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Ruthenium-Catalyzed Oxidative Dearomatization of Phenols to 4-(*tert*-Butylperoxy)cyclohexadienones: Synthesis of 2-Substituted Quinones from *p*-Substituted Phenols

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Keywords: Ruthenium / Oxidation / Peroxides / Phenols / Quinones

The ruthenium-catalyzed oxidation of phenols with *tert*-butyl hydroperoxide efficiently gives the corresponding 4-(*tert*-butylperoxy)cyclohexadienones. The oxidation proceeds selectively because of ruthenium's ability for rapid single-electron transfer. This biomimetic oxidation reaction is highly useful to obtain the metabolic compounds desired for confirming the safety of medicines and related compounds. Typically, the first metabolic compound of the female hormone estrone is readily obtained by this biomimetic oxidation reaction. The resulting 4-(*tert*-butylperoxy)cyclohexadienones are versatile synthetic intermediates, which can be transformed into 2-substituted 1,4-benzoquinones by treatment with acid catalysts. Acid-promoted rearrangement followed by a Diels–Alder reaction provides a new strategy for the synthesis of fused cyclic compounds, such as naphthoquinone and anthraquinone derivatives, from readily available phenols. The nonnatural 1,4-diacetoxy steroidal skeleton is obtained by the oxidation of estrone followed by zinc-mediated migration. Vitamin K_3 is synthesized selectively from *p*-cresol in an overall 79 % yield in 4 steps, and the synthesis includes the ruthenium-catalyzed oxidation.

Introduction

The oxidation of phenols has attracted interest because of their importance from a biochemical and synthetic standpoint.[1] Transition-metal-catalyzed oxidative transformations of phenols result in the formation of cyclohexadienones,[2] oxidative coupling,[3] *ortho*-hydroxylation,[4] and ring-cleavage reactions.[5] Among them, the catalytic oxidative transformation of *p*-alkylphenols to cyclohexadienones is very important, as aromatic compounds can be readily converted to synthetically important aliphatic compounds.[6] The catalytic oxidation of phenols is preferable for large-scale preparation, but selective transition-metal-catalyzed oxidations have never been achieved, because the initial intermediates of phenoxyl radicals undergo various side reactions giving a complex mixture of products.[7] For example, the iron-catalyzed oxidation of *p*-cresol typically gives various products.[7a] Selective oxidative transformations of phenols to cyclohexadienones can be carried out only with specific phenols bearing bulky substituents at the 2-, 4-, and 6-positions.[8–10] In biological systems, cytochrome P-450 enzymes selectively catalyze oxidative transformations of flavonoids to isoflavonoids, where the key step is the oxidation of the phenol moiety to the corresponding cyclohexadienone functionality.[11]

A general and practical catalytic method for the selective oxidative transformation of phenols waits to be explored. During the course of our systematic study on the simulation of the function of cytochrome P-450 with low-valent ruthenium complex catalysts,[12] we found that ruthenium-catalyzed oxidations of tertiary[13] and secondary amines,[14] amides,[15] β-lactams,[15,16] nitriles,[17] hydrocarbons,[18] alkenes,[19] alcohols,[20] and others proceed efficiently to give the corresponding oxidized products. We found in 1996 that the ruthenium-catalyzed oxidation of *para*-substituted phenols **1** with *tert*-butyl hydroperoxide gave the corresponding 4-(*tert*-butylperoxy)cyclohexadienones **2** as shown in Equation (1).[21] This was the first example of the selective transformation of phenols to cyclohexadienones without substituents at the 2- and 6-positions. Recently, Doyle and coworkers reported on the oxidation of phenols by treatment with 70% aqueous *tert*-butyl hydroperoxide and dirhodium caprolactamate $[Rh_2(cap)_4]$ as the catalyst.[22] Also, it is noteworthy that many organocatalytic oxidative transformations of phenols to cyclohexadienones using various oxidants, such as *m*-chloroperbenzoic acid and oxone, in the presence of hypervalent iodine catalysts, such as phenyliodine(III) bis(trifluoroacetate), have recently been explored,[23] in addition to the other methods including oxidation with singlet oxygen.[24]

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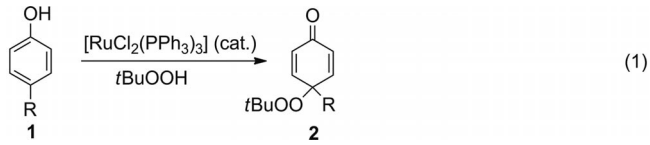
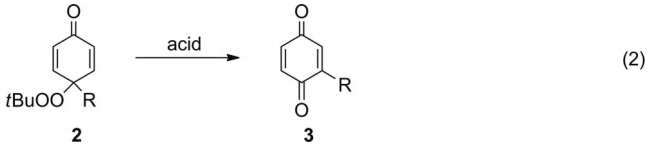


(1)

The resulting 4-(*tert*-butylperoxy)cyclohexadienones **2** are versatile synthetic intermediates for C–C bond formation through both Diels–Alder and Michael reactions. Furthermore, the present oxidation provides a new method for direct access to 2-substituted quinones **3** from *p*-substituted phenols by ruthenium-catalyzed oxidation and subsequent treatment with acid as shown in Equation (2).[21]



(2)

The advantage of the reaction is its applicability to selectively synthesize quinones bearing two or three substituents such as 2,5-dialkyl- and 2,3,5-trialkyl-*p*-benzoquinone, which are difficult to prepare. The rearrangement reaction proceeds in the presence of various acids such as Lewis and protic acids. Sequential migration followed by a Diels–Alder reaction provides feasible access to polycyclic compounds. As a practical application, we demonstrate the synthesis of various compounds including the metabolic compounds of estrone, naphthoquinones, anthraquinones, and vitamins K_1 and K_3.[25] In this paper, full details regarding the scope and reaction mechanism of the ruthenium-catalyzed oxidative transformations of *p*-substituted phenols to the corresponding cyclohexadienones as well as the synthetic applications are described.[21,25]

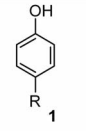
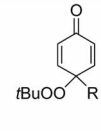
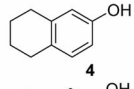
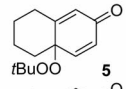
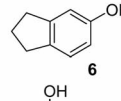
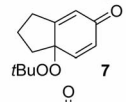
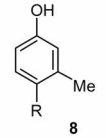
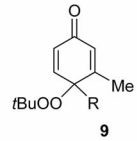
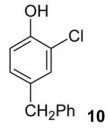
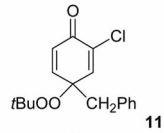
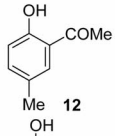
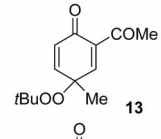
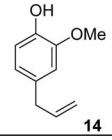
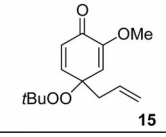
Results and Discussion

Ruthenium-Catalyzed Oxidative Transformation of Phenols to 4-(*tert*-Butylperoxy)-2,5-cyclohexadienones

The ruthenium-catalyzed oxidation of phenols proceeded selectively to give 4-(*tert*-butylperoxy)-2,5-cyclohexadienones. The catalytic activity of various metal complexes was examined for the oxidation of 4-isopropyl-3-methylphenol (**8b**) with *t*BuOOH. For the selective formation of 4-(*tert*-butylperoxy)-4-isopropyl-3-methyl-2,5-cyclohexadienone (**9b**), $RuCl_2(PPh_3)_3$ was proven to be the most effective catalyst. Other ruthenium catalysts such as $RuCl_3{\cdot}nH_2O$ also gave satisfactory results, whereas other metal catalysts such as $CoCl_2$, and $CrCl_2$ gave complex mixtures.

