux for 3 h with 0.15 g (0.8 mmol) tosylhydrazine in 4 mL absolute ethanol. Evaporation of the solvent and elution of the residue through a plug of silica gel with EtOAc/hexane 1:5 to remove the excess hydrazine afforded 0.34 g of hydrazone, pure by TLC. The hydrazone was stirred under N_2 in 2.5 mL DMF plus 2.5 mL sulfolane containing ca. 20 mg bromocresol green. The mixture was warmed to 110°C and $NaBH_3CN$ (0.38 g, 6 mmol) was added, followed by sufficient 2N HCl to give a tan color. Heating was continued for 80 min during which time several portions of 2N HCl were added to maintain proper acidity, as indicated by the tan color. The mixture was cooled, poured into H_2O and extracted with ether. The residue obtained after drying, filtering and evaporating the organic phase was chromatographed (20:1 hexane/Et_2O) to give 0.155 g (70% overall) of oily product. IR ($CHCl_3$): 2940, 1445, 1404, 1328, 1295, 1095, 1045, 1000, 970, 940, 875 cm^{-1}. NMR (200 MHz): δ 6.70 (s, 1H), 5.50 (s, Wh/2=8.8 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.74 (d, J=16 Hz, 1H), 3.24 (septet, J=7, 1H), 3.0 (d, J=16, 1H), 2.83-2.64 (m, 2H), 2.10-1.85 (m, 3H), 1.82-1.71 (m, 1H), 1.40-1.14 (m, 3H), 1.17 (2d, J=7, 6H), 0.87 (s, 3H), 0.81 (s, 3H). MS, m/e (rel. intensity): 328 (M^+, 94), 285 (31), 270 (63), 193 (100), 165 (36), 141 (30).

Preparation of 1,2-dimethoxy-3-isopropyl-6[(E)-2-methyl-2-butenyl]benzene (14). 3-Isopropylveratrole[9] (3.42 g, 19 mmol) was metalated as described in the preparation of **3c** using one equivalent (7.6 mL of 2.5M) n-butyllithium and 3 mL TMEDA in 20 mL ether. At the end of the metalation period (1.5 h), the mixture was cooled to -75°C, and (E)-1-bromo-2-methyl-2-butene (4.1 g, 28 mmol) in 10 mL THF was added. The cooling bath was removed and the mixture was stirred at 25°C for 30 min. Extraction with 2N HCl followed by a water wash, drying, filtration and

evaporation gave crude **14** which was purified by flash chromatography (hexane; hexane/ethyl acetate, 25:1) to afford 2.64 g (56%) of **14**. IR (CCl_4): 3050, 2960, 1450, 1410, 1275, 1050, 1035 cm^{-1}. NMR (200 MHz): δ 6.94, 6.84 (doublets, J=9 Hz, 2H), 5.23 (m, 1H), 3.85, 3.80 (singlets, 6H), 3.34 (septet, J=7, 1H), 3.30 (s, 2H), 1.61 (broad s, 6H), 1.20 (d, J=7, 6H). MS, m/e (rel. intensity): 248 (M^+, 100), 233 (47), 205 (94), 191 (37), 177 (65), 105 (32).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.12; H, 9.32.

Demethylation of 14; preparation of catechol 15. Ethanethiol (1 mL, 0.013 mol) was added dropwise to a stirred suspension of NaH (6.42 mmol, 0.26 g of 60% dispersion in oil) in dry DMF under N_2. Ether **14** (0.26 g, 1.07 mmol) was added and the mixture was held at reflux for 3 h. Dilution with H_2O, acidification (2N HCl) and extraction with ether gave crude product which was purified by chromatography (ethyl acetate/hexane, 1:20), yielding 142 mg (60%) of catechol **15** as a colorless oil which darkened on standing. Examination of the forerun by NMR showed what appeared to be an inseparable mixture of monodemethylation products; these showed no signs of olefin isomerization. Data for **15**: IR (CCl_4): 3540, 3480, 2960, 1450, 1300, 935 cm^{-1}. 200 MHz NMR: δ 6.65 (d, J=9 Hz, 1H), 6.56 (d, J=9, 1H), 5.54 (broad q, J=7, 1H), 5.50 (s, 2H), 3.46 (broad s, 2H), 3.20 (septet, J=7, 1H), 1.68 (d, J=7, 3H), 1.62 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H), MS, m/e (rel. intensity): 220 (M^+, 70), 205 (32), 163 (35), 149 (100).

