

A Convenient Synthesis of Estrone and 11-Methylequilenines based on the Thermal Elimination of β -Ketosulfoxides

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The thermal elimination of β -ketosulfoxides (3, 4, 5) derived easily from methyl 4-(3-methoxyphenyl)butyrate (1) gave 6-(3-methoxyphenyl)hex-1-en-3-one (6), which was condensed with 2-methylcyclopentane-1,3-dione (8) to yield the triketone (7), one of key intermediates of Smith's estrone synthesis. Compound 7 was cyclized to the unsaturated diketone (9), which was converted to estrone methyl ether (13) by the established procedures. When the mixture of 3 (or 4) and 8 was heated, 7 was directly formed in a good yield. Moreover, heating of 5 and 8 gave 9, though in less satisfactory yield. The over-all yield of this simple and short cut synthesis of estrone methyl ether (13) from the starting material (1) was 34%, nearly twice of the original Smith method. This method also applied for the synthesis of 11 α -methylequilenine methyl ether (20) and 11 α -methylisoequilenine methyl ether (19) *via* the prior introduction of a methyl group to 3 yielding the β -ketosulfoxide (14) in 40% over-all yield.

Keywords—short cut synthesis; estrone; 11 α -methylequilenine; 11 α -methylisoequilenine; thermal elimination; β -ketosulfoxide; stereochemistry

The Smith method,²⁾ as well as Torgov's is well known as an efficient and highly stereospecific synthesis of estrone.³⁾ However, some processes, especially those to the vinyl ketone (6) by the usual Hofmann degradation, still need to be improved. As part of our study on reactions and synthetic applications of β -ketosulfoxides,⁴⁾ we report here their thermal elimination to vinyl ketones, which may provide a practical improvement of the Smith method.⁵⁾

A β -ketosulfoxide (2) prepared quantitatively from methyl 4-(3-methoxyphenyl)butyrate (1) and dimethyl anion by the usual method⁶⁾ was treated with methyl iodide in the presence of potassium hydride to give an enone precursor (3) in 89% yield. The structural assignment of 3 rests on its spectral data. In its mass spectrum, 3 has no molecular ion, but a peak due to $M^+ - CH_3SOH$ at m/e 204 corresponding to that of the enone (6). Its nuclear magnetic resonance (NMR) spectrum shows that 3 is a diastereomeric mixture in the ratio of 1:2 attributed to the two asymmetric centers of the methine and the sulfoxide. Without further separation into its components, 3 was heated in dioxane-diglyme (1:1) under reflux for 4 hr. The thermal elimination of methanesulfenic acid took place smoothly and, after passing through a short column of silica gel, the pure enone (6) was easily isolated in 85% yield.⁷⁾

- 1) Location: a) Ishikari-Tobetsu, Hokkaido 061-02 Japan; b) Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.
- 2) G.H. Douglas, J.M.H. Graves, D. Hartley, G.H. Hughes, B.J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, **1963**, 5072.
- 3) For a review, see: P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968).
- 4) Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976); *idem*, *J.C.S. Perkin I*, **1976**, 1479; *idem*, *Heterocycles*, **5**, 233 (1976).
- 5) The preliminary communication of this paper appeared in Y. Oikawa, T. Kurosawa, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **23**, 2466 (1975).
- 6) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
- 7) The thermal elimination of 3 to 6 in other solvents under similar conditions gave less satisfactory results: xylene (60%), diglyme (62%), dioxane (80%).

