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Probing the Influence of an Allylic Methyl Group in Zearalenone Analogues on Binding to Hsp90

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Dedicated to Professor Richard R. Schmidt on the occasion of his 75th birthday

Abstract: By the replacement of an acetate with propionate by means of organic synthesis, a range of zearalenone analogues were prepared that feature an allylic methyl group. For the synthesis of the aliphatic region of the analogues, we used an asymmetric alkylation to yield pentenol derivatives **16** and *ent*-**16**. By means of hydroboration the corresponding aldehydes were secured. These were coupled with 2-pentynol derivate **23** by means of a Carreira acetylide addition. Further routine steps led to the sulfones **29** and **45**, respectively. After merging them with 2-bromobenzaldehyde **9** in a Julia–Kocienski reaction, metalation, carboxylation, and protecting-group manipulations gave the seco acids **35** and **49**. By means of lactonization under Mitsunobu (alcohol activation) or Trost–Kita conditions (carboxyl activation), all four possible macrocyclic ketone stereoisomers were accessible. In all, considering various protecting-group decorations, 16 analogues were obtained and tested for cytotoxicity (L929 mouse fibroblast cell line). Whereas most of the analogues were less active than zearalenone (IC_{50} = 9.4 μM), the resorcinol derivatives were comparable, with one stereoisomer (**40b**) being slightly more active (IC_{50} = 6.6 μM). These results were also reflected in the binding assays to Hsp90 in which **40b** showed a dissociation constant (K_d) value of 130 nM.

Keywords: asymmetric synthesis · Hsp90 · macrolactonization · natural products · zearalenone

Introduction

Various bioinformatic studies that employ chemical descriptors highlight the difference in chemical space occupied by natural products versus drugs.[1] In particular, it seems that the structural diversity among natural products is broader as compared with synthetic small molecules. Moreover, only about half of the natural-product-based drugs fully comply with the Lipinski Rule of Five. The other half violate these rules with the exception of the log*P* value.[2] On the other hand, natural products share a common feature with synthetic drugs, namely, clustering of similar compounds. In medicinal chemistry, similar structures with comparable mode of action are known as "me-too" drugs. With natural products, their diversity and similarity can be traced back to biosynthetic strategies. Thus, only a few building blocks are in use, but repeated incorporation and branching leads to different scaffolds.[3] The tailoring of reactions—such as redox reactions—on certain structures produce the compound clusters. Despite their structural similarity, compounds from a cluster (for example, steroids) may still have large differences in biological activity. Even though a large number of natural products is known, many more seem theoretically possible. Thus, about 10000 polyketide structures have been isolated up to now.[4,5] However, according to a theoretical analysis of polyketide biosynthesis, a billion structures seem possible.[4c] In this regard, some key questions arise, such as

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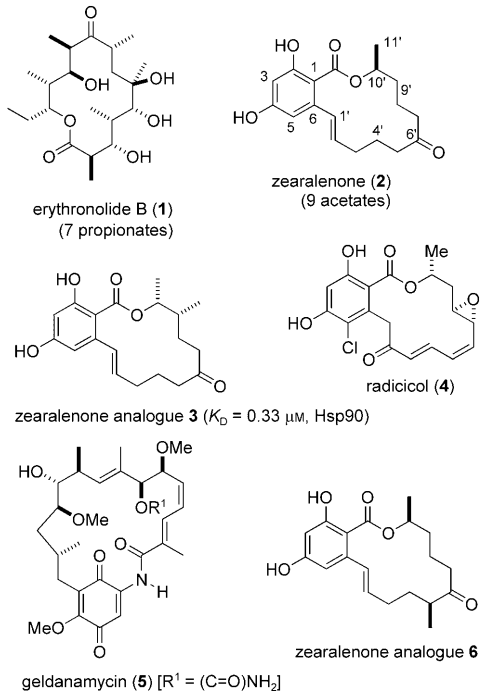
why only such a small number is made biosynthetically and why many conceivable structures are not known. Certainly, nature might have missed some opportunities. For example, polyketides are typically comprised of acetates and propionate building blocks in various ratios. Surprisingly, some polyketides are made up only of propionates, such as erythronolide B (**1**), whereas others such as zearalenone (**2**) represent pure polyacetates. The latter are typical for fungi,

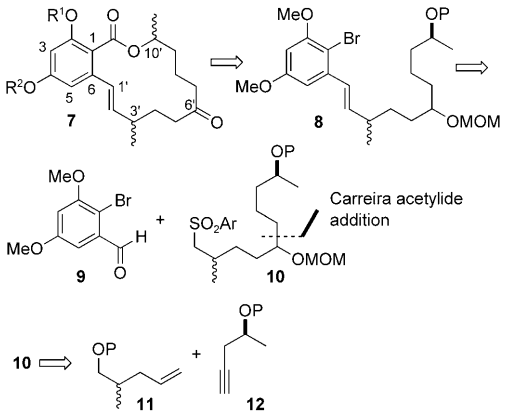


since their biosynthetic machinery only can incorporate acetates. Accordingly, incorporating the other lacking building block into these structures, either in erythronolide B or polyacetate-based macrolactones, should provide interesting analogues. Considering this, we conceived the concept of propionate scanning and applied it to the macrolide zearalenone (**2**).[6,7] This benzolactone, which is of fungal origin, consists of nine acetates.[8] Replacing the second acetate led to propionate analogues of zearalenone that bind to the heat shock protein 90 (Hsp90).[7] Compounds **3** and *ent*-**3** showed dissociation constant (K_d) values of 0.33 and 0.25 μM, respectively. Hsp90 and related proteins are chaperones that promote folding of denatured proteins. Since several client proteins of Hsp90 are involved in cancer, Hsp90 is a promising target for cancer treatment.[9] Whereas a range of heterocycles bind to the adenosine triphosphate (ATP) pocket of Hsp90,[10] the natural products radicicol[11] (**4**) and geldanamycin[12] (**5**) were also found to bind to Hsp90. Both natural products stimulated the development of synthetic analogues.[13–17]

Benzolactone **6**, which features a propionate in place of the fourth acetate, turned out to be an inhibitor for human carbonyl reductase 1.[6] In contrast to zearalenone (**2**) itself, analogue **6** does not bind to Hsp90 as determined by thermal shift assay. Whereas the biosynthesis of polyketides is akin to an assembly line, organic synthesis strives to be convergent and treelike. As a consequence, the replacement of an acetate by a propionate in zearalenone requires a different synthesis strategy for each acetate replacement. In this paper, we describe the synthesis and biological studies of zearalenone analogues with a methyl group in the allylic position; that is, the fifth acetate was replaced by a propionate.

