Monatsh Chem
DOI 10.1007/s00706-016-1797-4

ORIGINAL PAPER

Studies on [2 + 3] cycloaddition reaction of nitrile oxides to linear dipolarophiles bearing multiple double bonds

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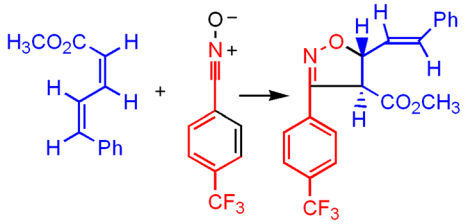
Received: 26 April 2016 / Accepted: 5 June 2016

Abstract Site selectivity, regioselectivity, and stereoselectivity of [2 + 3] cycloaddition of benzonitrile oxides to polyunsaturated esters were examined. Site selectivity was correlated with electron charges of unsaturated carbon atoms. Structure of the products has been established by an extensive application of ^{1}H and ^{13}C NMR spectroscopy and electrospray ionization mass spectrometry.

Graphical abstract



Keywords Alkenes · Polyunsaturated esters · Site selectivity · NMR spectroscopy · Mass spectroscopy

Introduction

The [2 + 3] cycloaddition of nitrile oxides to alkenes is the most convenient method for the preparation of 2-isoxazolines [1]. These heterocycles are valuable intermediates in the synthesis of several pharmaceuticals [2] and natural product [3]. The easy cleavage of their weak hetero N–O bond affords several synthetically important compounds, such as *β*-hydroxy ketones, *β*-hydroxy esters, *α*,*β*-unsaturated carbonyl compounds, or iminoketones [4]. The nitrile oxides can be formed either by Huisgen method from aldoximes by chlorination and base-induced dehydrochlorination [1] or by dehydration of primary nitro compounds by phenyl isocyanates [5] (Mukayama method) or ethyl chloroformate (Shimizu method) [6].

A key feature of the cycloaddition is the *cis*-stereospecificity—from *E*-alkenes 4,5-*anti* isomers are produced and from *Z*-alkenes 4,5-*syn* products are obtained [4]. Reactions of monosubstituted and 1,1-disubstituted alkenes furnish regioselectively 5-substituted 2-isoxazolines while 1,2-disubstituted olefins usually afford mixtures of regio- and stereoisomers. These problems were treated by two approaches. In the first method a substrate control was applied, where optically active reagents, much more often dipolarophiles than dipoles were used. One variant of this method was based on the use of chiral auxiliaries temporarily linked usually by an ester or amide bond to the dipolarophiles [7–9]. The second more effective method relied on chiral metal catalysts or organocatalysts. Shortage of reports on metal assisted 1,3-dipolar cycloadditions of nitrile oxides was due to interference of catalyst with generation of these dipoles and formation of unreactive complexes [10].

Cycloaddition of nitrile oxides to polyunsaturated alkenes was examined to a limited extent and concerned mostly a conjugated 1,3-diene system. In cycloaddition of benzonitrile oxide to 2-alkoxy-1,3-butadienes only the unsubstituted vinyl group participated in the reactions while in case of phenylglyoxylonitrile oxide both double bonds reacted [11]. This result indicated the dominance of steric effect over the electronic one in the first case, where more sterically

Electronic supplementary material The online version of this article (doi:10.1007/s00706-016-1797-4) contains supplementary material, which is available to authorized users.

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Published online: 19 July 2016

demanding dipole did not interact with the activated double bond. 2-Highly substituted diastereoisomerically pure butadiene derivative underwent a chemoselective and regioselective nitrile oxide cycloaddition to provide isoxazoline system en route to carbon skeleton of myriaporone [12]. 1,3-Dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-dienes occurred in a regioselective manner at 1,1-substituted double bond [13]. Tricarbonyl[(1-4-η)-2-methoxy-5-methyl-enecyclohexa-1,3-diene]iron underwent 1,3-dipolar cycloaddition reaction regio-, stereo-, and chemoselectively at its exocyclic double bond [14].

In reactions of nitrile oxides with dimethyl 7-(diphenylmethylene)bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate only disubstituted norbornene double bond participated [15]. Similarly in lately examined by us cycloadditions of aryl nitrile oxides to norbornenes substituted with an acrylate-derived moiety only adducts to norbornene system were formed with good site and *exo* selectivity [16].

We have described recently [2 + 3] cycloaddition reaction of nitrile oxides to cyclohexenes [17], medium ring cycloalkenes [18], crotonamides and cinnamides [19], as well as to α,β-unsaturated esters [20].

Studies on synthesis of cholecalciferol (vitamin D_3) analogs directed towards optimization of biological activity were carried out [21, 22].

Herein we present results of our research concerning site selectivity, regioselectivity, and stereochemistry of 1,3-dipolar cycloaddition reaction of two benzonitrile oxides to conjugated and unconjugated dienes, an allene, to conjugated and unconjugated trienes, and to an alkene–alkyne. Structure of the products has been established by an application of ^{1}H and ^{13}C NMR spectroscopy and electrospray ionization mass spectrometry. Some of the obtained products showed moderate fungicidal activities.

Results and discussion

Synthesis of the dipolarophiles

(2*E*,4*E*)-2,4-Dienoic acids **2a**, **2b** were obtained by the Knoevenagel condensation [27] of the corresponding aldehydes with malonic acid. Esters **3**, **4**, and **6** were prepared by acidic esterification (Scheme 1). Acetates **8**, **10**, and **12** were prepared by reaction with acetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). Ester **18** was purchased from Aldrich (Scheme 2).

Structural analysis of the cycloadducts

We have examined [2 + 3] cycloaddition of 4-(trifluoromethyl)benzonitrile oxide (**13a**) to conjugated dienes **3** and **4**, to the unconjugated diene **6**, to the allene **18**, to the conjugated triene of acetylcholecalciferol (vitamin D_3, **12**), to the unconjugated triene **8** (*cis*-neridiol acetate) and to the alkene–alkyne acetate **10** as well as cycloaddition of 4-(2-propyl)benzonitrile oxide (**13b**) to the latter dipolarophile. These reactions are presented in Schemes 3, 4 and 5. The spectroscopic data for the cycloadducts are presented in the experimental section.

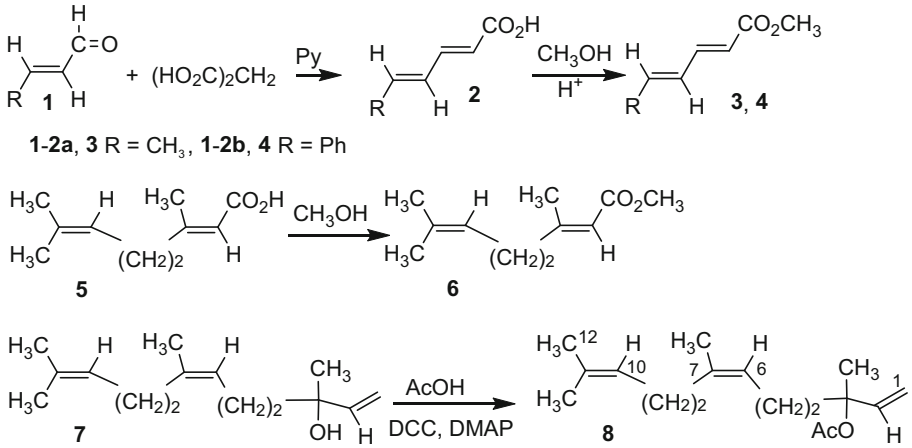
Reaction of the dipole **13a** and the diene **3** gave a 1:1 mixture of cycloadducts **14** and **15** to the C2–C3 double bond (30 %) and a cycloadduct **16** to the C4–C5 bond (23 %), separated by a column chromatography (Scheme 3). In the ^{1}H NMR spectrum of compound **14** a diagnostic proton H5 was a doublet of doublets at 5.40 ppm, showing a vicinal coupling with H4 (doublet at 4.25 ppm, $J = 6.9$ Hz) and with the olefinic proton H6 (ddq, $J = 7.8$, 1.5, 15.0 Hz), part of the *E*-propenyl side chain; H5 was also correlated in the 2D NMR HSQC spectrum with C5 (87.25 ppm). In the other regioisomer **15** the diagnostic H5 (d, $J = 4.5$ Hz) correlated in the 2D NMR HSQC spectrum with C5 (84.70 ppm) showed only vicinal coupling with H4 (dd at 4.25 ppm, $J = 4.5$, 9.0 Hz). In the third adduct **16** an acrylic side chain was attached at C5. H5 was an apparent triplet of doublets at 4.94 ppm, because of similar vicinal couplings with H4 (dq, $J = 5.3$, 6.3 Hz) and with H7 (dd, $J = 5.3$, 15.6 Hz).

