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New Chiral Ligands from Myrtenal and Caryophyllene for Asymmetric Oxydation of Sulfides Catalyzed by Metal Complexes

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Abstract—From myrtenal and caryophyllene, widespread terpene compounds, three new chiral Schiff bases were prepared suitable for ligands in vanadium ions catalyzed sulfides oxidation to chiral sulfoxides.

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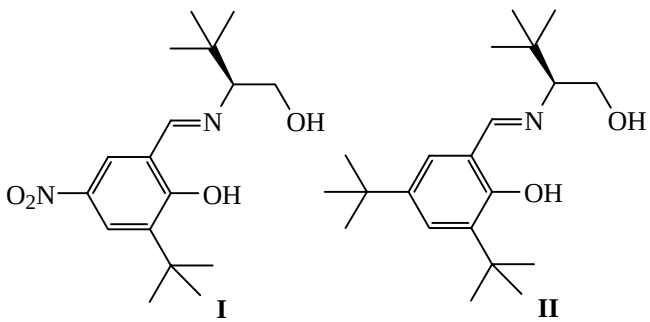
Chiral sulfoxides constitute an important class of organic compounds extensively used in asymmetric synthesis [1, 2]. The interest in chiral sulfoxides is also supported by discovery of natural substances containing an asymmetric sulfoxide group [3, 4] and by finding biologically active sulfoxides of certain configuration [5, 6]. Relatively recently optically active sulfoxides were patented with an outstanding antiulcer action, derivatives of 2-mercaptobenzimidazole and 2-mercapto-4,5-diphenylimidazole [7]. Therefore the development of efficient procedures for preparation of chiral sulfoxides by asymmetric oxidation of sulfides was stimulated.

In the beginning of nineteen eighties Kagan et al. [8] and Modena et al. [9] independently of one another succeeded in asymmetric oxidation of thioanisole and its homologs applying a modified Sharpless system [Ti(*i*-PrO)$_4$–(+)-diethyl tartrate–*t*-BuOOH]. Further development of the procedure of asymmetric sulfides oxidation in the presence of chiral titanium alcoholates was directed to increasing enantioselectivity and chemical yields of target sulfoxides [10]. The disadvantage of these system lies in the necessity to carry out the reaction under an inert gas atmosphere, to control moisture, and to use as a rule equivalent amount of the oxidating system with respect to sulfides.

As an alternative to the methods of Kagan and Modena a procedure for asymmetric sulfides oxidation was developed exploiting hydrogen peroxide in the presence of obtained in situ complexes of vanadium(IV) acetylacetonate with chiral Schiff bases [11, 12]. These complexes are used in a catalytic amount (~1%), permit the application of water solution of hydrogen peroxide, and the process is carried out in the presence of air. The system is sufficiently general and often can be used in oxidation of polyfunctional sulfides. Nowadays only several accessible ligands exist successfully used in this catalytic system, for instance, compounds **I** and **II**. These ligands are obtained by reaction of substituted salicylaldehydes with amino acids derivatives. These ligands made it possible to oxidize various methyl aryl sulfides into the corresponding sulfoxides with sufficient chemical and optical yields. Yet it is highly desirable to have available versatile optically active ligands for conversion of complex polyfunctional compounds with the use of chiral metal



complex systems, and therefore the research in the field of synthesis of new salicylaldimines remains urgent [10].

The target of this study was the synthesis of new ligands suitable for application to the oxidizing system with vanadium acetylacetonate based on widespread optically active terpenes.

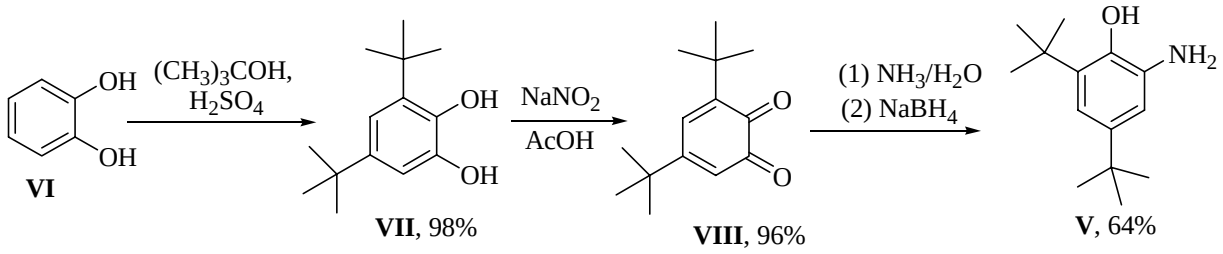
We selected for initial compounds monoterpenoid (–)-myrtenal (**III**) and sesquiterpene (–)-caryophyllene (**IV**), widely spread in the nature and accessible optically active substances.

The chiral salicylaldimines are commonly prepared by reaction of optically active amines with substituted salicylaldehydes. Since at the use of myrtenal (**III**) the chiral precursor was aldehyde, in order to obtain Schiff base containing a phenol hydroxy group, we synthesized 2,4-di-*tert*-butyl-6-aminophenol (**V**). To this end we prepared from pyrocatechol (**VI**) 3,5-di-*tert*-butylbenzene-1,2-diol (**VII**) [13], whose oxidation with sodium nitrite led to the formation of 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (**VIII**) [14]. The reaction of compound **VIII** with aqueous ammonia followed by reduction [15] resulted in the desired aminophenol **V** in overall yield of all the three stages 60% (Scheme 1).

(–)-Myrtenal (**III**) reaction with aminophenol **V** in acetonitrile under an argon atmosphere led to the formation of chiral Schiff base **IX** in 91% yield. Another optically active Schiff base we obtained from myrtenal epoxide (**X**) and aminophenol **V** in 96% yield. Myrtenal epoxide (**X**) was prepared by oxidation of (–)-myrtenal (**III**) with hydrogen peroxide in the presence of NaOH in 74% yield (Scheme 2).

