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A Corticoid Synthesis from 9α-Hydroxyandrost-4-ene-3,17-dione *via* a Steroidal Allene

David R. Andrews*, Robert A. Giusto and Anantha R. Sudhakar*

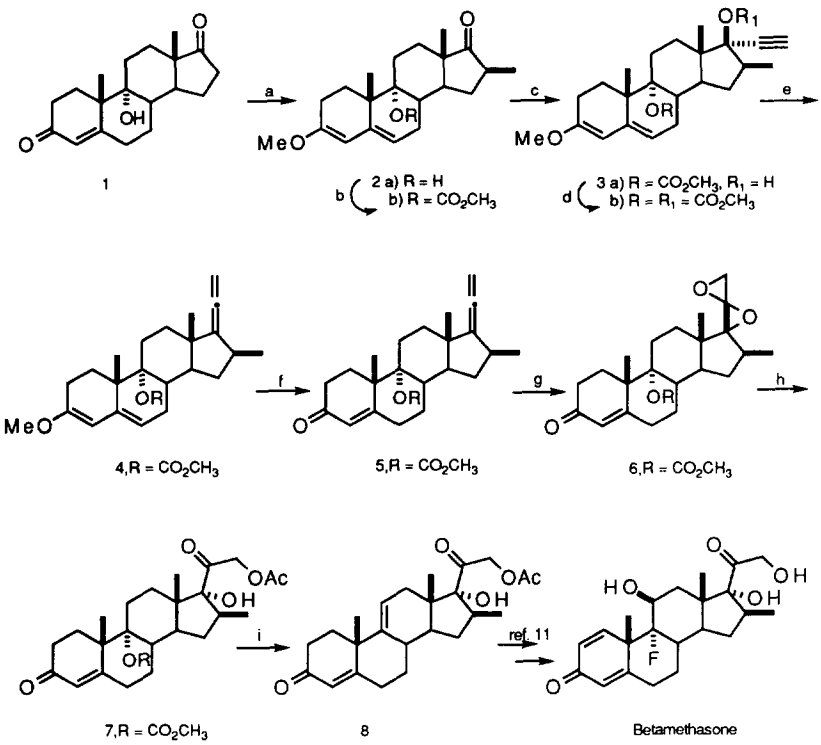
Chemical Process Development, Schering-Plough Research Institute, 1011 Morris Ave., Union, New Jersey, 07083, U.S.A.

Abstract: An alternative synthesis of 17α, 21-dihydroxy-16β-methylpregna-4,9(11)-diene-3,20-dione, an intermediate to the potent anti-inflammatory corticoid, Betamethasone, is described. The key reactions are the bis epoxidation of a C-17,20 allene and the regiospecific elimination of a 9α-methyl carbonate. Copyright © 1996 Elsevier Science Ltd

The efficient production of corticoids is of considerable commercial interest, and a variety of methods for their preparation have been developed over the past few decades.[1] However, not all of these methods are practical in cases where a C-16 methyl substituent is present.[2] Our interest in corticoids such as Betamethasone, and the availability of 9α-hydroxyandrost-4-ene-3,17-dione **1**, led us to examine routes to the key Betamethasone intermediate **8**, from **1**. Some solutions to this problem were described in our earlier papers[2] involving C-17-hydroxy pregnane and C-17 oxazoline intermediates. In this paper, we describe an alternative approach for effecting this important transformation *via* a C-17 allene, together with new, mild and selective conditions for the introduction of 9,11 unsaturation.

Oxidation of steroidal allenes has been reported[3] previously using OsO_4 or per-acid. These methods suffer from the use of a volatile and toxic oxidant and low yields, respectively. Recent reports[4] demonstrated that simple allenes can be converted to bis(epoxides) under mild and essentially neutral conditions using dimethyldioxirane and that these bis(epoxides) react with a number of nucleophiles to give ring opened products. With the introduction of this remarkably mild oxidant for the oxidation of allenes, it was of interest to study its reactivity with steroidal allenes such as **5** with the objective of obtaining corticosteroids.