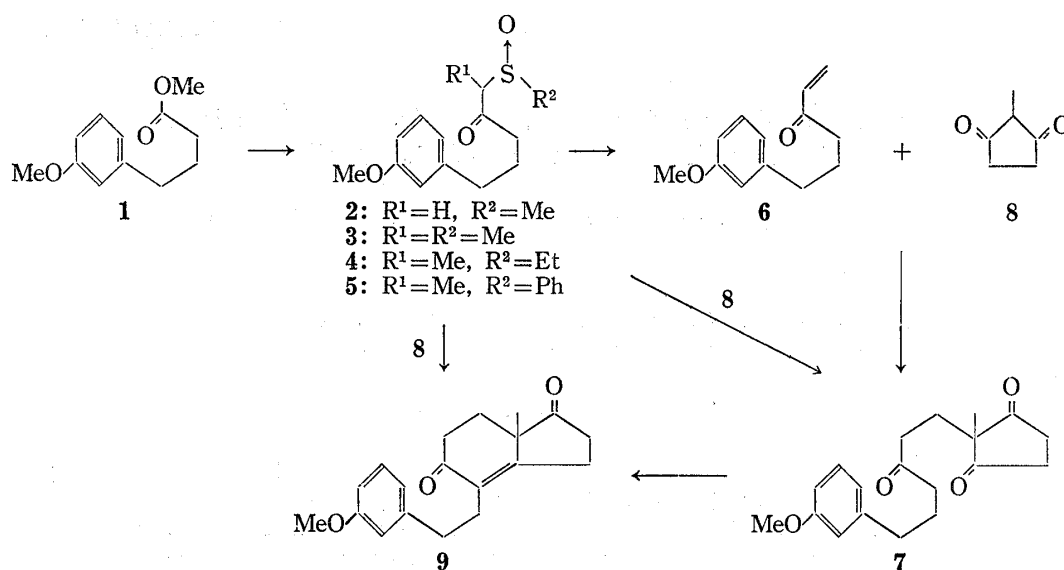


Fig. 1

The condensation of **6** and 2-methylcyclopentane-1,3-dione (**8**) to the trione (**7**) was carried out at room temperature in the presence of triethylamine in 80% yield.⁸⁾ As a more convenient way, however, when a diglyme solution of **3** and **8** (1.3 eq) was heated under reflux for 4.5 hr, **7** was formed directly in 70% yield through the thermal elimination of **3** and the subsequent Michael addition.

Moreover, to dispense with the methylation step (**2**→**3**), **1** was condensed with a carbanion prepared from diethyl sulfoxide and lithium diisopropylamide to give **4** in 97% yield. Its NMR spectrum shows that **4** was also a diastereomeric mixture. In its mass spectrum, **4** has again no molecular ion, but has entirely the same peaks as **3**. In analogy with **2**, **4** was heated with the dione in diglyme to yield the trione (**7**) though in less satisfactory yield (41%), probably because the thermal elimination of ethanesulfenic acid took place simultaneously in the unfavorable direction. In order to facilitate the thermal elimination, **5** was next prepared from **1** and a carbanion of ethyl phenyl sulfoxide. This compound

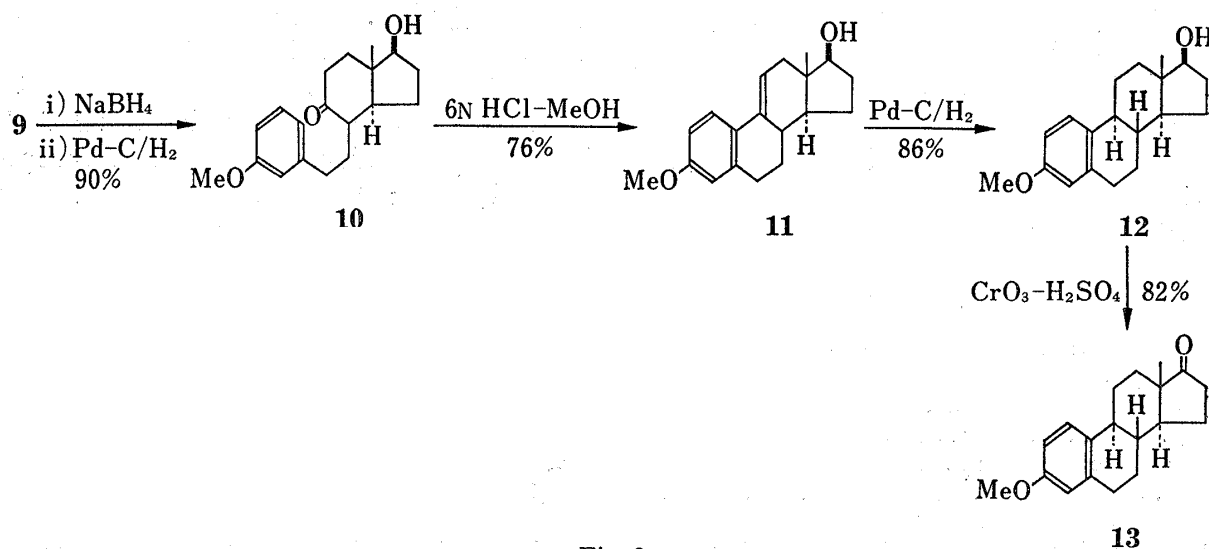


Fig. 2

8) cf. S. Danishefsky and P. Cain, *J. Org. Chem.*, **39**, 2925 (1974); G. Bauduin, H. Christol, and Y. Pietrasanta, *Bull. Soc. Chim. Fr.*, 1973, 359.

