ON CARDIOACTIVE STEROIDS VI.[1] THE SYNTHESIS OF 17α-METHYL
CARDENOLIDES

Karnail S. Atwal, Soumya P. Sahoo, Thomas Y. R. Tsai, and
Karel Wiesner[*]

Natural Products Research Centre, University of New Brunswick,
Bag Service #45222, Fredericton, New Brunswick, Canada E3B 6E2

Abstract -- Two methods for the simple synthesis of the $\Delta^{14,15}$-
17α-methyl cardenolide 1 are disclosed. This material may be
functionalized to a variety of 17α-methyl derivatives for
pharmacological testing. As an example, the preparation of 17α-
methyl digitoxigenin 20 is described.

In connection with our systematic studies of structure-activity-toxicity relation-
ships in the series of cardioactive steroids, we were interested in the synthesis
of 17α-methyl cardenolides. We disclose herein two simple methods for the pre-
paration of the unsaturated lactone 1 and the conversion of this derivative to
17α-methyl digitoxigenin 20.
The starting material for the first method was the furyl derivative 2.[2] Oxidation
of the C-15 hydroxyl by μ-oxo-bis(chlorotriphenylbismuth)[3] in CH_2Cl_2 at reflux
for 7 h gave the ketone 3[†] (mp 150-152°C) in a yield of 94%; ir $(CHCl_3)$ ν_{max}:
1695, 1600 cm^{-1} (conjugated C=O); pmr $(CDCl_3)$ δ: 1.03, 1.23 (s, 3H each, 19-
and 18-CH_3, respectively), 6.00 (s, 1H, vinylic H).
Most methods currently used for 1-4 additions to conjugated ketones failed with
compound 3. We have finally succeeded to prepare compound 4 (mp 126-127°C) in a
yield of 81% by treating the ketone 3 with trimethyl aluminum and nickel acetyl
acetonate in ether-THF according to Bagnell et al.[4]; ir $(CHCl_3)$ ν_{max}: 1730 cm^{-1}

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[†] All compounds gave molecular ions in mass spectroscopy and all spectral data in
agreement with the structures assigned to them. All crystalline compounds gave
satisfactory values in C/H analysis.

(C=O); pmr (CDCl$_3$) δ: 0.60, 0.98, 1.43 (s, 3H each, 18-, 19- and 17-CH$_3$, respectively).

The ketone 4 was reduced with NaBH$_4$ in THF and the oily mixture of the epimeric alcohols 5 and 6 was obtained in quantitative yield. It was immediately oxidized to the cardenolides 7 and 8 by our previously described[2] procedure with m-chloroperbenzoic acid followed by NaBH$_4$. The yield of both epimers was 95%. Compounds 7 and 8 were separated by chromatography on silica gel and they were obtained in a ratio 3:1.[††] The major epimer 7 remained oily; ir (CHCl$_3$) ν_{max}: 3610, 3500 (OH), 1790, 1750, 1620 cm^{-1} (conjugated lactone); pmr (CDCl$_3$) δ: 0.93, 1.02, 1.12 (s, 3H each, 3-CH$_3$), 4.30 (m, 1H, C15α-H).

The C15β-alcohol 7 was treated with methanesulfonyl chloride in pyridine for 30 min at 0°C and for 5 h at 60°C. The 14-15 unsaturated compound 1 (mp 128.5-130°C) was obtained in a yield of 77%; ir (CHCl$_3$) ν_{max}: 1780, 1750, 1625 (conjugated lactone); pmr (CDCl$_3$) δ: 4.80 (d, J = 2 Hz, 2H, allylic H of lactone), 5.23 (broad s, 1H, C15-H), 5.93 (broad s, 1H, vinylic H of lactone).

The second method for the preparation of the derivative 1 was based on the studies of Solo et al. concerning the Diels-Alder addition of steroidal ring D dienes.[5] The diene 10 (mp 53-55°C) was prepared in a yield of 88% by the reaction of the ketone 9[2] with methyl lithium in ether at 0°C, followed by refluxing the resulting tertiary allylic alcohol with hydrochloric acid in acetone; pmr (CDCl$_3$) δ: 1.80 (s, 3H, C17-CH$_3$), 5.77 (m, 1H, C16-H), 5.90 (m, 1H, C15-H). The diene 10 was heated to 90°C with an excess of ethyl propiolate and a single adduct (mp 103-105°C) 11 was isolated in a yield of 75%; ir (CHCl$_3$) ν_{max}: 1705 cm^{-1} (C=O); pmr (CDCl$_3$) δ: 0.97, 1.03, 1.40 (s, 3H each, 19-, 18- and 17-CH$_3$, respectively), 6.50 (d, J = 4 Hz, 1H, C16-H), 6.62 (d, J = 4 Hz, 1H, C15-H), 7.53 (s, 1H, H-C=C-C=O).

