Mendeleev Commun., 2005, 15(6), 217–221

Ozonolysis in the chemistry of low-molecular bioregulators

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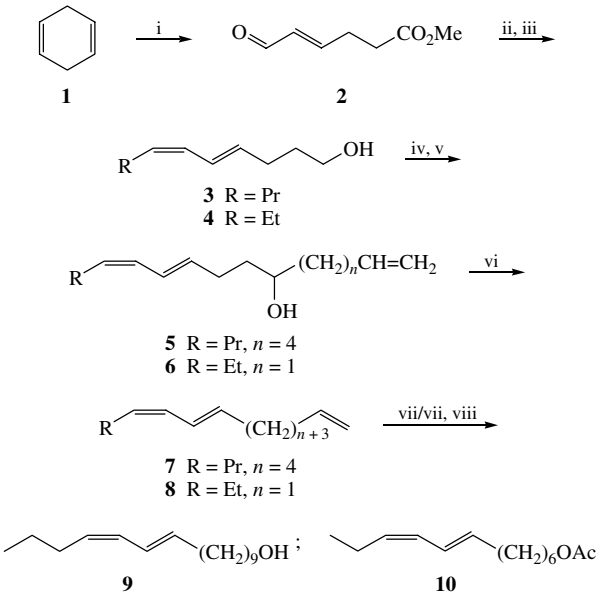
DOI: 10.1070/MC2005v015n06ABEH002237

Numerous records in the chemistry of pheromones, juvenile hormone analogues (juvenoids), ecdysteroids, tocopherols and related compounds demonstrate the effectiveness and, in many cases, the uniqueness of ozonolysis in the synthesis of low-molecular biologically active compounds.

Ozonolysis is of considerable interest in the modern chemistry of olefins.[1] The use of ozone in the synthesis and modification of complicated natural products is growing in both popularity and efficiency.[2–11] Its importance in the chemistry of low-molecular bioregulators was promoted by the appearance of advanced procedures for selective ozonolysis of acyclic[12,13] and cyclic alkenes, dienes, trienes[1,14,15] and enynes.[16]

New prospects in the synthesis of low-molecular bioregulators have been opened by a methodology of the ozonolytical splitting of cycloalkenes to obtain products with two functionally different terminal groups (*e.g.*, aldehydo esters, aldehydo acetals and acetal ethers),[17,18] because these products are less accessible by other methods.

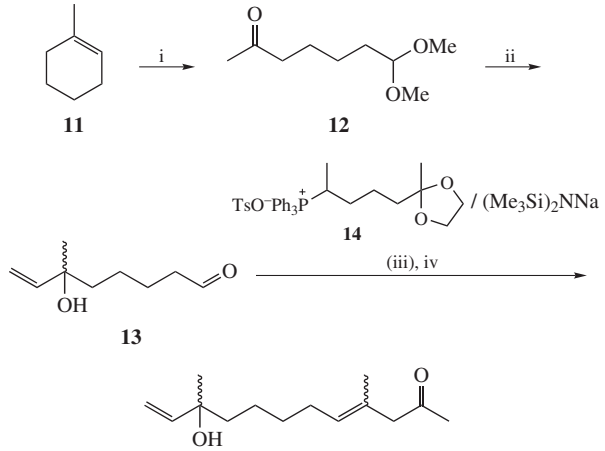
During the partial ozonolysis of 1,4-cyclohexadiene **1**, one of the double bonds can migrate into conjugation (which, in the case of a MeOH–CH_2Cl_2 medium, afforded methyl 6-oxo-4*E*-hexenoate **2**).[19] This observation was recently used for synthesising two conjugated dienes of agrochemical value (Scheme 1): 10*E*,12*Z*-hexadecadienol **9** (bombikol, the sex pheromone of the silk worm moth)[20] and 7*E*,9*Z*-dodecadien-1-yl acetate **10** (the pheromone of the codling moth).[21] Different reactivity of terminal functional groups in compound **2** makes it possible to perform necessary transformations at the CHO group and then to elongate the carbon chains to required lengths *via* intermediates **3**, **5**, **7** or **4**, **6**, **8**, respectively.