was easily converted to the enone (6) in refluxing benzene or monoglyme, and when heated with 8 in diglyme, the unsaturated diketone (9), one of key intermediates in the Smith method, was interestingly isolated in 37% yield, that is, the initially formed trione (7) further underwent an acid catalyzed cyclization. Benzenesulfenic acid, though unstable, formed as the elimination of 5 proceeded probably acted as a catalyst. If this assumption was correct, an excess of the dione (8) was expected to also act as a catalyst in this type of acid catalyzed cyclization, because 8 has almost the same acidity as acetic acid. Actually, when 3 was heated with three-fold excess of 8, the yield of 9 increased to 52%.

The conversion of 9 to estrone methyl ether (13) essentially followed the established procedures as shown in the scheme.^{2,9)} The overall yield of estrone methyl ether (13) from the starting material (1) was 34%, nearly twice of the original Smith method.

An additional advantage of the elimination method presented in this paper is that a substituent can be easily introduced at the C-11 position of the steroid skeleton through the prior introduction of the substituent at the active methylene between the sulfinyl and carbonyl groups of the starting β -ketosulfoxides.

As an example illustrating this feature the synthesis of 11-substituted steroids is next described. Treatment of 2 with 2.4 equivalents of methyl iodide in the presence of potassium hydride or sodium hydride gave 14 in 90% yield. In its mass spectrum, a peak owing to the elimination of methanesulfenic acid appears at 218. Its NMR spectrum has two singlets of methyl substituents at δ 1.70 and 2.10 ppm. On heating in dioxane, 14 readily gave an enone (15) in 89% yield. Then 15 was condensed with 8 in ethyl acetate containing 5% triethylamine at 70° for 7 days to give a ketol (17) in 70% yield accompanied by a small amount (7%) of a triketone (16). The mass spectrum of 17, though without its parent peak, has a fairly strong peak at 312 ($M^+ - 18$) from loss of water. The infrared (IR) spectrum, which contains a hydroxy (35000 cm^{-1}) and two carbonyl groups ($1740, 1705\text{ cm}^{-1}$), indicates that 17 is an aldol cyclization product.

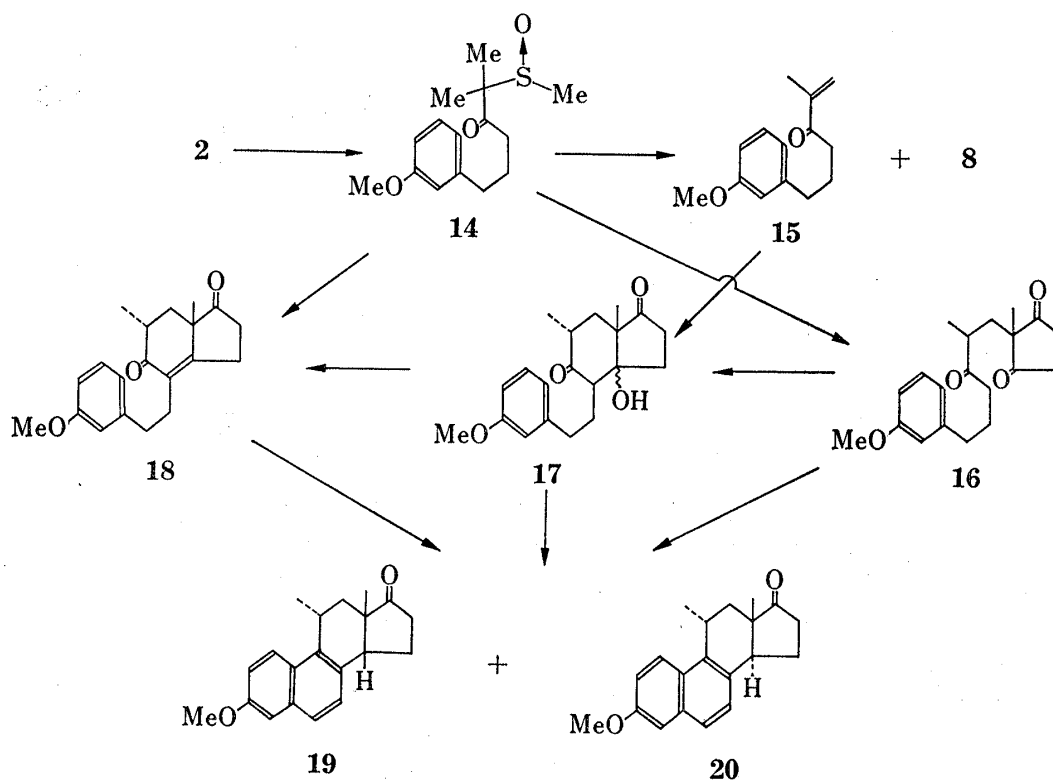


Fig. 3

9) R.P. Stein, G.C. Buzby Jr., G.H. Douglas, and H. Smith, *Tetrahedron Lett.*, 1967, 3603.