Demethylation of 1b; preparation of (±)-barbatusol. Methyl ether **1b** (100 mg, 0.3 mmol), was combined with EtSH (3.6 mmol, 0.3 mL) and 2.4 mmol NaH (100 mg of 60% dispersion in oil) in 2 mL DMF. The reaction mixture was heated at reflux under N_2 for 4 h and worked up as in the preparation of **15**. Rapid chromatography (ether/hexane, 1:9 → 2:3) gave 50 mg (56%) of **1a** which darkened rapidly in air. The remainder of the product, eluted before **1a**, appeared to be a mixture of monomethyl ethers. 200 MHz ^1H NMR of **1a**: δ 6.52 (s, 1H), 5.51 (broad t, Wh/2=8 Hz, 1H), 5.05 (broad, 2 phenolic H's), 3.70 (d, J=16, 1H), 3.17-2.98 (m, 2H), 2.82-2.64 (m, 2H), 2.10-1.88 (m, 3H), 1.79 (broad d, J=12, 1H), 1.40-1.10 (m, 2H), 1.20 (d, J=7, 3H), 1.22 (d, J=7, 3H), 0.89 (s, 3H), 0.85 (s, 3H).

References and Notes

(1) Kelecom, A. Tetrahedron **1983**, 39, 3603.
(2) For a review on the chemistry and biology of forskolin, see: Seamon, K. B.; Daly, J. W. in "Advances in Cyclic Nucleotide and Protein Phosphorylation Research", Greengard, P.; Robison, G. A., eds., Raven: New York, **1986**, 20, pp 1-150.
(3) Previous synthetic work: a) For the preparation of **1a** as a mixture of double bond isomers from carnosol, see ref. 1. b) Total synthesis of ± pisiferin (11-deshydroxy barbutusol): Matsumoto, T.; Imai, S.; Yoshinari, T.; Matsuno, S. Bull. Chem. Soc. Japan **1986**, 59, 3103. c) Conversion of pisiferin to **1a**: Hasegawa, S.; Hirose, Y.; Yatagai, M.; Takahashi, T. Chem. Lett. **1984**, 1837.
(4) The numbering system for all intermediates is that of ref. 1.
(5) Meyer, N.; Seebach, D. Angew. Chem. Int. Ed. Engl. **1978**, 17, 521; Taber, D. F.; Dunn, B. S.; Mack, J. F.; Saleh, S. A. J. Org. Chem. **1985**, 50, 1987.
(6) Comins, D. L.; Brown, J. O. J. Org. Chem. **1984**, 49, 1078. In this study, a 2-methoxy group was found to interfere with the 6-lithiation of a benzaldehyde-trimethyl ethylene diamine adduct.
(7) Mao, C-L., Barnish, I. T.; Hauser, C. R. J. Het. Chem. **1969**, 6, 475.
(8) Functionality at this position might be desirable for the synthesis of more complex members of this structural class, such as icetexone; Taira, Z.; Watson, W. H.; Dominquez, X. A., J.C.S. Perkin II **1976**, 1728.
(9) a) Stevens, R. V.; Bisacchi, G. S.; J. Org. Chem. **1982**, 47, 2396. b) Edwards, J. D.; Cashaw, J. L. J. Org. Chem. **1955**, 26, 847.
(10) Hosomi, A.; Sakurai, H. J. Am. Chem. Soc. **1977**, 99, 1673.
(11) Newman, M. S., Sankovan, V., Olson, D. R. J. Am. Chem. Soc. **1976**, 98, 3237.
(12) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, Jr., W. R.; Silverman, S. B. J. Org. Chem. **1978**, 43, 374.
(13) Hutchins, R. O.; Milewski, C. A.; Marxanoff, B. E. J. Am. Chem. Soc. **1973**, 95, 3662.
(14) Bhatt, M. V.; Kulkarni, S. U. Synthesis **1983**, 249.
(15) The o-quinone corresponding to barbatusol has been synthesized from the natural product via Ag_2O oxidation: see ref. 1.
(16) Feutrill, G. I.; Mirrington, R. N. Tetrahedron Lett. **1970**, 1327.