Our synthetic route to **8** is outlined in Scheme 1. Compound **1** was converted to the 16β-methyl, A-ring protected derivative **2a** (70%) as previously described.[2] When treated with LiHMDS (2eq) followed sequentially by methyl chloroformate and MeOH/MeONa, compound **2a** produced **2b** together with the 16α methyl epimer (ratio 96:4). The yield for this sequence was about 80%. Some base-water soluble material was also formed which was not characterised, but might reasonably be attributed to methoxycarbonylation at C-16. To prevent this from occuring, the enolate was initially trapped with TMS-Cl (1.1eq.) followed by subsequent treatment with methyl chloroformate. This produced the 16β methyl compound **2b** in an improved 93% yield after desilylation with methanol. The ratio of C-16 β:α was 98:2. This C-9 protected C-17 ketone **2b** was found to react readily with lithium acetylide (THF, excess acetylene gas, LDA, -40° to -20°C) to form **3a** requiring 4.8 equivalents LDA to give a ratio of **3a**:**2b** of 97:3.[5] Using 2.4 equivalents of LDA the ratio changed to a significantly less favourable 87:13. It occurred to us that the requirement for a large excess of



a) ref. 2. b) THF, i) LiHMDS, ii) TMSCl, iii) MeOCOCl, iv) MeOH. c) THF, acetylene, LDA, LiCl. d) THF, NaH, $MeOCO_2Ph$. e) DMSO/MeOH, $Pd(OAc)_2$ - Bu_3P, ammonium formate. f) THF, aq. TFA. g) CH_2Cl_2, dimethyl dioxirane. h) CH_2Cl_2 / H_2O, NBu_4 OAc. i) CH_2Cl_2, TFA.

Scheme 1

lithium acetylide might be a consequence of "aggregation" of the organometallic; and, indeed, it was found that a mixture of 2.4 eq LDA and 2 eq LiCl served to promote the reaction to give a ratio of **3a**:**2b** of 96:4. From this procedure **3a** could be isolated in about 95% yield.

We next envisaged a Pd(0) mediated propargylic ester reductive rearrangement to form the allene **4**, and for this we chose reaction of a propargylic carbonate as these had been observed to be superior to, for example, acetates in other systems.[6] In principle, the lithium acetylide reaction could be quenched directly with methylchloroformate, but given the potential to form the reportedly unstable tris(ethynyl) methanol[7] from the excess acetylide, we decided a second acylation step would be preferable.

Treatment of **3a** with the usual acylating conditions (MeOCOCl with DMAP) failed to provide **3b** in a clean manner. Alkoxide formation with 1 eq of base (n-BuLi or LiHMDS) followed by quenching with methyl chloroformate also failed to provide a clean esterification product; and similarly, reaction with NaH in the presence of methyl chloroformate (in THF) failed to acylate the alcohol function. To overcome this difficulty an alternative method of acylation was developed whereby the alcohol **3a** was treated with NaH (2eq) in THF in the presence of methyl phenyl carbonate. Presumably, in this system, phenol (initially present adventiously)

acts as a "carrier" for the irreversible base without ameliorating the reactivity of the acylating reagent. Utilising this method an efficient C-17 esterification was achieved (**3a** to **3b** 95% yield).[8]

The reaction of **3b** in an equal mixture of DMSO and methanol [$Pd(OAc)_2$-Bu_3P (2.5 mol %), ammonium formate (4eq), 45°C] produced the desired allene **4** (86%), along with unreacted starting material (4%). Also formed were by-products derived from elimination, (4%), rearrangement, (2%), and over-reduction, (3%). Hydrolysis (THF, aq TFA) of the dienol-ether protecting group from this mixture, followed by isolation from methanol, provided the enone **5** in 93% yield.

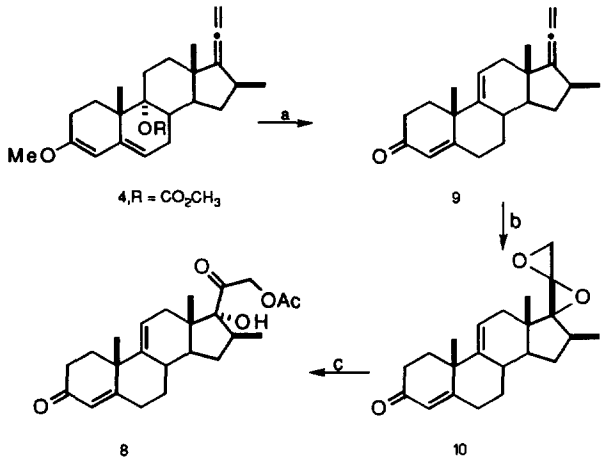
The literature procedures for the oxidation of allenes with dimethyldioxirane involve the use of isolated reagent.[4] We decided to study the oxidation with dimethyldioxirane, generated *in situ* , in the belief that this would offer some practical advantages. The reaction, in methylene chloride, in the presence of acetone and pH 7 phosphate buffer, with the slow addition of aqueous oxone® to substrate **5**, while maintaining the pH at 7.6 by the concomitant slow addition of 5M potassium carbonate, resulted in the clean conversion to two new products. Substituting either toluene or ethylacetate for methylene chloride in this reaction was detrimental. These new products have been characterised only by ^{1}Hnmr which indicates that they are a mixture of two diastereomeric (at C-20) bis(epoxides) **6** in about a 2:1 ratio. Their structure was further corroborated by their subsequent chemical reactivity with nucleophiles. Thus the mixture of epoxides **6** when treated with tetrabutylammonium acetate in methylene chloride-water gave the corticoid **7**.[9] The overall yield from **5** was measured at 85%.