On treatment with polyphosphoric ester (PPE) in refluxing chloroform for 4 hr, **17** readily lost water to yield an unsaturated diketone (**18**) in 80% yield. Its mass spectrum gives the fragmentation pattern identical with that of **17**, in which a strong and characteristic peak formed by the McLafferty rearrangement appears at 178. Its NMR spectrum shows that **18** is not a diastereomeric mixture, but a single product, whose two C-methyl groups must be in the *trans* configuration to avoid an unfavorable 1,3-diaxial interaction in the *cis* configuration. Then **18** was treated with polyphosphoric acid (PPA) in refluxing chloroform for 30 min, and gave two steroidal products, **19** and **20**, which were separated by silica gel column chromatography in 43% and 36% yield, respectively. Under the same conditions, **17** also gave directly **19** (38%) and **20** (30%) without isolation of the intermediary **18**.

As a more practical way, a mixture of **14** and **8** in diglyme was heated under reflux for 7 hr to give triketone (**16**) in 60% yield. Then **16** was treated with PPA in refluxing chloroform as described above, and interestingly gave **19** (41%) and **20** (33%), which were formed probably *via* **17** and **18**. The over-all yield of combined **19** and **20** from **2** was over 40%. When **14** was heated in the presence of three-fold excess of **8**, a mixture of **16** and **18** was formed, though only in 19% and 30% yield, respectively.

The structural assignment of **19** and **20** was established spectroscopically, and was supported by some chemical reactions and by mechanistic considerations. On the basis of the elemental analyses and the mass spectra, both **19** and **20** have the composition $C_{20}H_{22}O_2$. Their NMR spectra have no vinyl proton. In their UV spectra, both compounds have the chromophore of equilenine type, not **21**-type.^{2,10,11)} Therefore, they must be isomeric each other with regard to the configuration at C-14. Compound **20** having absorption maxima at a little longer wavelength can be assigned as 11 α -methylequilenine methyl ether with C-14 α -hydrogen, and hence **19** is 11 α -methylisoequilenine methyl ether with C-14 β -hydrogen.¹¹⁾ This assignment is supported by the following reactions.

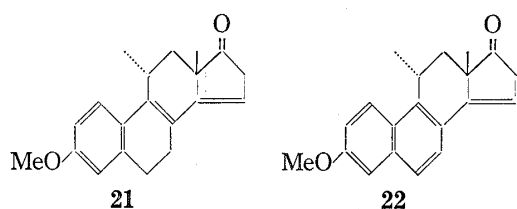


Fig. 4

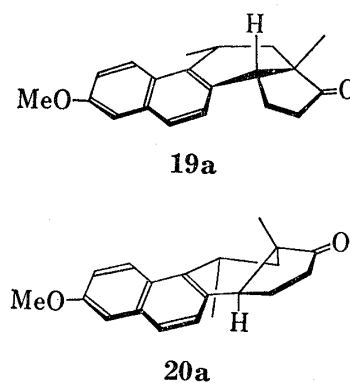


Fig. 5

Compound **19** was dehydrogenated by the treatment with dichlorodicyanobenzoquinone (DDQ) in refluxing benzene to **22**, which was then subjected to hydrogenation with 5% palladium on carbon to give **20** as well as **19**. On the other hand, **20** was unreactive to DDQ. Three-dimensional drawings (**19a** and **20a**) of **19** and **20** may account for their different reactivities, namely the α -side of **20** being hindered by the C-11 α -methyl group, it is hardly possible to form a charge transfer complex, the formation of which must be the initial step of the DDQ oxidation, between DDQ and the electron-donating naphthalene moiety of **20a**, whereas the β -side of **19a** is open to the attack of DDQ.

10) G.A. Smith and H. Smith, *Chem. and Ind.*, 1960, 1022.

11) T. Miki, K. Hiraga, and T. Asako, *Chem. Pharm. Bull.* (Tokyo), 13, 1285 (1965).

