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Review

Steroids as chiral model compounds for selective reactions with metals

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Abstract

Our own work on steroid compounds with defined conformation as chiral model compounds for investigations of chemo-, regio- and stereoselectivity of metal-mediated new reactions is reviewed. Reactions with nickelacycles, (π-allyl)zirconoxycarbene complexes, iron tricarbonyl complexes of dienes and 1-azadienes, the Ru-catalyzed synthesis of 1,3-dihydropyrrol-2-ones from 1-azadienes, the Pd-catalyzed cyclopropanation of 1-azadienes, syntheses with cuprio steroids, copper complexes of amino alcohol derivatives and the copper-mediated hydroxylation of nonactivated C–H bonds with molecular oxygen are discussed.

Keywords: Steroids; Selectivity; Metallation; Cyclopropanation; Copper; Hydroxylation

Contents

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1. Introduction

Steroids are a well-known class of tetracyclic chiral natural products with differing biological activities. In the past, the total syntheses of those compounds have been developed, especially in the case of estra-1,3,5(10)-trienes and 19-nor-androstanes. In addition to the pharmaceutical and medicinal interests, steroid compounds are also quite suitable homochiral model compounds for chemo-, regio- and stereoselective investigations. They possess a well-defined conformation of the steroid framework, which allowed the placement of substituents in different spatial environments. In addition, there is a great structure variability, caused by different tetracyclic frameworks (estratrienes, androstanes, cholestanes, etc.) with different ring junctions (5α/5β, 14α/14β, etc.) and differing positions (1–27) at the framework or at side chains with two configurations (α and β). For several years, we have been interested in binding metals to steroid compounds with the aim to find new selective reactions. The results are summarized in this report together with a recent work of cooperation (D. Walther, Jena, G. Erker, Münster, W. Imhof, Jena, H. Görls, Jena, E.-G. Jäger, Jena).

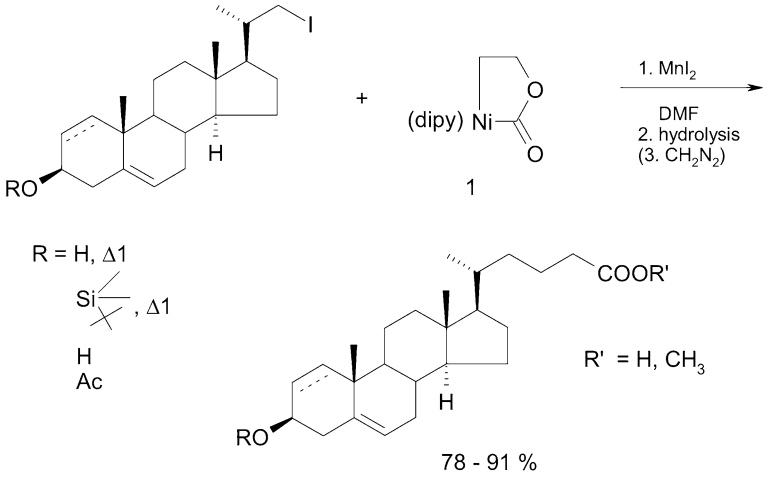
2. Syntheses with metallacycles

In the course of our work on vitamin-D_3 metabolites and their analogs, we have become interested in nickelacycles such as compound **1** (Scheme 1). Together with D. Walther (Jena), we could demonstrate that **1** can act as a propionate homoenolate C_3 building block. **1** can be alkylated with organic iodides in dimethylformamide under addition of MnI_2. In this way, we succeeded in synthesizing C_{25} steroid carboxylic acids or methyl esters (after the addition of diazomethane solution) from C_{22} steroid iodides (Scheme 1) in good yields. Remarkably, this procedure tolerates quite a few functional groups (OH, COOR, allylic alcohols, silylated alcohols) [1].

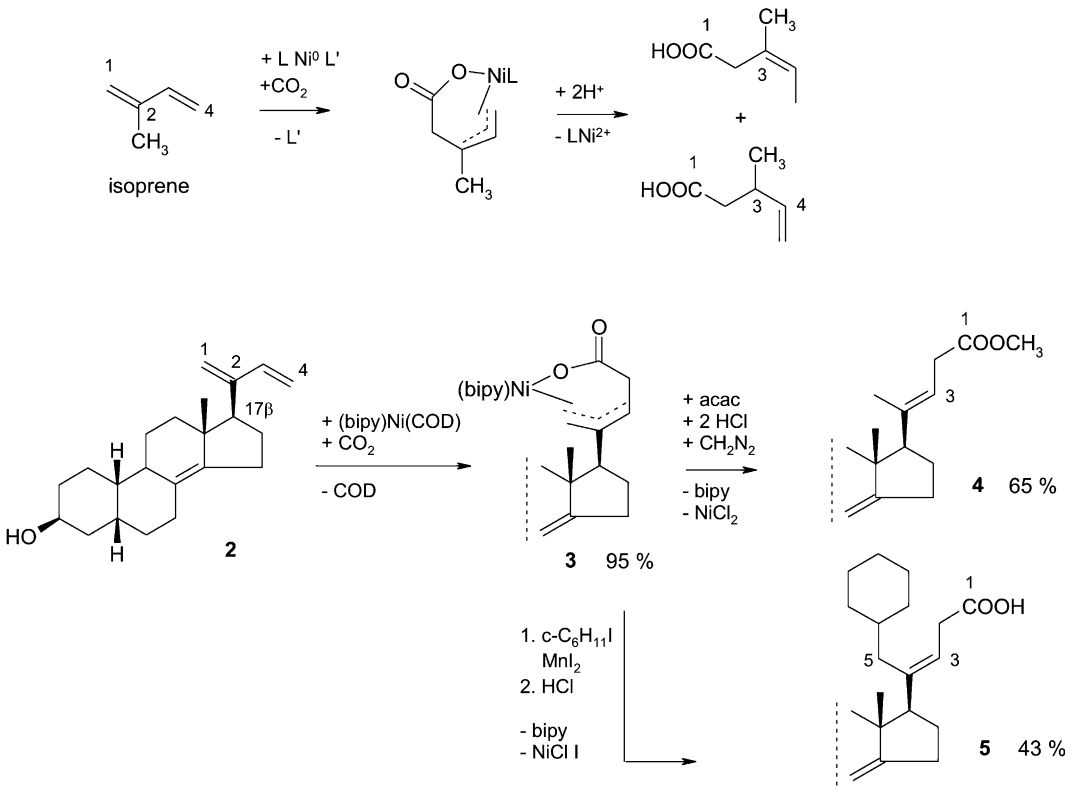
Nickelacycles with a nickel-η^3-allyl function can be synthesized from Ni(0) complexes, butadienes and CO_2 [2]. When 2-substituted butadienes are employed, coupling of CO_2 in the 1- or 4-position is possible. For isoprene, a regioselective coupling in positon 1 takes place and 3-substituted pentene acids are the main products obtained after hydrolysis (Scheme 2).

When one employs butadiene, which has been connected in the 2-position to a steroid (17β-position, compound **2**), the very stable nickelalactone **3** with a η^3-allyl function could be obtained when reacted with (dipy)Ni(COD) and CO_2. **3** gave, after reaction with acetylacetone, hydrolysis and the successive reaction with diazomethane, the methyl ester of a (*E*)-3-pentene acid substituted in 4-position by the steroid (17β-position, compound **4**). The nickelalactone **3** could also be regioselectively alkylated with cyclohexyl iodide, giving the (*E*)-3-pentene-acid substituted in 5-position (compound **5**). Alkylations with methyl or ethyl iodide are not regioselective. These results [3] clearly demonstrate that, in contrast to isoprene, a coupling of **2** with CO_2 takes place in 4-position caused by the steric demanding steroid group in position 2.

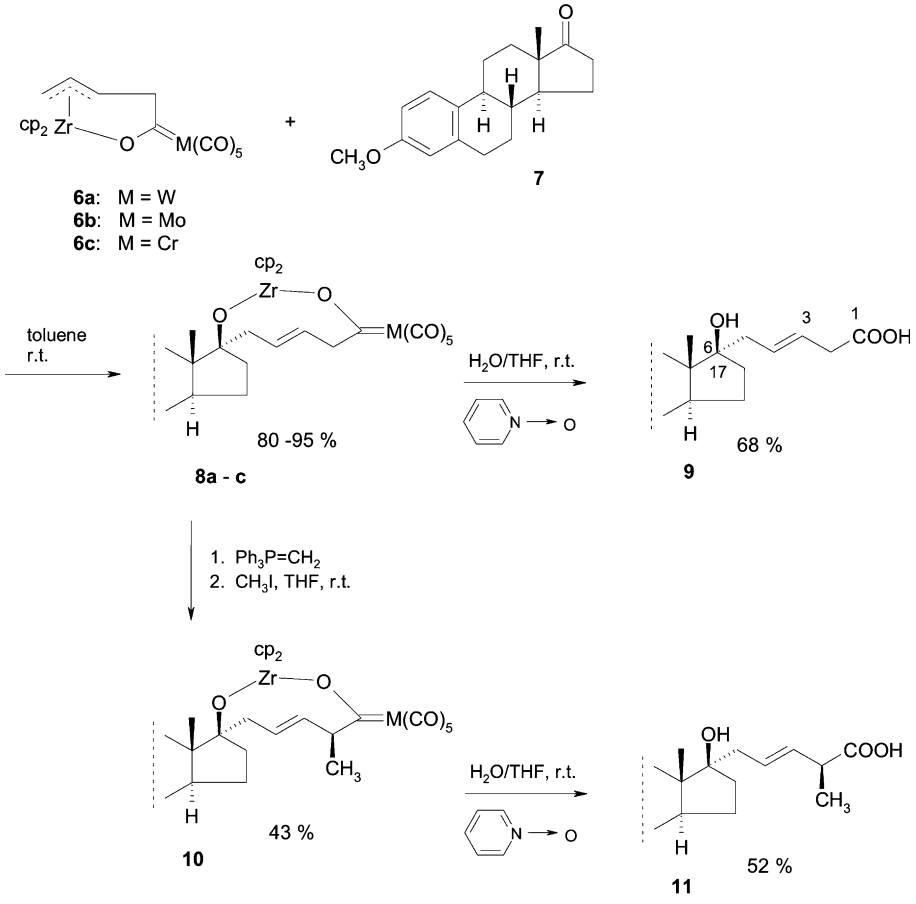
G. Erkers group has developed an interesting method for obtaining seven-membered (π-allyl)zirconoxycarbene complexes **6** (Scheme 3, M = Cr, Mo, W). Complexes **6** are quite simple to prepare by reacting (butadiene) zirconocene with a metal hexacarbonyl. **6** can react with ketones under C–C coupling to form nine-membered zirconoxycarbene complexes. Hydrolysis of the Zr–O bonds and the following oxidative cleavage of the metal carbene opens the way to metal-free (*E*)-3-unsaturated-6-hydroxy carboxylic acids. The reaction of 3-methoxy-estra-1,3,5(10)-triene-17-one (**7**) with complexes **6** gave high yields of the nine-membered metallacycles **8**. Investigations of the tungsten complex **8a** demonstrated that the new C–C bond at C17 of the steroid has, as expected, the 17α-configuration (>98%). In addition, the selectivity of the second chirality element (planar chirality initiating from the E-configuration of the double bond in the nine-membered metallacycle



Scheme 1. Nickelacycle **1** as propionate building block.



