HETEROSTEROIDS VIA ORGANOIRON COMPLEXES: A SIMPLE ROUTE TO 6-OXA AS WELL AS 6-KETO-6a-OXA-D-HOMO-AROMATIC STEROIDS

Enrico Mincione, Paolo Bovicelli, and Maria Luigia Forcellese

Centro di Studio per la Chimica delle Sostanze Organiche Naturali del C.N.R., c/o Dipartimento di Chimica dell' Universita' di Roma "La Sapienza", Piazzale Aldo Moro, 5 - 00185 Rome, Italy

Abstract - A simple route via organoiron complexes to 6-oxa as well as 6-keto, 6a-oxa D-homo-aromatic steroids is reported.

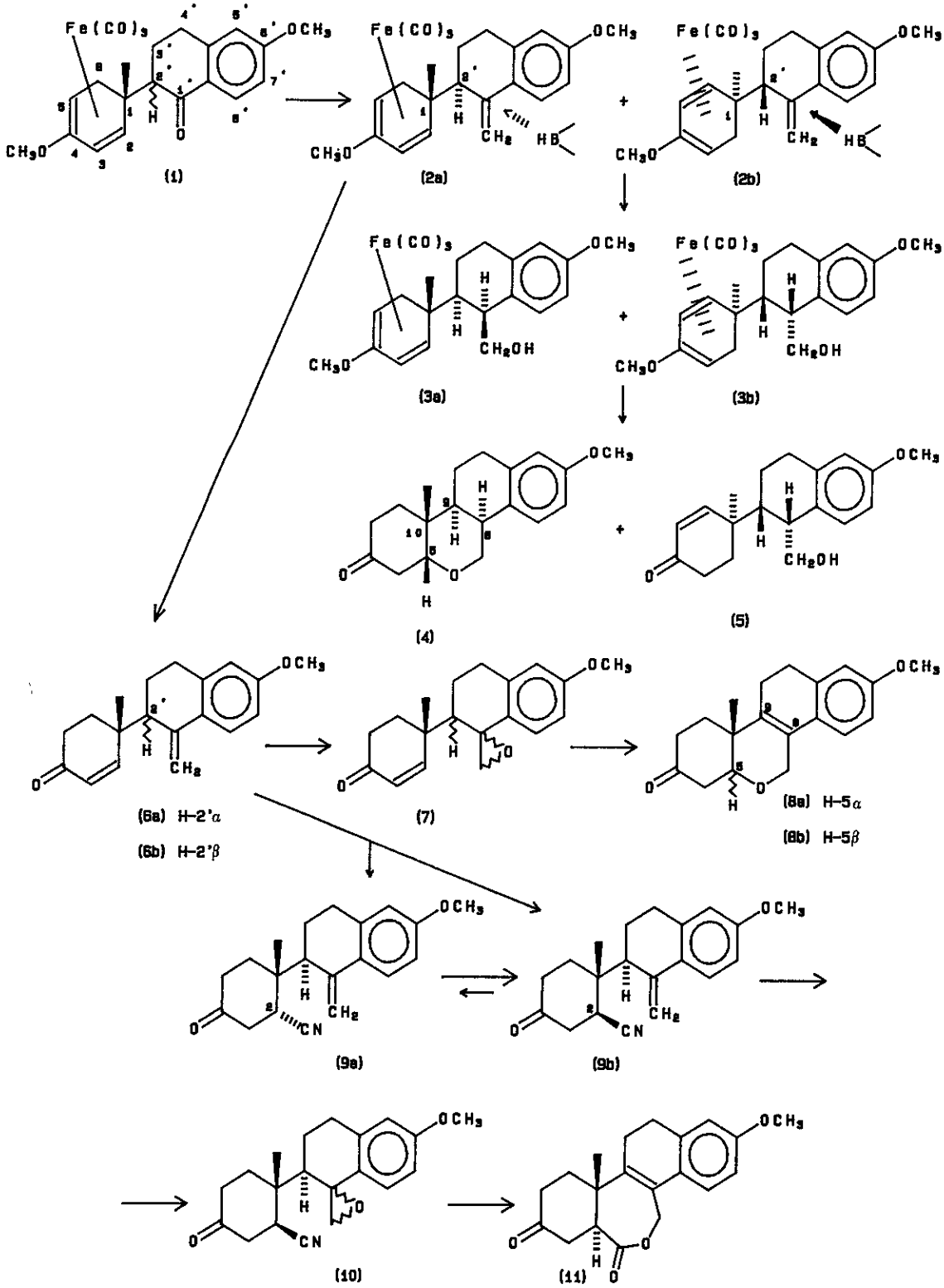
The synthesis of steroidal and heterosteroidal compounds by elaboration of suitable iron tricarbonyl-cyclohexadienyl complex, is currently under investigation in our laboratories.[1a,b,c]

