Polyalkoxybenzenes from plant sources
2.* Synthesis of isoxazoline analogs of combretastatin from natural allyl(methylenedioxy)methoxybenzenes

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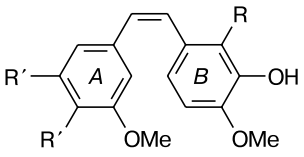
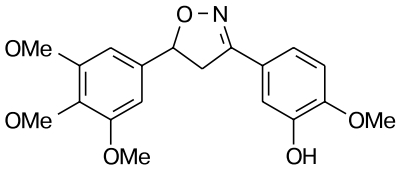
A series of analogs of the natural mitostatic agent combretastatin were synthesized by the reaction of nitrile oxides with natural allylbenzenes, such as myristicin, apiol, and dillapiol. The 1,3-dipolar cycloaddition reactions in allylic systems proceed regiospecifically. The reactions with *trans* isomers of propenylbenzenes, *viz.*, isomyristicin, isoapiol, and isodillapiol, as dipolarophiles produce regioisomers.

Key words: isoxazolines, nitrile oxides, 1,3-dipolar cycloaddition, myristicin, apiol, dillapiol.

Combretastatins **1** (CA-1, CA-2, and CA-4), which are natural antimitotic compounds isolated from the bark of the South African bush willow tree (*Combretum caffrum*),[2], are potent tubulin polymerization inhibitors bound to the colchicine site.[3] The O-phosphorylated derivative of combretastatin CA-4 is currently under clinical trials as an antitumor drug.[4]



1



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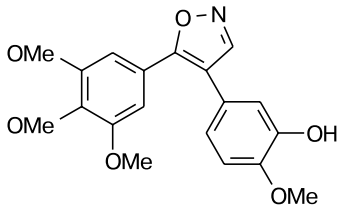


3

R = OH, R′ = Me (CA-1)
R = H, R′R′ = —CH_2— (CA-2)
R = H, R′ = Me (CA-4)

To search for more effective combretastatin derivatives, a series of their analogs have been synthesized in recent years, and compounds superior to natural combretastatins in activity were found.[5]

The affinity of combretastatin for tubulin is determined by the presence of two polyoxybenzene rings bridged by an appropriate linker, which provides the biologically active spatial configuration of the molecule and forces the rings to be located at a strictly specified distance from each other necessary for the interaction with the colchicine site of tubulin.[5]

To prevent isomerization of the active *cis* form of combretastatin to the inactive *trans* form taking place in living organisms, *i.e.*, to fix the relative arrangement of the rings, many researchers used[6—9] heterocycles (most often, five-membered heterocycles), in particular, isoxazolines (for example, **2**) and isoxazoles **3**, as linkers. 3,5-Diaryl derivatives were found to be less active than the 4,5-isomers.

The introduction of various substituents (OH, NH_2, or F) into the ring *B* was documented.[5] However, studies on modifcations of the ring *A* are lacking due, apparently, to low accessibility of polyalkoxybenzenes containing more than three alkoxy groups.

In the only study,[6] the modification of the ring *A* by introducing the 2-NH_2 group was demonstrated to give a combretastatin analog with the same activity level. We expected that the replacement of the NH_2 group by the bioisosteric methoxy group would lead to the formation of highly active combretastatin analogs.

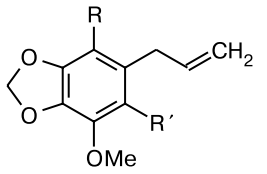
The aim of the present study was to synthesize new combretastatin analogs containing a larger number of methoxy groups in the ring *A* starting from natural allylpolyalkoxybenzenes **4**—**7** and to investigate their anti-

* For Part 1, see Ref. 1.

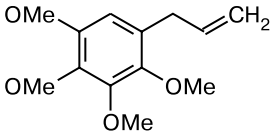
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2375—2380, December, 2007.

1066-5285/07/5612-2460

proliferative activity. The replacement of the double bond by the isoxazoline or isoxazole fragments seemed to be most reasonable, because these analogs were demonstrated to be most active among known azolocombretastatins.[6—9] According to our unpublished data, the starting polymethoxybenzenes isoapiol and isodillapiol exhibit the antiproliferative activity, *i.e.*, arrest the cell division of sea urchin embryo at concentrations of 5—20 μmol L^{-1}.



4—6



7

R = R′ = H (**4**, myristicin)
R = OMe, R′ = H (**5**, apiol)
R = H, R′ = OMe (**6**, dillapiol)

We found[1] that allylpolymethoxybenzenes **4—7** are present at high concentrations in commercial essence oils from seeds of certain varieties of dill and parsley and developed procedures for the isolation of these compounds at the kilogram scale.

