CYCLOADDITIONS IN SYNTHESES. XXXVI. 6-HYDROXY-1,2-DIHYDROCYCLOBUTA [a] NAPHTHALENE-2-CARBOXYLIC ACID: A NEW SYNTHON FOR A,B-RING AROMATIZED STEROIDS

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Received October 19, 1987
Revised March 2, 1988

ABSTRACT

A synthetic method of 6-hydroxy-1,2-dihydrocyclobuta-[a]naphthalene-2-carboxylic acid as well as a new methodology for the synthesis of A,B-ring aromatized steroids from its 6-deoxy derivative are elaborated.

INTRODUCTION

Previously, we have synthesized 1,2-dihydrocyclobuta[a]naphthalene-2-carboxylic acid (B) from 2-methoxynaphthalene via photoaddition to acrylonitrile

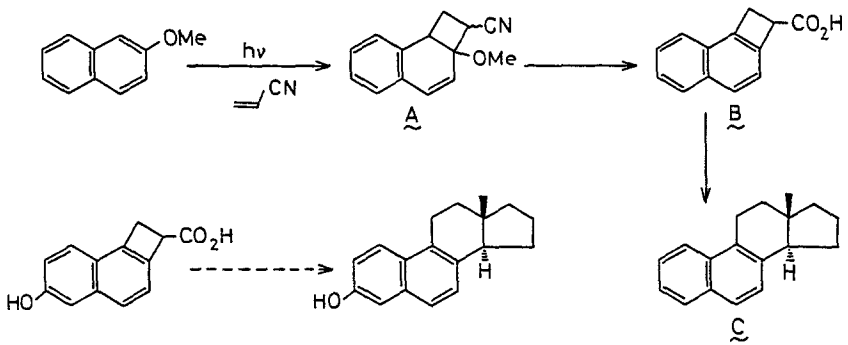

Chart 1

followed by elimination of methanol from the adduct (A) by base (1). In this paper, we wish to report on (i) successful conversion of B to A,B-ring aromatized steroidal compound (C: C/D-trans) and (ii) synthesis of 6-hydroxy derivative of B, which would serve as a new synthon for these steroids.

EXPERIMENTAL

All melting points were determined on a micro-hot stage (Yanagimoto Ltd., Tokyo) and are uncorrected. Infrared (IR) spectra were recorded on an A-102 spectrometer (Jasco Inc., Tokyo), ultraviolet (UV) spectra with a 320 spectrometer (Hitachi Ltd., Tokyo), and ^{1}H-NMR spectra on a JNM-PMX 60 SI or JNM-FX-100 spectrometer (JEOL Inc., Tokyo) with tetramethylsilane as an internal standard. Mass spectra (MS) were taken either with a Hitachi M-52 spectrometer or with a JEOL JMS-01SG-2 spectrometer. The photoreactions were carried out using Rayonet Photochemical Reactor (RPR 3500 Å, The Southern New England Ultraviolet Company, Hamden, Conn.).

Methyl 2-(4-Methyl-4-pentenyl)-1,2-dihydrocyclobuta[a]naphthalene-2-carboxylate (2). Sodium hydride (60% oil dispersion, 53 mg, 1.34 mmol) was added with stirring to an ice-cooled solution of methyl 1,2-dihydrocyclobuta[a]naphthalene-2-carboxylate (1, 189 mg, 0.89 mmol) (1) and 4-methyl-4-pentenyl iodide (281 mg, 1.34 mmol) in dimethylformamide (DMF, 3 mL). The whole was stirred under ice-cooling for 1 h and then at room temperature for 30 min. The mixture was acidified with 5% hydrochloric acid and extracted with ether. The organic layer was washed with water and dried over magnesium sulfate. The residue obtained after evaporation of the solvent was chromatographed [silica gel, hexane-ether (20:1)] to give 158 mg (60%) of 2 as an oil. IR($CHCl_3$): 1725, 1770 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.13-2.08(6H, m), 1.67(3H, br s), 3.27(1H, d, J=14 Hz), 3.67(3H, s), 3.85(1H, d, J=14 Hz), 4.85(2H, br s), 7.13-8.08(6H, m). High-resolution MS m/z:M^+ Calcd for $C_{20}H_{22}O_2$: 294.1639. Found: 294.1658.

