CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801398

Total Synthesis and Biological Activity of Neopeltolide and Analogues

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Abstract: Combining the core structure of neopeltolide, lactone **16a**, with the oxazole-containing side chain **23** via a Mitsunobu reaction provided the cytotoxic natural product neopeltolide (**2**). The side chain **23** was prepared from oxazolone **24** via the corresponding triflate. Key steps in the preparation of **23** were a Sonogashira coupling, an enamine alkylation, and a Still–Gennari Horner–Emmons reaction. By changing the Leighton reagent in the allylation step, the 11-epimer of lactone **16a**, compound **50** was prepared. This led to 11-*epi*-neopeltolide **51**. The 5-epimer of neopeltolide, compound **52**, could be obtained from the minor isomer of the Prins cyclization. Furthermore, a range of analogues with modifications in the side chain were prepared. All derivatives were checked for toxicity effects on mammalian cell cultures and inhibitory effects on NADH oxidation in submitochondrial particles of bovine heart. Modifications in the lactone part are tolerated to some degree. On the other hand, shortening the distance between the oxazole and the lactone causes a significant drop in activity. Analogue **65** with an additional double bond is equally or even more active than neopeltolide itself.

Keywords: allylation · mitochondria · natural products · neopeltolide · prins cyclization

Introduction

In recent years the search for secondary metabolites in marine organism revealed a range of novel natural products with interesting structures and biological activities.[1] Two illustrative examples include leucascandralide A (**1**) and neopeltolide (**2**) (Scheme 1). Both feature an elaborate macrolactone to which an oxazole-containing side chain is attached at C5 via an ester bond. Interestingly, this side chain is identical in both compounds. Leucascandrolide A was isolated in 1996 from the sponge *Leucascandra careolata* which was collected at the east coast of New Caledonia.[2] In the meantime it turned out that **1** is most likely the product of a bacterium that colonized the sponge.[3] Leucascandrolide A shows strong in vitro cytotoxicity against KB and P 388 cell lines. Meanwhile, a range of total syntheses[4] or formal total syntheses[5] for leucascondrolide A have appeared. However, only recently the mode of action could be clarified. Thus, the Kozmin group identified the cytochrome bc_1 complex of the mitochondrial respiratory chain as the principal cellular target of these two natural products.[6,7] Recognizing the differences in the macrolactone part of these two natural product Kozmin et al. surmised that structural simplifications should be tolerated. In fact, a simplified leucascandrolide analogue (see below) was prepared and screened against a commercially available library of 4900 yeast strains with different haploid nonessential gene deletions. Among the sensitive mutants one was haploid in the SNF4 gene. The corresponding gene product is a key regulator of glucose metabolism in that it senses the cellular AMP/ATP ratio. This led to the hypothesis that the two natural products interfere with mitochondrial oxidative phosphorylation. This could be supported by further studies, which revealed that the cytochrome bc_1 complex is the molecular target of leucascandrolide A and neopeltolide. This technique of target fishing clearly is an interesting alternative to classical pull-down approaches. Neopeltolide (**2**) was also isolated from a sponge.[8] The sponge of the family *Neopeltidae* was collected off the North Jamaican coast. Neopeltolide turned out to

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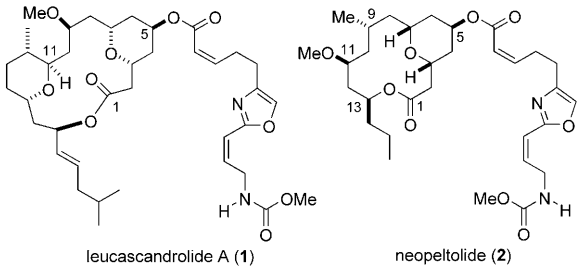
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801398.

be a very potent antitumor agent, inhibiting the proliferation of various cell lines in the low nanomolar range. Through total synthesis the stereochemistry of neopeltolide was assigned[9,10] as shown herein. In the original paper, the configurations at C11 and C13 were inverted. Since then other syntheses of **2** have been published.[6,11,12]



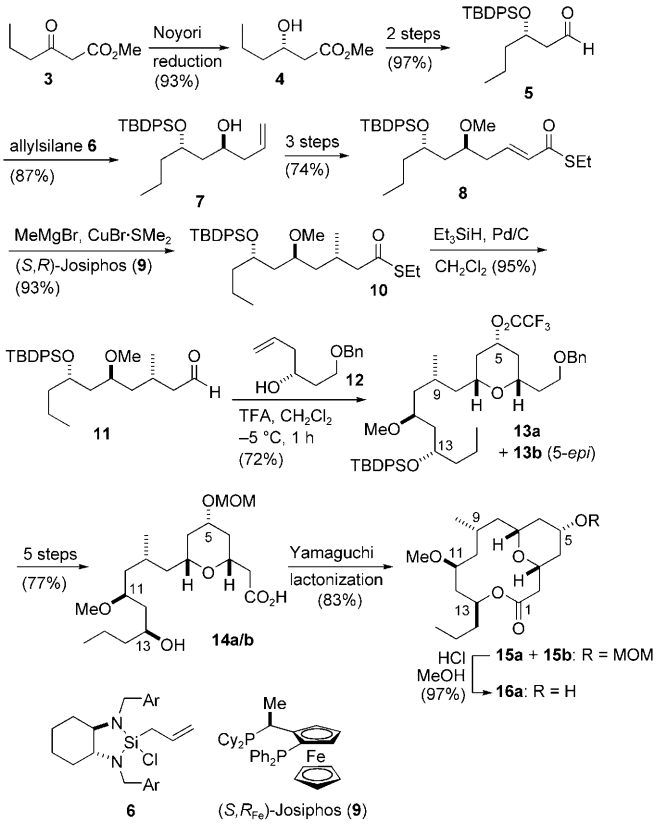
Scheme 1. Structures of the related natural products leucascandrolide A (**1**) and neopeltolide (**2**).