The elimination of the 9α-hydroxy group poses another challenge in order that **1** can be used commercially; and it has been reported that this transformation can be difficult to achieve.[10] An extremely facile elimination of the methyl carbonate group was observed to take place when **7** was subjected to a brief treatment with TFA in methylene chloride at ambient temperature, giving rise to the 9,11 olefin **8** in essentially quantitative yield. This product was identical in all respects to an authentic sample. Under similar reaction conditions, we observed that a 9α-hydroxy group was stable. Notably, the use of the C-9 carbonate permits a selective dehydration at C-9 in the presence of the unprotected C-17 hydroxy substituent of the corticoid side-chain.

Alternatively, an extended deprotection of **4** resulted in the direct formation of the tetra-ene **9** in good yield. This material, when oxidised and treated with acetate as described above, (Scheme 2), produced **8** in about 80% yield. In the crude product no evidence for epoxidation of $\Delta^{9,11}$ was detected by ^{1}Hnmr.

Intermediate **8** can be converted to Betamethasone by known procedures.[11]

In summary, we have demonstrated new syntheses of the Betamethasone intermediate **8**, from 9α-hydroxyandrost-4-ene-3,17-dione **1**. Key features of this approach are a high yielding diastereoselective oxygenation of steroidal allenes (**5** and **9**) containing the pharmaceutically important 16β-methyl substituent; and the carbonate ester as a new derivative of the 9α-hydroxy substituent. We have found that the 9α-carbonate group is readily prepared, is stable to many reaction conditions, and permits a facile and selective introduction to 9,11 unsaturation without the need to protect the C-17 alcohol of corticoid side-chains.



a) THF, aq. TFA. b) CH_2Cl_2, dimethyl dioxirane. c) CH_2Cl_2 / H_2O, NBu_4 OAc.

Scheme 2

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References and notes:

1. Nitta, I.; Ueno, H. *New Synthesis of Corticoids*, in *Yuki Gosei Kagaku Kyokaishi*, **1987**, 45, 445.
2. Carruthers, N.I.; Andrews, D.R.; Garshasb, S.; Giusto, R.A. *Perkin I*, 1992, 1195. Carruthers, N.I.; Garshasb, S.; McPhail, A.T. *J. Org. Chem.* **1992**, *57*, 961.
3. Biollaz, M.; Haefliger, W.; Velarde, E.; Crabbe, P.; Fried, J.H. *J. Chem. Soc., Chem. Comm.*, **1971**, 1322; Crabbe, P.; Velarde, E. U.S.Patent, **1972**, 3,681,410.
4. Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338.
5. The use of amine bases helps suppress the formation of the insoluble dilithium acetylide., Timko, J.M.; VanRheenen, V.H.; Cha, D.Y. European Patent, **1986**, 148616 A2.
6. Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196; Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis*, **1987**, 603.
7. Dillard, R.D.; Pavey, D.E.; *J. Org. Chem.*; **1971**, *36*, 749.
8. In a control experiment with the 9,17-diol corresponding to **3**, the C-9 alcohol was inert to these acylating conditions.
9. The importance of the C-16 methyl substituent in influencing the epoxidation reaction was indicated by the observation that the C-17 allene derived from Ethisterone (C-16 des methyl) produced a mixture of isomers at C-17.
10. VanRheenen, V.; Shephard, K.P. *J. Org. Chem.* **1979**, *44*, 1582.
11. Charney, W.; Herzog, H.L. *Microbial Transformations of Steroids*; Academic Press, New York, 1967. Rauser, R.; Oliveto, E.P. U.S. Patent 3,164,618, 1965.

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