Various *para*-substituted phenols (Entries 1–5) were selectively oxidized as shown in Table 1. The reaction proceeded chemoselectively in the presence of the easily oxidizable isopropyl and benzyl groups (Table 1, Entries 2 and 5) to give the corresponding 4-substituted *p*-(*tert*-butylperoxy)dienone derivatives. It is noteworthy that the copper-catalyzed oxidation of *p*-methyl-substituted phenols with H_2O_2 gave *p*-formylphenol.[27] Phenols bearing carbonyl, ester, and carboxylic acid groups at the *para* position also gave dienones in high yields (Table 1, Entry 6). The oxidation of bicyclic phenols gave *p*-(*tert*-butylperoxy)dienones selectively (Table 1, Entries 7 and 8). The oxidation of 3,4-disubstituted phenols **8** selectively occurred at the *para* position to give *p*-(*tert*-butylperoxy)dienone **9** (Table 1, Entries 9 and 10). The oxidation of 2,4-disubstituted phenols bearing electron-withdrawing groups such as 2-chloro and 2-acetyl or an electron-donating group such as 2-methoxy gave the corresponding *p*-(*tert*-butylperoxy)dienones (Table 1, Entries 11–13). It is noteworthy that the chemoselectivity for the oxidation of **14** (Table 1, Entry 13) is dif-

Table 1. Ruthenium-catalyzed oxidation of phenols with *t*BuOOH.[a]

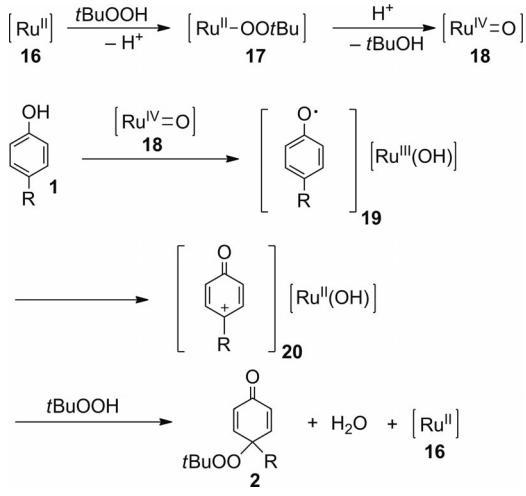
Entry	Substrate	Product	Yield [%][b]
	 **1**	 **2**	
1	**a**: R = Me		85
2	**b**: R = *i*Pr		86
3[c]	**c**: R = *t*Bu		68
4	**d**: R = Ph		76
5[c]	**e**: R = CH_2Ph		78
6[c]	**f**: R = $CH_2CO_2CH_3$		82
7	 **4**	 **5**	85
8	 **6**	 **7**	68
	 **8**	 **9**	
9[c]	**a**: R = Me		77
10	**b**: R = *i*Pr		92
11[c]	 **10**	 **11**	91
12[c]	 **12**	 **13**	71
13[c]	 **14**	 **15**	54

[a] Reagents and conditions: substrate (1 equiv.), $RuCl_2(PPh_3)_3$ (3 mol-%), *t*BuOOH (3.16 M in benzene,[26] 4 equiv.), solvent (benzene or ethyl acetate). [b] Isolated yield. [c] $RuCl_2(PPh_3)_3$ (1.5 mol-%) was used.

ferent than that of the oxidation of **14** with $PdCl_2/H_2O_2$ where allylic oxidation takes place.[28]

Mechanism for the Ruthenium-Catalyzed Oxidation of Phenols with *tert*-Butyl Hydroperoxide

The oxidation can be rationalized by the mechanism depicted in Scheme 1. The ruthenium(II) complex **16** undergoes reaction with *t*BuOOH to give the (alkylperoxido)-ruthenium(II) complex **17**,[18a,29] which subsequently undergoes heterolytic cleavage of the O–O bond to give the (oxido)ruthenium(IV) species **18**.[18] Abstraction of a hydrogen atom from the phenols by **18** would form the phenoxyl radical–Ru^{III}(OH) intermediate **19**.[30] Electron transfer from the phenoxyl radical to the ruthenium atom[31] would quickly take place to give the cationic intermediate **20**. Selective formation of **2** occurs, before the coupling of radical **19**, because of the rapid single-electron transfer to ruthenium from the phenoxyl radical to form the cationic intermediate **20**. The cationic intermediate **20** is trapped with the second molecule of the more basic and reactive nucleophile *t*BuOOH to give the *tert*-butylperoxy product **2**, water, and the ruthenium(II) complex to complete the catalytic cycle. The involvement of an Ru^{III}/Ru^{V} cycle to form an (oxido)-ruthenium(V) species cannot be excluded.[32]



Scheme 1. Proposed mechanism for ruthenium-catalyzed oxidation of phenols.

An alternative mechanism is unlikely where the *t*BuOO· radical forms followed by hydrogen abstraction to give the phenoxyl radical, which then recombines with the *t*BuOO· radical to form the product. Previously, we reported that the ruthenium-catalyzed oxidation of alkylated arenes with *t*BuOOH in the presence of the $RuCl_2(PPh_3)_3$ catalyst efficiently gives the corresponding aryl ketones.[18a] Thus, fluorene was converted to fluorenone in 97% yield, whereas 9-methylfluorene gave 9-(*tert*-butylperoxy)-9-methylfluorene in 98% yield. A similar ruthenium-catalyzed oxidation of indane in methanol gave 1-methoxyindane (20%) along with 1-indanone (12%) with a 36% conversion of indane. These results indicate the intermediacy of a carbocation species. A precise kinetic study, the deuterium isotope effect, and Minisci's test to distinguish the reactivities of the *t*BuO· and *t*BuOO· radicals revealed that the oxidation is derived from an (oxido)ruthenium species and not from the *t*BuOO· or *t*BuO· radicals.[18a] Furthermore, the oxidation of the hydrocarbons proceeds efficiently in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol. These results for the ruthenium-catalyzed reaction are in contrast to the rhodium-catalyzed oxidation with *t*BuOOH, where the *t*BuOO· radical is involved as a key intermediate.[22] These results are also in contrast to the iron- [33] and cobalt-catalyzed oxidations[7b] with *t*BuOOH, where various radical coupling products through the *t*BuO· and *t*BuOO· radicals are formed.

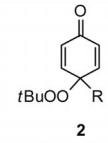
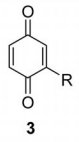
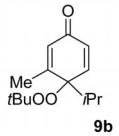
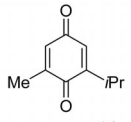
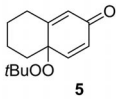
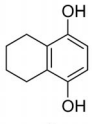
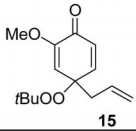
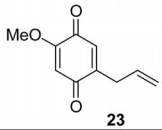
Lewis Acid Mediated Rearrangement of 4-(*tert*-Butylperoxy)cyclohexadienones to Quinones

Quinones are versatile synthetic intermediates and play an important role in biological systems because of their electron-transfer ability.[34] The ruthenium-catalyzed oxidation of *p*-alkylphenols gave 4-alkyl-4-(*tert*-butylperoxy)-cyclohexadienones **2**. We found that in the presence of acid catalysts the rearrangement of the alkyl group in 4-alkyl-4-(*tert*-butylperoxy)cyclohexadienones **2** selectively occurred to give the corresponding 3-alkyl-1,4-benzoquinones **3**.

The effect of various acids was examined for the rearrangement of 4-(*tert*-butylperoxy)-4-isopropyl-2,5-cyclohexadienone (**2b**). $TiCl_4$,[35] $BF_3{\cdot}OEt_2$, and TMSOTf (trimethylsilyl trifluoromethanesulfonate) proved to be highly effective acids for the selective formation of 2-isopropyl-*p*-benzoquinone (**3b**). Other acids such as $AlCl_3$ and $SnCl_4$ gave satisfactory results, whereas $Ti(OiPr)_4$ showed no activity. This reaction also proceeded with catalytic amounts of acids such as H_2SO_4 and TMSOTf. The optimized reaction conditions depended on the migratory aptitude of the substrates. The migration of the benzyl group in substrate **2e** proceeded efficiently in the presence of a catalytic amount of HCl.