Our group recently reported a concise synthesis of the neopeltolide lactone **16a**.[13] The seco acid **14a/b** was fashioned from pyran **13a/b**; the latter is the product of a Prins cyclization between aldehyde **11** and homoallylic alcohol **12** (Scheme 2). Key steps in the synthesis of aldehyde **11** were a Noyori reduction[14] of ketoester **3**, a Leighton allylation[15] on aldehyde **5**, and a Feringa-Minnaard stereoselective methyl cuprate addition[16,17] to the unsaturated thioester **8**. The overall sequence from ketoester **3** to macrolactone **16a** consists of 17 steps providing lactone **16a** with a good overall yield of 23%.

In order to complete the total synthesis of neopeltolide, the side chain acid was required. In this paper we describe a novel synthesis of the neopeltolide side chain from a simple oxazolone, the synthesis of neopeltolide, and the synthesis of some analogues.

Results and Discussion

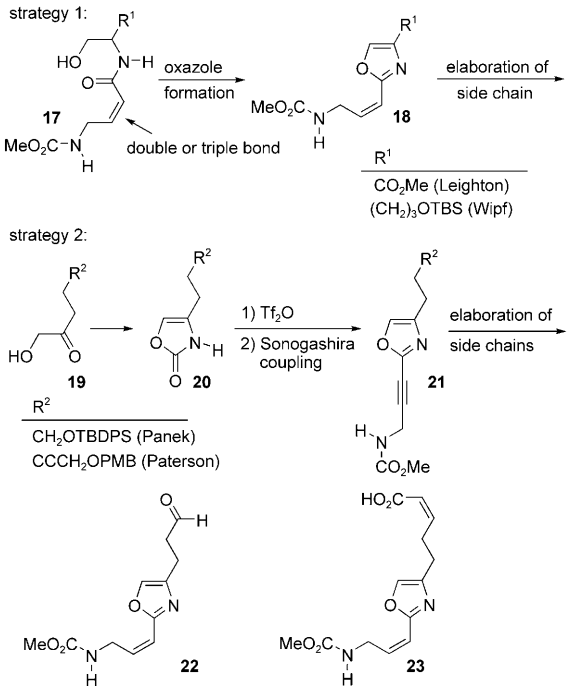
In the literature five syntheses for this acid or precursors have been described. Typically they require roughly 10–13 steps (Scheme 3). In some of them an oxazole **18** is formed from an amide **17** containing an ethanolamine subunit. In these cases the carboxylic acid part contains the carbamate terminus. This approach was used by the groups of Leighton,[4a] Wipf,[18] and Kozmin.[4b] The Kozmin route is unique in that a rhodium-catalyzed reaction of dimethyl diazomalonate with an alkynyl nitrile was used. Another strategy starts from a 2-hydroxyketone **19** from which an oxazolone **20** is created. In the approaches of Panek[4e] and Paterson,[4d] all or most of the atoms of the C-terminus of the side chain are part of the starting hydroxyketone. Target compounds are usually the aldehyde **22** or the acid **23**. Our strategy is based on a simple oxazolone as starting material which is then extended on both sides. This way we also hoped to



Scheme 2. Key steps in the synthesis of the neopeltolide hydroxylactone **16a**; Ar = pBrC$_6$H$_4$.

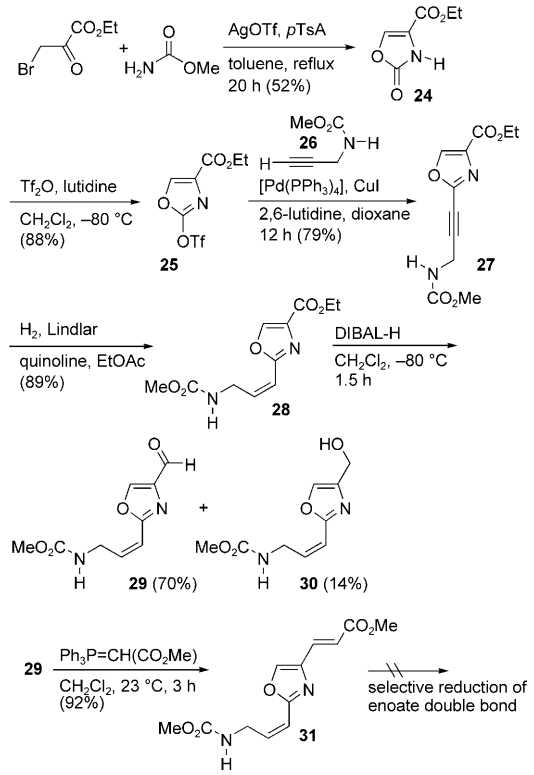
obtain modified side chains suitable for some structure activity studies.