Reaction with the phenyl diene **4** showed on the other hand a good site- and regioselectivity and only one adduct **17** to the C2–C3 bond was observed. It was a phenyl analog of the cycloadduct **14**, and its structure was similarly established by analysis of NMR spectra.

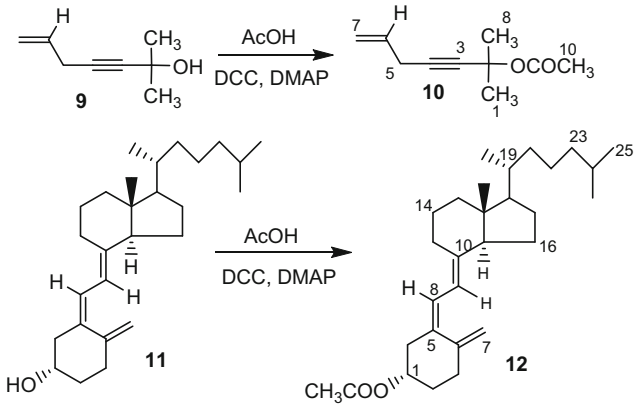
A high selectivity towards cycloaddition to the terminal double bond was found in case of the allenyl ester **18**, which gave only one ester **19**. ^{1}H NMR spectrum showed only one olefinic proton of H6 at 6.62 ppm and 2H singlet of H4 at 3.93 ppm. In the other possible cycloadducts, two alkenyl protons are expected and one or zero H4. This corollary was confirmed by ^{13}C NMR spectrum where C4 gave a high field signal at 32.71 ppm and C5 absorbed at a very low field (167.2 ppm).

Cycloaddition to the unconjugated diene **6** occurred mainly to the α,β-unsaturated ester moiety affording regioisomeric products **20** and **21** in 3:2 ratio and 50 % overall yield (Scheme 4). Unexpectedly, an addition of methanol components occurred to the C6–C7 double bond, originating presumably from the methyl ester group. No olefinic protons were observed and another quaternary methoxy group was identified in the ^{1}H and ^{13}C NMR spectra of both esters. A similar side reaction was observed by us before [17]. 2D NMR HMBC spectra of **20** and **21** showed correlation peaks between $OC^{12}H_3$ at 3.16 ppm and C9 at 74.4 ppm. A diagnostic correlation was also observed in 2D HMBC spectrum of compound **20** between H4 at 3.67

Scheme 1



Scheme 2



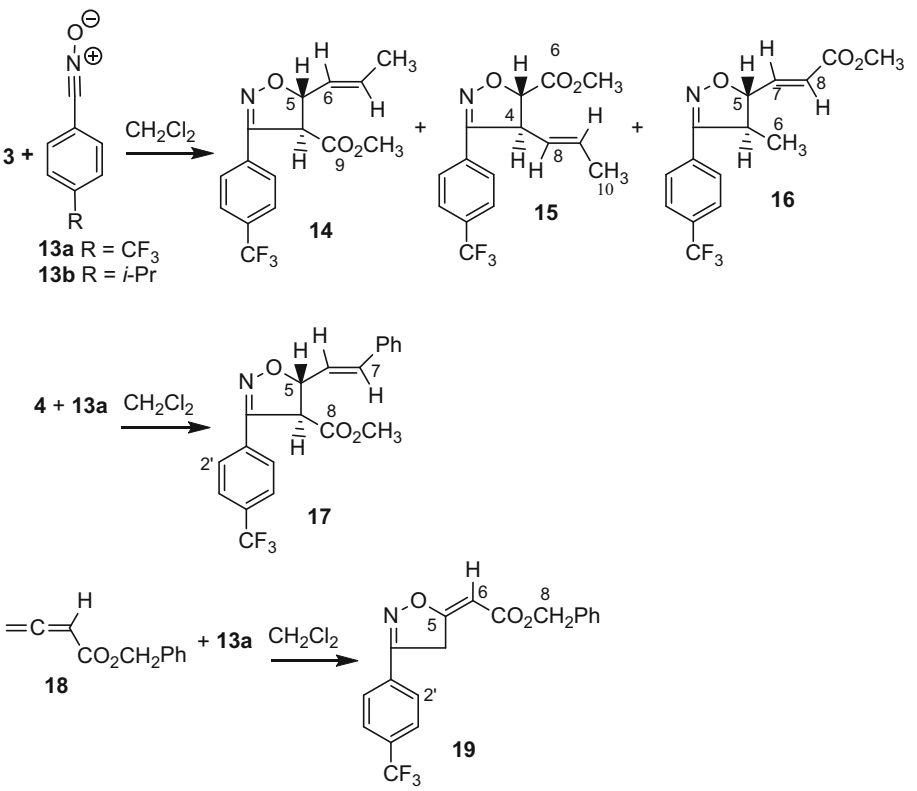
and C3 at 155.6 ppm which was missing in the spectrum of regioisomer **21**. A minor product **22** was formed by cycloaddition to the C6–C7 double bond. Regiochemistry of the cycloaddition leading to **22** and the major adduct **20** can be explained by Frontier Molecular Orbital (FMO) considerations. Reactions of the alkenes with electron-donating substituents and moderately electron-withdrawing substituents (such as an ester group) are controlled by $LUMO_{dipol}$–$HOMO_{alkene}$ ($\Delta E = 8.28$ eV) interaction since $LUMO_{alkene}$–$HOMO_{dipol}$ energy gap ($\Delta E = 9.87$ eV) is higher. Bond formation occurs between atoms of the larger orbital coefficients and leads to isoxazolines with the oxygen atom next to the more-substituted carbon atom [23].

Cycloaddition to *cis*-neridiol acetate (**8**) afforded an unseparable mixture of *anti* **23** and *syn* **24** adducts to the most exposed terminal double bond in 40:35 ratio (Scheme 4). Regiochemistry of the reaction results from FMO factors. *Anti* configuration was proposed to the major isomer **23** based on literature data concerning stereoselection in 1,3-dipolar cycloadditions of benzonitrile oxides to terminal alkenes bearing an allylic stereocenters [24]. In the absence of hydrogen bonding the major diastereoisomers had always 5,6-*anti* relative configuration like that of compound **23** at Scheme 4.