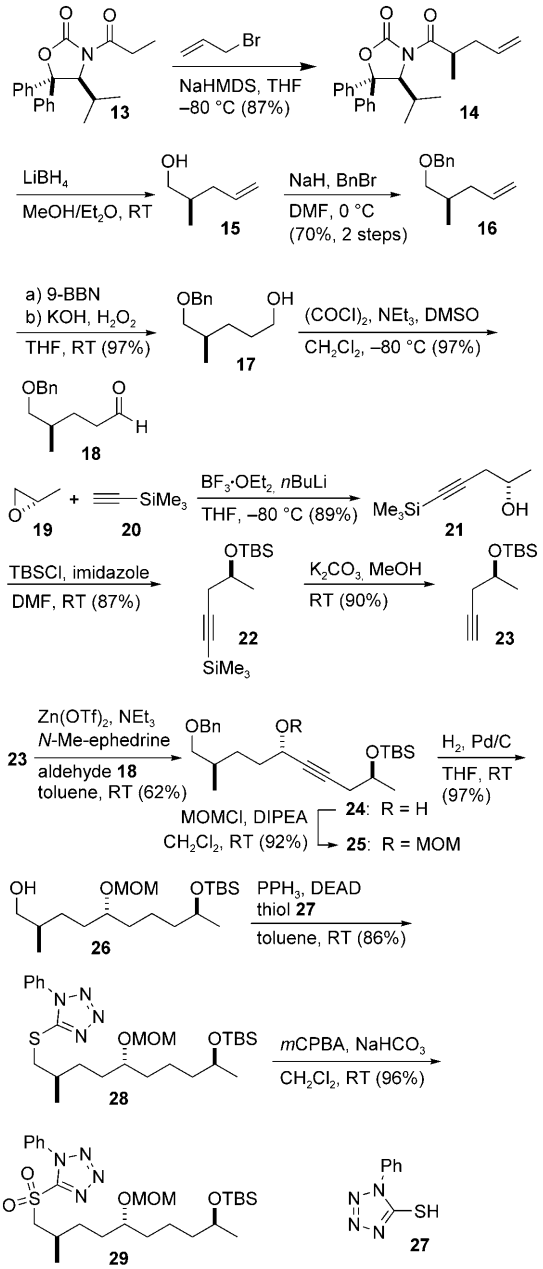
Results and Discussion

Chemistry: Although ring-closing metathesis (RCM) seems like the best option for the formation of the macrolactone ring,[18] we thought that the allylic methyl group might have a detrimental influence on the outcome of the RCM. Therefore, we opted for a classical macrolactonization approach. Also, we wanted to prepare all possible diastereomers with the methyl-bearing centers in a stereocontrolled manner. Accordingly, the plan was to form the *E* double bond by means of Julia–Kocienski olefination. In this setup, C-3′-Me would be installed by asymmetric alkylation. As has been described by Pan et al.[19] in the synthesis of aigialomycin D, the carboxylic function of the orsellinic subunit would be installed at a late stage through an aryl lithium intermediate (Scheme 1). Two aliphatic subunits **11** and **12**, each containing a stereogenic center, would be combined by means of a Carreira acetylide–aldehyde coupling.



Scheme 1. Retrosynthetic analysis for zearalenone analogues of type **7**; P = protecting group.

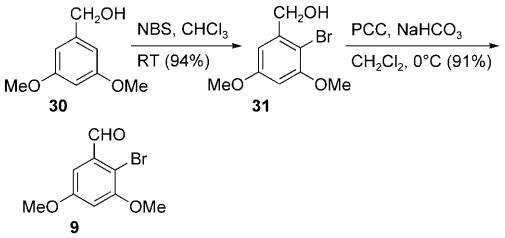
The synthesis of the aliphatic building block **29** is shown in Scheme 2. Allylation of propionyloxazolidinone[20] **13**, which contained the Seebach auxiliary,[21] provided pentenoyl derivative **14**. Reductive removal of the auxiliary and benzylation of alcohol **15** furnished ether **16**. Hydroboration of the double bond and Swern oxidation[22] of alcohol **17** gave rise to aldehyde **18**, which corresponds to the C6′–C2′ region of the designed zearalenone analogues. The aldehyde **18** would be used as electrophile in an addition reaction



Scheme 2. Synthesis of aliphatic building block **29**. NaHMDS = sodium bis(trimethylsilyl)amide, Bn = benzyl, 9-BBN = 9-borabicyclo-[3.3.1]nonane, TBS = *tert*-butyldimethylsilyl, DIPEA = *N*,*N*-diisopropylethylamine, DEAD = diethyl azodicarboxylate, *m*CPBA = *meta*-chloroperbenzoic acid.

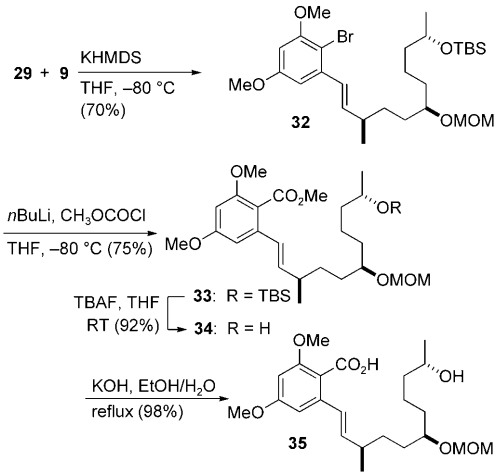
with an alkyne. A suitable alkyne could be obtained from (*S*)-propylenoxide **19** and trimethylsilyl acetylide. Alcohol protection of homopropargylic alcohol[23] **21** to silyl ether[24] **22** and removal of the trimethylsilyl group provided fragment **23**. Aldehyde **18** and alkyne[25] **23** were now combined by means of a Carreira reaction.[26] This secured uniform intermediates in subsequent transformations. Thus, *N*-methylephedrine (1.1 equiv), Et_3N, and zinc triflate (1.1 equiv) were combined followed by addition of alkyne **23** (1.1 equiv) and finally aldehyde **18** (1.0 equiv), thereby resulting in propargylic alcohol **24** (62%) as a single diastereomer. After methoxymethyl ether (MOM) protection, catalytic hydrogenation removed the triple bond and the benzyl ether to provide primary alcohol **26**. By means of Mitsunobu substitution with 1-phenyl-1*H*-tetrazole-5-thiol (**27**) and subsequent oxidation of thioether **28**, sulfone **29** could be secured on a gram scale.

Preparation of the aromatic aldehyde **9** commenced with benzylalcohol[27] **30**. Bromination with *N*-bromosuccinimide (NBS)[28] provided aryl bromide **31**, which was oxidized with pyridinium chlorochromate to yield aldehyde[28,29] **9** (Scheme 3).



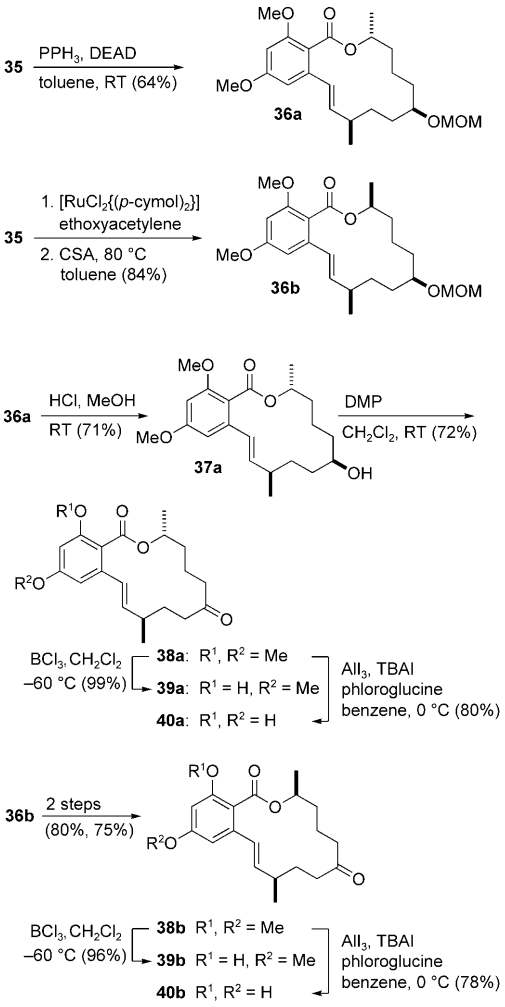
Scheme 3. Synthesis of 2-bromo-3,5-dimethoxybenzaldehyde (**9**). PCC = pyridinium chlorochromate.

The two building blocks, benzaldehyde **9** and sulfone **29**, were combined by means of Julia–Kocienski coupling[30] by using $KN(SiMe_3)_2$ as base in THF at −80 °C (Scheme 4). This gave *E* alkene **32** in good yield. The subsequent metalation and carboxylation proved challenging. Thus, metalation with *n*BuLi (THF, −80 °C) followed by quenching the aryllithium intermediate with CO_2 (solid or gas) did not give high yields of the corresponding benzoic acid. More consistent results were obtained with methyl chlorocarbonate (5 equiv), thereby providing ester **33** in good yield. Cleavage of the silyl ether and saponification of the ester function led to seco acid **35**.



