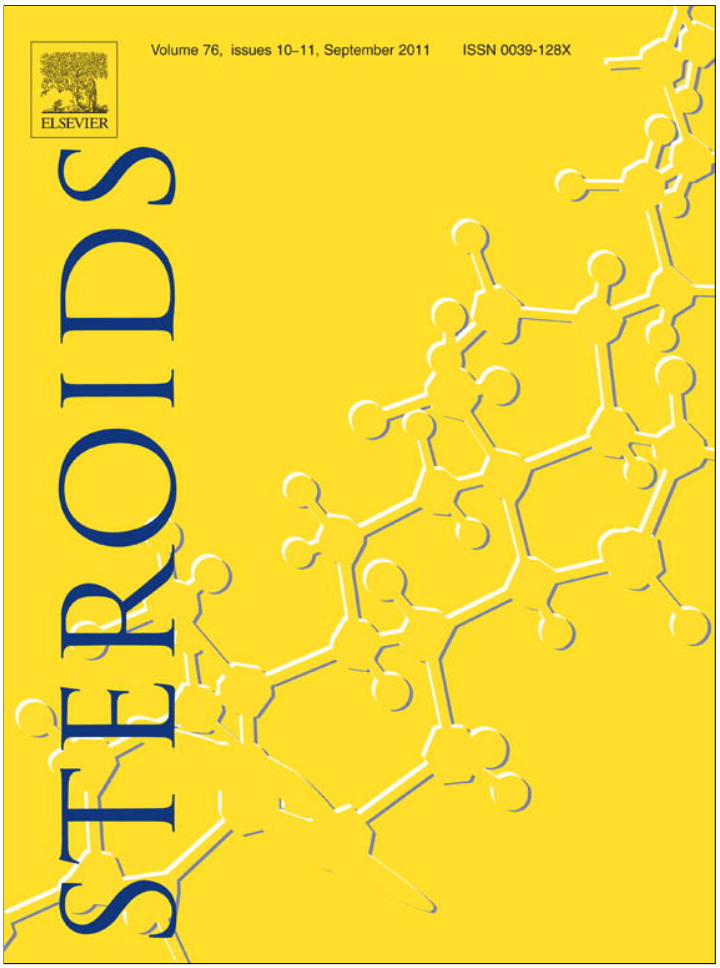

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Review

Application of olefin metathesis in the synthesis of steroids

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ABSTRACT

Over the past decade, ruthenium-mediated metathesis transformations, including cross-metathesis, ring-closing metathesis, enyne metathesis, ring-opening metathesis polymerization, and also tandem processes, belong to the most intensively studied reactions. Many applications of olefin metathesis in the synthesis of natural products have been recently described. Also in the field of steroid chemistry new methods of total synthesis and hemisynthesis based on metathesis reactions have been elaborated. Various biologically active compounds, e.g. vitamin D and hormone analogues, steroid dimers and macrocycles, etc. have been prepared using a variety of olefin-metathesis protocols.

Contents

1. Introduction

The "olefin scrambling" reaction, though discovered in the mid-1950s, for a long period of time remained a field of interest of industrial chemists only, working on large scale synthesis of simple bulk chemicals and polymers [1]. The reaction (so-called olefin metathesis) was rediscovered by the academic world in the early 1990s due to rapid development of well-defined catalysts. With the advent of the commercially available molybdenum and ruthenium complexes that present good application profiles for a range of metathesis reactions, olefin metathesis became one of the most powerful and attractive tools for the formation of carbon-carbon double bonds widely used in organic synthesis. The spectacular improvements in this reaction achieved over the last two decades are well known to most chemists. The importance of the development of metathesis methods in organic synthesis has been recognized by the award of the Nobel Prize in Chemistry for 2005 jointly to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock.

The number of publications per year on the olefin metathesis (Fig. 1) has reached a very high level and remained relatively steady during the last years (about one thousand per year according to the Scopus database). An increasing number of papers devoted to applications of olefin metathesis in the synthesis of natural products are observed. Many review articles [2–26] on olefin metathesis have appeared in the last years (over 20 in the last two years); some of them concerned natural products in general (e.g. synthesis of diverse polycyclic compounds [2] or catalytic enantioselective synthesis [5]) or a particular group of compounds like carbohydrates

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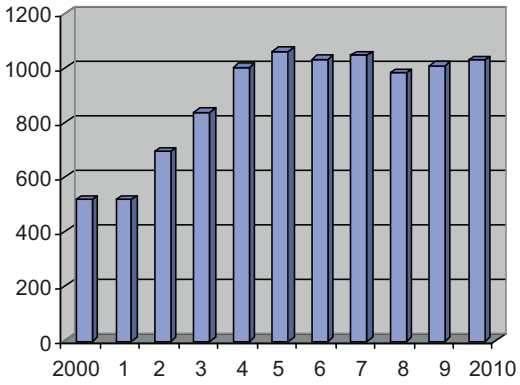


Fig. 1. The number of articles per year on the olefin metathesis published within the last decade (according to the Scopus database).

[8,9] peptides [10] or fatty acids [14]. However, none of them was devoted to the application of olefin metathesis in the synthesis of steroids.

Organic chemists are now provided with different commercially available molybdenum and ruthenium complexes (Fig. 2) that present good application profiles for a range of metathesis reactions. In contrast to the molybdenum Schrock' catalyst (S), most of the ruthenium catalysts can be handled in air and are compatible with functionalized substrates, including carbonyl, hydroxyl or carboxylic acid groups. For this reason they are commonly used in natural product syntheses, e.g., first and second generation Grubbs' catalysts (G I and G II), first and second generation Hoveyda-Grubbs' catalysts (H I and H II), Blechert catalyst (B) and others.

The popularity of olefin metathesis is due to the numerous types of metathesis transformations (Fig. 3) that have been developed, for example, cross-metathesis (CM), ring-closing metathesis (RCM), inter- and intramolecular enyne metathesis (RCEYM), ring-closing dienyne metathesis (RCDEYM), ring-opening metathesis (ROM), and many others. Examples of all these reactions from the steroid chemistry will be provided in this review article.

2. Total synthesis of steroids

Cascade reactions have proven effective in the assembly of complex polycyclic systems from simple acyclic precursors. These cascade cyclizations are characterized by the formation of a reactive intermediate that undergoes a series of ring-forming steps before termination. The application of homogeneous transition metal catalysts to cascade cyclizations of polyenes and polyynes appears very promising for the synthesis of polycyclic structures. The steroid skeletons have been prepared in one step from linear precursors by Negishi (Pd(0)-catalyzed process) [27] and Grubbs [28] groups (Scheme 1). The mechanism of the Ru-catalyzed polycyclizations involves the initial formation of a ruthenium alkylidene that undergoes a series of intramolecular metatheses with the relay units prior to termination by a final ring closure.

A diastereoselective method for the synthesis of the estrone skeleton from a substituted styrene based on sequential threefold use of Cp_2ZrBu_2 (oxidative addition-cyclization-alkylation sequences) and a Ru-catalyzed RCM reaction was developed by Kotora and co-workers (Scheme 2) [29]. The oxidative addition of the starting dibenzyl ether to dibutyl zirconocene, allylation of the organozirconium intermediate, and methoxylation of the formed allyl chloride afforded the diene, which was further transformed using zirconium chemistry [30]. The cyclization in the presence of dibutyl zirconocene followed by CuCl-catalyzed alkylation with 2,3-difluoropropene afforded the bicyclic diene, which was subjected to Zr-mediated cyclization followed by alkylation with methallyl chloride. The RCM reaction of the obtained tricyclic diene catalyzed by the Grubbs' II complex afforded the tetrasubstituted olefin in excellent yield (82%). Since the tetracyclic olefin is a known intermediate and was previously converted to 3-methoxyestrone in two steps [31], the formal short synthesis of (+/−)-estrone was accomplished.

A versatile D → BCD steroid construction strategy based on a C-ring closing metathesis and a B-ring Heck cyclization was developed by Linclau and co-workers [32].

Starting from the dibromide accessible in one step from 3-methylanisole (Scheme 3), benzylic displacement with allenyl magnesium bromide followed by one-carbon extension led to the propargylic alcohol. Diastereoselective alkyne reduction was achieved with $Zn/BrCH_2CH_2Br$. Conversion of the *Z*-allyl alcohol to the corresponding chloride using hexachloroacetone, and final Arbuzov reaction with triethyl phosphite or with homochiral phospholane afforded the corresponding phosphonates. The conjugate addition/allylation sequence yielded the key intermediates (a: racemic and b: optically active) for synthesis of estrone. The RCM reaction with the H II catalyst afforded a racemic tricyclic product in 61% yield. Unfortunately, the RCM reaction worked poorly (6% yield) for the optically active substrate due to the steric hindrance (after prior hydrolysis of the phosphonamide group the yield increased to 58%). The subsequent Heck reaction (B-ring closing) of the racemic material was carried out under conditions developed by Tietze et al. [33]. The cyclization product with the wrong 9β-configuration was subjected to the isomerization/hydrogenation procedure, which resulted in the 7:3 mixture of *O*-methyl estrone and its 9β-epimer. The pure (+/−)-estrone methyl ether was obtained by crystallization of the mixture. The same procedure was repeated for the optically active material affording (+)-estrone, identical with an authentic sample, proving that this approach allows also for enantioselective synthesis.

3. Hemisynthesis of steroid analogues

The Beckmann fragmentation/RCM route was applied in the synthesis of 18-nor-$\Delta^{13(17)}$-androgens and their 18-nor-13,17-epoxide derivatives (Scheme 4) [34]. Such compounds are expected to be potent modulators of ion channels in the central nervous system [35]. The Beckmann fragmentation of 17-oxime afforded 13,17-seco-nitrile, which was further transformed to the aldehyde. The Wittig olefination was followed by the G II catalyzed RCM. The obtained 18-nor-$\Delta^{13(17)}$-olefin was epoxidized with MCPBA.

Blechert and co-workers [36] have studied CM reactions of 1,3-dienes with electron-deficient olefins. Terminal monosubstituted 1,3-dienes afforded low yields of the desired CM products due to competing cleavage of the internal double bond. This undesirable cleavage is successfully suppressed in the case of 1,3-dienes containing a sterically more congested internal double bond, exemplified by various olefins, including steroidal substrates. Methyl vinyl ketone (MVK) as the coupling partner was shown to provide the best yields (Scheme 5).

The dienyne RCM/Diels-Alder approach for the construction of novel steroid-like polycyclic systems was described by Granja and co-workers [37]. The synthesis started from the Grundmann ketone (available by ozonolysis of vitamin D_3), which was α-alkylated with a propargyllic bromide (Scheme 6). Then the addition of allylmagnesium bromide to the carbonyl group was carried out stereoselectively (α). The ring-closing dienyne metathesis catalyzed by the G I catalyst afforded the 1,3-diene in good yield (66% for R = H; 93% for R = Me). The diene was subjected to Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) affording cycloaddition products in 82% yield as a mixture of two isomers

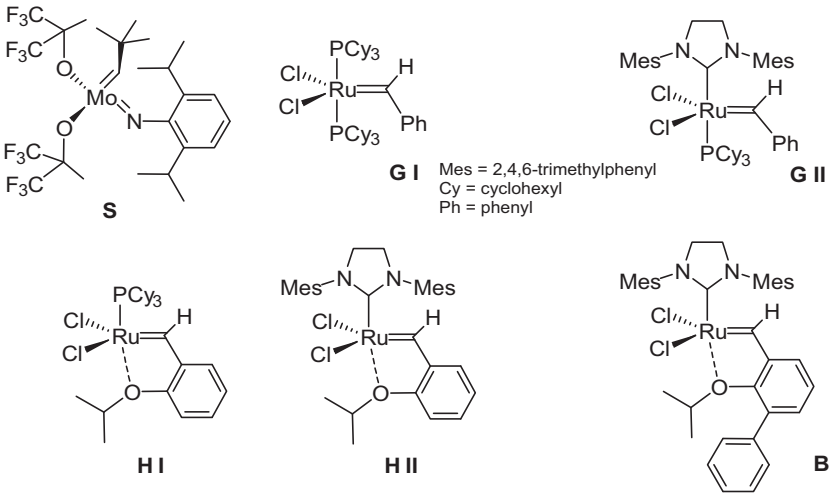


Fig. 2. Most frequently encountered complexes for metathesis transformations.

in the 2:1 ratio. Both hexacyclic steroid-like compounds were assigned as the endo-adducts.

