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SYNTHESIS OF 1,11α-ETHANO CORTICOSTEROIDS

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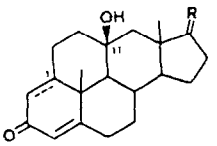
ABSTRACT: 11α-Formyl-methyl derivative 5 of prednisolone has been reductively cyclized to give the versatile pentacyclic intermediates 7 and 9 of novel 1,11α-ethano-bridged corticosteroid analogues.

Two different effects are thought to be responsible for the positive influence of a 9α-fluoro atom on the biological activity of corticosteroids [1,2]: The fluorine stabilizes the reduced (11β-hydroxy) active form of the drug in comparison to the oxidized (11-oxo) inactive one [3], at the same time inducing a stronger bending of ring A, thereby generating a special arrangement which might be closer to the biologically active conformation.

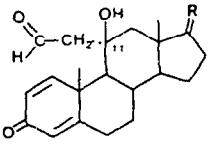
Attempts to obtain a similar effect by introducing a methyl group into the 11α-position have failed [4]. Compounds containing a tertiary 11β-hydroxy group were shown to be inactive. These negative results, however, could be attributed to additional steric interactions between C(1) and the 11α-methyl group, unfavourably influencing the conformation of the molecule. To test this hypothesis, we endeavoured to exclude the possible interaction by bridging C(1) and C(11) of hydrocortisone and prednisolone with a C_2 unit [5]. Simultaneously, ring A of the planned compounds of type I (Scheme 1) could be fixed in specific chosen conformations, depending on the configuration and/or hybridization of C(1). We report here on a stereoselective synthesis of this novel class of pentacyclic steroids [6].

The crucial step in our approach consisted in the reductive ring-closure of a keto-aldehyde (II) via an intermediate dianionic species III [7]. The necessary intermediate of type II was prepared as depicted in Scheme 2. The protected cortisone derivative 1 [8] was first transformed to the

