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Synthesis of natural products and analogs using multiple Pd-catalyzed transformations*

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Abstract: Palladium-catalyzed transformations are of great importance in modern synthetic organic chemistry. The vast number of reactions that can be catalyzed by Pd^0- as well as Pd^{2+}-complexes in combination with the relative stability of the intermediates offers the intriguing opportunity of carrying out multiple consecutive bond-forming processes. They can be even performed in a domino fashion and in the presence of chiral ligands to allow the efficient preparation of almost enantiopure compounds. In this article, the use of double Heck, Tsuji–Trost–Heck, and Wacker–Heck reactions for the total syntheses of estradiol, spinosyn A analogs, cephalotaxine, and vitamin E is described.

Keywords: Pd^0- and Pd^{2+}-transformations; Heck; Suzuki; Stille; Sonogashira; Tsuji–Trost; Wacker oxidation; domino reactions; spinosyn A; cephalotaxine.

INTRODUCTION

Pd-catalyzed transformations are of major importance in synthetic organic chemistry, since they allow the formation of C–C, C–O, and C–N bonds as well as other connections under mild reaction conditions, and, moreover, they tolerate many functional groups. One distinguishes Pd^0- and Pd^{2+}-catalyzed reactions. The most common Pd^0-transformations are the Heck and the cross-coupling transformations such as the Suzuki, the Stille, and the Sonogashira reaction, which allow the arylation or alkenylation of C–C double bonds, boronic acid derivates, stannanes, and alkynes, respectively [1]. Another important Pd^0-transformation is the nucleophilic substitution of usually allyl acetates or carbonates known as the Tsuji–Trost reaction [2]. The most versatile Pd^{2+}-catalyzed transformation is the Wacker oxidation, which is industrially used for the synthesis of acetaldehyde from ethylene [3].

The value of these reactions can be greatly enhanced by combining two or more Pd-catalyzed transformations either in a successive way or as a domino process [4]. Clearly, the latter approach is not only more efficient and elegant but has also ecological and economical advantages. We have introduced the concept of domino reactions into synthetic organic chemistry and have defined them as *processes of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond-forming reactions.* Domino processes are time-resolved transformations that can be nicely illustrated by domino tiles, where one tile tips over the next, which tips over the next, and so on. We have classified domino reactions according to the mechanism of the different steps, which would lead to 512 new types of domino reactions for a three-fold domino process, taking eight different types of transformation into account (Table 1).

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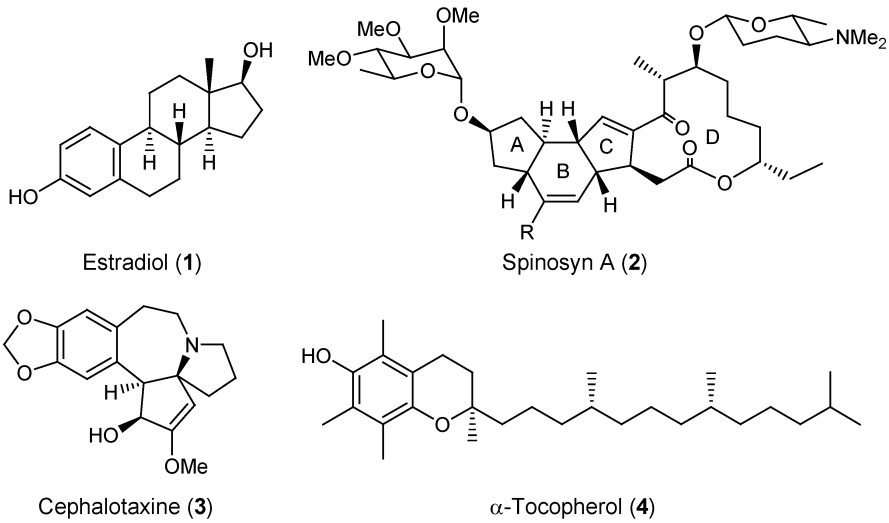
Table 1 Classification of domino reactions.

I. Transformation	II. Transformation	III. Transformation
1. Cationic	1. Cationic	1. Cationic
2. Anionic	2. Anionic	2. Anionic
3. Radical	3. Radical	3. Radical
4. Pericyclic	4. Pericyclic	4. Pericyclic
5. Photochemical	5. Photochemical	5. Photochemical
6. Transition-metal catalyzed	6. Transition-metal catalyzed	6. Transition-metal catalyzed
7. Oxidative or reductive	7. Oxidative or reductive	7. Oxidative or reductive
8. Enzymatic	8. Enzymatic	8. Enzymatic

In this short overview of parts of our work, we demonstrate the usefulness of multiple Pd-catalyzed transformations by presenting the enantioselective total syntheses of estradiol [5] (**1**), analogs of the insecticidal spinosyn A [6] (**2**), cephalotaxine [7] (**3**), and α-tocopherol [8] (**4**) (Scheme 1). Whereas in the syntheses of **1**, **2**, and **3**, a successive approach was used, **4** was prepared in a domino fashion.

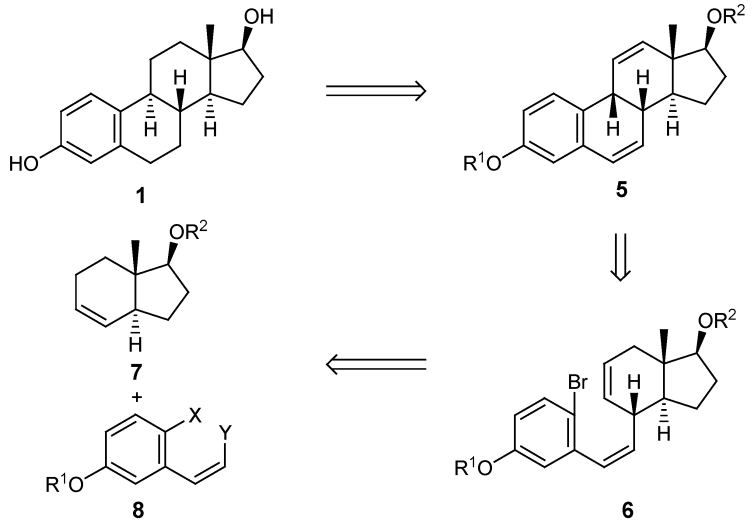


Scheme 1 Synthesis of natural products using multiple Pd-catalyzed transformations.

ESTRADIOL

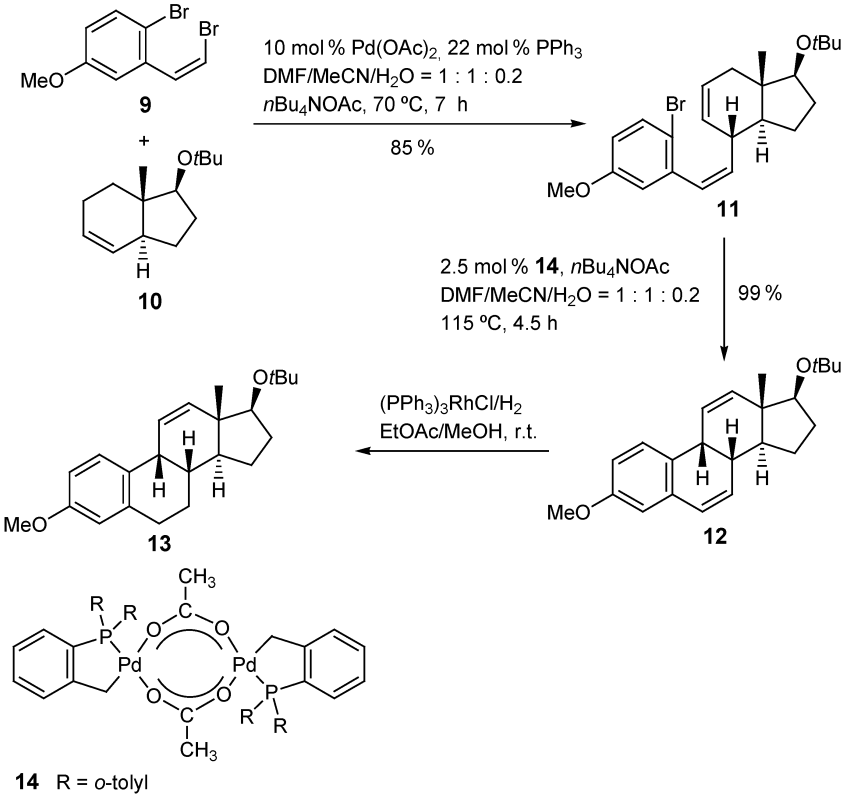
A necessity for multiple Pd-catalyzed transformations, which is true for all reactions of this type, is a careful adjustment of the reactivity of the functionalities involved in the different reaction steps. This may be done, for example, in the case of combining Heck reactions by taking advantage of the different reactivity of aryl iodides compared to aryl bromides or, on the other hand, of vinyl bromides compared to aryl bromides. For the enantioselective total synthesis of estradiol (**1**), we have used a combination of two Heck transformations for the formation of ring B according to the retrosynthetic analysis leading to the hydrinden **7** and the halogenated benzene **8** containing a vinyl halide side chain (Scheme 2).