Here we report a simple way to 6-oxa as well as 6-keto, 6a-oxa D-homo-aromatic steroids by elaboration of the iron tricarbonyl dienyl complex (1) previously obtained in high yield.[1a]

The conversion of (1) into the corresponding 6-oxa steroids was developed through the following steps: a) addition of a methylene unit at C-1'; b) conversion of the protected dienyl moiety into the corresponding α-β unsaturated ketone; c) addition of the hydroxymethyl to the enone to give the hetero ring B (scheme).

The olefination of (1) to give a diastereomeric mixture (2a) and (2b) proceeded in high yield by utilizing a large excess (10:1 ratio) of Takai's reagent (methylene bromide, zinc, titanium chloride).[2] This is a very mild methylenating agent useful in the presence of the liable iron tricarbonyl dienyl moiety; low yields of (2) are otherwise obtained utilizing the Wittig reagents. The mixture of (2a) and (2b) was then submitted to the hydroboration reaction under controlled conditions (thexylborane, tetrahydrofuran, r.t. 12 h) to give a

Scheme


Fe(CO)3
OCH3
CH3O
CH2
HB
CH2OH
O
H
(1)
(2a)
(2b)
(3a)
(3b)
(4)
(5)
(6a) H-2'α
(6b) H-2'β
(7)
(8a) H-5α
(8b) H-5β
CN
(9a)
(9b)
(10)
(11)

mixture of organoboranes, which by oxidation (water, hydrogen peroxide, sodium acetate), provided mainly a mixture of only the two stereoisomeric alcohols (3a) and (3b) resulting from a stereoselective trans addition of borane to iron tricarbonyl moiety. Considering that the C-1 and C-2′ axial substituents in (2a) and (2b) are oriented in a relative trans conformation (scheme, X Ray results),[1a] we can conclude that the corresponding alcohols (3a) and (3b) have the reported configurations.

The one-step decomplexation of the alcohols mixture (10 equiv. anhydrous trimethylamine N oxide, benzene, 60°C, 1 h) then the hydrolysis of the corresponding dienolethers (oxalic acid, methanol, water, 25°C, 30 min.) afforded the 6-oxa D-homo steroid (4)[3] resulting from the addition of the alcoholic hydroxy to the enone under the hydrolytic reaction conditions, as well as some enone alcohol (5) less suitable for the conformational arrangement (scheme) to cyclize.

By Dreiding models examination, the structure (4) with the A/B cis junction appears to be thermodynamically favoured with respect to the other possible trans junction. Alternatively, the mixture of (2a) and (2b) submitted to the decomplexation reaction, followed by hydrolysis of the corresponding dienolether, yielded a mixture of methylene enones, (6a) and (6b). This mixture by epoxidation (m-chloroperbenzoic acid 1:1 molar ratio, chloroform, r.t. 12 h) gave (7) as a diastereomeric mixture at C-8 and C-9. By chromatography on silica gel (eluting with benzene-ether 90:10) (7) gave in one step, as the main compound (70%), the 6-oxa Δ^{8-9}-D-homo aromatic steroids (8a) and (8b).