The synthesis started with the known oxazolone[19] **24** which was obtained by a condensation reaction between ethyl 3-bromopyruvate with methyl carbamate (5 equiv) in presence of pTsOH (0.1 equiv) and AgOTf (1 equiv) (Scheme 4). Similar to the Paterson and Panek synthesis, the oxazolone was converted to the corresponding triflate using triflic anhydride (Tf_2O) in presence of 2,6-lutidine. Triflate **25**, obtained in 88% yield was immediately subjected to a Sonogashira coupling with alkyne[18] **26**, using conditions {[Pd(PPh$_3$)$_4$], CuI, 2,6-lutidine, 1,4-dioxane} developed by Panek et al.[4e,20] Subsequent Lindlar reduction of alkyne **27** provided the oxazole-4-carboxylate **28** with the Z-double bond in the C2 substituent. The next task was to realize a two-carbon extension to an aldehyde **22** or the corresponding ester. We thought of preparing enoate **31** via a Wittig reaction followed by selective reduction of the enoate double bond. Accordingly, ester **28** was reduced with DIBAL-H in CH_2Cl_2 furnishing aldehyde **29** (70% yield) along with small amounts of alcohol **30**. The latter could be converted to the aldehyde **29** by simple Dess–Martin oxidation. Stirring of aldehyde **29** with (methoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 led to enoate **31** in high yields. However, we could not find conditions that would selectively reduce the enoate double bond without affecting the Z-double



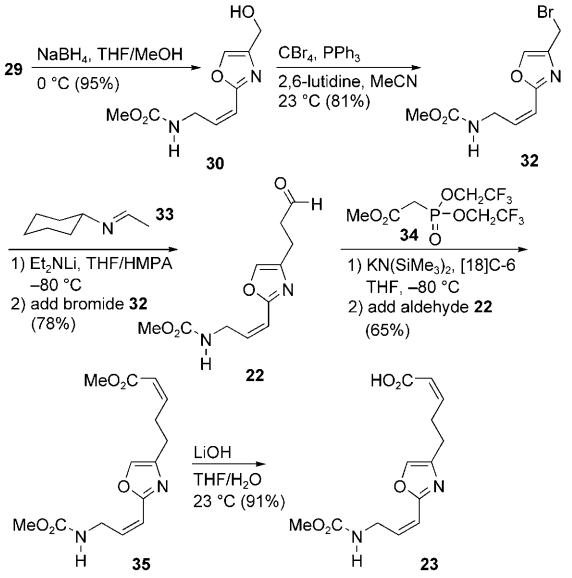
Scheme 3. General strategies for the synthesis of the oxazole containing side chain of leucascandrolide A and neopeltolide.

bond. Thus, neither Mg in MeOH[21] nor the combination of $NiCl_2/NaBH_4$ in MeOH,[22] were successful in this regard. In both cases, LC-MS showed significant amounts of over-reduction products.



Scheme 4. Synthesis of oxazole-4-carboxylate **28** and enoate **31**.

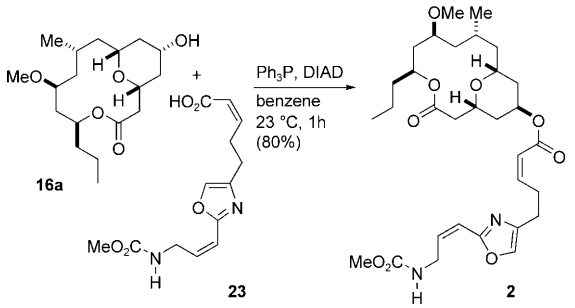
Therefore, we decided to use the two-carbon homologation method used by Kozmin[4b] in a similar context. Thus, aldehyde **29** was reduced to alcohol **30** using $NaBH_4$ (Scheme 5). Conversion of the primary alcohol **30** to the corresponding bromide **32** was achieved using CBr_4, PPh_3, and 2,6-lutidine in CH_3CN.[23] In order for this reaction to succeed the CBr_4 should be very pure and without any trace of water. Bromide **32** was then used as electrophile in the alkylation[24] of the lithium anion of imine[25] **33**, derived from acetaldehyde. Aqueous work-up afforded aldehyde **22** in 78% yield. A final olefination reaction with the Still–Gennari reagent[26] **34** delivered *Z*-enoate **35** with high selectivity (*Z*/*E* 11:1). Saponification of ester **35** with LiOH in H_2O/THF completed the synthesis of the side chain **23**.



Scheme 5. Completion of the synthesis of acid **23** by alkylation of imine **33** with bromide **32**.

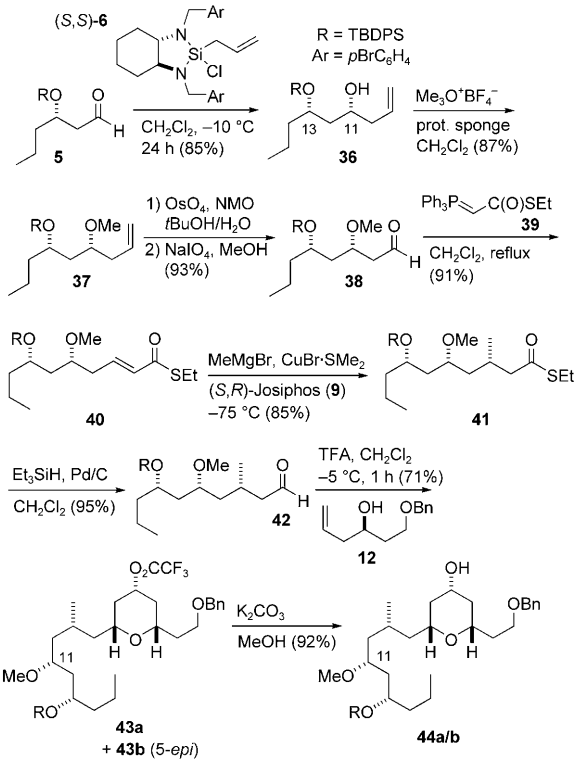
Since the Prins cyclization furnished the pyran **16a** with an all-equatorial arrangement of the substituents, a Mitsunobu esterification was required in order to obtain neopeltolide (**2**). Indeed, treatment of the two fragments **16a** and **23** (1.6 equiv) with PPh_3 and DIAD afforded neopeltolide (**2**) in 80% yield (Scheme 6). The NMR spectra of **2** were in excellent agreement with those reported in the literature.[8] In the longest linear sequence this synthesis required 18 steps with an overall yield of 18.7%. So far it is the most efficient synthesis of neopeltolide. The other known syntheses seem to be less efficient [Panek synthesis[9] (19 steps, 1.3%), Scheidt synthesis[10] (19 steps, 0.52%), Lee synthesis[11] (15 steps, 6.7%), Fuwa/Sasaki synthesis[12] (23 steps, 7.2%), Kozmin synthesis[6] (15 steps, 5.3%, racemic material)].