In the adjustment of the reactivity of the two substrates, compounds **9** and **10** emerged as most suitable, whereas compound **8** with X = I did not lead to the desired product. **10** can easily be obtained



Scheme 2 Retrosynthesis of estradiol.

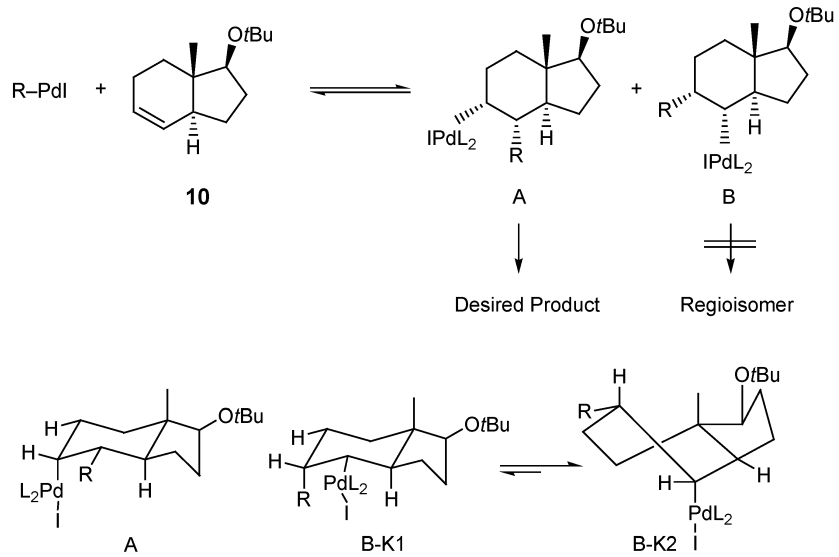
from enantiopure Hajos–Wiechert ketone in five steps [9], and **9** is accessible from 3-methoxybenzaldehyde in two steps with an excellent *Z*-selectivity of 98:2 by bromination followed by a Wittig reaction with $[BrCH_2–PPh_3]^+Br^-$ (Scheme 3).



Scheme 3 Double Heck reaction toward the synthesis of estradiol.

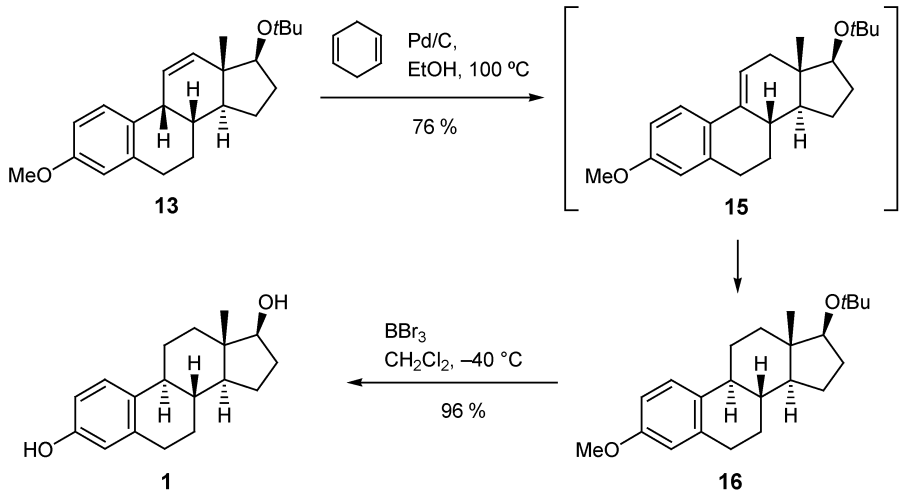
The Heck reaction of **9** and **10** reacting exclusively at the vinyl bromide moiety in **9** led to **11** in 85 % yield. Moreover, the attack of the Pd-intermediate formed from **9** occurs at the α-face of **10** anti to the angular methyl group. Whereas the diastereoselective attack from below corresponds with the expectation, the reaction at the more hindered position of the double bond in **10** needs an explanation.

We assume that this is due to a stereoelectronic effect. In the first reversible step, the two possible adducts A and B might be formed from **10** and the Pd-species (Scheme 4).



Scheme 4 Explanation of the regioselectivity of the Heck reaction of the hydrinden **10**.

However, only in A the necessary syn-coplanar orientation of Pd and the adjacent H-atom exists to allow a Pd-H elimination with formation of the desired product **11**. Thus, in the more stable conformation K2 of B the orientation of Pd toward the vicinal hydrogens is unfavorable [10]. For the intramolecular Heck reaction of **11** to give **12**, a variety of catalyst systems was employed. However, only the palladacycle **14**, developed by Herrmann and Beller [11], allowed this transformation leading to **12** with 99 % yield as a single diastereomer. Noteworthy, **12** has a *cis*-junction of rings B and C. Such steroids are not formed in nature. For the synthesis of estradiol (**1**), it was necessary to hydrogenate the two olefinic bonds and isomerize the stereogenic center C-9 in **12** to provide the necessary *trans*-ring junction of the rings B and C. A homogenous hydrogenation employing the Wilkinson catalyst allowed the selective hydrogenation of the more accessible $\Delta^{6,7}$-double bond of **12** to give **13** (Scheme 5). The synthesis of estradiol (**1**) was finally established by a transfer hydrogenation of **13** using Pd/C in the presence of 1,4-cyclohexadiene to give **16** via **15** followed by cleavage of the methyl ether in **16** with BBr_3 in 73 % overall yield.



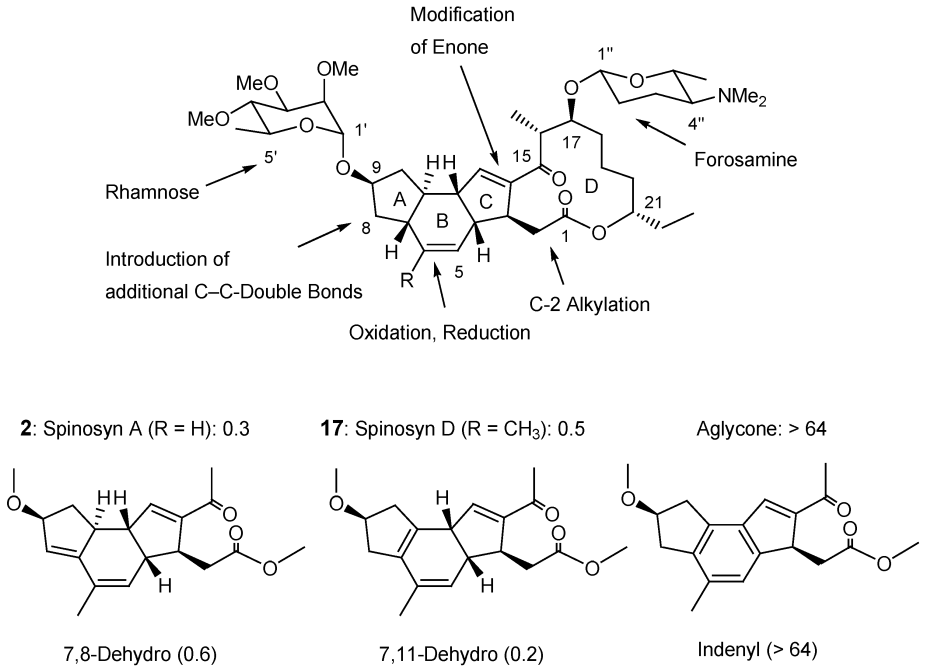
Scheme 5 Synthesis of estradiol.

SPINOSYN A

Based on the simple access to the *cis*-fused tetracycle **12** containing two double bonds as an intermediate in the synthesis of estradiol (**1**), we developed a novel and efficient entry to analogs of spinosyn A (**2**) [6]. The spinosyn natural product class comprises a group of more than 20 structurally related compounds which have been isolated from culture broths of the bacterium *Saccharopolyspora spinosa* [12,13]. The most important members of this group are spinosyn A (**2**) and D (**17**), which are used world-wide in agriculture as highly potent and selective insecticides [14] under the name Spinosad [15]. The spinosyns attack the neuronal activity of insects mainly by interacting with nicotinergic acetylcholine receptors (n-AchR) [13a,16].