Selective hydrogenation of the disubstituted double bond in the adduct 11 was achieved with Pd-CaCO$_3$ in benzene. The dihydro derivative 12 (mp 118-120°C) was obtained in a yield of 93%; ir (CHCl$_3$) ν_{max}: 1700 cm^{-1} (CO); pmr (CDCl$_3$) δ: 6.90 (s, 1H, H-C=C-C=O).
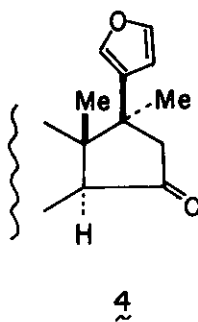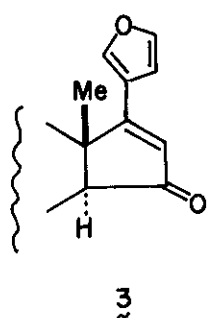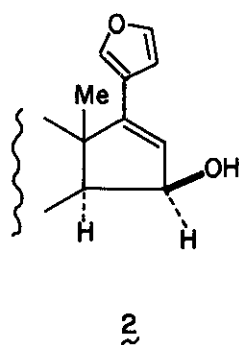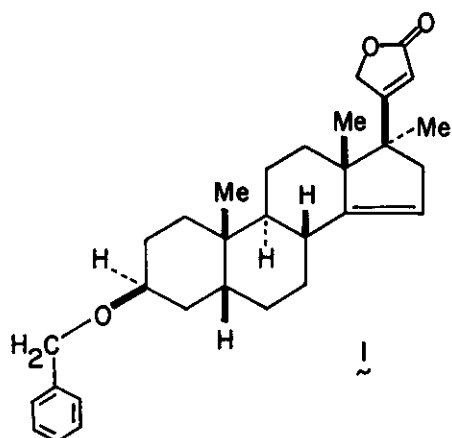
The compound 12 was oxidized in a mixture of acetone and water with an excess of

††The minor epimer 8 was oxidized with CrO$_3$-dipy in CH$_2$Cl$_2$ and reduced with NaBH$_4$ at 0°C to a 3:1 mixture of 7 and 8. The configuration of the 15-hydroxy group in the major epimer 7 follows from the regiospecific elimination of the corresponding mesylate to yield the Δ 14-15 derivative 1.