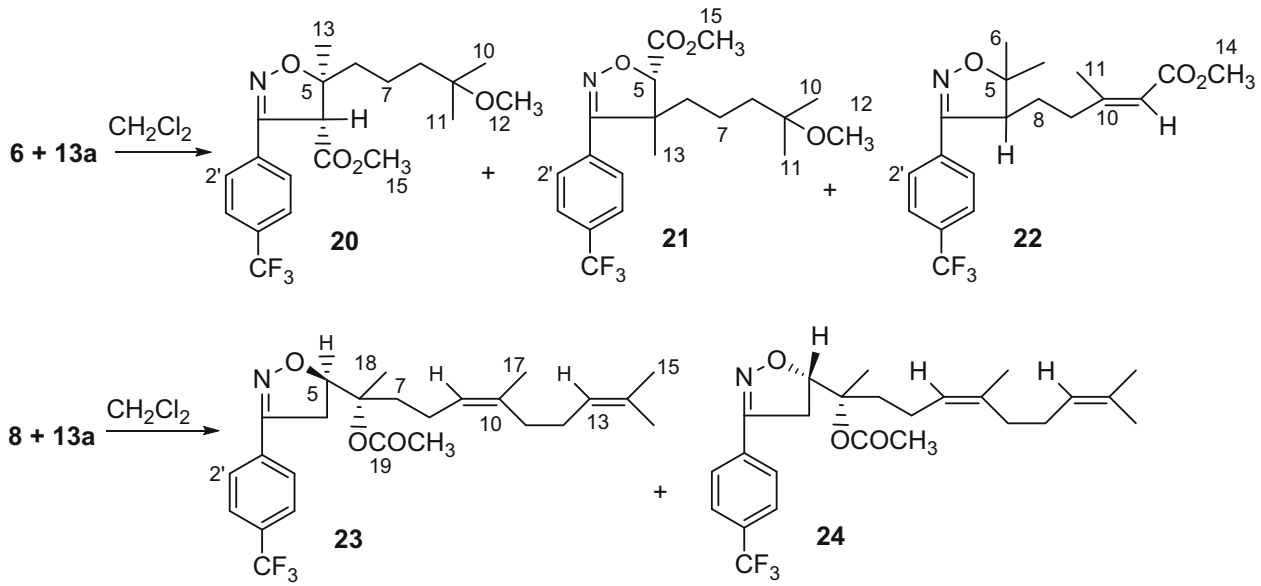
Reaction of both benzonitrile oxides **13a**, **13b** with the alkene–alkyne acetate **10** yielded mixtures of major monoadducts to the double bond **25**, **26** and minor bisadducts **27** and **28** (Scheme 5). Comparison of product amounts demonstrates that a double bond is seven times more reactive than the triple bond in reaction of dipole **13a** and in case of the dipole **13b** with an electron-donating substituent this ratio of reactivities is greater than 9. Regiochemistry of the second addition to alkyne system was as expected from FMO considerations where oxygen atom of the dipole tends to attack the more-substituted carbon atom [24]. It was confirmed by 2D ROESY NMR spectra where proximity of aryl H2"/H6" protons (7.85 ppm) and H6a (2.67 ppm) for compound **27** and proximity of H2"/H6" protons (7.61 ppm) and H6a (2.66 ppm) for compound **28** were found. These correlations were not possible in the other regioisomer.

Finally cycloaddition of 4-(trifluoromethyl)benzonitrile oxide (**13a**) to acetylcalciferol acetate (**12**) afforded a mixture of 5,8-*syn* **29** and 5,8-*anti* **30** adducts to the most easily excessible exocyclic double bond with the expected regiochemistry (Scheme 5). Structures of both diastereoisomers were proposed based on ^{1}H NMR spectra. In the *syn*-adduct **29,** the diagnostic H4 was a pair of geminally coupled protons (3.42, 3.31 ppm, $J = 16.5$ Hz), while in the *anti*-adduct **30** H4 were a two proton singlet at 3.36 ppm. In a preferred pseudo diequatorial conformation of the acetate substituent and C4–C5 bond H4 chemical shifts can be differentiated by interaction with C6–C13 diene system.

Scheme 3



Scheme 4



Rationalization of the observed site selectivity

Table 1 gives electron charges at the alkenyl (alkynyl) carbon atoms of the dipolarophiles **3**, **4**, **6**, **8**, **10**, **18**, and the observed site selectivity in the cycloaddition reaction.

Generally the greater was the amount of negative charges at both carbon atoms of the unsaturated bond, the higher was the reactivity of the cycloaddition reaction. The total charges for the diene **6** at C6–C7 of −0.289 correspond to the formation of 50 % of the products **22** and **21**, while the C2–C3

Scheme 5

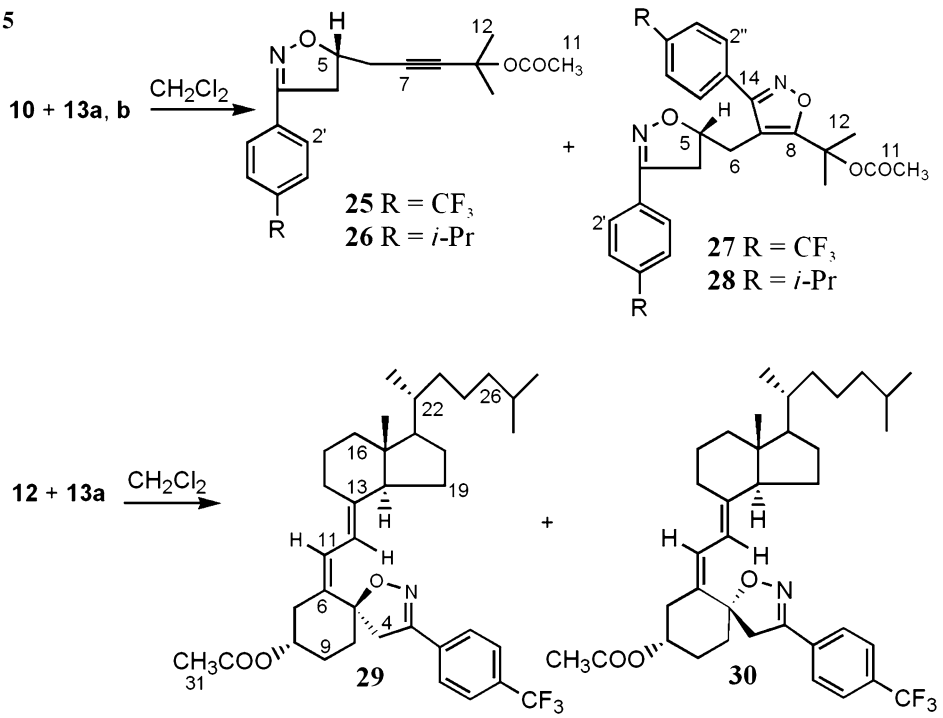


Table 1 Electron charges at the alkenyl carbon atoms of the dipolarophiles **3**, **4**, **6**, **8**, **10**, **12**, **18** and site selectivity in the cycloaddition reaction

Dipolarophile/C atom	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Site selectivity
3	–	−0.201	−0.039	−0.176	−0.111	–	–	–	–	–	–	–
4	–	−0.197	−0.041	−0.161	−0.075	–	–	–	–	–	–	C2/C3
6	–	−0.228	−0.008	–	–	−0.185	−0.104	–	–	–	–	C2/C3
8	−0.18	−0.182	–	–	–	−0.173	−0.108	–	–	−0.174	−0.107	C1/C2
10	–	–	−0.111	−0.175	–	−0.160	−0.210	–	–	–	–	C6/C7
12	–	–	–	−0.067	−0.075	–	−0.220	−0.102	−0.164	−0.064	–	C4/C7
18	–	−0.158	−0.066	−0.171		–	–	–	–	–	–	C3/C4

bond with total −0.236 gave rise to only 10 % of the product **22**. For the alkene–alkyne **10** the total charges at C6–C7 bond of −0.37 corresponded to 52.5 % (and 56 % for the other dipole) of cycloadducts, and to the C3–C4 bond with the total electron charges of −0.286 only 7.5 % (and 6 %) of cycloaddition took place. In case of trienes **8** and **12** exclusively an addition to the terminal double bonds with the highest electron densities was observed. This direction of the reaction was favored also by steric factors. The latter effects were decisive in case of compound **4** where in spite of similar electron densities at both double bonds the reaction showed good site selectivity. It could be explained by steric interactions of the phenyl substituent and a more difficult approach of the dipole to the double bond of the dipolarophile.