The stereoselective synthesis of furanic-steroid derivatives (Scheme 7) involving ring-closing metathesis as a key step was described by the Poirier group [38]. The furanic-estrane derivative initially targeted as a potential inhibitor of 17β-hydroxysteroid dehydrogenase type 1 by a docking experiment was found to inhibit the enzyme. Estrogens are known to be an important factor in the development of estrogen-dependent breast cancer [39]. A complementary approach to the treatment of this type of cancer with an antiestrogen is to lower the level of estradiol by inhibiting enzymes involved in its biosynthesis. 17β-Hydroxysteroid dehydrogenase participates in the process of hydride transfer to the α-face of estrone leading to the most potent estrogen estradiol. The synthetic

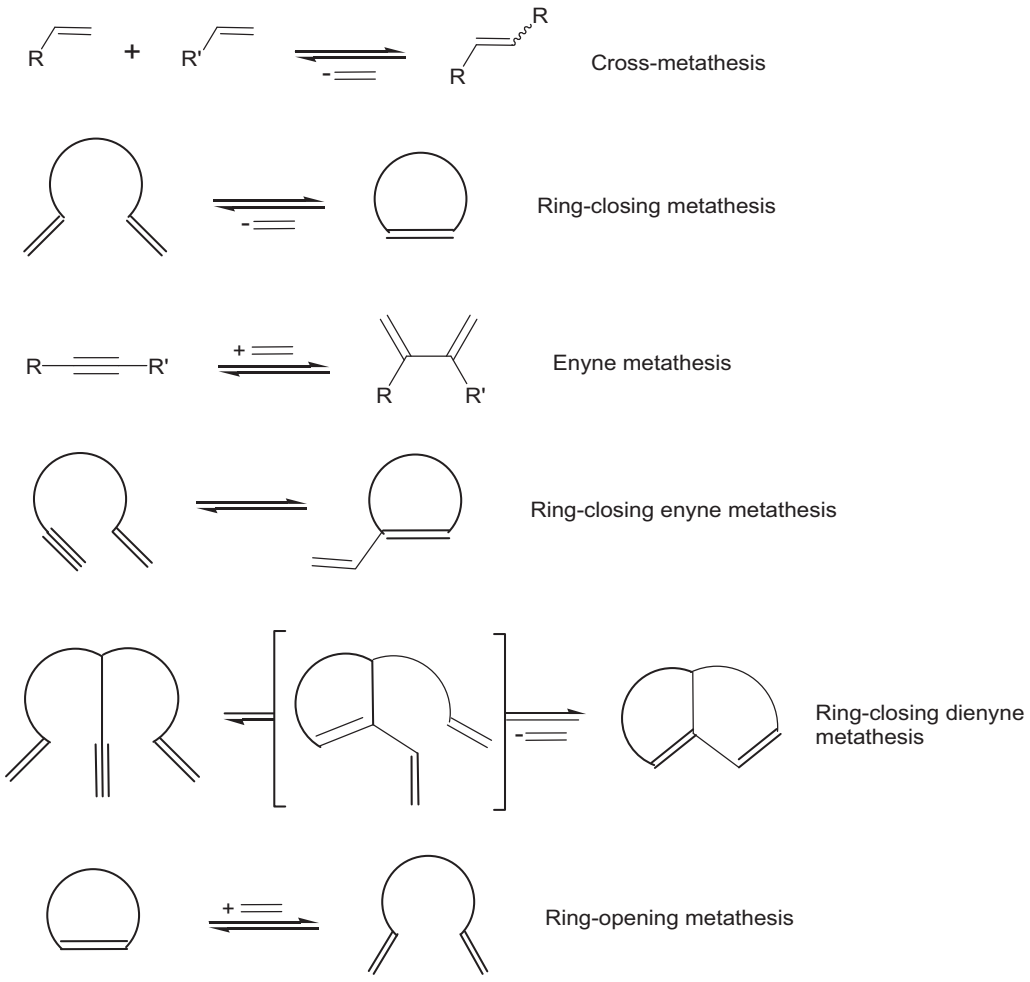
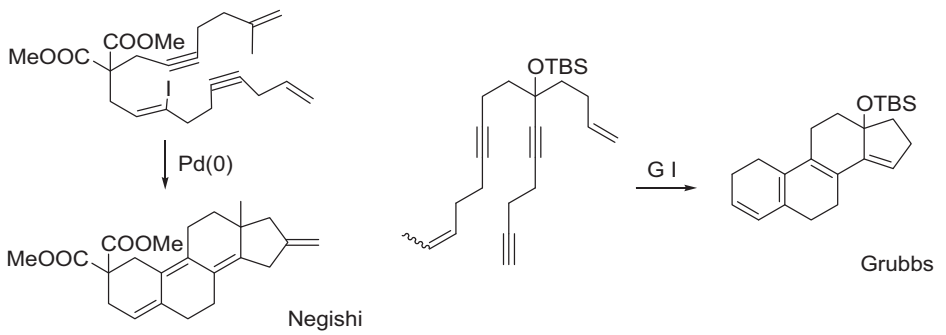
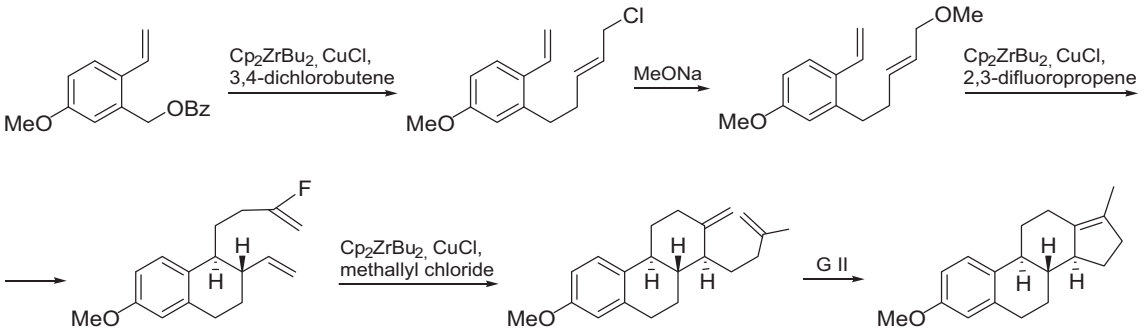


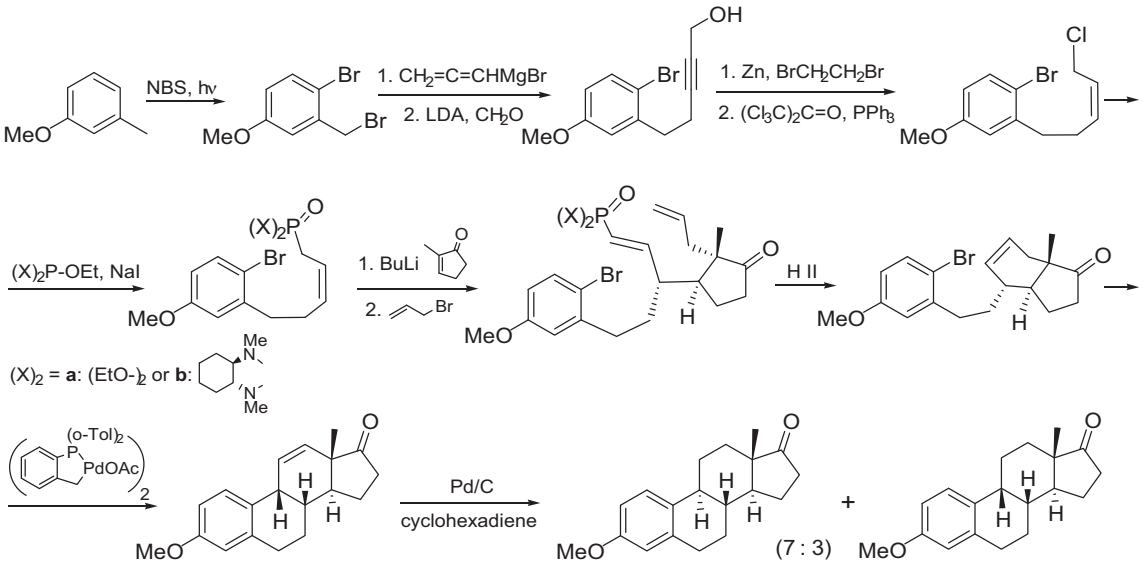
Fig. 3. Types of metathesis transformations.



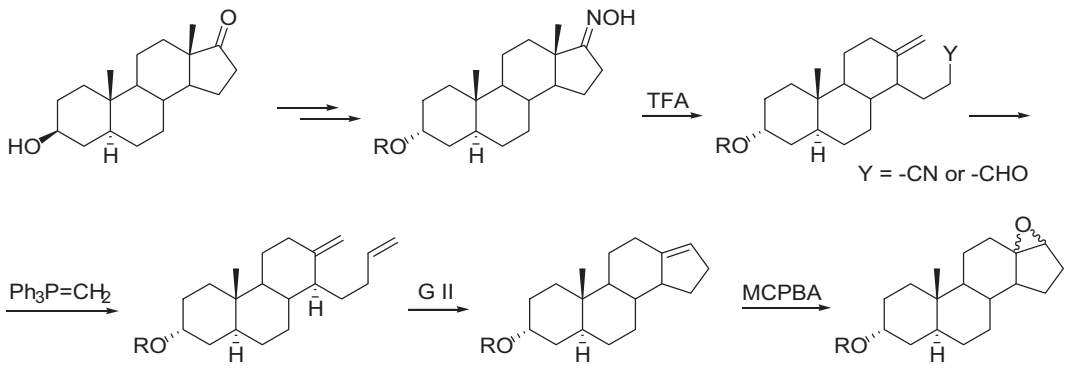
Scheme 1.



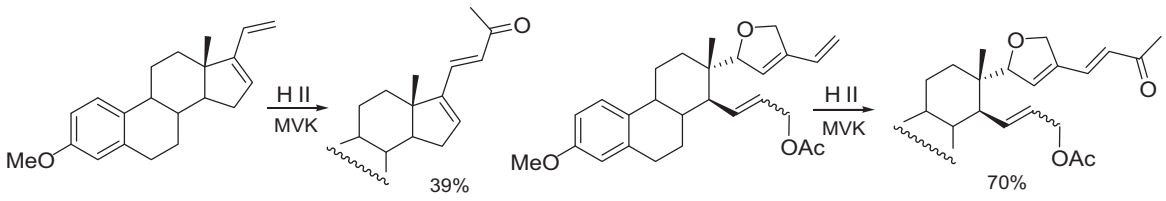
Scheme 2.