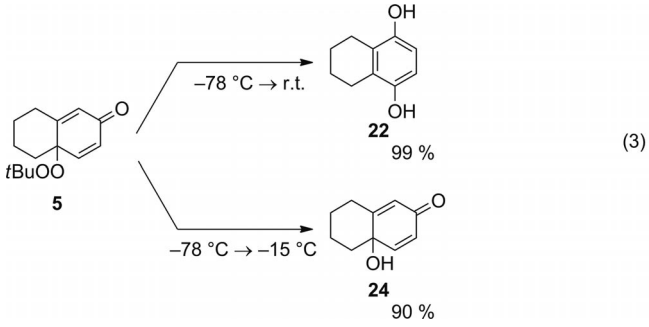
Representative results for the rearrangement reaction of the (*tert*-butylperoxy)cyclohexadienones are summarized in Table 2. The $TiCl_4$-promoted reactions of 4-substituted 4-(*tert*-butylperoxy)cyclohexadienones went to completion even at low temperatures (Table 2, Entries 1–4). The migratory aptitude of the substituents in **2** is in the order of $PhCH_2 \approx Ph > iPr > Me$. Importantly, disubstituted quinones were obtained selectively (Table 2, Entries 5 and 7). The substrate 4-(*tert*-butylperoxy)-4-isopropyl-3-methyl-2,5-cyclohexadienone (**9b**) underwent a 1,2-migration of the isopropyl group exclusively to give 2-isopropyl-6-methyl-*p*-benzoquinone (**21**) (Table 2, Entry 5). The selective formation of disubstituted benzoquinones is remarkable, as the conventional methods of alkylation of monosubstituted benzoquinones give a mixture of isomers.[36]

Table 2. $TiCl_4$-induced rearrangement reaction of (*tert*-butylperoxy)dienones to benzoquinones.[a]

Entry	Substrate	Temperature	Product	Yield [%][b]
	 **2**		 **3**	
1	**a**: R = Me	–78 °C → 0 °C		92
2	**b**: R = *i*Pr	–78 °C → –15 °C		98
3	**d**: R= Ph	–78 °C		91
4	**e**: R = CH_2Ph	–78 °C		93
5	 **9b**	–78 °C → 0 °C	 **21**	93
6	 **5**	–78 °C → r.t.	 **22**	99
7	 **15**	–78 °C	 **23**	93

[a] To a stirred solution of $TiCl_4$ (1.2 equiv.) in CH_2Cl_2 was added 4-(*tert*-butylperoxy)cyclohexadienone (1.0 equiv.) in CH_2Cl_2 dropwise at –78 °C. [b] Isolated yield.

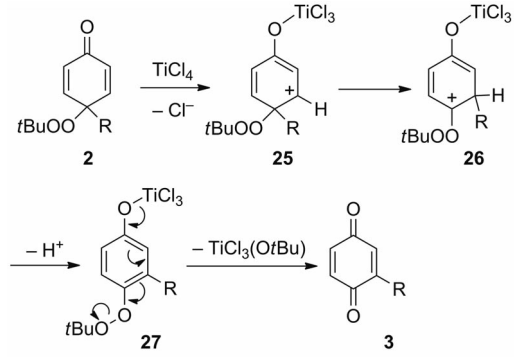
The reaction of peroxide **5**, derived from bicyclic phenol **4** (85%), gave 1,4-dihydroxynaphthalene derivative **22** (99%), where the carbon atom at the 4-position of the cyclohexadienone ring underwent migration to the 2-position. The same reaction at a lower temperature gave the corresponding hydroxy compound **24** in 90% yield [see Equation (3)].



(3)

The reaction of 4-allyl-4-(*tert*-butylperoxy)-2-methoxy-2,5-cyclohexadienone (**15**) derived from eugenol **14** with $TlCl_4$ at –78 °C gave 5-allyl-2-methoxy-*p*-benzoquinone (Table 2, Entry 7, 93%). Selective formation of the 5-substituted benzoquinone rather than the 3-substituted product is due to steric rather than electronic effects.

The reaction promoted by $TiCl_4$ can be rationalized by the mechanism depicted in Scheme 2. Dienone **2** is activated by the reaction with $TiCl_4$ to give cation **25**. 1,2-Migration of the alkyl group at the 4-position to give cation **26** is followed by deprotonation to form aromatic intermediate **27**. Elimination of *tert*-butoxytitanium affords 2-alkylquinone **3**. Electron-donating alkyl groups show a higher potential for migration. This tendency was observed in other cationic 1,2-migration reactions such as the dienone/phenol[37] and pinacol rearrangements.[38]

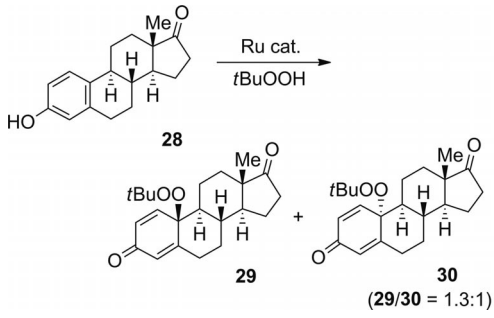


Scheme 2. Proposed mechanism for Lewis acid promoted migration.

Synthetic Application of the Cyclohexadienones

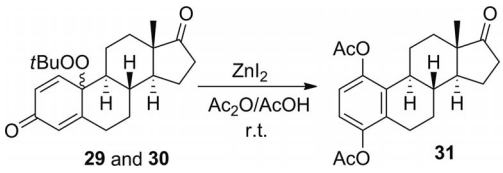
Synthesis of Estrone Derivatives

This biomimetic oxidation reaction is highly useful for confirming the safety of medicines and related compounds, because the metabolic compounds can be readily obtained. For example, the first metabolic compound of the female hormone estrone can be obtained by this biomimetic oxidation reaction. Thus, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of estrone **28** with *t*BuOOH gave a diastereomeric mixture (1:1) of the corresponding dienones **29** and **30**. Each diastereomer was easily separated and isolated [see Equation (4)], and reduction of the compounds led to a primary metabolic product of the hormone. This method is highly useful for the evaluation and exploitation of biological activity in medical supply.



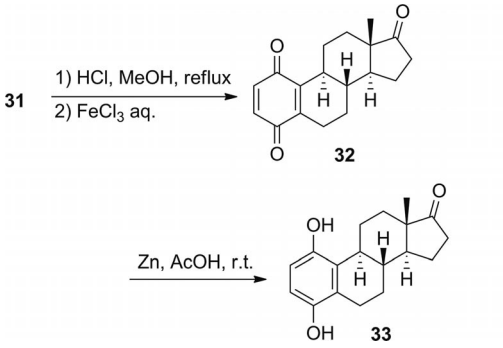
(4)

The biomimetic catalytic oxidation of natural products followed by their transformation can provide new types of compounds that are hardly accessible. The diastereomeric mixture of **29** and **30** underwent a ZnI_2-promoted reaction in a mixture of acetic acid/acetic anhydride to give diacetylhydroquinone **31** [see Equation (5), 69%].



(5)

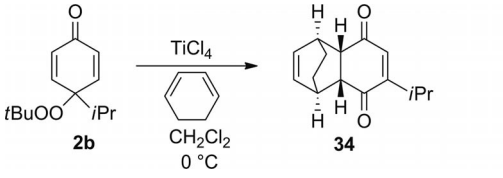
Hydrolysis of **31** with a hydrochloric acid solution followed by oxidation with an aqueous solution of $FeCl_2$ gave **32** [see Equation (6), 63%]. The reduction of quinone **32** with zinc in acetic acid gave the biologically interesting hydroquinone **33** quantitatively [see Equation (6)].



(6)

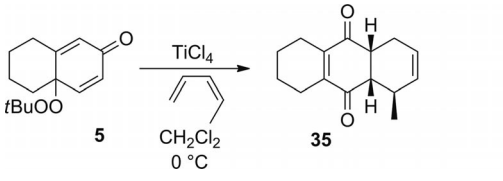
Selective Synthesis of Polycyclic Compounds

An application of this catalytic oxidation of phenols is illustrated by a sequential alkyl group migration and Diels–Alder reaction. Thus, the treatment of **2b**, derived from the oxidation of 4-isopropylphenol (**1b**), with $TiCl_4$ in the presence of 1,3-cyclohexadiene gave the corresponding tricyclic compound **34** (78%) stereoselectively through an isopropyl group migration and subsequent Diels–Alder reaction [see Equation (7)].



(7)

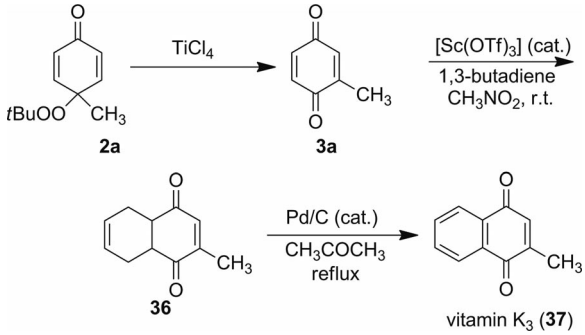
A similar one-pot reaction of (*tert*-butylperoxy)dienone **5** in the presence of (*Z*)-1,3-pentadiene gave *cis*-fused octahydroanthraquinone **35** (73%). The two-step synthesis of **35** from **4** shows great promise for further synthetic applications, which include asymmetric Diels–Alder reactions [see Equation (8)].