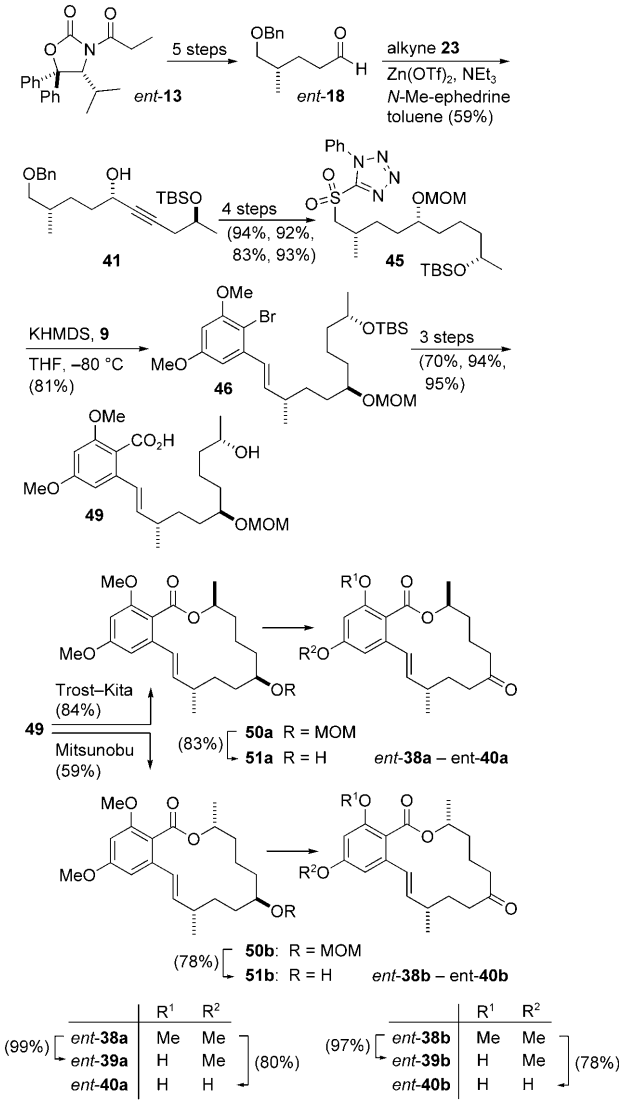
Scheme 4. Synthesis of seco acid **35** by means of Julia coupling and carboxylation. TBAF = tetrabutylammonium fluoride.

According to previous experience, macrolactonization is generally possible with such sterically hindered hydroxy acids under Mitsunobu conditions.[6,7,31] Indeed, lactonization of hydroxy acid **35** (0.005 M) in toluene using PPh_3 (2.3 equiv) and diethyl azodicarboxylate delivered lactone **36a** in 64% yield (Scheme 5). Since we also wanted to access the other diastereomer at C-10′, lactonization with carboxyl activation was also tried. Whereas Yamaguchi conditions were unsatisfactory (10% yield), the Kita–Trost variant worked well.[32,33] Thus, hydroxy acid **35** was converted to the mixed ketene acetal by ruthenium(II)-catalyzed addition to ethoxyacetylene. Thereafter, a solution of the intermediate 1-ethoxyvinyl benzoate was slowly added to a hot solution of camphorsulfonic acid (CSA) in toluene to produce lactone **36b** in 84% yield. Cleavage of the MOM protecting group (HCl/MeOH) gave alcohol **37a**, the oxidation of which furnished ketone **38a**. Selective cleavage of the 2-OMe ether was possible in essentially quantitative yield to give phenol **39a**. Removal of both aromatic methyl ether functions proved to be more troublesome. Whereas aluminum triiodide (AlI_3) in benzene did work to some degree on dimethyl ether **38a**, the reaction led to iodinated derivatives as side products and gave variable yields of resorcinol **40a**. Reproducible yields of dihydroxy lactone **40a** were possible in presence of phloroglucine (5 equiv), which served as a scavenger for iodine. In the same manner, diastereomeric lactone **36b** was converted to zearalenone analogues **37b**–**40b** with comparable yields for all steps.



Scheme 5. Lactonization of hydroxy acid **35** and refunctionalization of lactones **36a** and **36b**. DMP = Dess–Martin periodinane, TBAI = tetrabutylammonium iodide.

Access to the enantiomeric series of zearalenone analogues was started with propionyloxazolidinone *ent*-**13** ((+)-**13**). As described before, alkylation, reductive removal of the auxiliary, protection of the primary alcohol as benzyl ether, double-bond hydroboration, and oxidation led to *ent*-**18** (Scheme 6). By means of Carreira acetylide addition, alkynol **41** and then sulfone **45** could be reached. Coupling with benzaldehyde **9**, metalation, carboxylation, and protect-



Scheme 6. Synthesis of the enantiomeric series of lactones *ent*-**38**–*ent*-**40** from propionyloxazolidinone *ent*-**13**; for procedures and yields in this series, see the Supporting Information.

ing-group manipulations secured seco acid **49**. Macrolactonization under Kita–Trost conditions to give **50a** proceeded in 84% yield, whereas Mitsunobu conditions furnished 59% of diastereomer **50b**. Through hydrolysis of the MOM acetal to **51a** and **51b**, respectively, oxidation of the 6′-OH, and cleavage of the methyl ether functions, analogues *ent*-**38a**–*ent*-**40a** and *ent*-**38b**–*ent*-**40b** were obtained.

Biology

Growth inhibition: To assess the biological activity, analogues **37a**, **38a**–**40a**, **37b**, **38b**–**40b, 51a**, *ent*-**38a**–*ent*-**40a**, **51b**, and *ent*-**38b**–*ent*-**40b** (16 compounds) were tested for growth inhibition on L929 mouse fibroblast cells. The obtained IC_{50} values are included in Table 1. As can be seen,

Table 1. Cytoxicity of the tested macrolactones.

Compound	IC_{50} [μM]
37a	39
37b	69
51b	44
51a	18
38a	36
38b	111
ent-**38b**	47
ent-**38a**	39
39a	27
39b	26
ent-**39b**	20
ent-**39a**	20
40a	18
40b	6.6
ent-**40b**	14
ent-**40a**	12

the di-*O*-methyl ethers are much less active than zearalenone ($IC_{50}=9.4$ μM). The least-active compounds are the 10′*S*,3′*R* diastereomers (10′up,3′up). There are four analogues that show roughly half of the activity of zearalenone. These are the monomethoxy analogues **39a**, **39b**, *ent*-**39a**, and *ent*-**39b**. The fully deprotected analogues **40a**, **40b**, *ent*-**40a**, and *ent*-**40b** turned out to be significantly more active. Analogue **40b** ($IC_{50}=6.6$ μM) is clearly more active than zearalenone.

Binding to Hsp90: The most promising analogues were then further evaluated for binding Hsp90 by employing a thermal shift assay.[34–36] To obtain the K_d values, the melting temperature (T_m) measurements were performed at various concentrations for compounds *ent*-**40a**, *ent*-**40b**, **40a**, and **40b**, for reasons of comparison with radicicol (**4**). The corresponding Hsp90N melting temperature data as a function of ligand concentration is plotted in Figure 1. Curves that show the dependence of fluorescence on temperature for two ligands (*ent*-**40a** and **40b**) are shown on the lower panels. The stronger binder, **40b**, shifted the T_m to a greater extent than the weak binders. The Hsp90N protein was prepared as previously described.[37]

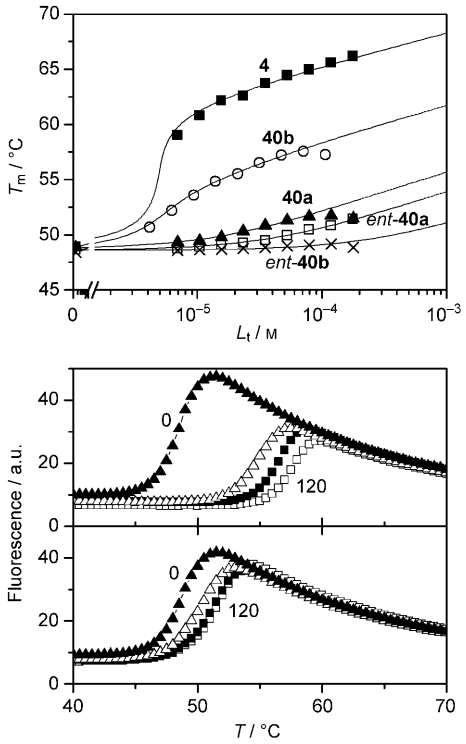


Figure 1. Hsp90N melting temperature (T_m) data as a function of added ligand concentration L_t. Panels on the bottom compare denaturation curves observed by fluorescence at 0 to 120 μM added ligand concentrations. The top of the bottom panels shows data for **40b**, the lower panel for *ent*-**40a**.

The melting curves allowed for a determination of the K_d values, which are shown for resorcinols **40** in Table 2.

Although the strong binding of radicicol could not be reached, zearalenone analogue **40b** did display a K_d value of 130 nM.

Table 2. Dissociation constants of selected compound binding to Hsp90N as determined by the thermal shift assay.