Results and Discussion

Isoxazolines were synthesized by the 1,3-dipolar cycloaddition reaction of nitrile oxides with unsaturated compounds[10] (myristicin, apiol, dillapiol, and the *trans* isomers of the corresponding isomeric propenylbenzenes) in the temperature range of 0—20 °C. Unstable nitrile oxides were generated from hydroximoyl chlorides using triethylamine as a base. In addition to the target isoxazolines, the corresponding furoxans were obtained as by-products in moderate yields. The latter compounds were removed by crystallization. To decrease the amount of furoxans, a small excess of an unsaturated compound and dilute solutions of the reagents were used.

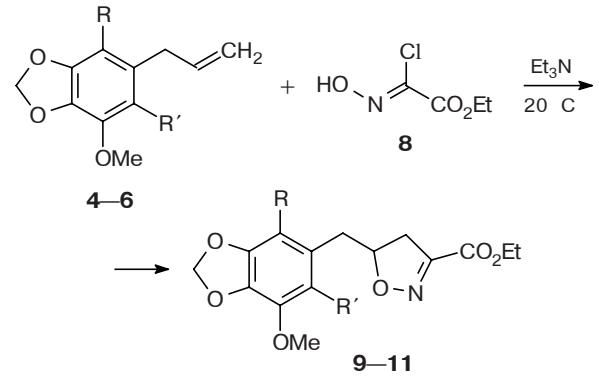
Ethoxycarbonylformonitrile oxide (hydroximoyl chloride **8** [10,11] is a precursor of this compound) served as the model 1,3-dipole (Scheme 1).

The yields of crystalline isoxazolines **9—11** were 60—70%; the purity was higher than 95%. In addition, small amounts of the regioisomers were produces. The latter were detected by NMR spectroscopy.

The reaction of compounds **4—6** with 4-methoxybenzonitrile oxide (the corresponding hydroximoyl chloride **12** is a precursor of the latter compound) (Scheme 2) was carried out at 0—5 °C. The yields of isoxazolines **13—15** were 65—80%.

Closer analogs of combretastatin in which the aromatic moiety of the fragment *B* is directly bound to isoxazoline were synthesized from the readily available *trans* isomers isomyristicin **16**, isoapiol **17**, and isodillapiol **18**

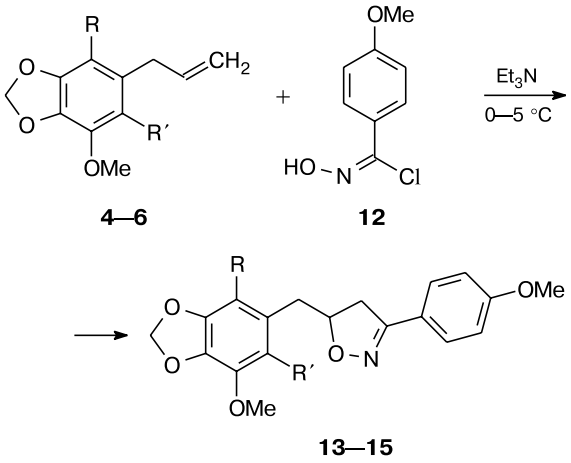
Scheme 1



4—6 **8** **9—11**

4, **9**: R = R′ = H
5, **10**: R = OMe, R′ = H
6, **11**: R = H, R′ = OMe

Scheme 2



4—6 **12** **13—15**

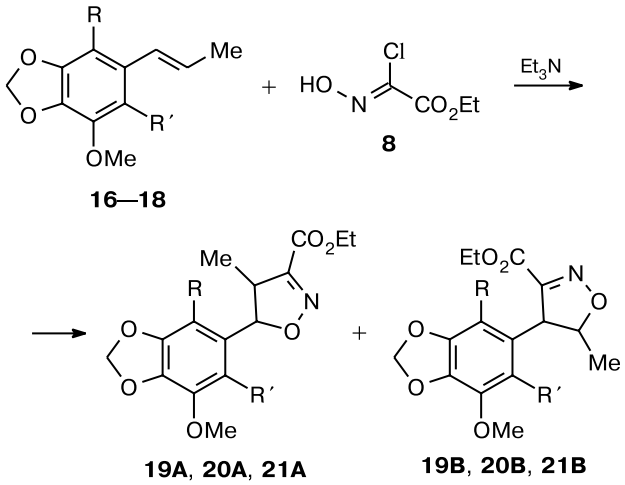
4, **13**: R = R′ = H
5, **14**: R = OMe, R′ = H
6, **15**: R = H, R′ = OMe

(generated from compounds **4—6**). The yields of the corresponding isoxazolines **19A**, **20A**, and **21A** in the reactions with hydroximoyl chloride **8** are somewhat lower due to the formation of regioisomeric products **19B**, **20B**, and **21B** in noticeable amounts (Scheme 3).