Experimental

5-(3-Methoxyphenyl)-1-methylsulfinylpentan-2-one (2)—To a stirring suspension of KH (0.8 g) washed with dry hexane in THF (5 ml), DMSO (2 ml) was added dropwise at 0° under argon. After evolution of hydrogen ceased, 4-(3-methoxyphenyl)butyrate (1, 1.02 g) in THF (5 ml) was added to the solution and the stirring was continued for 30 min at room temperature. The reaction mixture was then poured into sat. NH_4Cl solution and extracted with CH_2Cl_2 . The extract was washed with water and sat. NaCl, then dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residual oil was purified by silica gel column chromatography to yield 1.25 g of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1700, 1040. NMR (CDCl_3) δ : 1.8—2.2 (2H, m), 2.62 (2H, t, $J=6$ Hz), 2.67 (2H, t, $J=6$ Hz), 2.69 (3H, s), 3.72 (1H, d, $J=14$ Hz), 3.77 (1H, d, $J=14$ Hz), 3.82 (3H, s), 6.6—6.8 (3H, m), 7.20 (1H, t, $J=8$ Hz).

6-(3-Methoxyphenyl)-2-methylsulfinylhexan-3-one (3)—To a stirring suspension of KH (0.4 g) washed with dry hexane in THF (10 ml), 2 (1.27 g) in THF (10 ml) was added dropwise at 0° under argon. After evolution of hydrogen ceased, MeI (0.79 g) was added and the stirring was continued for 3.5 hr at room temperature. Work-up as described above gave 1.19 g (89%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1700, 1040. NMR (CDCl_3) δ : 1.30 (2H, d, $J=7$ Hz), 1.42 (1H, d, $J=7$ Hz), 1.8—2.1 (2H, m), 2.3—2.8 (7H, m), 3.74 (0.33H, q, $J=6$ Hz), 3.80 (3H, s), 3.84 (0.67H, q, $J=6$ Hz), 6.65—6.8 (3H, m), 7.18 (1H, t, $J=8$ Hz). MS m/e (%): 204 ($\text{M}^+ - \text{MeSOH}$, 11), 134 (100), 121 (15), 91 (16).

6-(3-Methoxyphenyl)-2-ethylsulfinylhexan-3-one (4)—To a stirring THF solution (8 ml) of diisopropylamine (1.21 g), 7.5 ml of *n*-BuLi (10% in hexane) was added dropwise at -20 — -30° under nitrogen and the stirring was continued for 20 min. Then a THF solution (2 ml) of diethylsulfoxide (1.5 g) was added and the solution was stirred for additional 20 min. After the temperature was allowed to raise to -10° , 1.01 g of the ester (1) in THF was added and the solution was stirred at room temperature for 1 hr. The reaction mixture was worked up as described above to give 1.33 g (97%) of a colorless oil: IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1700, 1040. NMR (CDCl_3) δ : 1.35 (3H, t, $J=7.5$ Hz), 1.35 (1.2H, d, $J=7.5$ Hz), 1.45 (0.8H, d, $J=7.5$ Hz), 1.7—2.3 (2H, m), 2.4—2.8 (6H, m), 3.70 (0.6H, q, $J=7.5$ Hz), 3.73 (0.4H, q, $J=7.5$ Hz), 3.80 (3H, s), 6.6—6.8 (3H, m), 7.05—7.3 (1H, dd, $J=7, 9$ Hz). MS m/e (%): 204 ($\text{M}^+ - \text{EtSOH}$, 6), 134 (100), 121 (10), 105 (9), 91 (15).

6-(3-Methoxyphenyl)-2-phenylsulfinylhexan-3-one (5)—To a THF solution (5 ml) of diisopropylamine (1.01 g), 6.4 ml of *n*-BuLi (10% in hexane) was added under nitrogen at -30 — -40° and the temperature was gradually raised to 0° during 20 min. Then ethyl phenyl sulfoxide (1.54 g) in THF (2 ml) was added dropwise, and after 20 min the ester (1, 0.52 g) was added. The stirring was continued for additional 2 hr and the reaction mixture was worked up as described above to give 0.73 g (88.5%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1700, 1040. NMR (CDCl_3) δ : 1.22 (1.35H, d, $J=6$ Hz), 1.37 (1.65H, d, $J=6$ Hz), 1.6—2.0 (2H, m), 2.3—2.65 (4H, m), 3.74 (1H, q, $J=6$ Hz), 3.80 (3H, s), 6.65—6.8 (3H, m), 7.20 (1H, t, $J=8$ Hz), 7.53 (5H, s). MS m/e (%): 218 ($\text{C}_6\text{H}_5\text{SSC}_6\text{H}_5$, 7), 204 ($\text{M}^+ - \text{C}_6\text{H}_5\text{SOH}$, 7), 134 (100), 121 (9), 110 (25), 104 (9), 91 (8).