The reported 6-oxa D-homo aromatic steroids are useful to get the biologically interesting 6-oxa steroids[4] via the ring-D contraction by the usual method.[5]

The enonic mixture (6a) and (6b) has been also utilized as the starting material to synthesize steroidal structures with a seven-membered lactonic ring B. The presence of a such lactonic ring is actually responsible for the biological activity of the brassinosteroids, a class of steroids with a very high plant growth regulating activity.[6]

Therefore, the diastereomer (6a)[7] with the natural steroidal stereochemistry at C-2′ was separated by chromatography from (6b) and then submitted to hydrocyanation[8] (diethylaluminum cyanide, benzene, r.t. 12 h) to give a mixture of the corresponding C-5α and C-5β cyano derivatives (9a) and (9b). Moreover, this mixture yielded mainly (7:3 molar ratio) the thermodynamically favoured equa-

torial epimer (9b) after acidic equilibration (p-toluenesulfonic acid, benzene, reflux, 36 h). Nitrile (9b) by epoxidation (m-chloroperbenzoic acid, 0°C, 12 h) gave (10) as a diastereomeric mixture at C-8. Epoxide (10) was submitted to acid hydrolysis, (a: gaseous HCl, r.t. overnight, b: conc. HCl, dioxane, 100°C, 12 h) giving eventually the expected lactone (11) (66%).[9]

Present work is in progress to get natural steroids with the seven-membered lactonic ring B, starting from suitable iron tricarbonyl dienyl complexes.[1c]

EXPERIMENTAL

Ir spectra were recorded in chloroform with a Perkin-Elmer 257 Infracord; ^{1}H-nmr spectra with a Varian EM-360 (60 MHz) in $CDCl_3$ using TMS as an internal standard; mass spectra of the reaction products were recorded with an AEI MS12 apparatus at 70eV. Kieselgel from Merck was used for TLC.

Tricarbonyl[6'-methoxy-2'-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-1'methylene-1',2',3',4'-tetrahydronaphthalene]iron Diastereoisomers (2a) and (2b).

Powdered zinc (4.68g) was added to a solution of methylene bromide (2.04g) in anhydrous tetrahydrofuran (11.8 ml) under N_2. To this suspension a solution of titanium tetrachloride in methylene chloride (7.15 ml of a 1M solution) was added in a few minutes under stirring and the resulting mixture was stirred for additional 15 min. Then 1 (0.715 g) in 4 ml of tetrahydrofuran was added and the mixture was stirred overnight. After filtration of the solid the solution was washed with acidic water then neutralized, dried and evaporated; the residue was chromatographied on silica gel. By elution with benzene, an unseparable mixture of 2a and 2b was obtained (75% yield). Mass 436 (M^+); ir 1610, 1640, 1980, 2020 cm^{-1}; ^{1}H-nmr δ 0.84 (3H, s, 19-H), 3.20 (1H, m, 5-H), 3.60 (3H, s, OCH_3), 3.75 (3H, s, aromatic OCH_3), 4.83 and 5.22 (2H, pseudo d, J=20 Hz, $=CH_2$), 5.09 (1H, dd $J_{2,3}$=7 Hz, $J_{3,5}$=2 Hz, 3-H), 6.59-7.20 (3H, m, aromatic H).

Tricarbonyl[6'-methoxy-2'-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-1'hydroxymethyl-1',2'-3'-4'-tetrahydronaphthalene]iron Diastereoisomers (3a) and (3b).

A solution of thexylborane was prepared as follows: $BH_3.Me_2S$ (2 mmol) and 2,3-dimethyl-2-butene (4 mmol) in tetrahydrofuran (0.2 ml) were mixed at 0°C and

stirred for 2h under N_2. To this solution, 2a+2b (1 mmol) in tetrahydrofuran (2 ml) were added at room temp. The solution was left overnight under stirring, then water (0.5 ml) sodium acetate 5M (3.40 ml) and 30% hydrogen peroxide (1.40 ml) were added. After 1h the reaction mixture was extracted with diethyl ether, neutralized, dried and evaporated. The liquid residue was chromatographied on silica gel. By eluting with benzene-diethyl ether 95:5 2a+2b were before obtained (20% yield) then 3a+3b (65% yield).

3a+3b: Mass 454 (M^+); ir 1610, 1980, 2020, 3600 cm^{-1}; ^{1}H-nmr δ 1.15 (3H, s, 19-H), 3.20 (1H, m, 5-H), 3.60 (3H, s, OCH_3), 3.70 (2H, m, $-CH_2OH$), 3.75 (3H, s, aromatic OCH_3), 5.10 (1H, dd $J_{2,3}$=7 Hz, $J_{3,5}$=2 Hz, 3-H), 6.50-7.10 (3H, m, aromatic H).

