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Introduction of C17 side chains in steroids. The use of phosphoryl substituted methyl isocyanides as connective reagents

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SUMMARY

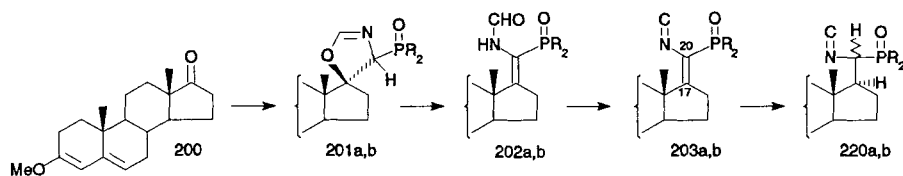
Steroids are an important group of natural products, which play a prominent role in life. In many steroids the basic ring system is equipped with a side chain at C17. Sub-classes of steroids carry characteristic side chains, which may differ considerably in length and functional groups. The physiological activity of steroids relies in part on size and structure of the side chain. This explains continued interest in the search for general applicable methods for the construction of steroid side chains, and especially for methods that allow ready introduction of additional functionality. Recently, there has been a revival in steroid chemistry, due to the discovery of new steroid activities. The discovery of the potential cytostatic action of 1α -25-dihydroxy vitamin D_3 is one example, which has served as a source of inspiration for many organic chemists to (re)enter the field of steroid chemistry. Furthermore, a new interesting area in steroid chemistry is formed by the action of steroids as inhibitors (antagonists) of enzymes, which are responsible for *in vivo* steroid synthesis and metabolism. Continuous industrial interest for new alternative steroid syntheses exists, not only to improve steroid applications or to find new active compounds, but also to dodge the many patents applied in the steroid field.

Nowadays microbiological degradation of vegetable sterols, such as β -sitosterol, provides an efficient low-cost method of manufacturing 17-oxosteroids. This makes 17-oxosteroids ideal starting materials for chemical manipulation into more elaborated steroidal molecules. The results of our investigation towards new methods for the introduction of various side chains in 17-oxosteroids are described in this thesis.

A general introduction on steroids is given in Chapter I. A short survey of natural steroid sources and physiological action is described, as well as a brief review on partial and total synthesis of steroids. Furthermore, an introduction is presented on aspects of the chemistry of the isocyanide functional group, which plays an important role throughout this thesis.

Chapter II describes reactions of commercially available diethyl (isocyanomethyl)-phosphonate (PhosMIC) with 17-oxosteroids. *t*-Butyl methyl ketone was used as a model substrate for these reactions, and solvent/base variations have been investigated. By the use of this model-system problems of low reactivity and selectivity in the reaction of PhosMIC with ketones were solved. It was established that the combination potassium hydride with dichloromethane gave oxazolines of type **201** with a remarkably high selectivity.

Next, the results obtained with *t*-butyl methyl ketone were transferred to 17-oxosteroids. In an one-pot process, 17-oxosteroids such as compounds **200** were converted *via* oxazolines **201** as intermediates into formamido steroids **202**. The formamido groups of **202** were easily dehydrated to yield (*E*)-17-[(dialkylphosphoryl)isocyanomethylene] steroids **203**, which represent a new class of compounds. Furthermore, the reduction of the exocyclic double bond of steroids **203** enabled us to synthesize steroids **220**, with two additional stereogenic centers. One hydrogen was introduced stereospecifically in the important C17-position, and the other hydrogen was introduced at C20.

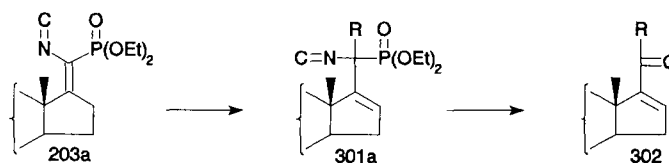


An example of the conversion of 17-oxosteroids **200** to intermediates **203** and **220**

Summary

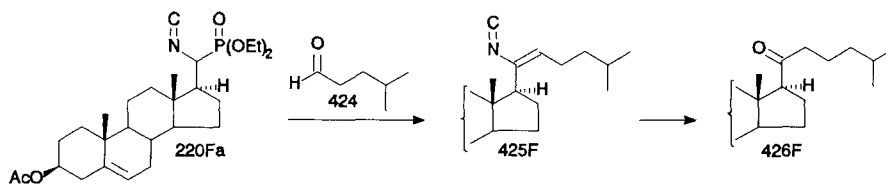
The new intermediates **203** and **220** carry short side chains with functional groups suitable for further elaboration. These side chains, the "handles", offer the possibility to develop new methods for the introduction of polyfunctional steroid side chains into 17-oxosteroids. Thus, the isocyano- and phosphorus groups of steroids **203** and **220** were used in a connective approach to attach one or more carbon fragments to 17-oxosteroids.