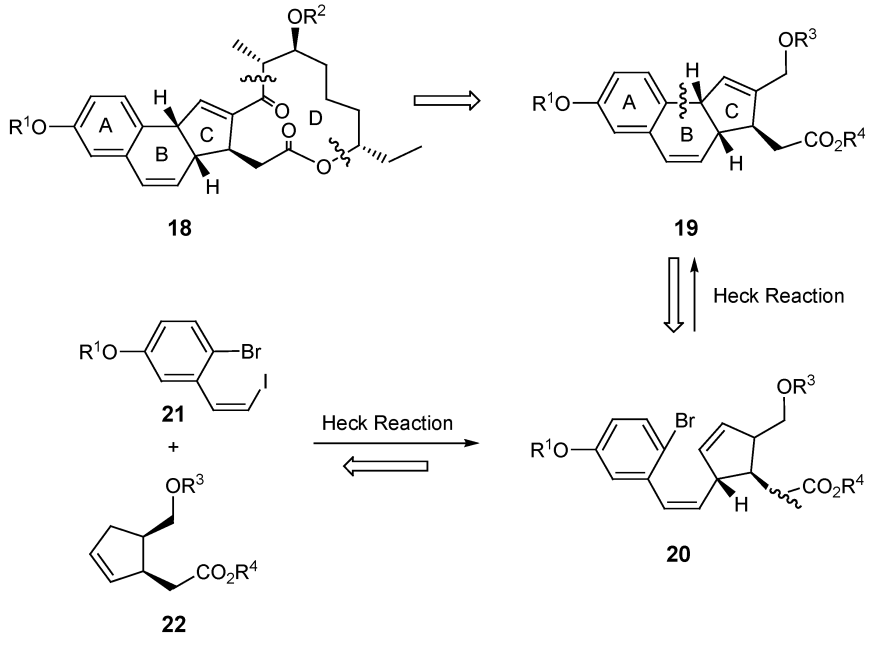
Unfortunately, first cases of resistance toward Spinosad have been reported recently [17]. Therefore, it is necessary to develop new analogs of the spinosyns that retain their insecticidal activity but can also be used against already resistant insects.

Several investigations on the structure–activity relation have been performed, indicating that the two sugar moieties in **2** are important (Scheme 6). Moreover, the two double bonds in the tricyclic core and the *cis*-fusion of the rings B and C are necessary for bioactivity [13]. Thus, spinosyn derivatives containing an aromatic ring B show a much lower potency, whereas additional double bonds in ring A have no negative effect. We therefore decided to develop spinosyn analogs of type **18** with an aromatic ring A.



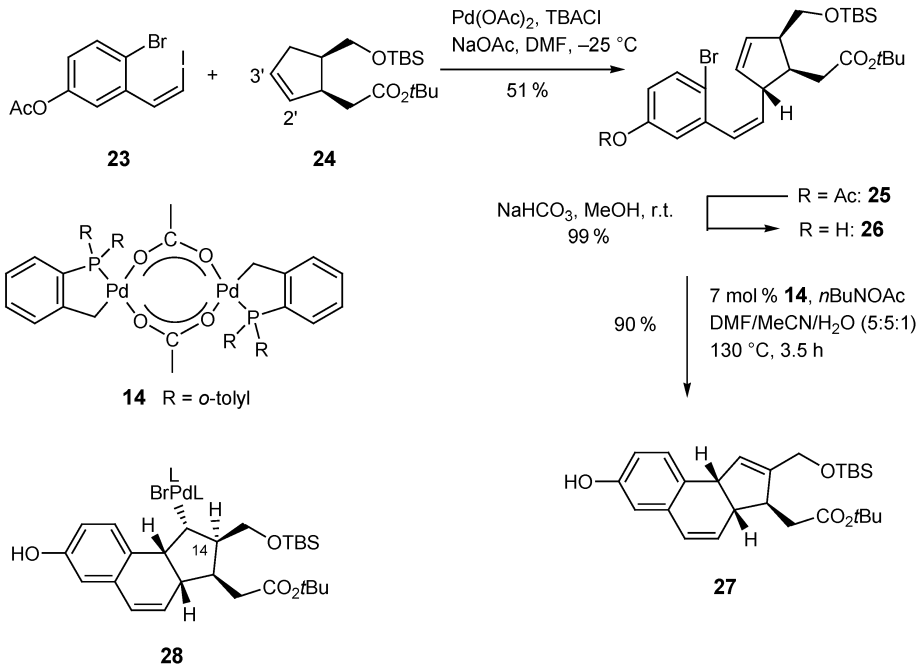
Scheme 6 Biological activity of spinosyns and derivatives (LC_{50} in ppm).

According to the retrosynthetic analysis shown in Scheme 7, the macrocyclic lactone in **18** was constructed in a later part of the synthesis from **19**, which could be formed from **21** and **22** by a double Heck reaction via **20**. After optimization, the bromoarene **23** with an iodovinyl side chain and the



Scheme 7 Retrosynthesis of spinosyn analogs.

enantiopure cyclopentene derivative **24** were used as substrates for the synthesis (Scheme 8). Thus, the analysis of the envisaged two-fold Pd-catalyzed reaction has revealed that the attack of the Pd-species formed from the vinyl iodide moiety in **23** at the cyclopentene **24** should take place anti to the side chain at C-1 to give the intermediate **25**, which then undergoes the second Heck reaction leading to the Pd species **28**. To allow the Pd-hydride elimination to give **27**, the H atom at C-14 must have an α-orientation. Thus, the *cis*-disubstituted cyclopentene **24** must be used as substrate and not the corresponding *trans*-diastereomer. Enantiopure **24** was accessible from 1,4-dihydroxycyclopentene with 99 % ee by enzymatic acetylation [18].

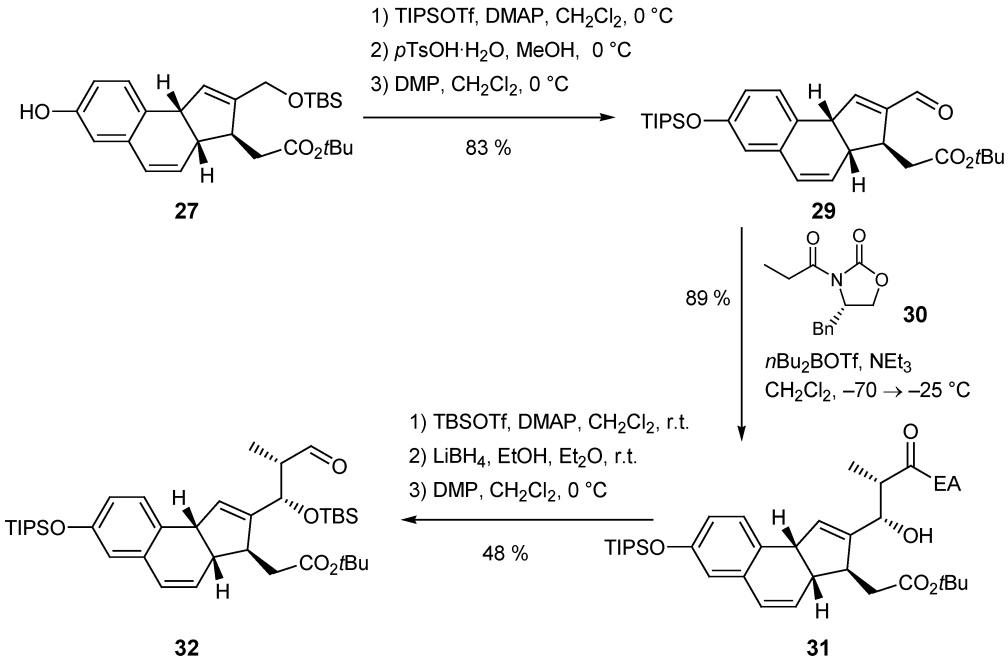


Scheme 8 Double Heck reaction for the synthesis of spinosyn analogs.

The intermolecular Heck reaction of **23** and **24** using $Pd(OAc)_2$ in DMF led to the desired product **25** in 51 % yield. As in the synthesis of estradiol (**1**), the diastereoselectivity was very high; however, the regioselectivity was less pronounced, since 24 % of the undesired regioisomer was also formed and in addition a partial isomerization of the double bond in the product occurs even when performing the reaction at –25 °C, which is quite unusual for a Heck reaction. After solvolysis of the acetate moiety at the aromatic ring, the second Heck reaction—this time in an intramolecular mode—could be carried out with 90 % yield using the palladacycle **14** [11] to give the desired *cis*-fused product **27** with the double bonds at the correct positions exclusively. The *cis*-connection of the rings B and C in **27** was established by a nuclear Overhauser enhancement spectroscopy (NOESY)-NMR experiment.