Scheme 1 *Reagents and conditions*: i, O_3/MeOH–CH_2Cl_2, Et_3N/Ac_2O; ii, $[RCH_2PPh_3]^+Br^-$/$(Me_3Si)_2NNa$; iii, $LiAlH_4$; iv, PCC; v, CH_2=$CH(CH_2)_n$-MgBr; vi, MsCl/Et_3N, $LiAlH_4$; vii, 9-BBN, H_2O_2/NaOH; viii, Ac_2O/Py.

Ozonolysis of 1-methylcyclohexene **11** in the presence of MeOH was chosen as the overture step in the synthesis of a mixture of racemic *Z*- and *E*-isomers of echinolone **15** (which is a potent juvenile hormone analogue). The subsequent transformation of the ozonolysis product, keto acetal **12**, into vinyl carbinol **13**, and the condensation of **13** with a complementary phosphorane (generated from phosphonium tosylate **14**) afforded the above echinolone derivative (Scheme 2).[22]

Partial ozonolysis of regular (*Z*)-1,4-(poly)butadiene **16** offers unique opportunities for the expedient synthesis of acyclic



Scheme 2 *Reagents and conditions*: i, O_3/MeOH, –70 °C, H_2/Pd–$CaCO_3$, MeOH/NH_4Cl; ii, CH_2=$CHMgBr$, H_2O/TsOH·Py; iii, **14**/$(Me_3Si)_2NNa$, iv, H_2O/TsOH, Me_2CO.

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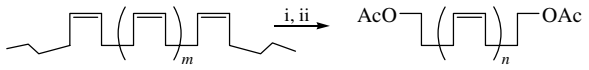
α,ω-bifunctional compounds **17**, which contain *Z*-configured bis-homoallylic double bonds (Scheme 3).[23] Molecules of this type are in demand for the synthesis of insect pheromones and other biologically active compounds with *Z*-configured polyene moieties.



16 **17**

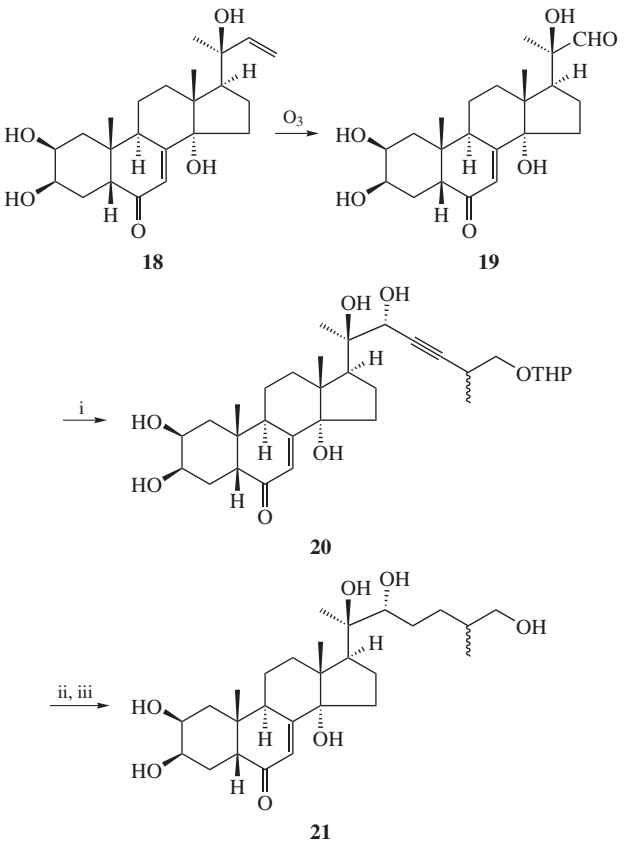
$m = (10–11)\times10^3$, $n = 1–5$

Scheme 3 *Reagents and conditions*: i, O_3/C_6H_6/MeOH, H_2/Pd–$CaCO_3$–PbO; ii, Ac_2O/Py, vacuum distillation.