Synthesis of neopeltolide analogues: The larger macrolactone ring in leucascandrolide A shows that variations in the lactone part of both compounds should be possible. By slight variations in the synthesis we hoped to probe the role



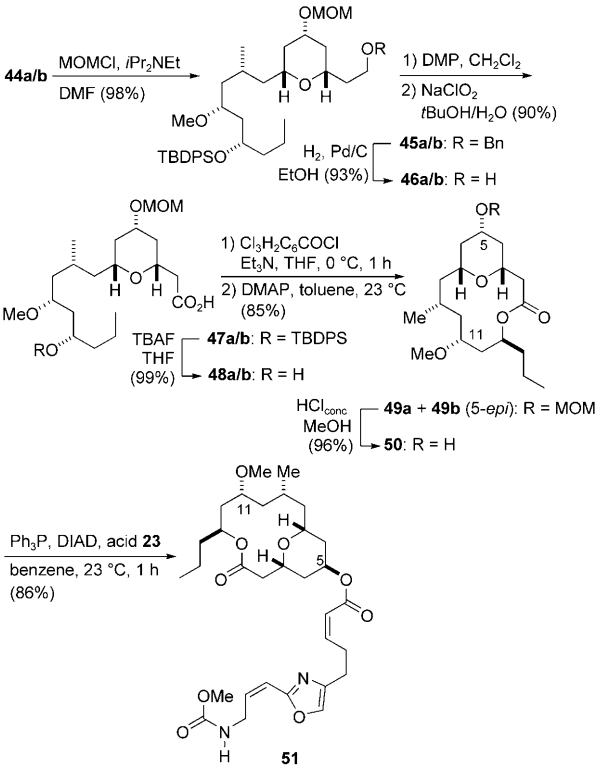
Scheme 6. Completion of the synthesis of neopeltolide (**2**) by Mitsunobu esterification.

of some of the configurations in the macrolactone part. Moreover, we planned to probe the distance between the macrolactone part and the oxazole ring. A first target became 11-*epi*-neopeltolide (**51**) (Schemes 7 and 8). Accord-



Scheme 7. Synthesis of the carbon skeleton of 11-*epi*-neopeltolide.

ingly, the Leighton alkylation of aldehyde **5** was performed with the (*S*,*S*)-reagent **6**. The alcohol **36** was methylated using the Meerwein salt in presence of proton sponge. Oxidative degradation of the double bond allowed for chain extension of the resulting aldehyde to the unsaturated thioester **40** with the Wittig reagent[27] **39**. The stereoselective methyl cuprate addition to **40** under Feringa–Minnaard conditions[16] generated thioester **41** as a single diastereomer. A subsequent Fukuyama-type reduction[28] of **41** produced aldehyde **42**. Stirring of aldehyde **42** and homoallylic alcohol



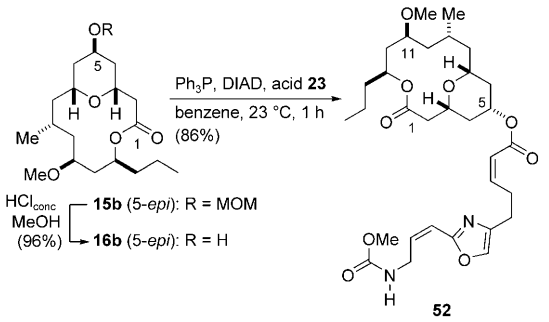
Scheme 8. Completion of the synthesis of 11-*epi*-neopeltolide (**51**). DMP = Dess Martin periodinane; DIAD = Diisopropylazodicarboxylate.

12 (1.3 equiv) in presence of trifluoroacetic acid (10 equiv) induced the Prins cyclization[29,30] yielding pyran **43a/b** in 71% yield. Treatment of the trifluoroacetate **43a/b** with K_2CO_3 in MeOH led to hydroxypyran **44a/b**. As in the case of the epimeric aldehyde **11**, the Prins cyclization of **42** and **12** afforded a small amount (ratio major/minor = 9:1) of the 5-*epi*-diastereomer **43b**. This isomer could be separated at the stage of lactone **49** (Scheme 8).

From pyran **44a/b** the same sequence of reactions that were used in the synthesis of neopeltolide lactone were used (Scheme 8). Thus, MOM protection of the secondary alcohol **44a/b** furnished pyran **45a/b**. Debenzylation to **46a/b**, oxidation of **46a/b**, and removal of the silyl ether from acid **47a/b** delivered *seco*-acid **48a/b** in good yields. The crucial Yamaguchi lactonization[31,32] provided the separable lactones **49a** and **49b** with high efficiency. Cleavage of the MOM acetal of **49a** led to hydroxy lactone **50**. Combination of lactone **50** with the acid **23** via Mitsunobu esterification gave rise to 11-*epi*-neopeltolide (**51**).

