Tetrahedron Letters, Vol. 33, No. 34, pp. 4913-4916, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .0
Pergamon Press Ltd

A CONVENIENT ACCESS TO 16-METHYLENE AND 16β-METHYL CORTICOSTEROIDS BY A NOVEL TRANSFORMATION OF GEMINAL BIS(PHENYLSULPHINYL) INTERMEDIATES

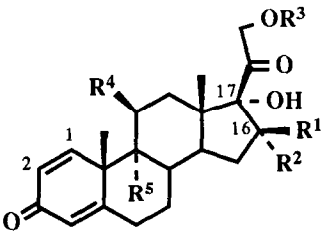
Jean Boivin, Christine Chauvet, and Samir Z. Zard*

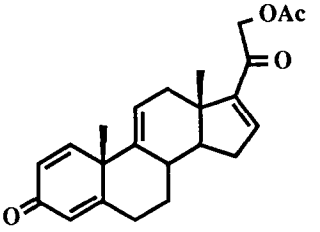
Laboratoire de Synthèse Organique associé au C.N.R.S.,
Ecole Polytechnique, F-91128 Palaiseau, France.

Abstract: 16α–Bis(phenylsulphinyl) methyl pregnane derivative 7 gives, by a series of eliminations and rearrangements, the corresponding 16-methylene intermediate 4 on heating in the presence of triphenylphosphine. Regio- and stereoselective hydrogenation of the latter using Wilkinson's catalyst furnishes 16β–methyl corticosteroid 5.

Following the discovery of the therapeutic potential of cortisone nearly forty years ago, a tremendous amount of work has been devoted to the search for more potent and more selective analogues as well as for developing viable routes for their large scale preparation[1,2]. Indeed, the commercial production of corticosteroids constitutes one of the most complex processes in the pharmaceutical industry.

Early on, it was found that a methyl group in the 16-position not only reduced the usually undesired mineralocorticoid activity but also protected the side-chain against metabolic degradation, and therefore increased the lifetime of the drug in the organism[1]. This has led to clinically very valuable corticosteroids such as dexamethasone **1** and betamethasone **2**.



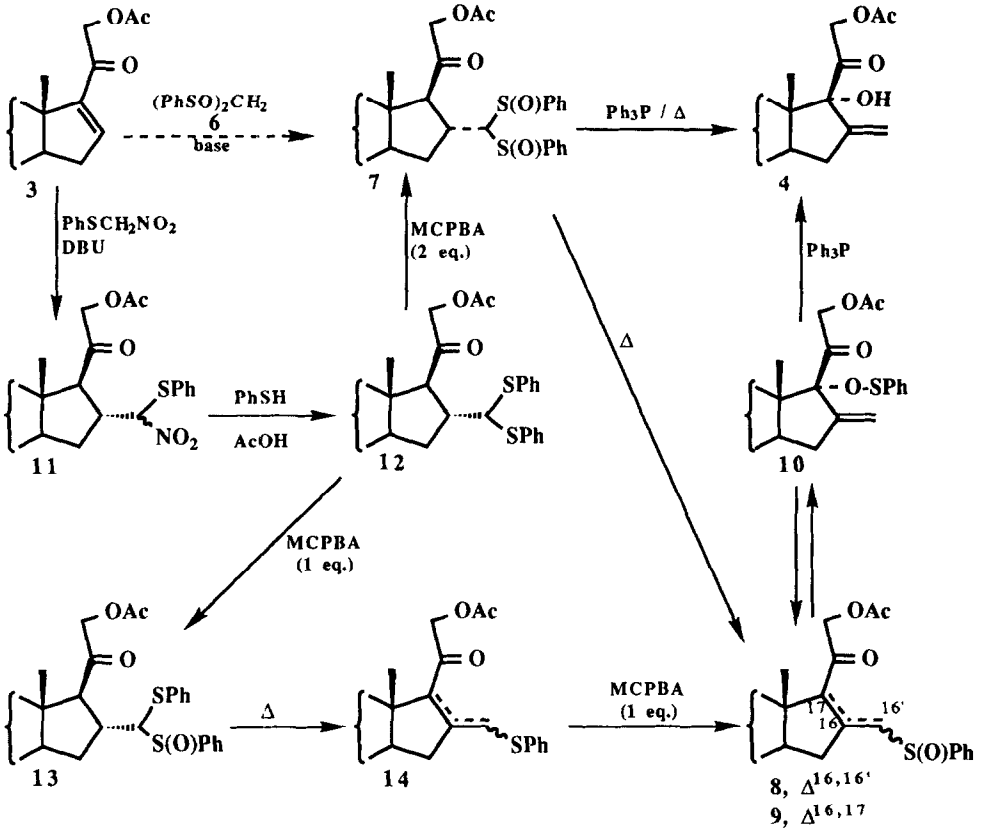


3

1, R^1= R^3= H; R^2= Me; R^4= OH; R^5= F
2, R^1= Me; R^2= R^3= H; R^4= OH; R^5= F
4, R^1, R^2= CH_2; R^3= Ac; R^4, R^5= $\Delta^{9,11}$
5, R^1= Me; R^2= H; R^3= Ac; R^4, R^5= $\Delta^{9,11}$

Because the β-face in steroids is generally less accessible, the 16β- methyl group is much harder to introduce than the corresponding α-isomer[1,2]. Moreover, existing methods are not compatible with many of the functionalities present in the final molecules, especially with the dienone system in ring A[2,3]. The 16β-methyl must therefore be grafted on less functionalised precursors causing the synthetic tree leading for example to **1** and **2** to branch quite early. The result is an expensive increase in the number of synthetic operations that have to be duplicated in the 16α- and 16β-methyl series.