Of special interest is the partial ozonolysis of cyclodimers and cyclotrimers of isoprene,[15] as well as linear all-(*Z*)-1,4- and all-(*E*)-1,4-(poly)isoprenes (*e.g.*, natural caoutchouk, guttapercha, and their synthetic analogues).[24–26] This strategy was applied to many syntheses of pheromones and juvenoids of isoprenoid origin.[27] Thus, it can be stated that ozonolysis is firmly established in the chemistry of insect pheromones and juvenoids.[14,27–30]

Ecdysteroids, hormonal substances of arthropods responsible for the processes of ecdysis, metamorphosis and diapause, were detected in insect bodies. More recently, they were isolated from many plants, and their structures were identified; this achievement was a real scientific sensation. The low toxicity of ecdysteroids towards warm-blooded organisms paired with their high content in some plant taxons (up to 2.5–3%) makes it feasible to use ecdysteroids in medicine and agriculture.[31]

Compositions ('bouquets') of ecdysteroids in plants can be rather various. But to the exclusion of one or two main ingredients, the concentrations of plant ecdysteroids usually are quite poor. Thus, the best way to obtain reasonable amounts of minor ecdysteroids appears to be chemical transformation of their most accessible congeners. Unexpectedly, a chemical study of ecdysteroids revealed that being in conjugation with a keto group the Δ^7 bond in the cycle B does not react with ozone, whereas similar double bonds in cyclic terpenoids are readily ozonised.[32–36] This peculiarity made it possible to perform a number of syntheses of ecdysteroids and their analogues, where ozonolysis was used as the key step.

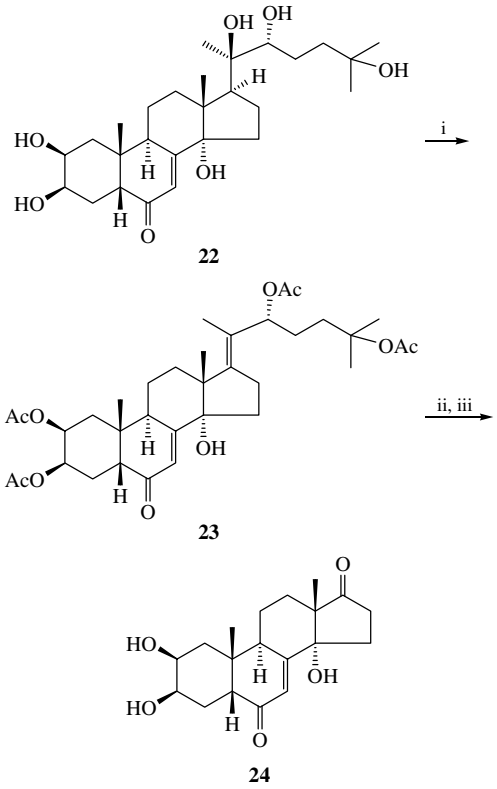


18 **19** **20** **21**

Scheme 4 *Reagents and conditions*: i, HC≡CCH(Me)CH_2OTHP/EtMgBr/THF; ii, H_2/10% Pd–C/Pyperidine/EtOH; iii, HCl/10% THF–H_2O.

In the total synthesis of inocosterone **21**,[37] key intermediate **19** was obtained by the ozonolysis of 20-vinylpregnane **18**.[38] The subsequent conversion of aldehyde **19** into acetylene carbinol **20**, its hydrogenation and, finally, hydrolysis (Scheme 4) resulted in a mixture of 25*R* and 25*S* epimers of inocosterone **21**. Earlier, this product, isolated from the roots of *Achyranthes fauriei* (China), was identified as a 1:2 mixture of 25*R* and 25*S* epimers.[37]

Acetylation of 20-(hydroxy)ecdysone **22** under drastic conditions to give anhydro tetraacetate **23**, followed by the ozonolysis of the latter, and subsequent hydrolysis afforded rubrosterone **24**[39] (Scheme 5).