metaperiodate and potassium permanganate. The pure compound 13 was isolated as
a foam by chromatography on silica gel using ether-hexane (1:10) as eluent in a
yield of 69.3%; ir (CHCl$_3$) ν_{max}: 1750 (-CH=O), 1730 (ester C=O), 1720 cm^{-1}
(C=O); pmr (CDCl$_3$) δ: 0.97 (s, 3H, 19-CH$_3$), 1.27 (s, 6H, C17- and 18-CH$_3$),
1.00 (t, J = 7 Hz, 3H, CH$_2$-CH$_3$), 4.23 (q, J = 6 Hz, 2H, CH$_2$-CH$_3$), 8.87 (s, 1H, CH=O).
The aldehyde group in compound 13 was oxidized with Jones' reagent at 0°C to a
carboxy group. Remarkably the unreactive α-ketoester group remained intact and
the carboxyl was immediately subjected to a decarboxylation in dry benzene and
pyridine (20:1) with lead tetraacetate and cupric acetate. The pure unsaturated
ketoester 14 was isolated by chromatography on silica gel as a foam in a yield
of 60%; ir (CHCl$_3$) ν_{max}: 1740 (ester C=O), 1720 cm^{-1} (C=O); pmr (CDCl$_3$) δ: 0.97
(s, 6H, 19- and 18-CH$_3$), 1.35 (t, J = 7 Hz, 3H, -CH$_2$-CH$_3$), 1.30 (s, 3H,
C17-CH$_3$), 4.33 (q, 2H, J = 6 Hz, -CH$_2$-CH$_3$), 5.10 (broad s, 1H, C15-H).
The configuration of the 17-methyl group in compound 14 follows from the known
stereochemistry of the Diels-Alder addition.[cf. 5] It also follows from the
correlation with compound 1 and from the comparison of the pmr spectrum of the
17α-methyl digitoxigenin 20 with that of digitoxigenin.
The ketoester 14 was quantitatively reduced with an excess of LiAlH$_4$ in ether and
the crude diol was selectively acetylated for 1 h at room temperature in a mixture
of dioxane-pyridine and acetic anhydride. The monoacetate 15 (mp 56-58°C) was
obtained in a yield of 92%; ir (CHCl$_3$) ν_{max}: 3625 (OH), 1735 cm^{-1} (C=O); pmr
(CDCl$_3$) δ: 2.08 (s, 3H, CO-CH$_3$). Compound 15 was oxidized with Jones' reagent
and the oily ketone 16 was purified by preparative tlc on silica gel. It was
obtained in a yield of 85%; ir (CHCl$_3$) ν_{max}: 1710 (C=O), 1730 cm^{-1} (CH$_3$-CO-);
pmr (CDCl$_3$) τ: 2.13 (s, 3H, CO-CH$_3$), 4.83 (s, 2H, -CH$_2$-O-Ac), 5.17 (broad s, 1H,
C15-H).
The acetoxy ketone 16 was converted to the alcohol 17 by methanolysis in the
presence of potassium carbonate and this material was tetrahydro-pyranylated in
methylene chloride in the presence of pyridinium p-toluenesulfonate. The
tetrahydro-pyranyl derivative 18 was subjected to a reaction with lithium ethoxy-
acetylide in benzene-ether and the crude material thus obtained was stirred with
methanolic hydrochloric acid. The product was purified by chromatography and
crystallization (mp 129-130°C). It was obtained in an overall yield of 55% from
the acetoxy ketone 16 and it was identical by mixed mp, tlc, and all spectral

1

2

3

4

5　$R_1 = H$,　$R_2 = OH$

6　$R_1 = OH$,　$R_2 = H$

7　$R_1 = H$,　$R_2 = OH$

8　$R_1 = OH$,　$R_2 = H$

9

—COOEt

—COOEt

10

11

12
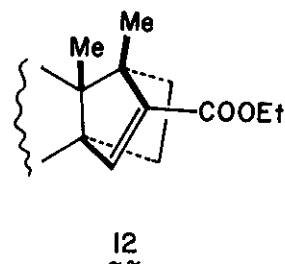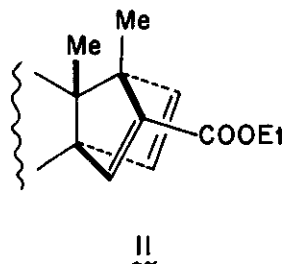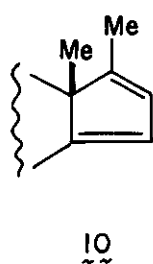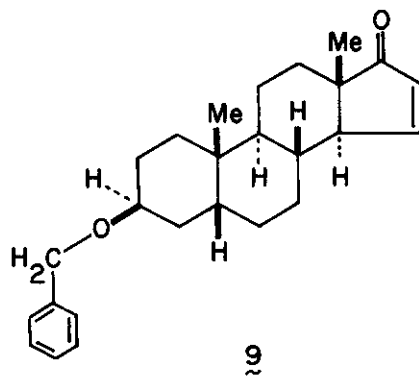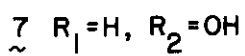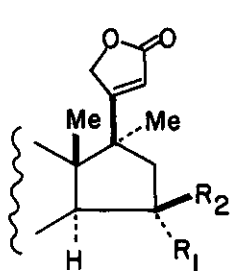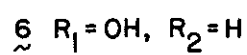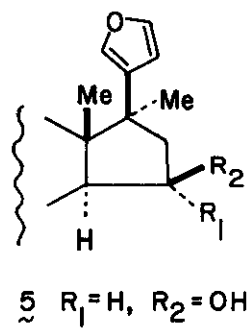
data with the unsaturated lactone 1. While it is clear that the Diels-Alder

approach to compound 1 is less efficient than the furan approach, it is neverthe-

less of considerable interest. The readily obtainable compound 13 may, for

example, serve as starting material for a variety of C14-β carbon substituted

cardenolide analogues which we have tried to prepare without much success by

other routes.

