Preparation of a Tricyclic A-Ring Analog of Quassin

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(±)-3-Methoxy-1α,4αβ,8αβ-trimethyl-1,4,4a,6,7,8,8a,9,10,10α-decahydrophenanthrene-4,8-dione, a tricyclic A-ring analog of quassin, was synthesized from a known tricyclic ketone through seven reaction steps, including phenylselenation in a neutral medium and the Wharton reaction.

Keywords—synthesis; quassinoid; Wharton reaction; 1,3-carbonyl transposition; phenylselenation

In the course of our synthetic studies on quassinoids, an easily available tricyclic hydroxy ketone (1) has been used as a key intermediate.1,2) The hydroxyl group of 1 was utilized to construct the D-ring of the picrasane skeleton (2) and to functionalize the C- and D-rings. On the other hand, the carbonyl group at the C-33) position is considered to provide a foothold for A-ring functionalization. We have already obtained 12β-hydroxyopicrasan-3-one (3) on the synthetic route to quassin (4) from 1.2) The next step of this synthetic study would be a transposition of the carbonyl group from the C-3 to the C-1 position. A number of procedures for 1,3-carbonyl transposition have already been developed.4) 17β-Hydroxy-5α-androst-1-en-3-one was converted into 2-methoxy-4α-methyl-5α-androst-2-ene-1,17-dione5) by successive reactions including the Wharton reaction.6) This paper deals with a method for preparation of a tricyclic A-ring analog (5) of quassin from the hydroxy ketone (1).

A transformation of 1 into the 1α,2α-epoxy ketone (6)3) was initially attempted by the use of successive reactions: namely, i) protection of the hydroxyl group at C-14 with methoxy-methyl ether, ii) the Birch reduction, iii) phenylselenation of the C-2 position with lithium disopropylamide/benzeneselenenyl chloride, and then iv) treatment with alkaline hydrogen peroxide.7) However, the yield of the phenylselenation reaction in the third step was found to be poor (the best yield: 43%,) and more than half of the starting material was recovered even when hexamethylphosphoric triamide was added to the reaction solution. Sharpless et al. reported that cholestan-3-one was transformed into cholest-1-en-3-one by utilizing a substitution reaction of the phenylselenenyl group followed by oxidation–elimination reaction in a neutral medium.8) This substitution reaction of the phenylselenenyl group under neutral conditions was now examined. The hydroxy ketone (7), obtained from 1 by Birch reduction (88% yield), was stirred with 1.2 mol equivalent of benzeneselenenyl chloride in ethyl acetate.
followed by addition of pyridine and m-chloroperbenzoic acid to afford the \( \alpha,\beta \)-unsaturated ketone (8) in 80% yield. When the 14-\( O \)-methoxymethyl analog of 7 was subjected to the same reaction, the corresponding \( \alpha,\beta \)-unsaturated ketone was obtained in ca. 27% yield. Epoxidation of the \( \alpha,\beta \)-unsaturated ketone (8) was carried out with alkaline hydrogen peroxide to give the epoxide (9) in 83% yield. Treatment of 9 with hydazine hydrate afforded the allylic alcohol (10) by the Wharton reaction. The Collins oxidation of 10 gave a diketone (11) in 38% yield from 9. Epoxidation of 11 was carried out under the same conditions as used for 8 to give the epoxide (12) in 73% yield. A mixture of 12 and sodium methoxide in methanol was refluxed under a nitrogen atmosphere to afford the title compound (5) in 50% yield. Overall yield of 5 from 1 was 8.1%.