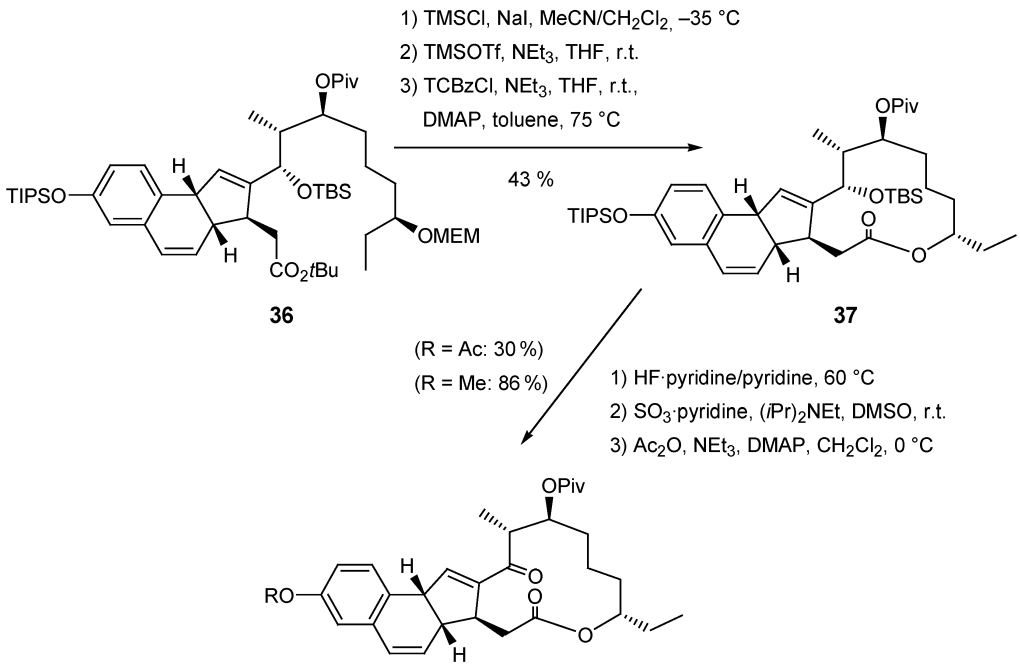
After protection of the phenolic hydroxy group in **27** as a triisopropylsilane (TIPS) ether, cleavage of the *tert*-butyldimethylsilyl (TBS) ether and oxidation of the resulting primary alcohol led to the aldehyde **29**, into which a C_3 fragment **30** was inserted via a boron enolate in an Evans aldol addition [19]. The reaction took place with high diastereoselectivity, presumably through a closed six-membered transition state [20], with exclusive formation of **31** in a yield of 89 % (Scheme 9).

The secondary hydroxy group in **31** was then protected as a TBS ether, and the imide was converted into the corresponding primary alcohol using $LiBH_4$, which by oxidation with Dess–Martin periodinane (DMP) gave the aldehyde **32** (Scheme 9). Reaction of **32** with the enantiomerically pure



Scheme 9 Stereoselective introduction of a C_3-unit.

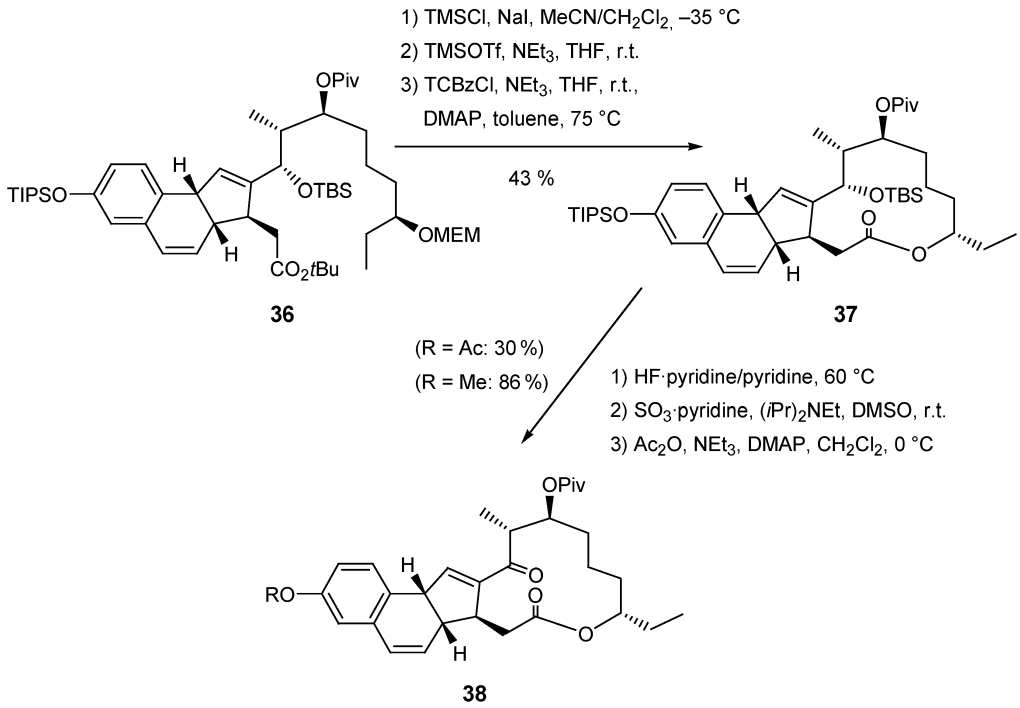
organomagnesium species **33**, obtained from **34** [21] and subsequent transformation of the formed secondary alcohol into a pivaloyl ester provided the two diastereomers **35** and **36** in a ratio of approximately 4:1 in a total yield of 78 % (Scheme 10).



Scheme 10 Stereoselective introduction of a C_6-unit.

The preferred formation of diastereoisomer **35** with *S*-configuration at C-3" required for further synthesis can be explained by a Felkin–Anh transition state.

The methoxyethoxymethyl (MEM) protecting group in **35** was then removed with trimethylsilyl iodide (TMSI) prepared in situ, and subsequently the *tert*-butyl ester group was cleaved with TMSOTf (Scheme 11). The hydroxy acid obtained was converted into the mixed anhydride with trichlorobenzoyl chloride (TCBzCl) by the method of Yamaguchi et al. [22], from which the macrolactone **37** was formed by slow addition to a solution of dimethylaminopyridine (DMAP).

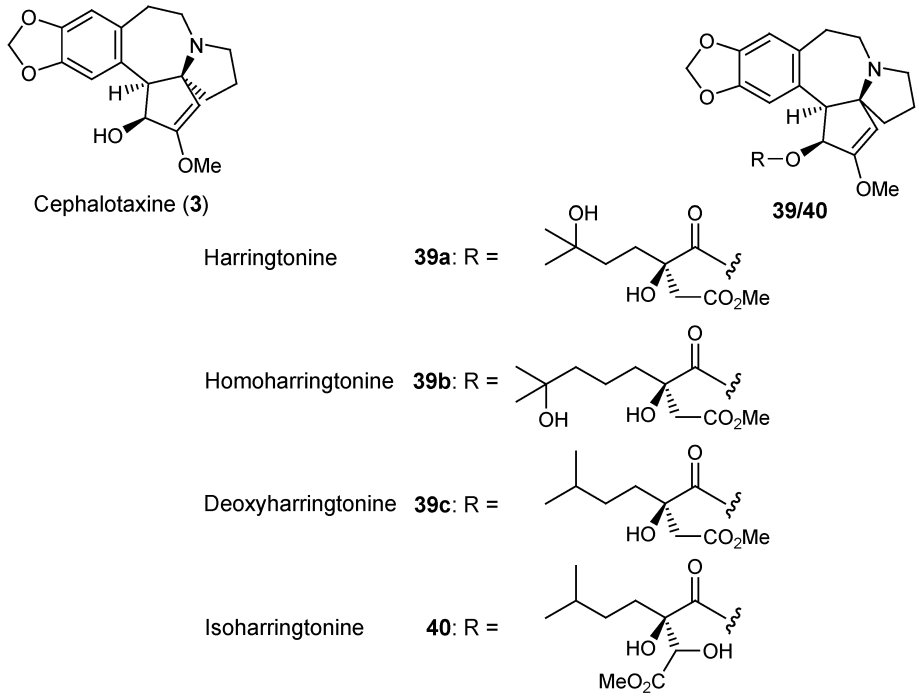


Scheme 11 Formation of the macrocyclic lactone.

To conclude the synthesis of the analog of spinosyne-A aglycone, the two silyl groups in **37** were removed with HF·pyridine, the formed secondary allylic alcohol oxidized using the method of Parikh and Doering [23], and the phenolic hydroxy group was protected as acetate for the reason of stability. The low overall yield of the last three steps of 30 % is due to the sensitivity of the unprotected phenol in the oxidation step. Using the corresponding methyl ether and DMP as oxidizing agent, however, the yield could be improved to 86 %. We are now on the way to introduce the two sugar moieties, which are necessary for the bioactivity.

CEPHALOTAXINE

Whereas in the synthesis of estradiol (**1**) and the spinosyn analog (**38**), two successive Heck reactions had been used, for the preparation of (–)-cephalotoxine (**3**) a combination of a nucleophilic substitution of an allyl acetate (Tsuji–Trost reaction) and a Heck reaction was employed. Cephalotaxine (**3**) is the parent compound of a group of alkaloids called harringtonines (Scheme 12). They occur in about eight known species of the genus *Cephalotaxus* (Cephalotaxaceae), evergreen plum yews, which are indigenous to southeast Asia [24].