We failed to isolate the minor regioisomers of isoxazolines in the pure form, but the presence of these compounds in the reaction mixture was unambiguously confirmed by NMR spectroscopy based on the ratio of the signals for H(5) of the isoxazoline ring. The formation of regioisomers is associated with the less pronounced polarization of the double bond in compounds **16—18** (compared to the allylic system of myristicin, apiol, and dillapiol).

The cycloaddition of benzonitrile oxide to isoapiol (**17**) has been studied earlier.[12] The reaction gave the target product in low yield. The formation of regioisomers was not observed. However, we obtained compounds **22A**+**22B**, **23A**+**23B**, and **24A**+**24B** in the reactions with 4-methoxybenzonitrile oxide as the 1,3-dipolarophile (Scheme 4).

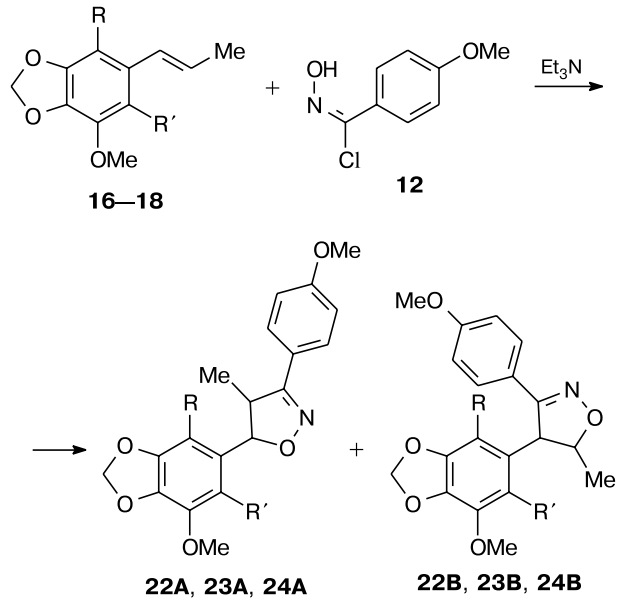
Scheme 3



16, **19A**, **19B**: R = R′ = H
17, **20A**, **20B**: R = OMe, R′ = H
18, **21A**, **21B**: R = H, R′ = OMe

Isoxazoline	Yield (%)	Ratio **A** : **B**
19A	41.0	2.3 : 1.0
20A	39.0	3.1 : 1.0
21A	40.0	13.1 : 1.0

Scheme 4



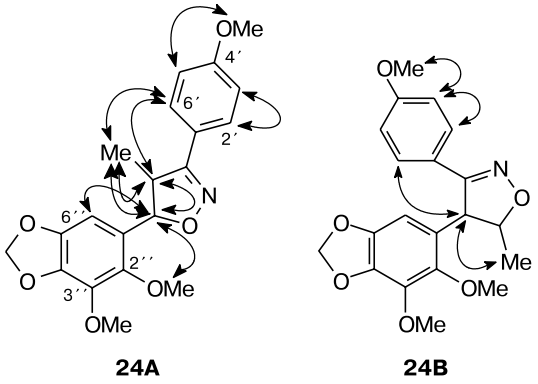
16, **22A**, **22B**: R = R′ = H
17, **23A**, **23B**: R = OMe, R′ = H
18, **24A**, **24B**: R = H, R′ = OMe

Isoxazoline	Yield of regio-isomers (%)	Ratio **A** : **B**
22A+**22B**	58.0	3.7 : 1.0
23A+**23B**	67.3 (47.5*)	4.0 : 1.0
24A+**24B**	68.5	4.2 : 1.0

* The yield of isoxazoline **23A** after crystallization.

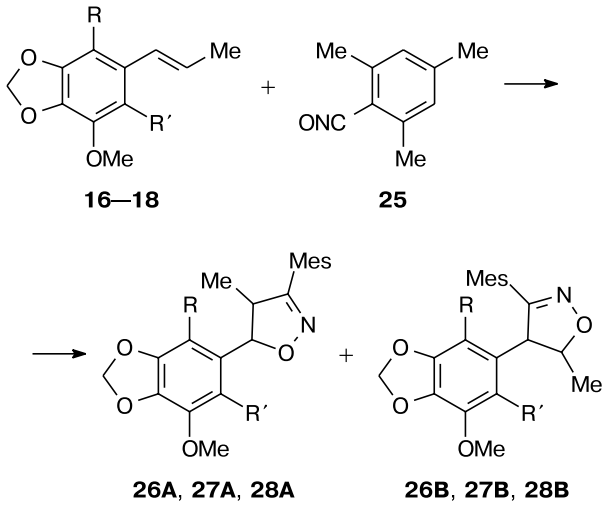
Only isoxazoline **23A** was isolated in the individual state. Isoxazolines **22A**+**22B** and **24A**+**24B** were obtained as chromatographically inseparable mixtures. The ratios of the regioisomers were determined by NMR spectroscopy. The structures of compounds **24A** and **24B** were confirmed by the NOESY spectrum of the mixture of these compounds. The observed contacts are presented in Scheme 5.