In Chapter III a series of new derivatives of α -isocyanomethylphosphonates **301a** is described, which were formed by allylic alkylation of (*E*)-17-[(diethylphosphono)isocyanomethylene] steroids **203a** at C20. Simultaneous with alkylation at C20 a double bond formed at C16-C17, which is desirable in steroid chemistry for further functionalization. It was possible to hydrolyze compounds **301a** under relatively mild conditions with diluted perchloric acid to Δ^{16} -20-ketosteroids **302**. By doing so we were the first to show that geminal N and P substituted carbon compounds do react as *N,P*-acetals. We have proposed a mechanism for this conversion of *N,P*-acetals to ketones, in which oxidation of an intermediate at nitrogen by perchloric acid plays a crucial role. After this oxidation, an 'aza-Wittig' reaction is assumed to occur. Some evidence for this mechanism was obtained by detecting the eliminated phosphate group by *in situ* ^{31}P NMR measurements.



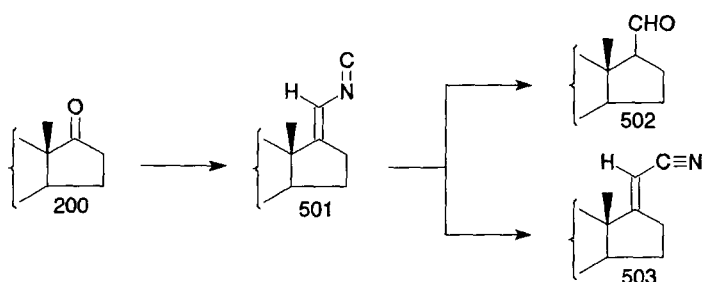
An example of the conversion of steroids **203** into Δ^{16} -pregnanes **302**

Chapter IV describes Wittig-Horner-Emmons reactions of steroids **203a** and **220a** with several aldehydes and with acetone. In this way, a series of polyfunctional unsaturated $\Delta^{16,20}$ -20-isocyanosteroids (**412**, comparable to **425F**) was formed. It proved possible to hydrolyze steroids of type **412** with diluted sulfuric acid in high yield to a variety of both new and known Δ^{16} -20-ketosteroids **413** (comparable to **426F**). Neutral hydrolysis of steroids **412** was possible also, *via* an intermediate $\Delta^{16,20}$ -20-isocyanosteroid, leading to A-ring protected 16-dehydropregesterone. The Wittig-Horner-Emmons reaction, together with the described hydrolyses, provides a new method particularly suitable for the introduction of steroid side chains with a variety of size, structure and functional groups. This is demonstrated by a stereoselective synthesis of progesterone, and by a stereoselective synthesis of 20-keto-21-norcholesterol **426F**.



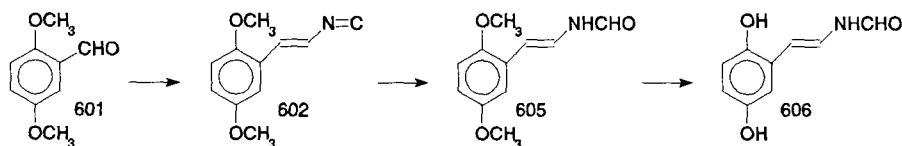
The stereoselective synthesis of 20-keto-21-norcholesterol **426F**

In Chapter V, a series of α,β -unsaturated isocyanosteroids **501** is described, which are formed by a *n*-BuLi induced Wittig-Horner-Emmons reaction of PhosMIC and 17-oxosteroids **200**. Acid hydrolysis of the α,β -unsaturated isocyanosteroids **501** gave 17-formylsteroids **502** in high yields. Thus, our application of the Wittig-Horner-Emmons reaction, followed by acid hydrolysis, provides a straightforward method for one carbon homologation of 17-oxosteroids **200** to 17-formylsteroids **502** in a short and effective manner. Furthermore, the introduction of a second carbon-atom into steroids **200** proved possible with PhosMIC. To our surprise, a thermal rearrangement takes place upon heating at 200 °C, which converts α,β -unsaturated isocyanosteroids **501** stereospecifically and in high yield to α,β -unsaturated cyanosteroids **503**. This means that the isocyano-carbon also can be used in steroidal carbon-carbon bond forming reactions. We obtained a nearly quantitative conversion when the rearrangements were carried out without solvents. With these results, we are the first to describe actual examples of the thermal rearrangement of α,β -unsaturated isocyanides to α,β -unsaturated cyanides.



Conversion of **200** into 17-formylsteroids **502** and into α,β -unsaturated cyanosteroids **503**

In Chapter VI, as a spin off of the synthesis of α,β -unsaturated isocyanosteroids, a new synthesis is developed of erbstatin **606**, which is an antibiologically active fermentation product equipped with an α,β -unsaturated formamide group. Erbstatin has been shown to inhibit the growth of human epidermoid carcinoma cells in tissue cultures. Such inhibitors have the potential of providing leads to new classes of therapeutic agents for treatment of skin cancer. We have introduced the α,β -unsaturated formamide functionality into the phenolic aldehyde **601** by a Wittig-Horner-Emmons reaction of aldehyde **601** with PhosMIC, followed by controlled hydration of the α,β -unsaturated isocyanide group of **602**.



Synthesis of erbstatin **606** via α,β -unsaturated isocyanide **602**