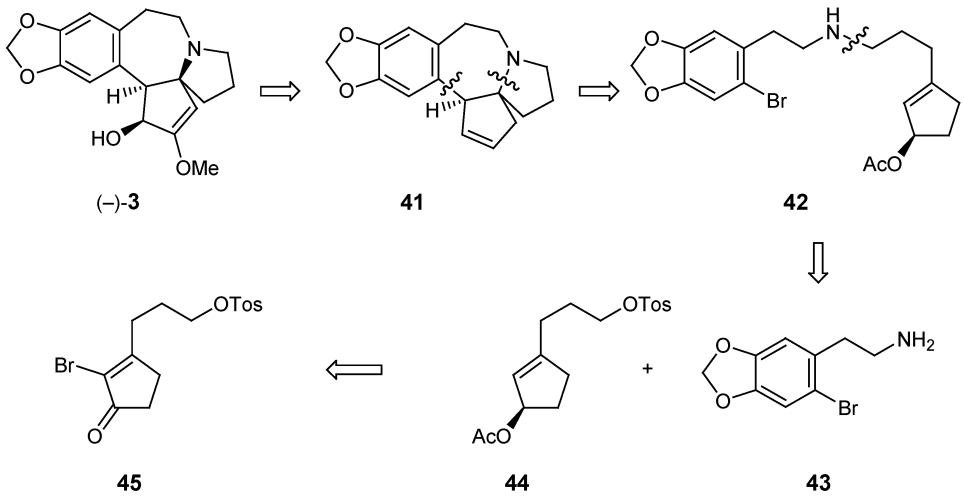
Scheme 12 Cephalotaxine and harringtonines.

Cephalotaxine has become an interesting synthetic target, not only because of its unique ring skeleton containing a 1-azaspiro[4.4]nonane moiety fused to a benzazepine system, but also as a result of the antileukemic activity of several of its 2-alkylhydroxysuccinates at C-3, especially harringtonine (**39a**), homoharringtonine (**39b**), deoxyharringtonine (**39c**), and isoharringtonine (**40**); cephalotaxine (**3**) itself is biologically largely inactive. Clinical trials have reached phase II–III [24,25], and more recently homoharringtonine (**39b**) has been investigated in the treatment of chloroquine-resistant malaria [26].

Since the first isolation of **3** in 1963 by Paudler [27] and its characterization [28] in the 1960s and 1970s, about a dozen total syntheses of racemic cephalotaxine (**3**) have been reported [29]; in addition, two syntheses of enantiopure (–)-cephalotaxine (**3**) using D-(+)-proline as starting material [30] and a resolution of an intermediate [31], respectively, were known, before we started our research in this field.

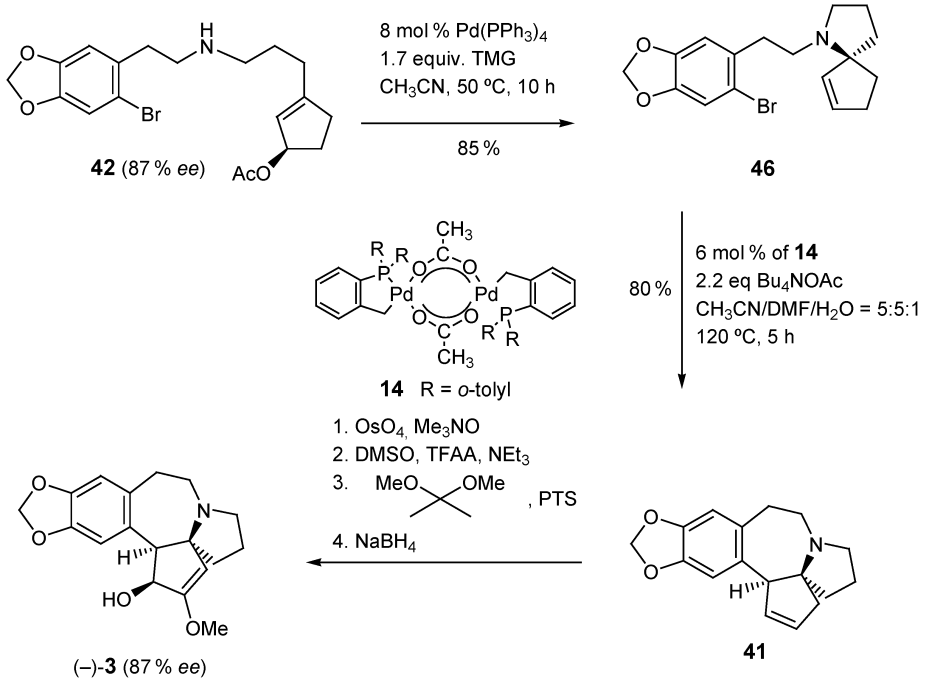
Our retrosynthesis of (–)-**3** led to the pentacyclic core **41**, which would be accessible by a combination of a Tsuji–Trost allylation [2] and a Heck reaction starting from the secondary amine **42** (Scheme 13).

The amine could be obtained by an alkylation of phenylethylamine **43** with the chiral cyclopentene derivative **44**, which is easily reached by an enantioselective Corey–Bakshi–Shibata (CBS) reduction (*B*-Me-oxazaborolidine, BH_3·THF) [32] of **45** followed by acetylation with 87 % ee and 96 % yield.



Scheme 13 Retrosynthesis of cephalotaxine.

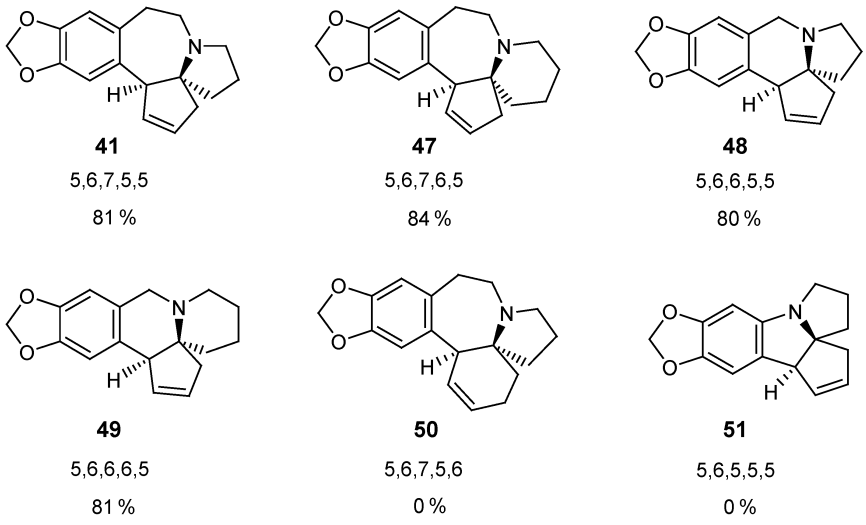
The Pd-catalyzed reaction of **42** at 45 °C using tetramethylguanidine (TMG) as base yielded the desired spirocycle **46** in 88 % (Scheme 14). In contrast, the corresponding iodo compound (**42**, I instead of Br) did not lead to **46**, which may be explained by an insufficient reactivity of the allyl acetate in comparison to the iodoaryl moiety; thus, the Pd seems to undergo preferably an oxidative addition at the aryl-I bond. Moreover, the reaction of **42** stops if the temperature exceeds 50 °C, which can be traced back again to a competing reaction at the haloaryl moiety. It should be noted that the reaction takes place with retention, which is agreement with the investigations about the steric control of the Tsuji–Trost reaction using weak nucleophiles.



Scheme 14 Synthesis of (–)-cephalotaxine (**3**).

The following Heck reaction of **46**, which gives the pentacyclic core **41** of (–)-cephalotaxine (**3**) in 81 % yield, was performed using 4 mol % of the Herrmann–Beller catalyst **14**. This palladacycle again was the only Pd catalyst out of five being used by us, which allowed the described transformation. The cyclization occurs once more highly stereoselectively; thus, the double bond in **42** is attacked exclusively from the Re face syn to the nitrogen. No double-bond isomers were detected; furthermore, there is no loss of stereointegrity. The transformation of **41** into cephalotaxine (**3**) by bishydroxylation of the cyclopentene moiety using OsO_4, oxidation of the diol to the diketone, formation of the methyl enol ether, and diasteroselective reduction of the remaining keto group was performed according to a known procedure [30,33].