Scheme 2. Synthesis and reactivity of nickelacycles.



Scheme 3. Reactivity of zirconoxycarbene complexes.

8a) was very high ($\geqslant$98%) and was achieved under thermodynamic control. This implies that two new chirality elements have been introduced with a very high diastereoselectivity. Successive hydrolysis and oxidative cleavage resulted in **9**, a compound with a new side chain [(*E*)-3-pentenoic acid] in the 17α-position and a hydroxy group in the biologically important 17β-position [4,5]. Starting with **8a**, a third chiral center could be introduced, also with high stereoselectivity. Deprotonation of **8a** with methylene triphenylphosphorane and methylation with methyl iodide gave the (*S*)-2-methyl compound **10** with a very high diastereoselectivity (97:3) and regioselectivity. From **10**, compound **11** with a 17α-[(2*S*,3*E*)-2-methyl-3-pentenoic acid] side chain is available [5]. These investigations show that the reactions with high diastereo- and regioselectivities are possible when metallacycles are employed as templates.

3. Iron tricarbonyl complexes

3.1. Ergosterol

Ergosterol with its sensitive 5,7-diene system is a suitable starting material for the synthesis of biologically very interesting vitamin D metabolites. One of the protecting groups for the 5,7-diene system is the iron tricarbonyl group [6,7]. After protection, the side chain double bond can be hydroxylated with OsO_4 [7]. We could show that the iron tricarbonyl group of diol **12** is stable against oxidation with MnO_2 in chloroform or $Pb(OAc)_4$ in pyridine/dichloromethane. Under these conditions, aldehyde **13** could be obtained with good yields without epimerization at C22. In addition, **13** can be reduced with calcium borohydride to alcohol **14** and oxidized with $KMnO_4$ to carboxylic acid **15** under preservation of the iron tricarbonyl group [8] (see Scheme 4).

3.2. 1-Azadienes from steroid amines and amino alcohols

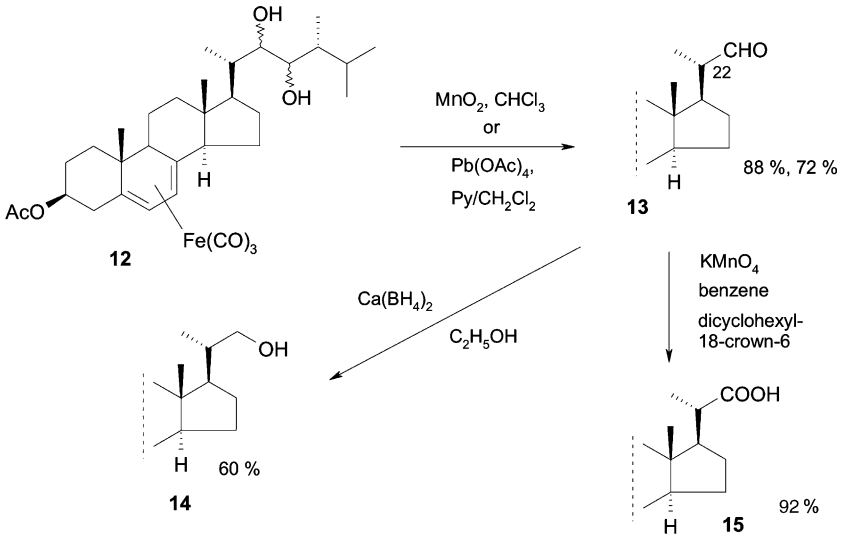
Planar-chiral (1-azadiene)$Fe(CO)_3$ complexes can usually be obtained from chiral 1-azadienes normally as diastereomeric pair [9–11]. In some cases, the diastereomers could be separated by crystallization [12–15]. In solution, epimerization of pure diastereomers has been observed.

W. Imhof (Jena) has succeeded in showing that the condensation products of 16- and 17-amines and 16,17-amino alcohols of the estra-1,3,5(10)-triene series with cinnamic aldehyde (chiral steroid 1-azadienes) react with $Fe_2(CO)_9$ to form chiral $Fe(CO)_3$ complexes. In this manner, high diastereoselectivies could be obtained for the first time. The pure diastereomers have a remarkable configurational stability in solution [16].

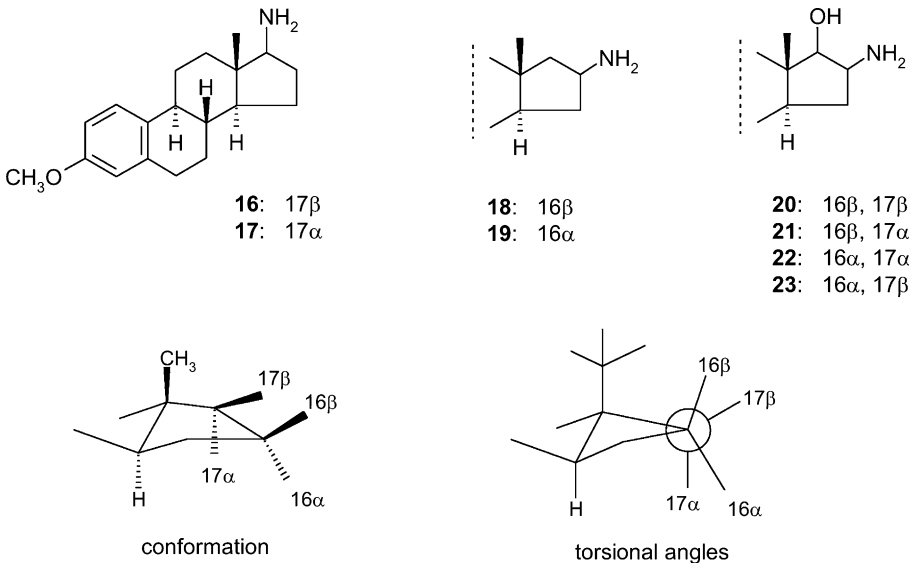
In this study, model compounds with a well defined conformation have been chosen. These include the 16- [17] and 17-amines [18] and the 16-amino-17-hydroxy compounds of 3-methoxy-estra-1,3,5(10)-triene [19] and their derivatives.

Depending upon the position and the configuration of the amino group in our model compounds, the steric relations are quite different and well defined. The quasiequatorial 17β-position is hindered by the *cis*-13β-methyl group. The quasiaxial 17α-, the bisectional 16β- and especially the bisectional 16α-amine are not influenced much by the 13β-methyl group. The 16-amino group in the *cis*-amino alcohols is strongly influenced by the 17-OH group (small torsional angles). In contrast, the 16-amino group in *trans*-amino alcohols has little contact with the 17-OH group (larger torsional angles, see Scheme 5).

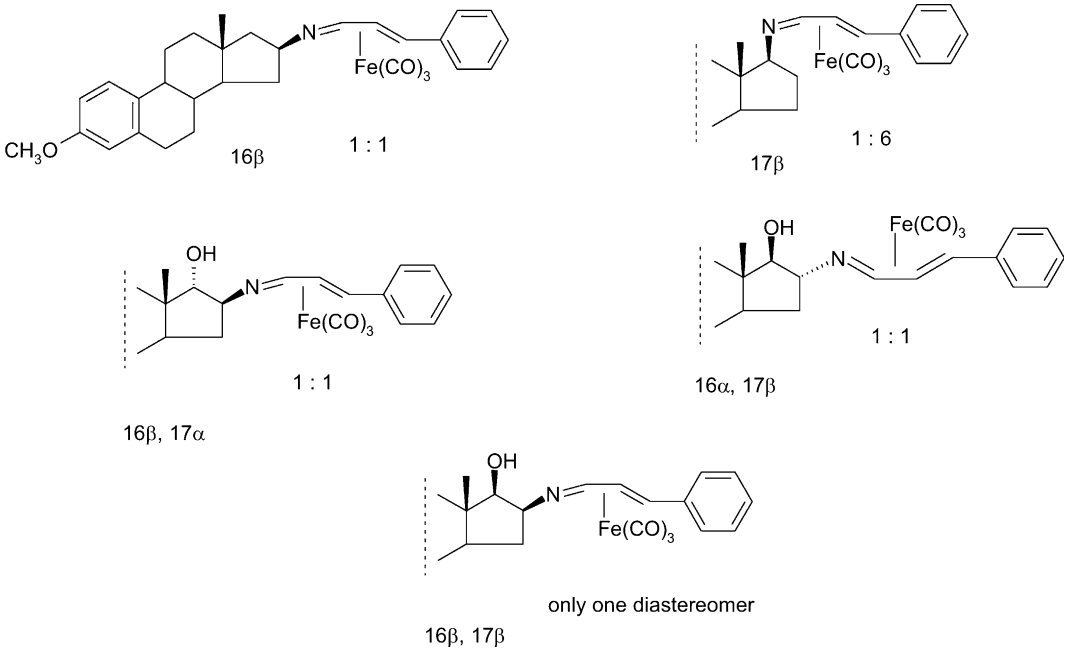
These stereochemical relations are also valid for the 1-azadienes (Scheme 6), which allowed a fine substituent tuning for the reaction with the $Fe(CO)_3$ unit. In addition, we could show that imines and also the 1-azadienes possess a preferred conformation. The torsional angle between the



Scheme 4. Iron tricarbonyl as protecting group for ergosteryl acetate.



Scheme 5. Model compounds.



Scheme 6. Configuration and diastereoselectivity.

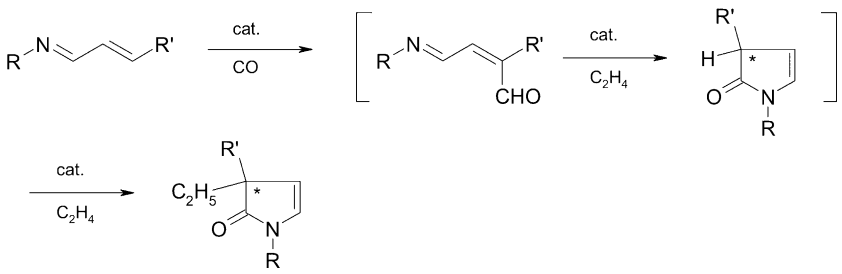
N=C bond and the C–H bond (H–C_{ring}–N=C) is normally quite small [20] (see also Scheme 11).