17-Methoxy-3-keto-6-oxa-8α-D-homo-18-norandrosta-13,15,17-triene (4) and 6'-Methoxy-2'-(4-keto-1-methylcyclohex-2,3-enyl)-1'-hydroxymethyl-1',2',3',4'-tetrahydronaphthalene (5).

To a solution of Me_3NO (253 mg) in benzene (4 ml) the mixture 3a+3b (180 mg) was added. This solution was stirred under N_2 for 4 h at 55-60°C, then water was added and the mixture extracted with diethyl ether. The ethereal extracts were neutralized, dried and evaporated. The crude mixture obtained (110 mg) was hydrolized by adding at room temp. acetic acid (1.95 ml), water (6.4 ml), and dioxane (1.6 ml) then leaving overnight. The hydrolized solution was extracted with diethyl ether and the ethereal extracts, neutralized, were dried and evaporated to give a residue oil. This oil was chromatographied on silica gel; by eluting with hexane-diethyl ether 90:10, 4 (50 mg) was obtained, then 5 (45 mg). 4 liquid compound; Mass 300 (M^+); ir 1610, 1715 cm^{-1}. ^{1}H-nmr δ 1.01 (3H, s, 19-H), 3.70 (2H, m, 7-H), 3.75 (3H, s, aromatic OCH_3), 4.30 (1H, pseudo t J=4 Hz, 5-H), 6.60-7.22 (3H, m, aromatic H). 5 solid with low melting point; Mass 300 (M^+); ir 1610, 1680, 3600 cm^{-1}; ^{1}H-nmr δ 1.1 (3H, s, 19-H), 3.70 (3H, s, aromatic OCH_3), 3.80 (2H, m, CH_2OH), 5.70 (1H, d J=10 Hz, 3-H), 6.50-7.30 (4H, aromatic H and 2-H).

6'-Methoxy-2'-(4-keto-1-methylcyclohex-2,3-enyl)-1'-methylene-1',2',3',4'-tetrahydronaphthalene Diastereoisomers (6a) and (6b).

To a solution of Me_3NO (650 mg) in benzene (9.6 ml) the mixture 2a+2b (310 mg), was added. This solution was stirred at 60°C for 4h then worked up as usual.

The crude decomplexed product (210 mg) was dissolved in methanol (6.8 ml) then a solution of oxalic acid (140 mg) in water (1.6 ml) was added and the resulting solution leaved at room temp. for 40 min. After extractive work up with diethyl ether, the crude product obtained was chromatographied on silica gel eluting with hexane-diethyl ether 95:5. A diastereoisomeric mixture of 6a and 6b was obtained (65%); Mass 282 (M^+); ir 1620, 1645, 1680 cm^{-1}; ^{1}H-nmr δ 1.05 (3H, s, 19-H), 3.70 (3H, s, aromatic OCH_3), 5.0 (2H, d J=20 Hz, $=CH_2$), 5.70 (1H, d J=10 Hz, 3-H), 6.50-7,20 (4H, aromatic H and 2-H).

17-Methoxy-3-keto-6-oxa-D-homo-18-norandrosta-8,13,15,17-tetraene (8a) and 17-Methoxy-3-keto-6-oxa-5β-D-homo-18-norandrosta-8,13,15,17-tetraene (8b).

To a mixture of 6a and 6b (2 mmol) in methylene chloride (5.74 ml), m-chloroperbenzoic acid (4.7 mmol) was added and the resulting solution leaved at room temp. for 12h. The excess of peracid was destroyed by adding sodium metabisulphite (1 g in 10 ml of water). After extractive work up with diethyl ether, the crude product formed was chromatographied on silica gel. Eluting with benzene-diethyl ether 95:5 two main products 8a then 8b (2:1 ratio) were obtained (total yield 70%). 8a: liquid compound; Mass 298 (M^+); ir 1610, 1710 cm^{-1}; ^{1}H-nmr δ 1.25 (3H, s, 19-H), 3.80 (5H, pseudo s, OCH_3 and 7-H), 4.40 (1H, dd J_1=7 Hz, J_2=14 Hz, 5-H), 6.25-7.30 (3H, m, aromatic H); 8b: liquid compound, Mass 298 (M^+); ir 1610, 1710 cm^{-1}; ^{1}H-nmr δ 1.12 (3H, s, 19-H), 3.78 (5H, m, aromatic H and 7-H), 4.30 (1H, pseudo t J=7 Hz, 5-H), 6.75-7.30 (3H, m, aromatic H).