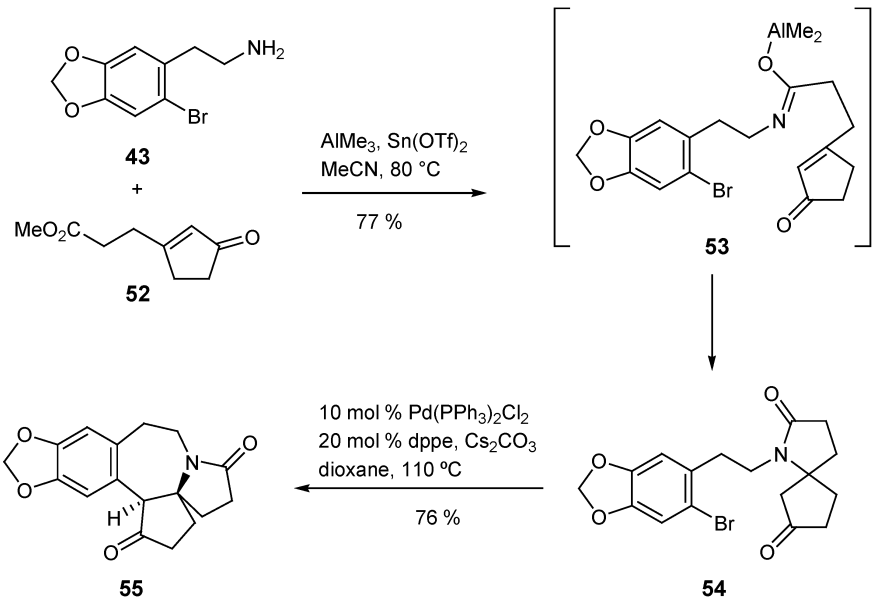
By changing the number of methylene units between the reacting bromoaryl functionality and the allyl acetate in the substrate **42**, several ring-size analogs of the 5,6,7,5,5-pentacycle **41**, such as the 5,6,7,6,5-compound **47**, the 5,6,6,5,5-compound **48**, and the 5,6,6,6,5-compound **49**, could be synthesized (Scheme 15).



Scheme 15 Synthesis of cephalotaxine analogs.

However, the procedure failed in the syntheses of **50** and **51**. To allow a synthesis of these compounds as well as of the cephalotaxine derivative **55**, we developed a new type of domino reaction, which is exemplified in the preparation of **55**. The retrosynthetic approach is based on a Pd-catalyzed α-arylation of a ketone and a novel domino-amidation-Michael addition.

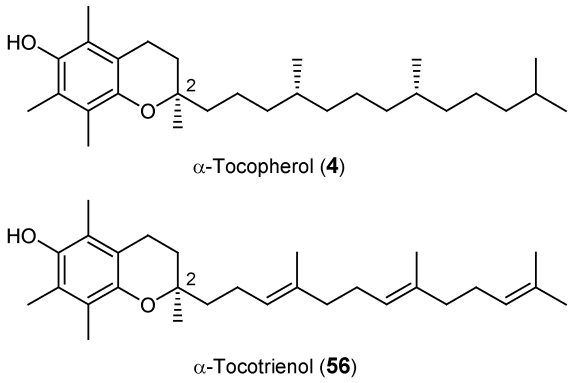
Reaction of **43** and **52** in the presence of $AlMe_3$ and catalytic amounts of $Sn(OTf)_2$ led to the spiro compound **54** with the azaenolate **53** as a proposed intermediate in 77 % yield (Scheme 16). The Pd-catalyzed transformation of **54** gave **55** in 76 % yield, which was further transformed into the corresponding enantiopure analog of homoharringtonine **39b**.



Scheme 16 Novel domino reaction for the synthesis of cephalotaxine derivatives.

α-TOCOPHEROL

Finally, for the synthesis of α-tocopherol (**4**) of the vitamin E family, we used a domino-Wacker–Heck reaction starting with a chiral Pd^{2+}-compound as the catalyst. Vitamin E is one of the fat-soluble vitamins and a collective term for all tocopherols and tocotrienols. It consists of eight natural occurring compounds which, depending upon the number and position of the methyl groups at the aromatic ring, are specified as α, β, γ, and δ-tocopherol as well as α, β, γ, and δ-tocotrienol (Scheme 17).

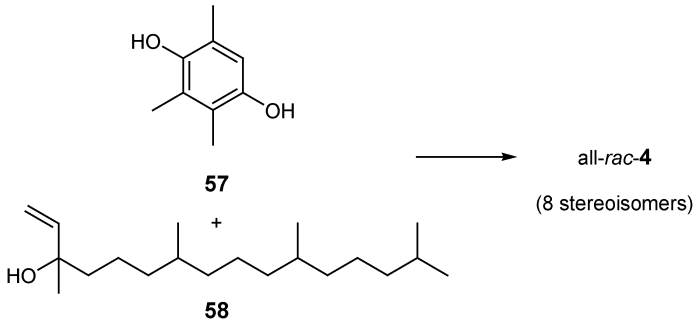


Scheme 17 α-Tocopherol (**4**) and α-tocotrienol (**56**).

All are derivatives of 6-chromanol with a stereogenic center at C-2. The tocopherols have a saturated 16-carbon phytyl moiety, whereas the tocotrienols have two *E*-configurated double bonds in the side chain [examples: α-tocopherol (**4**), α-tocotrienol (**56**)] [34]; α-tocopherol (**4**) with the *R*-configuration at all stereogenic centers has the most pronounced biological activity. It acts as an antioxidant and is considered to be an essential protective factor against lipid peroxidation; in particular, it protects polyunsaturated fatty acids and other components of the cell membrane and low-density lipoproteins

(LDLs) by capturing highly reactive free radicals formed in the body as by-products of the normal oxidative metabolism [35,36].

α-Tocopherol (all-*rac*-**4**) is produced industrially on a large scale by an acid-catalyzed reaction of trimethylhydroquinone (**57**) with all-*rac*-isophytol (**58**) as a mixture of all eight possible stereoisomers (Scheme 18) [37].



Scheme 18 Industrial production of racemic α-tocopherol (all-*rac*-**4**) by reaction of trimethylhydroquinone with all-*rac*-isophytol.

Recent studies have shown that 2*S*-configurated tocopherols are not transported into the human tissue due to the C-2-enantiotopos-differentiating α-tocopherol transfer protein (TTP), whereas the configuration of the stereogenic centers in the side chain seems to have no influence (Table 2) [38].

Table 2 Biological activity of tocopherols and tocotrienols.

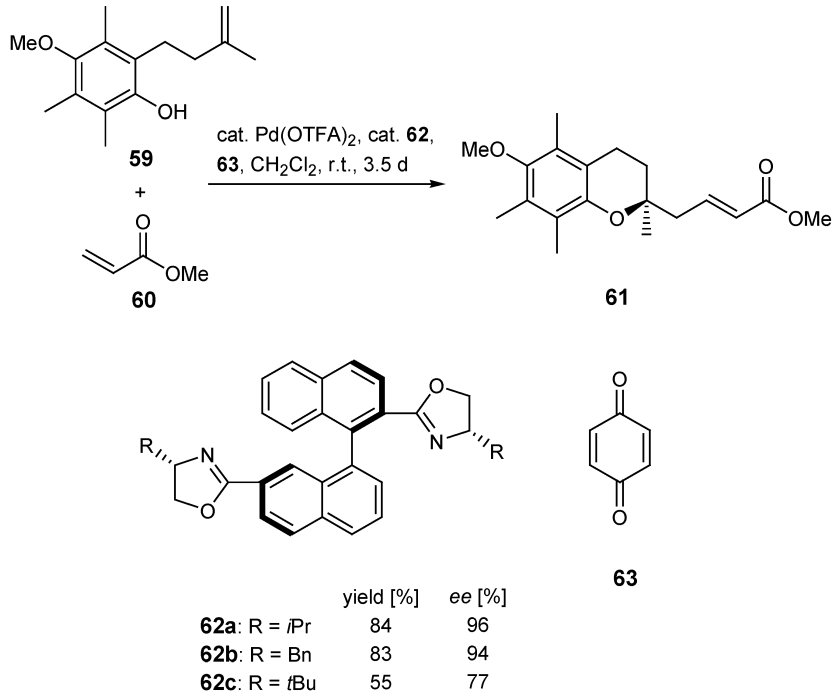
Tocopherol acetate[a]		Tocopherols/tocotrienols	
RRR-(α)	100 %	*RRR*-(α)	100 %
RRS-(α)	100 %	*RRR*-(β)	57 %
RSR-(α)	100 %	*RRR*-(γ)	31 %
RSS-(α)	100 %	*RRR*-(δ)	1.4 %
SSS-(α)	0 %	*R*-(α)	30 %
SRS-(α)	0 %		
SRR-(α)	0 %		
SSR-(α)	0 %		

RRR: Natural configuration.
Method: Fetal resorption gestation test with rats.
[a]New US FNB standard, 2000.