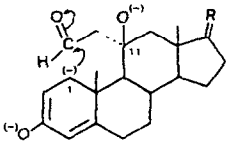
Scheme 1



I



II



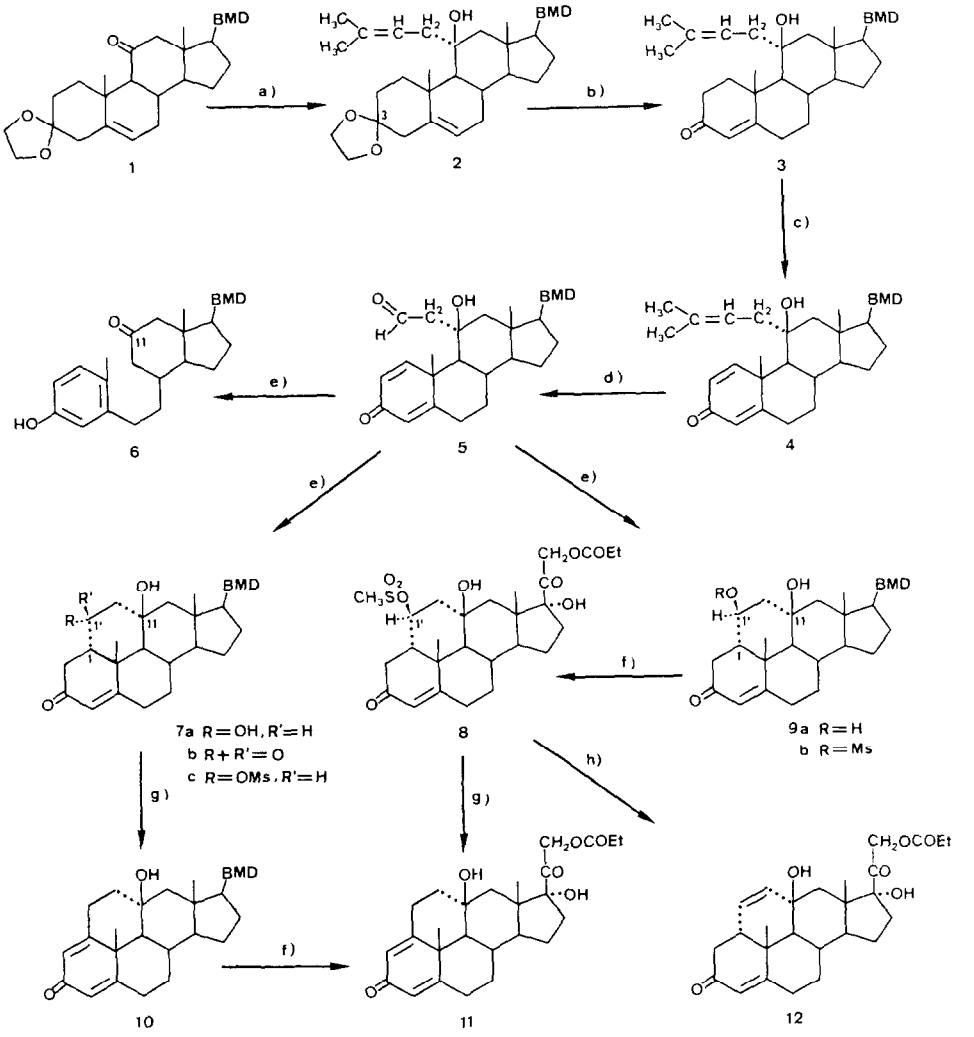
III

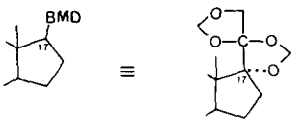
11α-dimethallyl carbinol 2 [9] (59 %; F: 154-156°). After deprotection at C(3) (82 %; F: 181-183°), the resulting compound 3 was dehydrogenated via the corresponding 2-phenylselenyl derivative to yield the $\Delta^{1,4}$-3-ketone 4 (55 %; F: 194-197°). By subsequent ozonization, the desired aldehyde 5 (82 %; F: 212-213°) was obtained.

Treatment of 5 with lithium and diphenyl in THF[10] as a source of radical anions generated, as expected [11], the two epimeric diols 7a (5.5 %; F: 208-248°) [12] and 9a (25.5 %; F: 267.5-272°)[13]. In addition, the secoketone 6 [14] (5.2 %; F: 234-238°) was formed. Both diols were oxidized (CrO_3/H_2SO_4/acetone/0°) to the same hydroxydiketone 7b (F: 269-272°). The configurations of the chiral centers at C(1) and C(1)' of 7 and 9 were deduced from mechanistic considerations and the physical properties of these compounds. Subsequent transformations established the correctness of the assumed stereochemistry at C(1).

Compound 7a was selectively mesylated at the equatorial 1'-hydroxy group and the crude mesylate 7c treated (18 hrs.) with NaOAc in AcOH at 80°. The 17-side-chain of the isolated monool 10 (F: 248-258° dec.) was deprotected and the 21-hydroxy group of the free ethanoprednisolone directly esterified yielding the corresponding 21-propionate 11 (F: 213-219°). The same compound was obtained starting from the epimeric 1'β-mesylate 9b (F: 151-153°) by subsequent deprotection of the side-chain and propionylation (8), followed by elimination of methane sulfonic acid using the above procedure. When $LiBr/Li_2CO_3$/DMF was used instead of NaOAc/AcOH, the non-conjugated dienone 12 (F:204-206°) was obtained. The structures of 11 and 12 were confirmed by X-ray analyses [15].

Scheme 2





Reagents: a) $(CH_3)_2C{=}CHCH_2MgBr$; b) AcOH, H_2O; c) LDA, C_6H_5SeCl, 2) H_2O_2; d) O_3; e) Li, $(C_6H_5)_2$; f) 1) HF, H_2NCONH_2, 2) $(EtCO)_2O$, Py; g) NaOAc, AcOH; h) LiBr, Li_2CO_3

References and Notes

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3. A. Eschenmoser and J. Schreiber (personal communication) studied the kinetics of the oxidation steroidal of 9,11-halohydrins in comparison to 9-unsubstituted 11β-hydroxy compounds, thereby confirming the predicted behaviour of 9α-fluoro derivatives.
4. R.E. Beyler, F. Hoffman and L.H. Sarett, J.Amer.Chem.Soc. 82, 178 (1960); G. Anner (Ciba-Geigy) unpublished experiments.
5. Biologically interesting compounds containing an oxygen bridge between C(1) and C(11) will be described in a forthcoming paper (J. Kalvoda, J. Grob and U. Joss, Helv.Chim. Acta 67 [1984] in preparation.
6. Aromatic pentacyclic steroid analogues have recently been synthesized by T.S. Bhatt, M.M. Coombs, A.-M. Kissonerghis, A.F.D. Clayton and M. McPartlin (J.C.S. Chem.Commun. 1979, 433); C.G. Pitt, J.Chem.Soc.Perkin Trans. I, 1977, 1144.
7. Qualitative MO arguments (high-lying HOMO ["filled LUMO"] of the dianion and low-lying LUMO of the carbonyl group) seem to favour the envisaged process.
8. J.H. Fried, G.E. Arth and L.H. Sarett, J.Amer.Chem.Soc. 81, 1235 (1959).
9. All new compounds described in this communication gave satisfactory analyses and spectral data compatible with the proposed structure. The mps are uncorrected.
10. H.L. Dryden, G.M. Webber and J.J. Wieczorek, J.Amer.Chem.Soc. 86, 742 (1964).
11. C.f. also P. Wieland and G. Anner, Helv.Chim.Acta 51, 1932 (1968).
12. The long and different melting points of several samples of 7a could be explained by the presence of varying small amounts of the 1αH-epimer.
13. On treatment of the much more stable 17,20,20,21-bismethylendioxy-11α-hydroxy-pregna-1,4-dien-3-one acetate with lithium in ammonia, M. Tanabe et al [14] were able to isolate a compound formed by uncleophilic attack of a carbanion at C_1 similar to the one depicted in III on the acetate carbonyl group.
14. M. Tanabe, J.W. Chamberlin and P.Y. Nishiura, Tetrahedron Letters 1961, 601.
15. For detailed X-ray data and biological behaviour of the new 1,11 bridged corticosteroids, c.f. P. Wieland, G. Rihs and J. Kalvoda, Helv.Chim.Acta 67, (1984) in preparation.

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