Scheme 5



Evidently, sterically hindered nitrile oxides should behave differently in this reaction. We chose stable nitrile oxide of the aromatic series, *viz.*, 2,4,6-trimethylbenzonitrile oxide **25**, as an example (Scheme 6).

Scheme 6



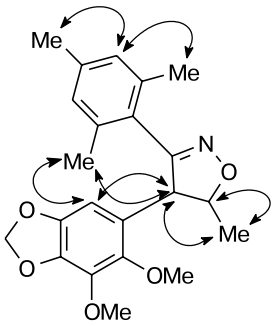
16: R = R′ = H
17: R = OMe, R′ = H
18: R = H, R′ = OMe

Isoxazoline	Yield of regio-isomers (%)	Ratio **A** : **B**
26A+**26B**	81.2	1.0 : 1.9
27A+**27B**	76.0	1.0 : 1.8
28A+**28B**	83.4 (39.5*)	1.0 : 1.4

* The yield of isoxazoline **28B** after crystallization.

In this case, the inverse ratio of the regioisomers was observed. 5-Methylisoxazolines **26B**, **27B**, and **28B** were the major products. This is apparently associated with considerable steric hindrance.[13] We succeeded in isolating isomer **28B** in moderate yield by chromatography and fractional crystallization in the reaction with isodillapiol **18**. In other cases, the reactions gave chromatographically inseparable mixtures of regioisomers. The structure of compound **28B** was confirmed by the observed contacts in the NOESY spectrum (Scheme 7).

Scheme 7



28B

To summarize, we demonstrated that the double bond in biologically active natural compounds, such as myristicin, apiol, and dillapiol, as well as in their isomers, is rather active in the 1,3-dipolar cycloaddition reactions with various nitrile oxides. According to the preliminary data, compounds **9**—**11**, **14**, **15**, and **21A** exert an effect on the cell division of sea urchin embryo.[14]

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were obtained on a Finningan MAT in INCOS 50 quadrupole mass spectrometer. TLC was carried out on Merck $60F_{254}$ plates. Preparative chromatography was performed on silica gel Acros 0.035—0.070 mm, 60 A. Melting points were determined on a Kofler hot stage. Elemental analysis was carried out on an automated Perkin—Elmer 2400 CHN microanalyzer. Etoxycarbonylformohydroximoyl chloride,[10] 4-methoxybenzohydroximoyl chloride,[15] 2,4,6-trimethylbenzonitrile oxide,[16] isomyristicin,[17] isoapiol,[17] and isodillapiol[17] were synthesized according to known procedures.

Cycloaddition of ethoxycarbonylformonitrile oxide to myristicin (4), apiol (5), dillapiol (6), and their isomers (16—18) (general procedure). A solution of triethylamine (17.3 g, 171 mmol) in CH_2Cl_2 (200 mL) was added dropwise to a solution of compound **8** (24.8 g, 163 mmol) and the unsaturated compound (180 mmol) in CH_2Cl_2 (600 mL) at 20 °C for 5 h. The reaction mixture was stirred for 24 h, washed with water (2×150 mL), and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The oily residue was crystallized from a 1 : 1 ethyl acetate—hexane mixture (200 mL), washed with hexane (2×50 mL), and dried in air.

Ethyl 5-(3-methoxy-4,5-methylenedioxybenzyl)-4,5-dihydroisoxazole-3-carboxylate (9). The yield was 69%, m.p. 84—86 °C. Found (%): C, 58.24; H, 5.37; N, 4.36. $C_{15}H_{17}NO_6$. Calculated (%): C, 58.63; H, 5.58; N, 4.56. ^{1}H NMR, δ: 1.25 (t, 3 H, MeCH_2O, J = 7.0 Hz); 2.76 and 2.87 (both dd, 1 H each, CH_2Ar, J = 7.9 Hz, J = 15.0 Hz); 2.91 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.17 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 3.80 (s, 3 H, OMe); 4.23 (q, 2 H, MeCH_2O); 5.01 (dq, 1 H, H(5)); 5.95 (s, 2 H, OCH_2O); 6.53 (s, 1 H, H(6′); 6.57 (s, 1 H, H(2′)).