Compound	K_d [μM]
40a	9.1
ent-**40a**	26
40b	0.13
ent-**40b**	182
radicicol (**4**)	0.001

Conclusion

The purpose of this study was to elucidate the effect of an additional methyl group in the binding of the fungal metabolite zearalenone to Hsp90. From a biosynthetic point of view, a methyl group on a polyketide corresponds to a replacement of an acetate building block by a propionate. Here we formally replaced acetate number five with a propionate, thereby resulting in zearalenone analogues with an allylic methyl group. All four possible stereoisomers and several differently methylated derivatives could be accessed.

Key steps in the synthesis of the analogues include a Carreira acetylide addition to an aldehyde to reach the aliphatic fragment. Its coupling with the aromatic building block was realized by a Julia–Kocienski olefination. Halogen–metal exchange on the aryl bromide followed by carboxylation of the anion led to the seco acids. Lactonization could be achieved by Trost–Kita or Mitsunobu lactonization in a stereodivergent manner. As determined by thermal shift assay, one analogue, **40b**, turned out to be a good binder (K_d = 130 nM) to Hsp90. Although this represents a focused case study, it does underscore two important facts. Namely, the resorcinol subunit (2,4-dihydroxy-6-alkenylbenzoic acid part) seems to be important for binding to Hsp90. Furthermore, a methyl group represents a privileged aliphatic substituent. It seems that the secondary and tertiary structures of proteins can provide hydrophobic pockets that can be matched perfectly with a methyl group. The same should be true for other privileged substituents, such as hydroxyl, keto, or nitrogen-based groups. Accordingly, these natural substituents should be preferentially employed in drug-discovery programs.

Experimental Section

(2*R*,5*S*,9*S*)-1-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-2-methyldec-6-yn-5-ol (24): Triethylamine (4.76 mL, 34.3 mmol, 1.5 equiv) was added to a solution of *N*-methyl ephedrine (4.51 g, 25.2 mmol, 1.1 equiv) in dry toluene (40 mL) under atmospheric pressure. In a separate flask, zinc triflate (9.15 g, 25.2 mmol, 1.1 equiv) was dried under high vacuum at 150 °C for 3 h. After cooling to room temperature, the triflate was treated with the suspension of ephedrine/triethylamine in toluene in one portion under a nitrogen atmosphere, and the light yellow suspension was stirred vigorously for 2 h at ambient temperature before alkyne **23** (4.99 g, 25.2 mmol, 1.1 equiv) in dry toluene (5 mL) was added. The reaction mixture was stirred for 1 h before aldehyde **18** (4.72 g, 22.9 mmol, 1.0 equiv) in dry toluene (10 mL) was added dropwise over 4 h by syringe pump. The light yellow mixture was allowed to warm to room temperature overnight, before saturated NH_4Cl solution (150 mL) and ethyl acetate (150 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 15:1) afforded propargyl alcohol **24** (5.7 g, 62 %) as a colorless oil. R_f = 0.25 (petroleum ether/EtOAc, 10:1); $[\alpha]_D^{20}$ = +1.5 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3H; $Si(CH_3)_2$), 0.07 (s, 3H; $Si(CH_3)_2$), 0.88 (s, 9H; $C(CH_3)_3$), 0.94 (d, J = 6.6 Hz, 3H; 2-CH_3), 1.19–1.34 (m, 1H; 4-H), 1.51–1.89 (m, 4H; 2-H, 3-H, 4-H), 2.25 (ddd, J = 16.4, 7.2, 1.9 Hz, 1H; 8-H), 2.37 (ddd, J = 16.4, 5.6, 1.8 Hz, 1H; 8-H), 3.26 (dd, J = 9.1, 6.6 Hz, 1H; 1-H), 3.32 (dd, J = 9.1, 6.1 Hz, 1H; 1-H), 3.86–3.93 (m, 1H; 9-H), 4.28–4.37 (m, 1H; 5-H), 4.49 (s, 2H; $PhCH_2$), 7.22–7.39 ppm (m, 5H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.64 ($Si(CH_3)_2$), 17.1 (2-CH_3), 18.1 ($C(CH_3)_3$), 23.3 (C-10), 25.8 ($C(CH_3)_3$), 29.2 (C-8), 29.6 (C-3), 33.3 (C-2), 35.5 (C-4), 63.0 (C-5), 67.6 (C-9), 73.0 (C-1), 75.7 ($PhCH_2$), 82.6 (C-6 or C-7), 82.9 (C-6 or C-7), 127.5 (ar C), 128.3 (ar C), 138.7 ppm (ar C); HRMS (ESI): m/z: calcd for $C_{24}H_{40}O_3SiNa$ $[M+Na]^+$: 427.26389; found: 427.26420.

[(2*R*,6*S*,9*R*)-10-(Benzyloxy)-6-(methoxymethoxy)-9-methyldec-4-yn-2-yloxy](*tert*-butyl)dimethylsilane (25): Diisopropylethylamine (5.38 mL, 30.9 mmol, 10 equiv), methoxy methylchloride (1.52 mL, 15.5 mmol, 5 equiv), and tetrabutylammonium iodine (114 mg, 0.31 mmol, 0.1 equiv) were added to a cooled (0 °C) solution of propagyl alcohol **24** (1.25 g, 3.09 mmol, 1 equiv) in dry CH_2Cl_2 (30 mL). The stirred, light yellow solution was allowed to warm to room temperature overnight. In the case of incomplete conversion, additional diisopropylethylamine (2.69 mL, 15.5 mmol, 5 equiv) and methoxy methylchloride (0.76 mL, 7.73 mmol, 2.5 equiv) were added at 0 °C under a nitrogen atmosphere and the mixture was stirred again overnight at ambient temperature before saturated $NaHCO_3$ solution (100 mL) and CH_2Cl_2 (100 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with saturated NaCl solution (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 30:1) afforded protected MOM ether **25** (1.3 g, 92 %) as a colorless oil. R_f = 0.50 (petroleum ether/EtOAc, 10:1); $[\alpha]_D^{20}$ = −90.8 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H; $Si(CH_3)_2$), 0.87 (s, 9H; $C(CH_3)_3$), 0.95 (d, J = 6.8 Hz, 3H; 9-CH_3), 1.20 (d, J = 6.1 Hz, 3H; 2-CH_3), 1.20–1.37 (m, 1H; 7-H), 1.51–1.88 (m, 4H; 7-H, 8-H, 9-H), 2.25 (ddd, J = 16.5, 7.3, 1.8 Hz, 1H; 3-H), 2.37 (ddd, J = 16.4, 5.3, 1.5 Hz, 1H; 3-H), 3.25 (dd, J = 9.1, 6.8 Hz, 1H; 10-H), 3.33 (dd, J = 9.1, 6.8 Hz, 1H; 10-H), 3.35 (s, 3H; OCH_3), 3.86–4.01 (m, 1H; 2-H), 4.24–4.31 (m, 1H; 6-H), 4.49 (s, 2H; $PhCH_2$), 4.56 (d, J = 6.8 Hz, 1H; OCH_2OCH_3), 4.93 (d, J = 6.8 Hz, 1H; OCH_2OCH_3), 7.21–7.39 ppm (m, 5H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7 ($Si(CH_3)_2$), 17.1 (9-CH_3), 18.1 ($C(CH_3)_3$), 23.4 (2-CH_3), 25.8 ($C(CH_3)_3$), 29.3 (C-3 or C-8), 29.6 (C-3 or C-8), 33.3 (C-9), 33.5 (C-7), 55.6 (OCH_3), 66.1 (C-6), 67.6 C-2), 73.0 (C-10), 75.8 ($PhCH_2$), 80.1 (C-5), 83.5 (C-4), 93.9 (OCH_2OCH_3), 127.5 (ar C), 128.3 (ar C), 138.8 ppm (ar C); HRMS (ESI): m/z: calcd for $C_{26}H_{44}O_4SiNa$ $[M+Na]^+$: 471.29011; found: 471.29003.