Methyl (13S', 14R')-13-Methyl-12,13,14,15,16,17-hexahydro-11H-cyclopenta[a]phenanthrene-14-carboxylate (3). A solution of 2 (80 mg, 0.27 mmol) in o-dichlorobenzene (10 mL) was refluxed for 3 h 15 min. The residue obtained after evaporation of the solvent was separated by preparative thin-layer chromatography (TLC) (benzene) to give 47 mg (59%) of 3 as an oil. IR($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08(3H, s), 0.90-3.30(10H, m), 3.55(3H, s), 6.95-8.13(6H, m). High-resolution MS m/z:M^+ Calcd for $C_{20}H_{22}O_2$: 294.1637. Found: 294.1620.

(13S', 14R')-13-Methyl-12,13,14,15,16,17-hexahydro-11H-cyclopenta[a]phenanthrene-14-carboxylic Acid (4). A solution of 3 (75 mg, 0.26 mmol) and potassium hydroxide (3 g) in methanol (4 mL) was refluxed for 4.5 h. After removal of the solvent, the residue was acidified with 10% hydrochloric acid and extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. The residue obtained after evaporation of the solvent was chromatographed [silica gel, hexane-ethyl acetate (1:1)] to give 71 mg (100%) of 4 as colorless prisms (from ether-hexane). mp 189-191 °C. IR($CHCl_3$): 2960, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14(3H, s), 0.79-3.80(10H, m), 7.10-8.23(6H, m), 10.05(1H, br s). High-resolution MS m/z: M^+ Calcd for $C_{19}H_{20}O_2$: 280.1480. Found: 280.1467.

13-Methyl-12,13,16,17-tetrahydro-11H-cyclopenta[a]-phenanthrene (5). Lead tetraacetate (131 mg) was added to a solution of 4 (85 mg, 0.3 mmol) in dry benzene (4.0 mL), and the mixture was refluxed for 1 h 10 min under an argon atmosphere. The precipitate was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was chromatographed (silica gel, 1% ether-hexane) to give 30 mg (42%) of 5 as colorless needles. mp 89-90 °C (from methanol) (2). UV λmax(MeOH): 253, 262, 283, 293, 304 nm. ^{1}H-NMR($CDCl_3$) δ: 1.07(3H, br s), 1.20-3.43(8H, m), 6.12(1H, t, J=3 Hz), 7.26-8.20(6H, m). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{18}$: 234.1385. Found: 234.1408.

13-Methyl-12,13,14,15,16,17-hexahydro-11H-cyclopenta[a]phenanthrene (6). A mixture of 5 (25 mg, 0.11 mmol) and 10% Pd-C (10 mg) in methanol (4 mL) was shaken in hydrogen under atmospheric pressure for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 21 mg (83%) of 6 as colorless needles (from methanol). mp 71-72 °C (2). ^{1}H-NMR($CDCl_3$) δ: 0.67(3H, s), 1.03-3.53(11H, m),

7.20-8.20(6H, m). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{20}$: 236.1543. Found: 236.1565.

2-Acetoxy-6-methoxynaphthalene (7). 2-Hydroxy-6-methoxynaphthalene (1.8 g, 10.3 mmol)(3) was acetylated by a usual manner. Recrystallization from ether-hexane gave 1.9 g (85%) of 7 as needles of mp 106-106.5 °C. IR($CHCl_3$): 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32(3H, s), 3.89(3H, s), 7.01-7.86(6H, m). MS m/z: 216(M^+), 174,159,131. Anal. Calcd for $C_{13}H_{12}O_3$: C,72.21; H,5.59. Found: C, 72.10; H,5.71.

6-Acetoxy-2-naphthol (8). A solution of potassium hydroxide (448 mg, 8 mmol) in methanol (20 mL) was added dropwise to a stirred and ice-cooled solution of 2,6-diacetoxynaphthalene (2.44 g, 10 mmol)(4) in tetrahydrofuran (100 mL). The mixture was stirred for 5 min and acidified with 10% hydrochloric acid. The solvents were evaporated off and the residue was collected by suction, washed with water, and dried. Recrystallization from dichloromethane-hexane gave 1.46 g (72%) of 8 as needles of mp 153-154 °C. IR($CHCl_3$): 3580, 1750 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.33(3H, s), 5.34(1H, br s), 6.87-7.73 (6H, m). MS m/z: 202(M^+). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.41; H, 4.93.