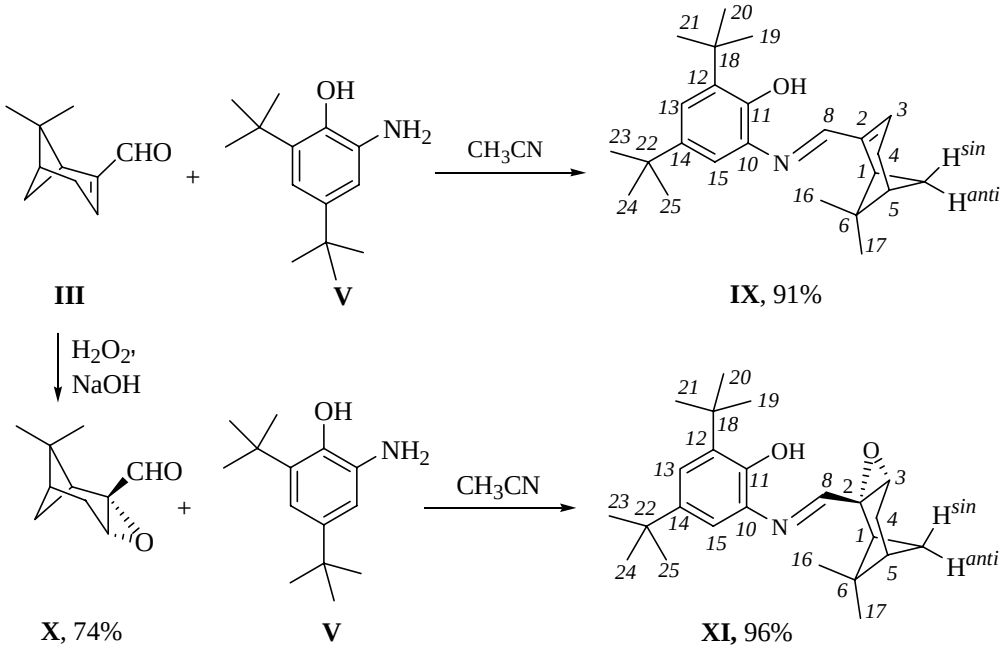
Compound **XI** proved to be unstable in air and within several days transformed into a complex mixture of substances. This transformation was considerably accelerated in the presence of chloroform. However under an argon atmosphere at –24°C aldimine **XI** can be stored for a long time.

Scheme 1.



VI **VII**, 98% **VIII**, 96% **V**, 64%

Scheme 2.



III **V** **IX**, 91%

X, 74% **V** **XI,** 96%

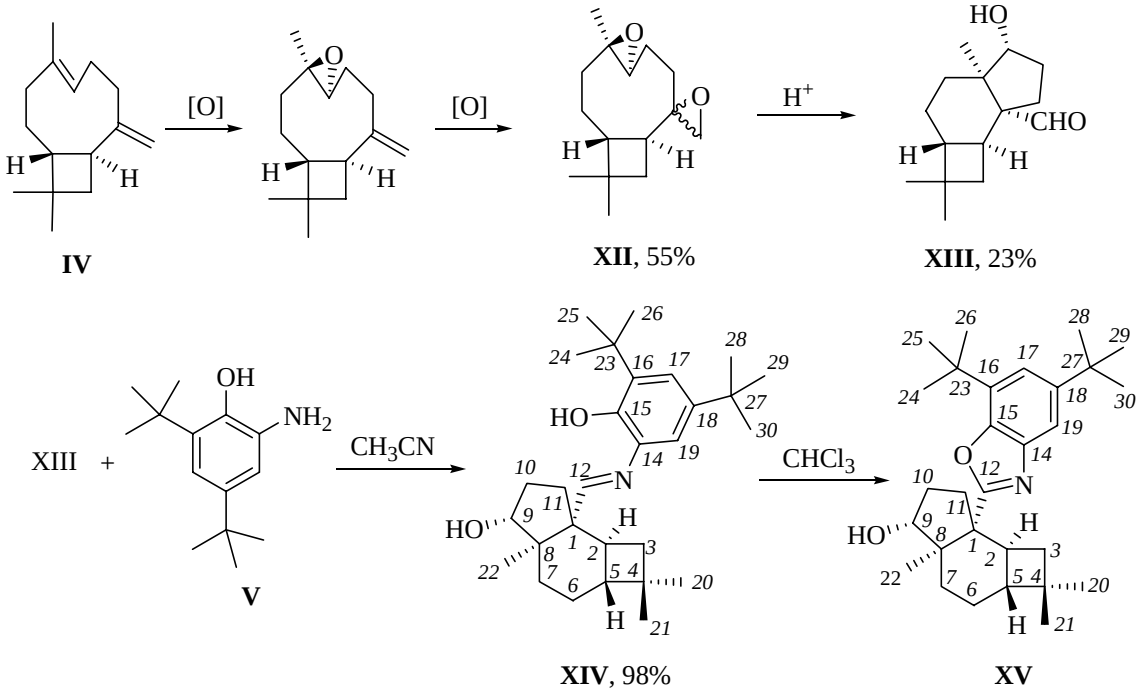
Another terpenoid chosen as initial chiral compound was widespread sesquiterpene caryophyllene (**IV**). We showed formerly that keeping caryophyllene diepoxide (**XII**) in the presence of H-β-zeolite led to the prevailing formation of hydroxyaldehyde **XIII** [16].