Biological activity of the products

Fungicidal inhibitory activities of dipolarophiles **3**–**12** and cycloadducts **14**–**30** against the following phytopathogenic fungi: *Alternaria alternata*, *Botrytis cinerea*, *Fusarium culmorum*, *Phytophthora cactorum*, and *Rhizoctonia solani* was examined. Generally only a moderate potency was found, particularly against *P. cactorum* and *R. solani*. Diene **4** was the most active from the dipolarophiles displaying a higher potency against *F. culmorum* and *P. cactorum* than the reference compound chlorothalonil. From the cycloadducts tested compounds **14**–**16** were the most active (Table 2).

Conclusions

High regio- and site selectivity of 1,3-dipolar cycloaddition reaction of 4-(trifluoromethyl)benzonitrile oxide to the conjugated dienyl ester **4**, to the allenyl ester **18**, to the conjugated **12** and the unconjugated trienic ester **8** were observed. A correlation of double bond reactivity with electron charges was found. Steric effects were also

Table 2 Fungicidal inhibitory activities of compounds **3**, **4**, **8**, **10**, **12**, **14**, **15**, **16**, **17**, **19**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30** at 200 μg/cm^3

Compound	*A. a.*[a]	*B. c.*	*F. c.*	*P. c.*	*Rh. s.*
3	16.0	14.8	22.0	29.0	30.0
4	–	12.0	40.0	68.0	27.0
8	–	0	22.0	0	17.0
10	17.4	22.2	20.0	42.2	0
12	14.0	14.8	6.0	12.9	38.0
14	38.0	17.0	33.0	44.0	49.0
15	–	40.0	33.0	–	51.0
16	44.0	40.0	33.0	56.0	67.0
17	–	0	16.0	0	0
19	21.7	17.8	0	11.1	0
23 + **24**	–	10.0	22.0	0	0
25	39.1	37.8	13.3	11.1	52.0
26	41.3	35.6	24.4	0	46.0
27	0	0	0	3.2	0
28	20.0	29.7	16.0	35.4	66.0
29	0	6.3	0	6.4	0
30	0	0	0	12.9	0
Chlorothalonil[b]	–	80.0	38.0	61.0	88.0

Percentage of linear growth inhibition

[a] *A. a. Alternaria alternata*, *B. c. Botrytis cinerea*, *F. c. Fusarium culmorum*, *P. c. Phytophthora cactorum*, *Rh. s. Rhizoctonia solani*

[b] Reference compound

important. The addition to the exocyclic and terminal alkene group was strongly favored. A much higher reactivity of the alkene than alkyne function was found (addition to the compound **10**). All diastereoisomeric products were fully characterized by ^{1}H and ^{13}C NMR 1D and some by 2D spectroscopy. Some dipolarophiles and adducts showed a moderate fungistatic activity. Further research is in progress to analyze the biological potency of the new products, and to improve regioselectivity of the cycloaddition reaction.

Experimental

Reagent grade chemicals were used without further purification unless otherwise noted. Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^{1}H NMR spectra and ^{13}C NMR spectra on Varian 500 UNITY plus-500 and Varian 300 UNITY plus 300 spectrometers in deuterated chloroform using TMS as internal standard. 2D HSQC (heteronuclear single quantum coherence) and 2D ROESY (rotating frame nuclear Overhauser effect spectroscopy) analyses were carried out on a Bruker AVANCE III 500 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard, coupling constants are reported in Hz. In ^{13}C NMR spectra, signals of fluorine-substituted carbon atoms and some alpha carbon atoms were sometimes not observed because of strong ^{19}F–^{13}C coupling. In order to further characterize these compounds, ^{19}F spectra were recorded. EI mass spectra were run on an AMD M-40 instrument, electrospray ionization-mass spectra (ESI–MS) on a LCT (Micromass) apparatus. Flash chromatography was carried out using silica gel S 230–400 mesh (Merck) and hexanes-ethyl acetate mixtures as eluents. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF [25]. Calculations of electron charges on alkenyl carbon atoms, molecular modeling and substrate HOMO/LUMO energies were calculated with the Hyperchem 7.5 program using semiempirical AM1 method [26]. Elemental analyses (C, H) were conducted using the Elemental Analyser Vario EL III, their results were found to be in good agreement (±0.3 %) with the calculated values.

Methyl (2E,4E)-hexa-2,4-dienoate (**3**)

A brown liquid (yield: 25 %) was obtained by the Knoevenagel condensation [27] of 2-(2*E*)-but-2-enal with malonic acid followed by acidic esterification. It was identical to the published ester [28].

Methyl (2E,4E)-5-phenylpenta-2,4-dienoate (**4**)

A yellowish wax (yield: 35 %) was obtained by the Knoevenagel condensation [27] of *trans* cinnamaldehyde with malonic acid followed by acidic esterification. Identical to the published ester [29].

Methyl (2E)-3,7-dimethylocta-2,6-dienoate (**6**)
A greenish liquid, yield: 75 %. Identical to the published ester [30].

(6E)-3,7,11-Trimethyldodeca-1,6,10-trien-3-yl propanoate (**8**)
N,N-Dicyclohexylcarbodiimide (DCC, 8 mmol in dry CH_2Cl_2) was added with stirring at room temperature to a solution of acetic acid (6 mmol), alcohol **7** (6 mmol) and 4-(dimethylamino)pyridine (1.8 mmol) in a mixture of dry dichloromethane/acetonitrile (5 cm^3, 1:1) under dry argon. Stirring was continued for 24 h. The reaction mixture was filtered and the filter paper was washed with dichloromethane. The solution was washed with water, dilute HCl, water, aqueous solution of sodium bicarbonate, and finally several times with water. The solution was dried ($MgSO_4$) and the product obtained after evaporation of the solvent was purified by flash chromatography on silica gel affording the expected ester **8** as a yellowish wax (50 %) [31].

2-Methylhept-6-en-3-yn-2-yl acetate (**10**, $C_{10}H_{14}O_2$)
It was prepared in the same way as ester **8**; a brownish liquid, yield: 50 %. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.80$ (ddt, $J = 17.0$, 10.2, 5.1 Hz, 1H, H6), 5.35 (dq, $J = 17.0$, 1.8 Hz. 1H, H7a), 5.11 (dq, $J = 10.2$, 1.8 Hz, 1H, H7b), 2.99 (dt, $J = 5.1$, 1.8 Hz, 2H, H5), 2.02 (s, 3H, H10), 1.66 (s, 6H, H1, H8) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 169.5$ (C9), 132.2 (C6), 116.1 (C7), 83.9 (C3), 80.0 (C4), 72.4 (C2), 29.2 (C8), 28.9 (C1), 22.9 (C5), 22.0 (C10) ppm.

Cholecalciferol acetate (**12**)
It was prepared in the same way as ester **8**; a brownish liquid, yield 40 %. ^{1}H NMR, ^{13}C NMR identical to the published data [32].

*Cycloaddition reaction of dipolarophiles **3**, **4**, **6**, **8**, **10**, **12**, and **18** with benzonitrile oxides. A general procedure for preparation of esters **14–30***
4-(Trifluoromethyl)benzonitrile oxide was generated as follows: a solution of 0.25 g of the corresponding chlorobenzaldoxime (1.12 mmol) in dry dichloromethane was passed through an Amberlyst-21 column and added dropwise over 30 min to the solution of a dipolarophile in dry dichloromethane, and the solution was stirred overnight at room temperature. Water was added, organic layer was separated and the aqueous one extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the product was purified by flash column chromatography. Chlorobenzaldoximes were prepared from the corresponding aryl aldehyde oximes and *N*-chlorosuccinimide (NCS) in *N,N*-dimethylformamide (DMF) [21, 22].