Ethyl 5-(2,5-dimethoxy-3,4-methylenedioxybenzyl)-4,5-dihydroisoxazole-3-carboxylate (10). The yield was 59%, m.p. 74—76 °C. Found (%): C, 57.12; H, 5.36; N, 3.92. $C_{16}H_{19}NO_7$. Calculated (%): C, 56.97; H, 5.68; N, 4.15. ^{1}H NMR, δ: 1.26 (t, 3 H, MeCH_2O, J = 7.0 Hz); 2.75 and 2.91 (both dd, 1 H each, CH_2Ar, J = 7.0 Hz, J = 15.0 Hz); 2.93 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.20 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 3.77 and 3.83 (both s, 3 H each, OMe); 4.25 (q, 2 H, MeCH_2O); 4.92 (dq, 1 H, H(5)); 6.00 (s, 2 H, OCH_2O); 6.55 (s, 1 H, H(6′)).

Ethyl 5-(2,3-dimethoxy-4,5-methylenedioxybenzyl)-4,5-dihydroisoxazole-3-carboxylate (11). The yield was 62%, m.p. 79—81 °C. Found (%): C, 56.25; H, 5.81; N, 4.01. $C_{16}H_{19}NO_7$. Calculated (%): C, 56.97; H, 5.68; N, 4.15. ^{1}H NMR, δ: 1.26 (t, 3 H, MeCH_2O, J = 7.0 Hz); 2.73 and 2.89 (both dd, 1 H each, CH_2Ar, J = 7.9, J = 10.0 Hz); 2.93 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.32 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 3.69 and 3.93 (both s, 3 H each, OMe); 4.25 (q, 2 H, MeCH_2O); 4.96 (dq, 1 H, H(5)); 5.97 (s, 2 H, OCH_2O); 6.07 (s, 1 H, H(6′)).

Ethyl 5-(3-methoxy-4,5-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole-3-carboxylate (19A). The yield was 41%, m.p. 81—82 °C. Found (%): C, 58.94; H, 5.79; N, 4.68. $C_{15}H_{17}NO_6$. Calculated (%): C, 58.63; H, 5.58; N, 4.56. ^{1}H NMR, δ: 1.27 (t, 3 H, MeCH_2O, J = 7.0 Hz); 1.33 (d, 3 H, MeCH, J = 7.0 Hz); 3.50 (m, 1 H, H(4)); 3.84 (s, 3 H, OMe); 4.27 (q, 2 H, MeCH_2O); 5.25 (d, 1 H, H(5), J = 7.0 Hz); 6.00 (s, 2 H, OCH_2O); 6.63 (s, 1 H, H(2′)); 6.70 (s, 1 H, H(6′)).

Ethyl 4-(3-methoxy-4,5-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole-3-carboxylate (19B). ^{1}H NMR, δ: 1.17 (t, 3 H, MeCH_2O, J = 7.0 Hz); 1.35 (d, 3 H, MeCH, J = 7.0 Hz); 4.10 (d, 1 H, H(4), J = 7.0 Hz); 4.17 (q, 2 H, MeCH_2O); 4.71 (m, 1 H, H(5)); 5.99 (s, 2 H, OCH_2O); 6.44 (s, 1 H, H(2′)); 6.47 (s, 1 H, H(6′)).

Ethyl 5-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole-3-carboxylate (20A). The yield was 39%, m.p. 97—98 °C. Found (%): C, 56.54; H, 5.79; N, 4.01. $C_{16}H_{19}NO_7$. Calculated (%): C, 56.97; H, 5.68; N, 4.15. ^{1}H NMR, δ: 1.28 (t, 3 H, MeCH_2O, J = 7.0 Hz); 1.34 (d, 3 H, MeCH, J = 7.0 Hz); 3.47 (m, 1 H, H(4)); 3.78 and 3.80 (both s, 3 H each, OMe); 4.28 (q, 2 H, MeCH_2O); 5.40 (d, 1 H, H(5), J = 7.0 Hz); 6.05 (s, 2 H, OCH_2O); 6.56 (s, 1 H, H(6′)).

Ethyl 4-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole-3-carboxylate (20B). ^{1}H NMR, δ: 1.16 (t, 3 H, MeCH_2O, J = 7.0 Hz); 1.47 (d, 3 H, MeCH, J = 7.0 Hz); 3.75 and 3.83 (both s, 3 H each, OMe); 4.08 (d, 1 H, H(4), J = 7.0 Hz); 4.17 (q, 2 H, MeCH_2O); 4.43 (m, 1 H, H(5)); 6.04 (s, 2 H, OCH_2O); 6.22 (s, 1 H, H(6′)).