As a result, all-*rac*-**4** exhibits only 50 % of the biological activity of *RRR*-**4** as the maximum. Thus, all tocopherols and tocotrienols with a *S*-configuration at the stereogenic center of the chroman moiety have no anti-oxidative activity in living tissue. From Table 2, it can also be seen that β, γ, and δ-tocopherol and the corresponding tocotrienols have a much lower bioactivity than **4**. Therefore, there is considerable interest in the development of an efficient process for the enantioselective synthesis of α-tocopherol (**4**) with special attention to the configuration of the stereogenic center C-2.

Several enantioselective approaches to **4**, based on resolution of the products, the use of enantiopure natural building blocks, enzymatic transformations as well as asymmetric oxidations and allylations have been used to build up the chiral chroman framework [39]. However, all these methods are not efficient enough for an industrial use. Recently we have developed a new approach, which not only allows the formation of the chiral chroman moiety of α-tocopherol (**4**) with very high enantioselectiv-

ity, but also the concurrent introduction of a part of the side chain using a novel enantioselective domino-Wacker–Heck process (Scheme 19) [8]. Thus, reaction of **59** with methyl acrylate (**60**) in the presence of catalytic amounts of palladium trifluoroacetate and the enantiopure ligand 2,2'-bis(oxazolyl)-1,1'-binaphthyl (BOXAX) [40] (**62a**) led to **61** with 96 % ee in 84 % yield. Using the (*S*,*S*)-Bn-BOXAX ligand **62b**, similar results were obtained, However, with the sterically more demanding ligand **62c**, the yield with 55 % and also the enantioselectivity with 77 % ee were significantly lower.



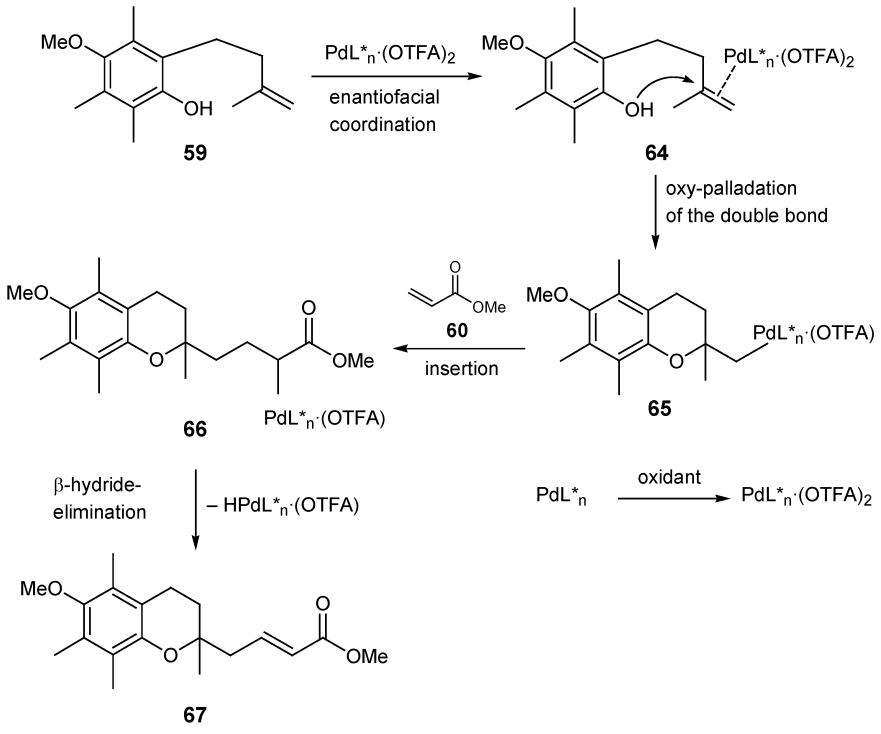
	yield [%]	*ee* [%]
62a: R = *i*Pr	84	96
62b: R = Bn	83	94
62c: R = *t*Bu	55	77

Scheme 19 Synthesis of the chiral chroman **61**.

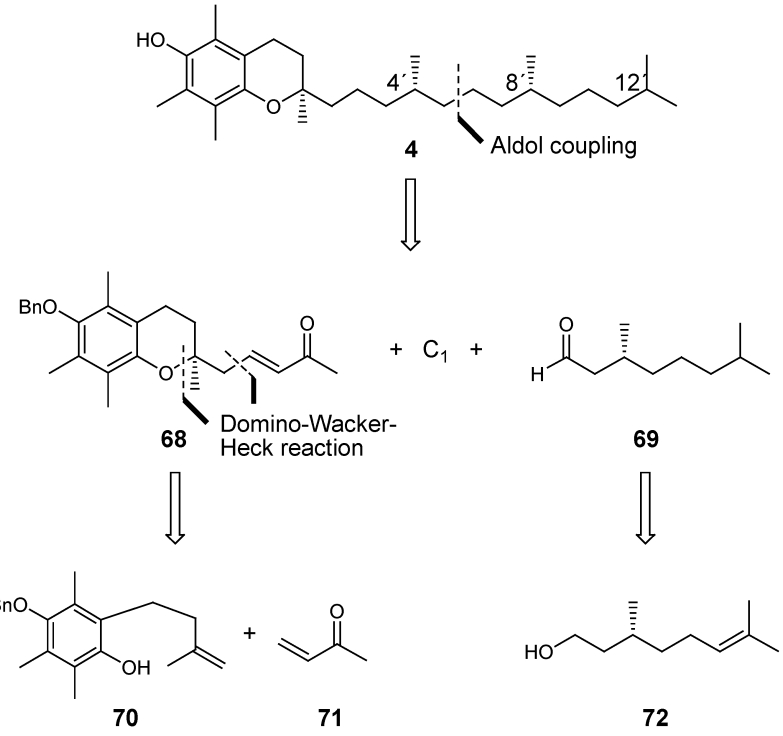
We assume that in the first step an enantiofacial complexation of the double bond in **59** with the chiral Pd^{2+}-compound takes place, inducing an umpolung of the double bond to allow a nucleophilic addition of the phenolic hydroxyl group to give **65** via **64** (Scheme 20). The Pd-compound **65** has a certain stability since a Pd–H elimination cannot occur due to the lack of a H atom in β-position. Therefore, **65** is intercepted by methyl acrylate (**60**) present in the reaction mixture to give **66**, which now can undergo a β-hydride elimination with formation of **67**.

In the reaction mixture with the substrates **59** and **60**, two double-bond systems are present which could react with Pd^{2+}; however, as anticipated, Pd^{2+} reacts preferentially at the more electron-rich double bond in **59**. Moreover, a homo-coupling of **65** with **59** does not take place, since α,β-unsaturated carbonyl compounds react much faster in a Heck reaction than simple alkenes. These considerations are in agreement with the observation that the reaction of **59** with simple alkenes instead of acrylate does not give any product.

For the enantioselective synthesis of α-tocopherol (**4**) according to the retrosynthetic analysis, we envisaged that the chroman moiety and the first part of the side chain as in **68** could be introduced by a domino-Wacker–Heck reaction of the alkenylphenol **70** with methyl vinyl ketone (**71**) (Scheme 21). For the missing part of the side chain, an aldol condensation of **68** with (*R*)-dihydrocitronellal (**69**) followed by the introduction of a C_1-unit would be most appropriate. **69** can be obtained from (*R*)-citro-



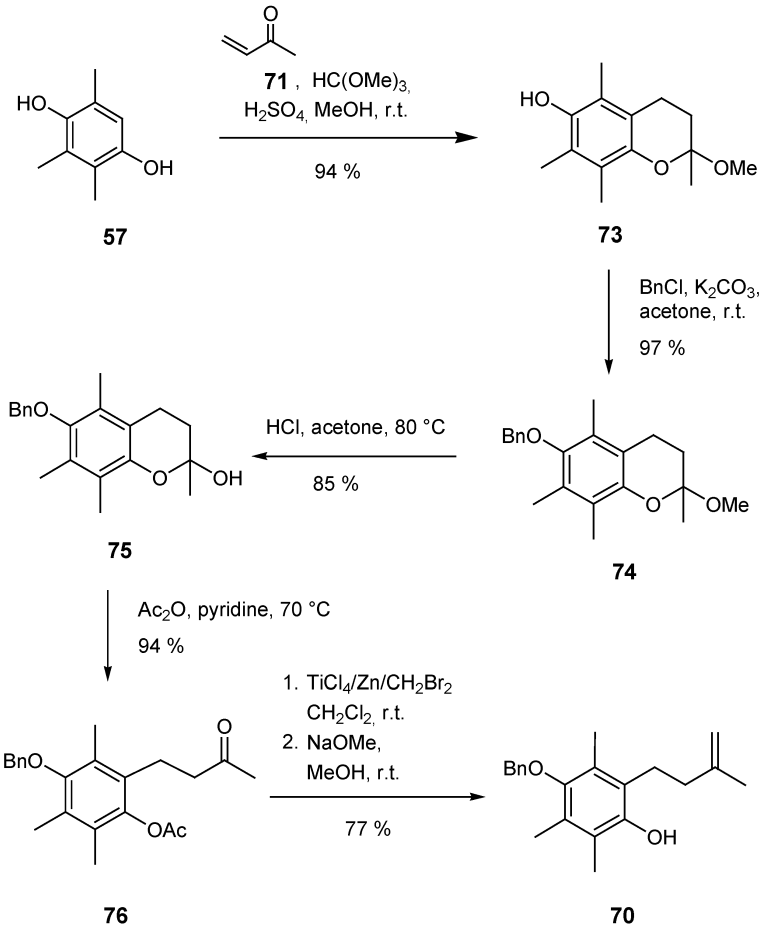
Scheme 20 Mechanism of the domino-Wacker–Heck reaction.