6-(3-Methoxyphenyl)hex-1-en-3-one (6)—a) A dioxane-diglyme (1:1) solution (50 ml) of 3 (1.34 g) was refluxed for 4 hr. After removal of the solvent *in vacuo*, the residual pale yellow oil was purified passing through a silica gel column to give 0.87 g (85%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1695 (sh), 1680. NMR (CDCl_3) δ : 1.9—2.15 (2H, m), 2.45—2.8 (4H, m), 3.80 (3H, s), 5.77 (1H, dd, $J=4, 9$ Hz), 6.23 (1H, d, $J=4$ Hz), 6.28 (1H, d, $J=9$ Hz), 6.65—7.2 (4H, m). MS m/e (%): 204 (M^+ , 6), 134 (100), 121 (10), 105 (9), 91 (11).

b) A xylene solution (50 ml) of 4 (1.41 g) was refluxed for 4 hr. The xylene was distilled off *in vacuo* and the residual oil was worked up as described above to yield of 0.55 g (54%) of 6.

c) A benzene solution (5 ml) of 5 (1.65 g) was refluxed for 7 hr. Work-up as described above gave 0.63 g (62%) of 6.

2-(6-3'-Methoxyphenyl-3-oxohexyl)-2-methylcyclopentane-1,3-dione (7)—a) A solution of 6 (204 mg; 1 mmol) and 2-methylcyclopentane-1,3-dione (8, 123 mg; 1.1 mmol) in EtOAc (4 ml) containing 5% Et_3N was stirred at room temperature for 36 hr. The reaction mixture was concentrated *in vacuo* and the residual oil was purified passing through a silica gel column to give 253 mg (80%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1760, 1720. NMR (CDCl_3) δ : 1.08 (3H, s), 1.7—2.0 (4H, m), 2.2—3.0 (10H, m), 3.80 (3H, s), 6.6—6.8 (3H, m), 7.14 (1H, t, $J=8$ Hz). MS m/e (%): 316 (M^+ , 16), 134 (100), 121 (45).

b) A diglyme solution (3.5 ml) of 3 (100 mg; 0.37 mmol) and 8 (55 mg; 0.49 mmol) was heated under reflux for 4.5 hr. Work-up as described above gave 83 mg (70.4%) of 7.

c) A xylene solution (10 ml) of 3 (536 mg; 2 mmol) was refluxed for 4 hr. After removal of the solvent, the residue was dissolved in EtOAc (6 ml) containing Et_3N (0.4 ml), and to the solution 8 (246 mg; 2.2 mmol) was added. The mixture was stirred for 36 hr at room temperature, then the solvent was removed *in vacuo* and the residue was chromatographed to give 447 mg (71%) of 7.

d) A diglyme solution (8 ml) of 4 (282 mg; 1 mmol) and 8 (134 mg; 1.03 mmol) was refluxed for 6 hr. Work-up as described above gave 130 mg (41%) of 7.

5,6,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-7a-methylindane-1,5-dione (9)—a) A diglyme solution (5 ml) of 5 (330 mg; 1 mmol) and 8 (115 mg; 1.03 mmol) was refluxed for 7 hr. After removal of the solvent, the residue was chromatographed on a silica gel column to yield 109 mg (36.6%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$

cm⁻¹: 1740, 1660. NMR (CDCl₃) δ : 1.20 (3H, s), 1.6–2.8 (12H, m), 3.79 (3H, s), 6.5–6.8 (3H, m), 7.14 (1H, t, $J=8$ Hz). MS m/e (%): 298 (M⁺, 45), 164 (100), 134 (66), 121 (90).

b) A diglyme solution (5 ml) of **3** (268 mg; 1 mmol) and **8** (336 mg; 3 mmol) was refluxed for 10 hr. Work-up as described above gave 155 mg (52%) of **9**.

c) A benzene solution (15 ml) of **7** (316 mg) was treated with trifluoroacetic acid (1.5 ml) at 80° for 4 hr. The solution was washed with 5% NaHCO₃, water, and sat. NaCl and dried over Na₂SO₄. The benzene was evaporated and the residual oil was purified by silica gel chromatography to yield 210 mg (70.5%) of **9**.