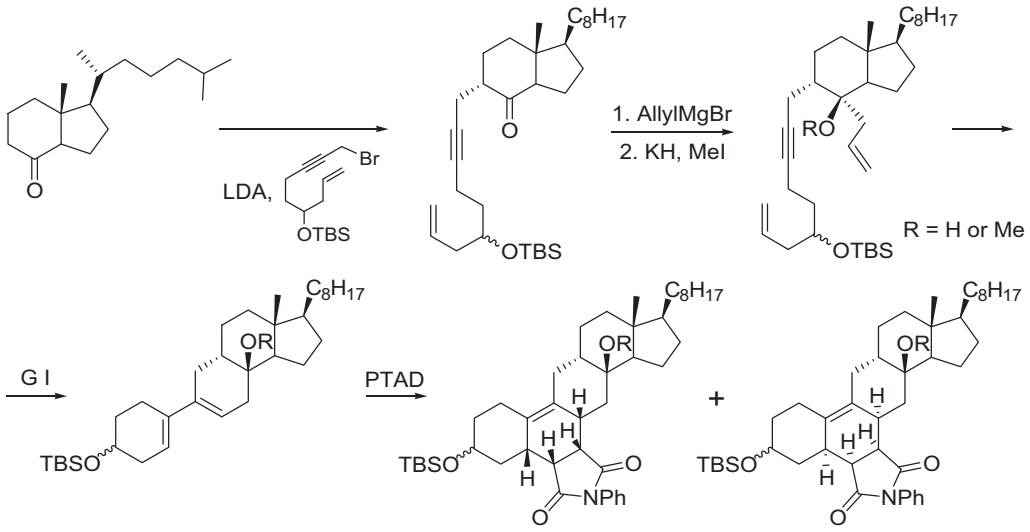
Scheme 3.



Scheme 4.



Scheme 5.



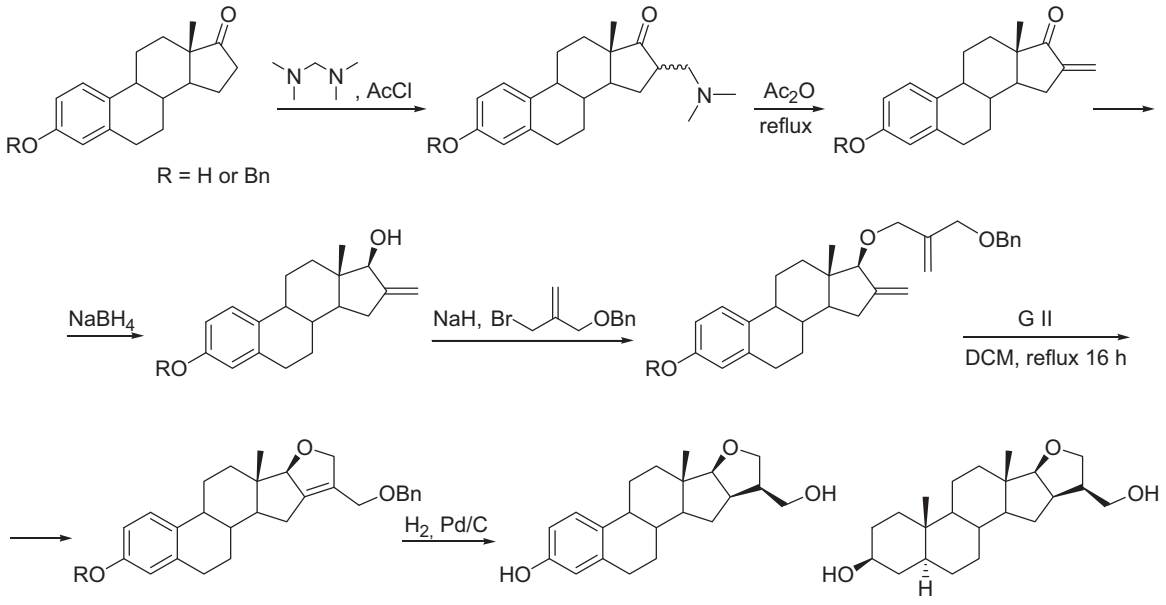
Scheme 6.

strategy was first illustrated by the synthesis of the from estrone and 2-methylene-propane-1,3-diol.

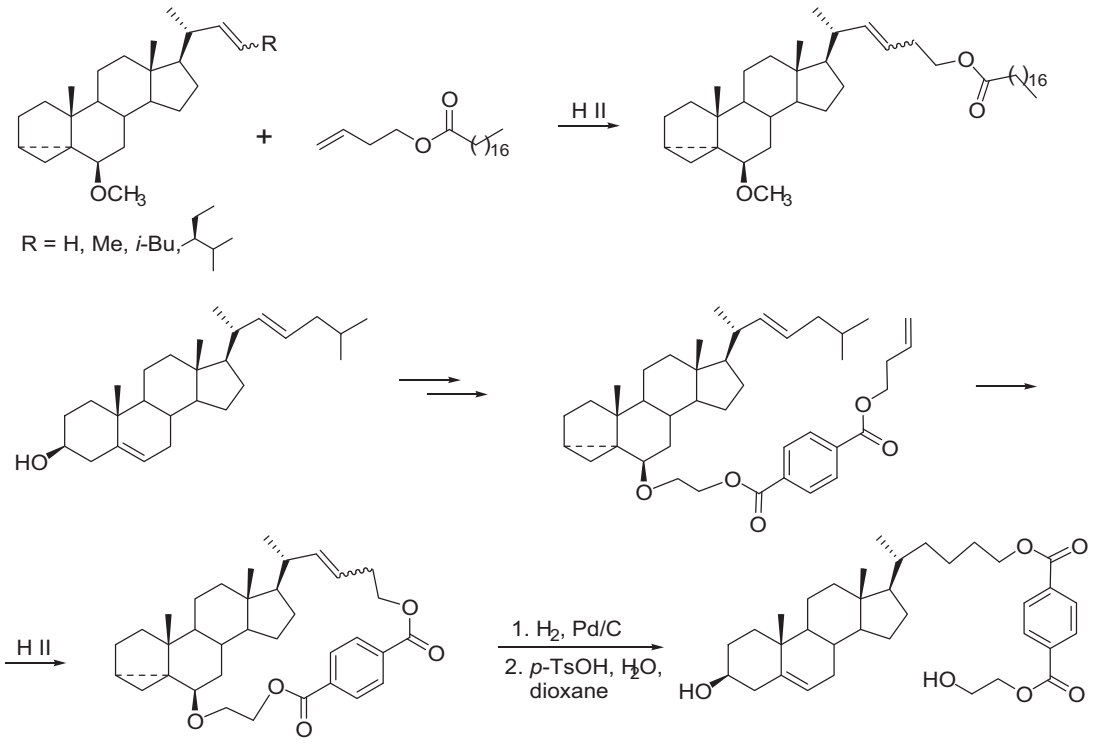
The starting estrone benzyl ether was transformed into 16-methylene derivative following known methodology [40] consisting of the Mannich base formation and its thermal elimination. The unsaturated ketone was stereoselectively reduced to the 17β-alcohol, which was *O*-alkylated with bromide readily prepared from 2-methylene-propane-1,3-diol. The RCM reaction of the diene catalyzed by G II afforded the tetrasubstituted cyclic olefin in 66% yield. The same strategy was also used for the preparation of the furanic-androstane derivative.

4. Modification of steroid side chain by cross-metathesis approach

The CM reactions have been frequently used for modification of steroid side chain. Czajkowska and Morzycki [41] have studied metathesis reactions of Δ^{22}-steroids. The CM reactions of



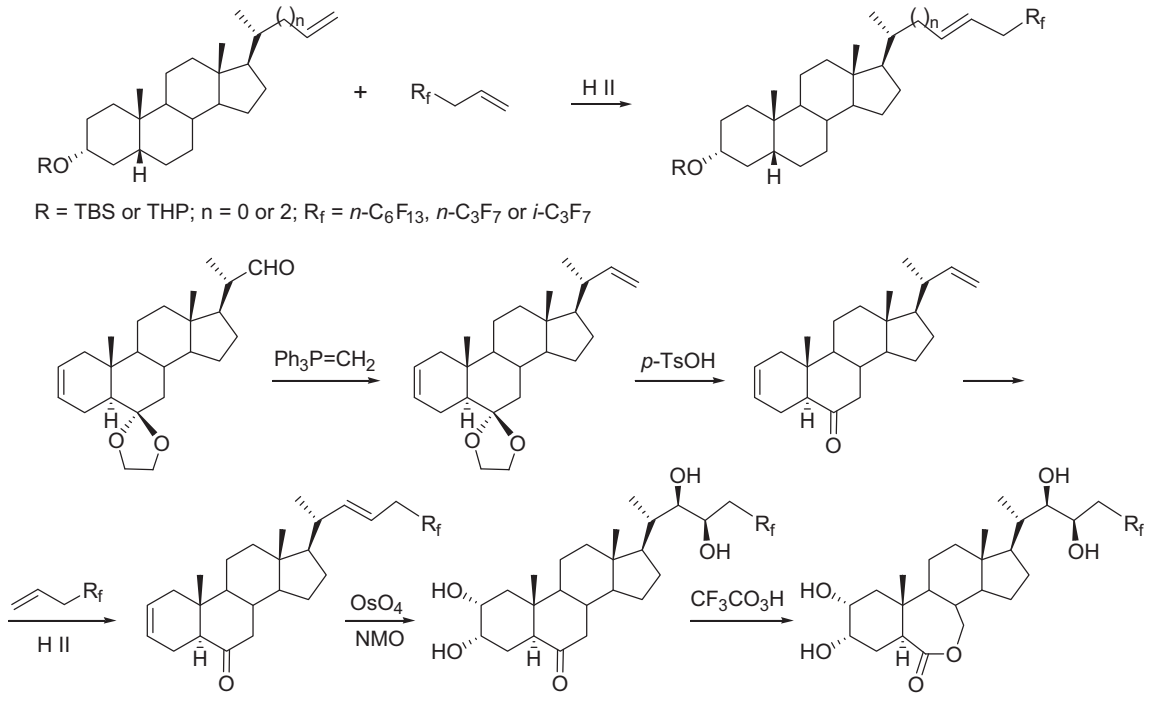
Scheme 7.



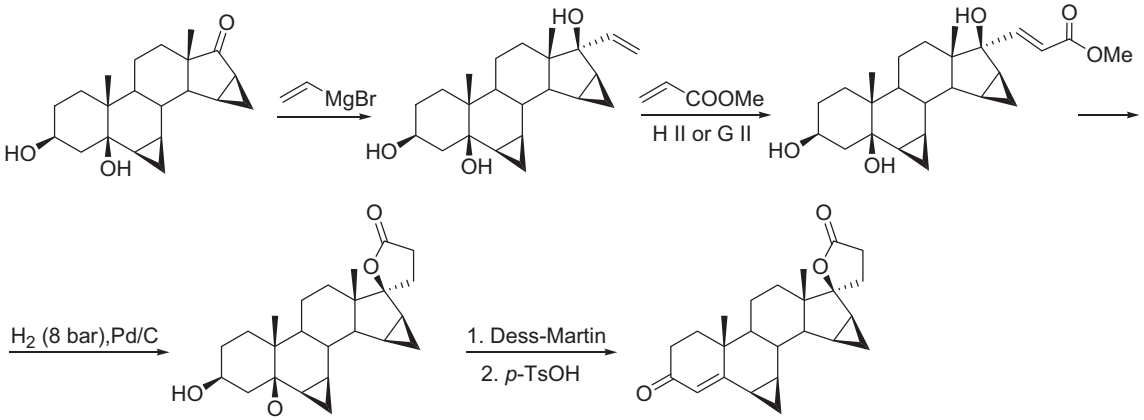
Scheme 8.

model Δ^{22}-steroids (Scheme 8) with excess of simple alkenes (e.g. 3-butenyl stearate) are rather sluggish and low-yielding (e.g. 12% yield achieved for the Δ^{22}-cholesterol derivative) or do not occur at all. In contrast, the intramolecular reaction (RCM) of the appropriate 3α,5α-cyclo-6β-substituted derivative of trans-Δ^{22}-cholesterol afforded the cyclic product in 64% yield. The product was further transformed to the 26,27-dinor-25-hydroxy-cholesterol derivative. Unfortunately, all attempts to apply stigmasterol (additional 24β-ethyl group) derivatives in metathesis reactions (CM or RCM) failed, probably due to the steric reasons.

The cross-metathesis reactions of (perfluoroalkyl)ethenes are known though they require use of at least a tenfold excess of the fluorinated alkene with respect to the non-fluorinated partner. However, the inductive effects of perfluoroalkyl groups is profoundly reduced with the distance from the reaction center.



