Synthetic Approach to (+)-Aldosterone and Its Relatives. 1. Synthesis of (+)-*trans*-4,5-(4-Methoxybenzo)-1β,7aβ-[2α-(methoxymethyl)-5-oxofuro]-hydrindan

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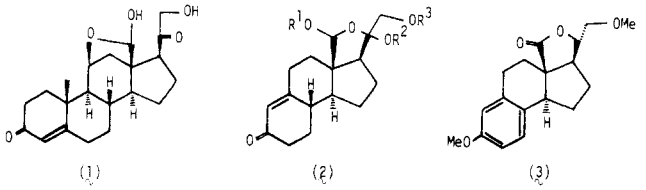
A new method for the synthesis of (+)-*trans*-4,5-(4-methoxybenzo)-1β,7aβ-[2α-(methoxymethyl)-5-oxofuro]-hydrindan (**3**), a potential intermediate for the synthesis of aldosterone (**1**), as an optically pure form is described. The key step is an intramolecular cycloaddition of the *o*-quinodimethane **16**, generated in situ from optically active 4β-[2-(1,2-dihydro-4-methoxybenzocyclobutenyl)ethyl]-4,5-dihydro-5α-(methoxymethyl)-3-[(phenylthio)methylene]furan-2(3*H*)-one (**15**) by a thermolysis. The stereochemical course of this cycloaddition is also discussed.

Much attention[1] has been paid to the synthesis of aldosterone (**1**) because of its physiological importance as a mineral corticoid. In connection with our interest[2] in a total synthesis of steroids by intramolecular cycloaddition of olefinic *o*-quinodimethanes, we planned an asymmetric total synthesis of aldosterone (**1**) through the des-A steroid

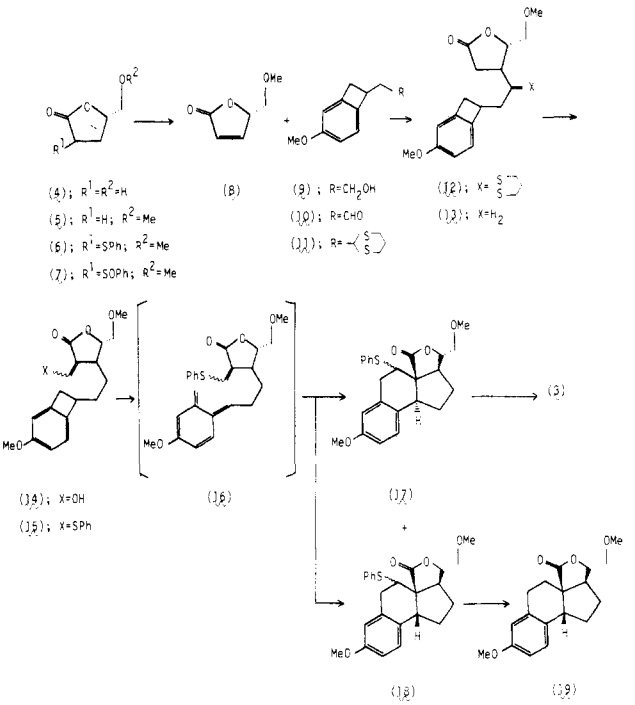


(1) (2) (3)

2, which in turn could be readily prepared from the des-A B-aromatic steroid **3**. Here we wish to report a new method for the synthesis of (+)-*trans*-4,5-(4-methoxybenzo)-1β,7aβ-[2α-(methoxymethyl)-5-oxofuro]hydrindan (**3**) in optically pure form.

The key intermediate **15** for the generation of the olefinic *o*-quinodimethane **16** was prepared as follows. The butenolide **8**, which has been obtained previously[3] from D-(+)-ribonolactone, was prepared more conveniently starting from (*S*)-(+)-γ-(hydroxymethyl)-γ-butyrolactone[4] (**4**) (Scheme I). The methoxymethyl derivative **5**, obtained by methylation (MeI, NaH, DMF, room temperature) of **4** in 60% yield, was converted (PhSSPh, LDA, THF–HMPA, −78 °C) to the phenylthio derivative **6** in 54% yield. After oxidation (MCPBA, CH_2Cl_2, −78 °C) of **6** in 98% yield, the resulting sulfoxide **7** was thermolyzed (toluene, reflux) to give the butenolide **8** (81%), which was identical with an authentic sample prepared by the known method.[3] Also 2-(1,2-dihydro-4-methoxybenzocyclobutenyl)acetaldehyde (**10**), prepared by oxidation (PCC, CH_2Cl_2, room temperature) of alcohol **9**[5] (87% yield), was