Methyl 5-[(1E)-prop-1-en-1-yl]-3-[4-(trifluoromethyl) phenyl]-4,5-dihydro-1,2-oxazole-4-carboxylate
(**14**, $C_{15}H_{14}F_3NO_3$)
A brownish liquid, yield: 15 %; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.81$ (d, $J = 8.5$ Hz, 2H, H2', H6'), 7.65 (d, $J = 8.5$ Hz, 2H, H3', H5'), 5.90 (dqd, $J = 15.0$, 6.6, 1.5 Hz, 1H, H7), 5.60 (ddq, $J = 15.0$, 7.8, 1.5 Hz, 1H, H6), 5.40 (dd, $J = 7.8$, 6.9 Hz, 1H, H5), 4.25 (d, $J = 6.9$ Hz, 1H, H4), 3.74 (s, 3H, H_3CO), 1.78 (dd, $J = 6.6$, 1.5 Hz, 3H, H8) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 169.4$ (C9), 152.8 (C3), 132.1 (C7), 131.8 (q, $J = 32.8$ Hz, C4'), 131.2 (C1'), 127.1 (C6), 127.0 (C2', C6'), 125.7 (q, $J = 3.8$ Hz, C3', C5'), 123.8 (q, $J = 272.4$ Hz, F_3C), 87.3 (C5), 58.6 (C4), 53.2 (C10), 17.7 (C8) ppm; MS (EI): $m/z = 313$ (M^+, 55), 294 ($[M - F]^+$, 30), 145 ($C_6H_5CF_3$, 100).

Methyl 4-[(1E)-prop-1-en-1-yl]-3-[4-(trifluoromethyl) phenyl]-4,5-dihydro-1,2-oxazole-5-carboxylate
(**15**, $C_{15}H_{14}F_3NO_3$)
A brownish liquid, yield: 15 %; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.83$ (d, $J = 8.0$ Hz, 2H, H2', H6'), 7.64 (d, $J = 8.0$ Hz, 2H, H3', H5'), 5.81 (dq, $J = 16.0$, 6.5 Hz, 1H, H9), 5.55 (ddd, $J = 16.0$, 9.0, 1.5 Hz, 1H, H8), 4.90 (d, $J = 4.5$ Hz, 1H, H5), 4.51 (dd, $J = 9.0$, 4.5 Hz, 1H, H4), 3.82 (s, 3H, H7), 1.71 (dd, $J = 6.5$, 1.5 Hz, 3H, H10) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 131.9$ (C9), 127.7 (C2', C6'), 126.2 (C8), 125.6 (C3', C5'), 84.7 (C5), 55.0 (C4), 53.0 (C7), 18.0 (C10) ppm; MS (EI): $m/z = 313$ (M^+, 23), 294 ($[M - F]^+$, 35), 212 (80), 127 (90), 111 (100), 69 (83).

Methyl (2E)-3-[5-methyl-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazol-4-yl]prop-2-enoate
(**16**, $C_{15}H_{14}F_3NO_3$)
A brownish liquid, yield: 23 %; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.77$ (d, $J = 8.7$ Hz, 2H, H2', H6'), 7.67 (d, $J = 8.7$ Hz, 2H, H3', H5'), 6.91 (dd, $J = 15.6$, 5.3 Hz, 1H, H7), 6.14 (dd, $J = 15.6$, 1.5, 1H, H8), 4.94 (app. td, $J = 5.3$, 1.5 Hz, 1H, H5), 3.74 (s, 3H, H10), 3.56 (qd, $J = 6.3$, 5.3 Hz, 1H, H4), 1.39 (d, $J = 6.3$ Hz, 3H, H6) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 166.3$ (C9), 159.2 (C3), 143.6 (C7), 132.0 (q, $J = 32.8$ Hz, C4'), 131.7 (C1'), 127.3 (C2', C6'), 125.9 (q, $J = 3.8$ Hz, C3', C5'), 123.9 (q, $J = 272.0$ Hz, F_3C), 122.2 (C8), 86.9 (C5), 51.9 (C10), 47.8 (C4), 17.4 (C6) ppm; MS (EI): $m/z = 313$ (M^+, 75), 294 ($[M - F]^+$, 30), 254 (45), 226 (50), 198 (87), 173 (88), 145 ($C_6H_4CF_3$, 100), 126 (30), 111 (75), 95 (35), 67 (45).

Methyl 5-[(E)-2-phenylethenyl]-3-[4-(trifluoromethyl) phenyl]-4,5-dihydro-1,2-oxazole-4-carboxylate
(**17**, $C_{20}H_{16}F_3NO_3$)
A brown liquid, yield: 35 %; IR (KBr): $\bar{\nu} = 3460$, 2970, 2930, 2850, 1739, 1650, 1620, 1599, 1580, 1497, 1440,

1410, 1330, 1257, 1150, 1120, 1112, 1072, 1018, 968, 920, 870, 846, 830, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.85$ (dm, $J = 8.1$ Hz, 2H, H2', H6'), 7.67 (dm, $J = 8.1$ Hz, 2H, H3', H5'), 7.43–7.27 (m, 5H), 6.77 (d, $J = 15.8$ Hz, 1H, H7), 6.26 (dd, $J = 15.8$, 7.5 Hz, 1H, H6), 5.64 (ddd, $J = 7.5$, 6.5, 1.0 Hz, 1H, H5), 4.39 (d, $J = 7.5$ Hz, 1H, H4), 3.76 (s, 3H, H9) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 169.1$ (C8), 152.9 (C3), 135.4 (C1"), 134.4 (C7), 132.1 (C1'), 131.9 (q, $J = 32.7$ Hz, C4'), 128.7 (C2', C6'), 128.6 (C3", C5"), 127.2 (C4"), 126.9 (C2", C6"), 125.8 (q, $J = 3.9$ Hz, C3', C5'), 124.7 (C6), 123.8 (q, $J = 272.2$ Hz, F_3C), 87.0 (C5), 58.9 (C4), 53.3 (C9) ppm; ^{19}F NMR ($CDCl_3$, 471 MHz): $\delta = -63.33$ (s, 3F, F_3CAr) ppm; MS (EI): $m/z = 374$ ($[M - H]^+$, 3), 356 ($[M - F]^+$, 25), 316 ($[M - O{=}COCH_3]^+$, 52), 212 (22), 144 (63), 145 ($C_6H_4CF_3$, 56), 129 (100), 115 27), 104 (48), 77 (C_6H_5, 18); MS (ESI): $m/z = 376$ ($[M+H]^+$).

Benzyl (2E)-[3-[4-(trifluoromethyl)phenyl]-1,2-oxazol-5(4H)-ylidene]ethanoate (**19**, $C_{19}H_{14}F_3NO_3$)
A brown liquid, yield: 50 %; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.90$ (dd, $J = 8.2$, 0.6 Hz, 2H, H2', H6'), 7.69 (d, $J = 8.2$ Hz, 2H, H3', H5'), 7.37 (m, 5H), 6.62 (s, 1H, H6), 5.22 (s, 2H, H8), 3.93 (s, 2H, H4) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 167.2$ (C5), 166.1 (C7), 161.4 (C3), 135.0 (C1"), 132.3 (C1'), 131.7 (q, $J = 32.5$ Hz, C4'), 128.6 (C3", C5"), 128.6 (C4"), 128.4 (C2", C6"), 127.1 (C2', C6'), 125.8 (q, $J = 3.8$ Hz, C3', C5'), 123.8 (q, $J = 270.7$ Hz, F_3C), 101.6 (C6), 67.5 (C8), 32.7 (C4) ppm; MS (ESI): $m/z = 361$ (M^+, 20), 360 ($[M - H]^+$, 95), 189 (70), 145 (20).