As seen in Scheme 6, the 1-azadienes from the 16β-amine and the *trans*-16,17-amino alcohols react in a non-stereospecific manner. The 1-azadiene from the 17β-amine gave an excess of one diastereomer. This could be crystallized for an X-ray analysis and demonstrates the described preferred conformation for the imine, which had previously been reported [20]. The $Fe(CO)_3$ group points away from the 13β-methyl group. The 1-azadiene from the 16β,17β-amino alcohol reacts with high diastereoselectivity. ^1H NMR-spectroscopy pointed out to only one diastereomer [16].

4. Ru-Catalyzed synthesis of steroid 1,3-dihydropyrrol-2-ones from 1-azadienes

W. Imhof has developed an interesting synthesis of substituted γ-lactams starting with 1-azadienes (α,β-unsaturated imines), CO and ethylene with $Ru_3(CO)_{12}$ as catalyst. The proposed mechanism is given in Scheme 7 [21].

Employing our model compounds in the form of unsaturated imines (condensation of the steroid amines with cinnamic aldehyde) will in the course of the catalytic reaction introduce a new stereocenter, which should result in two diastereomers (Scheme 8). The diastereoselectivity is low for the two 16-imines although the turnover numbers are

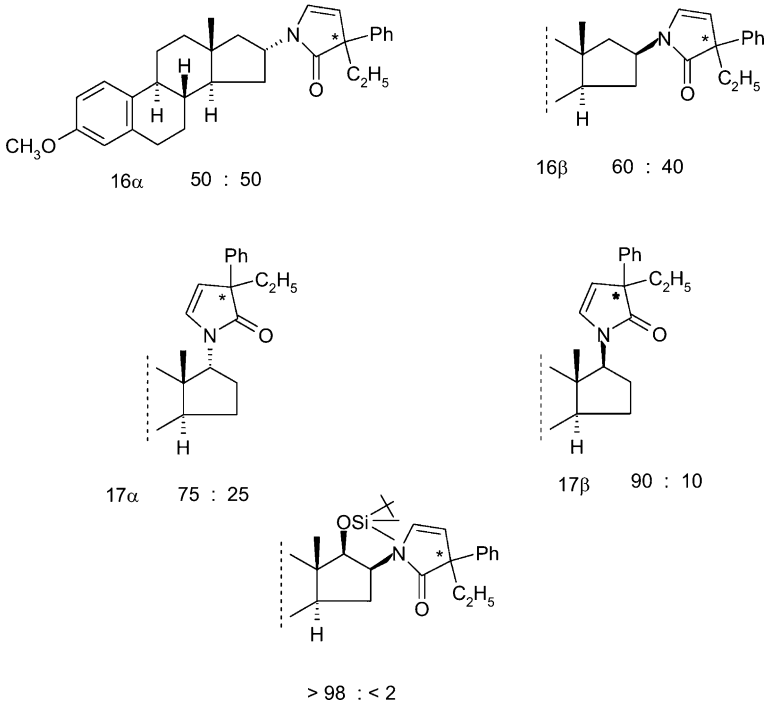


Scheme 7. 1,3-Dihydropyrrol-2-one synthesis.

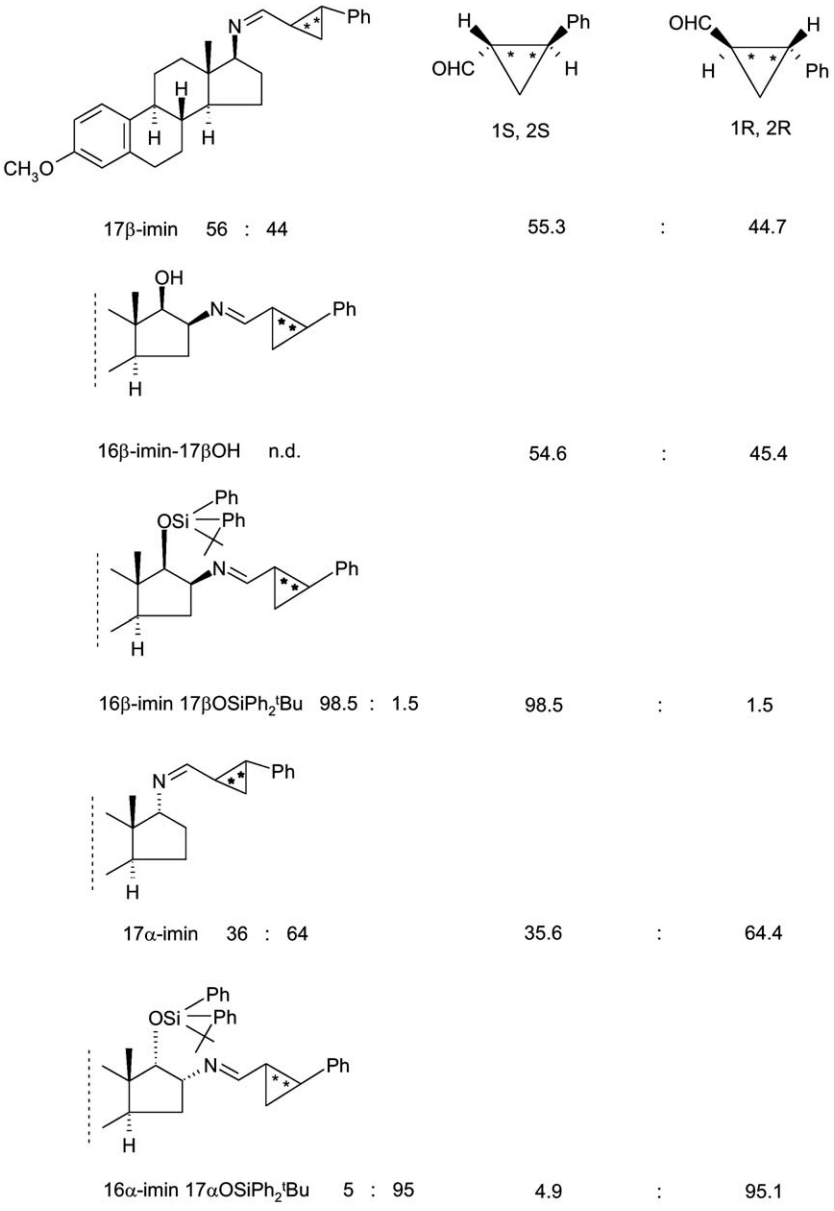
high (95% for 16α and >98% for 16β of the starting material is used). An intermediate diastereoselectivity was obtained with the 17-imines, most probably caused by the steric demands of the 13β-methyl group and the quaternary center of C13. In these cases, the turnover numbers are somewhat lower (55% for 17α and 71% for 17β of the starting material is used). The best diastereoselectivity was obtained with the 16β-imine of the *O*-silylated *cis*-16β-amino-17β-alcohol. The large 17β-silyloxy group is clearly responsible for the high diastereoselectivity [21]. An X-ray analysis of the reaction product with 17β-configuration shows a H-bridge between 17αH and the carbonyl group, a feature which could also be present in the transition state. On this model, an explanation for the diastereoselectivity could be given. In addition, these results demonstrate the successful use of our model compounds for stereochemical investigations of new reactions.

5. Pd-Catalysed cyclopropanation of α,β-unsaturated imines

The convenient Pd-catalyzed synthesis of 1,2-disubstituted cyclopropanes from 1,2-disubstituted olefins with diazomethane does not seem to operate in an enantioselective manner with chiral ligands, since only racemates could be obtained in this way [22]. The use of chiral auxiliaries is therefore quite desirable [23,24]. For this purpose, our α,β-unsaturated steroid imines could be useful. Up until now, the cyclopropanation of α,β-unsaturated imines with diazomethane has not been investigated. Using the 17β-unsaturated imine (obtained by the reaction of cinnamic aldehyde with the 17β-amine, Scheme 9) as a starting material for a Pd-catalyzed reaction with diazomethane, we observed a chemoselective reaction at the C=C double bond. The desired *trans*-1,2-disubstituted cyclopropane with two new chiral centers could be obtained in a high yield; however, with a very low diastereoselectivity (^{1}H NMR-investigation). A simple hydrolysis of the C=N double bond could be achieved via chromatography, which resulted in the 17β-amine and a mixture of the two enantiomers of the known *trans*-2-phenyl-cyclopropano-1-carbaldehyde (ratio determined by gas chromatography with a chiral column) [25]. A similar result was obtained starting with the α,β-unsaturated imine from the *cis*-16β-amino-17β-alcohol. Using the imine from the



Scheme 8. Structure and diastereoselectivity.



Scheme 9. Cyclopropanation of unsaturated imines – structures and stereoselectivities.

cis-16β-amino-17β-diphenyl-*tert*-butylsilyloxy compound resulted in a 98.6:1.4 ratio of the diastereomeric cyclopropanes. This very high diastereoselectivity is obviously caused by the large 17β-silyloxy group. Hydrolysis gave the (1*S*,2*S*)-*trans*-2-phenyl-cyclopropano-1-carbaldehyde in a high enantiomeric purity. With the α,β-unsaturated imine of the 17α-amine, a 36:64 ratio of the two diastereomers could be obtained. Hydrolysis furnished the mixture of the enantiomeric *trans*-2-phenyl-cyclopropano-1-carbaldehyde, which now had an excess of the (1*R*,2*R*)-compound. With the imine of the *cis*-16α-amino-17α-diphenyl-*tert*-butylsilyloxy compound, the diastereoselectivity could be improved to a ratio of 5:95. After hydrolysis, the (1*R*,2*R*)-*trans*-2-phenyl-cyclopropano-1-carbaldehyde is now the main enantiomer [25].

The stereochemical outcome can be rationalized from the preferred conformation of the α,β-unsaturated imine (small torsional angle between 16-N=C double bond and the C16–H bond, transoid arrangement of C–C bond between the double bonds). In the 17-silyloxy compounds, only one side of the reacting C=C double bond can be attacked by the cyclopropanation reagent. X-ray analyses of the *cis*-16α-imino-17α-silyloxy compounds [26] have confirmed these assumptions (see Fig. 1).

