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A SYNTHESIS OF BUFALIN FROM DEOXYCHOLIC ACID

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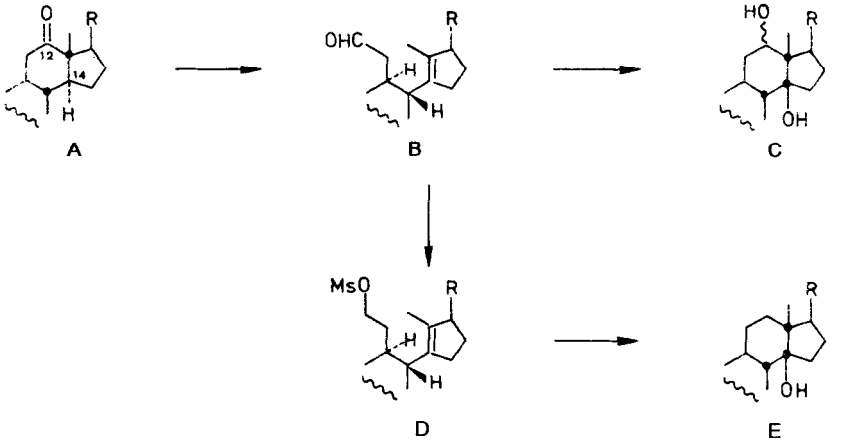
Abstract - Bufalin acetate (**14**) has been prepared from deoxycholic acid (**1**) in 12 steps.

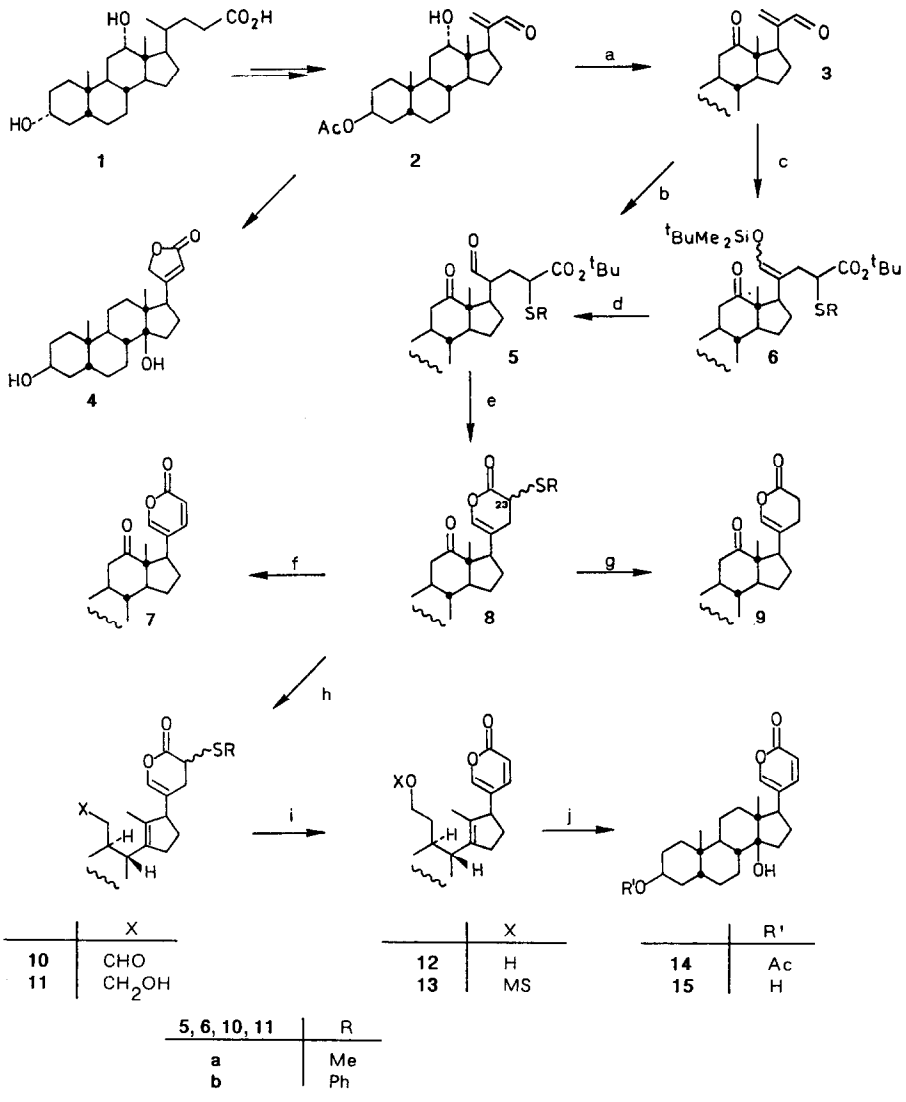
One of the main problems associated with the synthesis of the medicinally important cardioactive steroids,[1,2] such as digitoxigenin (**4**) and bufalin (**15**), from normal 14α-H steroids is the introduction of the 14β-OH group.[5] Recently, we have shown that photochemical isomerization of 12-oxo-14α-steroids (partial structure **A**) to unsaturated aldehydes of type **B**, followed by a Prins cyclization opens a simple access to 12,14ß-diols (partial structure **C**), whereas mesylates of type **D** (obtained from **B** in 2 steps) furnish 12-unsubstituted compounds of type **E** under solvolytic conditions.[6] Using this methodology, cardenolides such as **4** have been synthesized starting from deoxycholic acid (**1**).[7]



Scheme 1.