(2*R*,5*R*,9*S*)-9-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-2-methyldecan-1-ol (26): A catalytic amount of palladium (10 % Pd/C, 100 mg) was added to a solution of alkyne **25** (5.5 g, 12.24 mmol) in dry THF (100 mL). The black reaction mixture was stirred vigorously under a balloon of hydrogen at room temperature. After 72 h, the reaction was filtered through a pad of Celite, the filter cake was washed with THF (100 mL), and the filtrate concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:1) afforded alcohol **26** (4.3 g, 97 %) as a colorless oil. R_f = 0.20 (petroleum ether/EtOAc, 10:1); $[\alpha]_D^{20}$ = +16.2 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H; $Si(CH_3)_2$), 0.87 (s, 9H; $C(CH_3)_3$), 0.92 (d, J = 6.82 Hz, 3H; 2-CH_3), 1.10 (d, J = 6.1 Hz, 3H; 9-CH_3), 1.20–1.70 (m, 11H; 2, 3, 4, 6, 7, 8-H), 3.37 (s, 3H; OCH_3), 3.31–3.43 (dd, J = 10.6, 6.3 Hz, 1H; 1-H) 3.46–3.55 (m, 1H; 9-H), 3.50 (dd, J = 10.6, 6.3 Hz, 1H; 1-H), 3.71–3.84 (m, 1H; 5-H), 4.64 ppm (s, 2H; OCH_2OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.72 ($Si(CH_3)_2$), −4.40 ($Si(CH_3)_2$), 16.6 (2-CH_3), 18.1 ($C(CH_3)_3$), 21.7 (C-7), 23.8 (9-CH_3), 25.9 ($C(CH_3)_3$), 28.5 (C-4), 31.5 (C-3), 34.4 (C-6), 35.9 (C-2), 39.9 (C-8), 55.5 (OCH_3), 68.2 (C-1), 68.6 (C-9), 77.8 (C-5), 95.5 ppm (OCH_2OCH_3); HRMS (ESI): m/z: calcd for $C_{19}H_{42}O_4SiNa$ $[M+Na]^+$: 385.27446; found: 385.17449.

5-[(2*R*,5*R*,9*S*)-9-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-2-methyldecylthio]-1-phenyl-1*H*-tetrazole (28): A cooled (0 °C) solution of alcohol **26** (3.22 g, 8.88 mmol, 1 equiv) in dry toluene (120 mL) was treated with 1-phenyl-1*H*-tetrazole-5-thiol (**27**) (1.90 g, 10.66 mmol, 1.2 equiv) and triphenylphosphine (9.32 g, 35.5 mmol, 4 equiv) under a nitrogen atmosphere. Then diethyl azodicarboxylate (16.28 mL, 40 % in toluene, 35.5 mmol, 4 equiv) was added dropwise. The brown suspension was allowed to warm to room temperature over 2 h, before water (200 mL) and ethyl acetate (200 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with saturated NaCl (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) afforded thioether **28** (4.0 g, 86 %) as a colorless oil. R_f = 0.74 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$ = +11.5 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (d, J = 2.5 Hz, 6H; $Si(CH_3)_2$), 0.86 (s, 9H; $C(CH_3)_3$), 1.04 (d, J = 6.6 Hz, 3H; 2-CH_3), 1.10 (d, J = 6.1 Hz, 3H; 9-CH_3), 1.15–1.75 (m, 10H; 3, 4, 6, 7, 8-H), 1.86–2.00 (m, 1H; 2-H), 3.27 (dd, J = 12.6, 7.3 Hz, 1H; 1-H), 3.35 (s, 3H; OCH_3), 3.45 (dd, J = 12.6, 7.3 Hz, 1H; 1-H), 3.47–3.54 (m, 1H; 9-H), 3.71–3.83 (m, 1H; 5-H), 4.62 (s, 2H; OCH_2OCH_3), 7.46–7.63 ppm (m, 5H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.1 (2-CH_3), 21.6 (9-CH_3), 23.8 (C-7), 25.9 ($C(CH_3)_3$), 31.3 (C-4), 31.5 (C-1), 33.1 (C-2), 34.4 (C-3), 39.8 (C-6), 40.4

(C-8), 55.6 (OCH_3), 68.5 (C-9), 77.4 (C-5), 95.4 (OCH_2OCH_3), 123.9 (ar C), 129.8 (ar C), 130.1 (ar C), 133.8 (ar C), 154.6 ppm (hetaryl C); HRMS (ESI): *m/z*: calcd for $C_{26}H_{46}N_4O_3SSiNa$ $[M+Na]^+$: 545.29521; found: 545.294970.

5-[(2*R*,5*R*,9*S*)-9-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-2-methyldecylsulfonyl]-1-phenyl-1*H*-tetrazole (29): Predried *m*-chloroperbenzoic acid (1.42 g, 5.74 mmol, 3 equiv) in dry CH_2Cl_2 (5 mL) was added dropwise to a cooled (0 °C) solution of thioether **28** (1.0 g, 1.91 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) under a nitrogen atmosphere, and the white suspension was stirred 24 h at ambient temperature. In case of incomplete conversion (TLC control), additional *m*-chloroperbenzoic acid (0.95 g, 3.83 mmol, 2 equiv) in dry CH_2Cl_2 (5 mL) was added dropwise and the mixture stirred again 24 h at ambient temperature before aqueous sodium thiosulfate/1 M sodium hydroxide (70 mL) and CH_2Cl_2 (70 mL) were added. After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) afforded sulfone **29** (1.0 g, 96 %) as a colorless oil. R_f=0.6 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=+12.1 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.02 (s, 3H; $Si(CH_3)_2$), 0.03 (s, 3H; $Si(CH_3)_2$), 0.87 (s, 9H; $C(CH_3)_3$), 1.10 (d, *J*=6.1 Hz, 3H; 9-CH_3), 1.17 (d, *J*=6.6 Hz, 3H; 2-CH_3), 1.20–1.72 (m, 10H; 3, 4, 6, 7, 8-H), 2.27–2.40 (m, 1H; 2-H), 3.35 (s, 3H; OCH_3), 3.46–3.54 (m, 1H; 5-H), 3.59 (dd, *J*=14.5, 8.0 Hz, 1H; 1-H), 3.71–3.80 (m, 1H; 9-H), 3.81 (dd, *J*=14.7, 4.8 Hz, 1H; 1-H), 4.59–4.67 (m, 2H; OCH_2OCH_3), 7.55–7.72 ppm (m, 5H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.7 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.6 (2-CH_3), 21.6 (C-7), 23.8 (9-CH_3), 25.9 ($C(CH_3)_3$), 28.5 (C-2), 31.1 (C-4), 32.1 (C-3), 34.4 (C-6), 39.8 (C-8), 55.6 (C-1), 61.7 (OCH_3), 68.5 (C-9), 77.3 (C-5), 95.5 (OCH_2OCH_3), 125.1 (ar C), 129.7 (ar C), 131.5 (ar C), 133.1 (ar C), 154.0 ppm (hetaryl C); HRMS (ESI): *m/z*: calcd for $C_{26}H_{46}N_4O_5SSiNa$ $[M+Na]^+$: 577.28504; found: 577.28505.

2-Bromo-1-[(3′*R*,6′*R*,10′*S*,*E*)-10-*tert*-butyldimethylsilyloxy-6-(methoxymethoxy)-3-methylundec-1-enyl]-3,5-dimethoxybenzene (32): Potassium hexamethyldisilazane (0.47 mL, 0.5 M in toluene, 0.234 mmol, 1.3 equiv) was added dropwise to a cooled (−80 °C) solution of sulfone **29** (100 mg, 0.18 mmol, 1 equiv) in dry THF (8 mL) under a nitrogen atmosphere. After stirring the yellow solution for 45 min, aldehyde **9** (46 mg, 0.189 mmol, 1.05 equiv) in dry THF (2 mL) was added, and the colorless reaction mixture was stirred for 30 min at −80 °C. The solution was allowed to warm to room temperature for 1 h before saturated NaCl solution (70 mL) and ethyl acetate (70 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3× 100 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 15:1) afforded alkene **32** (88.0 mg, 83 %) as a colorless oil. R_f=0.63 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{20}$=−5.85 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.02 (s, 3H; $Si(CH_3)_2$), 0.02 (s, 3H; $Si(CH_3)_2$), 0.86 (s, 9H; $C(CH_3)_3$), 1.09 (d, *J*=6.1 Hz, 3H; 3′-CH_3 or 10′-CH_3), 1.10 (d, *J*=6.6 Hz, 3H; 3′-CH_3 or 10′-CH_3), 1.18–1.65 (m, 10H; 4′, 5′, 7′, 8′, 9′-H), 2.24–2.40 (m, 1H; 3′-H), 3.37 (s, 3H; OCH_2OCH_3), 3.48–3.59 (m, 1H; 6′-H), 3.68–3.84 (m, 1H; 10′-H), 3.81 (s, 3H; ar OCH_3), 3.85 (s, 3H; ar OCH_3), 4.64 (s, 2H; OCH_2OCH_3), 5.98 (dd, *J*=15.8, 8.0 Hz, 1H; 2′-H), 6.37 (d, *J*=2.5 Hz, 1H; ar H), 6.63 (d, *J*=2.5 Hz, 1H; ar H), 6.72 ppm (d, *J*=15.2 Hz, 1H; 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.7 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 20.6 (3′-CH_3), 21.7 (C-8′), 23.8 (10′-CH_3), 25.9 ($C(CH_3)_3$), 32.0 (C-4′), 32.3 (C-5′), 34.5 (C-6′), 37.5 (C-9′), 39.9 (C-3′), 55.5 (ar OCH_3), 56.3 (OCH_3), 68.6 (C-10′), 77.2 (C-6′), 95.4 (OCH_2OCH_3), 98.4 (ar CBr), 102.9 (ar C), 104.2 (ar C), 127.8 (C-1′), 139.3 (C-1), 139.7 (C-2′), 156.7 (ar $COCH_3$), 159.5 ppm (ar $COCH_3$); HRMS (ESI): *m/z*: calcd for $C_{28}H_{49}BrO_5SiK$ $[M+K]^+$: 611.21642; found: 611.21601.