6. Synthesis of 22-cupriosteroids and reactions

In connection with the syntheses of vitamin D_3 metabolites, we were interested in developing a short route to the silylated provitamin form of (24*R*)-24,25-dihydroxy-

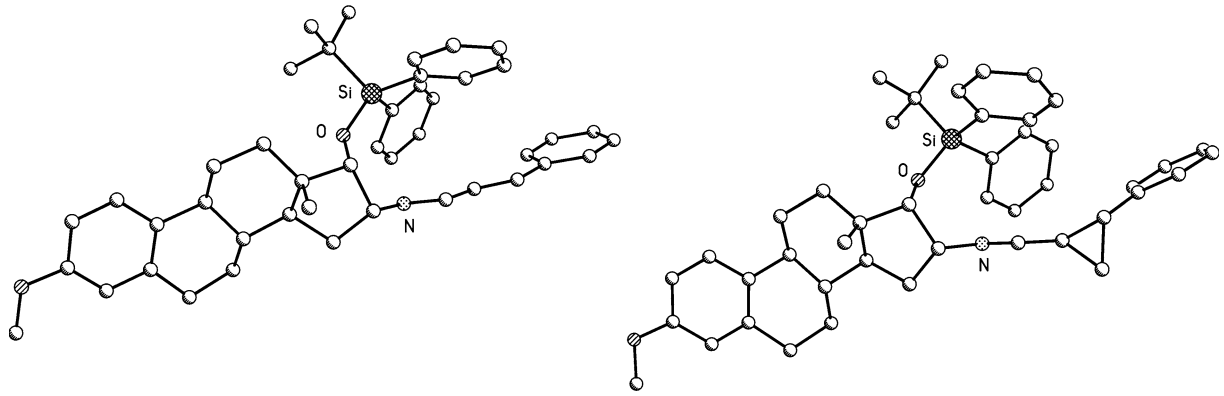
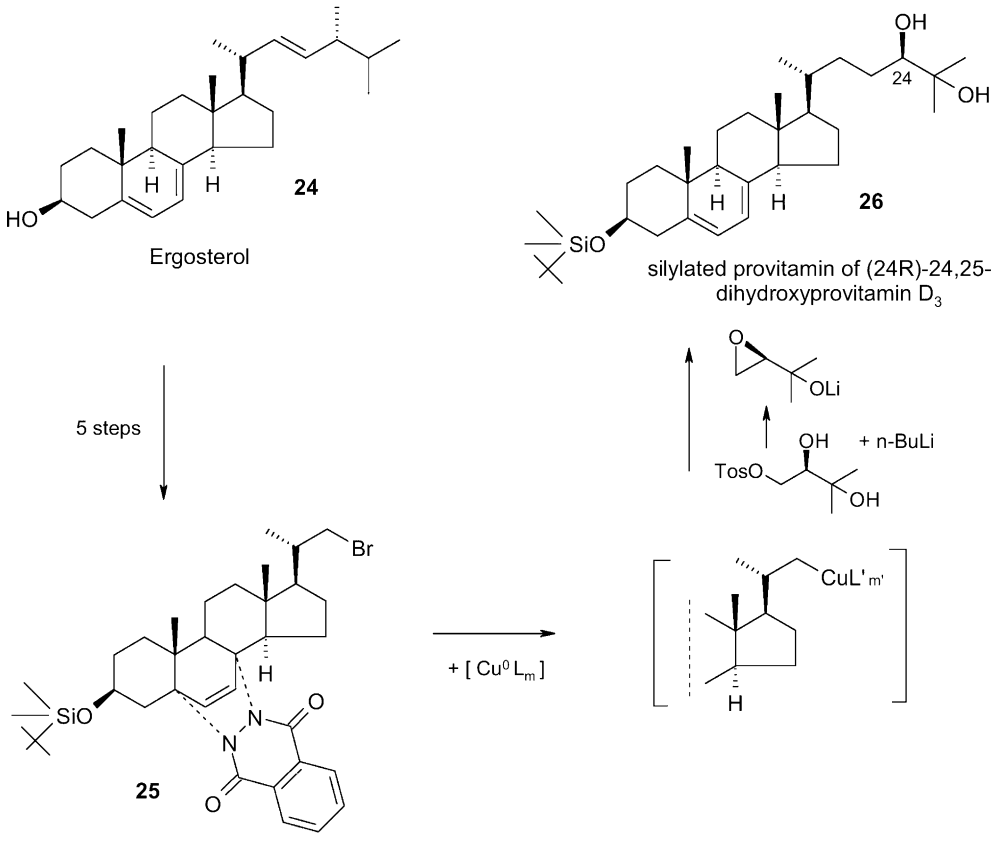


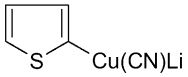
Fig. 1. Molecular structures for the 16α-unsaturated imine with a 17α-silyloxy group and the cyclopropanation product.

vitamin D_3 (**26**, Scheme 10) starting from ergosterol (**24**). It was our aim to synthesize a metallated compound from **25** (Scheme 10), which should be able to react with epoxides. **25** is easily available from a fivestep procedure starting with ergosterol (**24**). Other 22-bromo steroids have been employed as model compounds in lithiation procedures, but the yields after quenching were not very satisfactory [27]. Reactions with different species of Rieke copper [28–30] proved to be more successful. In particular, the reaction of Li 2-thienylcyanocuprate [28] with



Synthesis of [Cu^0 L_m] species:

yield of **26** from **25**:



\+ Li naphthalenide - 78 °C 32 %
- 100 °C 70 %

Scheme 10. Synthesis of the provitamin of (24*R*)-24,25-dihydroxyprovitamin D_3.

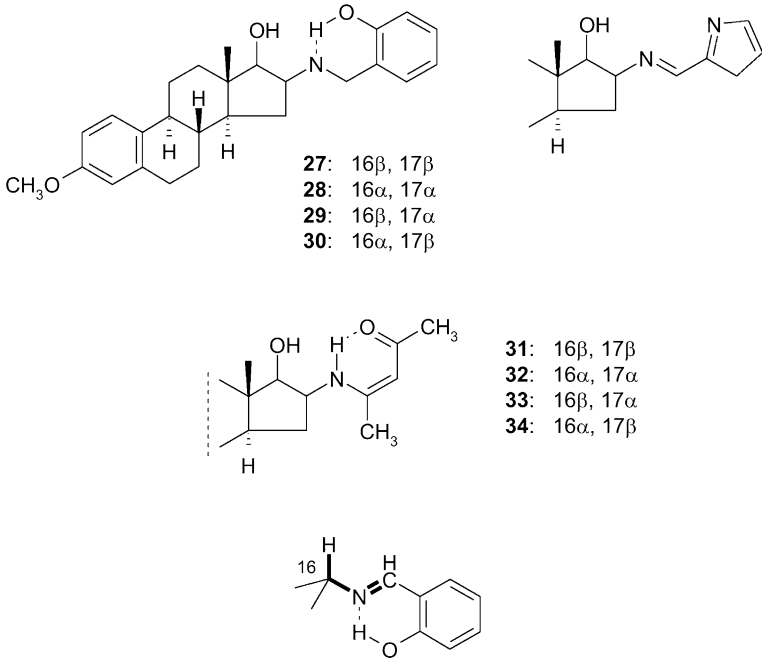
Li naphthalenide in THF at −78 °C gave a copper(0) species, which reacted well with 22-bromo steroids. 22-Cupriosteroids thus obtained were able to react with epoxides [27]. In addition, a chiral epoxide prepared in situ from (*R*)-3-methyl-1-tosyloxybutane-2,3-diol with *n*-butyl lithium and bearing a tertiary lithioalkoxy group reacts well with these 22-cupriosteroids. Reaction of **25** with this copper(0) species and quenching with an ammonium chloride solution gave a new product with the expected 20,20-dimethyl structure in a yield of 94%. However, and quite surprisingly, the 5,7-diene structure is present. Two results are very important: (1) the yield of the in situ prepared 22-cupriosteroid is very high and (2) a very mild and smooth cleavage of the protecting group for the 5,7-diene system has taken place under the reaction conditions. We could show later that an excess of Li naphthalenide is responsible for cleaving the protecting group [31]. The same reaction of **25**, but now with the addition of the chiral epoxide prepared in situ, gave the desired compound **26**, but in a low yield of 32%. Since Rieke has indicated that the temperature employed as well as the manner of preparing the copper(0) species can be critical, we prepared Cu(O) at −100 °C instead of −78 °C, then added **25** before adding the in situ prepared epoxide. This increased the yield of **26** to 70% (crystallized product). In this manner, especially since side chain construction and cleavage of the 5,7-diene protecting group has been achieved in one step, we have developed the shortest route known to date from ergosterol to the provitamin of (24*R*)-24,25-dihydroxy-vitamin D_3 (7 steps, overall yield >30%) [27].

7. Copper complexes of 16,17-amino alcohol derivatives

As described in Section 3.2, (Scheme 5), the four diastereomeric 16,17-amino alcohols **20**–**23** can serve as model compounds for stereoselective investigations. In order to create new chiral ligands for copper(II) ions, we have condensed the amino alcohols with salicylic aldehydes as well as heteroaromatic α-aldehydes and acetylacetone. Selected examples are illustrated in Scheme 11 [20].

Copper complexes of such ligands could possibly provide interesting catalysts for stereoselective syntheses and, in addition, serve as biomimetic models for copper-containing enzymes.

We succeeded in determining the molecular and crystal structures of these ligands by X-ray analyses of salicylideneimines **27**–**30** and enamines **31** and **33** [20]. All of these ligands have in common a preferred conformation for the imino functionality with a small torsional angle for H–C16–N=CH (Scheme 11 as well as Sections 3.2 and 5.). This means that a nearly eclipsed or skew arrangement for the H–C16 and the imine bond is present. Furthermore, small torsional angles for the functional groups of the *cis*-amino alcohols and the larger for the *trans*-amino alcohols (see also Section 3.2) were observed. Copper(II) complexes, which were suitable for X-ray analysis, could be obtained from *trans*-amino alcohol derivative **30** and *cis*-derivative **27**. Brown crystals, obtained from **30** and copper(II) acetate, showed a 2:1 ratio of the steroid ligand:copper (Fig. 2). Compound **30** is a bidentate ligand (deprotonated phenol and imino nitrogen), which provides a distorted tetrahedral environment for the copper(II) ion. The



Scheme 11. 16-Imines and preferred conformation.

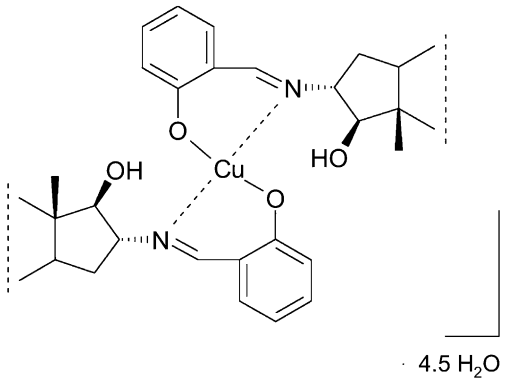


Fig. 2. Structure of the copper(II) complex of **30**.