Methyl 3-[4-(trifluoromethyl)phenyl]-5-(4-methoxy-4-methylpentyl)-5-methyl-4,5-dihydro-1,2-oxazole-4-carboxylate (**20**, $C_{20}H_{26}F_3NO_4$)
A brown liquid, yield: 30 %; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.77$ (d, $J = 8.0$ Hz, 2H, H2', H6'), 7.66 (d, $J = 8.0$ Hz, 2H, H3', H5'), 3.67 (s, 1H, H4), 3.68 (s, 3H, H15), 3.16 (s, 3H, H12), 1.82 (m, 2H, H6), 1.58–1.42 (m, 4H, H7, H8), 1.48 (s, 3H, H13), 1.14 (s, 3H), 1.13 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 170.5$ (C14), 155.6 (C3), 133.2 (d, $J = 1.3$ Hz, C1'), 131.6 (q, $J = 32.6$ Hz, C4'), 127.0 (C2', C6'), 125.7 (q, $J = 3.8$ Hz, C3', C5'), 123.8 (q, $J = 271.4$ Hz, CF_3), 87.8 (C5), 74.4 (C9), 60.4 (C4), 51.9 (C15), 49.1 (C12), 40.0 (C8), 39.0 (C6), 24.9 (C10), 24.8 (C11), 24.8 (C13), 18.0 (C7) ppm.

Methyl 3-[4-(trifluoromethyl)phenyl]-4-(4-methoxy-4-methylpentyl)-4-methyl-4,5-dihydro-1,2-oxazole-5-carboxylate (**21**, $C_{20}H_{26}F_3NO_4$)
A brown liquid, yield: 20 %; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.71$ (d, $J = 8.3$ Hz, 2H, H2', H6'), 7.65 (d, $J = 8.3$ Hz, 2H, H3', H5'), 4.13 (s, 1H, H5), 3.72 (s, 3H, H15), 3.16 (s, 3H, H12), 1.8–1.5 (m, 6H, H6, H7, H8), 1.46 (s, 3H, H13), 1.14 (s, 3H), 1.13 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 168.3$ (C14), 153.4 (C3), 132.9 (C1'), 131.6 (q, $J = 32.7$ Hz C4'), 126.6 (C2', C6'), 125.6 (q, $J = 3.9$ Hz, C3', C5'), 91.1 (C5), 74.4 (C9), 52.7 (C12), 50.9 (C15), 41.9 (C4), 40.2 (C8), 37.6 (C6), 24.9 (C10), 24.8 (C11), 20.4 (C13), 18.0 (C7) ppm.

Methyl (2E)-5-[5,5-dimethyl-3-[4-(trifluoromethyl) phenyl]-4,5-dihydro-1,2-oxazol-4-yl]-3-methylpent-2-enoate (**22**, $C_{20}H_{26}F_3NO_4$)
A brown liquid, yield: 10 %; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.76$ (d, $J = 8.3$ Hz, 2H, H2', H6'), 7.67 (d, $J = 8.3$ Hz, 2H, H3', H5'), 5.59 (q, $J = 1.0$ Hz, 1H, H12), 3.67 (s, 3H, H14), 3.17 (dd, $J = 8.0$, 3.5 Hz, 1H, H4), 2.17 (s, 3H, H11), 2.16–2.08 (m, 2H, H9), 1.86–1.78 (m, 2H, H8), 1.53 (s, 3H, H6), 1.37 (s, 3H, H7) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 166.8$ (C=O), 159.5 (C3), 158.2 (C10), 131.9 (q, $J = 32.7$ Hz, C4'), 130.8 (C1'), 127.3 (C2', C6'), 126.2 (q, $J = 3.8$ Hz, C3', C5'), 124.1 (q, $J = 272.1$ Hz, F_3C), 116.3 (C12), 87.6 (C5), 53.4 (C4), 51.2 (C14), 38.2 (C9), 28.7 (C8), 25.8 (C6), 20.9 (C7) ppm.

*(5,6)-Anti (5Z)-6,10-dimethyl-2-[3-[4-(trifluoromethyl) phenyl]-4,5-dihydro-1,2-oxazol-5-yl]undeca-5,9-dien-2-yl acetate (**23**) and (5,6)-syn (5Z)-6,10-dimethyl-2-[3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazol-5-yl]undeca-5,9-dien-2-yl acetate (**24**)*
IR (neat): $\bar{\nu} = 2970$, 2929, 2860, 1735, 1620, 1600, 1450, 1410, 1326, 1248, 1169, 1129, 1070, 1016, 916, 843, 770 cm^{-1}; MS (ESI): $m/z = 474$ ($[M + Na]^+$, 100), 178 (12); HRMS (ESI): m/z calcd for $C_{25}H_{32}F_3NO_3Na$ 474.2232, found 474.2217.

23 ($C_{25}H_{32}F_3NO_3$): A brown liquid, yield: 40 %; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.79$ (d, $J = 8.4$ Hz, 2H, H2', H6'), 7.67 (d, $J = 8.4$ Hz, 2H, H3', H5'), 5.28 (dd, $J = 10.0$, 9.0 Hz, 1H, H5), 5.16–5.08 (m, 2H, H9, H13), 3.34 (d, $J = 10.0$ Hz, 1H, H4a), 3.33 (d, $J = 9.0$ Hz, 1H, H4b), 2.20–1.80 (m, 8H, H7, H8, H11, H12), 2.02 (s, 3H, H20), 1.69 (s, 9H, H17, H16, H15), 1.41 (s, 3H, H18) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 170.0$ (C19), 155.4 (C3), 136.0 (C10), 132.8 (q, $J = 1.0$ Hz, C1'), 131.9 (C14), 131.7 (C4'), 126.9 (C2', C6'), 125.7 (q, $J = 3.9$ Hz, C3', C5'), 124.2 (C9), 124.1 (C13), 123.8 (q, $J = 272.16$ Hz, F_3C), 84.2 (C6), 84.7 (C5), 35.6 (C7), 35.5 (C4), 31.9 (C11), 25.7 (C12), 23.4 (C16), 22.2, 22.1, 21.9, 18.5 (C20), 17.7 (C15) ppm.

24 ($C_{25}H_{32}F_3NO_3$): A brown liquid, yield: 35 %; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.79$ (d, $J = 8.4$ Hz, 2H, H2', H6'), 7.67 (d, $J = 8.4$ Hz, 2H, H3', H5'), 5.25 (dd, $J = 11.0$, 8.8 Hz, 1H, H5), 5.11 (m, 2H, H9, H13), 3.32 (d, $J = 11.0$ Hz, 1H, H4a), 3.27 (d, $J = 8.8$ Hz, H4b), 2.20–1.80 (m, 8H, H7, H8, H11, H12), 2.01 (s, 3H, H20),

1.62 (s, 9H, H17, H16, H15), 1.52 (s, 3H, H18) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 170.3 (C19), 155.1 (C3), 136.0 (C10), 132.8 (q, J = 1.3 Hz, C1'), 131.9 (C14), 131.7 (C4'), 126.9 (C2', C6'), 125.7 (q, J = 3.9 Hz, C3', C5'), 124.1 (C9), 124.1 (C13), 123.8 (q, J = 272.2 Hz, F_3C), 84.3 (C6), 84.0 (C5), 35.6 (C7), 34.2 (C4), 31.9 (C11), 26.5 (C12), 23.4 (C16), 22.2, 22.1, 22.0, 19.8 (C20), 17.7 (C15) ppm.