Compound **XIII** we obtained from caryophyllene diepoxide (**XII**) in keeping with procedure [16] in 23% yield; its high optical activity was proved by ^{1}H NMR spectroscopy using chiral shift reagent Eu(hfc)$_3$ (on adding Eu(hfc)$_3$ to compound **XIII** most proton signals in the ^{1}H NMR spectrum shifted without separation) (Scheme 3).

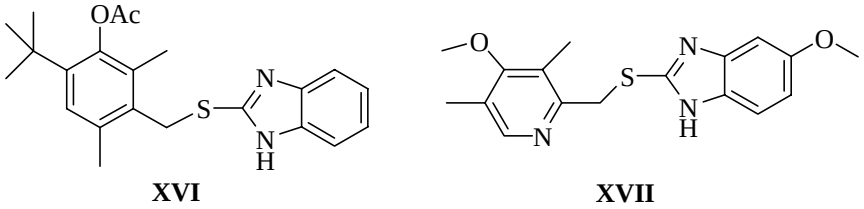
The reaction of hydroxyaldehyde **XIII** with aminophenol **V** in acetonitrile under an argon atmosphere gave rise to compound **XIV** in nearly quantitative yield. Thus we for the first time prepared from sesquiterpene caryophyllene (**IV**) a chiral Schiff base suitable for application as a ligand in metal complex catalysts. Compound **XIV** on storage in air at room temperature suffered slow oxidative cyclization into benzoxazole **XV**; the rate of conversion significantly increased in the presence of chloroform. It is known from published data that similar cyclization into benzoxazole derivatives was observed in reactions of *o*-aminophenols with aldehydes in the presence of various oxidizing systems {oxygen in the presence of activated carbon [17], Ag_2O [18], 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in DMF [19]}, and also at maintaining at 170°C a mixture of phosphorylated acetals with some *o*-aminophenols [20]. In our case the cyclization proceeded at room temperature without special catalysts: Apparently the air oxygen acted as oxidant, and chloroform, as promoter.

In order to test the possibility of using optically active Schiff bases **IX, XI**, and **XIV** in asymmetric sulfides oxidation catalyzed by vanadium acetylacetonate we selected for a substrate sulfide **XVI**, analog of compound **XVII**, the precursor of antiulcer drug esomeprazole [21], (*S*)-sulfoxide prepared from sulfide **XVII** (Scheme 4).

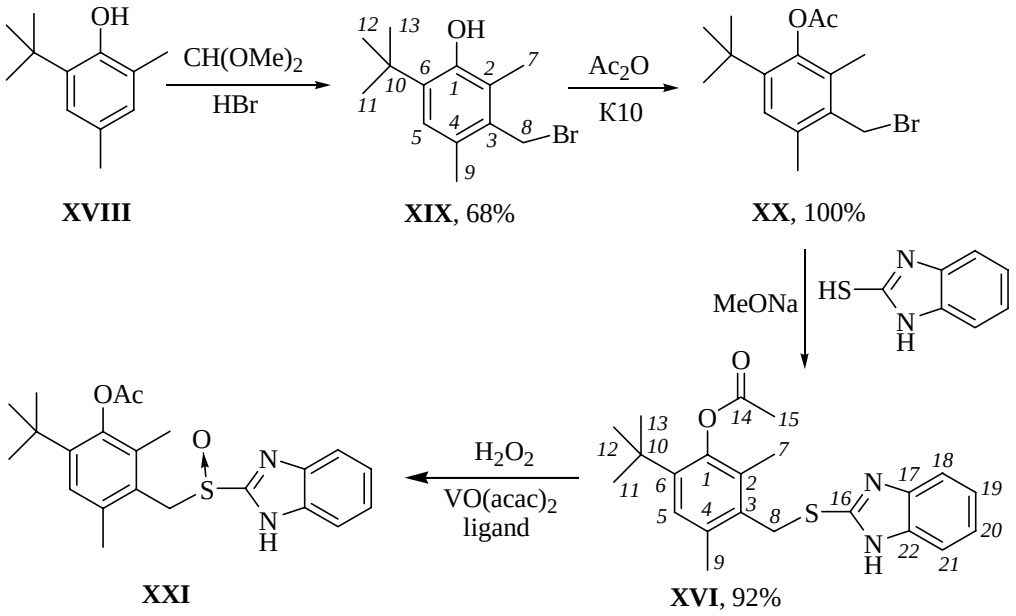
Scheme 3.



Scheme 4.



Scheme 5.



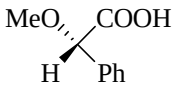
XVIII **XIX**, 68% **XX**, 100%

XXI **XVI**, 92%

Compound **XVI** was prepared from 6-*tert*-butyl-2,4-dimethylphenol **XVIII**. In the first stage by bromomethylation of compound **XVIII** in keeping with a modified procedure [22] we obtained 6-*tert*-butyl-3-bromomethyl-2,4-dimethylphenol (**XIX**) in 68% yield (Scheme 5).

Acylation of phenol **XIX** with acetic anhydride in the presence of nonactivated kaolin K10 by method [23] gave rise in quantitative yield to 6-*tert*-butyl-3-bromo-methyl-2,4-dimethylphenyl acetate (**XX**) that by reaction with 2-mercaptobenzimidazole in the presence of sodium methylate formed sulfide **XVI** in 92% yield.

Oxidation of sulfide **XVI** was performed with aqueous hydrogen peroxide in the presence of a complex obtained *in situ* of vanadium acetylacetonate with ligands **IX, XI, XIV**, or commercially available salicylaldimine **II**. The reaction progress was monitored by HPLC. Enantiomer excess was determined using ^{1}H NMR spectra registered in the presence of a chiral shift reagent, *S*-(+)-2-methoxy-2-phenylacetic acid (**XXII**), and also by comparison of the angles of optical rotation. The results of reactions are compiled in the table.