Ethyl 5-(2,3-dimethoxy-4,5-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole-3-carboxylate (21A). The yield was 40%, m.p. 92—94 °C. Found (%): C, 57.35; H, 5.31; N, 4.02. $C_{16}H_{19}NO_7$. Calculated (%): C, 56.97; H, 5.68; N, 4.15. ^{1}H NMR, δ: 1.28 (t, 3 H, MeCH$_2$O, J = 7.0 Hz); 1.33 (d, 3 H, MeCH, J = 7.0 Hz); 3.43 (m, 1 H, H(4)); 3.71 and 3.94 (both s, 3 H each, OMe); 4.28 (q, 2 H, MeCH$_2$O); 5.42 (d, 1 H, H(5), J = 7.0 Hz); 6.00 and 6.01 (both s, 1 H each, OCH$_2$O); 6.55 (s, 1 H, H(6′)).

Ethyl 4-(2,3-dimethoxy-4,5-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole-3-carboxylate (21B). ^{1}H NMR, δ: 1.17 (t, 3 H, MeCH$_2$O, J = 7.0 Hz); 1.35 (d, 3 H, MeCH, J = 7.0 Hz); 3.65 and 3.90 (both s, 3 H each, OMe); 4.08 (d, 1 H, H(4); J = 7.0 Hz); 4.17 (q, 2 H, MeCH$_2$O); 4.59 (m, 1 H, H(5)); 5.97 (s, 2 H, OCH$_2$O); 6.18 (s, 1 H, H(6′)).

Cycloaddition of 4-methoxybenzonitrile oxide to myristicin (4), apiol (5), and dillapiol (6) (general procedure). A solution of triethylamine (24.10 g, 239 mmol) in CH_2Cl_2 (300 mL) was added dropwise to a solution of hydroximoyl chloride **12** (42.10 g, 227 mmol) and the unsaturated compound (250 mmol) in CH_2Cl_2 (700 mL) at 0 °C for 8 h. The reaction mixture was stirred for 24 h, washed with water (2×150 mL), and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The oily residue was crystallized from a 1 : 2 ethyl acetate—hexane mixture (300 mL), washed with hexane (2×70 mL), and dried in air.

3-(4-Methoxyphenyl)-5-(3-methoxy-4,5-methylenedioxybenzyl)-4,5-dihydroisoxazole (13). The yield was 67%, m.p. 103—105 °C. Found (%): C, 66.62; H, 5.43; N, 3.84. $C_{19}H_{19}NO_5$. Calculated (%): C, 66.85; H, 5.61; N, 4.10. ^{1}H NMR, δ: 2.77 and 2.91 (both dd, 1 H each, CH$_2$Ar, J = 8.0 Hz, J = 15.0 Hz); 3.08 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.48 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 4.87 (dq, 1 H, H(5)); 5.96 (s, 2 H, OCH$_2$O); 6.58 (s, 1 H, H(2′)); 6.00 (s, 1 H, H(6′)); 7.00 (d, 2 H, H(2′), H(6′), J = 8.0 Hz); 7.60 (d, 2 H, H(3′), H(5′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-5-(2,5-dimethoxy-3,4-methylenedioxybenzyl)-4,5-dihydroisoxazole (14). The yield was 78%, m.p. 102—103 °C. Found (%): C, 64.21; H, 5.31; N, 3.56. $C_{20}H_{21}NO_6$. Calculated (%): C, 64.68; H, 5.70; N, 3.77. ^{1}H NMR, δ: 2.72 and 2.89 (both dd, 1 H each, CH$_2$Ar, J = 8.0 Hz, J = 15.0 Hz); 3.08 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.49 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 3.70 (s, 3 H, OMe); 3.80 (s, 3 H, OMe(4′)); 3.93 (s, 3 H, OMe); 4.83 (dq, 1 H, H(5)); 5.92 (s, 2 H, OCH$_2$O); 6.60 (s, 1 H, H(6′)); 7.00 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.60 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-5-(2,3-dimethoxy-4,5-methylenedioxybenzyl)-4,5-dihydroisoxazole (15). The yield was 67%, m.p. 98—100 °C. Found (%): C, 64.32; H, 5.45; N, 3.86. $C_{20}H_{21}NO_6$. Calculated (%): C, 64.68; H, 5.70; N, 3.77. ^{1}H NMR, δ: 2.73 and 2.90 (both dd, 1 H each, CH$_2$Ar, J = 8.0 Hz, J = 15.0 Hz); 3.08 (dd, 1 H, H(4), J = 8.0 Hz, J = 17.0 Hz); 3.36 (dd, 1 H, H(4), J = 10.0 Hz, J = 17.0 Hz); 3.77 (s, 3 H, OMe); 3.78 (s, 3 H, OMe(4′)); 3.81 (s, 3 H, OMe); 4.83 (dq, 1 H, H(5)); 5.98 (s, 2 H, OCH$_2$O); 6.07 (s, 1 H, H(6′)); 6.99 (d, 2 H, H(2′), H(6′), J = 8.0 Hz); 7.09 (s, 1 H, H(3′), H(5′), J = 8.0 Hz).