(8)

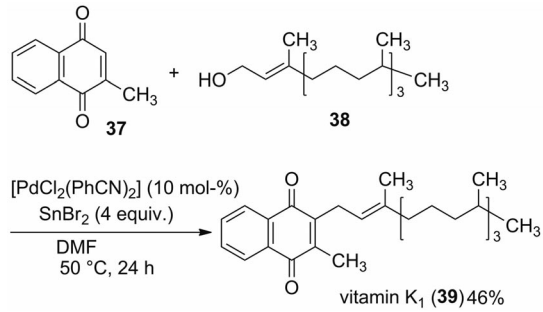
Synthesis of Vitamins K_3 and K_1

The oxidation/migration can be applied to the synthesis of vitamin K.[39] The key steps are the ruthenium-catalyzed oxidation of *p*-cresol (**1a**) to give **2a** and subsequent Lewis acid promoted migration to afford *p*-toluquinone (**3a**). A Diels–Alder reaction of **3a** with 1,3-butadiene in the presence of the $Sc(OTf)_3$ catalyst gave **36** (97% yield), which subsequently underwent dehydrogenation upon treatment with the Pd/C catalyst to give vitamin K_3 (**37**) in 100% yield (Scheme 3). The conventional method for the preparation of vitamin K_3 is the catalytic oxidation of 2-methylnaphthalene; however, side products such as 6-methylnaphthoquinone are obtained.[40] This present strategy provides a method for the selective synthesis of various biologically active bicyclic compounds such as vitamin K_3 (**37**) from readily available *p*-cresol (**1a**).



Scheme 3. Synthesis of vitamin K_3 (**37**).

The synthesis of vitamin K_1 (**39**) from vitamin K_3 (**37**) and phytol (**38**) was examined as shown in Scheme 4. A number of synthetic methods directed towards **39** have hitherto been developed, and the most straightforward method is the introduction of a phythyl chain to the 3-position of **37**.[41] However, there is no method for the direct synthesis of **39** from **37** and **38**. The reaction of **37** with **38** in the presence of a palladium catalyst and tin(II) bromide gave vitamin K_1 (**39**).[42] This is the first example for the direct synthesis of allylated quinones from quinones and allyl alcohols.



Scheme 4. Synthesis of vitamin K_1 (**39**).

Conclusions

We demonstrated a new catalytic oxidative dearomatization reaction of phenols upon treatment with *t*BuOOH. The reactions proceeded efficiently on a large scale to give the corresponding 4-(*tert*-butylperoxy)cyclohexadienones, because of the ruthenium's ability for rapid electron transfer. Thus, the resulting 4-(*tert*-butylperoxy)cyclohexadienones

can be transformed to 2-substituted quinones regioselectively by acid-catalyzed rearrangement. These methods are highly useful for the synthesis of various biologically active compounds. The biomimetic principle of these reactions will provide a powerful means to develop new types of catalytic oxidative transformation reactions, dearomatizations, and related reactions.

Experimental Section

General: All experiments were carried out under argon unless otherwise stated. Reagents were obtained from commercial sources and were used without further purification unless otherwise indicated. Benzene was distilled from calcium hydride under argon. Dichloromethane and diethyl ether were stored over molecular sieves (4 Å). $TiCl_4$ was purified by distillation under argon. Anhydrous solutions of *t*BuOOH in benzene were prepared and titrated by using the Sharpless method.[26] All melting points were measured with a Yanagimoto micro melting point apparatus. IR spectra were recorded with a Shimadzu FTIR-4100 spectrometer. NMR spectra were obtained with a JEOL JNM-GSX-270 spectrometer (^{1}H at 270 MHz, ^{13}C at 68 MHz). Chemical shifts were expressed in ppm downfield from tetramethylsilane. Mass spectra were obtained with a JEOL JMS-DX 303 spectrometer. Elemental analyses were performed with a Yanagimoto MT-3 CHN corder.

General Procedure for the Ruthenium-Catalyzed Oxidation of Phenols with *tert*-Butyl Hydroperoxide. Synthesis of 4-(*tert*-Butylperoxy)-4-methyl-2,5-cyclohexadien-1-one (2a): A round-bottomed flask (25 mL) equipped with a magnetic stir bar and a pressure-equalizing dropping funnel connected to a three-way stopcock was charged with *p*-cresol (**1a**, 0.652 g, 6.0 mmol), $RuCl_2(PPh_3)_3$[43] (0.173 g, 0.18 mmol), and dry benzene (6.0 mL) under argon. The mixture was stirred at room temperature, and a solution of *t*BuOOH (3.30 M) in dry benzene (7.3 mL, 24.0 mmol) was added dropwise over a period of 2 h. The mixture was stirred at room temperature for 3 h. Chromatography on Florisil (15.0 g) with diethyl ether (300 mL) gave **2a** (1.01 g, 85%) as a dark brown oil. An analytically pure sample was prepared by column chromatography (SiO_2, hexane/ethyl acetate, 5:1) to give a light yellow oil. R_f = 0.66 (SiO_2; hexane/ethyl acetate, 2:1). IR (neat): $\tilde{\nu}$ = 2986, 1671, 1631, 1445, 1393, 1302, 1199, 862, 731 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20, 1.38 (s, 3 H), 6.21 (d, J = 10.8 Hz, 2 H), 6.89 (d, J = 10.8 Hz, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.6, 151.2, 128.8, 80.0, 76.1, 26.3, 23.2 ppm. $C_{11}H_{16}O_3$ (196.25): calcd. C 67.32, H 8.21; found C 66.92, H 8.11.

4-(*tert*-Butylperoxy)-4-isopropyl-2,5-cyclohexadien-1-one (2b): IR (neat): $\tilde{\nu}$ = 2978, 1674, 1633, 1610, 1387, 1364, 1271, 1198, 1003, 877, 856, 766 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.93 (s, 3 H), 0.95 (s, 3 H), 1.20 (s, 9 H), 2.04 (sept, 1 H), 6.30 (d, J = 10.8 Hz, 2 H), 6.85 (d, J = 10.8 Hz, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.6, 149.7, 130.7, 80.1, 76.5, 34.7, 26.5, 17.1 ppm. $C_{13}H_{20}O_3$ (224.30): calcd. C 69.61, H 8.99; found C 69.34, H 8.76.

4-*tert*-Butyl-4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-one (2c): IR (KBr): $\tilde{\nu}$ = 2988, 1674, 1628, 1363, 1196, 1099, 875 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.21 (s, 9 H), 6.30 (d, J = 10.5 Hz, 2 H), 7.02 (d, J = 10.3 Hz, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.4, 150.4, 130.5, 82.6, 80.0, 39.9, 26.3, 25.9 ppm.

4-(*tert*-Butylperoxy)-4-phenyl-2,5-cyclohexadien-1-one (2d): IR (neat): $\tilde{\nu}$ = 2980, 1672, 1632, 1608, 1389, 1364, 1277, 1194, 1001, 874, 858, 752 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.28 (s, 9 H), 6.32 (d, J = 10.8 Hz, 2 H), 7.00 (d, J = 10.8 Hz, 2 H), 7.32–7.42 (m, 5 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 186.6, 150.0, 137.0, 128.9, 128.1, 125.9, 80.6, 76.3, 26.5 ppm. HRMS [CI (chemical ionization)]: calcd. for $C_{16}H_{19}O_3$ $[M + H]^+$ 259.1334; found 259.1318.

4-Benzyl-4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-one (2e): IR (neat): $\tilde{\nu}$ = 3030, 1672, 1631, 1496, 1454, 1385, 1261, 1194, 1068, 1018, 862 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 2.99 (s, 2 H), 6.21 (d, J = 10.3 Hz, 2 H), 6.83 (d, J = 10.3 Hz, 2 H), 7.13–7.31 (m, 5 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.5, 150.1, 134.3, 130.7, 129.7, 128.1, 127.2, 80.3, 78.6, 43.9, 26.4 ppm.