**Experimental**

**General Procedures**—All melting points were determined on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. Ultraviolet absorption (UV) and infrared (IR) spectra were measured on Hitachi 340 and Hitachi 260-30 spectrometers, respectively. Mass spectra (MS) were run on a JEOL JMS-D300 mass spectrometer operating at 70 eV. Proton nuclear magnetic resonance (\( ^1 \)H-NMR) spectra were taken using a Varian EM390 (90 MHz) spectrometer. Chemical shifts are expressed in \( \delta \) (ppm) downfield from tetramethylsilane as an internal standard and coupling constants in Hz. Thin-layer chromatography (TLC; including preparative) was carried out on Kieselgel 60 GF254 (0.25 mm thickness). Wakogel C-200 (Wako) and Florisil (100—200 mesh) were used for column chromatography. High-performance liquid chromatography (HPLC) was carried out with an NPDX-8 pump (Nihon Seimitsu Kagaku Co.) and an ERC-7520 type RI detector (Erma Optical Works) using a YMC-Pack A-012 SIL column. All the samples taken for high resolution MS were pure on TLC and/or HPLC examination.

\( \alpha,\beta \)-Hydroxy-1,4a,8a-\( \beta \)-trimethyl-1,2,4a,6,7,8,8a,9,10,10a,12-decahydrophenanthren-2-one (7)—At \(-78^\circ \text{C}, \) dry liquid ammonia (100 ml) was added to lithium (400 mg) under a nitrogen atmosphere, and the whole was stirred for 30 min to form a solution. A solution of \( \alpha,\beta \)-unsaturated ketone (1; 3.96 g) in tetrahydrofuran (50 ml) was added and the mixture was refluxed for about 1 h. After addition of ammonium chloride, ammonia was evaporated off, and the reaction mixture was extracted with chloroform as usual to afford a ketone (7; 3.52 g; 88% yield): white crystals, mp 152.5-154.5\(^\circ \text{C} \) (recrystallized from chloroform–hexane). IR (KBr) 3520, 1700 cm\(^{-1} \). \( ^1 \)H-NMR (CDCl\(_3\)) \( \delta = 1.00 \) (3H, d, \( J = 7 \) Hz), 1.18 (3H, s), 1.31 (3H, s), 3.41 (1H, dd, \( J = 9,8 \) Hz), 5.38 (1H, t, \( J = 4 \) Hz). MS \( m/z \) (rel. intensity) 262 (M\(^+\), 8), 247 (7), 244 (70), 218 (100), 203 (67). High-resolution MS. Found: m/z 262.1945. Calcd for C\(_{17}\)H\(_{26}\)O\(_2\): M, 262.1933. Anal. Found: C, 77.47; H, 10.04. Calcd for C\(_{17}\)H\(_{26}\)O\(_2\): C, 77.82; H, 9.99.

\( \alpha,\beta \)-Hydroxy-1,4a,8a-\( \beta \)-trimethyl-1,2,4a,6,7,8,8a,9,10,10a,12-decahydrophenanthren-2-one (8)—Benzene-selenenyl chloride (2.94 g, 1.2 eq) was added to a solution of the keto alcohol (7; 3.36 g) in dry ethyl acetate (50 ml) at 0\(^\circ \text{C} \), and the mixture was stirred at room temperature for 2 h. When the color of the solution changed from brown into yellow, a saturated aqueous solution of sodium hydrogen carbonate was added to bring the solution to pH >7, and most of the aqueous layer was removed. Pyridine (2.6 ml) and m-chloroperbenzoic acid (6.9 g; 2.5 eq) were added to the organic layer. After being stirred for 30 min at 40—50\(^\circ \text{C} \), the reaction mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate and saturated brine successively, and dried (MgSO\(_4\)). After removal of the solvent, the resulting yellow oily product was crystallized from hexane–ether to give a white
crystalline compound (8; 2.67 g; 80% yield). 8: white needles, mp 151—153°C (recrystallized from chloroform-hexane). UV (EtOH) 235 nm (ε 11000). IR (KBr) 3540, 1675 cm⁻¹. ¹H-NMR (CDCl₃) δ = 1.14 (3H, d, J = 7 Hz), 1.20 (3H, s), 1.32 (3H, s), 3.42 (1H, dd, J = 8, 7 Hz), 5.57 (1H, t, J = 4 Hz), 5.81 (1H, d, J = 10 Hz), 7.29 (1H, d, J = 10 Hz). MS m/z (rel. intensity) 260 (M⁺, 66), 242 (75), 216 (40), 201 (100). High resolution MS. Found: m/z 260.1769. Caled for C₁₇H₂₄O₂: M, 260.1774. Anal. Found: C, 75.54; H, 9.16. Caled for C₁₇H₂₄O₂·H₂O: C, 75.80; H, 9.35.