6-Acetoxy-2a-methoxy-1,2,2a,8b-tetrahydrocyclobuta-[a]naphthalene-2-carbonitrile (9). A solution of 7 (432 mg, 2 mmol) and acrylonitrile (10.6 g, 0.2 mol) in methanol (300 ml) was irradiated for 4 h. The residue obtained after evaporation of the solvent was chromatographed [silica gel, hexane-ethyl acetate (5:1)] to give 442 mg (83%) of 9 as an oil. The ^{1}H-NMR spectrum indicated that this sample was a mixture of two stereoisomers (endo/exo=3:1). IR($CHCl_3$): 2240, 1750 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ:1.5-2.7(2H, m), 2.30(3H, s), 3.10(3H, s), 3.0-4.1(2H, m), 5.95(1H, dd, J=10.0, 1.5 Hz), 6.8-7.4(4H, m). High-resolution MS m/z: M^+ Calcd for $C_{16}H_{15}NO_3$: 269.1051. Found: 269.1042.

2a,6-Dimethoxy-1,2,2a,8b-tetrahydrocyclobuta[a]naphthalene-2-carbonitrile (11a). A mixture of 9 (538 mg, 2 mmol), conc. ammonia (4 mL) and methanol (20 mL) was stirred at room temperature for 1 h. Evaporation of the solvent gave 474 mg (quantitative) of 10 as an oil. The mixture of 10 (77 mg, 0.34 mmol), iodomethane (920 mg, 6.5 mmol), potassium carbonate (1.53 g, 11 mmol), and acetone (5 mL) was refluxed with stirring for 1 h. The mixture was diluted with ether and washed with water. The organic layer was dried over magnesium sulfate and condensed. The residue was purified by preparative TLC

to give 65.5 mg (80%) of a mixture of stereoisomers (endo-11a: exo-11a=4:1) as an oil. IR($CHCl_3$): 2240 cm^{-1}. MS m/z: 241(M^+). ^{1}H-NMR($CDCl_3$) δ: 5.89(dd, J=9.5, 1.5 Hz, C_3H of endo-11a), 5.68(dd, J=9.5, 1.5 Hz, C_3H of exo-11a). High-resolution MS m/z: M^+ Calcd for $C_{15}H_{15}NO_2$: 241.1103. Found: 241.1121.

6-Benzyloxy-2a-methoxy-1,2,2a,8b-tetrahydrocyclobuta[a]naphthalene-2-carbonitrile(11b). Following the procedure given for 11a, compound 10 (474 mg, 2,1 mmol) was alkylated with benzyl bromide. Purification by column chromatography [silica gel, hexane-ethyl acetate (5:1)] gave 607 mg (91%) of a mixture of stereoisomers (endo-11b: exo-11b=5:1) as a solid. The major isomer was purified by recrystallization from hexane-ether. mp 85-86 °C (needles). IR($CHCl_3$): 2240 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ:1.73(1H, t, J=10 Hz), 3.07(3H, s), 3.38(1H, t, J=10.0 Hz), 3.53(1H, dt, J=10.0, 1.5Hz), 5.06(2H, s), 5.91(1H, dd, J=10, 1.5 Hz), 6.67-7.63(9H, m). High-resolution MS m/z: M^+ Calcd for $C_{20}H_{17}NO_2$: 317.1416. Found: 317.1372.

6-Methoxy-1,2-dihydrocyclobuta[a]naphthalene-2-carbonitrile (12a). A mixture of 11a (53.2 mg, 0.22 mmol), potassium tert-butoxide (74 mg, 0.66 mmol), and dry benzene (2 mL) was refluxed with stirring for 10 min. The mixture was acidified with 10% hydrochloric acid, diluted with chloroform, and washed with water. The organic layer was dried over magnesium sulfate. The residue obtained after evaporation of the solvent was purified by preparative TLC [hexane-ethyl acetate (10:1)] to give 8.5 mg (18%) of 12a as needles of mp 116.5-117 °C (from hexane). IR($CHCl_3$): 2240 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.74-4.12(2H, m), 3.92(3H, s), 4.35(1H, t, J=4.0 Hz), 7.10-7.87(5H, m). High-resolution MS m/z: M^+ Calcd for $C_{14}H_{11}NO$: 209.0841. Found: 209.0863.