Scheme I



converted ($HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temperature) to the corresponding thioacetal **11** (84%), and the thioacetal **12**, obtained in 20% yield by a Michael reaction (*n*-BuLi, THF–HMPA, −78 °C) between **8** and **11**, was hydrogenated (Raney nickel, THF, reflux) to give **13** (44%), which was then transformed (HCO_2Et, NaH, benzene, room temperature) into the hydroxymethylene derivative **14** (68%). Finally, the initial target compound **15** [*m/z* 410 (M^+)] was obtained in 52% yield by successive reactions (MsCl, pyridine, room temperature; PhSH, pyridine, DMAP, room temperature) of the hydroxymethylene derivative.

The thermolysis of the olefinic benzocyclobutene **15** was conducted in *o*-dichlorobenzene at 180 °C for 22 h to afford in 72% yield an inseparable mixture of **17** and **18**, whose IR spectra exhibited an absorption at 1760 cm^{-1} due to the carbonyl group. After desulfurization (Raney nickel, EtOH, reflux) and careful separation of the resulting

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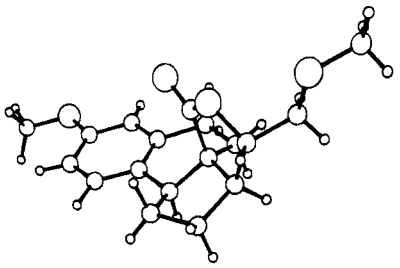
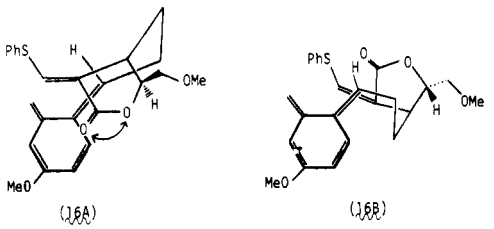


Figure 1.

mixture, the des-A B-aromatic steroids **3** [m/z 302 (M^+)] and **19** were obtained in 17% and 39% yields, respectively. The structure and stereochemistry of **3** and **19** were deduced from the spectral data described in the Experimental Section and unambiguously established by a single-crystal X-ray analysis[6] of **3** (Figure 1).

The stereochemical course of the cycloaddition of **16** can be explained by invoking a greater contribution of **16B** (giving **18**) than **16A** (affording **17**) because of steric re-



pulsion between *o*-quinodimethane and lactone rings in the latter. Thus, a new route for the synthesis of des-A B-aromatic steroid **3**, a potential intermediate for aldosterone (**1**), in an optically pure form has been developed.

Experimental Section

General. Melting points were determined on a Yanagimoto MP-22 apparatus and are uncorrected. Chemical shifts are reported as δ values relative to internal $SiMe_4$. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase "residue upon workup" refers to the residue when the organic layer was separated and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. All new compounds described in this Experimental Section were homogeneous on TLC.

(*S*)-(+)-γ-(Methoxymethyl)-γ-butyrolactone (5). To a suspension of sodium hydride (60% in oil; 1.63 g, 40 mmol) in anhydrous dimethylformamide (40 mL) was added a solution of (*S*)-(+)-γ-(hydroxymethyl)-γ-butyrolactone (**4**) (3.60 g, 31 mmol) in anhydrous dimethylformamide (10 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. To the reaction mixture was then added dropwise methyl iodide (13.2 g, 93 mmol) at 0 °C, after being stirred for 2 h at room temperature. The mixture was diluted with aqueous ammonium chloride and extracted with chloroform, and the extract was washed with saturated aqueous sodium chloride. The residue upon workup was chromatographed with methylene dichloride to afford **5** (2.13 g, 60%) as a colorless oil: $[\alpha]^{20}_D$ +27.90° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 1760 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.79–2.70 (4 H, m, CH_2CH_2), 3.40 (3 H, s, OMe), 3.53 (2 H, d, J = 3 Hz, OCH_2), 4.48–4.75 (1 H, m, OCH); mass spectrum, m/z 130 (M^+). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.33; H, 7.82.