2-Methyl-5-[3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazol-5-yl]pent-3-yn-2-yl acetate
(**25**, $C_{18}H_{18}F_3NO_3$)
A brown liquid, yield: 45 %; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (d, J = 8.1 Hz, 2H, H2', H6'), 7.66 (d, J = 8.1 Hz, 2H, H3', H5'), 4.95 (dddd, J = 10.2, 6.9, 6.5, 4.8 Hz, 1H, H5), 3.47 (dd, J = 16.9, 10.2 Hz, 1H, H4a), 3.38 (dd, J = 16.9, 6.9 Hz, 1H, H4b), 2.68 (dd, J = 16.8, 4.8 Hz, H6a), 2.68 (dd, J = 16.8, 6.5 Hz, H6b), 1.91 (s, 3H, H11), 1.58 (s, 3H), 1.54 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 169.2 (C10), 155.4 (C3), 132.9 (C1'), 131.5 (q, J = 32.4 Hz, 1C, C4'), 126.9 (C2', C6'), 125.3 (q, J = 3.9 Hz, C3', C5'), 123.8 (q, J = 272.3 Hz, F_3C), 83.9 (C7), 79.2 (C5), 78.8 (C8), 71.8 (C9), 38.7 (C4), 28.9 (C12, C13), 25.0 (C6), 21.7 (C11) ppm; MS (ESI): *m/z* = 376 ($[M + Na]^+$, 100); HRMS (ESI): *m/z* calcd for $C_{18}H_{18}F_3NO_3Na$ 376.1136, found 376.1127.

2-Methyl-5-[3-[4-(propan-2-yl)phenyl]-4,5-dihydro-1,2-oxazol-5-yl]pent-3-yn-2-yl acetate (**26**, $C_{18}H_{18}F_3NO_3$)
A brown liquid, yield: 50 %; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.62 (d, J = 8.2 Hz, 2H, H2', H6'), 7.26 (d, J = 8.2 Hz, 2H, H3', H5'), 4.86 (dddd, J = 9.9, 7.1, 6.6, 4.7 Hz, 1H, H5), 3.44 (dd, J = 16.9, 9.9 Hz, 1H, H4a), 3.31 (dd, J = 16.9, 6.6 Hz, 1H, H4b), 2.92 (septet, J = 6.9 Hz, 1H, H-C$(CH_3)_2$), 2.64 (dd, J = 16.7, 4.7 Hz, H6a), 2.55 (dd, J = 16.7, 7.1 Hz, H6b), 1.92 (s, 3H, H11), 1.59 (s, 3H), 1.56 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H, $(H_3C)_2CH$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 169.2 (C10), 156.2 (C3), 151.0 (C4'), 126.9 (C1'), 126.7 (C5', C3'), 126.6 (C2', C6'), 83.6 (C7), 79.2 (C8), 78.5 (C5), 71.9 (C9), 39.3 (C4), 33.9 ($\underline{C}Me_2$), 29.0, 28.9, 25.0 (C6), 23.7 ($\underline{Me}_2C$), 21.8 (C11) ppm; MS (ESI): *m/z* = 350 ($[M + Na]^+$, 100); HRMS (ESI): calcd for $C_{18}H_{18}F_3NO_3Na$ 350.1732, found 350.1723.

2-[3-[4-(Trifluoromethyl)phenyl]-4-([[3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazol-5-yl]methyl)-1,2-oxazol-5-yl]propan-2-yl acetate (**27**, $C_{26}H_{22}F_6N_2O_4$)
A brown liquid, yield: 15 %; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.06 (d, J = 8.0 Hz, 2H, H2', H6'), 7.85 (d, J = 8.0 Hz, 2H, H2", H6"), 7.68 (d, J = 8.0 Hz, 2H, H3", H5"), 7.69 (d, J = 8.0 Hz, 2H, H3', H5'), 4.28 (dddd, J = 11.3, 6.5, 4.5, 4.0 Hz, 1H, H5), 3.12 (dd, J = 13.3, 4.0 Hz, 1H, H4a), 2.73 (dd, J = 13.3, 11.3 Hz, 1H, H4b), 2.67 (dd, J = 17.0, 4.5 Hz, H6a), 2.57 (dd, J = 17.0, 6.5 Hz, H6b), 1.95 (s, 3H, H11), 1.59 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 169.3 (C10), 156.7 (C8), 142.1 (C3), 142.0 (C14), 132.8 (q, J = 32.8 Hz, C4'), 131.3 (q, J = 32.7 Hz, C4"), 128.7 (C1'), 128.7 (C1"), 126.3 (C2', C6', C2", C6"), 125.6 (m, C3', C5', C3", C5"), 123.9 (q, J = 272.4 Hz, F_3CAr'), 123.7 (q, J = 272.4 Hz, F_3C-Ar"), 108.7 (C7), 84.5 (C5), 78.1 (C9), 50.7 (C4), 29.1 (C12), 29.0 (C13), 21.9 (C6), 21.1 (C11) ppm; MS (ESI): *m/z* = 563 ($[M + Na]^+$, 100); HRMS (ESI): *m/z* calcd for $C_{26}H_{22}F_6N_2O_4Na$ 563.1381, found 563.1375.

2-[3-[4-(Propan-2-yl)phenyl]-4-[3-[4-(propan-2-yl)phenyl-4,5-dihydro-1,2-oxazol-5-yl]methyl]-1,2-oxazol-5-yl]propan-2-yl acetate (**28**, $C_{30}H_{36}N_2O_4$)
A brown liquid, yield: 12 %; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.87 (d, J = 8.2 Hz, 2H, H2', H6'), 7.61 (d, J = 8.0 Hz, 2H, H2", H6"), 7.27 (d, J = 8.2 Hz, 2H, H3', H5'), 7.25 (d, J = 8.0 Hz, 2H, H3', H5'), 4.26 (dddd, J = 7.2, 6.6, 4.8, 4.2 Hz, 1H, H5), 3.08 (dd, J = 13.2, 4.2 Hz, 1H, H4a), 2.97–2.87 (m, 2H, 2x $\underline{H}C(CH_3)_2$), 2.90 (dd, J = 13.2, 6.6 Hz, 1H, H4b), 2.66 (dd, J = 16.7, 4.8 Hz, H6a), 2.50 (dd, J = 16.7, 7.2 Hz, H6b), 1.96 (s, 3H, H11), 1.58 (s, 6H, H12, H13), 1.31–1.22 (m, 12H, 2x $(\underline{H}_3C)_2CH$) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 169.3 (C10), 157.5 (C8), 152.1 (C3), 149.6 (C14), 135.9, 129.9, 128.6, 127.8 (C4'), 126.8 (C3'), 126.6 (C5'), 125.8 (C2', C6'), 126.4, 108.3 (C7), 84.1 (C5), 78.6, 77.6 (C9), 72.0, 50.6 (C4), 34.3, 33.9, 29.7, 29.7, 29.1 (CH_3), 29.0 (CH_3), 23.9 (CH_3), 23.9 (CH_3), 23.8 (CH_3), 23.7 (CH_3), 22.0 ppm; MS (ESI): *m/z* = 489 ($[M+H]^+$, 35), 488 ($[M]^+$, 55), 450 (83), 448 (83), 389 (55), 388 (100).

*(5R, 6Z, 8S)-6-[2[(4E, 7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-octahydro-1H-inden-4-ylidene)-3-[trifluoromethyl)phenyl]-1-oxa-2-azaspiro[4, 5]dec-2-8-yl acetate (**29**) and (5S, 6Z, 8S)-6-[2[(4E, 7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-octahydro-1H-inden-4-ylidene)-3-[trifluoromethyl)phenyl]-1-oxa-2-azaspiro[4, 5]dec-2-8-yl acetate (**30**)*
29 ($C_{37}H_{50}F_3NO_3$): A yellowish semisolid, yield: 24 %; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.78 (d, J = 8.5 Hz, 2H, H2', H6'), 7.66 (d, J = 8.5 Hz, 2H, H3', H5'), 6.28 (d, J = 11.6 Hz, 1H, H12), 6.19 (d, J = 11.6, 1H, H11), 5.02 (quint, J = 4.0 Hz, 1H, H8), 3.42 (d, J = 16.5 Hz, H4a), 3.31 (d, J = 16.5 Hz, H4b), 2.76 (dd, J = 12.5, 4.0 Hz, 1H, H17a), 2.62 (dd, J = 12.5, 4.0 Hz, 1H, H9a), 2.49 (dm, J = 12.5 Hz, 1H, H9b), 2.27–2.21 (m, 2H, H17b, H21), 2.06 (s, 3H, H_3CC=O), 2.06–2.01 (m, 2H), 2.03–1.94 (m, 2H), 1.89–1.83 (m, 2H), 1.79–1.72 (m, 1H), 1.69–1.62 (m, 1H), 1.54–1.49 (m, 2H), 1.33–1.29 (m, 5H), 1.16–1.10 (m, 3H), 0.90–0.82 (m, 2H), 0.89 (s, 3H, H_3C), 0.90–0.82 (m, 9H, 3 CH_3) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz):