XXII

Asymmetric oxidation of sulfide **XVI** to sulfoxide **XXI**

Ligand	Yield, %	$[\alpha]_{580}^{20}$	Enantiomer excess, %
II	74	3.6	3
IX	69	1.5	1
XI	60	–33	21
XIV	95	7.1	5

As seen from the table, the application of ligand **II** was ineffective: The reaction product formed in a medium yield and of very low optical purity. The use of ligand **IX** also gave unsatisfactory results. The highest yield of the target sulfoxide **XXI** was obtained using the catalytic system with **XIV**, and the highest enantiomer excess was attained with compound **XI**. Note that on going from the catalytic system with compound **IX** to the system with epoxide **XI** not only sharply grew the optical purity of the sulfoxide obtained but also changed the sign of its optical rotation. The results of experiments show that the most promising for application as ligands are tridentate compounds **XI** and **XIV** with asymmetric centers in direct proximity to the complexing atoms.

We did not find in the literature mention of compounds **IX, XI, XIV–XVI**, and **XIX–XXI**. Their structure was established from ^{1}H, ^{13}C NMR, and high-resolution mass spectra. NMR spectra of compound **XXI** revealed that it was present in two forms in 1:1 ratio, apparently, due to slow proton exchange between the nitrogen atoms of the benzimidazole ring. On heating the solution to 35 and further to 45°C the corresponding signals of methyl groups, protons of aromatic rings, and of NH group coalesced into singlets; the signals in the ^{13}C NMR spec-

trum behaved similarly except the signals of aromatic C^{17}, C^{22}, C^{18}, and C^{21} which only suffered considerable broadening; the complete coalescence of these signals did not occur because apparently the temperature was not sufficiently high. The changes in the spectra are reversible: On cooling to 25°C the primary pattern of the spectra is recovered. The observed reversible changes in the spectra may be ascribed to the variations in the exchange rate.

The assignment of carbon signals in the aromatic part of compound **IX** was done using spectra LRJMD. On decoupling from the atom H^8 with a signal at 8.27 ppm in the downfield part of the LRJMD spectrum appeared singlets at 149.09 and 134.53 ppm and a doublet at 137.06 ppm that were assigned to atoms C^2, C^{10}, and C^3 respectively. Decoupling by turn from atoms H^{13} and H^{15} with signals at 7.15 and 7.05 ppm respectively made it possible to attribute all signals of aromatic carbons and signals of atoms C^{18} and C^{22}. The assignment of analogous signals in the spectrum of compound **XV** was confirmed by selective decoupling from protons of *tert*-butyl groups. The close values of the chemical shifts of signals of the corresponding aromatic carbon atoms and of *tert*-butyl groups permitted the assignment for compounds **IX, XI, XIV**, and **XV**.

Thus starting with widespread terpene compounds myrtenal and caryophyllene we synthesized three new chiral Schiff bases suitable for application as ligands in oxidation of sulfides into chiral sulfoxides catalyzed by vanadium ions.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-400 (operating frequencies 400.13 and 100.61 MHz respectively) from solutions of compounds in $CDCl_3$, in a mixture $CDCl_3$–CCl_4, ~1:1 v/v, in deuteroacetone, or DMSO-d_6. For internal reference were used signals of chloroform (δ_H 7.24, δ_C 76.90 ppm), deuteroacetone (δ_H 2.04, δ_C 29.80 ppm), or DMSO-d_6 (δ_H 2.50, δ_C 39.50 ppm). The structure of compounds obtained was established from analysis of ^1H NMR spectra involving also double resonance ^1H–^1H spectra, and also from analysis of ^{13}C NMR spectra using spectra with off-resonance decoupling from protons, two-dimensional correlation ^{13}C–^1H spectra on direct constants (COSY, $^1J_{C,H}$ 135 Hz), and one-dimensional correlation ^{13}C–^1H spectra on long range constants (LRJMD, $^nJ_{C,H}$ 10 Hz, n = 2, 3). High resolution mass spectra were measured on Finnigan MAT-8200 instrument, specific rotation $[\alpha]_{580}$ was determined on a spectrometer Polamat A from solutions in $CHCl_3$ of concentration c, g/100 ml of solvent.

The purity of initial compounds was checked and the reaction products were analyzed by HPLC on a Milikhrom A02 device (stationary phase ProntoSil-120-5-C18 AQ, eluent 90% aqueous MeOH with 0.1% of trifluoroacetic acid). Column chromatography was performed on silica gel (70–230 mesh, Merck).

6-Amino-2,4-di-*tert*-butylphenol (V). To a suspension of 2.75 g (25 mmol) of pyrocatechol (**VI**) in 7 ml (5.5 g, 74 mmol) of *tert*-butanol cooled by ice was added dropwise 2.5 ml of concn. H_2SO_4, and the mixture was stirred for 8 h at room temperature. Then a mixture of 25 ml of water and 1.2 ml of dioxane was added, the separated precipitate was filtered off, washed with water till neutral pH, and dried in air. We obtained 5.43 g (98%) of 3,5-di-*tert*-butylbenzene-1,2-diol (**VII**), the substance was recrystallized from hexane, mp 100–101°C. ^1H NMR spectrum of compound **VII** coincided with analogous spectrum published before [24].

To a suspension of 0.44 g (2 mmol) of compound **VII** in 1 ml of CH_3COOH was added by portions a solution of 0.28 g (4 mmol) of $NaNO_2$ in 1 ml of H_2O. The mixture was stirred for 1 h at room temperature, then diluted with water. The separated precipitate was filtered off, washed with water, and dried in air. We obtained 0.42 g (96%) of 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (**VIII**) of brick-red color, mp 114–115°C. ^1H NMR spectrum of compound **VIII** coincided with the spectrum previously published [25].