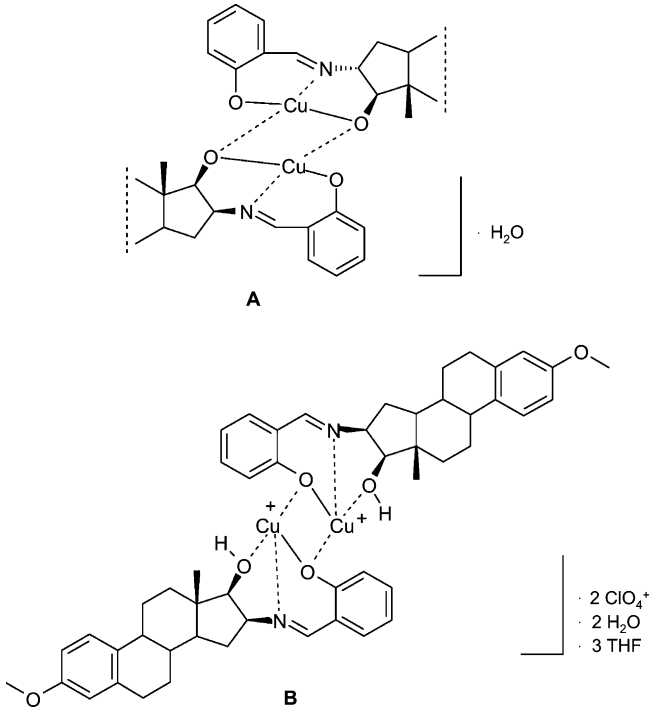
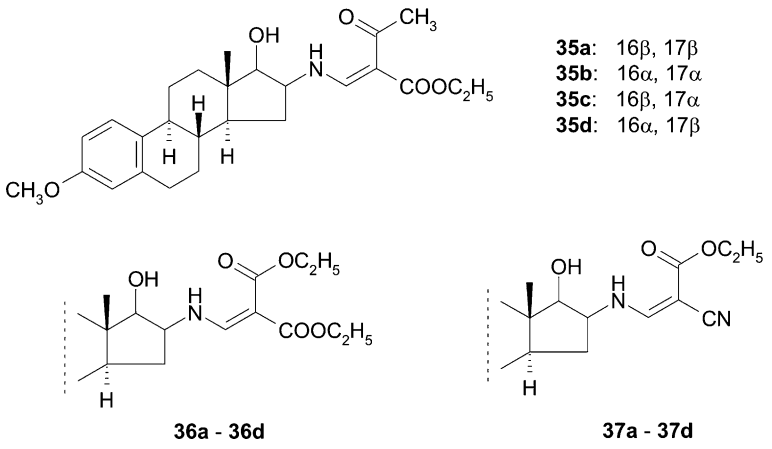


Fig. 3. Structure of the copper(II) complex of **27**: (A) with $Cu(OAc)_2$; (B) with $Cu(ClO_4)_2$.

trans-arrangment of the 17β-OH ensured that this group was not involved in metal complexation. The torsional angle for H–C16–N=C is quite similar to the free ligand **30** [20]. Reaction of *cis*-ligand **27** with copper(II) acetate gave green crystals in which the ligand has been deprotonated twice. The ratio of ligand to copper(II) was 1:1 (Fig. 3A). The central four-membered planar-quadratic ring containing two copper and two alcoholate oxygen atoms lies in the same plane as the deprotonated salicylideneimine unit. Reaction of **27** with copper(II) perchlorate resulted in another green dimeric 1:1 complex with two copper and the monodeprotonated ligand (Fig. 3B). The four-membered central ring containing two phenolate oxygens is now folded instead of being planar. The 16-nitrogens and the 17-OH groups provide the other coordination sites [32]. Intermolecular bridging of the molecules by perchlorate and water gave a sixfold coordination of the copper with a distorted octahedron. The protonation state of the ligands obviously determines the molecular structures for both complexes [32].

In contrast to the bidentate *trans*-ligand **30**, the *cis*-ligand **27** acted as tridentate ligand. In this case, complexation with the 17-oxygen causes a change in the preferred conformation of the imino functionality.

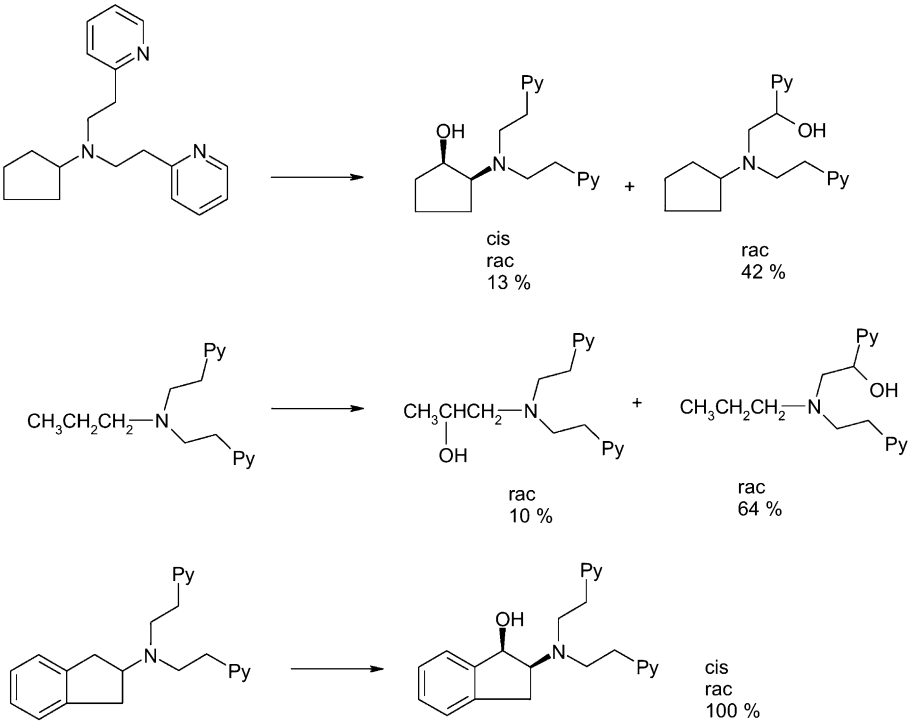
In cooperation with E.-G. Jäger and R. Wegner (Jena), the ligands described here as well as additional types (Scheme 12) have been investigated as possible models of the enzyme catechol oxidase [33]. 3,5-Di- *tert*-butyl-catechol can be oxidized by dioxygen to the *ortho*-chinone in the presence of in situ prepared catalysts [complexes of these ligands with $Cu(OAc)_2$]. In general, ligands derived from the *trans*-amino alcohols are more active than those prepared from the *cis*-amino alcohols. The *cis*-salicylideneimines (**27**, **28**) and the *cis*-derivatives (**35a** and **35b**) are inactive. Obviously, the nearly planar environment of the copper in complexes obtained with tridentate ligands and the higher stability of the dinuclear structure of the *cis*-compounds are not ideal for the catalyst. The bidentate *trans*-ligands provide better catalysts than the *cis*-ligands. The best catalysts found in this study were obtained with



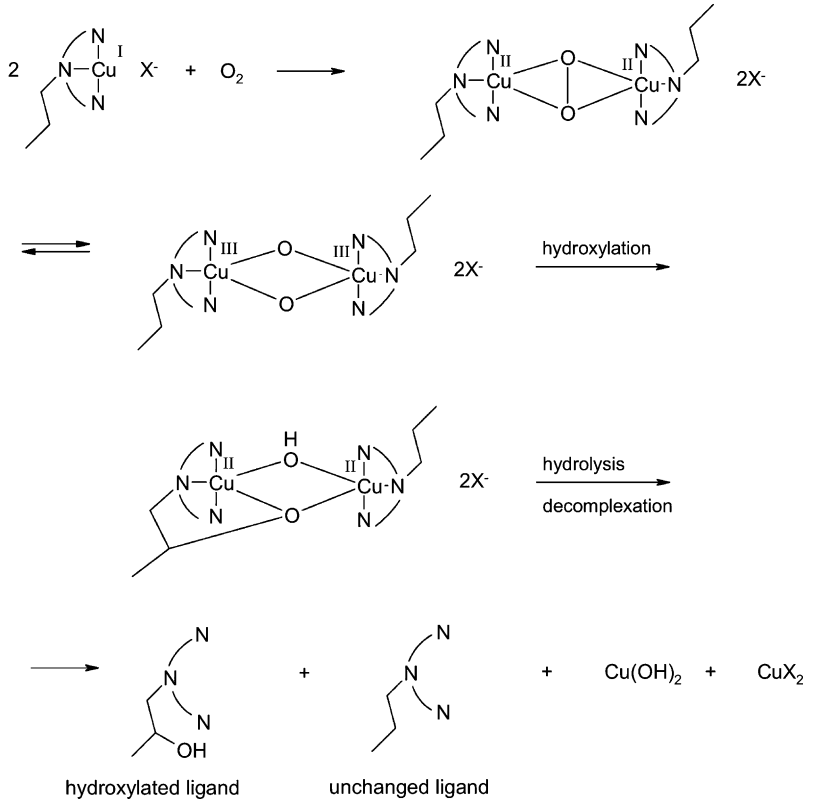
Scheme 12. Ligands for catechol oxidase activity.

ligands **35c** and **35d** followed by **37c** and **37d**. Compounds **33** and **34** (Scheme 11) exhibited the lowest activity in the *trans* series.

In the course of the reaction of the copper(II) complex obtained from the ligand **36b** and 3,5-di-*tert*-butyl-catechol under inert conditions, an intermediate with a catechol



Scheme 13. Regliers hydroxylation results.