The conversion of compound 1 to 17α-methyl digitoxigenin 20 was performed as

in our previous work,[2] but it proceeded in a poorer yield and with only low

stereoselectivity. Compound 1 was treated with NBS in aqueous acetone (10% H_2O)

and the resulting bromohydrin was debrominated with Raney nickel in a mixture of

methanol and methylene chloride. The benzyl derivative 19 (mp 182-183°C) was

obtained in a yield of 35% besides 20% of the 14α-hydroxy derivative and 20% of

starting material.   The 14α-hydroxy derivative was quantitatively dehydrated to

compound 1 and thus the effective yield was somewhat improved; ir ($CHCl_3$) ν_{max}:

3605, 3480 (OH), 1745, 1605 cm^{-1} (unsaturated lactone); pmr ($CDCl_3$) δ: 1.17

(s, 3H, 17α-CH_3), 0.97 (s, 3H, 19-CH_3), 0.92 (s, 3H, 18-CH_3).

Compound 19 was debenzylated with palladium on charcoal in an ethanol-benzene

mixture to yield 92% of 17α-methyl digitoxigenin 20 (mp 253-255°C); ir ($CHCl_3$)

ν_{max}: 3605, 3450 (OH), 1745, 1605 cm^{-1} (unsaturated lactone); pmr ($CDCl_3$) δ:

5.78 (t, J = 2 Hz, 1H, C22-H), 5.11, 4.97 (2d, J = 2 Hz, 1H each, C21-H_2), 1.17

(s, 3H, C17-CH_3), 0.97 (s, 3H, 19-CH_3), 0.93 (s, 3H, 18-CH_3).

The only feature in the pmr spectrum of compound 20 which is strikingly different

from the corresponding spectrum of digitoxigenin (except of course for the

presence of the C17-CH_3 singlet) is the pattern due to the two diastereotopic

C21-hydrogens. These in the case of digitoxigenin give rise to two doublets at

δ = 4.81 and 4.87 (J = 2 Hz). It is believed that differences in the rotational

barrier around the C_{17}-C_{20} bond and in the populations of different rotomers may

be the cause of the different pmr patterns and it is expected that these differ-

ent rotational properties will also influence the pharmacologic parameters of

compound 20.

COOEt
C=O
Me Me
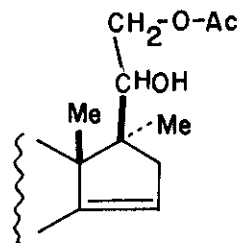
Me

H C=O

13

COOEt
C=O
Me Me

14

CH₂-O-Ac
CHOH
Me Me

15

CH₂-OR
C=O
Me Me
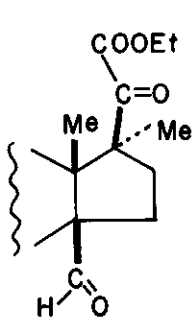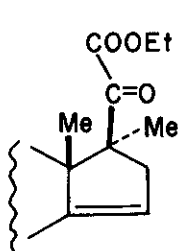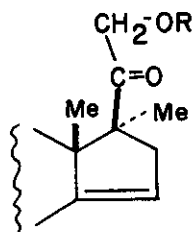
16 R = -CO-Me

17 R = H

18 R = THP

Me Me
Me H
Me H
OH
H
RO H
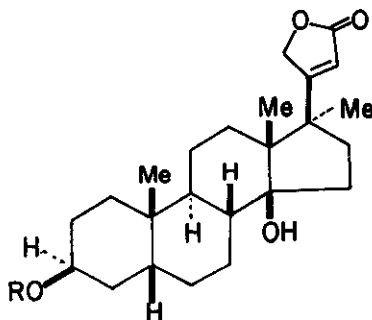
19 R = -CH₂–⬡

20 R = H

REFERENCES

1. For Communication V, see M. J. Shiao, T. Y. R. Tsai, and K. Wiesner, Heterocycles, 1981, 16, 1879.

2. T. Y. R. Tsai, A. Minta, and K. Wiesner, Heterocycles, 1979, 12, 1397.

3. D. H. R. Barton, J. P. Kitchin, and W. B. Motherwell, J. Chem. Soc., Chem. Commun., 1978, 1099.

4. L. Bagnell, E. A. Jabbery, A. Meisters, and T. Mole, Austr. J. Chem., 1975, 28, 801.

5. A. J. Solo, H. S. Sachdev, and S. S. Gilani, J. Org. Chem., 1965, 30, 769.