To a solution of 2.35 g (11 mmol) of compound **VIII** in 60 ml of methanol was added 20 ml of concn. NH_4OH, and the mixture was stirred for 10 min. The red solution turned yellow, $NaBH_4$ was added by portions till the solution became completely colorless (~0.4 g). The separated precipitate was filtered off, washed with a mixture methanol–aqueous ammonia, 3:1 v/v, dried, and recrystallized from a mixture chloroform–hexane. Yield 1.5 g (64%), mp 164–165°C. ^{13}C NMR spectrum of compound **V** coincided with the spectrum previously published [26].

4,6-Di-*tert*-butyl-2-{(6,6-dimethylbicyclo-[3.1.1]-hept-2-en-2-yl)methyleneamino}phenol (IX). To a solution of 0.044 g (0.2 mmol) of compound **V** in 4.5 ml of acetonitrile was added at stirring under an argon atmosphere 0.035 g (0.23 mmol) of (–)-myrtenal (**III**) {Aldrich, 98%, $[\alpha]_D^{22}$ –15° (oil); publ.: $[\alpha]_D^{20}$ –15.8° (oil)

[27]} in 1.3 ml of acetonitrile, and the mixture was stirred at 28°C for 4 h. The solvent was distilled off. Yield 0.064 g (91%), mp 141–142°C (from acetonitrile), $[\alpha]_D^{27}$ + 1.7° (*c* 2.6, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 0.84 s (3H, $C^{16}H_3$), 1.18 d (1H, H^{7anti}, $J_{7anti,7syn}$ 9.5), 1.32 s (9H, $C^{23}H_3$, $C^{24}H_3$, $C^{25}H_3$), 1.40 s (3H, $C^{17}H_3$), 1.42 s (9H, $C^{19}H_3$, $C^{20}H_3$, $C^{21}H_3$), 2.22 m (1H, H^5, $J_{5,7syn}$ 5.5, $J_{5,1}$ 5.5, $J_{5,4}$ 3, $J_{5,3}$ 1.2), 2.53 d.d.d (1H, H^{7syn}, *J* 9.5, $J_{7syn,1}$ 5.5, $J_{7syn,5}$ 5.5), 2.46–2.62 m (2H, H^4), 3.20 d.d.d (1H, H^1, $J_{1,5}$ 5.5, $J_{1,7sin}$ 5.5, $J_{1,3}$ 1.2), 6.29 m (1H, H^3, $J_{3,4}$ 3.5, $J_{3,1}$ 1.2, $J_{3,5}$ 1.2), 7.05 d (1H, H^{15}, $J_{15,13}$ 2.2), 7.15 d (1H, H^{13}, *J* 2.2), 8.27 s (1H, H^8). ^{13}C NMR spectrum, δ, ppm: 40.02 d (C^1), 149.09 s (C^2), 137.06 d (C^3), 32.82 t (C^4), 40.94 d (C^5), 37.77 s (C^6), 31.30 t (C^7), 155.72 d (C^8), 134.53 s (C^{10}), 148.68 s (C^{11}), 134.75 s (C^{12}), 122.52 d (C^{13}), 140.82 s (C^{14}), 109.58 d (C^{15}), 21.07 q (C^{16}), 26.15 q (C^{17}), 34.55 s (C^{18}), 29.50 q (C^{19}–C^{21}), 34.87 s (C^{22}), 31.76 q (C^{23}–C^{25}). Found *M* 353.27221. $C_{24}H_{35}NO$. Calculated *M* 353.27185.

4,6-Di-*tert*-butyl-2-{(7,7-dimethyl-3-oxatricyclo-[4.1.1.0^{2,4}]oct-2-yl)methyleneamino}phenol (XI). To a solution of 3 g (20 mmol) of (–)-myrtenal (**III**) in 30 ml of methanol at 12–15°C was added 6 ml of 30% H_2O_2, then 1.5 ml of 6 N aqueous NaOH, and the mixture was stirred for 2 h, maintaining the temperature in the indicated range. The reaction mixture was poured into water, the product was extracted into ethyl ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and the solvent was distilled off. We obtained 2.47 g (74%) of myrtenal epoxide (**X**), $[\alpha]_{580}^{20}$ –114.5° (*c* 2.3, $CHCl_3$) {publ.: $[\alpha]_D^{20}$ –89.4° ($CHCl_3$) [28]}. ^1H NMR spectrum of compound **X** coincided with the corresponding spectrum previously published [29].

To a solution of 0.023 g (0.1 mmol) of compound **V** in 2 ml of acetonitrile was added at 25°C while stirring under an argon atmosphere a solution of 0.022 g (0.13 mmol) of myrtenal epoxide (**X**) in 0.8 ml of acetonitrile. The stirring was continued for 0.5 h, the solvent was distilled off. We obtained 0.037 g (96%) of compound **XI**, $[\alpha]_{580}^{27}$ +2.6° (*c* 2.1, CH_3CN). ^1H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 0.91 s (3H, $C^{16}H_3$), 1.28 s (9H, $C^{23}H_3$, $C^{24}H_3$, $C^{25}H_3$), 1.40 s (3H, $C^{17}H_3$), 1.41 s (9H, $C^{19}H_3$, $C^{20}H_3$, $C^{21}H_3$), 1.70 d (1H, H^{7anti}, $J_{7anti,7syn}$ 10), 1.81 m (1H, H^5, $J_{5,7syn}$ 5.5, $J_{5,1}$ 5.5, $J_{5,4}$ 3, $J_{5,3}$ 2), 2.10 m (2H, H^4), 2.17 d.d.d (1H, H^{7syn}, $J_{7syn,7anti}$ 10, $J_{7syn,1}$ 5.5, $J_{7syn,5}$ 5.5), 2.94 d.d (1H, H^1, $J_{1,5}$ 5.5, $J_{1,7syn}$ 5.5), 3.63 m (1H, H^3, *J* 2–3), 7.23 d and 7.25 d (2H, H^{13}, H^{15}, *J* 2.2), 7.69 br.s (1H, OH), 7.88 s (1H, H^8). ^{13}C NMR spectrum, δ, ppm: 40.26 d (C^1), 63.47 C (C^2), 56.50 d (C^3), 27.89 t (C^4), 40.87 d (C^5), 40.95 s (C^6), 26.04 t (C^7), 162.43 d (C^8), 135.63 s (C^{10}), 149.05 s (C^{11}), 135.36 s (C^{12}), 123.82 d (C^{13}), 142.20 s (C^{14}), 111.80 d (C^{15}), 20.76 q (C^{16}), 26.72 q (C^{17}), 35.12 C (C^{18}), 29.80 q (C^{19}–C^{21}), 35.46 s (C^{22}), 31.87 q (C^{23}–C^{25}). Found *M* 369.26682. $C_{24}H_{35}NO_2$. Calculated *M* 369.26676.