4-(*tert*-Butylperoxy)-4-[(methoxycarbonyl)methyl]-2,5-cyclohexadien-1-one (2f): IR (neat): $\tilde{\nu}$ = 2955, 1741, 1676, 1635, 1439, 1365, 1194, 1001, 862 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.17 (s, 9 H), 2.72 (s, 2 H), 3.63 (s, 3 H), 6.25 (d, J = 10.2 Hz, 2 H), 7.00 (d, J = 10.2 Hz, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.1, 166.1, 147.8, 129.8, 80.5, 75.9, 51.8, 41.8, 26.2 ppm.

6-(*tert*-Butylperoxy)bicyclo[4.4.0]deca-1,4-dien-3-one (5): IR (neat): $\tilde{\nu}$ = 2940, 1672, 1640, 1617, 1474, 1389, 1364, 1271, 1198, 1003, 884, 806, 733 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.35 (m, 2 H), 1.58 (dddd, J = 13.4, 8.4, 4.0, 2.0 Hz, 1 H), 1.80 (dddd, J = 13.4, 13.4, 4.0, 4.0 Hz, 1 H), 2.01 (ddddd, J = 13.9, 4.8, 4.5, 2.0, 2.0 Hz, 1 H), 2.19 (ddddd, J = 13.9, 4.0, 4.5, 2.0, 2.0 Hz, 1 H), 2.39 (d, J = 13.0 Hz, 1 H), 2.66 (dddd, J = 13.0, 13.0, 4.8, 1.7 Hz, 1 H), 6.12 (dd, J = 1.7, 1.7 Hz, 1 H), 6.21 (dd, J = 10.0, 2.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 186.8, 163.2, 151.5, 129.2, 124.9, 79.6, 76.5, 37.4, 32.3, 28.2, 26.4, 20.7 ppm.

6-(*tert*-Butylperoxy)bicyclo[4.3.0]nona-1,4-dien-3-one (7): IR (neat): $\tilde{\nu}$ = 2934, 1676, 1649, 1474, 1387, 1364, 1198, 893 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 1.62 (m, 1 H), 1.90 (m, 1 H), 2.10 (m, 2 H), 2.46 (m, 1 H), 2.82 (m, 1 H), 6.11 (ddd, J = 3.2, 2.2, 1.1 Hz, 1 H), 6.21 (dd, J = 10.0, 1.7 Hz, 1 H), 6.01 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 186.8, 165.3, 145.2, 130.9, 124.7, 82.1, 79.6, 32.9, 28.9, 26.4, 21.8 ppm. HRMS: calcd. for $C_{13}H_{19}O_3$ $[M + H]^+$ 223.1334; found 223.1332.

4-(*tert*-Butylperoxy)-3,4-dimethyl-2,5-cyclohexadien-1-one (9a): IR (neat): $\tilde{\nu}$ = 2982, 1674, 1639, 1442, 1363, 1294, 1197, 1170, 1072, 881 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 1.33 (s, 3 H), 2.03 (d, J = 1.5 Hz, 3 H), 6.07 (dd, J = 2.0, 1.5 Hz, 1 H), 6.12 (dd, J = 10.0, 2.0 Hz, 1 H), 6.87 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 186.0, 161.4, 152.7, 128.3, 127.3, 79.7, 76.4, 26.4, 22.8, 17.9 ppm. $C_{12}H_{18}O_3$ (210.27): calcd. C 68.54, H 8.63; found C 68.64, H 8.52.

4-(*tert*-Butylperoxy)-4-isopropyl-3-methyl-2,5-cyclohexadien-1-one (9b): IR (neat): $\tilde{\nu}$ = 2978, 1767, 1676, 1637, 1363, 1197, 987, 895 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.68 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.21 (s, 9 H), 1.98 (d, J = 1.2 Hz, 3 H), 2.08 (qq, J = 6.8, 6.8 Hz, 1 H), 6.14 (dq, J = 1.9, 1.2 Hz, 1 H), 6.30 (dd, J = 10.2, 1.9 Hz, 1 H), 6.91 (d, J = 10.2 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 185.9, 161.3, 149.0, 130.9, 128.8, 83.7, 79.8, 33.6, 26.4, 17.8, 17.3, 16.7 ppm.

4-Benzyl-4-(*tert*-butylperoxy)-2-chloro-2,5-cyclohexadien-1-one (11): IR (neat): $\tilde{\nu}$ = 2984, 1680, 1365, 1194, 978 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 3.02 (s, 2 H), 6.28 (d, J = 10.0 Hz, 1 H), 6.83 (dd, J = 10.0, 2.6 Hz, 1 H), 7.00 (d, J = 2.6 Hz, 1 H), 7.10–7.40 (m, 5 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 178.4, 150.2, 146.0, 133.6, 130.7, 130.6, 128.5, 128.2, 127.4, 80.7, 80.5, 43.8, 26.3 ppm.

2-Acetyl-4-(*tert*-butylperoxy)-4-methyl-2,5-cyclohexadien-1-one (13): IR (neat): $\tilde{\nu}$ = 2934, 1697, 1674, 1639, 1365, 1250, 1197, 1157,

1068, 912, 873, 835 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.38 (s, 3 H), 2.51 (s, 3 H), 6.22 (d, J = 10.0 Hz, 1 H), 6.88 (dd, J = 10.0, 2.9 Hz, 1 H), 7.49 (d, J = 2.9 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 197.6, 183.4, 156.5, 150.3, 137.8, 129.4, 80.4, 76.4, 30.7, 26.3, 23.0 ppm.

4-Allyl-4-(*tert*-butylperoxy)-2-methoxy-2,5-cyclohexadien-1-one (15): IR (neat): $\tilde{\nu}$ = 2982, 1682, 1647, 1620, 1363, 1207, 1176, 987, 870, 848 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 2.50 (ddd, 2 H), 3.68 (s, 3 H), 5.07 (ddd, J = 10.2, 3.4, 1.3 Hz, 1 H), 5.12 (ddd, J = 7.3, 1.3, 1.2 Hz, 1 H), 5.68 (tdd, J = 10.2, 7.6, 7.3 Hz, 1 H), 5.72 (d, J = 2.8 Hz, 1 H), 6.26 (d, J = 10.3 Hz, 1 H), 6.88 (dd, J = 10.3, 2.8 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 181.1, 151.4, 150.1, 130.9, 128.8, 119.6, 116.0, 80.04, 79.98, 54.6, 42.0, 26.4 ppm. HRMS: calcd. for $C_{14}H_{21}O_4$ [M]$^+$ 253.1440; found 253.1465.

Titanium-Promoted Reaction of 4-(*tert*-Butylperoxy)-4-methyl-2,5-cyclohexadien-1-one (2a). Synthesis of Toluquinone (3a): A side-armed round-bottomed flask (25 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with $TiCl_4$ (0.13 mL, 1.2 mmol) and dry dichloromethane (1.0 mL) under argon. The solution was stirred at –78 °C with the help of a dry ice/acetone bath, and a solution of **2a** (0.195 g, 1.0 mmol) in dichloromethane (1.0 mL) was added dropwise over a period of 5 min. The mixture was stirred at –78 °C for 30 min, warmed to 0 °C, and then stirred for 1 h. The mixture was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and dichloromethane (5 mL). After the mixture had been stirred for 30 min, it was filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2; hexane/ethyl acetate, 10:1) to give **3a** (0.112 g, 92%) as a light brown oil. R_f = 0.30 (SiO_2; hexane/ethyl acetate, 20:1). IR (neat): $\tilde{\nu}$ = 3391, 2961, 1734, 1657, 1601, 1509, 1458, 1205, 1091, 903, 810 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.07 (d, J = 1.5 Hz, 3 H), 6.63 (dq, J = 2.2, 1.5 Hz, 1 H), 6.71 (dd, J = 10.0, 2.2 Hz, 1 H), 6.77 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 187.7, 187.6, 145.9, 136.5, 133.3, 15.8 ppm. HRMS (EI): calcd. for $C_7H_6O_2$ [M]$^+$ 122.0368; found 122.0407.