Cycloaddition of 4-methoxybenzonitrile oxide to isomyristicin (16), isoapiol (17), and isodillapiol (18) (general procedure). A solution of triethylamine (0.96 g, 9.52 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a solution of compound **12** (1.54 g, 8.28 mmol) and the unsaturated compound (7.52 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 2 h. The reaction mixture was stirred for 24 h, washed with water (2×30 mL), and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was subjected to column chromatography (ethyl acetate—hexane, 1 : 4, as the eluent). The oily fraction with R_f 0.58 was isolated (ethyl acetate—hexane, 1 : 2). Chromatographically indistinguishable regiosiomers accounted for 97% of the total content of this fraction. The ratio between the major and minor regioisomers was determined by ^{1}H NMR spectroscopy. In the case of the addition to isodillapiol, the major regioisomer (**23A**) was isolated by fractional crystallization from a 1 : 2 ethyl acetate—hexane mixture.

3-(4-Methoxyphenyl)-5-(3-methoxy-4,5-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole (22A). ^{1}H NMR, δ: 1.30 (d, 3 H, MeCH, J = 7.0 Hz); 3.79 (m, 1 H, H(4)); 3.80 and 3.83 (both s, 3 H each, OMe); 5.22 (d, 1 H, H(5), J = 7.0 Hz); 5.97 (s, 2 H, OCH$_2$O); 6.17 (s, 1 H, H(6′)); 6.58 (s, 1 H, H(2′)); 7.02 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.65 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-4-(3-methoxy-4,5-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole (22B). ^{1}H NMR, δ: 1.33 (d, 3 H, MeCH J = 7.0 Hz); 3.77 and 3.80 (both s, 3 H each, OMe); 4.53 (q, 1 H, H(4), J = 7.0 Hz); 4.56 (m, 1 H, H(5)); 5.89 and 5.91 (both s, 1 H each, OCH$_2$O); 6.41 (s, 1 H, H(2′)); 6.57 (s, 1 H, H(6′)); 6.92 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.55 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-5-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole (23A). The yield was 48%, m.p. 91—93 °C. Found (%): C, 65.04; H, 5.32; N, 3.51. $C_{20}H_{21}NO_6$. Calculated (%): C, 64.68; H, 5.70; N, 3.77. ^{1}H NMR, δ: 1.31 (d, 3 H, MeCH, J = 7.0 Hz); 3.72 (m, 1 H, H(4)); 3.73, 3.80, and 3.86 (all s, 3 H each, OMe); 5.31 (d, 1 H, H(5), J = 7.0 Hz); 6.03 (d, 2 H, OCH$_2$O, J_{gem} = 4.0 Hz); 6.49 (s, 1 H, H(6′)); 7.00 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.65 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-4-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole (23B). ^{1}H NMR, δ: 1.36 (d, 3 H, MeCH, J = 7.0 Hz); 3.67, 3.74, and 3.81 (all s, 3 H each, OMe); 4.52 (m, 1 H, H(5)); 4.66 (d, 1 H, H(4), J = 7.0 Hz); 6.02 (s, 2 H, OCH$_2$O); 6.24 (s, 1 H, H(6′)); 6.93 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.46 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-5-(2,3-dimethoxy-4,5-methylenedioxyphenyl)-4-methyl-4,5-dihydroisoxazole (24A). ^{1}H NMR, δ: 1.31 (d, 3 H, MeCH, J = 7.0 Hz); 3.41 (m, 1 H, H(4)); 3.77 (s, 3 H, OMe(2′)); 3.80 (s, 3 H, OMe(4′)); 3.95 (s, 3 H, OMe(3′)); 5.39 (d, 1 H, H(5), J = 7.0 Hz); 5.95 and 5.99 (both s, 1 H each, OCH$_2$O); 6.42 (s, 1 H, H(6′)); 7.00 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.65 (d, 2 H, H(2′), H(6′), J = 8.0 Hz).

3-(4-Methoxyphenyl)-4-(2,3-dimethoxy-4,5-methylenedioxyphenyl)-5-methyl-4,5-dihydroisoxazole (24B). ^{1}H NMR, δ: 1.34 (d, 3 H, MeCH, J = 7.0 Hz); 3.74 (s, 3 H, OMe(4′)); 3.76 (s, 3 H, OMe(2′)); 3.95 (s, 3 H, OMe(3′)); 4.50 (m, 1 H, H(5)); 4.67 (d, 1 H, H(4), J = 7.0 Hz); 5.92 and 5.96 (both s, 1 H each, OCH$_2$O); 6.14 (s, 1 H, H(6′)); 6.92 (d, 2 H, H(3′), H(5′), J = 8.0 Hz).