Scheme 9.



Scheme 10.

Therefore (3-perfluoroalkyl)propenes were used for the CM reactions with steroidal side-chain olefins [42]. The reactions of two steroidal terminal olefins (Scheme 9) with only two-fold excess of 3-perfluoroalkyl-propene reagent catalyzed by the H II ruthenium carbene afforded the desired products in 63–81% yields. Interestingly, reactions of the steroidal olefin with the shorter side chain ($n=0$) were completely *E*-stereoselective, while substrate with the longer one ($n=2$) afforded diastereomeric mixtures with the *E* olefin prevailing. The authors have found that (3-perfluoroalkyl)propenes can be classified as type I olefins, unlike (perfluoroalkyl)ethenes, which behave rather like type II olefins (according to the Grubbs categorization) [43].

The reaction has been applied to the synthesis of fluorinated brassinosteroids, which are important plant hormones with potential application in agrochemistry due to their ability to stimulate growth of plants under undesirable conditions [44]. The brassinosteroids are inactivated by the conversion to more hydroxylated derivatives (e.g. at C-26 or C-28). Since the metabolic stability of the C–F bond is very high, fluorine-containing brassinosteroids would have practical significance because of an enhanced stability of products. The synthesis started from the 22-aldehyde (Scheme 9) readily available from the commercial substrates. The Wittig olefination afforded the 22-alkene which was subjected, after deprotection the carbonyl group at C-6, to CM reactions with (3-perfluoroalkyl)propenes. The H II catalyzed reactions afforded the corresponding *E* alkenes in satisfactory yields. The following reaction with OsO_4/NMO proved to be stereoselective at both C_2–C_3 and C_{22}–C_{23} olefinic bonds due to the preferred approach of the reagent from the less hindered side. Finally, the Baeyer–Villiger oxidation of the ketone with trifluoroperoxy acetic acid afforded the brassinolide analogue fluorinated in the side chain. The biological activity of the analogue was in the range of that of brassinolide.

A new synthetic approach employing the CM reaction for the construction of the spirolactone moiety of the aldosterone antagonist, drospirenone, was elaborated by Bandini [45]. Drospirenone exhibits both antimineralocorticoid and antiandrogenic activity very similar to that of the natural hormone progesterone. It is used as an oral contraceptive in combination with ethinylestradiol. The spirolactone moiety was constructed in three steps from the starting 17-ketone (Scheme 10). The highly stereoselective addition of vinylmagnesium bromide afforded the 17α-vinyl derivative. The key step of synthesis was cross metathesis reaction of this compound and methyl acrylate catalyzed by a ruthenium carbene catalyst. The first generation Grubbs catalyst (G I) failed, while the second generation catalysts proved effective. The reaction promoted by G II required relatively high amount of catalyst (12 mol%) and the yield was modest (55%). However, the reaction catalyzed by the H II ruthenium complex (6 mol%) afforded the desired product in 80% yield and the active catalyst could be recovered. Then hydrogenation of the double bond under pressure was performed and the spirolactone was directly obtained in 60% yield. Finally, with the synthesis of the spirolactone already accomplished, the stereoselective oxidation-dehydration of ring A was carried out under mild conditions with Dess-Martin periodinane followed by acid catalyzed dehydration. Drospirenone was obtained in 60% yield.

The same catalyst was used by Kotora and co-workers [46], who have demonstrated that the CM reactions between 17α-vinyl- and 17α-allylestradiols with (3-perfluoroalkyl)propenes constitute a convenient synthetic route (Scheme 11) to the 17α-substituted estradiol derivatives bearing highly lipophilic perflouroalkylated side chains. Such analogues are expected to be potent and selective ligands for the estrogen receptor. The yields of the cross metathesis products (*E*-isomers) were satisfactory for 17α-allylestradiols (53–68%) and significantly lower for the 17α-vinyl substrates (12–36%).

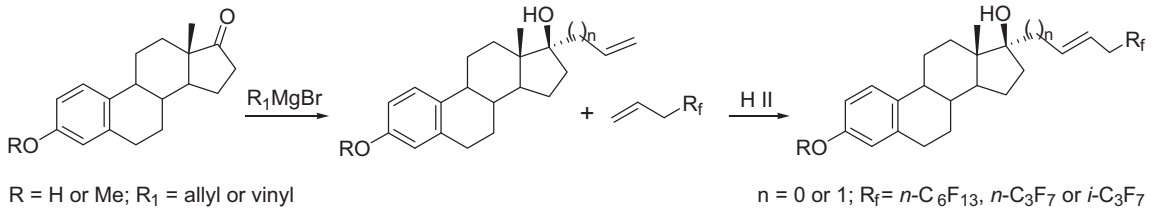
The efficient and convergent synthesis of simplified hybrid inhibitors of type I 17β-hydroxysteroid dehydrogenase was described by Bérubé and Poirier [47–49]. The synthesis of the designed inhibitors from estrone involves a cross-metathesis and a Sonogashira coupling reaction as key steps (Scheme 12).

Loozen [50] has prepared a series 7α-substituted 3-oxosteroids with an additional ring E attached to the steroidal ring D from the α-side (cis-fusion). These compounds are claimed to show contraceptive and antiosteoporosis activities. Two of these compounds were obtained by the ring closing metathesis approach. The five- or six-membered rings were closed using the first generation Grubbs' catalyst in high (75–85%) yields (Scheme 13).

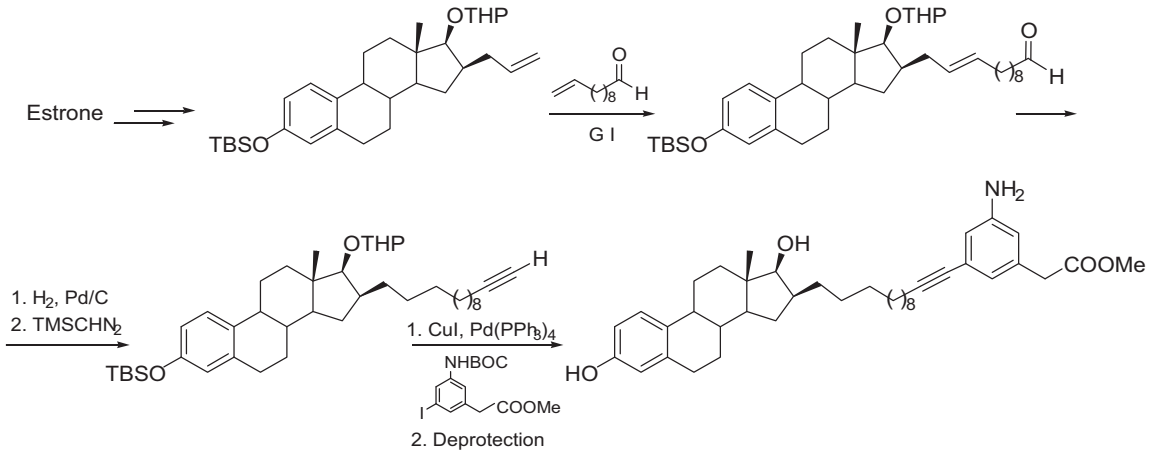
5. Synthesis of steroid dimers and macrocycles

Evidence that the dimerization or polymerization of the steroid skeleton leads to unique characteristics and functions gradually begin to emerge in diverse areas. Numerous dimeric and oligomeric steroids display micellular detergent activity and act as ligands for proteins. In this sense, dimers can trigger cellular processes or may promote the affinity of ligands to their binding locations by providing additional anchoring points to the active site of certain domains. Another area of interest is their behaviors as liquid-crystals, playing a key role as catalysts in some types of reactions, or producing new pharmaceutically active leads.

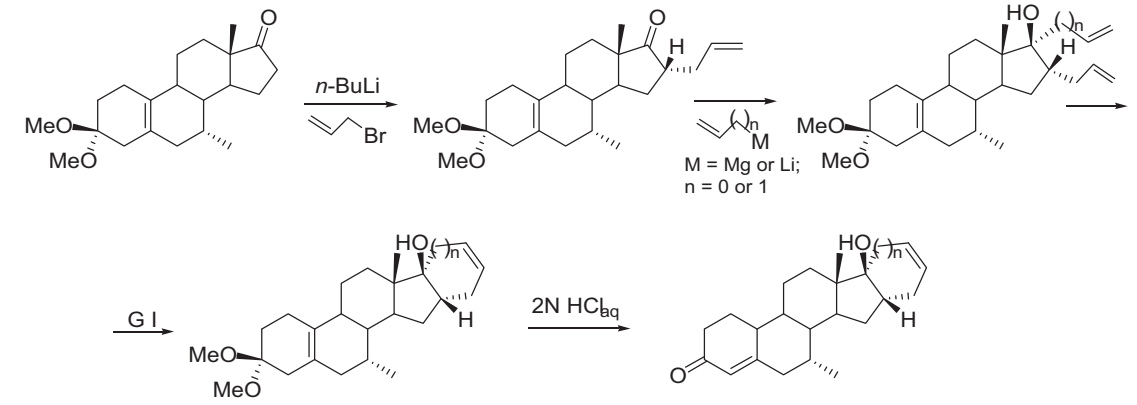
Having this in mind a synthesis of 6*E*-hydroximinosteroid homodimers was attempted (Scheme 14) [51]. The unusual 6*E*-hydroximino-3-oxo-4-ene steroids were discovered in the sponge *Cinachyrella alloclada*. A rapid and efficient synthesis of homodimers of these cytotoxic compounds was carried out. To 6-ketones (X = O) three or four carbon atom linkers with terminal double



Scheme 11.



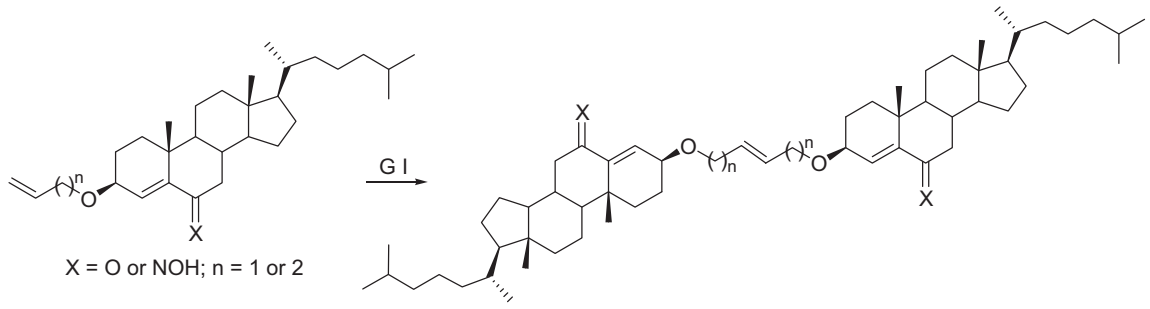
Scheme 12.