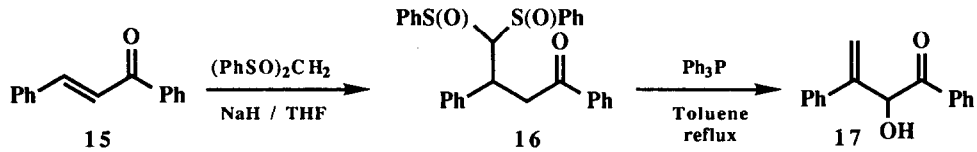
In this Letter, we describe a novel, more economical, approach to this problem which allows the introduction of the 16β-methyl group on a highly advanced intermediate, namely dienone **3**. The route we have adopted hinges on the possibility of acceding to the 16-methylene-17α-hydroxy intermediate **4** which upon selective hydrogenation from the α-side should lead to the desired steroid **5**.



Scheme 1

The planned access to precursor **4** is shown in scheme 1. It begins with a Michael addition of bis(phenylsulphinyl) methane **6**[4] followed by a novel and direct transformation (via **8**,**9**, and **10**) of adduct **7** into **4** mediated by heat and the presence of a thiophile such as a phosphine. Thus, thermal syn elimination of one of the sulphoxide groups would produce intermediate **8** which should isomerise easily into the better conjugated enone **9** through the now stabilised enolate of the 20-ketone. As remaining sulphoxide becomes allylic in the process, it should equilibrate through the well-known [2,3] sigmatropic rearrangement[5] with its sulphenate isomer **10**. In the presence of the phosphine, the latter would be selectively cleaved to give ultimately the desired 16-methylene-corticosteroid **4**. The correct stereochemistry of the hydroxy group should follow from the expected preferred rearrangement of the sulphoxide moiety from the α-face due to shielding of the β-face by the 13-methyl group[6].

We first tested this conception on chalcone **15**, a simple α,β-unsaturated ketone. Michael addition took place cleanly to give the expected adduct **16** as a mixture of diastereomers. Upon heating in toluene in the presence of two equivalents of triphenylphosphine, a smooth reaction occured to give the expected allylic alcohol **17** in 60% yield (scheme 2).



Scheme 2

Encouraged by these results, we attempted to apply the sequence on steroid **3**. Unfortunately, we were unable to perform the Michael addition of the bis(sulphoxide) **6** under a variety of conditions. Either no reaction occured or a complex mixture of compounds was obtained. We nevertheless found a less direct way to **7** based on the chemistry of the nitro group. Thus, in contrast to the less acidic bis(phenylsulphinyl)methane, (phenylthio)nitromethane[7] reacted smoothly and selectively with **3** in the presence of DBU in t-butanol-tetrahydrofuran to give adduct **11** in almost quantitative yield. On heating with thiophenol in acetic acid, this compound was easily converted (70%) into dithioacetal **12**. This mild and synthetically useful transformation of a geminal (phenylthio)nitro group into a dithioacetal does not seem to have been reported previously.

With the dithioacetal in hand, it only remained to oxidise it into the desired bis(sulphoxide) **7**. This was accomplished in 57% yield using two equivalents of MCPBA. We were delighted to find that heating the mixture of diasteriomers thus obtained in toluene to eliminate one of the sulphoxide groups, followed by addition of methanol and triphenylphosphine produced the long sought key 16-methylene intermediate **4** in 53% unoptimised yield.

This novel and crucial transformation involves a rather large number of discrete intermediates (including the various isomers arising from the chirality of the sulphoxide groups). In order to help monitoring the progress of the reaction, we prepared some of these intermediates by carrying out the sequence in a stepwise fashion. Thus oxidation of thioacetal **12** with one equivalent of peracid gave monosulphoxide **13** which was smoothly converted into a mixture of vinylic and allylic sulphides **14** (86% yield) upon thermolysis in toluene. Further oxidation with peracid produced the corresponding sulphoxides **8** and **9** which were directly treated with triphenylphosphine in refluxing toluene-methanol to give ultimately **4** in 57% yield.

Selective reduction of the exocyclic olefin could not be achieved by hydrogenation using palladium on carbon catalysts despite some indication in the patent literature[8] as to its feasibility. We were in fact surprised and dismayed to find that the 1,2-double bond was reduced faster than the 16-methylene group. However, reduction with Wilkinson's catalyst[9] proved much more useful giving about 90% yield of the

16β-methyl corticosteroid **5** identical to an authentic specimen. Less than 10% of unwanted further reduction of the 1,2-double bond took place.

Efforts to introduce the bis(sulphoxide) moiety directly via a Michael addition are being pursued as this will significantly shorten the synthetic scheme. Nevertheless we believe that the viability of this novel and concise approach towards 16-methylene and 16β-methyl steroids has been demonstrated. Moreover, this work has uncovered some interesting transformations of geminal bis(sulphoxides) and geminal (phenylthio)nitro derivatives which should find more general synthetic applications.

Acknowledgements: We wish to thank Dr. J. Buendia (Roussel-Uclaf) for a gift of dienone **3** and for fruitful discussions, and Roussel-Uclaf for generous financial support.

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(Received in France 22 May 1992)