Cycloaddition of 2,4,6-trimethylbenzonitrile oxide to isomyristicin (16), isoapiol (17), and isodillapiol (18) (general procedure). A solution of compound **25** (1.52 g, 9.44 mmol) and the unsaturated compound (9.44 mmol) in CH_2Cl_2 (50 mL) was stirred at

20 °C for 3 days. The solvent was removed on a rotary evaporator. The ratio between the major (**26B**, **27B**, and **28B**) and minor (**26A**, **27A**, and **28a**) regioisomers was determined by ^{1}H NMR spectroscopy. In the case of the addition to isodillapiol, the major regioisomer (**28B**) was isolated by fractional crystallization from a 1 : 2 ethyl acetate—hexane mixture.

5-(3-Methoxy-4,5-methylenedioxyphenyl)-4-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (26A). ^{1}H NMR, δ: 1.09 (d, 3 H, MeCH, J = 7.0 Hz); 2.16 (s, 6 H, Me(2′), Me(6′)); 2.25 (s, 3 H, Me(4′)); 3.53 (m, 1 H, H(4)); 3.85 (s, 3 H, OMe); 5.20 (d, 1 H, H(5), J = 7.0 Hz); 6.02 (s, 2 H, OCH_2O); 6.70 (s, 1 H, H(6′)); 6.73 (s, 1 H, H(2′)); 6.94 (s, 2 H, H(3′), H(5′)).

4-(3-Methoxy-4,5-methylenedioxyphenyl)-5-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (26B). ^{1}H NMR, δ: 1.42 (d, 3 H, MeCH, J = 7.0 Hz); 2.11 (s, 6 H, Me(2′), Me(6′)); 2.19 (s, 3 H, Me(4′)); 3.71 (s, 3 H, OMe); 4.37 (d, 1 H, H(4), J = 7.0 Hz); 4.87 (m, 1 H, H(5)); 5.93 (s, 2 H, OCH_2O); 6.40 (s, 1 H, H(6′)); 6.42 (s, 1 H, H(2′)); 6.72 (s, 2 H, H(3′), H(5′)).

5-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-4-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (27A). ^{1}H NMR, δ: 1.23 (d, 3 H, MeCH, J = 7.0 Hz); 2.29 (s, 6 H, Me(2′), Me(6′)); 2.25 (s, 3 H, Me(4′)); 3.53 (m, 1 H, H(4)); 3.79 and 3.86 (both s, 3 H each, OMe); 5.36 (d, 1 H, H(5); J = 7.0 Hz); 6.04 and 6.06 (both s, 1 H each, OCH_2O); 6.61 (s, 1 H, H(6′)); 6.94 (s, 2 H, H(3′), H(5′)).

4-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-5-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (27B). ^{1}H NMR, δ: 1.43 (d, 3 H, MeCH, J = 7.0 Hz); 2.11 (s, 6 H, Me(2′), Me(6′)); 3.37 (s, 3 H, OMe(2′)); 3.75 (s, 3 H, OMe(5′)); 4.67 (d, 1 H, H(4), J = 7.0 Hz); 4.87 (m, 1 H, H(5)); 5.95 and 5.96 (both s, 1 H each, OCH_2O); 6.46 (s, 1 H, H(6′)); 6.85 (s, 2 H, H(3′), H(5′)).

5-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-4-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (28A). ^{1}H NMR, δ: 1.00 (d, 3 H, MeCH, J = 7.0 Hz); 2.16 (s, 6 H, Me(2′), Me(6′)); 2.25 (s, 3 H, Me(4′)); 3.54 (m, 1 H, H(4)); 3.77 and 3.97 (both s, 3 H each, OMe); 5.37 (d, 1 H, H(5), J = 7.0 Hz); 6.02 (s, 2 H, OCH_2O); 6.61 (s, 1 H, H(6′)); 6.93 (s, 2 H, H(3′), H(5′)).

4-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-5-methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazole (28B). The yield was 40%, m.p. 128—130 °C. Found (%): C, 64.29; H, 5.81; N, 3.61. $C_{20}H_{21}NO_6$. Calculated (%): C, 64.68; H, 5.70; N, 3.77. ^{1}H NMR, δ: 1.42 (d, 3 H, MeCH, J = 7.0 Hz); 2.10 (s, 6 H, Me(2′), Me(6′)); 2.19 (s, 3 H, Me(4′)); 3.25 (s, 3 H, OMe(2′)); 3.84 (s, 3 H, OMe(3′)); 4.63 (d, 1 H, H(4), J = 7.0 Hz); 4.79 (m, 1 H, H(5)); 5.95 and 5.97 (both s, 1 H each, OCH_2O); 6.49 (s, 1 H, H(6′)); 6.84 (s, 2 H, H(3′), H(5′)).

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Received July 6, 2007;
in revised form November 23, 2007