Methyl 2-[(3*R*,6*R*,10*S*,*E*)-10-(*tert*-butyldimethylsilyloxy)-6-(methoxymethoxy)-3-methylundec-1-enyl]-4,6-dimethoxybenzoate (33): *n*BuLi (0.113 mL, 2.5 M in hexane, 0.192 mmol, 2.2 equiv) was added dropwise to a cooled (−80 °C) solution of aryl bromide **32** (50.0 mg, 0.087 mmol, 1 equiv) in dry THF (4 mL) under a nitrogen atmosphere, and the resulting yellow solution was stirred for 30 min. Then freshly distilled methyl chlorocarbonate (0.036 mL, 0.436 mmol, 5 equiv) was added dropwise at −80 °C and the reaction was stirred for 1 h at −80 °C. The colorless solution was allowed to warm to room temperature over 1 h, before saturated NH_4Cl solution (50 mL) and ethyl acetate (50 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:1) afforded benzoate **33** (35.8 mg, 75 %) as a colorless oil. R_f= 0.25 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{20}$=−13.0 (*c*=0.6 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.02 (s, 6H; $Si(CH_3)_2$), 0.86 (s, 9H; $C(CH_3)_3$), 1.06 (d, *J*=6.6 Hz, 3H; 3′-CH_3 or 10′-CH_3), 1.09 (d, *J*=6.1 Hz, 3H; 3′-CH_3 or 10′-CH_3), 1.18–1.66 (m, 10H; 4′, 5′, 7′, 8′, 9′-H), 2.15–2.35 (m, 1H; 3′-H), 3.36 (s, 3H; OCH_2OCH_3), 3.47–3.55 (m, 1H; 6′-H), 3.72–3.81 (m, 1H; 10′-H), 3.79 (s, 3H; OCH_3), 3.82 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 4.63 (s, 2H; OCH_2OCH_3), 6.00 (dd, *J*=15.7, 7.8 Hz, 1H; 2′-H), 6.29 (d, *J*=15.7 Hz, 1H; ar H), 6.33 (d, *J*=2.3 Hz, 1H; ar H), 6.56 ppm (d, *J*=2.0 Hz, 1H; 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.7 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 20.5 (3′-CH_3), 21.7 (C-8′), 23.8 (10′-CH_3), 25.9 ($C(CH_3)_3$), 32.0 (C-7′), 32.3 (C-5′), 34.5 (C-4′), 37.6 (C-3′), 39.9 (C-9′), 52.2 (CO_2CH_3), 55.5 (OCH_3), 56.0 (OCH_2OCH_3), 68.6 (C-10′), 77.4 (C-6′), 95.45 (OCH_2OCH_3), 97.4 (ar C), 101.6 (ar C), 115.4 (C-1), 125.3 (C-1′), 138.0 (C-2′), 139.8 (C-2), 158.0 (C-1), 161.4 (ar $COCH_3$), 168.6 ppm (CO_2CH_3); HRMS (ESI): *m/z*: calcd for $C_{24}H_{52}O_7SiNa$ $[M+Na]^+$: 575.33745; found: 575.33750.

Methyl 2-[(3*R*,6*R*,10*S*,*E*)-10-hydroxy-6-(methoxymethoxy)-3-methylundec-1-enyl]-4,6-dimethoxybenzoate (34): Tetra-*N*-butylammonium fluoride (275 mg, 0.872 mmol, 2 equiv) was added to a solution of ester **33** (235 mg, 0.436 mmol, 1 equiv) in dry THF (2 mL) under a nitrogen atmosphere. After stirring for 24 h at ambient temperature, saturated NaCl solution (50 mL) and Et_2O (50 mL) were added. After separation of the layers, the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic layers were washed with saturated NaCl (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 1:1) afforded hydroxy ester **26** (176 mg, 92 %) as a colorless oil. R_f=0.1 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=−15.7 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.06 (d, *J*=6.6 Hz, 3H; 3′-CH_3), 1.16 (d, *J*=6.3 Hz, 3H; 10′-CH_3), 1.15–1.69 (m, 10H; 4′, 5′, 7′, 8′, 9′-H), 2.15–2.38 (m, 1H; 3′-H), 3.37 (s, 3H; OCH_2OCH_3), 3.48–3.57 (m, 1H; 6′-H), 3.68–3.89 (m, 1H; 10′-H), 3.78 (s, 3H; OCH_3), 3.82 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 4.64 (s, 2H; OCH_2OCH_3), 5.99 (dd, *J*=15.7, 8.3 Hz, 1H; 2′-H), 6.29 (d, *J*=15.7 Hz, 1H; 1′-H), 6.33 (d, *J*=2.0 Hz, 1H; ar H), 6.57 ppm (d, *J*=2.0 Hz, 1H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.6 (3′-CH_3), 21.5 (C-8′), 23.5 (10′-CH_3), 31.9 (C-7′), 32.2 (C-5′), 34.3 (C-4′), 37.5 (C-3′), 39.4 (C-9′), 52.2 (CO_2CH_3), 55.4 (OCH_3), 55.6 (OCH_3), 56.0 (OCH_3), 68.0 (C-10′), 77.5 (C-6′), 95.4 (OCH_2OCH_3), 97.4 (ar C), 101.6 (ar C), 115.4 (C-1), 125.3 (C-1′), 137.9 (C-2), 139.7 (C-2′), 158.0 (ar $COCH_3$), 161.4 (ar $COCH_3$), 168.6 ppm (CO_2CH_3); HRMS (ESI): *m/z*: calcd for $C_{29}H_{38}O_7Na$ $[M+Na]^+$: 461.25097; found: 461.250741.

2-[(3*R*,6*R*,10*S*,E)-10-Hydroxy-6-(methoxymethoxy)-3-methylundec-1-enyl]-4,6-dimethoxybenzoic acid (35): A solution of hydroxy ester **34** (50.0 mg, 0.114 mmol) in a 10 % solution of potassium hydroxide in a mixture of ethanol/water (1.5 mL, v/v=95:5) was heated at reflux for 36 h. After cooling, the mixture was diluted with water (20 mL) and Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×30 mL), before it was carefully acidified (pH 3) with 1 M hydrochloric acid. The acidified aqueous layers were extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/methanol, 9:1) afforded hydroxy acid **35** (48.0 mg, 98 %) as a colorless oil. R_f=0.28 (petroleum ether/EtOAc/AcOH, 1:3:0.01); $[\alpha]_D^{20}$= −9.3 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (d, *J*= 6.8 Hz, 3H; 3′-CH_3), 1.19 (d, *J*=6.1 Hz, 3H; 10′-CH_3), 1.21–1.68 (m, 10H; 4′, 5′, 7′, 8′, 9′-H), 2.17–2.38 (m, 1H; 3′-H), 3.38 (s, 3H; OCH_3), 3.42–3.59 (m, 1H; 6′-H), 3.83 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 3.78–3.95 (m, 1H; 10′-H), 4.51–4.55 (m, 2H; OCH_2OCH_3), 5.89 (dd, *J*=15.7,

8.3 Hz, 1H; 2′-H), 6.36 (d, J=2.3 Hz, 1H; ar H), 6.55 (d, J=2.3 Hz, 1H; ar H), 6.65 ppm (d, J=15.7 Hz, 1H; 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.2 (3′-CH_3), 21.5 (C-8′), 23.6 (10′-CH_3), 31.4 (C-7′), 31.8 (C-5′), 34.0 (C-4′), 37.1 (C-3′), 39.1 (C-9′), 55.4 (ar OCH_3), 56.2 (OCH_2OCH_3), 68.6 (C-10′), 77.6 (C-6′), 95.2 (OCH_2OCH_3), 97.4 (ar C), 103.3 (ar C), 114.0 (ar C), 127.0 (C-1′), 139.6 (C-2′), 140.1 (C-2), 158.3 (ar $COCH_3$), 161.6 (ar $COCH_3$), 169.0 ppm (CO_2H); HRMS (ESI): m/z: calcd for $C_{23}H_{36}O_7Na$ $[M+Na]^+$: 447.23532; found: 447.23534.