2-Isopropyl-*p*-benzoquinone (3b): IR (neat): $\tilde{\nu}$ = 3316, 2965, 1717, 1633, 1507, 1456, 1312, 1196, 1035, 909, 812 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.8 Hz, 6 H), 3.04 (qq, J = 6.8, 1.2 Hz, 1 H), 6.55 (dd, J = 2.2, 1.2 Hz, 1 H), 6.70 (dd, J = 10.0, 2.2 Hz, 1 H), 6.76 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 188.1, 187.1, 154.9, 137.1, 135.9, 130.3, 26.8, 21.8 ppm. HRMS (EI): calcd. for $C_9H_{10}O_2$ [M]$^+$ 150.0681; found 150.0652.

2-Phenyl-*p*-benzoquinone (3d): IR (neat): $\tilde{\nu}$ = 3973, 3345, 2986, 2909, 1593, 1502, 1489, 1445, 1395, 1242, 1046, 938 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.83 (dd, J = 10.0, 2.2 Hz, 1 H), 6.87 (dd, J = 2.2 Hz, 1 H), 6.88 (d, J = 10.0 Hz, 1 H), 7.47–7.51 (m, 5 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 187.6, 186.6, 145.9, 137.0, 136.2, 132.7, 130.1, 129.2, 128.5 ppm. HRMS (EI): calcd. for $C_{12}H_8O_2$ [M]$^+$ 184.0524; found 184.0542.

2-Benzyl-*p*-benzoquinone (3e): M.p. 43–44 °C. IR (neat): $\tilde{\nu}$ = 1661, 1559, 1497, 1455, 1352, 1292, 1080, 1060, 895, 850, 758, 704 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.73 (d, J = 1.5 Hz, 2 H), 6.37 (dt, J = 2.4, 1.5 Hz, 1 H), 6.68 (dd, J = 10.2, 2.4 Hz, 1 H), 6.76 (d, J = 10.2 Hz, 1 H), 7.19 (dt, J = 6.3, 1.6 Hz, 2 H), 7.25 (td, J = 8.3, 6.3 Hz, 2 H), 7.32 (tt, J = 8.3, 1.6 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 187.6, 187.1, 148.6, 136.6, 136.4, 136.3, 133.3, 129.3, 128.8, 127.0, 35.1 ppm. HRMS (EI): calcd. for $C_{13}H_{10}O_2$ [M]$^+$ 198.0681; found 198.0712.

2-Isopropyl-6-methyl-*p*-benzoquinone (21): IR (neat): $\tilde{\nu}$ = 2966, 1653, 1612, 1466, 1375, 1294, 916 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.8 Hz, 6 H), 2.06 (d, J = 1.7 Hz, 3 H), 3.06 (m, 1 H), 6.47 (dd, J = 2.7, 1.2 Hz, 1 H), 6.54 (dq, J = 2.7, 1.7 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 188.1, 155.0, 146.1, 132.8, 130.7, 26.9, 21.4, 16.0 ppm. HRMS: calcd. for $C_{10}H_{12}O_2$ [M]$^+$ 164.0837; found 164.0850.

5,6,7,8-Tetrahydro-1,4-dihydroxynaphthalene (22): M.p. 172.5–173.0 °C. IR (KBr): $\tilde{\nu}$ = 3222, 2923, 1597, 1485, 1373, 1306, 1264, 1044, 968, 802, 741 cm^{-1}. ^{1}H NMR (270 MHz, CD_3OD): δ = 1.72 (m, 4 H), 2.58 (m, 4 H), 6.40 (s, 2 H) ppm. ^{13}C NMR (68 MHz, CD_3OD): δ = 149.6, 127.01, 113.3, 25.5, 24.5 ppm.

5-Allyl-2-methoxy-*p*-benzoquinone (23): M.p. 92.5–93.5 °C. IR (KBr): $\tilde{\nu}$ = 1657, 1599, 1373, 1348, 1302, 1097, 925 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.20 (dddd, J = 6.8, 1.3, 1.3, 1.3 Hz, 2 H), 3.82 (s, 3 H), 5.16 (ddt, J = 11.8, 1.3, 1.3 Hz, 1 H), 5.21 (ddt, J = 6.2, 1.3, 1.3 Hz, 1 H), 5.81 (ddt, J = 11.8, 6.2, 6.8 Hz, 1 H), 5.93 (s, 1 H), 6.51 (t, J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 187.0, 182.1, 158.7, 148.6, 132.8, 130.9, 118.9, 107.6, 56.2, 32.9 ppm. HRMS: calcd. for $C_{10}H_{10}O_3$ [M]$^+$ 178.0630; found 178.0629.

Titanium-Promoted Reaction of 6-(*tert*-Butylperoxy)bicyclo[4.4.0]-deca-1,4-dien-3-one (5). Synthesis of 6-Hydroxybicyclo[4.4.0]deca-1,4-dien-3-one (24):[44] A side-armed round-bottomed flask (25 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with $TiCl_4$ (0.07 mL, 0.6 mmol) and dry dichloromethane (1.0 mL) under argon. The solution was stirred at –78 °C with the help of a dry ice/acetone bath, and a solution of **5** (0.107 g, 0.5 mmol) in dichloromethane (1.0 mL) was added dropwise over a period of 5 min. The mixture was stirred at –78 °C for 30 min, warmed to –15 °C, and then stirred for 5 h with the help of a dry ice/ethylene glycol bath. The mixture was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and dichloromethane (5 mL). After the mixture had been stirred for 30 min, it was filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with Na_2SO_4. Evaporation of the solvent gave **24** (0.067 g, 90%) as a yellow solid. Recrystallization from ethyl acetate/hexane gave colorless microcrystals. R_f = 0.13 (SiO_2, hexane/ethyl acetate, 6:1); m.p. 117.5–118.0 °C (ref.[44] m.p. 125 °C). IR (KBr): $\tilde{\nu}$ = 3273, 2945, 1661, 1397, 1271, 1117, 1071, 1036, 999, 887 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.35 (m, 2 H), 1.66 (dm, J = 13.4 Hz, 1 H), 1.94 (dddd, J = 13.4, 13.4, 3.9, 3.9 Hz, 1 H), 2.02 (m, 1 H), 2.10 (ddddd, J = 13.6, 3.9, 3.9, 2.0, 2.0 Hz, 1 H), 2.32 (dddd, J = 12.9, 2.0, 2.0 Hz, 1 H), 2.4–2.8 (br., 1 H), 2.71 (dddd, J = 12.9, 12.9, 5.1, 1.7 Hz, 1 H), 5.97 (dd, J = 1.7, 1.7 Hz, 1 H), 6.09 (dd, J = 10.0, 2.0 Hz, 1 H), 6.81 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 186.7, 164.8, 152.6, 127.3, 123.0, 68.2, 39.0, 32.2, 27.9, 20.2 ppm. $C_{10}H_{12}O_2$ (164.20): calcd. C 73.15, H 7.37; found C 72.76, H 7.52.

Ruthenium-Catalyzed Oxidation of Estrone (28) with *t*BuOOH: A round-bottomed flask (25 mL) equipped with a magnetic stir bar and a pressure-equalizing dropping funnel connected to a three-way stopcock was charged with estrone (**28**, 0.810 g, 3.0 mmol), $RuCl_2(PPh_3)_3$ (0.086 g, 0.09 mmol), and dry benzene (3.0 mL) under argon. The mixture was stirred at room temperature, and a solution of *t*BuOOH (3.83 M) in dry benzene (3.2 mL, 12.0 mmol) was added dropwise over a period of 2 h. The mixture was stirred at room temperature for 3 h. Chromatography on Florisil (8.0 g)