A further analogue, namely 5-*epi*-neopeltolide (**52**) was accessible from the minor diastereomer obtained in the Prins cyclization of **11** and **12** (Schemes 2, 9). After the Prins cyclization, the diastereomers were separated at the stage of the MOM-protected lactone **15a/b**. The minor isomer **15b** (5-*epi*) has an axial OH-group at C5. Accordingly, cleavage of the MOM protecting group of **15b** provided hydroxy lactone **16b**. This reacted with acid **23** under Mitsunobu conditions to 5-*epi*-neopeltolide (**52**). The alternative

formation of **52** from hydroxy lactone **16a** by classical esterification with acid **23** was not tried, because of a possible isomerization of the side chain double bond.

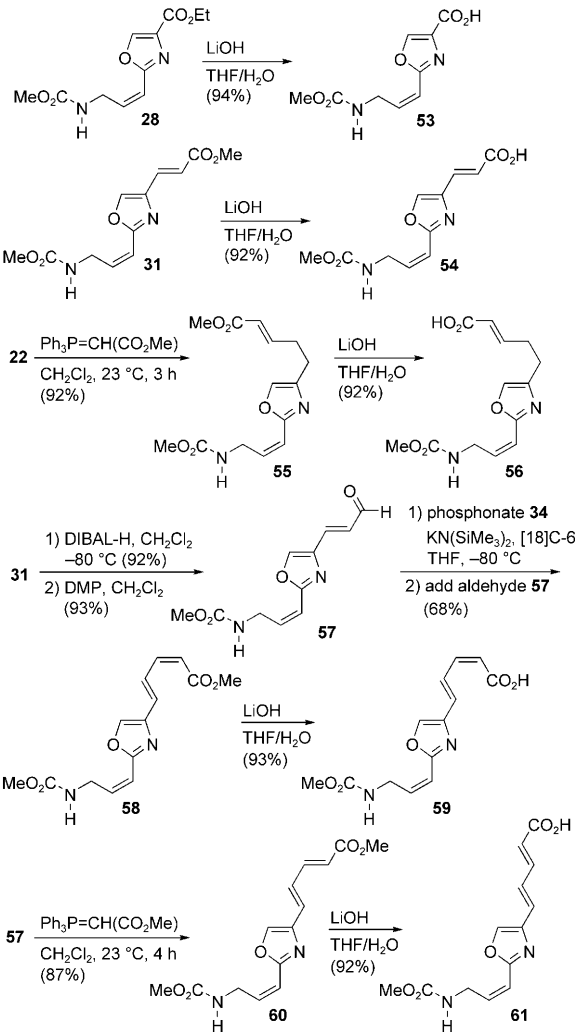


Scheme 9. Synthesis of 5-*epi*-neopeltolide (**52**).

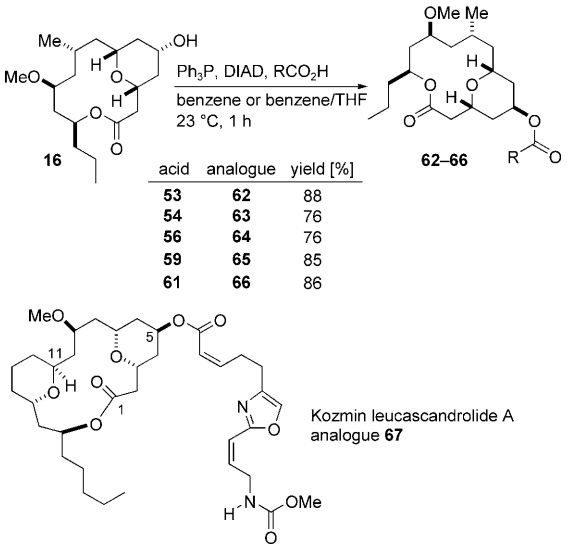
Using the 1,3-oxazole-4-carboxylate **28** and other derived compounds a few side chain analogues were prepared (Scheme 10). Accordingly, saponification of ester **28** provided acid **53**. In a similar manner enoate **31** was hydrolyzed to unsaturated acid **54**. Extending aldehyde **22** via Wittig reaction using stabilized ylide (methoxycarbonylmethylene)triphenylphosphorane gave (*E*)-enoate **55**. Saponification of the latter furnished acid **56**. Enoate **31** served also as a precursor to unsaturated aldehyde **57**, which could be obtained from **31** via a reduction/oxidation sequence. Reaction of aldehyde **57** with the Still–Gennari reagent **34** provided the *Z*,*E*-dienoate **58** in reasonable yield. This was hydrolyzed to the corresponding acid **59**. Likewise, reaction of aldehyde **57** with (methoxycarbonylmethylene)triphenylphosphorane gave the *E*,*E*-dienoate **60** and the acid **61**, respectively.

Condensation of the neopeltolide hydroxylactone **16a** with acids **53**, **54**, **56**, **59**, and **61** using the proven Mitsunobu conditions (PPh_3, DIAD, benzene or benzene/THF) produced the neopeltolide analogues **62–66** in very good yields (Scheme 11). The benzene/THF mixture was used to enhance solubility of some of the carboxylic acids.