(3′*R*,10′*R*)-Macrolactone 36a: Triphenylphosphine (114 mg, 0.433 mmol, 2.3 equiv) was added to a cooled (0 °C) solution of hydroxy acid **35** (80.0 mg, 0.188 mmol, 1 equiv) in dry toluene (40 mL) under a nitrogen atmosphere followed by dropwise addition of *N*,*N*-diethyl azodicarboxylate (1.90 mL, 40 % in toluene, 0.415 mmol, 2.2 equiv) over 5 h with a syringe pump. The reaction mixture was allowed to warm to room temperature overnight before it was concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) afforded lactone **36a** (49.0 mg, 64 %) as a colorless oil. R_f=0.65 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=−215 (c=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (d, J=6.8 Hz, 3H; 3′-CH_3), 1.34 (d, J=6.3 Hz, 3H; 10′-CH_3), 1.32–1.80 (m, 10H; 9′-H, 8′-H, 7′-H, 5′-H, 4′-H), 2.15–2.33 (m, 1H; 3′-H), 3.37 (s, 3H; OCH_2OCH_3), 3.55–3.71 (m, 1H; 6′-H), 3.79 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 4.57–4.68 (m, 2H; OCH_2OCH_3), 5.13–5.26 (m, 1H; 10′-H), 6.20 (dd, J=16.2, 7.1 Hz, 1H; 2′-H), 6.34 (d, J=2.0 Hz, 1H; ar H), 6.41 (d, J=16.2 Hz, 1H; 1′-H), 6.56 ppm (d, J=2.0 Hz, 1H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (10′-CH_3), 20.6 (C-8′), 21.2 (3′-CH_3), 22.6 (C-5′), 27.6 (C-7′*C*), 29.0 (C-9′), 30.9 (C-4′), 35.4 (C-3′), 35.7 (OCH_2OCH_3), 55.2 (OCH_3), 55.9 (OCH_3), 64.2 (OCH_2OCH_3), 70.7 (C-10′), 75.2 (C-6′), 94.6 (OCH_2OCH_3), 97.5 (ar C), 101.5 (ar C), 116.5 (C-1), 124.5 (C-1′), 136.8 (C-6), 138.8 (C-2′), 157.8 (C-2), 161.0 (C-4), 168.0 ppm (CO_2); HRMS (ESI): m/z: calcd for $C_{23}H_{34}O_6Na$ $[M+Na]^+$: 429.22476; found: 429.22476.

(3′*R*,10′*S*)-Macrolactone 36b: A cooled (0 °C) solution of hydroxy acid **35** (150 mg, 0.35 mmol, 1 equiv) in dry toluene (15 mL) was treated with di-μ-chloro-bis[chloro(*p*-cymol)ruthenium(II) complex (4.3 mg, 0.007 mmol, 0.02 equiv) and ethoxy acetylene (0.113 mL, 40 % in hexane, 0.53 mmol, 1.5 equiv) under a nitrogen atmosphere, and the resulting dark brown solution was stirred at ambient temperature for 3 h. The mixture was then concentrated in vacuo and the residue was dissolved in toluene (15 mL) again. This resulting brown solution was added dropwise to a stirred solution of (±)-camphorsulfonic acid (16.4 mg, 0.071 mmol, 0.2 equiv) in toluene (100 mL) by syringe pump over 3 h at 80 °C under a nitrogen atmosphere. After further stirring at 80 °C for 30 min, the reaction mixture was allowed to cool to room temperature overnight before saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (100 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) afforded lactone **36b** (64.0 mg, 84 %) as a colorless oil. R_f=0.65 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=+5.5 (c=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01 (d, J=6.6 Hz, 3H; 3′-CH_3), 1.23 (d, J=6.3 Hz, 3H; 10′-CH_3), 1.16–1.86 (m, 10H; 9′, 8′, 7′, 5′, 4′-H), 2.28–2.44 (m, 1H; 3′-H), 3.31 (s, 3H; OCH_2OCH_3), 3.42–3.57 (m, 1H; 6′-H), 3.72 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 4.50 (d, J=7.1 Hz, 1H; OCH_2OCH_3), 4.64 (d, J=6.8 Hz, 1H; OCH_2OCH_3), 5.30–5.41 (m, 1H; 10′-H), 5.75 (dd, J=15.7, 9.4 Hz, 1H; 2′-H), 6.28 (d, J=1.8 Hz, 1H; ar H), 6.32 (d, J=15.7 Hz, 1H; 1′-H), 6.54 ppm (d, J=2.0 Hz, 1H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.4 (10′-CH_3), 20.2 (C-8′), 21.9 (3′-CH_3), 30.9 (C-5′), 32.2 (C-7′), 33.6 (C-9′), 35.0 (C-4′), 36.3 (C-3′), 55.4 (OCH_3), 55.9 (OCH_3), 60.3 (OCH_2OCH_3), 70.7 (C-10′), 75.0 (C-6′), 94.9 (OCH_2OCH_3), 97.6 (ar CH), 101.1 (ar CH), 116.7 (C-1), 126.7 (C-1′), 136.8 (C-6), 139.2 (C-2′), 157.4 (C-2), 161.2 (C-4), 167.8 ppm (CO_2); HRMS (ESI): m/z: calcd for $C_{23}H_{34}O_6Na$ $[M+Na]^+$: 429.22476; found: 429.225013.

(3′*R*,10′*R*)-Macrolactone 37a: Concentrated hydrochloric acid (0.12 mL) was added to a cooled (0 °C) solution of lactone **36a** (50.0 mg, 0.123 mmol) in methanol (2.5 mL), and the mixture was allowed to warm to room temperature over 1 h before it was stirred for 36 h at ambient temperature. The reaction mixture was then treated carefully with saturated sodium hydrogen carbonate at 0 °C until the mixture was neutralized, then ethyl acetate (50 mL) was added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 2:1) afforded hydroxy lactone **36a** (36.1 mg, 81 %) as a colorless oil. R_f=0.21 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=−24.3 (c=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (d, J=6.8 Hz, 3H; 3′-CH_3), 1.34 (d, J=6.3 Hz, 3H; 10′-CH_3), 1.14–1.88 (m, 10H; 9′, 8′, 7′, 5′, 4′-H), 2.17–2.33 (m, 1H; 3′-H), 3.67–3.85 (m, 1H; 6′-H), 3.78 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 5.12–5.27 (m, 1H; 10′-H), 6.16 (dd, J=16.0, 7.0 Hz, 1H; 2′-H), 6.34 (d, J=2.3 Hz, 1H; ar H), 6.42 (d, J=16.2 Hz, 1H; 1′-H), 6.55 ppm (d, J=2.0 Hz, 1H; ar H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.6 (3′-CH_3), 21.3 (10′-C), 22.5 (C-8′), 27.4 (C-9′), 31.4 (C-5′), 34.2 (C-7′), 35.4 (C-4′), 35.6 (C-3′), 55.4 (OCH_3), 56.0 (OCH_3), 70.3 (C-6′ or C-10′), 70.7 (C-6′ or C-10′), 97.5 (ar CH), 101.6 (ar CH), 116.4 (C-1), 124.7 (C-1′), 137.0 (C-6), 138.9 (C-2′), 157.8 (C-2), 161.1 (C-4), 168.0 ppm (CO_2); HRMS (ESI): m/z: calcd for $C_{21}H_{30}O_5Na$ $[M+Na]^+$: 385.19855; found: 385.19871.