It is the purpose of this communication to demonstrate that the new method can also be used for the synthesis of bufadienolides such as **15**.[8,9,10] Unlike the cardenolide case, however, the introduction of the 14ß-OH group cannot be postponed to the last stage of the synthesis. It appears impossible to effect selective photochemical rearrangement of 12-oxobufadienolide **7** into the corresponding secoaldehyde of type **B** by irradiation into the $n \rightarrow \pi^*$ band of the keto group since it is well-known that α-pyrones absorb at the same wavelength (300 nm) and react from the excited state(s) to give formyl ketenes.[11] Our conceptual approach was, therefore, to use for the photochemical rearrangement a 20-bufenolide such as **8** [12] and to introduce the missing double bond later via a sulfoxide.[12,13]

The results are summarized in Scheme 2.



	X
10	CHO
11	CH_2OH

	X
12	H
13	MS

	R'
14	Ac
15	H

5, 6, 10, 11	R
a	Me
b	Ph

Scheme 2. Reagents, conditions, yields.

[a](i) $(COCl)_2$/DMSO (1 equiv) + **2** in CH_2Cl_2, 30 min at -55°C, (ii) Et_3N,-55°C→20°C: 90%.- [b] **3** + tert-butyl phenylsulfanylacetate (2 equiv) + KO^tBu (1.7 equiv) in DME, 1h at 20°C: 75%.- [c] (i) **3** + dry $ZnCl_2$ (0.14 equiv) + 1-tert-butoxy-1-(tert-butyldimethylsilyloxy)-2-methylsulfanyl-ethylene (2 equiv) in CH_3CN, 105 min at 20°C, (ii) Et_3N: 58% (43% **3** were recovered).- [d] **6a** + KF (4 equiv) in 2:1 THF-methanol, 10h at 20°C: 96%. [e] **6a** + p-toluenesulfonic acid (1 equiv) in benzene, 7h reflux (water trap): 83%.- [f](i) **7a** + m-chloroperbenzoic acid (1 equiv) in CH_2Cl_2, 35 min at -78°C, (ii) work-up, (iii) 36h at 20°C in CH_2Cl_2: 84%.- [g] **8b** in CH_2Cl_2, UV light (Philips HPK 125, pyrex filter), 100 min at 8°C: 30% (30% **8b** were recovered).- [h](i) in CH_2Cl_2, UV light (Philips HPK 125, pyrex filter), 139 min at 8°C, (ii) solvent evaporation, (iii) + $LiAlH(O^tBu)_3$ (1 equiv) in THF, 25 min at 20°C: 36% (48% **8a** were recovered).- [i] (i) **11a** + m- chloroperbenzoic acid (1 equiv) in CH_2Cl_2, 30 min at -78°C, (ii) work-up, (iii) 24h at 20°C in CH_2Cl_2: 49%.- [j] (i) **12** + Et_3N (2 equiv) + methanesulfonyl chloride (2 equiv) in CH_2Cl_2, 85 min at -78°C, (ii) work-up, (iii) + oxalic acid (2 equiv) in 1:3 acetone-water, 1 h at 50°C: 62% (based on **12**).

Deoxycholic acid (**1**) was transformed into **2** in 4 steps as already described.[7] Swern oxidation of **2** gave **3** (90%). Reaction of **3** with the stabilized anion prepared from tert-butyl phenylsulfanylacetate proceeded cleanly in the 1,4-mode to give **5b** (mixture of 4 stereoisomers) in 75% yield. In the analogous reaction of **3** with the ester enolate of tert-butyl methylsulfanylacetate, **5b** (mixture of stereoisomers) was obtained in only 38% yield. However, the $ZnCl_2$-catalyzed reaction of **3** with the tert-butyldimethylsilyl ketene acetal derived from tert-butyl methylsulfanylacetate [14] provided the corresponding Michael adducts **6a** in 58% yield. [15,24] Reaction of **6a** with potassium fluoride in THF-methanol led to the cleavage product **5a** (mixture of stereoisomers) in 96% yield.

As was hoped for and in contrast to a report by Kreiser et al.,[27] refluxing a benzene solution of **5b** (mixture of stereoisomers) in the presence of p-toluenesulfonic acid (1 equiv) provided **8b** (1:1 mixture of 23-isomers) directly in 90% yield. Similarly, cyclization of **5a** furnished **8a** (83%, 1:1 mixture of 23-epimers).

In a model experiment, the **8a** isomers were oxidized with m-chloroperbenzoic acid to the corresponding sulfoxides.[13] After work-up, a CH_2Cl_2 solution of the sulfoxides was allowed to stand at 20°C for 36h. **7** was then isolated in 84% yield.

Unfortunately, the photorearrangement of **8a** and **8b**, respectively, posed a number of problems which could be solved only partly until now. In the case of **8b**, the keto, the aromatic, and the enollactone UV bands were overlapping. In keeping with this after irradiation with UV light not the desired **10b** but only **9** could be isolated (30%). In the case of **8a**, selective irradiation into the CO band ($_{max}$= 308 nm in CH_3CN solution, taken from the CD spectrum [28]) was possible. However, the rearrangement product, secoaldehyde **10a**, turned out to be very unstable. At present, the best procedure involves irradiation until about 50% of **8a** are consumed, followed by immediate reduction of **10a** with $LiAlH(O^tBu)_3$ (which does not react with **8a** under the experimental conditions). The yield of **11a** is then 36 % (based on **8a**).

Introduction of the missing double bond to give **12** was performed as described above for the preparation of **7**.

Finally, mesylation and subsequent solvolysis of **13** under Masamune's conditions [29] gave **14** in 62%. The formation of **15** from **14** by ester hydrolysis has already been reported. [9a,10a]

In conclusion: **14** has been prepared form **1** in 12 steps. At present, this seems to be the shortest synthetic approach to **15** starting from a steroidal raw material.

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