6-Benzyloxy-1,2-dihydrocyclobuta[a]naphthalene-2-carbonitrile (12b). Following the procedure given for 12a, compound 11b (95 mg, 0.3 mmol) was treated with the base to give 23.6 mg (28%) of 12b as needles of mp 151-152°C (from ether). IR($CHCl_3$): 2250 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.72-3.92(2H, m), 4.35(1H, t, J=4.0 Hz), 5.18(2H, s), 7.15-7.85(10H, m). Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found; C, 84.25; H, 5.32; N, 5.01.

Methyl 6-Acetoxy-2a-hydroxy-1,2,2a,8b-tetrahydrocyclobuta[a]naphthalene-2-carboxylate (13). A solution of 8 (606 mg, 3 mmol) and methyl acrylate (25.8 g, 0.3 mol) in methanol (600 mL) was irradiated for 5 h. The solvent was evaporated off, and the residue was

purified by chromatography [silica gel, hexane-ethyl acetate (3:1)] to give 487 mg (56%) of 13 as crystals. The ^{1}H-NMR spectrum indicated that this sample was a mixture of two stereoisomers (endo-13: exo-13=5:1). Recrystallization from ether gave pure endo-13 as needles of mp 129.5-130 °C. IR($CHCl_3$): 3580, 1755, 1735 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.62(1H, brs), 1.73-2.41(2H, m), 2.30(3H, s), 3.53(1H, dd, J=11.0, 9.0 Hz), 3.43-3.67(1H, m), 3.73(3H, s), 5.79(1H, dd, J=9.5, 1.5 Hz), 6.64(1H, d, J=9.5 Hz), 6.81-7.23(3H, m). MS m/z: 288(M^+). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.36; H, 5.45.

Methyl 6-Acetoxy-1,2-dihydrocyclobuta[a]naphthalene-2-carboxylate (14). Triethylamine (242 mg, 2.4 mmol) was added dropwise to a stirred solution of 13 (86.4 mg, 0.3 mmol) and methanesulfonyl chloride (69 mg, 0.6 mmol) in dichloromethane (5 mL) under ice-salt cooling. Stirring was continued for 1 h at ice-salt cooling temperature and then at room temperature for 1 h. The mixture was diluted with chloroform, washed with 10% hydrochloric acid, and then with 10% sodium carbonate solution. The organic layer was dried over magnesium sulfate. The solvent was evaporated off, and the residue was purified by prepartaive TLC (dichloromethane) to give 14 (32 mg, 40%) and 16 (oil, 30 mg, 37%). 14. mp 77-78 °C (from ether-hexane). IR($CHCl_3$): 1750, 1728 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.33(3H, s), 3.69(2H, d, J=3.5 Hz), 3.75(3H, s), 4.43(1H, t, J=3.5 Hz), 7.13-7.88(5H, m). MS m/z: 270(M^+). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.20; H, 5.27. 16. mp 72-73 C (from pentane). IR($CHCl_3$): 1760, 1720 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.35(3H, s), 3.85(3H, s), 6.02, 6.44(each 1H, d, J=1.5 Hz), 7.12-8.00(6H, m). High-resolution MS m/z: M^+ Calcd for $C_{16}H_{14}O_4$: 270.0891. Found: 270.0909.

6-Hydroxy-1,2-dihydrocyclobuta[a]naphthalene-2-carboxylic Acid (15). Compound 14 (26.3 mg 0.12 mmol) was stirred in 5% sodium hydroxide solution at room temperature for 30 min. The solution was acidified with 10% hydrochloric acid and extracted with ether. The oragnic layer was dried over magnesium sulfate. The solvent was evaporated off, and the residue was recrystallized from ethyl acetate to give 24.1 mg (94%) of 15 as needles of mp 197-198 °C. IR(KBr): 3400, 1690, 1600 cm^{-1}. ^{1}H-NMR($CDCl_3/CD_3COCD_3$, 3/1) δ: 3.57(2H, J=3.5 Hz), 4.34(1H, t, J=3.5 Hz), 6.98-7.77(5H, m). High-resolution MS m/z :M^+ Calcd for $C_{13}H_{10}O_3$: 214.0630. Found: 214.0620.