Biological testing: Neopeltolide (**2**), as well as the analogues **51**, **52** and **62–66** were tested for cytotoxicity against the L929 mouse fibroblasts and A549 human lung carcinoma cells, as well as for their inhibitory efficacy on NADH-oxidation in submitochondrial particles of bovine heart. The obtained IC_{50} values are listed in Table 1. The compounds are ordered according to increasing IC_{50} values against the L929 cell line, which mostly run parallel with the IC_{50} against A549 and the inhibition of NADH oxidation in submitochondrial particles of bovine heart, yet with some smaller aberrations. Referring to the cytotoxicity of neopeltolides against L929 mouse cells, Table 1 shows that the lactone alone is not sufficient for biological activity (entry 9 and 10). With regard to the lactone part one can conclude that some modifications are tolerated (entry 4, 11-*epi*, entry 6, 5-*epi*). In this context the recent study by Kozmin et al.[6] is supporting our findings. Thus, natural (+)-leucascandrolide A



Scheme 10. Synthesis of various acids analogues of the neopeltolide side chain.



acid	analogue	yield [%]
53	**62**	88
54	**63**	76
56	**64**	76
59	**65**	85
61	**66**	86

Scheme 11. Synthesis of neopeltolide analogues with modifications in the side chain.

and the unnatural enantiomer, both obtained by chromatographic separation of the racemic mixture, showed similar cytotoxic profiles against various cell lines with the natural isomer being only two to three times more active. Accordingly, modifications in the lactone part seem to be well tolerated. The Kozmin leucascandrolide A analogue **67** (Scheme 11) which lacks the methyl group at C12 and C21, as well as the side-chain double bond also is still quite active [IC_{50} (A549 cell line) = 0.8 nM]. Racemic neopeltolide showed an IC_{50} of 0.5 nM against the same cell line[6] (cf. entry 2, natural neopeltolide has an IC_{50} of 0.16 nM with this cell line).

Table 1. Biological activity of neopeltolide (**2**) and the analogues.

Entry	Compound	IC_{50} L929		IC_{50} A549		IC_{50} of NADH oxidation		Description
		[ng mL^{-1}]	[nM]	[ng mL^{-1}]	[nM]	[ng mL^{-1}]	[nM]	
1	**65**	0.094	0.16	0.12	0.22	7.6	12.9	neo-diene-*Z*,*E*
2	**2**	0.15	0.25	0.095	0.16	6.0	10.2	neopeltolide
3	**66**	1.2	2.0	1.2	2.0	38	64.6	neo-diene-*E*,*E*
4	**51**	1.3	2.2	0.53	0.90	8.2	13.9	11-*epi*-neo
5	**64**	2.6	4.4	3.4	5.8	34.5	58.4	neo-*trans*
6	**52**	5.0	8.5	3.3	5.6	9.8	16.6	5-*epi*-neo
7	**63**	630	1120	800	1300	2700	4800	neo-enoate
8	**62**	2400	4500	2800	5200	1850	3450	neo-oxazole
9	**16**	> 4000	> 12000	> 4000	> 12000	> 8097	> 24650	neo-lactone
10	**50**	> 4000	> 12000	> 4000	> 12000	> 8097	> 24650	11-*epi*-lactone

The analogues with modified side chain show that the distance of the oxazole ring to the macrolactone ring is important. Thus, analogue **62** with a very short distance is essentially inactive (entry 8). Analogue **64** with an *E*-double bond is roughly 20 times less active (entry 5). A similar trend is seen for the dienoate analogues **66** and **65**. Surprisingly, the *Z*,*E* compound is more active (IC_{50} = 160 pM) than neopeltolide itself (IC_{50} = 250 pM). The *E*,*E*-isomer **66** is about 12 times less active than the *Z*,*E*-isomer **65**. It seems that the diene part in **65** somehow corresponds to the bioactive conformation of the side chain. The inhibition seen in the NADH oxidation study does roughly correlate with the cellular assay data. However, the relative weak inhibition observed with analogue **66** (entry 3) and analogue **64** (entry 5) in comparison to analogue **51** (entry 4) and analogue **52** (entry 6) is striking. Compounds **51** and **52** are the analogues with modifications in the lactone part but with an intact side chain. This clearly underscores the importance of the correct oxazole containing side chain at the target. It seems that an *E*-double bond next to the carboxyl function of the side chain slightly reduces the inhibition of the NADH oxidation. This is evident by comparing the pairs **2**/**64** and **65**/**66**. In both pairs the corresponding *E*-isomer is less active.

With the L929 fibroblasts we observed typical morphological alterations under the light microscope. The cells became bigger and more circular in shape with an outspread cytoplasm (Figure 1). These changes resembled alterations that were also induced by myxothiazol, an inhibitor of the respiratory chain from myxobacteria.[33] This first hint about the mode of action of neopeltolide was proven by NADH oxidation assays with submitochondrial particles of bovine heart as given in Table 1.

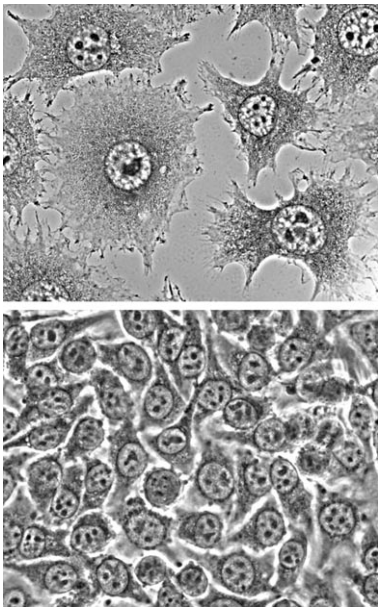


Figure 1. L929 mouse fibroblasts (top) were incubated with **2** (50 ng mL^{-1}) for 1 d and stained with Giemsa. The treated cells are bigger and show a widely outspread cytoplasm. The bottom picture shows control cells.