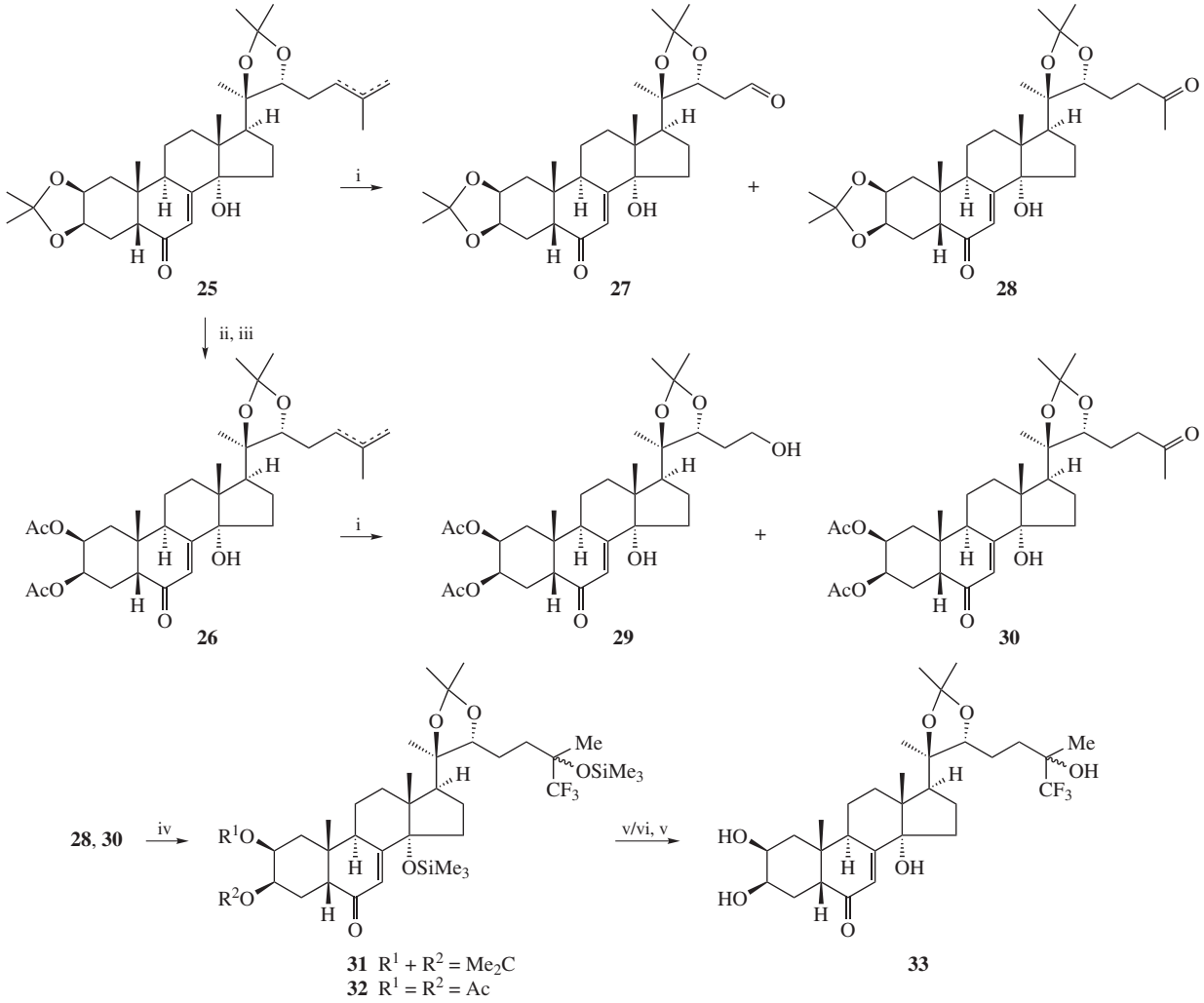
22 **23**

24

Scheme 5 *Reagents and conditions*: i, Ac_2O/AcONa, 140 °C, 30 min; ii, $O_3/CHCl_3$; iii, K_2CO_3/MeOH–H_2O.

The ozonolysis of binary mixtures of protected Δ^{24}- and Δ^{25}-ecdysone derivatives (2,3:20,22-bis-acetonides **25**[40] or 2,3-di-*O*-acetyl-20,22-*O*-isopropylidene compounds **26**[41]) affords a ~2:1 mixture of aldehyde **27** with ketone **28** or alcohol **29** with ketone **30**, respectively. Trifluoromethylation of ketones **28** and **30**, followed by the hydrolysis of intermediates **31** and **32**, gives an ω-trifluorosubstituted analogue of 20-(hydroxy)ecdysone **33** (Scheme 6).