(±)-3x,4x-Epoxy-8x-hydroxy-1x,4a,8x-β-trimethyl-1,2,3,4,4a,6,7,8,8a,9,10,10az-decayohydrophenanthrene-2-one (9)—A 30% aqueous solution (23 ml) of hydrogen peroxide in methanol (50 ml) was added dropwise at 0°C to a mixture of the α,β-unsaturated ketone (8; 2.67 g) in tetrahydrofuran (200 ml) and 2M aqueous sodium hydroxide (30 ml), and the mixture was stirred at room temperature for 3h. After addition of a saturated aqueous solution of sodium sulfite at 0°C and then a 5% aqueous solution of sodium hydroxide, the organic solvents were evaporated off and the residue was extracted with ether. The ethereal extract was treated as usual to afford the epoxy ketone (9; 2.33 g; 83% yield): white crystals, mp 132—134°C (recrystallized from chloroform). IR (KBr) 3450, 1705, 1100, 1075, 1010, 990, 900 cm⁻¹. ¹H-NMR (CDCl₃) δ = 1.15 (3H, d, J = 6 Hz), 1.17 (6H, s), 3.32 (1H, d, J = 4 Hz), 3.48 (1H, t, J = 7.5 Hz), 3.77 (1H, d, J = 4 Hz), 5.78 (1H, t, J = 3 Hz). MS m/z (rel. intensity) 276 (M⁺, 10), 258 (45), 232 (100). High resolution MS. Found: m/z 276.1768. Caled for C₁₇H₂₄O₂: M, 276.1726. Anal. Found: C, 71.74; H, 9.89. Caled for C₁₇H₂₄O₂·H₂O: C, 71.55; H, 9.99.

(±)-1x,4aβ,8aβ-Trimethyl-1,4,4a,6,7,8,8a,9,10,10az-decayohydrophenanthrene-4x,8x-diol (10)—Hydrate hydrate (6 ml) was added to the epoxy ketone (9; 493 mg), and the mixture was heated for 1h at 150—160°C (bath temperature) under a nitrogen atmosphere. After the addition of saturated brine at 0°C, chloroform extraction was carried out as usual to give the allylic alcohol as a crude oil (10; 474 mg). The crude oily compound (10) was used for the next oxidation reaction without purification. On the other hand, to obtain pure 10, a part of this crude oil (36 mg) was charged on top of a silica gel (2 g) column. Elution with hexane-ethyl acetate (1 : 1) gave 12 mg of the pure allylic alcohol (10): pale yellow crystals, mp 150—151.5°C (recrystallized from chloroform-hexane). IR (KBr) 3380, 1640 cm⁻¹. ¹H-NMR (CDCl₃) δ = 1.05 (3H, d, J = 7 Hz), 1.06 (3H, s), 1.14 (3H, s), 1.30 (1H, t, J = 8 Hz), 4.03 (1H, d, J = 4.5 Hz), 5.47 (1H, t, J = 4 Hz), 5.73 (2H, m). MS m/z (rel. intensity) 262 (M⁺, 19), 244 (49), 229 (13), 226 (14), 211 (21), 134 (100). High resolution MS. Found: m/z 262.1961. Caled for C₁₇H₂₆O₂: M, 262.1933. Anal. Found: C, 77.58; H, 9.98. Caled for C₁₇H₂₆O₂·H₂O: C, 77.82; H, 9.99.

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3) Numberings of most of the compounds described in the main text are adopted from those of the picrasane skeleton (2). All the synthetic compounds are racemic; only one enantiomer is shown for convenience.