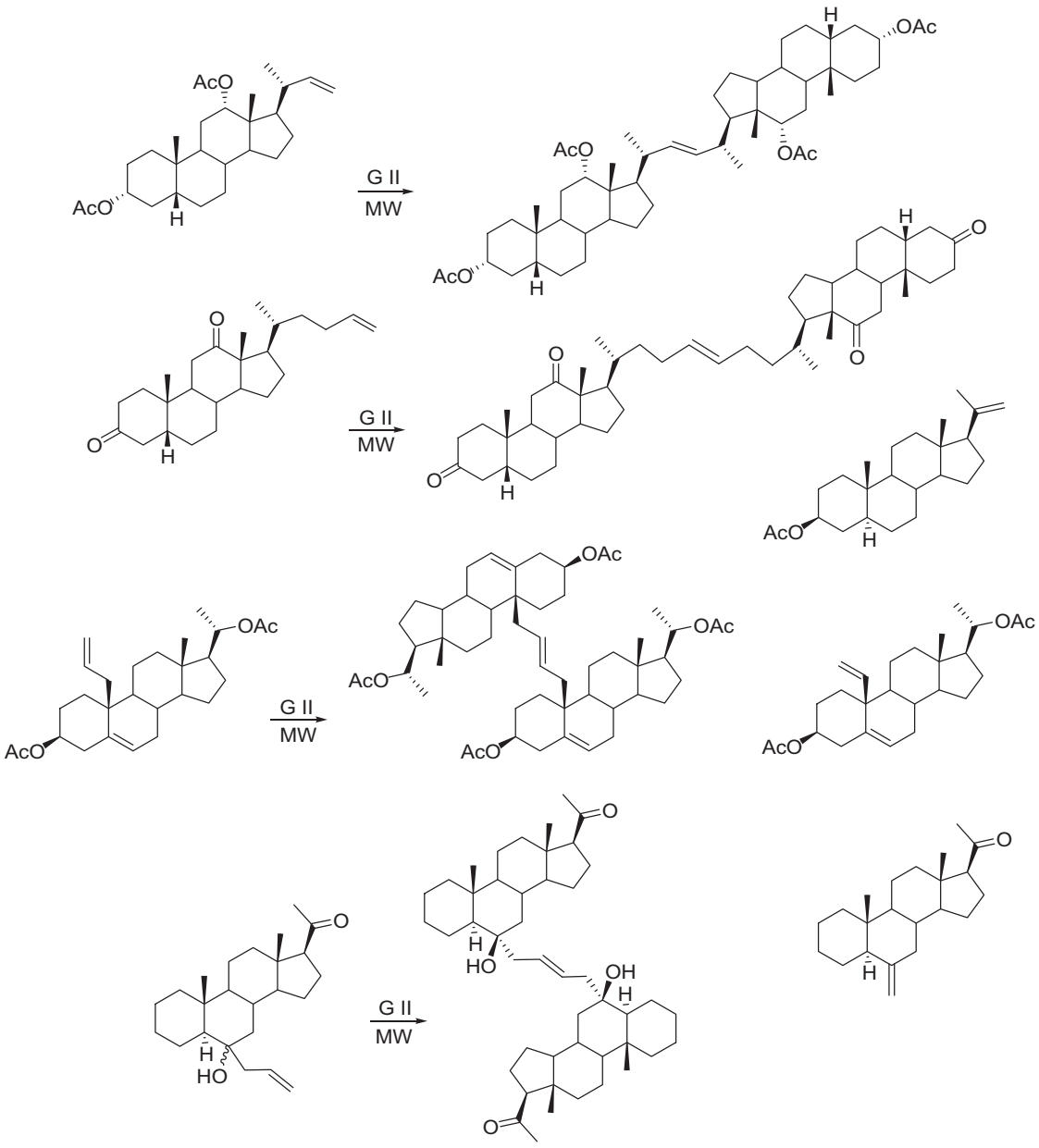
Scheme 13.

bonds were attached at 3β-position. The monomers were subjected to a G I catalyzed self-metathesis. The allylic ether ($n = 1$) afforded *E*-homodimer in 82% with small amounts of the sterically less favored *Z*-isomer. In the case of homoallylic ether (yield 80%) the ratio *E*/*Z* was 1.5:1. After chromatographic purification, the dimers were converted to the 6*E*-oximes. However, homodimers were proved to be not very cytotoxic when compared with monomer counterparts.

The steric hindrance was an important factor in studies on dimerization of steroidal olefins by metathesis [52]. A series of steroidal homodimers derived from deoxycholic acid, preg-



Scheme 14.

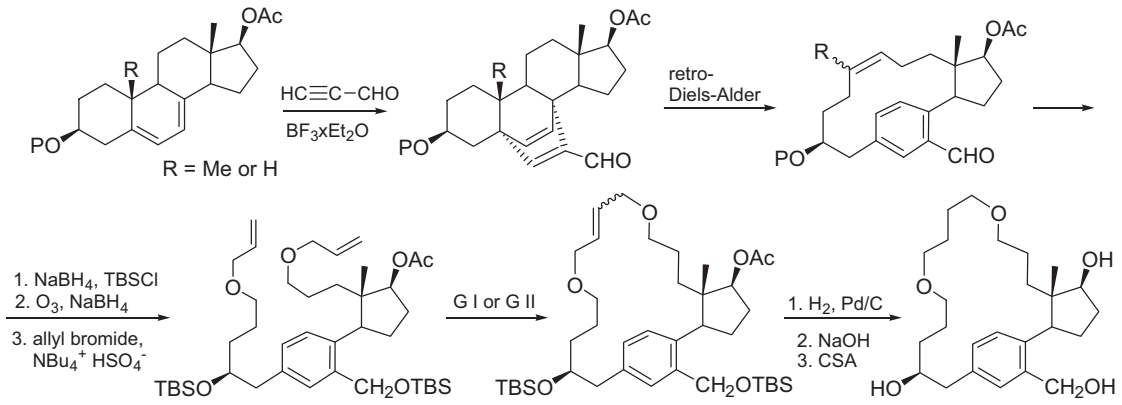


Scheme 15.

nenolone, and progesterone was synthesized by olefin metathesis reactions assisted by microwave heating (Scheme 15). The application of microwaves accelerated the reactions and allowed for the use of less catalyst without diminishing yields. Due to the bulky nature of the steroidal skeleton the more favorable *E*-dimers were formed as the sole or major products depending on the linker length. Thus compounds with a double bond in the side chain significantly differ in reactivity. While the $\Delta^{20(22)}$-olefin prepared from progesterone acetate by the Wittig reaction proved resistant to metathesis conditions (G II) due to the steric hindrance, the Δ^{24}-olefin derived from deoxycholic acid readily reacted with G II affording the corresponding homodimer as a mixture of *E*/*Z* isomers (ratio 9:1) in 89% yield. The Δ^{22}-olefin afforded exclusively the *E* isomer but yield of the homodimerization reaction was lower (49%). Similar results were obtained for compounds with an olefinic bond in the alkenyl substituent at 10β-position. The 10β-vinyl compound did not undergo self-metathesis. However, the allyl analogue afforded the *E*-homodimer in 64% yield. Progesterone derivative with exo-methylene double bond at C-6 failed to react under metathesis conditions, apparently from steric reasons. Also the axial 6β-allyl compound did not react, probably for the same reasons (steric hindrance from the proximal axial methyl group). However, the equatorial isomer (6β-allyl) reacted promptly (97% yield) affording the *E*-homodimer as the major product with 5% of the *Z*-isomer detected by NMR.

Ring enlargement of ansa-steroids leads to a variety of novel templates suitable for the preparation of diverse libraries of natural product derivatives [53] (Scheme 16). Due to the enhanced flexibility within the macrocycle, the compounds should show a higher adaptability towards the molecular targets. The ansa-steroids are readily available by the Winterfeldt–Diels-Alder/retro-Diels-Alder sequence [54].

The ansa-steroid ring enlargement consisted of a sequence: ozonolysis of a double bond, $NaBH_4$ reduction, diallylation, and RCM. This last reaction was catalyzed by the G I catalyst and led to the 20-membered macrocycle as a mixture of *E*/*Z* isomers (36%

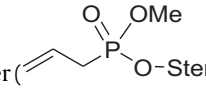


Scheme 16.

yield). The mixture was hydrogenated and the protecting groups were removed.

6. Synthesis of vitamin D analogues

The synthesis of vitamin D analogues functionalized at C-19 via ring-closing metathesis was attempted for the first time by Barrett and co-workers [55]. The use of tethered heteroatoms in ring-closing metathesis reactions has been shown to be synthetically very useful in the preparation of di- and trisubstituted alkenes [56–58]. This methodology has been also applied to the regioselective C-19 monosubstitution of 1α,25-dihydroxyvitamin D_2 (Scheme 17). The desired selectivity was achieved due to the greater susceptibility of the terminal alkenes to RCM and the proximity of the tethered allylic substituent. It was expected that removal of the heteroatom tether following RCM should afford a range of functionalized C-19 alkenes. According to this strategy 1α-hydroxy-5,6-*trans*-vitamin D_2 allyldimethylsilyl ether was subjected to RCM with the Grubbs' II carbene. The desired product was obtained in 82% yield. Analogously an allylphosphonate ester



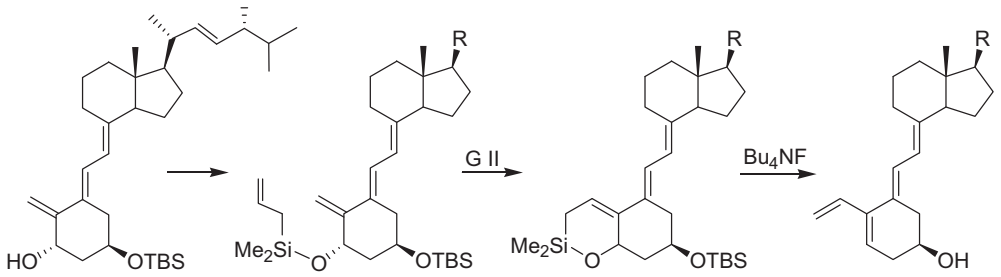
tether ( ) attached at C-3 to 5,6-*trans*-1α-OH-D_2 was proved to be a suitable substrate for RCM reaction affording cyclic steroid phosphonate in 79% yield. Unfortunately attempts to remove tethers led to elimination products.

A few years later a similar approach was attempted by Wojtkielewicz and Morzycki [59,60], but instead of heteroatom tethers, the carboxylate ester tethers with a terminal double bond were used. It have been shown that such ester derivatives of 1α-OH-D_3 (Scheme 18) do not react when treated with ruthenium carbenes, probably due to the steric reasons (steric hindrance from the CD moiety). However, the ω-unsaturated esters of 5,6-*trans*-1α-OH-D_3 yielded the corresponding γ- and δ-lactones with the second generation ruthenium catalysts in addition to self metathesis products. The lactones were further transformed into 19-substituted 5,6-*trans*-1α-OH-D_3 derivatives by reduction with DIBAL-H or LAH (Scheme 19). Photochemical isomerization around the C_5–C_6 double bond yielded the desired analogues of 1α-OH-D_3 with a substituent at C-19.

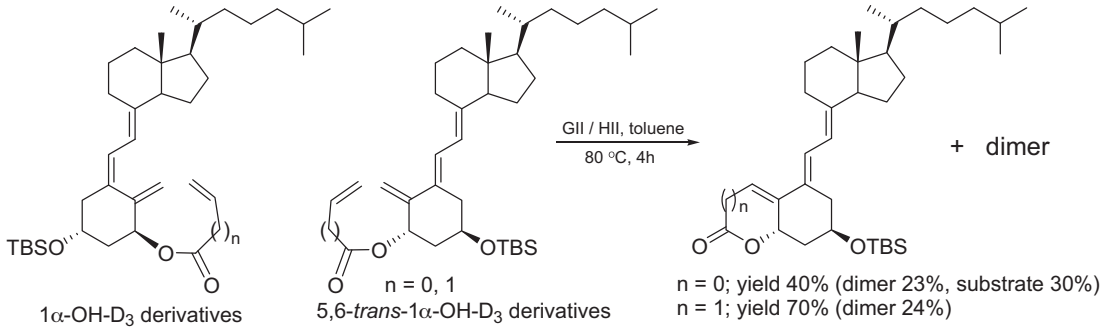
DeLuca et al. have prepared 1α,25-dihydroxy-19-norvitamin D_3 analogues constrained in a single A-ring conformation by RCM as a key step [61]. The conformation of the ring A and, as a consequence, the position occupied by 1α-OH group is pivotal for binding to the vitamin D receptor. It is well established that in vitamin D compounds equilibration between the two dominating chair conformations is rapid. Of these conformations, the one with equatorial 1α-OH substituent (β-chair form) is necessary for ligand binding to the receptor. The hemisynthesis of new analogues started from (−)-quinic acid (Scheme 20), which was converted into the ring A synthons with constrained cyclohexanone conformation. The RCM steps were accomplished using G II catalyst in high yields for both dihydrofuran and tetrahydropyran derivatives. However, the five-membered ring was formed using a TBS-protected substrate (n = 1; R = TBS), while the analogous substrate (homoallylic ether; n = 2; R = TBS) failed to react. This was probably due to steric hindrance caused by a bulky *tert*-butyldimethylsilyl group. Once it was removed (R = H), the RCM reaction leading to the six-membered ether ring occurred smoothly. Upon removal of the thioacetal protecting group with thalium triflate, the resultant ketones were subjected to Julia olefination with the phenylthiazoline sulfone separately prepared from ergocalciferol, followed by acid deprotection of the hydroxyl groups [62]. The reaction afforded the mixture of isomeric 19-norvitamins with restricted ring A conformation. According to expectations they have exhibited enormous difference in biological activities.