(*S*)-(+)-γ-(Methoxymethyl)-α-(phenylthio)-γ-butyrolactone (6). To a stirred solution of lithium diisopropylamide [from *n*-butyllithium (1.56 M *n*-hexane solution; 3.4 mL, 5.3 mmol) and diisopropylamine (0.8 mL, 5.72 mmol)] in anhydrous tetrahydrofuran (17 mL) was added a solution of **5** (574 mg, 4.4 mmol) in anhydrous tetrahydrofuran (2.5 mL) at −78 °C, and the reaction mixture was stirred for 1 h at the same temperature. After addition of hexamethylphosphoramide (948 mg, 5.3 mmol), diphenyl disulfide (1.16 g, 5.3 mmol) in anhydrous tetrahydrofuran (2.0 mL) was added at −78 °C, and the reaction mixtrure was stirred for 40 min at the same temperature. After being quenched with saturated aqueous ammonium chloride, the mixture was extracted with ether, and the extract was washed with water. The residue upon workup was chromatographed with *n*-hexane–ethyl acetate (5:1, v/v) to yield sulfide **6** (565 mg, 54%) as a colorless oil: $[\alpha]^{20}_D$ +34.24° (*c* 1.76, $CHCl_3$); IR ($CHCl_3$) 1765 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.91–2.50 (2 H, m, SCH=CH_2), 3.33 (3 H, s, OMe), 3.42 (2 H, d, J = 3 Hz, OCH_2), 3.87 (1 H, dd, J = 7, 8 Hz, SCH), 4.21–4.60 (1 H, m, OCH<); mass spectrum, m/z 238 (M^+). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.53; H, 6.17.

(*S*)-5-(Methoxymethyl)furan-2(5*H*)-one (8). To a stirred solution of sulfide **6** (332 mg, 1.39 mmol) in anhydrous methylene dichloride (15 mL) was added a solution of *m*-chloroperbenzoic acid (70%; 288 mg, 1.67 mmol) in anhydrous methylene dichloride (3 mL) at −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was diluted with water (5 mL), and the organic layer was separated. The aqueous layer was extracted with methylene dichloride, and the combined extracts were washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue upon workup was chromatographed with methylene dichloride–chloroform (4:1, v/v) to give sulfoxide **7** (347 mg, 98%) as a colorless oil: $[\alpha]^{20}_D$ +10.12° (*c* 0.086, $CHCl_3$); IR ($CHCl_3$) 1760 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 2.00–2.70 (2 H, m, SCHCH_2), 3.31, 3.42 (3 H, s, each OMe), 3.50, 3.66 (2 H, d, J = 3 Hz, each OCH_2), 4.46–4.90 (1 H, m, OCH), 7.36–7.80 (5 H, m, Ar H); mass spectrum, m/z 254 (M^+).

A solution of sulfoxide **7** (95 mg, 0.39 mmol) in anhydrous toluene (10 mL) was refluxed for 30 min. After removal of the solvent, the residue was chromatographed with methylene dichloride to give butenolide **8** (39 mg, 81%) as a colorless oil: $[\alpha]^{20}_D$ −115.36° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1758 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.30 (3 H, s, OMe), 3.46 (2 H, dd, J = 1, 5 Hz, OCH_2), 4.80–5.06 (1 H, m, OCH), 5.93 (1 H, dd, J = 2, 6 Hz, CHCO), 7.33 (1 H, dd, J = 1.5, 6 Hz, C*H*=CHCO); mass spectrum, m/z 128 (M^+). Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 55.91; H, 6.20.

2-(1,2-Dihydro-4-methoxybenzocyclobutenyl)acetaldehyde (10). To a stirred solution of pyridinium chlorochromate (10.8 g, 50.0 mmol) in anhydrous methylene dichloride (80 mL) was added a solution of 2-(1,2-dihydro-4-methoxybenzocyclobutenyl)ethanol (**9**) (6.0 g, 33.7 mmol) in anhydrous methylene dichloride (20 mL) at room temperature, and the mixture was stirred for 2 h. The mixture was diluted with ether (150 mL) and filtered through Celite. The filtrate was washed successively with water and saturated aqueous sodium hydrogen carbonate. The residue upon workup was chromatographed with *n*-hexane–ethyl acetate (19:1, v/v) to afford aldehyde **10** (5.2 g, 87%) as a colorless oil: IR ($CHCl_3$) 1725 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.66 (3 H, s, OMe), 6.50–6.91 (3 H, m, Ar H), 9.70 (1 H, t, J = 1 Hz, CHO); mass spectrum, m/z 176 (M^+). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.94; H, 6.59.