with diethyl ether (150 mL) gave a mixture of **29** and **30** (0.952 g, 89%) as a yellow solid. An analytically pure sample was prepared by column chromatography (SiO_2; diethyl ether/hexane, 9:1). Data for compound **29**: R_f = 0.57 (SiO_2; diethyl ether/hexane, 6:1); m.p. 138.5–139.0 °C. $[\alpha]_D$ = +89.3 (c = 0.65, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3866, 3447, 2942, 1740, 1670, 1456, 1364, 1289, 1198, 1047, 956, 899, 870 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.80 (s, 3 H), 1.19 (s, 9 H), 1.20–2.18 (m, 10 H), 2.32–2.50 (m, 3 H), 2.91 (dddd, J = 12.8, 10.0, 2.0, 2.0 Hz, 1 H), 6.14 (dd, J = 2.0, 2.0 Hz, 1 H), 6.22 (dd, J = 10.0, 2.0 Hz, 1 H), 6.93 (d, J = 10.0 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 219.6, 186.1, 162.9, 149.8, 128.8, 126.9, 80.6, 79.5, 53.1, 50.3, 47.9, 36.3, 35.5, 31.5, 28.6, 26.0, 25.2, 24.3, 21.5, 13.9 ppm. $C_{22}H_{30}O_4$ (358.48): calcd. C 73.71, H 8.44; found C 73.36, H 8.38. Data for compound **30**: R_f = 0.54 (SiO_2, diethyl ether/hexane, 6:1); m.p. 140.5–141.0 °C. $[\alpha]_D$ = +28.1 (c = 0.56, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3958, 2950, 2355, 1744, 1636, 1474, 1364, 1290, 1196, 1178, 997, 889, 854 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.22 (s, 9 H), 1.25–2.18 (m, 10 H), 2.36–2.52 (m, 3 H), 2.74 (dddd, J = 12.8, 10.0, 2.0, 2.0 Hz, 1 H), 6.11 (dd, J = 1.6, 1.6 Hz, 1 H), 6.27 (dd, J = 10.3, 2.0 Hz, 1 H), 7.11 (d, J = 10.3 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 220.1, 185.9, 164.6, 150.7, 129.9, 124.6, 80.0, 78.6, 55.7, 50.3, 47.6, 35.5, 35.2, 32.6, 31.7, 31.2, 26.5, 22.6, 21.9, 13.6 ppm. HRMS: calcd. for $C_{22}H_{31}O_4$ $[M + H]^+$ 359.2223; found 359.2203.

1,4-Diacetoxyestra-1,3,5(10)-trien-17-one (31):[45] A side-armed round-bottomed flask (200 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with ZnI_2 (9.57 mg, 30 mmol), acetic acid (10 mL), and acetic anhydride (40 mL) under argon. The solution was stirred at room temperature, and 10-(*tert*-butylperoxy)estra-1,4-dien-3,17-dione (**29** and **30**, 3.58 g, 10 mmol) was added in one portion. After stirring at room temperature for 3 h, the mixture was quenched by pouring it into a mixture of an aqueous solution of NaOH (2 N, 200 mL) and ethyl acetate (150 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (150 mL) and an aqueous solution of Na_2SO_3 (1 M, 100 mL) and then dried with Na_2SO_4. After evaporation of the solvent, column chromatography (SiO_2; hexane/diethyl ether, 3:1) gave **31** (2.57 g, 69%) as a colorless solid. R_f = 0.20 (SiO_2; hexane/ethyl acetate, 3:1); m.p. 161.5–162.5 °C (ref.[45] m.p. 163–163.6 °C). $[\alpha]_D$ = +270 (c = 0.50, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.93 (s, 3 H), 1.18–2.20 (m, 10 H), 2.26 (s, 3 H), 2.30 (s, 3 H), 2.30–3.85 (m, 5 H), 6.83 (d, J = 8.8 Hz, 1 H), 6.90 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 220.0, 168.9, 147.5, 146.6, 133.2, 132.1, 121.1, 120.2, 50.2, 48.2, 44.8, 39.4, 35.5, 32.2, 25.6, 25.1, 24.1, 21.5, 21.1, 20.7, 14.2 ppm. HRMS: calcd. for $C_{22}H_{26}O_5$ $[M]^+$ 370.1780; found 370.1746.

Estra-2,5(10)-diene-1,4,17-trione (32):[45] A round-bottomed flask (200 mL) equipped with a magnetic stir bar and a reflux condenser was charged with 1,4-diacetoxyestra-1,3,5(10)-trien-17-one (**31**, 1.00 g, 2.70 mmol), concentrated HCl (12 mL), and MeOH (40 mL). After heating at reflux for 12 h, the mixture was concentrated. To the residue, an aqueous solution of $FeCl_3$ (1 M, 100 mL) and ethyl acetate (50 mL) were added. After stirring for 1 h, the organic layer was separated. The organic layer was washed with brine (2 × 100 mL) and dried with Na_2SO_4. After evaporation of the solvent, column chromatography (SiO_2; hexane/diethyl ether, 4:1) gave **32** (485 mg, 63%) as a yellow solid. R_f = 0.20 (SiO_2; hexane/ethyl acetate, 3:1); m.p. 171.5–172.5 °C (ref.[45] m.p. 173.8–174.4 °C). $[\alpha]_D$ = +272 (c = 0.50, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2993, 1730, 1649, 1591, 1298, 1066, 862, 837 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 1.08–2.81 (m, 15 H), 6.66 (s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 219.7, 187.8, 187.3, 144.8, 143.4, 137.4, 135.4, 49.7, 48.2, 43.4, 38.4, 35.5, 32.0, 25.3, 24.0, 23.5, 21.4, 14.1 ppm. HRMS: calcd. for $C_{18}H_{20}O_3$ $[M]^+$ 284.1412; found 284.1390.

1,4-Dihydroxyestra-1,3,5(10)-trien-17-one (33):[45] A round-bottomed flask (50 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with Zn (10 g), acetic acid (12 mL), and estra-2,5(10)-diene-1,4,17-trione (**32**, 380 mg, 6.0 mmol) under argon. After stirring at room temperature for 1 h, the mixture was quenched by pouring it into a mixture of brine (60 mL) and ethyl acetate (60 mL). The organic layer was separated, washed with brine (3 × 40 mL), and then dried with Na_2SO_4. Evaporation of the solvent gave **33** as a colorless solid; m.p. 270 °C (decomposed) [ref.[45] m.p. 300–305 °C (evacuated capillary)]. $[\alpha]_D$ = +296 (c = 0.5, dioxane). IR (KBr): $\tilde{\nu}$ = 3368, 2926, 1718, 1487, 1375, 1311, 1259, 808 cm^{-1}. ^1H NMR (270 MHz, [D$_6$]DMSO): δ = 0.87 (s, 3 H), 0.98–2.12 (m, 10 H), 2.23–2.55 (m, 3 H), 2.76 (dd, J = 12.8, 2.1 Hz, 1 H), 3.22 (dd, J = 12.8, 2.1 Hz, 1 H), 6.41 (s, 2 H), 8.32 (s, 1 H), 8.40 (s, 1 H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 219.5, 148.7, 147.2, 126.5, 125.5, 112.7, 111.7, 49.6, 47.8, 44.7, 39.3, 35.2, 31.9, 25.0, 24.8, 24.4, 21.1, 14.0 ppm.

4-Isopropyltricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene-3,6-dione (34): A side-armed round-bottomed flask (25 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with $TiCl_4$ (0.092 mL, 0.84 mmol) and dichloromethane (2.0 mL) under argon. The solution was stirred at 0 °C, and a solution of **2b** (0.146 g, 0.70 mmol) in dichloromethane (1.0 mL) was added dropwise over a period of 5 min. After stirring at 0 °C for 1 h, cyclohexadiene (67 mg, 0.84 mmol) was added dropwise to the solution, and the mixture was stirred at 0 °C for 2 h. The mixture was quenched by pouring it into a mixture of a saturated aqueous solution of $NaHCO_3$ (10 mL) and dichloromethane (10 mL). The mixture was stirred for 30 min and filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with $MgSO_4$. Evaporation of the solvent gave **34** (0.125 g, 78%) as a yellow liquid. R_f = 0.54 (SiO_2; hexane/ethyl acetate, 6:1). IR (neat): $\tilde{\nu}$ = 2863, 1684, 1676, 1388, 1211, 1141, 939, 875, 731 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.8 Hz, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.36 (m, 2 H), 1.70 (m, 2 H), 2.97 (d, J = 2.4 Hz, 2 H), 3.00 (qdd, J = 6.8, 6.8, 1.0 Hz, 1 H), 3.18 (m, 2 H), 6.18 (m, 2 H), 6.46 (d, J = 1.0, Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 199.5, 198.5, 160.9, 136.1, 133.5, 133.0, 49.8, 49.6, 35.6, 35.3, 26.9, 24.8, 24.7, 21.1, 20.7 ppm.