6'-Methoxy-2'-(2α-cyano-4-keto-1-methylcyclohexanyl)-1'-methylene-1',2',3',4'-tetrahydronaphthalene (9a) and 2β-Cyano Isomer (9b).

A mixture of 6a and 6b (500 mg) was separated by chromatography on silica gel eluting with hexane-ethyl acetate 90:10; 6a (180 mg), a mixture of 6a and 6b (120 mg) then 6b (170 mg) were in order eluted.

To 6a (150 mg) dissolved in anhydrous tetrahydrofuran (2.35 ml) a 1.7M solution of diethylaluminum cyanide in benzene (1.57 ml) was added. The resulting solution was stirred at room temp. under N_2 for 12h; then HCl 2N and ice were added and the mixture was extracted with diethyl ether. After washing with saturated sodium bicarbonate solution and neutralization, the organic layer was dried and evaporated. The crude product obtained (170 mg) chromatographied on

silica gel eluting with benzene-diethyl ether 90:10, furnished 9a (70 mg) liquid compound; Mass 309 (M^+); ir 1640, 1715, 2240 cm^{-1}; ^{1}H-nmr δ 1.25 (3H, s, 19-H), 3.3 (1H, pseudo t J=8 Hz, 2-H), 3.75 (3H, s, OCH_3), 4.85 (2H, d J=18 Hz, $=CH_2$), 6.50-7.15 (3H, m, aromatic H), then 9b (60 mg) liquid compound, ^{1}H-nmr δ 1.20 (3H, s, 19-H), 3.27 (1H, m, 2-H).

Equilibration of (9a) to (9b).

The C-5α-cyano derivative 9a (70 mg) was dissolved in anhydrous benzene (3 ml) then some crystals of p-toluensulfonic acid were added and the solution leaved under reflux for 36h. After the usual work up and chromatographic separation of the reaction mixture 9a, (18 mg) and 9b (45 mg) were isolated.

6'-Methoxy-2'-(2β-cyano-4-keto-1-methylcyclohexanyl)-1'-methylene Oxide-1',2',3',4'-tetrahydronaphthalene (10) and 7-Methoxy-3,6-diketo-B,D-homo-6a-oxa-18-nor Androsta-8,13,15,17-tetraene (11).

9b (130 mg) was dissolved in methylene chloride (4.9 ml). M-chloroperbenzoic acid (290 mg) was added and the solution leaved at room temp. for 12h. After the usual work up the crude 10 (no methylene bands present in the ir spectrum of 10) was dissolved in anhydrous dioxane (6 ml), and this solution, saturated with gaseous HCl, was leaved overnight under stirring at room temp. After evaporation and extractive work up with diethyl ether, the reaction mixture was examined on TLC. 9b was reacted in part (40%) to give the lactonic compound 11. This reaction mixture was dissolved in dioxane (2 ml), conc. HCl was added (2 ml) and the resulting solution leaved overnight under stirring at 100°C. After extractive work up with diethyl ether the crude reaction mixture was chromatographied on acidic alumina B IV to give after elution with hexane-diethyl ether 70:30 11 as the main product (68% yield).

11 liquid compound; Mass 326 (M^+); ir 1720, 1735 cm^{-1}; ^{1}H-nmr δ 1.10 (3H, s, 19-H), 3.70 (1H, m, 5-H), 3.75 (3H, s, OCH_3), 4.10 (2H, broad s, 7-H), 6.75-7.30 (3H, m, aromatic H).

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7. 6a was recognized by comparison (rf, ir, nmr) with a sample prepared from the corresponding known 3β-acetate by reduction with lithium aluminum hydride then PCC oxidation.[1b]

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9. A treatment of (10) with only gaseous HCl at room temp., then addition of water furnished the same the lactone (11) (40%). The unusual hydrolysis of the cyano group in these very mild conditions is explainable via an intramolecular addition of the alcoholic function, derived from the opening of the epoxidic ring, to the nitrile function.

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