(2a*R*,4a*R*,5*R*,7a*R*,7b*S*)-[7a-(3,5-Di-*tert*-butyl-2-hydroxyphenylimino)methyl]-2,2,4a-trimethyldecahydro-1-cyclobuta[*e*]indene-5-ol (XIV). (2a*R*,4a*R*,5*R*,7a*R*,7b*S*)-5-Hydroxy-2,2,4a-trimethyldecahydro-1*H*-cyclobuta[*e*]indene-7a-carbaldehyde (**XIII**) was obtained from caryophyllene diepoxides (**XII**) in keeping with procedure [16] in 23% yield, $[\alpha]_{580}^{20}$ –5.3° (*c* 3.7, $CHCl_3$). To a solution of 0.032 g (0.14 mmol) of compound **V** in 4.5 ml of acetonitrile was added at 28°C while stirring under an argon atmosphere a solution of 0.040 g (0.16 mmol) of aldehyde **XIII** in 1.3 ml of acetonitrile, and the stirring was continued for 4 h. The solution was dried with Na_2SO_4, then filtered, and the solvent was distilled off. Yield 0.063 g, $[\alpha]_{580}^{20}$ +33.2° (*c* 2.35, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 1.09 s (3H, $C^{21}H_3$), 1.10 s (3H, $C^{22}H_3$), 1.18 s (3H, $C^{20}H_3$), 1.22-1.50 m (5H, H^3, 2H^6, 2H^7), 1.29 s (9H, $C^{28}H_3$, $C^{29}H_3$, $C^{30}H_3$), 1.41 s (9H, $C^{24}H_3$, $C^{25}H_3$, $C^{26}H_3$), 1.61 m (1H, H^5), 1.73 d.d (1H, H^{32}, $J_{32,3}$ 10, $J_{32,2}$ 7), 1.89 m (1H, H^{10}), 2.11 m (2H, H^{11}), 2.40 m (1H, H^2), 2.43 m (1H, H^{102}), 3.77 d.d (1H, H^9, $J_{9,102}$ 6.5, $J_{9,10}$ 1.5), 6.84 d (1H, H^{19}, $J_{19,17}$ 2.2), 7.12 d (1H, H^{17}, *J* 2.2), 8.20 c (H^{12}). ^{13}C NMR spectrum, δ, ppm: 55.71 s (C^1), 37.54 d (C^2), 38.70 t (C^3), 38.70 s (C^4), 46.28 d (C^5), 23.24 t (C^6), 37.00 t (C^7), 52.96 s (C^8), 82.11 d (C^9), 32.88 t (C^{10}), 26.47 t (C^{11}), 170.74 d (C^{12}), 135.59 s (C^{14}), 147.50 s (C^{15}), 134.74 s (C^{16}), 121.95 d (C^{17}), 141.05 s (C^{18}), 110.61 d (C^{19}), 21.01 q (C^{20}), 30.39 q (C^{21}), 17.13 q (C^{22}), 34.44 s (C^{23}), 29.57 q (C^{24}–C^{26}), 34.87 s (C^{27}), 31.75 q (C^{28}–C^{30}). Found *M* 439.34822. $C_{29}H_{45}NO_2$. Calculated *M* 439.35624.

On keeping in chloroform solution for 48 h compound **XIV** virtually completely converted into **(2a*R*,4a*R*,5*R*,7a*R*,7b*S*)-7a-(5,7-di-*tert*-butylbenzo[*d*]-oxazol-2-yl)-2,2,4a-trimethyldecahydro-1*H*-cyclobuta[*e*]inden-5-ol (XV)**, $[\alpha]_{580}^{20}$ +37.0° (*c* 0.7, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 0.99 s (3H, $C^{22}H_3$), 1.11 s (3H, $C^{21}H_3$), 1.20 s (3H, $C^{20}H_3$), 1.23–1.52 m (4H, 2H^6, 2H^7), 1.35 s (9H, $C^{28}H_3$, $C^{29}H_3$, $C^{30}H_3$), 1.46 s (9H, $C^{24}H_3$, $C^{25}H_3$, $C^{26}H_3$), 1.52 d.d (1H, H^3, $J_{3,32}$ 10, $J_{3,2}$ 10), 1.68 m (1H, H^5), 1.92 d.d (1H, H^{32}, $J_{32,3}$ 10, $J_{32,2}$ 7), 2.05 d.d.d (1H, H^{11}, $J_{11,112}$ 10, $J_{11,10}$ 10, $J_{11,102}$ 3), 2.11 m (1H, H^{10}), 2.31 m (1H, H^{112}),