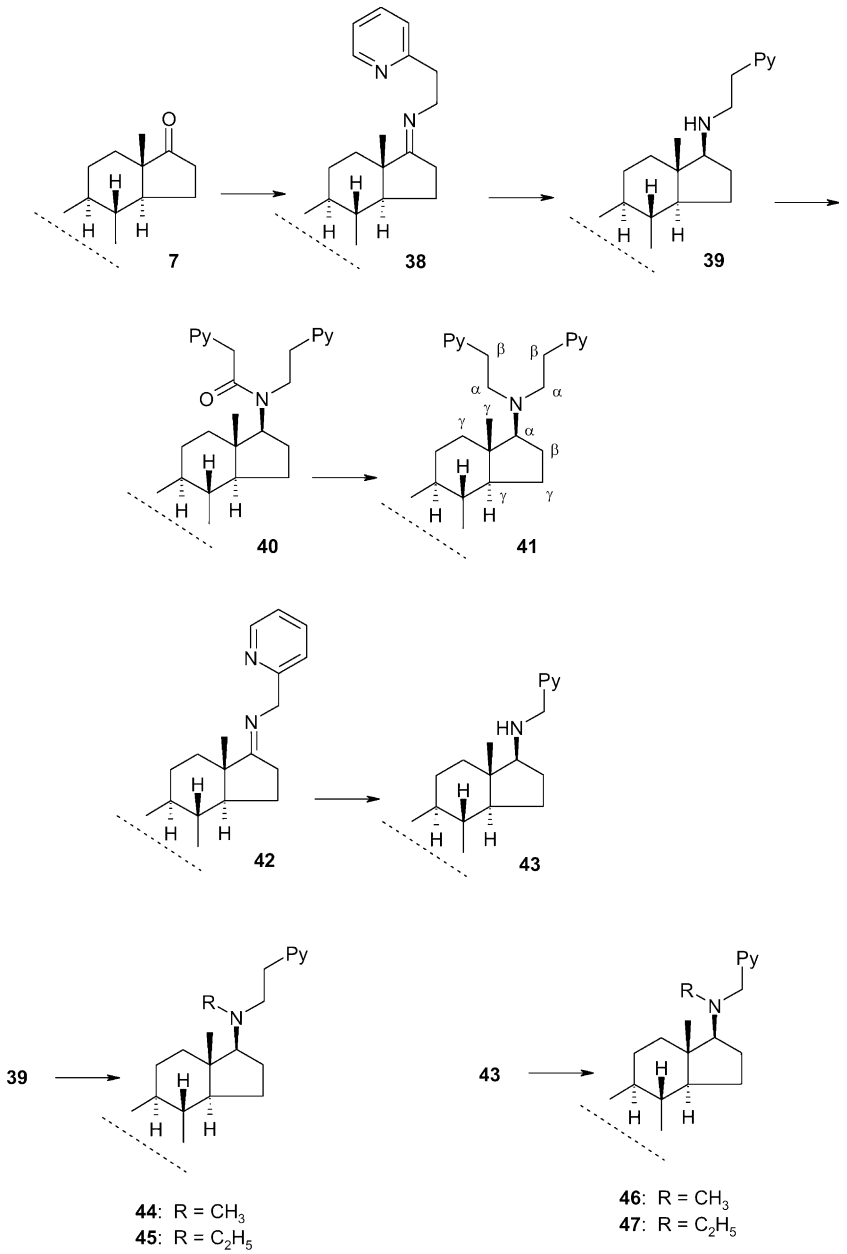
Scheme 14. Ligand hydroxylation process (method A).

bridge to the copper(I) complexes could be isolated, in addition to the *ortho*-chinone, for the first time.

8. Copper-mediated hydroxylation reactions of nonactivated C–H bonds with molecular oxygen

8.1. β-Hydroxylations with aminoalkyl-2-pyridino ligands

Copper-containing enzymes such as tyrosinase or dopamin-β-hydroxylase are able to hydroxylate *aromatic* or *benzylic* C–H bonds, in the latter case in an enantioselective manner. Hydroxylations of aromatic or benzylic C–H bonds using simpler nitrogen-containing ligands have been quite successful [34–40]. Normally, the ligands themselves are hydroxylated in the reaction. In the hopes of achieving hydroxylation of a *nonactivated* C–H bond, we have now examined steroid ligands, because in these cases the diastereoselectivity and regioselectivity of the reactions can be studied too. Only a few examples have been described in the literature for the hydroxylation of a nonactivated C–H bond using copper complexes and molecular oxygen [34]. The yields are normally very low (10–14%). Reglier and coworkers [41] could show that with the tridentate ligand *N*,*N*-bis[2-(2-pyridyl)ethyl]amine connected with the *n*-propyl or the cyclopentyl group, the CH_2 group in β-position to the central nitrogen could be hydroxylated in yields of 10–13% (β-hydroxylation). The main products are the alcohols resulting from β-hydroxylation of the acti-



Scheme 15. Synthesis of 17β-substituted steroidal bi- and tridentate ligands.

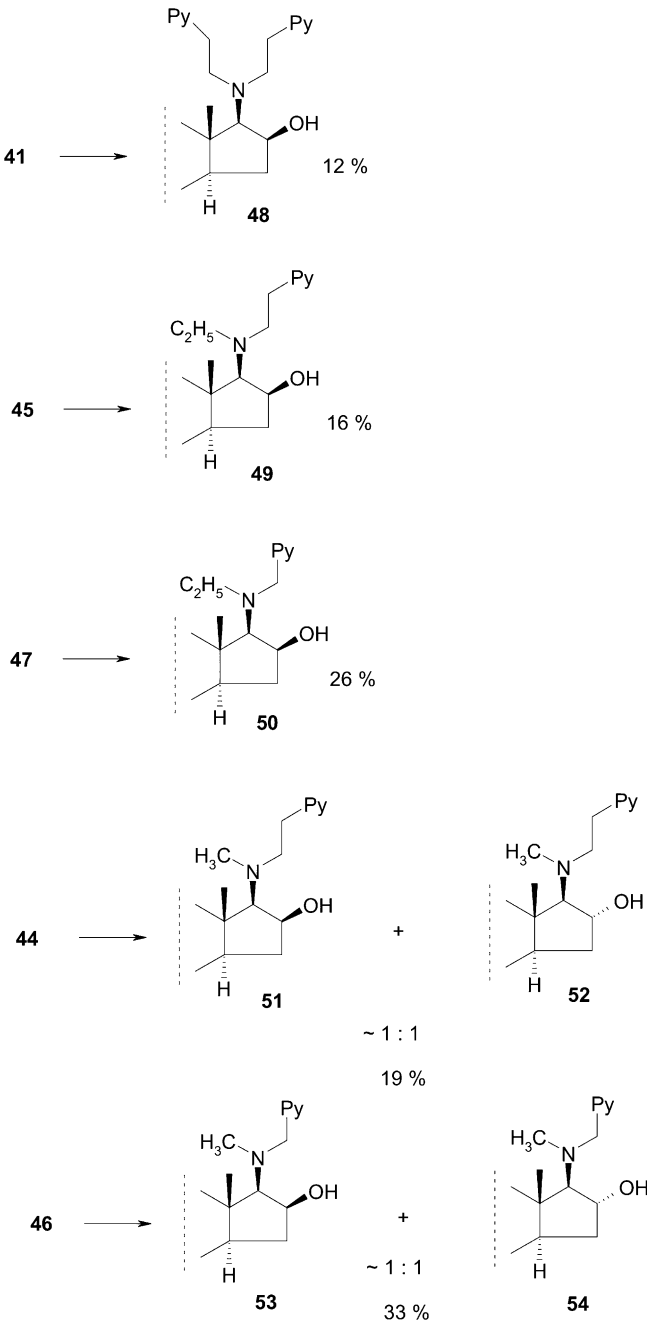
vated CH_2 groups adjacent to the pyridine ring. The hydroxylation of a benzylic CH_2 group is much easier as demonstrated using this ligand in 2- position of indane. Under these conditions indane can be quantitatively β-hydroxylated in position 1 (Scheme 13). It should be mentioned that a stereospecific *cis*-hydroxylation has been observed for indane and cyclopentane. A binuclear complex with a central four-membered $[Cu^{III}–O]_2$ unit has been postulated as being the oxidizing species. This bis(μ-oxo)dicopper(III) complex is in equilibrium with the initially generated (μ-η^2:η^2-peroxo)dicopper(II) complex from the reaction of the copper(I) complex with molecular oxygen (Scheme 14) [35,38]. After the hydroxylation process, only half of the ligand is oxidized; the other half is unchanged. In this manner, maximum yield of only 50% of the hydroxylated ligand can be achieved (method A, Scheme 14). In an attempt to obtain a quantitative hydroxylation of the ligand, Itoh and Fukuzumi started with a copper(II) complex and an excess of benzoin and triethylamine for reduction to copper(I) followed by the reaction with molecular oxygen (method B, Scheme 14) [42]. This method has also been employed by Reglier et al. In addition, Itoh and Fukuzumi could show that bidentate *N*-[2-(2-pyridyl)ethyl]amino ligands are also suitable for the hydroxylation of benzylic CH_2 groups [43].

We started our work with the synthesis of tridentate *N*,*N*-bis[2-(2-pyridyl)ethyl]amino ligands connected with steroids. Classical synthetic procedures consisting of a double Michael addition of *primary* amines (in our case steroid amines) to 2-vinyl pyridine were not very successful. The sterically hindered 17β-amine was especially inert under these conditions. Another route, starting with the 17-ketone **7**, allowed the synthesis of the desired tridentate ligands as well as the interesting bidentate *N*-[2-(2-pyridyl)ethyl]amino ligands (Scheme 15). Illustrated for the tridentate ligand **41**, the definition for α-, β- and hitherto not observed γ-hydroxylations for nonactivated C–H bonds is also given in Scheme 15. From the viewpoint of organic synthesis, α-hydroxylation which is often observed is not desired, because due to the instability of the hydroxylation products the chelating part of the ligand could be destroyed. Desirable are β- or γ-hydroxylations which result in stable compounds with potential applications in organic chemistry.

Ligands **41** (tridentate), **44**, **45**, **46** and **47** (all bidentate) were complexed with copper(II) triflate in dichloromethane, reduced with benzoin/triethylamine, oxidized with pure oxygen (method B) and then decomplexed with aqueous ammonia and chromatographed on silica gel. The polar hydroxylation products were isolated. From **41**, 12% of 16β-hydroxy compound **48** (product of a *cis*-β-hydroxylation, Scheme 16) was obtained, which is directly comparable to the results of Reglier et al. This reaction was also observed for the hydroxylation of *N*-ethyl compounds **45** and **47** (16% and 26%, **49** and **50**). Interestingly, a nearly 1:1 mixture of 16β- (**51** and **53**) and 16α-alcohol (**52** and **54**) (19% and 33%) for *N*-methyl compounds **44** and **46** was found. These are the first examples reported in the literature for a *trans*-β-hydroxylation. It is also important that the yields for the hydroxylation of aminomethylpyridino ligands **46** and **47** are somewhat higher than for aminoethylpyridino ligands **44** and **45**. This fact along with the high diastereoselectivity observed for the *N*-ethyl compounds demonstrated the importance of restricted conformations for successful hydroxylations [44].