4-Methyltricyclo[8.4.0.0^{3,8}]tetradeca-1(10),5-diene-2,9-dione (35): A side-armed round-bottomed flask (25 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with $TiCl_4$ (0.092 mL, 0.84 mmol) and dry dichloromethane (5.0 mL) under argon. The solution was stirred at 0 °C, and a solution of **5** (0.165 g, 0.70 mmol) in dichloromethane (1.0 mL) was added dropwise over a period of 5 min. After stirring at 0 °C for 18 h, (*Z*)-1,3-pentadiene (71 mg, 1.05 mmol) was added dropwise to the solution. After stirring at 0 °C for 1 h, the mixture was quenched by pouring it into a mixture of a saturated aqueous solution of $NaHCO_3$ (10 mL) and dry dichloromethane (10 mL). The mixture was stirred for 30 min and filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with $MgSO_4$. Evaporation of the solvent gave **35** (0.118 g, 73%) as a yellow liquid. R_f = 0.73 (SiO_2; hexane/ethyl acetate, 6:1). IR (neat): $\tilde{\nu}$ = 1703, 1680, 1618, 1404, 1365, 1250, 1182, 993, 964 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.16 (d, J = 7.1 Hz, 3 H), 1.68 (m,

4 H), 2.40 (m, 4 H), 2.92 (ddd, J = 24.1, 6.5, 2.2 Hz, 1 H), 3.14 (ddd, J = 24.1, 4.6, 2.2 Hz, 1 H), 3.41 (m, 1 H), 5.77 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 187.1, 186.6, 143.5, 142.2, 141.7, 138.7, 130.1, 121.3, 28.8, 24.0, 22.5, 22.4, 21.9, 21.2, 21.1 ppm.

Sc(OTf)$_3$-Catalyzed Diels–Alder Reaction of Toluquinone (3a) and 1,3-Butadiene. Synthesis of 2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (36):[46] To a suspension of $Sc(OTf)_3$ (10 mol-%) in CH_3NO_2 (2.5 mL) was added a mixture of **3a** (0.122 g, 1.0 mmol) and 1,3-butadiene (0.25 mL, 3.0 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h and quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (4 mL). The aqueous layer was extracted with ethyl acetate (3 × 4 mL), and the combined organic layers were dried with Na_2SO_4. Evaporation of the solvent gave **36** (0.174 g, 99%); m.p. 86.0–86.5 °C (ref.[46] m.p. 80–81 °C). IR (KBr): $\tilde{\nu}$ = 3029, 2924, 1674, 1620, 1443, 1431, 1379, 1368, 1345, 1327, 1283, 1204, 1088, 1046, 986, 922, 899, 648 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.00 (d, J = 1.5 Hz, 3 H), 2.12 (m, 2 H), 2.41 (m, 2 H), 3.21 (m, 1 H), 3.21 (m, 1 H), 5.69 (dd, 2 H), 6.53 (q, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 16.2, 24.3, 46.2, 46.4, 124.4, 124.4, 136.1, 148.9, 199.8, 200.3 ppm. HRMS (EI): calcd. for $C_{11}H_{12}O_2$ $[M]^+$ 176.0837; found 176.0857.

Synthesis of Vitamin K$_3$ (37).[47] **Pd/C-Catalyzed Dehydrogenation of 2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (36) in Acetone:** A 10 mL sealed tube equipped with a magnetic stir bar was charged with **36** (0.035 g, 0.20 mmol), 10% Pd/C (22.0 mg, 0.02 mmol) and acetone (2.0 mL) under argon. The mixture was stirred at reflux temperature for 24 h, then filtered through a pad of Celite. Evaporation of the solvent gave **37** (0.034 g, 100%) as a yellow solid; m.p. 106.0–107.0 °C (ref.[47] m.p. 107 °C). IR (KBr): $\tilde{\nu}$ = 3069, 1665, 1624, 1595, 1354, 1302, 1267, 1157, 1019, 941, 779, 693, 667 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.19 (d, J = 1.5 Hz, 3 H), 6.84 (q, J = 1.5 Hz, 1 H), 7.71 (d, J = 5.9 Hz, 1 H), 7.72 (d, J = 5.6 Hz, 1 H), 8.06 (dd, J = 10.4, 5.61 Hz, 1 H), 8.07 (dd, J = 10.4, 5.9 Hz, 1 H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 16.4, 126.1, 126.5, 132.2, 132.3, 133.5, 133.6, 135.7, 148.2, 184.9, 185.5 ppm. HRMS: *m/z*: calcd. for $C_{11}H_8O_2$ $[M^+]$; 172.0524; found 172.0536.

Synthesis of Vitamin K$_1$ (39). Palladium-Catalyzed Allylation of Vitamin K$_3$ (37) with Phytol (38) in the Presence of Tin(II) Bromide: A side-armed round-bottomed flask (25 mL) equipped with a magnetic stir bar and a three-way stopcock was charged with **37** (172 mg, 1.0 mmol), **38** (593 mg, 2.0 mmol), and dimethylformamide (DMF, 3.0 mL) under argon at room temperature. The mixture was stirred at room temperature, and $PdCl_2(PhCN)_2$ (38.4 mg, 0.10 mmol) and tin(II) bromide (1114 mg, 4.0 mmol) were added. The mixture was stirred at room temperature for 24 h and then quenched by the addition of an aqueous solution of 10% HCl (5.0 mL). The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL) and then dried with Na_2SO_4. Evaporation of the solvent gave a dark brown oil (1048 mg). Purification by preparative TLC gave **39** as a yellow oil (209 mg, 46%) and 2,3-benzo-5-methyl-5-phytylcyclohexane-1,4-dione as a pale yellow oil (192 mg, 42%). Data for compound **39**:[33a] R_f = 0.57 (SiO_2; hexane/ethyl acetate, 10:1). IR (neat): $\tilde{\nu}$ = 3015, 2919, 2870, 1661, 1618, 1597, 1462, 1377, 1331, 1296, 1258, 1229, 1173, 1159, 1136, 1094, 1070, 972, 949, 893, 787, 714, 693, 666, 639 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 6 H), 0.96–1.57 (m, 19 H), 1.78 (d, J = 1.2 Hz, 3 H), 1.94 (t, J = 7.7 Hz, 2 H), 2.19 (s, 3 H), 3.37 (d, J = 7.1 Hz, 2 H), 5.00 (tq, J = 7.1, 1.2 Hz, 1 H), 7.65–7.74 (m, 2 H), 8.05–8.12 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.7, 16.3, 19.7, 22.6, 22.7, 24.4, 24.8, 25.2, 26.0, 28.0, 32.6, 32.8, 36.6, 37.26, 37.35, 37.38, 37.44, 39.4, 40.0, 118.8, 133.26, 133.31, 137.9, 143.3, 146.2, 184.5, 185.5 ppm. HRMS (EI): calcd. for $C_{31}H_{46}O_2$ $[M]^+$ 450.3498; found 450.3491. Data for 2,3-benzo-5-methyl-5-phytylcyclohexane-1,4-dione:[27] R_f = 0.50 (SiO_2; hexane/ethyl acetate, 10:1). IR (neat): $\tilde{\nu}$ = 3071, 2926, 1698, 1597, 1462, 1414, 1377, 1316, 1291, 1258, 1213, 1159, 1063, 980, 920, 799, 756, 725, 694 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.80–0.88 (m, 12 H), 1.03–1.55 (m, 19 H), 1.29 (s, 3 H), 1.48 (s, 3 H), 1.89 (t, J = 7.1 Hz, 2 H), 2.28 (dd, J = 14.2, 7.6 Hz, 1 H), 2.46 (dd, J = 14.2, 7.6 Hz, 1 H), 2.84 (d, J = 16.1 Hz, 1 H), 3.03 (d, J = 16.1 Hz, 1 H), 5.04 (t, J = 7.6 Hz, 1 H), 7.68–7.78 (m, 2 H), 7.98–8.11 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.1, 19.67, 19.72, 22.6, 23.8, 24.4, 24.8, 25.2, 28.0, 32.6, 32.8, 36.6, 37.26, 37.32, 37.35, 37.40, 39.3, 40.2, 49.5, 49.7, 118.2, 125.9, 127.4, 133.8, 134.1, 134.3, 134.4, 135.0, 196.5, 200.9 ppm. HRMS (EI): calcd. for $C_{31}H_{48}O_2$ $[M]^+$ 452.3654; found 452.3634.

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