RESULTS AND DISCUSSION

As reported already (1), 2-(4-methylpent-4-enyl) derivative (2) of the naphthocyclobutene-2-carboxylate (1) afforded upon heating in o-dichlorobenzene C/D-cis tetracyclic compound (3-cis), almost exclusively. In order to construct the C/D-trans steroidal skeleton, it is necessary not only to effect decarboxylation at the 14-position in the corresponding acid (4-cis), but also to convert C/D-cis juncture to trans. These two requirements were simultaneously satisfied by the use of oxidative decarboxylation/Kochi reaction (5) and subsequent hydrogenation. Thus, when the acid (4-cis) was subjected to the reaction [$Pb(OAc)_4$/benzene/reflux], 14-ene (5) (2) was obtained in 42% yield

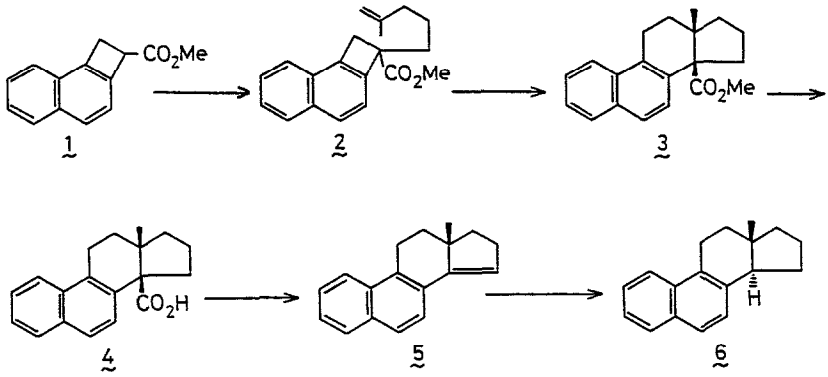

Chart 2

(6). Catalytic hydrogenation of 5 then afforded C/D-trans isomer (6) in almost quantitative yield (7). This fact reveals that the sequential reactions shown in Chart 2 provide a new methodology for the synthesis of A,B-ring aromatized steroids, if the 6-hydroxy derivative of 1 can be synthesized. This aim was achieved by the routes as described below.

Akhtar and McCullough reported that irradiation of 2,6-dimethoxynaphthalene and acrylonitrile resulted in the expected 2+2 adduct (8). However, the yield of the adduct was low (ca. 20% based on the consumed naphthalene), even if the reaction was terminated at the point of ca. 1/3 consumption of the naphthalene. Two derivatives of naphthalene-2,6-diol, however, were found to photoadd efficiently to both acrylonitrile and methyl acrylate. These are (a) acetate (7) of 6-methoxy-2-naphthol and (b) mono-acetate (8) of the diol. Though the photoaddition reactions of 7 and 8 with the olefins proceed efficiently, it is noteworthy that the adducts obtained are unstable to the irradiation and hence, the addition reactions should be terminated at ca. 70% consumption of the starting naphthalenes. The poor yield of the adduct of 2,6-dimethoxynaphthalene to acrylonitrile reported by Akhtar and McCullough (8) is

probably due to the same photo-instability (9). Two methods that provide effective routes to the desired compound are termed as a and b, depending upon the starting materials (7 and 8) used.