In search for vitamin D receptor antagonists a series of 1α-hydroxyvitamin D_3 26,23-lactones (analogues of the natural 1α-OH-D_3 metabolite) were synthesized [63,64]. The antagonists have attracted interest because of their potential utility in the treatment of Paget's disease, which is known as the most flagrant example of disordered bone remodeling and the second most common bone disease after osteoporosis.

The synthesis of 24,24-ethano-25-dehydro-1α-hydroxyvitamin D_3 26,23-lactone (Scheme 21) started from the 23-aldehyde prepared from ergocalciferol in a few steps. The addition of lithium sililoxymethylacetylide to the aldehyde and subsequent tetrapropylammonium perruthenate (TPAP) oxidation afforded ketone, which was subjected to metathesis reaction. The Ru-catalyzed intermolecular enyne metathesis with ethylene [65] to introduce methylene units both at position C-24 and at position C-25 was investigated under various conditions. The best yield (92%) was achieved with the Blechert catalyst, ethylene (1 atm) at 0 °C. In the next step the regioselective cyclopropanation through 1,4-addition of trimethylsulfoxonium iodide afforded the cyclopropyl ketone. The ketone was reduced with DIBAL-H to afford a mixture of epimeric at C-23 alkohols. After deprotection of the hydroxyl groups with TBAF, the epimers were separated, and both 23*R* and 23*S* diols were converted to 26,23-lactones by MnO_2 oxidation. Construction of the vitamin D3 triene skeleton was accomplished by Pd-catalyzed alkenylative cyclization [66] of enyne with the appropriate CD-ring counterparts followed by removal of the *tert*-butyldimethylsilyl groups. (23S)-24,24-Ethanovitamin D_3 lactone showed a very strong VDR-binding affinity and antagonistic activity. In contrast, the (23*R*)-isomer showed almost no antagonism.



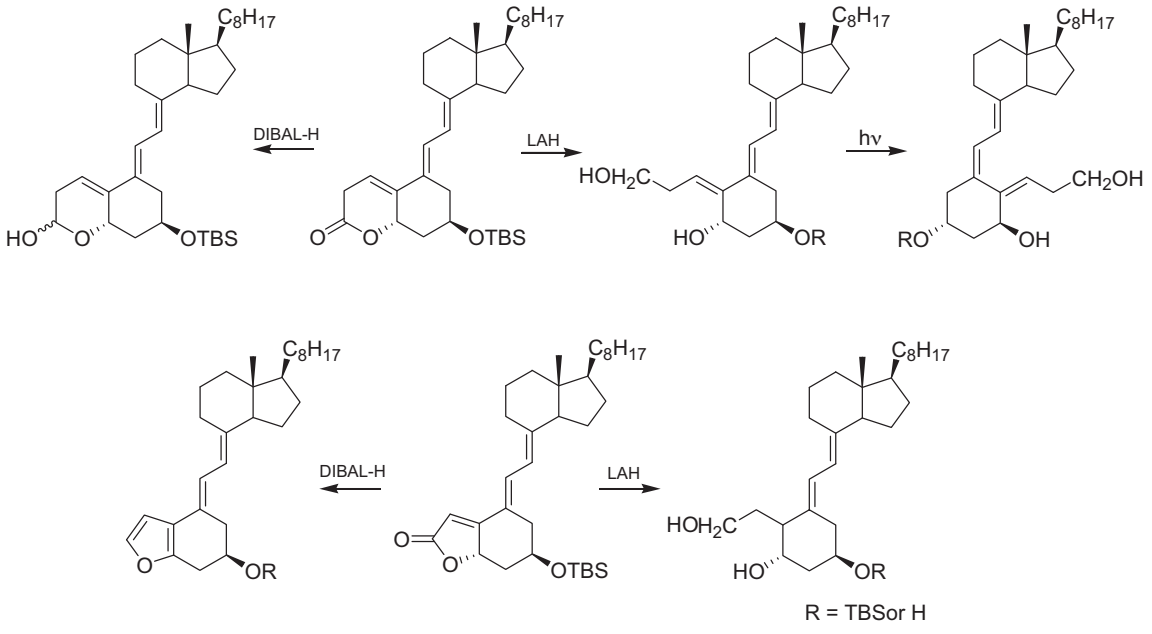
Scheme 17.



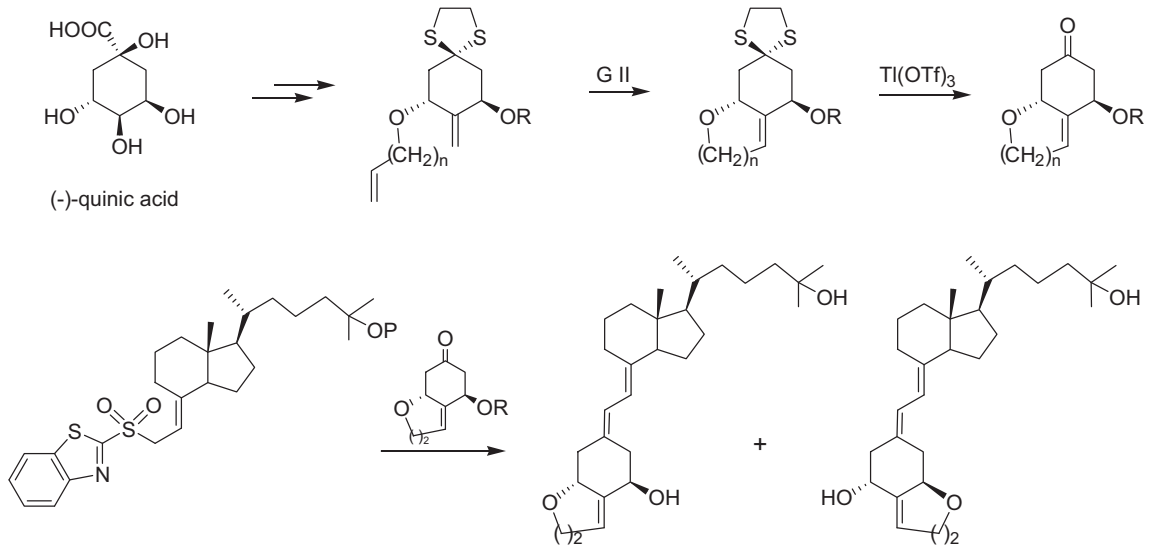
Scheme 18.

The dimers comprising two 1α,25-dihydroxyvitamin D_3 (calcitriol) units, linked at C-11 by an alkyl side chain of six or ten carbon atoms, were designed and synthesized with a view to the simultaneous binding of two vitamin D_3 receptor molecules and the consequent induction of its dimerization [67,68]. The ring C region was chosen as a site of linkage of two calcitriol molecules because it is probably the least active part of the vitamin D structure. The synthesis of the dimers started from the known hydroxyester (Scheme 22), which was routinely converted to the 8-ketone with protected hydroxyl group in the side chain. For the ketone dehydrogenation the Saegusa reaction conditions were used. The stereoselective cuprate addition to the enone afforded substrates for metathetic homodimerization reactions. The reactions ($n = 1$ or 3) catalyzed by the Grubbs' first generation catalyst led to the corresponding mixtures of *E* and *Z* isomers, which were hydrogenated using a rhodium catalyst. Finally, the Wittig–Horner approach was used to construct the vitamin D triene from the dimeric ketones. The reverse order of transformations (the reaction with phosphonium oxide first and then olefin metathesis) was also attempted. However, this approach failed since the selective hydrogenation of the linker double bond in dimers could not be carried out in the presence of the triene systems.

The tandem metathesis of dienynes was employed to the synthesis of linearly fused 6–8–6 carbocyclic systems [69]. Using this approach an analogue of the transition state of previtamin $D_3 \rightarrow$ vitamin D_3 was obtained (Scheme 23). This isomerization,



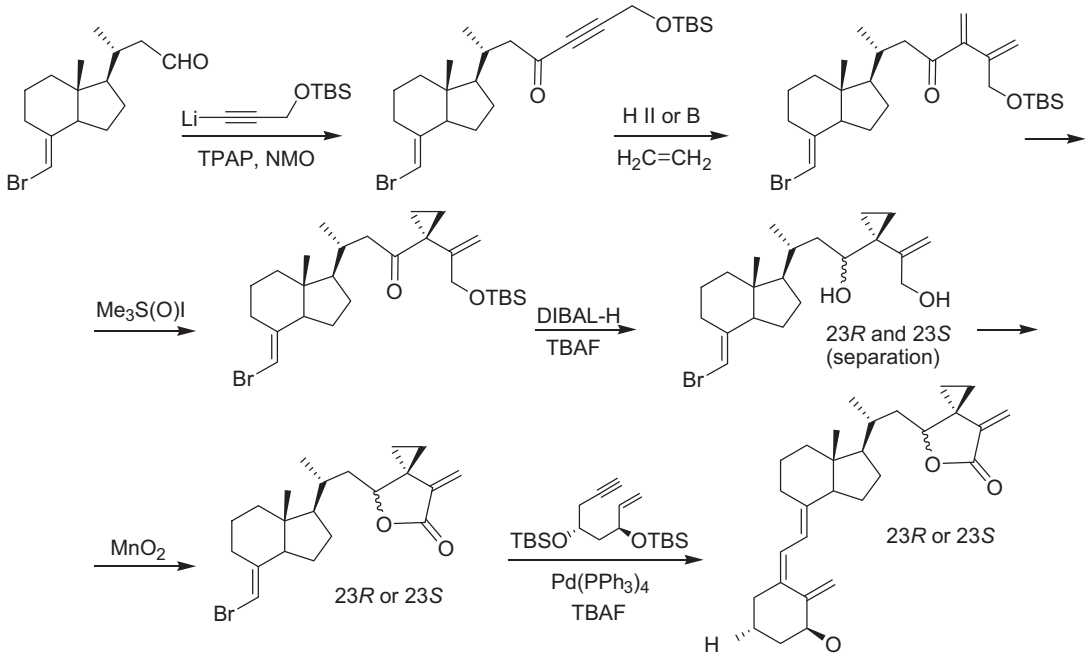
Scheme 19.