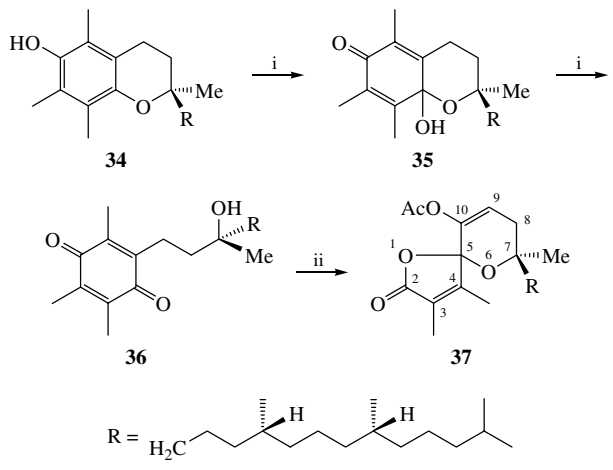
Vitamin E, the most important fat-soluble antioxidant complex of nutritional vegetable oils, consists of several vitamin E-active components (tocopherols) in species-dependent proportions;[42] usually, the main of these is (*R*,*R*,*R*)-α-tocopherol **34**.[43] Interaction of α-tocopherol **34** with O_3 had been reported. Ozonolysis in MeCN gives rise to α-tocopherolquinone **36** and its precursor, 8a-(hydroxy)tocopherone **35** (Scheme 7). When ozonisation is carried out in an acidic medium, and is stopped at a less than 50% conversion, the concentration of quinone **36** in the converted material is about 30%. Longer exposure of **36** to O_3 results in *ca.* twofold decrease of the quinone concentration. This implies the ability of quinone **36** to further oxidation, which presumably starts as the addition of O_3 to the quinone ring. Subsequent rearrangement of this adduct into acyclic hydroxy acids, followed by their dehydration, leads to the



Scheme 6 *Reagents and conditions*: i, O_3/AcOH, CH_2Cl_2, $NaBH(OAc)_3$; ii, 70% AcOH; iii, Ac_2O/Py/DMAP; iv, $Me_3SiCF_3/Bu_4N^+F^-$, THF; v, 5% HCl/$Bu_4N^+F^-$, THF; vi, NaOH/MeOH.

heterocyclic spiro compounds. By means of preparative HPLC, two of such spiro compounds (**37**, epimers at C-5) were isolated and identified. They can be considered as markers for the interaction of ozone with lipidous structures in vitamin E-containing tissues.[44]

Racemic (2*RS*,4′*RS*,8′*RS*)-α-tocopherol, manufactured by acid-catalysed condensation of (3*RS*,7*RS*,11*RS*)-isophytol with trimethylhydroquinone (TMHQ),[45] is a mixture of eight stereoisomers, while the syntheses of natural (2*R*,4′*R*,8′*R*)-α-tocopherol are complicated and involve many steps.[43,46,47] On the other hand, (2*RS*,4′*R*,8′*R*)-α-tocopherol **41** (otherwise known as



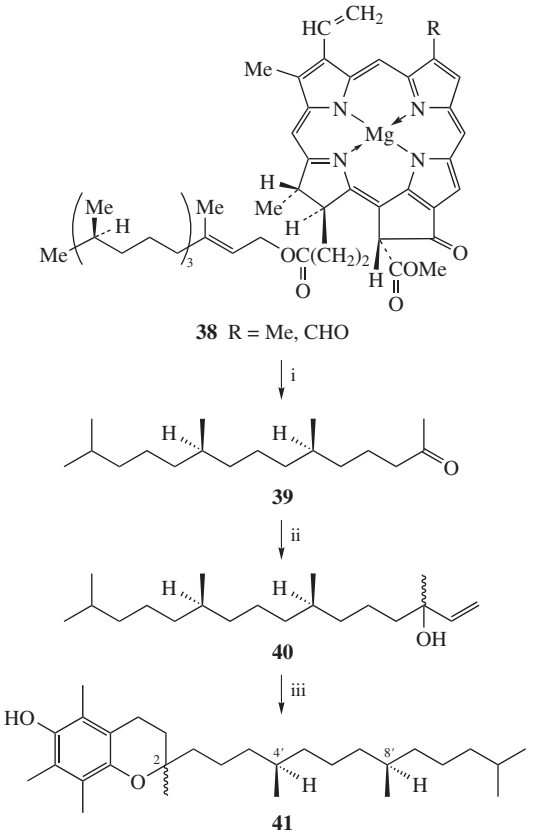
Scheme 7 *Reagents and conditions*: i, O_3/MeCN; ii, O_3/AcOH.