δ = 170.9 (C30), 154.7 (C3), 145.3 (C6), 139.5 (C13), 133.4, 130.9, 129.5, 126.7 (C2', C6'), 125.7 (q, J = 3.9 Hz, C3', C5'), 123.8, 122.1, 119.2, 116.0, 90.4 (C5), 69.5 (C8), 56.6 (C13, H_3CC=O), 46.0 (C4), 40.4, 40.3, 39.5, 36.1, 33.4, 29.7, 28.3, 28.2 (CH_3), 27.6, 27.3, 23.9, 23.6, 22.8 (CH_3), 22.5, 22.2, 21.4 (CH_3), 18.8 (CH_3) ppm.

30 ($C_{37}H_{50}F_3NO_3$): A yellowish semisolid, yield: 29 %; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.77 (d, J = 8.0 Hz, 2H, H2', H6'), 7.65 (d, J = 8.0 Hz, 2H, H3', H5'), 6.37 (d, J = 11.6 Hz, H11), 6.25 (d, J = 11.6, H12), 4.89 (ddd, J = 11.0, 9.0, 4.5 Hz, 1H, H8), 3.36 (s, 2H, H4), 2.79 (dm, J = 11.0 Hz, 1H, H7a), 2.72 (dd, J = 13.8, 3.3 Hz, 1H, H9a), 2.33–2.28 (m, 2H, H9b, H7b), 2.17 (s, 3H, H_3C), 2.20–2.10 (m, 2H), 2.06 (s, 3H, H31), 2.04–1.96 (m, 3H), 1.84–1.81 (m, 1H), 1.66–1.51 (m, 4H), 1.37–1.24 (m, 3H), 1.17–1.04 (m, 2H), 0.98–0.85 (m, 5H), 1.70–1.45 (m, 1H, H10), 0.92 (d, J = 6.5 Hz, 3H, H23), 0.87 (d, J = 6.5 Hz, 3H, H28), 0.86 (d, J = 6.5 Hz, 3H, H29), 0.57 (s, 3H, H_3C) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 170.4 (C30), 154.7 (C3), 145.7 (C6), 139.5 (C13), 133.4 (q, J = 1.1 Hz, C1'), 131.0, 129.2, 126.7 (C2', C6'), 125.7 (q, J = 3.6 Hz, C3', C5'), 123.7 (C11), 116.1 (C12), 90.4 (C5), 71.4 (C8), 56.7, 56.0, 46.0 (C4), 45.4, 41.6, 40.5, 39.5, 36.1, 34.8, 29.7, 28.2, 28.0, 27.6, 23.9, 23.6, 23.0, 22.6, 21.3, 18.9 ppm.

Fungicidal testing

The compounds were screened for fungicidal activity in vitro. The tests were carried out for *Alternaria alternata* (*A. a.*), *Botrytis cinerea* (*B. c.*), *Fusarium culmorum* (*F. c.*), *Phytophthora cactorum* (*P. c.*), and *Rhizoctonia solani* (*R. s.*), and involved determination of mycelial growth retardation in potato glucose agar (PGA). Test strains of pathogenic fungi were obtained from the Department of Plant Pathology and Entomology of the University of Warmia and Mazury in Olsztyn, Poland. The strains were stored on agar slants (PDA medium, Oxoid) in a refrigerator at 4 °C and were subcultured every 5–8 weeks onto a fresh medium.

Stock solutions of test chemicals in acetone were added to agar medium to give a concentration of 200 μg/cm^3 and dispersed into Petri dishes. Four discs containing the test fungus were placed at intervals on the surface of the solidified agar and the dishes were then inoculated for 4–8 days depending on the growth rate of the control samples, after which fungal growth was compared with that in untreated control samples. The fungicidal activity was expressed as the percentage of fungi linear growth inhibition compared to that of the control.

Acknowledgments This work was supported in part by the Polish Ministry of Science and Higher Education (Research Grant NR EMC: 0150 084 31), which is gratefully acknowledged.

References

1. Bast K, Christl M, Huisgen R, Mack W, Sustman R (1973) Chem Ber 106:3258
2. Zimmermann PJ, Blanarikova I, Juger V (2000) Angew Chem Int Ed 39:910
3. Ghorai S, Mukhopadhyay R, Kundu AP, Bhattacharjya A (2005) Tetrahedron 61:2999
4. Caramella P, Grunanger P (1984) In: Padwa A (ed) 1,3-Dipolar cycloaddition chemistry. Wiley, New York, p 177
5. Mukayama T, Hoshino T (1960) J Am Chem Soc 82:5339
6. Shimizu T, Hayashi T, Shibafuchi H, Teramura K (1986) Bull Chem Soc Jpn 59:2827
7. Gothelf KV, Jørgensen KA (1998) Chem Rev 98:863
8. Pellisier H (2007) Tetrahedron 63:3235
9. Kissane M, Maguire AR (2010) Chem Soc Rev 39:845
10. Kanemasa S, Nishiuchi M, Kamimura A, Hori K (1994) J Am Chem Soc 116:2324
11. Kheruze YI, Galishev VA, Petrov AA (1988) Zh Org Khim 24:944
12. Taylor RE, Hearn BR, Ciavarri JP (2002) Org Lett 4:2953
13. Hwang SH, Kurth MJ (2002) Tetrahedron Lett 43:53
14. Ong CW, Chien T-L (1996) Organometallics 15:1323
15. Fisera L, Ondrus V, Timpe HJ (1990) Collect Czech Chem Commun 55:512
16. Gucma M, Gołębiewski WM, Krawczyk M (2013) J Braz Chem Soc 24:805
17. Gucma M, Gołębiewski WM, Michalczyk AK (2014) J Mol Struct 1060:223
18. Gucma M, Gołębiewski WM, Michalczyk AK (2016) J Braz Chem Soc. doi:10.5935/0103-5053.20160078
19. Gucma M, Gołębiewski WM (2011) Catal Sci Technol 1:1354
20. Gucma M, Gołębiewski WM, Krawczyk M (2015) RSC Adv 5:13112
21. Gerdes JM, Norman AW, Okamura WH (1981) J Org Chem 46:599
22. Mouriño A, Blair P, Wecksler W, Norman AW, Okamura WH (1978) J Med Chem 21:1025
23. Liu KC, Shelton BR, Howe RK (1980) J Org Chem 45:3916
24. Hyperchem 7.5. Hypercube company, Gainesville, Florida, 32601 USA
25. McNulty J, Steere JA, Wolf S (1998) Tetrahedron Lett 39:8013
26. Houk KH, Sims J, Watts CR, Jenkins LJ (1973) J Am Chem Soc 95:7301
27. Raimondi L (1997) Gazz Chim Ital 127:167
28. Lewis FD, Howard DK, Barancyk SV, Oxman JD (1986) J Am Chem Soc 108:3016
29. Lau KCY, Chiu P (2011) Tetrahedron 67:8769
30. Comenskey DJ, Rowan DD, Matich AJ (2006) J Label Compd Radiopharm 49:47
31. Khomenko TM, Tatarova LE, Korchagina DV, Barthash VA (2002) Russ J Org Chem 38:498
32. Curci R, Detomaso A, Prencipe T, Carpenter GB (1994) J Am Chem Soc 116:8112