(3′*R*,10′*R*)-Macrolactone 38a and *ent*-38a: A cooled (0 °C) solution of hydroxy lactone **37a** (32.0 mg, 0.088 mmol, 1 equiv) in dry CH_2Cl_2 (1.5 mL) was treated with Dess–Martin periodinane (74.9 mg, 0.177 mmol, 2 equiv) under a nitrogen atmosphere, and the mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with a mixture of saturated $Na_2S_2O_3$/saturated $NaHCO_3$/water (1:1:1, 30 mL) and with CH_2Cl_2 (30 mL). After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) afforded ketolactone **38a** (22.8 mg, 72 %) as a white solid. R_f=0.39 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$ =+9.0 (c=1.0 in CH_2Cl_2 for **38a**), −7.3 (c=1.0 in CH_2Cl_2 for *ent*-**38a**); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.06 (d, J=6.6 Hz, 3H; 3′-CH_3), 1.33 (d, J=6.6 Hz, 3H; 10′-CH_3), 1.41–1.54 (m, 1H; 4′-H), 1.57–1.71 (m, 2H; 9′-H), 1.66–1.85 (m, 2H; 8′-H), 1.83–1.95 (m, 1H; 4′-H), 2.17 (dt, J=13.1, 7.5 Hz, 1H; 7′-H), 2.24–2.37 (m, 1H; 3′-H), 2.43 (dd, J=7.6, 5.8 Hz, 2H; 5′-H), 2.55 (dt, J=13.4, 6.7 Hz, 1H; 7′-H), 3.80 (s, 3H; OCH_3), 3.82 (s, 3H; OCH_3), 5.24–5.37 (m, 1H; 10′-H), 5.94 (dd, J=15.9, 8.1 Hz, 1H; 2′-H), 6.37 (d, J=2.0 Hz, 1H; ar H), 6.51 (d, J=2.0 Hz, 1H; ar H), 6.58 ppm (d, J=15.9 Hz, 1H; 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.3 (10′-CH_3), 21.5 (C-8′), 21.9 (3′-CH_3), 29.5 (C-4′), 35.4 (C-9′), 36.1 (C-3′), 38.0 (C-5′), 42.8 (C-7′), 55.4 (OCH_3), 56.0 (OCH_3), 70.7 (C-10′), 97.7 (ar CH), 102.5 (ar CH), 115.5 (C-1), 126.8 (C-1′), 138.0 (C-6), 138.7 (C-2′), 158.4 (CO_2 or C-4 or C-2), 161.4 (CO_2 or C-4 or C-2), 167.4 (CO_2 or C-4 or C-2), 212.0 ppm (C-6′); HRMS (ESI): m/z: calcd for $C_{21}H_{28}O_5Na$ $[M+Na]^+$: 383.18290; found: 383.18313 (**38a**), 383.182893 (*ent*-**38a**).

(3′*R*,10′*R*)-Macrolactone 39a and *ent*-39a: Boron trichloride (0.386 mL, 1 M in CH_2Cl_2, 0.386 mmol, 20 equiv) was added dropwise to a cooled (−60 °C) solution of keto lactone **38a** (7.0 mg, 0.019 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL) under a nitrogen atmosphere. The dark brown solution was allowed to warm to room temperature over 1 h. After complete conversion, the reaction mixture was again cooled to −60 °C before methanol (1 mL) was added dropwise. The brown mixture was allowed to warm to room temperature and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/Et_2O, 3:1) afforded mono-deprotected lactone **39a** (6.5 mg, 99 %) as a white solid. R_f=0.65 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=147.8 (c=1.0 in CH_2Cl_2 for **39a**), −130.1 (c=1.0 in CH_2Cl_2 for *ent*-**39a**); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01 (d, J=6.8 Hz, 3H; 3′-CH_3), 1.01–1.28 (m, 2H; 5′-H), 1.31 (d, J=6.3 Hz, 3H; 10′-CH_3), 1.38–1.79 (m, 4H; 9′-H, 8′-H, 5′-H), 1.96–2.15 (m, 2H; 7′-H, 4′-H), 2.18–2.36 (m, 1H; 3′-H), 2.48–2.61 (dt, J=12.4, 8.8, 3.8 Hz, 1H; 7′-H), 2.70–2.85 (dt, J=18.7, 12.6, 2.3 Hz, 1H; 4′-H), 3.76 (s, 3H; OCH_3), 4.93–5.05 (m, 1H; 10′-H), 5.45 (dd, J=15.3, 10.0 Hz, 1H; 2′-H), 6.33 (s, 1H; ar H), 6.38 (s, 1H; ar H), 6.96 (d, J=15.4 Hz, 1H; 1′-H), 12.11 ppm (s, 1H; 2-OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.1 (10′-CH_3), 22.4 (C-8′), 22.7 (3′-CH_3), 29.6 (C-4′), 34.7 (9′-C), 36.7 (C-3′), 37.3 (C-7′), 42.9 (C-5′), 55.4 (OCH_3), 73.4 (C-10′), 99.8 (ar

CH), 103.5 (C-1), 108.5 (ar CH), 131.9 (C-1′), 138.2 (C-2′), 143.4 (C-6), 164.0 (C-2), 165.8 (C-4), 171.4 (CO_2), 211.1 ppm (C-6′); HRMS (ESI): m/z: calcd for $C_{20}H_{26}O_5Na$ $[M+Na]^+$: 369.16725; found: 369.16735 (**39a**), 369.167249 (*ent*-**39a**).

(3′*R*,10′*R*)-Macrolactone 40a and *ent*-40a: A suspension of aluminum powder (29.0 mg, 1.074 mmol, 43 equiv) in dry benzene (2 mL) was treated with iodine (101 mg, 0.400 mmol, 16 equiv) under a nitrogen atmosphere and the violet mixture was stirred under reflux for 30 min until the color had changed to a colorless mixture. After cooling to 5 °C, a few crystals of tetra-*N*-butylammonium iodide and phloroglucine (15.8 mg, 0.125 mmol, 5 equiv) were added before a solution of lactone **38a** (9.0 mg, 0.025 mmol, 1 equiv) in dry benzene (0.3 mL) was added in one portion. The resulting green brown suspension was stirred for 30 min at 5 °C before saturated $Na_2S_2O_3$ solution (30 mL) and ethyl acetate (30 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:1) afforded zearalenone derivative **40a** (28.5 mg, 80%) as a white solid. R_f=0.54 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$=+107.1 (c=0.5 in CH_2Cl_2 for **40a**), −109.1 (c=0.5 in CH_2Cl_2 for *ent*-**40a**); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01 (d, J=6.6 Hz, 3H; 3′-CH_3) 1.04–1.27 (m, 1H; 5′-H), 1.31 (d, J=6.1 Hz, 3H; 10′-CH_3), 1.43–1.77 (m, 5H; 9′, 8′, 5′-H), 1.98–2.15 (m, 2H; 7′-H, 4′-H), 2.21–2.35 (m, 1H; 3′-H), 2.56 (dd, J=9.2, 4.3 Hz, 1H; 7′-H), 2.79 (ddd, J=18.7, 12.5, 2.2 Hz, 1H; 4′-H), 4.88–4.98 (m, 1H; 10′-H), 5.46 (dd, J=15.3, 10.0 Hz, 1H; 2′-H), 6.31 (d, J=2.5 Hz, 1H; ar H), 6.96 (d, J=2.5 Hz, 1H; ar H), 7.01 (d, J=15.2 Hz, 1H; 1′-H), 12.07 ppm (s, 1H; 2-OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.1 (10′-CH_3), 22.4 (C-8′), 22.7 (3′-CH_3), 29.6 (C-9′), 34.7 (C-4′), 36.8 (C-3′), 37.3 (C-5′), 42.9 (C-7′), 73.5 (C-10′), 102.4 (ar CH), 103.9 (C-1), 108.5 (ar CH), 131.8 (C-1′), 138.4 (C-2′), 144.2 (C-6), 160.4 (CO_2, C-4, C-2), 165.6 (CO_2, C-4, C-2), 171.3 (CO_2, C-4, C-2), 211.3 ppm (C-6′); HRMS (ESI): m/z: calcd for $C_{19}H_{24}O_5Na$ $[M+Na]^+$: 355.15159; found: 355.151720 (**40a**), 355.151846 (*ent*-**40a**).

Cytotoxicity assay: The toxicity of the compounds with L929 cells was tested with an 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay after 5 d of incubation of serial dilutions of the samples.[38,39] The cell line was from DSMZ and kept in 1,2-dimethoxyethane (DME) medium as reported. Radicicol was purchased from Sigma, GEA from Serva.

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