2-*ambo*-α-tocopherol,[48] an equimolecular mixture of 2*R* and 2*S* epimers) was conveniently synthesised from either (2*E*,7*R*,11*R*)-phytol[49] or (3*RS*,7*R*,11*R*)-isophytol.[50] The mixture of 3*R* and 3*S* epimers of isophytol **40** was obtained from chlorophyll **38** (extractable from nettle with acetone) by submitting it to ozonolysis and then by vinylating phytone **39**[50,51] (Scheme 8).

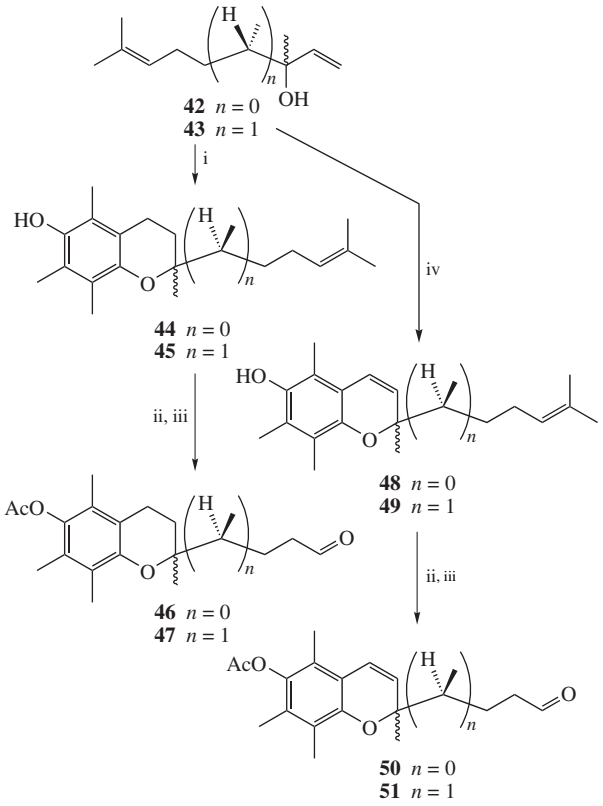
Interest in the synthesis of α-tocopherol analogues with shortened side chains was expressed.[52,53] Hydrophilic analogues of α-tocopherol with ω-positioned functional groups seem particularly attractive.[47] Ozonolysis of chromanols like **44** and **45**, which bear isoprenoid side chains with terminal isopropylidene groups, is a promising approach to ω-functionalised α-tocopherol analogues like **46** and **47**. Intermediates **44**, **45** can be obtained by the condensation of isoprenoid tertiary vinyl carbinols **42**, **43** with TMHQ[54,55] (Scheme 9).

The reaction of vinyl carbinols **42**, **43** with TMHQ under different conditions[56] leads to corresponding chromenes **48**, **49**. Special conditions of ozonolysis were elaborated to convert these chromenes into aldehydes **50**, **51** by selectively cleaving the double bond in the side chain (Scheme 9).[56]