Conclusion

In this paper we describe the total synthesis of the potent antitumor compound neopeltolide (**2**). This marine natural product consists of a macrolactone part and an oxazole containing side chain at C5. The macrolactone part was available by our previous developed route.[13] Key steps in this very concise sequence include a Noyori reduction of a keto ester, a Leighton allylation to create the 1,3-diol subunit, a stereoselective methyl cuprate addition to an unsaturated thioester, a Prins cyclization, and a Yamaguchi lactonization. The required side chain, acid **23**, was fashioned from the known ethyl 2-oxo-2,3-dihydro-1,3-oxazole-4-carboxylate (**24**). Using established methods the required functionalities were introduced via a Sonogashira coupling reaction and elongation on the carboxylate position. This way acid **23** could be obtained from oxazolone **24** in nine steps with an overall yield of 18%. Mitsunobu esterification led to neopeltolide. Using the 5-epimer lactone **16b**, 5-*epi*-neopeltolide **52** was obtained. In addition, the 11-

epimer of lactone **16a**, hydroxylactone **50**, was made by employing the appropriate Leighton reagent and otherwise the same reaction sequence used for the natural product. Finally, derivatives of the oxazole **28** were prepared leading to a range of side chain acids. These were condensed with hydroxy lactone **16a** under Mitsunobu conditions. Biological testing revealed some interesting structure-activity information. Thus, modifications in the stereochemistry of the macrolactone part are tolerated to some degree. The drop in activity is more pronounced if the modification is closer to the side chain (5-*epi*- vs 11-*epi*-neo). With regard to the side chain it seems that the distance between the lactone and the oxazole ring is of relevance. For example, analogue **62** where the oxazole is close to the lactone is not active. The configuration of the enoate double bond of the side chain contributes roughly with a factor of 10 to the activity with the *Z*-isomers being more active. Analogue **65** with an additional double bond is equally or even more potent than the natural product itself ($IC_{50}=160$ vs 250 pM, L929 cells). Neopeltolides exert their effects by inhibition of respiration as was clearly shown by NADH oxidation assays with submitochondrial particles of bovine heart. The target within the mitochondrial respiratory chain by neopeltolides has been published recently.[6]

Experimental Section

General details and the experimental details for Schemes 7, 8, 10, 11, and compounds **31**, **52** are given in the Supporting Information.

Ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1,3-oxazole-4-carboxylate (25): A solution of oxazolone[19] **24** (2.01 g, 12.8 mmol) in CH_2Cl_2 (70 mL) was cooled to −80 °C, before 2,6-lutidine (3.0 mL, 25.6 mmol, 2 equiv) was added via syringe followed by the addition of Tf_2O (3.21 mL, 19.2 mmol, 1.5 equiv). The reaction mixture was then allowed to warm to ambient temperature with stirring for 40 min. The mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give triflate **25** (3.30 g, 88%) as a slightly yellow amorphous solid. Triflate **25** was used immediately after preparation. TLC (petroleum ether/EtOAc 4:1): $R_f=0.52$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.31$ (t, $J=7.2$ Hz, 3H, CH_3), 4.33 (q, $J=7.2$ Hz, 2H, CH_2), 8.09 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.0$ (CH_3), 61.7 (CH_2), 118.3 (q, $J=322.0$ Hz, CF_3), 133.8 (C-4), 142.9 (C-5), 150.0 (C-2), 159.4 ppm (CO_2Et).

Ethyl 2-{3-[(methoxycarbonyl)amino]prop-1-ynyl}-1,3-oxazole-4-carboxylate (27): Triflate **25** (3.25 g, 11.1 mmol) and 2,6-lutidine (6.3 mL, 54.4 mmol) were dissolved in degassed 1,4-dioxane (45.0 mL) and alkyne[18] **26** (2.51 g, 22.2 mmol), [$Pd(PPh_3)_4$] (1.27 g, 1.11 mmol), and CuI (422 mg, 2.22 mmol) were added. The reaction mixture was stirred at ambient temperature for 12 h, diluted with EtOAc (200 mL), filtered through a thin pad of SiO_2 and the filtrate concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc 7:3→1:1) afforded alkyne **27** (2.21 g, 79%) as a slightly yellow oil which crystallized upon standing in the fridge (−20 °C). M.p. 76–78 °C; TLC (CH_2Cl_2/EtOAc 85:15): $R_f=0.35$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.33$ (t, $J=7.2$ Hz, 3H, CH_2CH_3), 3.66 (s, 3H, OCH_3), 4.19 (d, $J=5.6$ Hz, 2H, CH_2NH), 4.33 (q, $J=7.2$ Hz, 2H, CH_2CH_3), 5.36 (brs, 1H, NH), 8.14 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.1$ (CH_2CH_3), 31.1 (CH_2NH), 52.5 (OCH_3), 61.4 (CH_2CH_3), 70.1 (C≡CCH_2), 89.7 (C≡CCH_2), 134.1 (C-4), 144.2 (C-5), 146.3 (C-2), 156.5 (CO_2CH_3), 160.3 ppm (CO_2Et); HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{12}NaN_2O_5$: 275.06384, found 275.06386 $[M+Na]^+$.

Ethyl 2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazole-4-carboxylate (28): Alkyne **27** (1.21 g, 4.8 mmol, 1 equiv) and quinoline (0.94 mL, 7.7 mmol, 1.6 equiv) were dissolved in EtOAc (280 mL), which was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned by lead (Fluka, No. 62145), 940 mg, 100 wt%). The reaction was placed under H_2 atmosphere and stirred until HPLC-MS analysis showed complete consumption of the starting material (ca. 5–6 h). The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The obtained oil was triturated with hexane (50 mL), resulting in the crystallization of product. Hexane was decanted and this procedure was repeated once more. Flash chromatography of the residue (CH_2Cl_2/EtOAc 9:1→85:15→4:1) afforded ester (*Z*)-alkenoate **28** (1.085 g, 89%) as a slightly yellow solid. M.p. 92–93 °C. TLC (CH_2Cl_2/EtOAc, 85:15): $R_f=0.36$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.33$ (t, $J=7.1$ Hz, 3H, CH_2CH_3), 3.62 (s, 3H, OCH_3), 4.28–4.37 (m, 4H, CH_2NH, CH_2CH_3), 5.47 (brs, 1H, NH), 6.10–6.19 (m, 1H, HC=$CHCH_2$), 6.30 (d, $J=11.9$ Hz, 1H, HC=$CHCH_2$), 8.14 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.1$ (CH_2CH_3), 39.6 (CH_2NH), 52.1 (OCH_3), 61.2 (CH_2CH_3), 115.2 (HC=$CHCH_2$), 134.3 (C-4), 139.3 (HC=$CHCH_2$), 143.1 (C-5), 157.1 (CO_2CH_3), 160.6 (CO_2Et), 161.0 ppm (C-2); HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{14}NaN_2O_5$: 277.07949, found 277.07937 $[M+Na]^+$.