Scheme 21 Retrosynthetic analysis of α-tocopherol (**4**).

nellol (**72**), which is commercially available in high enantiopurity. The substrate **70** contains a benzyl protecting group, which can be removed under mild conditions without the danger of an isomerization at C-2 in **4**.

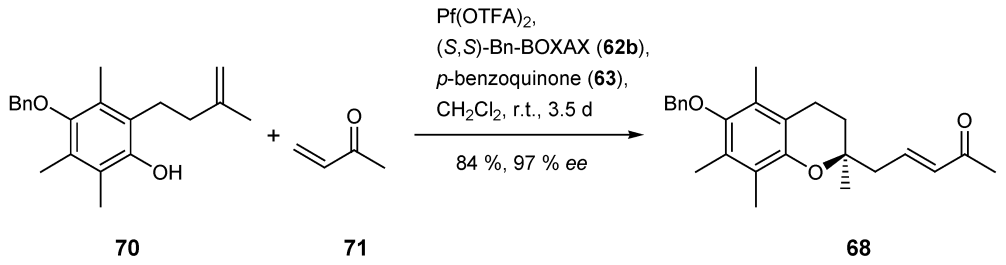
The required alkenylphenol **70** was prepared via reaction of the trimethylhydroquinone (**57**) with methyl vinyl ketone (**71**) in the presence of trimethyl orthoformate to give **73**, which was benzylated at the phenolic hydroxyl group with formation of **74** (Scheme 22) [41].



Scheme 22 Synthesis of the alkene **70**.

The acetal moiety in **74** was then cleaved with hydrochloric acid to afford **75**, which was transformed into the phenyl ester **76** using acetic anhydride in pyridine in 94 % yield. Finally, formation of the double bond using the Lombardo-reagent [42], followed by a Zemplén-saponification afforded the desired substrate **70** in six steps with 56 % yield based on **57**.

The domino reaction of the benzyl-protected phenol **70** and methyl vinyl ketone (**71**) in dichloromethane in the presence of catalytic amounts of $Pd(OTFA)_2$, the chiral ligand (*S*,*S*)-Bn-BOXAX (**62b**) and *p*-benzoquinone (**63**) afforded the chroman **68** with 97 % ee in 84 % yield (Scheme 23).

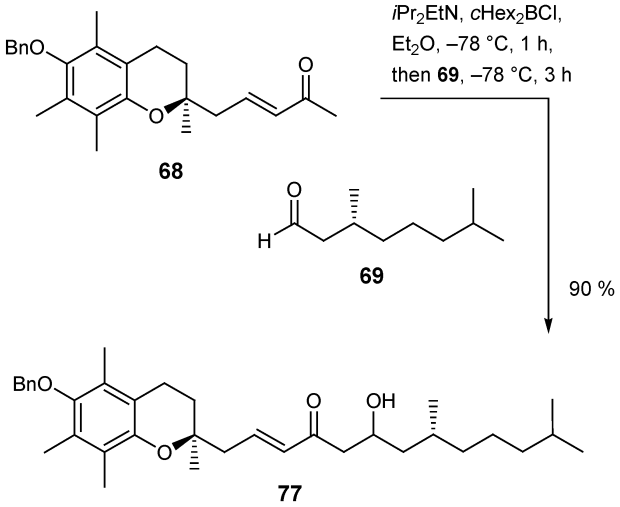


Scheme 23 Synthesis of the chiral chroman **68**.

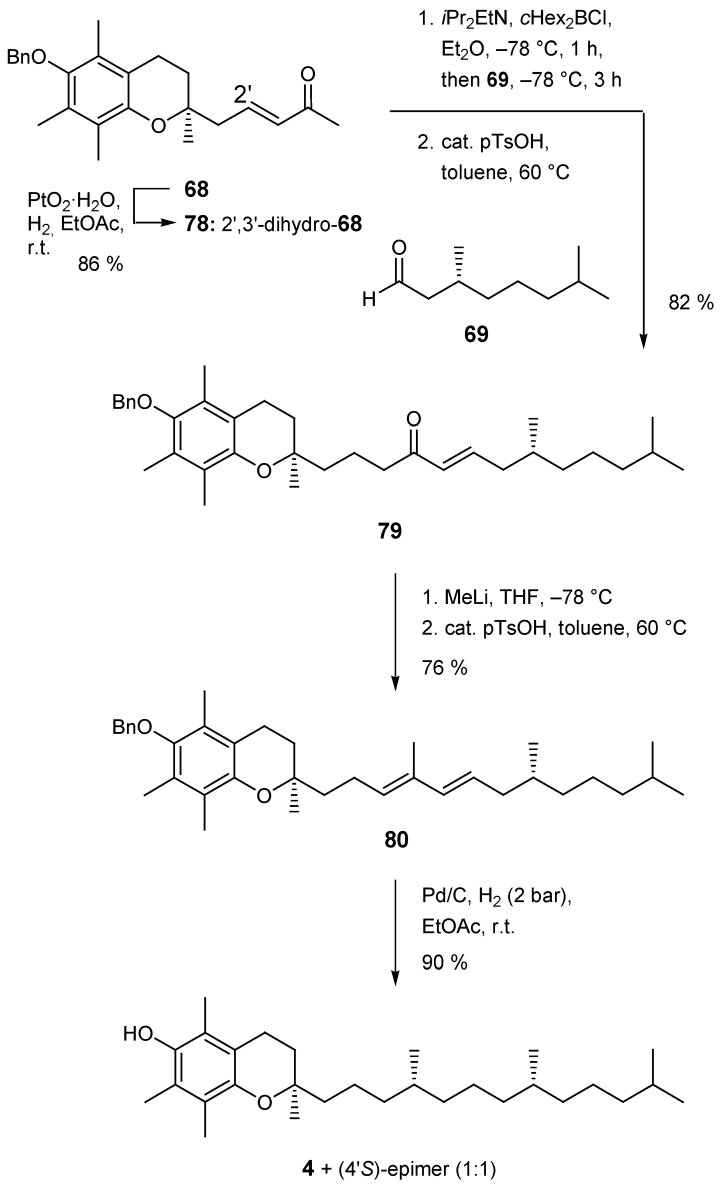
63 was used to reoxidize Pd^0 to Pd^{2+}. All attempts to employ the system O_2/CuCl, being used in industry for the Wacker oxidation, were not successful, since under these conditions an oxidation of the substrate **70** to give a quinone took place.

For the introduction of the missing part of the side chain in α-tocopherol (**4**), we first tried to perform an aldol condensation of **68** with (*R*)-citronellal, which, however, was not satisfying due to the formation of a by-product caused by an intramolecular Prins reaction of (*R*)-citronellal. In contrast, (*R*)-dihydrocitronellal (**69**) reacted smoothly with the ketone **68** to give **77** using the corresponding boron enolate in a yield of 90 % (Scheme 24) [43]. Unfortunately, **77** was not ideal for the following transformations. We therefore repeated the sequence using the chroman **78** containing a saturated side chain, which is accessible from **68** by a simple hydrogenation (Scheme 25).

Thus, reaction of the boron enolate of **78** with **69** followed by an acidic work-up gave the enone **79** in 82 % yield. The synthesis of α-tocopherol (**4**) was then completed by a 1,2-addition of methyl lithium to the carbonyl moiety in **79** to give the corresponding tertiary alcohol, which was transformed into the diene **80** by an acid-catalyzed elimination using *p*-TsOH in 76 % yield over two steps. Finally, hydrogenation of the diene moiety in **80** with the simultaneous cleavage of the benzyl phenyl ether with hydrogen in the presence of catalytic amounts of Pd/C resulted in the formation of (2*R*,4'*R*,8'*R*)-α-tocopherol (**4**) together with its (4'*S*)-epimer as an almost 1:1-mixture in 90 % total yield. Since the configuration of the stereogenic centers in the side chain has no influence on the bioactivity of α-tocopherol (**4**), no attempts were made to perform a facial selective hydrogenation.



Scheme 24 Synthesis of **77**.



Scheme 25 Synthesis of (2*R*,4'*R*,8'*R*)-α-tocopherol **4**.

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