6-(3-Methoxyphenyl)-2-methyl-2-methylsulfinylhexan-3-one (14)—To a suspension of KH (0.8 g) washed with dry hexane in THF (10 ml), **2** (2.54 g) in THF (10 ml) was added dropwise at 0° under nitrogen. After evolution of hydrogen ceased, MeI (3.4 g) in THF (5 ml) was added and the solution was stirred for 2 hr at room temperature. The reaction mixture was poured into ice-water and extracted with CH₂Cl₂. The extract was washed with water and sat. NaCl, then dried over Na₂SO₄. The solvent was evaporated and residual oil was purified by silica gel column chromatography to give 2.53 g (89.7%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1700, 1040. NMR (CDCl₃) δ : 1.32 (3H, s), 1.54 (3H, s), 1.8–2.1 (2H, m), 2.36 (3H, s), 2.5–2.8 (4H, m), 3.80 (3H, s), 6.65–6.8 (3H, m), 7.20 (1H, t, $J=8$ Hz). MS m/e (%): 218 (M⁺–MeSOH, 8), 134 (100), 121 (13), 103 (13), 91 (2).

6-(3-Methoxyphenyl)-2-methylhex-1-en-3-one (15)—A dioxane solution (30 ml) of **14** (2.82 g) was heated under reflux for 4.5 hr. After evaporation of the solvent, the residue was purified as described above to give 1.95 g (89.4%) of a colorless oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1680. NMR (CDCl₃) δ : 1.85 (3H, d, $J=1$ Hz), 1.75–2.1 (2H, m), 2.61 (2H, t, $J=7$ Hz), 2.70 (2H, t, $J=7$ Hz), 3.78 (3H, s), 5.73 (1H, q, $J=1$ Hz), 5.89 (1H, s), 6.7–6.8 (3H, m), 7.1–7.2 (1H, m). MS m/e (%): 218 (M⁺, 8), 134 (100).

3a,4,5,6,7,7a-Hexahydro-6a,7a β -dimethyl-3a-hydroxy-4-(3-methoxyphenethyl)indane-1,5-dione (17), **2-(6-3'-Methoxyphenyl-3-oxo-2-methylhexyl)-2-methylcyclopentane-1,3-dione (16)**, and **5,6,7,7a-Tetrahydro-6a,7a β -dimethyl-4-(3-methoxyphenethyl)indane-1,5-dione (18)**—a) A EtOAc solution (5 ml) containing 5% Et₃N of **15** (2.18 g) and **8** (1.23 g) was heated at 70° for 7 days. The solution was concentrated and the residual oil was purified by silica gel chromatography to give two fractions. The first fraction was 231 mg (7%) of a colorless oil of **16**. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1760, 1720. NMR (CDCl₃) δ : 1.04 (3H, d, $J=7$ Hz), 1.08 (3H, s), 1.2–2.0 (4H, m), 2.1–2.9 (9H, m), 3.80 (3H, s), 6.6–6.8 (3H, m), 7.20 (1H, t, $J=8$ Hz). MS m/e (%): 330 (M⁺, 1), 178 (8), 134 (100), 121 (28).

The second fraction was 2.31 g (70%) of a colorless oil of **17**. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3500, 1740, 1705. NMR (CDCl₃) δ : 0.95 (3H, d, $J=6$ Hz), 0.96 (3H, s), 1.1–2.9 (12H, m), 3.80 (3H, s), 6.6–6.8 (3H, m), 7.16 (1H, t, $J=8$ Hz). MS m/e (%): 312 (M⁺–H₂O, 29), 178 (65), 134 (49), 121 (100), 91 (99).

b) A CHCl₃ solution (15 ml) of **17** (660 mg) and PPE (2.2 g) was heated under reflux for 4 hr. After the addition of sat. NaHCO₃ (75 ml), the mixture was stirred for 12 hr. The organic layer was dried and evaporated to leave an oil, which was purified by passing through a silica gel column to give 500 mg (80%) of a colorless oil of **18**. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1740, 1660. NMR (CDCl₃) δ : 1.20 (3H, s), 1.20 (3H, d, $J=6.5$ Hz), 1.4–2.9 (10H, m), 3.1–3.4 (1H, m), 3.80 (3H, s), 6.6–6.8 (3H, m), 7.16 (1H, t, $J=8$ Hz). MS m/e (%): 312 (M⁺, 29), 178 (64), 134 (48), 121 (100).

c) A diglyme solution (3 ml) of **14** (296 mg; 1.05 mmol) and **8** (140 mg; 1.25 mmol) was refluxed for 7 hr. Work-up as described above gave 209 mg (60%) of **16**.

d) A diglyme solution (10 ml) of **16** (564 mg; 2 mmol) and **8** (672 mg; 6 mmol) was refluxed for 44 hr. Work-up as described above gave 125 mg (19%) of **16** and 188 mg (30%) of **18**.