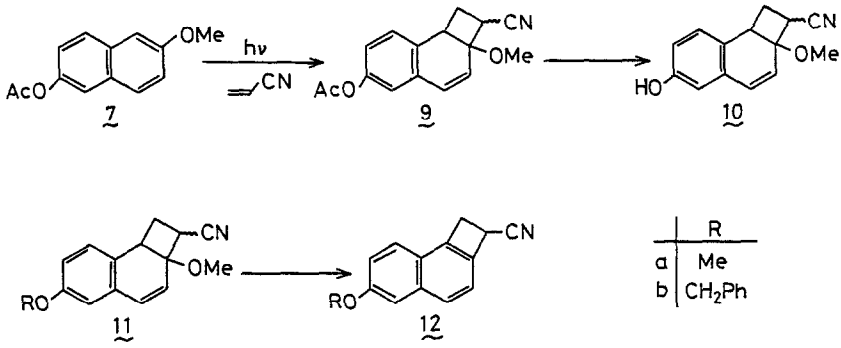

Chart 3

In method a, irradiation of 7 in methanol containing 100 mol equivalents of acrylonitrile afforded the adduct (9) as a mixture of endo- and exo-isomers (ratio of endo/exo ca. 3:1) in 83% yield. The phenol (10) obtained by hydrolysis of 9 with aqueous ammonium hydroxide was alkylated under usual manner (RX/K_2CO_3/reflux) to give the ethers (11a and 11b). Treatment of 11 with base (t-BuOK/benzene/reflux) gave the naphthocyclobutene-2-carbonitriles (12a and 12b) in ca. 40% yields, respectively.

The use of the adduct (13) obtained from 8 in ca.

85% yield provides a more direct route to the desired compound (method b). Thus, when the adduct (13) was mesylated (MsCl/triethylamine/CH_2Cl_2), the naphthocyclobutene (14) was obtained in 40% yield. Hydrolysis of 14 led to unprotected hydroxycarboxylic acid (15) in a quantitative yield. In this mesylation reaction, 2-(2-naphthyl)acrylate derivative (16) was formed as the by-

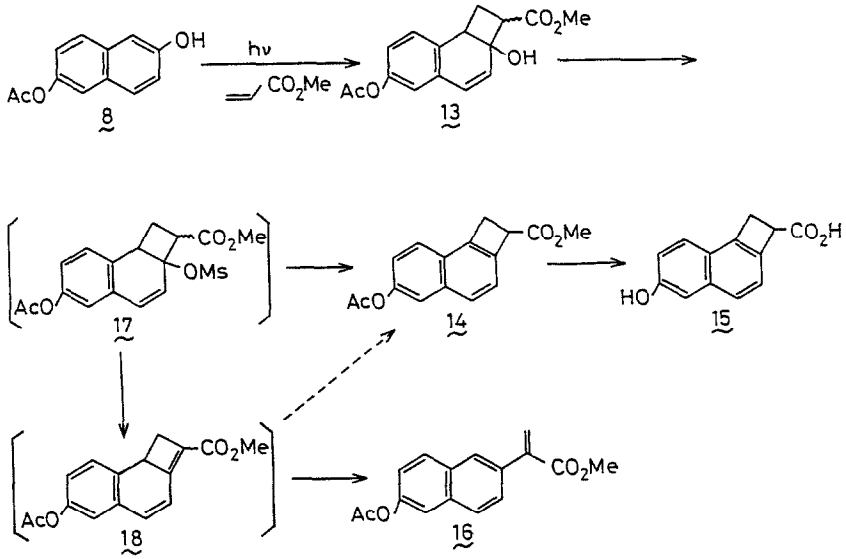

Chart 4

product. Formation of 16 is best explained by assuming 18 as the intermediate.

In conclusion, we have elaborated a new methodology to construct A,B-ring aromatized steroid carbon-skeleton compound (6), which is characterized not only

by the use of naphtho[a]cyclobutene-2-carboxylic acid (4) as the key intermediate, but also by the use of oxidative decarboxylation as the key reaction. A new synthon/6-hydroxy derivative (15) of 4, which would enable an introduction of a hydroxyl group at the 3-position in the final compound (essential requisite for the steroids), was also synthesized.

ACKNOWLEDGMENT

This work was supported in part by Ministry of Education, Science and Culture, Japan.

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6. This oxidative decarboxylation reaction proceeds smoothly, irrespective of the stereochemistry of 4. Hence, the methodology shown in Chart 2 should have wide applicability to construct C/D-trans compound either from C/D-cis or-cis, trans mixture having a carboxylic acid at the 14-position.

7. A small amount of the C/D-cis isomer (less than 1/10 to the trans isomer) was also formed, because NMR spectrum of the residue obtained after recrystallization of the product (pure 6) from methanol showed a methyl signal at δ 1.10.
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9. Though the photoadduct previously obtained from 2-methoxynaphthalene and acrylonitrile partly reverted to the original naphthalene when irradiated (300 nm) in the absence of the acrylate, the adducts (9 and 13) merely decomposed to tarry materials without such photo-cycloreversion.