2.58 m (1H, H^{102}), 2.61 m (1H, H^2), 3.61 br.d (1H, H^9, $J_{9,102}$ 7), 7.18 d (1H, H^{17}, $J_{17,19}$ 2), 7.46 d (1H, H^{19}, J 2). ^{13}C NMR spectrum, δ, ppm: 53.12 s (C^1), 37.49 d (C^2), 39.39 t (C^3), 38.39 s (C^4), 46.03 d (C^5), 23.42 t (C^6), 37.30 t (C^7), 52.43 s (C^8), 82.46 d (C^9), 34.12 t (C^{10}), 29.99 t (C^{11}), 173.13 s (C^{12}), 140.53 s (C^{14}), 146.02 s (C^{15}), 133.38 s (C^{16}), 118.66 d (C^{17}), 147.36 s (C^{18}), 113.76 d (C^{19}), 20.93 q (C^{20}), 30.32 q (C^{21}), 17.51 q (C^{22}), 34.30 s (C^{23}), 29.91 q (3C, C^{24}–C^{26}), 35.06 s (C^{27}), 31.94 q (3C, C^{28}–C^{30}). Found *M* 437.33213. $C_{29}H_{43}NO_2$. Calculated *M* 437.34059.

3-{(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)methyl}-6-*tert*-butyl-2,4-dimethylphenyl acetate (XVI). 3-(Bromomethyl)-6-*tert*-butyl-2,4-dimethylphenol (**XIX**) was obtained in 68% yield by bromomethylation of 2-*tert*-butyl-4,6-dimethylphenol (**XVIII**) with methylal in the presence of HBr in keeping with a modified procedure [22]. mp 76–77°C. ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 1.43 s (9H, $C^{11}H_3$, $C^{12}H_3$, $C^{13}H_3$), 2.28 s (3H, C^7H_3), 2.37 s (3H, C^9H_3), 4.56 s (2H, H^8), 4.75 s (1H, OH), 6.98 s (1H, H^5). ^{13}C NMR spectrum, δ, ppm: 150.81 s (C^1), 122.95 s (C^2), 132.10 s (C^3), 128.58 s (C^4), 126.40 d (C^5), 136.29 s (C^6), 11.29 q (C^7), 29.88 t (C^8), 18.97 q (C^9), 34.26 s (C^{10}), 29.67 q (3C, C^{11}–C^{13}). The assignment of carbon signals belonging to the aromatic part of compound **XIX** was carried out with the help of LRJMD spectra. Found *M* 270.06005. $C_{13}H_{19}BrO$. Calculated *M* 270.06197.

6-*tert*-Butyl-3-bromomethyl-2,4-dimethyl-phenyl acetate (XX). To a solution of 8.00 g (30 mmol) of compound **XIX** in 40 ml of CH_2Cl_2 was added at stirring 6 g of clay kaolin K10 (Fluka) and 6.5 ml (6.02 g, 59 mmol) of acetic anhydride. The solution was heated at reflux with stirring for 4 h. The solvent was distilled off, the residue was diluted with 100 ml of ethyl ether and thoroughly washed with water. The ether solution was dried with $MgSO_4$, the solvent was distilled off. Yield 9.23 g (100%), yellow oily substance solidifying at standing, mp 41°C. ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 1.33 s (9H, $C^{11}H_3$, $C^{12}H_3$, $C^{13}H_3$), 2.12 s (3H, C^7H_3), 2.34 s (3H, $COCH_3$), 2.40 s (3H, C^9H_3), 4.50 m (2H, H^8), 7.05 s (1H, H^5). ^{13}C NMR spectrum, δ, ppm: 146.36 s (C^1), 130.76 s (C^2), 132.94 s (C^3), 134.38 s (C^4), 126.86 d (C^5), 141.34 s (C^6), 12.62 q (C^7), 29.08 t (C^8), 19.40 q (C^9), 34.44 s (C^{10}), 30.37 q (3C, C^{11}–C^{13}), 168.46 s ($\underline{C}OCH_3$), 21.20 q ($CO\underline{C}H_3$). Found *M* 312.07043. $C_{15}H_{21}BrO_2$. Calculated *M* 312.07253.

To a solution of 4.16 g (13.3 mmol) of compound **XX** and 2.00 g (13.3 mmol) of 2-mercaptobenzimidazole in 20 ml of methanol was added dropwise at stirring a solution of sodium methylate in methanol prepared from 0.31 g (13.5 mmol) of sodium and 12 ml of methanol. After several minutes white precipitate started to form. The suspension was stirred for 2.5 h at room temperature. The precipitate was filtered off, washed on the filter with 40 ml of 50% aqueous methanol, 40 ml of 25% aqueous methanol, and 40 ml of water, and dried in a vacuum. We obtained 4.68 g (92%) of compound **XVI**, mp 219°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 s (9H, $C^{11}H_3$, $C^{12}H_3$, $C^{13}H_3$), 2.08 s (3H, C^7H_3), 2.33 s (3H, $C^{15}H_3$), 2.37 s (3H, C^9H_3), 4.57 m (2H, H^8), 7.09 s (1H, H^5), 7.14 m (2H, H^{19}, H^{20}), 7.47 m (2H, H^{18}, H^{21}). ^{13}C NMR spectrum, δ, ppm: 146.24 s (C^1), 130.78 s (C^2), 131.55 s (C^3), 134.44 s (C^4), 126.67 d (C^5), 140.36 s (C^6), 12.93 q (C^7), 31.47 t (C^8), 19.48 q (C^9), 34.20 s (C^{10}), 30.31 q (3C, C^{11}–C^{13}), 169.15 s (C^{14}), 21.13 q (C^{15}), 149.89 s (C^{16}), 139.61 s (C^{17}, C^{22}), 114.05 d (C^{18}, C^{21}), 121.72 d (C^{19}, C^{20}). In the ^{13}C NMR spectrum the signals at 139.61 and 114.05 ppm are strongly broadened presumably due to a slow proton exchange between nitrogen atoms of benzimidazole ring. On heating to 30 and then to 45°C the signals in the spectra recorded at these temperatures contain these signals in somewhat narrower form. In the ^1H NMR spectrum the signals of two H^8 protons proved to be sensitive to the temperature, and at 45°C these signals became one singlet. At recording the ^1H NMR spectrum in a mixture $CDCl_3$–CCl_4 at 25°C the spectral pattern slightly changed apparently due to the slower exchange. ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 1.29 s (9H, $C^{11}H_3$, $C^{12}H_3$, $C^{13}H_3$), 2.12 s (3H, C^7H_3), 2.25 s (3H, C^9H_3), 2.35 s (3H, $C^{15}H_3$), 4.39 br.d (1H, H^8, $J_{8,82}$ 12) and 4.54 br.d (1H, H^{82}, J 12), *AB* system, 6.90 s (1H, H^5), 7.14 br.s and 7.15 br.s (2H, H^{19}, H^{20}), 7.65 br.s and 9.35 br.s (2H, H^{18}, H^{21}). In the ^{13}C NMR spectrum recorded in the mixture $CDCl_3$–CCl_4 the signals from atoms C^{17}, C^{18}, C^{21}, and C^{22} were not observed because of great width of the signals; the chemical shifts of the other peaks were close to the values given for the spectrum in DMSO-d_6. Found *M* 382.18917. $C_{22}H_{26}N_2O_2S$. Calculated *M* 382.17149.