11a-Methylisoequilenine Methyl Ether (19) and **11a-Methylequilenine Methyl Ether (20)**—a) A CHCl₃ solution (30 ml) of **18** (624 mg) and PPA (2.0 g) was refluxed for 30 min. After the reaction mixture was washed with sat. NaHCO₃ and water, the organic layer was dried and evaporated to leave a gummy product, which was chromatographed on a silica gel column to give two fractions. The first fraction was a crude solid of **19**, which was recrystallized from MeOH to give 253 mg (43%) of colorless needles, mp 104–106°. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 230 (4.84), 254 (3.94), 264 (3.83), 274 (3.82), 285 (3.60), 304 (3.00), 318 (3.29), 327 (3.25), 334 (3.38). NMR (CDCl₃) δ : 1.28 (3H, s), 1.45 (3H, d, $J=7$ Hz), 1.4–2.5 (6H, m), 3.0–3.3 (1H, m), 3.5–3.8 (1H, m), 3.90 (3H, s), 7.1–7.3 (3H, m), 7.56 (1H, d, $J=8$ Hz), 7.88 (1H, d, $J=10$ Hz). MS m/e (%): 294 (M⁺, 100), 279 (33), 235 (25), 221 (33), 208 (18). Anal. Calcd. for C₂₀H₂₂O₂: C, 81.63; H, 7.48. Found: C, 81.58; H, 7.49.

The second fraction was crude **20**, which was recrystallized from MeOH to give 212 mg (36%) of colorless prisms, mp 142.5–144°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 235 (5.83), 254 (3.79), 265 (3.76), 275 (3.76), 286 (3.57), 307 (3.01), 321 (3.26), 328 (3.25), 335 (3.38). NMR (CDCl₃) δ : 1.13 (3H, s), 1.24 (3H, d, $J=8$ Hz), 1.4–2.7 (6H, m), 3.2–3.3 (1H, m), 3.4–3.8 (1H, m), 3.90 (3H, s), 7.1–7.3 (3H, m), 7.58 (1H, d, $J=8$ Hz), 7.86 (1H, d, $J=10$ Hz). MS m/e (%): 294 (M⁺, 100), 279 (39), 237 (18), 235 (18), 223 (32), 208 (21). Anal. Calcd. for C₂₀H₂₂O₂: C, 81.63; H, 7.48. Found: C, 81.62; H, 7.47.

b) A CHCl₃ solution (15 ml) of **17** (240 mg) and PPA (900 mg) was refluxed for 30 min. Work-up as described above gave 83 mg (38%) of **19** and 65 mg (30%) of **20**.

c) A CHCl₃ solution (5 ml) of **16** (135 mg) and PPA (450 mg) was refluxed for 30 min. Work-up as described above gave 49 mg (41%) of **19** and 40 mg (33%) of **20**.

14-Dehydro-11 α -methylequilenine Methyl Ether (22)—A benzene solution (5 ml) of **19** (28 mg) and DDQ (25 mg) was refluxed for 3 hr. The reaction mixture was washed with 10% NaOH and sat. NaCl, then dried over Na₂SO₄. The organic layer was evaporated *in vacuo* to yield a gummy product, which was chromatographed on silica gel to give 19 mg of crude **22**. Recrystallization from MeOH gave 14 mg of pale yellow plates, mp 140.5–142°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1755, 1620, 1600. NMR (CDCl₃) δ : 1.06 (3H, s), 1.34 (3H, d, $J=5$ Hz), 1.5–2.6 (2H, m), 3.1–3.3 (2H, m), 3.6–3.9 (1H, m), 3.96 (3H, s), 6.23 (1H, t, $J=3$ Hz), 7.1–8.1 (5H, m). MS m/e (%): 292 (M⁺, 100), 264 (95), 249 (91), 234 (38).

Reduction of 22—A EtOH solution (10 ml) of **22** (10 mg) was hydrogenated in the presence of 5% Pd-C (5 mg). The product was chromatographed on a silica gel column to yield 5 mg of **19** and 2 mg of **20**.