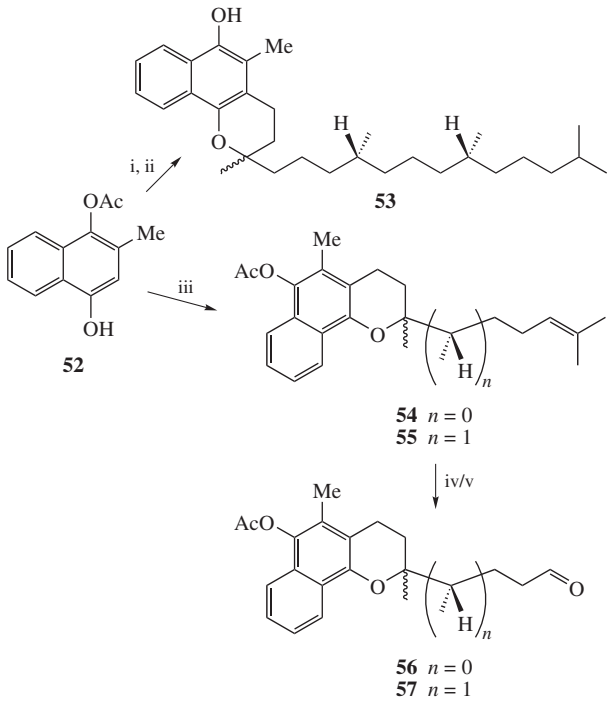
Akin to the chroman structure of α-tocopherol is that of naphthotocopherol,[57] the cyclic form of 1*O*,4*O*-dihydrovitamin K_1. It was identified as a product of enzymatic reduction of vitamin K_1,[58] and proved the strongest antioxidant among phenolic compounds (including α-tocopherol, the potency of which is lower than that of naphthotocopherol by a factor of 6.9).[59] Early syntheses of racemic (2*RS*,4′*RS*,8′*RS*)-naphthotocopherol had been recorded.[45,59] Recently, the first synthesis of optically active (2*RS*,4′*R*,8′*R*)-naphthotocopherol **53** has been implemented.[60] This synthesis of **53** was performed by con-



Scheme 8 *Reagents and conditions*: i, O_3/Me_2CO/$Ba(OH)_2$; ii, CH_2=CH-MgBr/THF; iii, TMHQ/H$^+$/*n*-C_9H_{20}, reflux.



Scheme 9 *Reagents and conditions*: i, TMHQ/H$^+$/*n*-C_9H_{20}, reflux; ii, Ac_2O/Py; iii, O_3/Me_2CO/$Ba(OH)_2$; iv, TMHQ/H$^+$, *n*-C_7H_{16}, reflux, O_2/SiO_2, Py/reflux.



Scheme 10 *Reagents and conditions*: i, **40**/H$^+$, PhMe; ii, $LiAlH_4$/Et_2O; iii, **42** or **43**/CSA, *n*-C_8H_{18}, reflux; iv, O_3/$Ba(OH)_2$, Me_2CO, ~20 °C; v, O_3/$NaHCO_3$, CH_2Cl_2–MeOH (10:1), –70 °C, then Me_2S.

densing isophytol **40** with 1-acetoxy-4-hydroxy-2-methylnaphthalene **52** and then deacetylating the condensation product (Scheme 10).

Because of a very high antioxidant potency of naphthotocopherol, the synthesis of its analogues is also of interest.[61] Benzochromans with unsaturated side chains are particularly attractive. Their ozonolysis affords the derivatives with ω-positioned functional groups, which are promising synthons for obtaining various naphthotocopherols (including water-soluble antioxidants). The interaction of phenol **52** with vinyl carbinol **42** or **43** in the presence of (+)-camphor-10-sulfonic acid (CSA) gave the analogues of naphthotocopherol with ω-isopropylidene group in the side chain (**54** or **55**, respectively). Their ozonolysis resulted in corresponding aldehydes **56** and **57** (Scheme 10).[62]

In summary, ozonolysis, an effective and selective methodology in organic synthesis, is being expanding and finding new promising applications in the chemistry of pheromones, juvenoids, ecdysteroids and tocopherols. The controlled partial ozonolysis of alkenes, cycloalkenes and polyenes provides a plethora of α,ω-bifunctional compounds with double bonds of required geometry or chiral centres of required configuration. In many syntheses of structurally complicated natural products, ozonolysis has played a pivotal role. Certainly, ozone will be widely used in the chemistry of natural products as a unique and selective reagent.

This work was supported by the Russian Foundation for Basic Research (grant no. 04-03-33103).

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Received: 6th September 2005; Com. 05/2575