8.2. γ-Hydroxylations with iminoalkylpyridino ligands

Bidentate imines **38** and **42** (Scheme 15) possess, especially for **42** (*im*ino*m*ethyl*py*ridino ligand; IMPY ligand),



Scheme 16. β-Hydroxylation of chiral ligands.

very restricted conformations. The 17-imino double bond has the *anti* configuration and determines the complex functionality. **38** and **42** were reacted with method B for hydroxylation. Since the imino double bond was not stable under chromatographic conditions, the reaction products were reduced with $NaBH_4$ after the hydroxylation procedure to give stable 17β-amino compounds after decomplexation. Crystalline main products **55** and **56** could be obtained in yields of nearly 40% and were determined as the 12β-hydroxy compounds (Scheme 17). Another work-up procedure (hydrolysis of the imino group to the carbonyl group with aqueous ammonia) gave 12β-hydroxy-17-ketone **57** (Scheme 17) in yields of 40% from **38** and 50% from **42**.

Using the same definition for α-, β- and γ-hydroxylation as described in Scheme 15 and now referring to the imino nitrogen, a regio- and stereoselective γ-hydroxylation of a nonactivated CH_2 group has taken place for the first time in preparative useful yields. In the case of the hydrolytic work-up procedure, the iminomethylpyridine (IMPY ligand) and the iminoethylpyridine ligand play an auxiliary role and can be simply removed after the hydroxylation procedure [44,45]. Conformational analysis by X-ray analysis and MMFF94 force field calculations for IMPY compound **42** indicate that a seven-membered ring with six atoms nearly in a plane (Fig. 4) plays an important role in the course of the hydroxylation process. It seems to be very important that the H-atom which is to be abstracted must lie in this plane.

Using this model, we selected the IMPY-compounds of the 13α-CD-*cis*-configured 17-ketone [46] (**59**) and of (1*R*)-camphor (**63**) [47] for γ-hydroxylations (Scheme 18). In the first case, a 12β-hydroxylation seems to be possible (Fig. 5A). In the latter case, only one (C10) of the three methyl groups has a suitable arrangement for γ-hydroxylation. Both compounds (**59** and **63**) could be hydroxylated in yields of 6% (**60**) and 4% (**64**) in the expected positions with method B. Surprisingly, and in contrast to the results obtained with compound **42** (method B 50%, method A 29%), hydroxylation with method A [starting with copper(I) salts] resulted in better yields (34% for **60** and 31% for **64**). In the case of (1*R*)-IMPY-camphor, we could isolate the stable γ-hydroxylated IMPY-compound (**64**), which could be hydrolyzed to the (1*R*)-10-hydroxy-camphor (**65**) [45]. Reaction of the IMPY-compound **59** gave an interesting dependence of the stereoselectivity from the

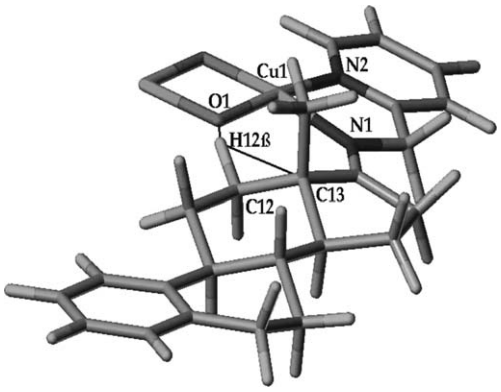
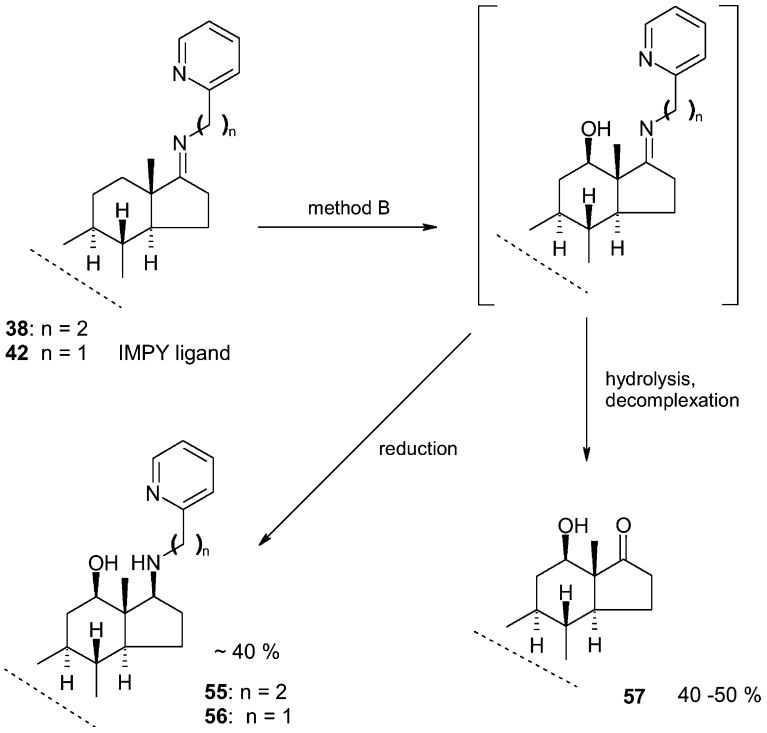
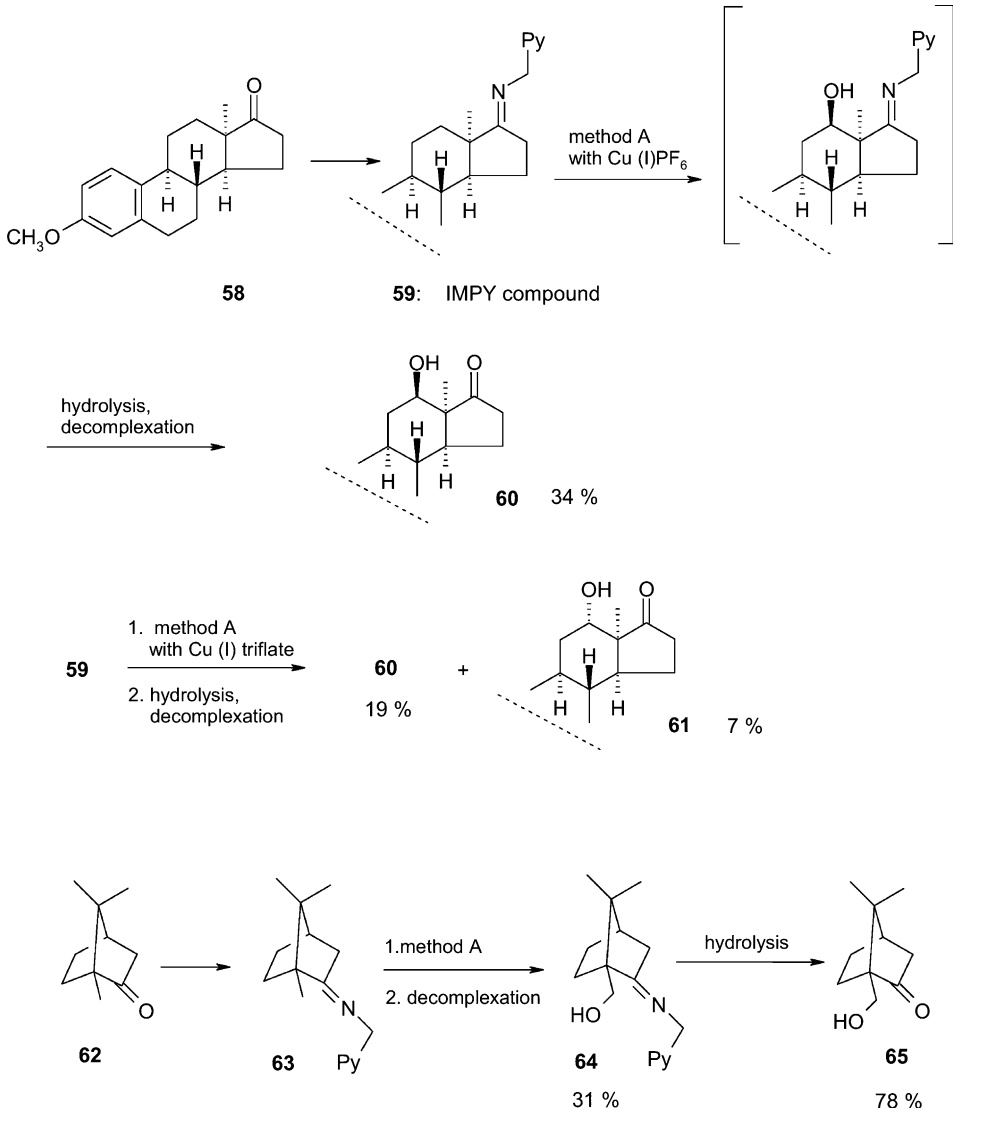


Fig. 4. Model for the active complex of IMPY compound **42**.



Scheme 17. Regio- and stereoselective γ-hydroxylation of a nonactivated CH_2-group.



Scheme 18. γ-Hydroxylation of 13α-17-ketone **58** and (1*R*)-camphor **62**.

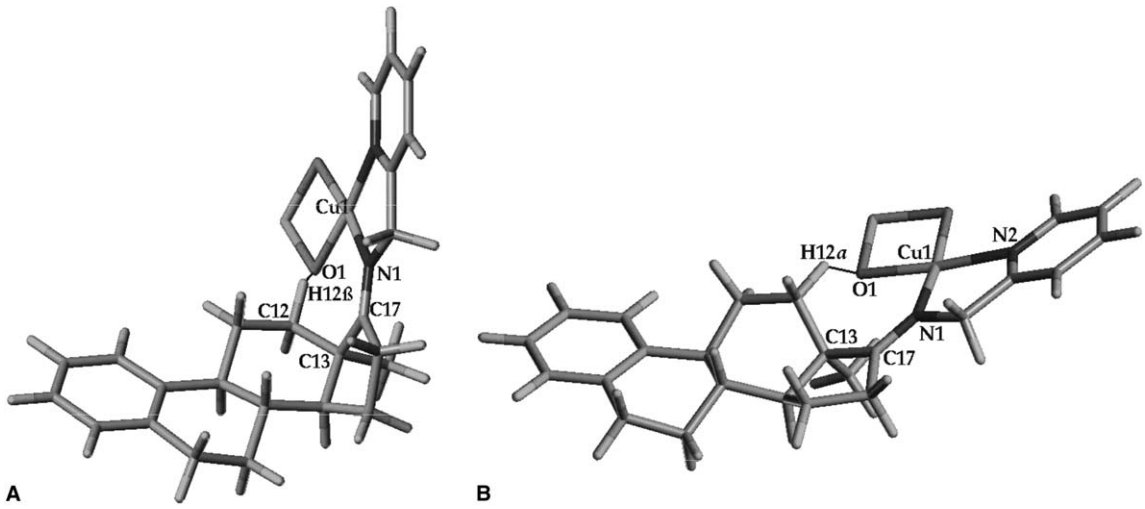


Fig. 5. Model for the active complex of IMPY compound **59**: (A) responsible for 12β-hydroxylation; (B) responsible for 12α-hydroxylation.

used Cu(I) salt. With copper(I) triflate instead of the PF_6 salt, we could isolate only 19% of 12β-hydroxy compound **60**, but this was accompanied by 7% of 12α-hydroxy compound **61**.