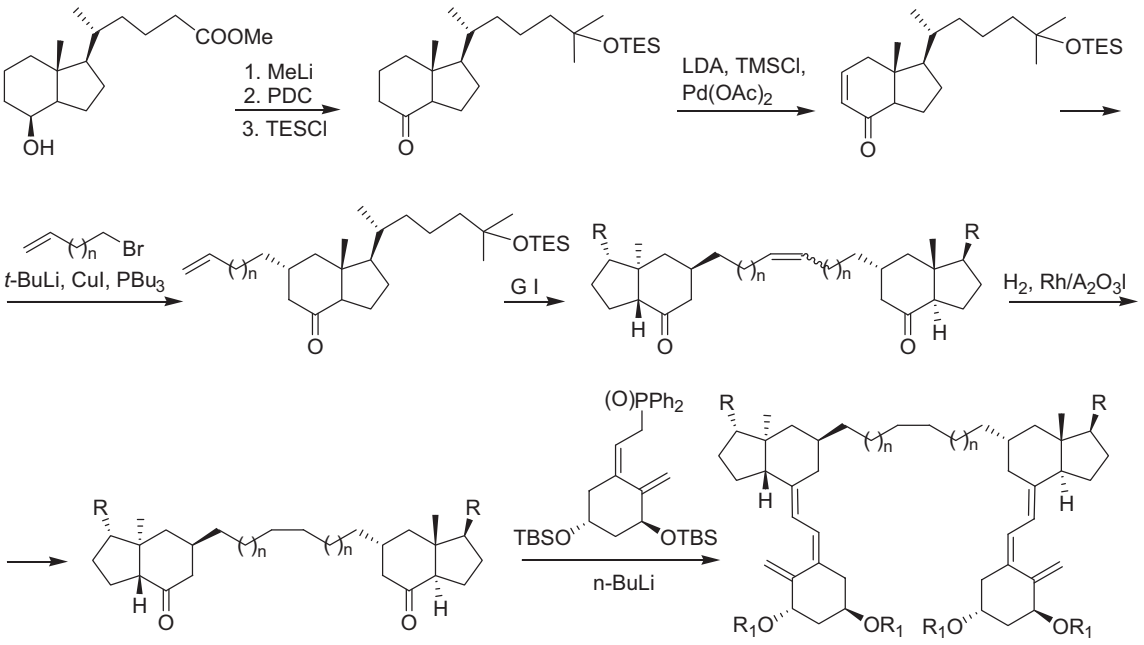
Scheme 20.

one of two consecutive pericyclic reactions in the synthesis of vitamin D_3 from 7-dehydrocholesterol, consists of a thermally induced antarafacial [1,7]-sigmatropic hydrogen shift from C-19 to C-9. The product, obtained as an inseparable 1:1 diastereomeric mixture at C-10 in 48% yield upon treatment of dienyne (prepared from the Grundmann ketone) with a ruthenium carbene catalyst (G I), mimics the cyclic transition state of this isomerization.

The above tetracyclic system was also prepared on a different route in the enantiopure form (Scheme 24) [70,71]. The route consisted of two successive cyclizations (RCM and Heck). The formation of a medium-size ring by RCM was studied in detail. A series of dienes was prepared from the Grundmann ketone and subjected to RCM reactions with G I and G II. The desired eight-membered rings ($n = m = 1$) were obtained in yields of 86–99%. Elongation of the longer alkenyl chain by one carbon atom ($n = 1$, $m = 2$) allowed also for the formation of a nine-membered ring in good yield. On the other hand, attempts to cyclize substrates without the methylene group between the oxygenated carbon atom and the double bond ($n = 0$, $m = 2$) proved unsuccessful. Also the cyclohexyl derivative ($R_1R_2 = (CH_2)_4$) completely failed to cyclize, even using G II at elevated temperature. The formation of the eight-membered ring is not impeded by the stereochemistry of a substituent at C-10, since approximately 1:1 diastereomeric mixtures of cyclooctenes were obtained. The mixtures were usually difficult to separate including TBS-ethers but in the case of free alcohols obtained upon treatment of the crude product with tetrabuthylammonium fluoride (TBAF), the C-10 epimers were easily separated. Further transformations (oxidation and olefination by Stork's method [72]) allowed isolation of *Z*-vinyl iodides, suitable substrates for the Heck reaction. Treatment of both epimers with palladium tetrakistriphenylphosphine afforded the expected products in 64% and 15% in the case of 10*R* and 10*S* diastereomers, respectively. In the latter case a major product (40%) was formed by replacement of iodine by hydrogen atom. These differences in reactivity of iodides are due to confor-



Scheme 21.



Scheme 22.

mational restrictions introduced by the eight-membered ring fused to the CD-bicyclic system.

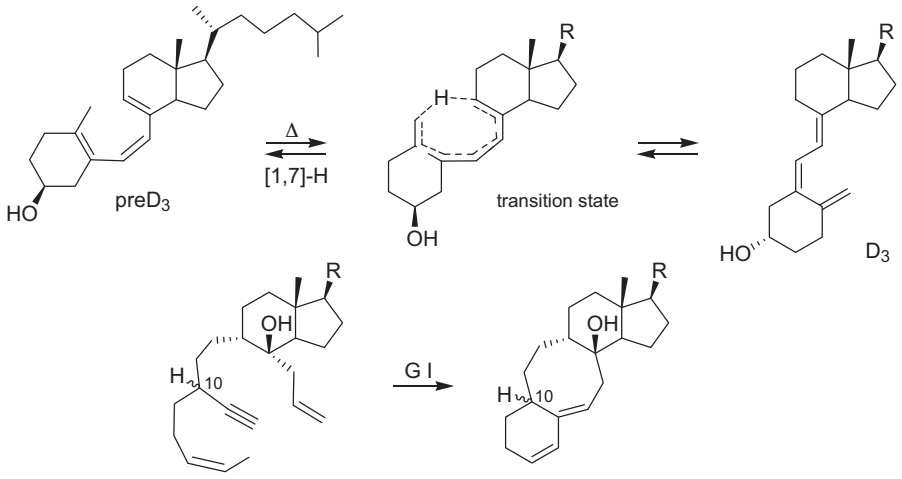
7. Synthesis of hybrid compounds

The chemical synthesis of hybrid natural products is a promising approach to obtain structurally diverse chemical substances for pharmaceutical testing. A new class of sugar–oxasteroid–quinone hybrid molecules has been designed and synthesized (Scheme 25) by approach involving an efficient enyne metathesis/Diels-Alder reaction strategy [73]. The D-allofuranose derived ketone was treated with methylmagnesium iodide followed by allylation of the tertiary alcohol. Selective deprotection of the more exposed 5,6-*O*-isopropylidene group afforded a diol, which was subsequently cleaved with $NaIO_4$ to provide the aldehyde.

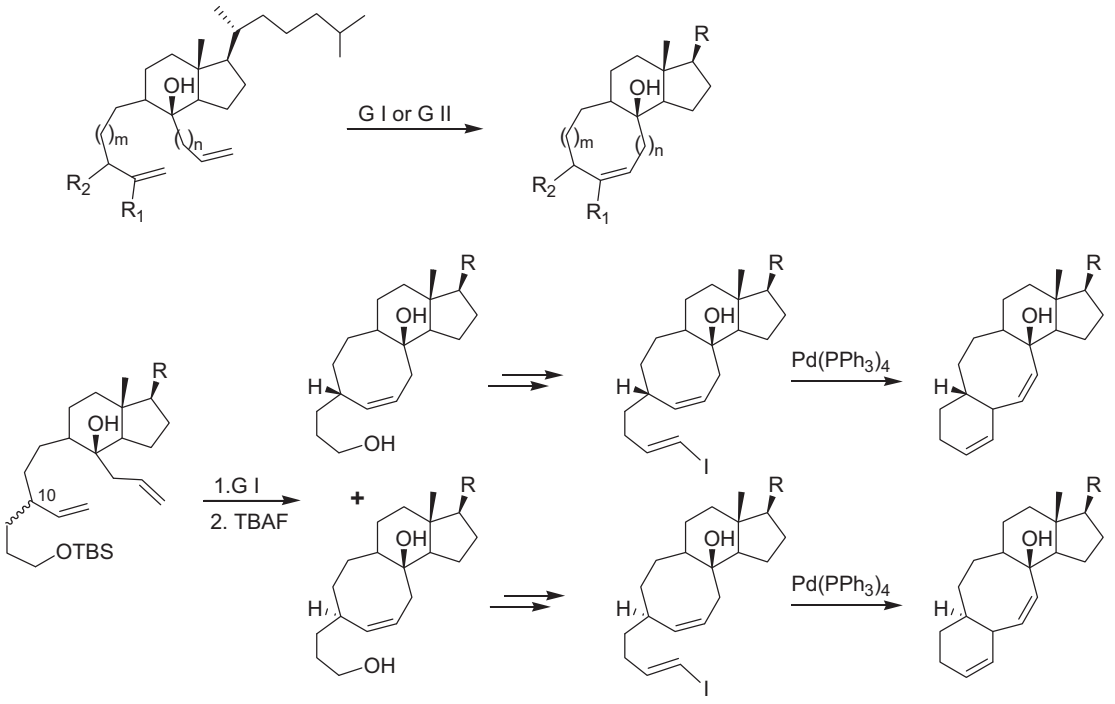
The key precursor enyne was obtained from the aldehyde using the Bestmann protocol [74]. The enyne underwent a smooth intramolecular metathesis with the Grubbs' first generation catalyst to afford the diene in 74% yield. The Diels-Alder reaction of the diene with 1,4-benzoquinone was carried out under thermal conditions. The initially formed cycloadduct proved unstable and underwent aromatization/oxidation during chromatography on a silica gel column.

A synthesis of new hybrid compounds called 'glycospirostanes' comprising steroid and sugar moieties from steroidal 22,16-lactones was described [75] (Scheme 26). The starting lactones were treated with allylmagnesium bromide followed by trifluoromethanesulfonimide catalyzed reaction with allylic alcohol. The key step of synthesis was ring-closing metathesis of the C,O-diallyl derivative. Excellent yields were achieved with the Grubbs first generation catalyst. Further elaboration of the six-membered ring F consisted of regio- and stereoselective allylic hydroxylation with SeO_2 followed by OsO_4 dihydroxylation of the C_{24}–C_{25} double bond from the less hindered side. The obtained final products proved to be simultaneously O- and C-L-arabinopyranosides.

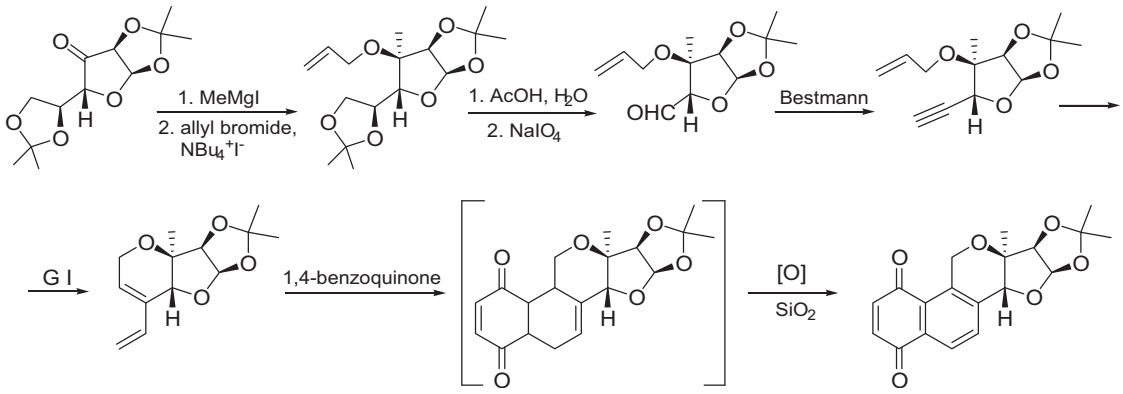
A cascade dienyne ring-closing metathesis approach has been also applied [76,77] to the synthesis (Scheme 27) of the tetracyclic carbon framework of a new class of hybrid compounds – the taxosteroids – possessing carbon frameworks incorporating moieties characteristic of both taxanes (such as AB rings) and steroids



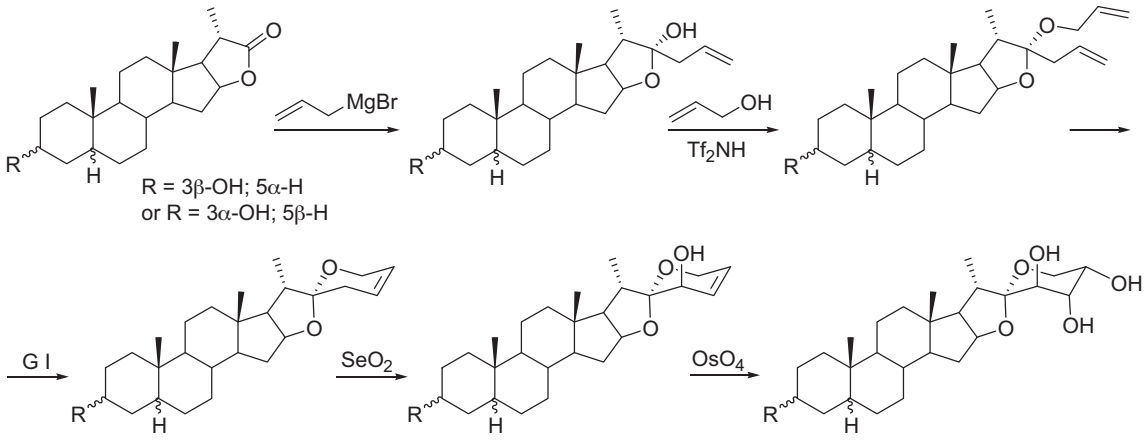
Scheme 23.