2-[2-(1,2-Dihydro-4-methoxybenzocyclobutenyl)ethyl]-1,3-dithiane (11). To a stirred solution of aldehyde **10** (417 mg, 2.37 mmol) and 1,3-propanedithiol (307 mg, 2.84 mmol) in methylene dichloride (10 mL) was added a catalytic amount of boron trifluoride–diethyl ether at room temperature, and the mixture was stirred for 3 h. The resulting mixture was then diluted with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with methylene dichloride, and the extract was washed with saturated aqueous sodium chloride. The residue upon workup was chromatographed with *n*-hexane–ethyl acetate (19:1, v/v) to afford thioacetal **11** (528 mg, 84%) as a colorless oil: ^1H NMR (CCl_4) δ 1.95–2.26 (2 H, m, $SCH_2CH_2CH_2S$), 2.70–2.85 (4 H, m, $SCH_2CH_2CH_2S$), 3.71 (3 H, s, OMe), 4.16 (1 H, t, J = 7 Hz, SCHS), 6.52–7.03 (3 H, m, ArH); mass spectrum, m/z 266 (M^+). Anal. Calcd for $C_{14}H_{18}OS_2 \cdot 0.5H_2O$: C, 61.05; H, 6.95. Found: C, 60.95; H, 6.70.

4β-[2-(1,2-Dihydro-4-methoxybenzocyclobutenyl)-1,1-(trimethylenedithio)ethyl]-4,5-dihydro-5α-(methoxymethyl)furan-2(3*H*)-one (12). To a stirred solution of thioacetal **11** (2.7 g, 10.2 mmol) in anhydrous tetrahydrofuran (70 mL) was added *n*-butyllithium (1.56 M *n*-hexane solution; 11 mL, 17.2

(6) Monoclinic, space group $P2_12_12_1$ with a = 12.641 Å, b = 21.758 Å, and c = 5.886 Å; D_c = 1.241 g/cm³ for Z = 4. The final R value was 0.046.

mmol) at −78 °C. After the mixture was stirred for 1 h at −20 °C, hexamethylphosphoramide (4.0 g, 22.3 mmol) and (*S*)-5-(methoxymethyl)furan-2(5*H*)-one (**8**) (1.4 g, 10.9 mmol) in anhydrous tetrahydrofuran (5 mL) were added to the mixture at −78 °C, and the reaction mixture was stirred for 2.5 h at the same temperature. After being quenched with saturated aqueous ammonium chloride (10 mL), the mixture was extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon workup was chromatographed with *n*-hexane–ethyl acetate (5:1, v/v) to afford thioacetal **12** (0.77 g, 19%) as a colorless oil: $[\alpha]^{20}_D$ +1.40° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 1765 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.29 (3 H, s, OMe), 3.70 (3 H, s, OMe), 4.72 (1 H, br s, furanone C(5)HCH_2), 6.51–7.10 (3 H, m, Ar H); mass spectrum, *m/z* 394 (M^+). Anal. Calcd for $C_{20}H_{26}O_4S_2$: C, 60.88; H, 6.64. Found: C, 61.17; H, 6.68.

4β-[2-(1,2-Dihydro-4-methoxybenzocyclobutenyl)ethyl]-4,5-dihydro-5α-(methoxymethyl)furan-2(3*H*)-one (13). To a suspension of Raney nickel (3.5 g) in anhydrous tetrahydrofuran (20 mL) was added a solution of thioacetal **12** (313 mg, 0.79 mmol) in anhydrous tetrahydrofuran (10 mL). The reaction mixture was refluxed for 4 h. After cooling, the mixture was filtered through Celite, and evaporation of the solvent afforded a crude product, which was chromatographed with *n*-hexane–ethyl acetate (5:1, v/v) to afford **13** (102 mg, 44%) as a colorless oil: IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.30 (3 H, s, OMe), 3.74 (3 H, s, OMe), 4.56 (1 H, br s, furnanone C(5)*H*CH_2), 6.52–6.98 (3 H, m, Ar H); mass spectrum, *m/z* 320 (M^+). Anal. Calcd for $C_{17}H_{22}O_4 \cdot 0.5H_2O$: C, 68.20; H, 7.74. Found: C, 67.95; H, 8.10.