These facts can be rationalized by assuming an equilibrium of two conformations for the active complex in the case of the triflate anion. The conformation with a chair form of ring C is responsible for the 12β-hydroxylation (Fig. 5A). A C-ring conformation with a twist-boat form (Fig. 5B) will allow the hydroxylation in the 12α-position [45].

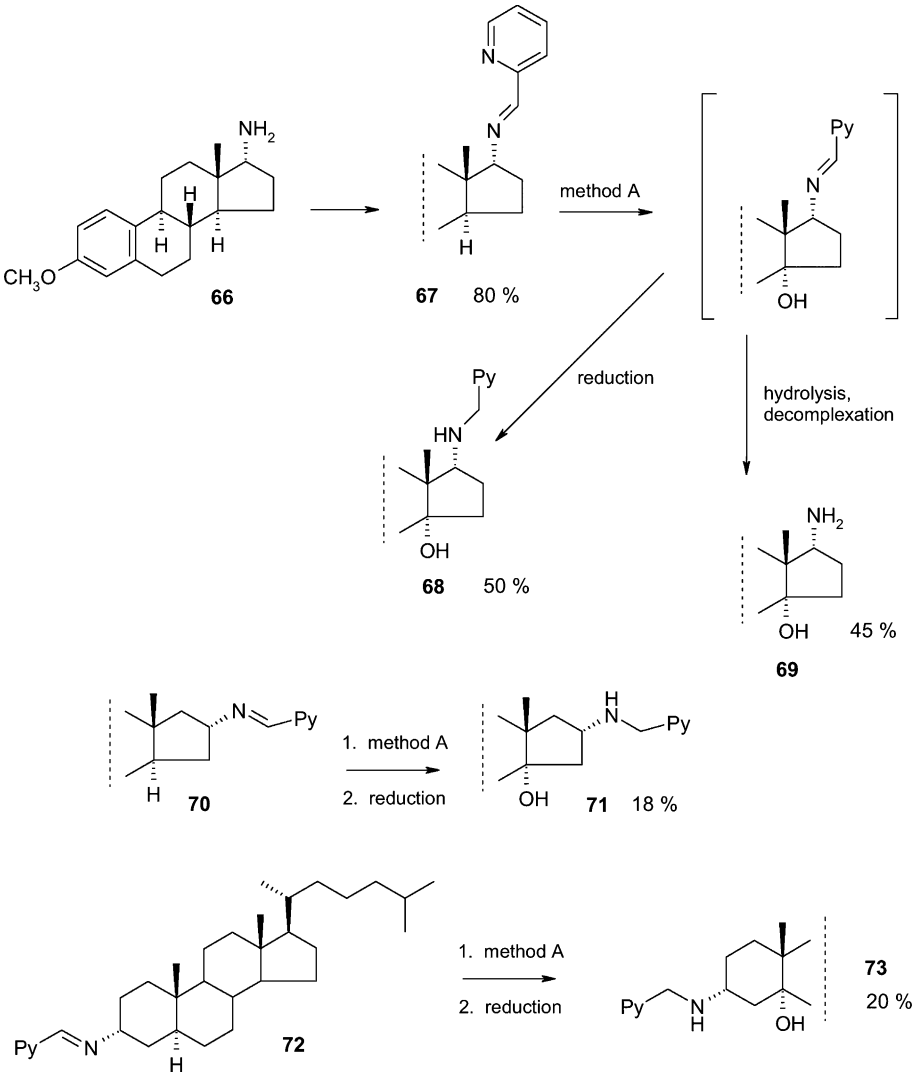
In earlier investigations, we could demonstrate the existence of both conformations for 13α-steroids [46].

8.3. γ-Hydroxylations with aminomethylenepyridino ligands (AMPY ligands) [45]

In addition to the iminomethylpyridino ligands (IMPY ligands), we became interested in the isomeric aminomethylenepyridino ligands (AMPY ligands) [45]. These compounds are also simple to prepare by condensation of *primary* amines with pyridine-2-carboxaldehyde (Scheme 19). In contrast to IMPY ligands, AMPY ligands have a ring C–N single bond and a C–N double bond in conjugation to the pyridine ring. The preferred conformation of imino compounds with a small torsional angle H–Cring–N=C is important for modelling. Fig. 6 demonstrates that γ-hydroxylation of 17α-AMPY compound **67** can be expected for the 14α-position.

Other suitable arrangements also have 16α-AMPY compound **70** and 3α-AMPY cholestane compound **72**. For all three AMPY compounds, γ-hydroxylation of a nonactivated methine C–H bond was successful with method A. The yields after reduction of the C=N double bond or after hydrolysis are nearly 50% (**68** and **69**), 18% (**71**) and 20% (**73**). The yields are lower with method B. The steric relations are given in Fig. 7. Possible γ-hydroxylations of CH_2 groups (C12, C1) have not been observed.

Hydrolysis of the AMPY group after hydroxylation opens a route to 1,3-*primary* amino alcohols [45].



Scheme 19. γ-Hydroxylations with aminomethylenepyridine ligands (AMPY ligands).

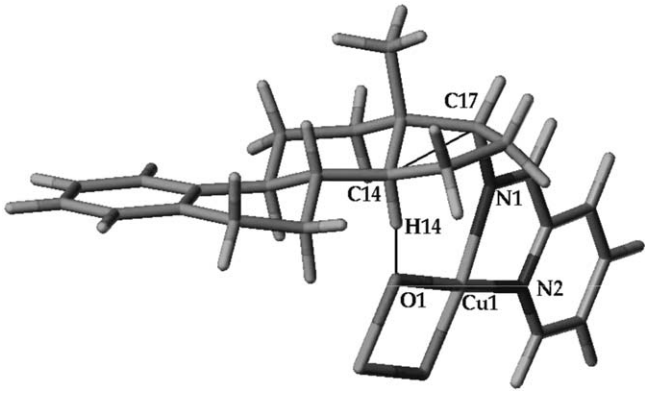


Fig. 6. Model for active complex of AMPY compound **67**.

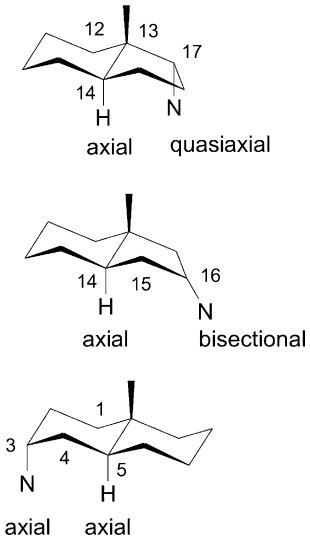


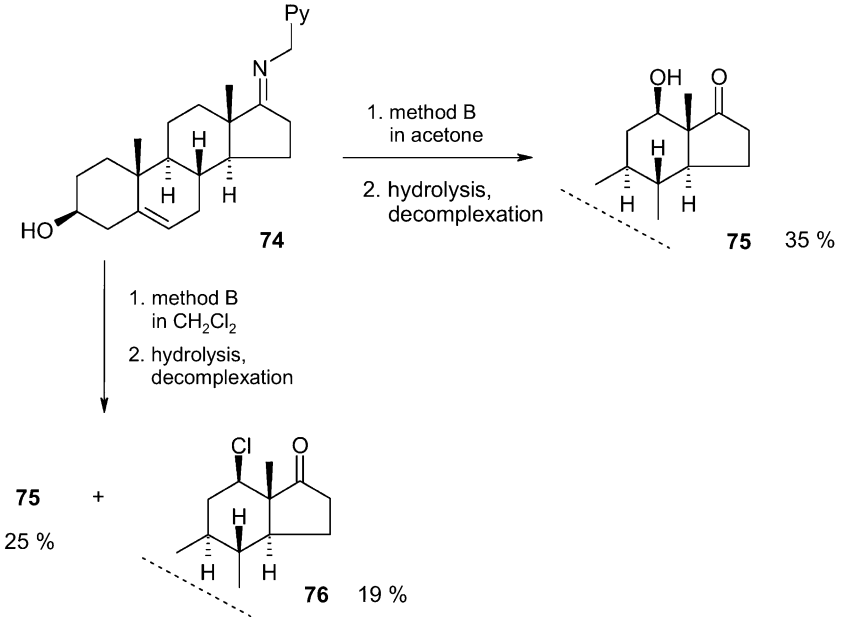
Fig. 7. Steric relations for the γ-hydroxylations with AMPY ligands **67**, **70** and **72**.

8.4. Solvent influence on γ-hydroxylations [48]

Using method A for **67**, comparable yields of γ-hydroxylated products were obtained in acetone (the preferred solvent), dichloromethane, methanol and dioxane. In contrast to this, hydroxylation of the *trans*-CD-configured 17-IMPY compound **74** of dehydroepiandrosterone (DHEA) using method B (Scheme 20) demonstrated a strong solvent dependence. In acetone, 35% of the 12β-hydroxylated 17-ketone **75** was isolated after hydrolysis. In dichloromethane only 25% of **75** was obtained, but this was surprisingly accompanied by an additional 19% of a new compound, identified as being the 12β-chloro17-ketone **76**. A comparison with method A in acetone and dichloromethane gave only the 12β-hydroxy compound **75** in nearly 20% [48]. It seems that the basic conditions of method B (benzoin, triethylamine) generate chloride ions from the solvent, which, in connection with the copper–oxygen complex, are responsible for the surprising regio- and stereoselective chlorination. Indeed, by addition of chloride ions to the reaction mixture of method A or B in acetone, chlorination product **76** could be isolated in low yields. These new reactions should have a great potential for selective functionalization of unactivated C–H bonds using copper–oxygen complexes coupled with other bridging anions.

8.5. Summary

The described IMPY and AMPY ligands allow regio- and stereoselective γ-hydroxylations of unactivated CH, CH_2 and CH_3 groups with copper ions and molecular oxygen – a fact which opens new routes for obtaining 3-hydroxy-1-



Scheme 20. γ-Chlorination with IMPY ligands.

oxo and 3-hydroxy-1-*primary* amino compounds by the simple removal of the complexing groups. Alternatively, simple reduction of the imino bond with $NaBH_4$ leads to 3-hydroxy-1-*sec*amino compounds.

Acknowledgements

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