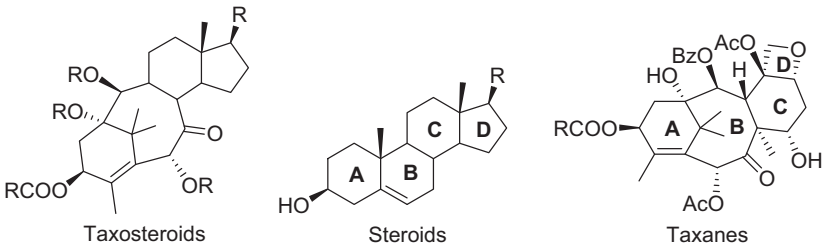
Scheme 24.



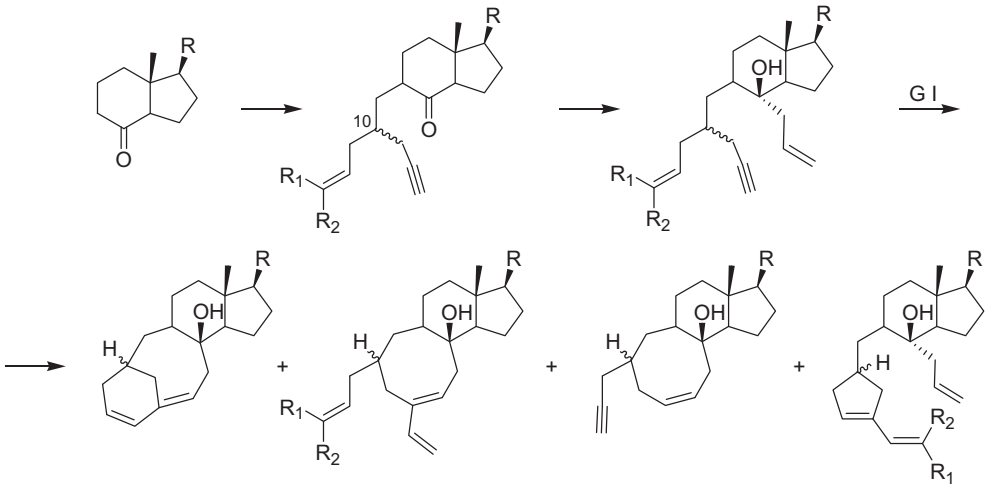
Scheme 25.



Scheme 26.



Scheme 27.



Scheme 28.

(i.e. the CD system and side chain). This tandem cyclization is highly stereoselective, allowing the one-step formation of the bicycle[5,3,1]undecene system characteristic of taxol.

The starting compound for his study (Scheme 28) was obtained by alkylation of the kinetic enolate of an easily available ketone containing the steroidal CD fragment (e.g. Grundmann ketone) with the appropriate alkylating agent separately prepared. The metathesis reactions were catalyzed by the Grubbs' complexes of the first or second generation. The four products were formed in variable yields depending on the substituents R_1 and R_2, configuration at C-10 and the reaction conditions. The desired taxosteroid was usually a minor product. The reactions promoted by the Grubbs' II catalyst afforded mostly products containing the cyclopentene ring. Only in the case, when R_1 = H and R_2 = isopropyl, the 10*R* configuration, using the Grubbs' I catalyst, the yield of the taxosteroid was satisfactory (a 9:1 mixture of this compound and its intermediate was obtained in a global yield of 90%).

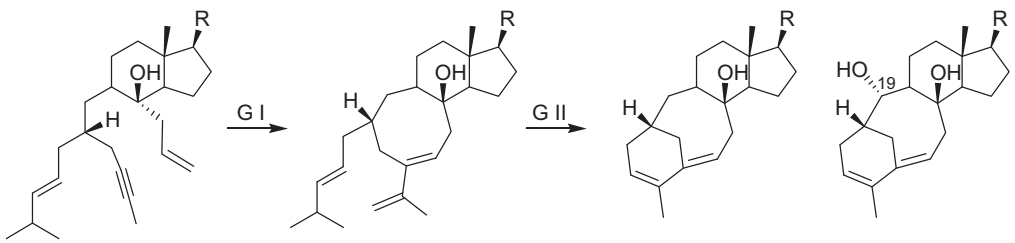
In further study an enantioselective synthesis of a 3-methyltaxosteroid was attempted (Scheme 29). To achieve this goal a substrate with an alkyne chain terminated by a methyl group, isopropyl group at the double bond, and the *R* configuration at C-10 was used.

Unfortunately, the reaction promoted with the Grubbs' I catalyst afforded mostly the triene intermediate with a 3-methyltaxosteroid as a very minor product. This was probably so due to the steric hindrance. However, treatment of the triene with the Grubbs' II catalyst led to the 3-methyltaxosteroid. It was subsequently demonstrated that the final product may be directly obtained from the dienyne with the same catalyst in 69% yield, without any cyclopentene formation that was expected on the basis of the initial study. More complex substrates were also prepared to synthesize the 19-substituted taxosteroids by a cascade dienyne ring-closing metathesis approach.

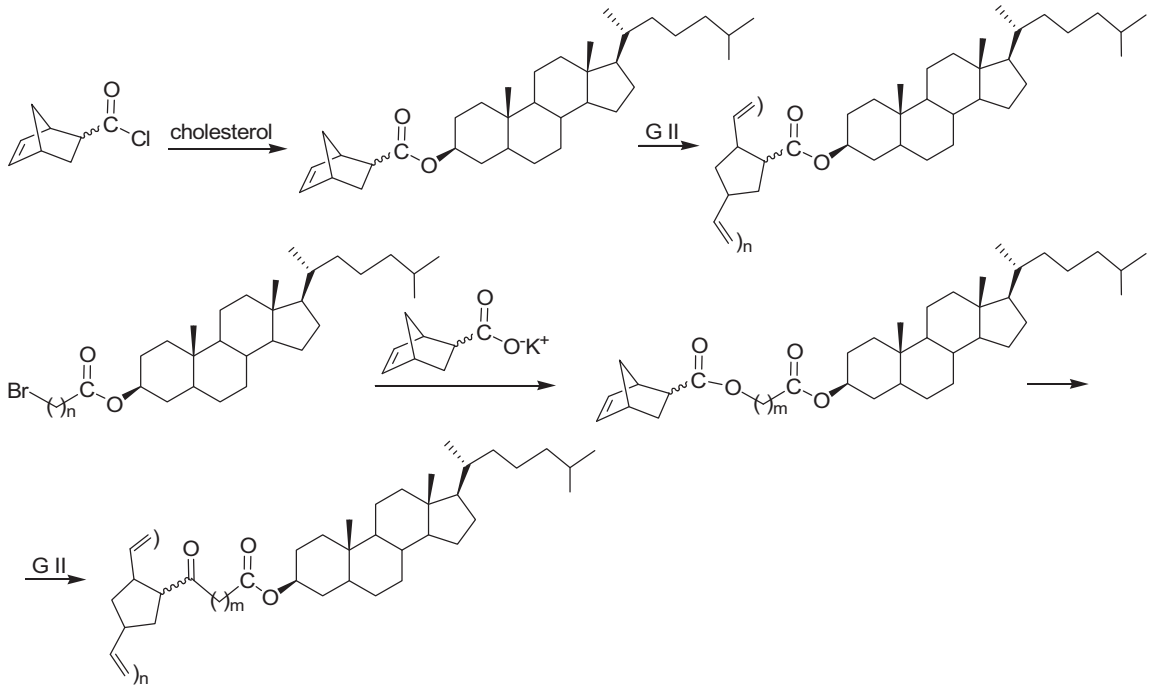
8. Miscellaneous

A series of norbornene carboxylic cholesteryl ester monomers with and without spacers between the two moieties (Scheme 30) were prepared and the corresponding liquid crystalline homopolymers were obtained with the Grubbs' second generation catalyst. The thermal and liquid crystalline properties of the homopolymers were investigated by different techniques [78].

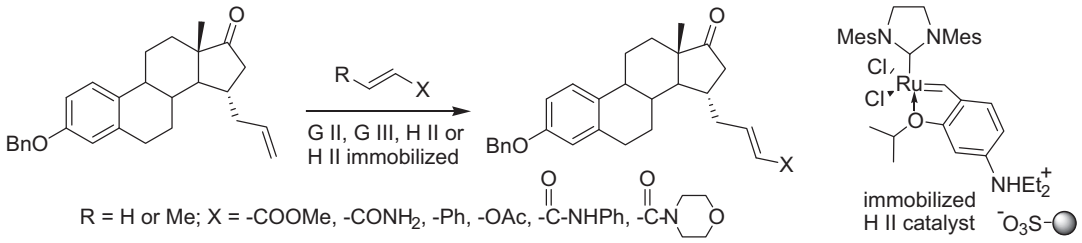
Other steroids (estrone, estradiol, ursodeoxycholic acid, chenodeoxycholic acid, cortisone, prednisone, and dexamethasone)



Scheme 29.



Scheme 30.



Scheme 31.

were also reacted with either 5-norbornene-2-carboxylic acid chloride or 5-norbornene-2-methanol to form norbornene derivatives with bioactive steroid residues bound with an ester linkage [79]. These norbornene based monomers were polymerized by a ring-opening metathesis polymerization initiated by the Grubbs' II catalyst or the ruthenium–vinylidene complex (Fig. 4).

The polymers were soluble in THF, and casting the solutions produced films. Solid-state hydrolysis of the estrone containing film showed a slow but steady release of estrone under mild conditions (pH 5.5 at 37 °C).

In search for new inhibitors of enzyme 17β-hydroxysteroid dehydrogenase type I, a series of 15α-substituted derivatives of estradiol were prepared by the cross-metathesis of 15α-allylestrone with various conjugated olefins (Scheme 31) [80]. As previously noted [39], the enzyme is involved in the conversion of estrone to the potent estrogen estradiol and plays a key role in controlling the tissue level of this compound. The reactions catalyzed by different homogenous and heterogeneous Ru-catalysts were studied. Hoveyda-type catalyst containing

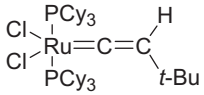


Fig. 4. The ruthenium–vinylidene complex.

an additional diethylamino group turned out to be comparably active as homogenous Grubbs' II catalyst after immobilization on an acidic ion exchange resin which greatly facilitates workup.

9. Conclusion

Two decades after the first reports on ruthenium-mediated olefin metathesis transformations, this powerful reaction still attracts significant attention. In recent years a growing number of papers is observed devoted to synthesis of natural products, including steroids, employing olefin metathesis as a key step. All types of metathesis transformations have been applied in the steroid chemistry, such as cross-metathesis, ring-closing metathesis, enyne RCM, ring-opening polymerization metathesis, and also tandem reactions, e.g. dienyne metathesis or enyne metathesis in combination with a Diels-Alder reaction. The catalysts used in the steroid synthesis are mainly commercially available first and second generation Grubbs and Hoveyda ruthenium complexes. Other catalysts may offer higher activity and different chemoselectivity but they are rarely used in practice [11]. Although various chiral olefin metathesis catalysts are known [5], none of them was used in the synthesis of steroids. It seems that there is a need for commercialization of new catalysts.

Acknowledgement

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