Asymmetric oxidation of 3-{(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)methyl}-6-*tert*-butyl-2,4-dimethylphenyl acetate (XVI). *a*. A mixture of 1 mg (4 μmol) of vanadium acetylacetonate, 2 mg (6 μmol) of (*S*)-(–)-2-(3,5-di-*tert*-butylsalicylideneamino)-3,3-dimethyl-1-butanol (**II**) (Aldrich), and 1 ml of CH_2Cl_2 was stirred till complete dissolution of components (~ 30 min). To the solution obtained was added at stirring 200 mg (0.52 mmol) of compound **XVI** in 4 ml of CH_2Cl_2, and

60 μl (0.58 mmol) of 33% H_2O_2 was added within 30 min in three portions 20 μl each. The reaction mixture was stirred at room temperature for 5.5 h (HPLC monitoring), twice washed with water, and the washings were extracted with CH_2Cl_2. The combined organic solutions were dried with $MgSO_4$, and the solvent was distilled off. The yellow residue (0.234 g) was recrystallized from 2 ml of ethanol. Yield 155 mg (74%), $[\alpha]_5^{20}{}_{80}$ +3.6° (*C* 1.1, acetone); enantiomer excess 3% according to ^{1}H NMR spectrum with a chiral shift reagent. **XXI,** mp 168°C. ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 1.33 s (9H, $C^{11}H_3$, $C^{12}H_3$, $C^{13}H_3$), 2.10 br.s (3H, C^7H_3), 2.28 br.s and 2.30 br.s (3H, $C^{15}H_3$), 2.38 br.s and 2.39 br.s (3H, C^9H_3), 4.69 br.s (2H, $2H^8$), 7.07 br.s and 7.09 br.s (1H, H^5), 7.27 m (2H, H^{19}, H^{20}), 7.38 br.s and 7.76 br.s (2H, H^{18}, H^{21}), 12.08 br.s and 12.14 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 146.72 s (C^1), 125.94 s and 126.19 s (C^2), 131.89 s and 132.42 s (C^3), 135.46 s and 136.29 s (C^4), 127.25 d (C^5), 141.68 C (C^6), 14.00 q and 14.18 q (C^7), 57.07 t and 57.22 t (C^8), 20.86 q and 21.03 q (C^9), 34.55 s (C^{10}), 30.95 q (3C, C^{11}–C^{13}), 168.55 s (C^{14}), 21.19 q (C^{15}), 152.85 s (C^{16}), 134.47 s and 144.06 s (C^{17}, C^{22}), 112.40 d and 120.15 d (C^{18}, C^{21}), 123.02 d and 124.19 d (C^{19}, C^{20}). Found *M* 398.16737. $C_{22}H_{26}N_2O_3S$. Calculated *M* 398.16640.

b. By oxidation of 200 mg (0.52 mmol) of compound **XVI** with 60 μl (0.58 mmol) of 33% H_2O_2 in the presence of 1 mg (4 μmol) of vanadium acetylacetonate and 3 mg (8 μmol) of compound **IX** in 4 h we obtained 143 mg (69%) of compoundÿ **XXI**, $[\alpha]_{580}^{20}$+1.5° (*c* 1.2, acetone), enantiomer excess 1%.

c. By oxidation of 200 mg (0.52 mmol) of compound **XVI** with 60 μl (0.58 mmol) of 33% H_2O_2 in the presence of 1 mg (4 μmol) of vanadium acetylacetonate and 3 mg (8 μmol) of compound **XI** in 4 h 45 min we obtained 124 mg (60%) of compoundÿ **XXI**, $[\alpha]_{580}^{20}$ –33° (*c* 1.5, acetone), enantiomer excess 21%.

d. By oxidation of 200 mg (0.52 mmol) of compound **XVI** with 60 μl (0.58 mmol) of 33% H_2O_2 in the presence of 1 mg (4 μmol) of vanadium acetylacetonate and 3 mg (7 μmol) of compound **XIV** in 4 h we obtained 197 mg (95%) of compound **XXI**, $[\alpha]_{580}^{20}$ +7.1° (*c* 1.4, acetone), enantiomer excess 5%.

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