4β-[2-(1,2-Dihydro-4-methoxybenzocyclobutenyl)ethyl]-4,5-dihydro-5α-(methoxymethyl)-3-[(phenylthio)-methylene]furan-2(3*H*)-one (15). To a suspension of sodium hydride (60% in oil; 79 mg, 1.98 mmol) in anhydrous benzene (10 mL) was added a solution of **13** (120 mg, 0.38 mmol) in anhydrous benzene (2 mL) at room temperature, and the mixture was stirred for 30 min at the same temperature. To the reaction mixture was then added dropwise ethyl formate (122 mg, 1.65 mmol), and, after being stirred for 1 h at room temperature, the mixture was diluted with water (3 mL), acidified with 10% hydrochloric acid, and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon workup was chromatographed with chloroform to afford hydroxymethylene **14** (90 mg, 68%) as a pale yellow oil: IR ($CHCl_3$) 1780, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.30 (1 H, br s, furanone (5)*H*CH_2), 6.60–7.08 (3 H, m, Ar H); mass specltrum, *m/z* 318 (M^+).

To a stirred solution of hydroxymethylene **14** (90 mg, 0.283 mmol) in anhydrous pyridine (1 mL) was added methanesulfonyl chloride (37 mg, 0.323 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was treated with thiophenol (49 mg, 0.447 mmol) and a catalytic amount of 4-(dimethylamino)pyridine for 4 h at room temperature. The resulting mixture was then diluted with 10% hydrochloric acid and extracted with chloroform, and the extract was washed with aqueous potassium hydrogen sulfate and saturated aqueous sodium chloride. The residue upon workup was chromatographed with benzene to afford (phenylthio)methylene compound **15** (39 mg, 52% from **13**) as a pale yellow oil: IR ($CHCl_3$) 1740 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.37 (3 H, s, OMe), 3.70 (3 H, s, OMe), 4.26 (1 H, br s, furanone C(5)*H*CH_2), 6.52–7.01 (3 H, m, Ar H), 7.22–7.59 (6 H, m, Ar H, SCH=C); mass spectrum, *m/z* 410 (M^+); exact mass calcd for $C_{24}H_{26}O_4S$ 410.1550, found 410.1505.

Thermolysis of 15 and Synthesis of *cis*-4,5-(4-Methoxybenzo)-1β,7aβ-[2α-(methoxymethyl)-5-oxofuro]hydrindan (19) and *trans*-4,5-(4-Methoxybenzo)-1β,7aβ-[2α-(methoxymethyl)-5-oxofuro]hydrindan (3). A solution of benzocyclobutene **15** (25 mg, 0.061 mmol) in *o*-dichlorobenzene (2 mL) was heated at 180 °C for 22 h. After removal of the solvent, the residue was chromatographed with benzene to give an inseparable mixture of **17** and **18** (18 mg, 72%) as a pale yellow oil: IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR (CCl_4) δ 3.42 (3 H, s, OMe), 3.68 (3 H, s, OMe), 6.40–7.05 (3 H, m, Ar H), 7.18–7.58 (5 H, m, Ar H); mass spectrum, *m/z* 410 (M^+). To a suspension of Raney nickel (300 mg) in ethanol (4 mL) was added a solution of the mixture of **17** and **18** (18 mg, 0.044 mmol) in ethanol (1 mL). The reaction mixture was refluxed for 4 h. After cooling, the mixture was filtered through Celite, and evaporation of the solvent afforded a crude product, which was chromatographed with *n*-hexane–ethyl acetate (19:1, v/v) to afford **19** (7 mg, 39%) as an oil: IR ($CHCl_3$) 1758 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.40 (3 H, s, OMe), 3.70 (3 H, s, OMe), 4.03 (1 H, br s, furanone C(5)*H*CH_2), 6.42–7.10 (3 H, m, Ar H); mass spectrum, *m/z* 302 (M^+); exact mass calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1526. From the latter fractions, **3** (3 mg, 17%) was obtained as colorless needles after recrystallization from ethanol: mp 91–92 °C; $[\alpha]^{20}_D$ +57.1° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 1754 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.43 (3 H, s, OMe, 3.80 (3 H, s, OMe), 4.23 (1 H, br s, furanone C(5)*H*CH_2), 6.51–6.98 (3 H, m, ArH); mass spectrum, *m/z* 302 (M^+). Anal. Calcd for $C_{18}H_{22}O_4 \cdot 0.25H_2O$: C, 70.45; H, 7.39. Found: C, 70.00; H, 7.32.

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