Methyl (2*Z*)-3-(4-formyl-1,3-oxazol-2-yl)prop-2-enylcarbamate (29): DIBAL-H (1 M in hexane, 7.1 mL, 7.1 mmol, 2.5 equiv) was added dropwise at −80 °C to a solution of ester **28** (0.72 g, 2.83 mmol) in dry CH_2Cl_2 (15 mL). The reaction was stirred at −80 °C for 90 min, then quenched with saturated aqueous NH_4Cl solution and warmed up to room temperature. It was then treated with saturated potassium and sodium tartrate (Rochelle salt)/EtOAc (100:100 mL) and the mixture was vigorously stirred for 10 min. After the layers were separated, the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (CH_2Cl_2/MeOH 97:3→95:5) afforded aldehyde **29** (415 mg, 70%) as a colorless solid. Besides aldehyde **29** some overreduced alcohol **30** (85 mg, 14%) was isolated. M.p. 75–76 °C; TLC (CH_2Cl_2/MeOH 9:1): $R_f=0.61$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.66$ (s, 3H, OCH_3), 4.32–4.42 (m, 2H, CH_2NH), 5.39 (brs, 1H, NH), 6.20–6.29 (m, 1H, HC=$CHCH_2$), 6.33 (d, $J=11.6$ Hz, 1H, HC=$CHCH_2$), 8.21 (s, 1H, 5-H), 9.93 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=39.7$ (CH_2NH), 52.2 (OCH_3), 115.0 (HC=$CHCH_2$), 140.4 (C-4), 141.5 (HC=$CHCH_2$), 143.5 (C-5), 157.1 (CO_2CH_3), 161.1 (C-2), 184.1 ppm (CHO).

Methyl (2*Z*)-3-[4-(hydroxymethyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (30): To a cooled (0 °C) solution of aldehyde **29** (380 mg, 1.81 mmol) in a mixture of THF/MeOH (6:2 mL) was added sodium borohydride (87 mg, 2.35 mmol) and the reaction mixture was stirred at this temperature for 1 h. Then it was treated with saturated NH_4Cl solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×40 mL), and the combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 95:5) afforded alcohol **30** (364 mg, 95%) as a colorless solid. M.p. 125–126 °C, lit.[4a] m.p. 124–125 °C; TLC (CH_2Cl_2/MeOH 9:1): $R_f=0.42$; ^{1}H NMR (400 MHz, CD_3OD): $\delta=3.53$ (s, 3H, OCH_3), 4.16–4.22 (m, 2H, CH_2NH), 4.38 (d, $J=5.1$ Hz, 2H, CH_2OH), 5.21 (t, $J=5.1$ Hz, 1H, OH), 5.92–6.01 (m, 1H, HC=$CHCH_2$), 6.28 (dt, $J=11.9$, 2.0 Hz, 1H, HC=$CHCH_2$), 7.46 (t, $J=5.2$ Hz, 1H, NH), 7.89 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=39.8$ (CH_2NH), 51.4 (OCH_3), 55.7 (CH_2OH), 114.5 (HC=$CHCH_2$), 135.3 (C-4), 138.4 (HC=$CHCH_2$), 142.7 (C-5), 156.8 (CO_2CH_3), 159.6 ppm (C-2); HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{14}NaN_2O_5$: 235.06948, found 235.06952 $[M+Na]^+$.

Methyl (2*Z*)-3-[4-(bromomethyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (32): A solution of alcohol **30** (62 mg, 0.29 mmol) and PPh_3 (152 mg, 0.58 mmol) in CH_3CN (3 mL) was treated with 2,6-lutidine (17 mL, 0.15 mmol) and CBr_4 (Fluka, Nr. 86770) (192 mg, 0.58 mmol). After 1 h the reaction mixture was partitioned between 5% solution of $NaHCO_3$ (10 mL) and Et_2O (20 mL). The organic layer was separated and the

aqueous layer extracted with Et_2O (3×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexane 2:1→1:1→1:2) to give bromide **32** (64 mg, 81%) as a white solid. M.p. 85–86°C, lit.[4a] m.p. 86–87°C; TLC (hexane/EtOAc 1:2): R_f=0.62; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.67 (s, 3H, OCH_3), 4.28–4.36 (m, 2H, CH_2NH), 4.37 (s, 2H, CH_2Br), 5.42 (br s, 1H, NH), 6.10–6.20 (m, 1H, HC=C*H*CH$_2$), 6.29 (d, J=11.6 Hz, 1H, *H*C=CHCH$_2$), 7.60 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=39.8 (CH_2NH), 51.4 (OCH_3), 55.7 (CH_2OH), 114.5 (HC=CHCH$_2$), 135.3 (C-4), 138.4 (HC=*C*HCH$_2$), 142.7 (C-5), 156.8 (CO_2CH_3), 159.6 ppm (C-2); HRMS (ESI): m/z: calcd for $C_9H_{11}BrNaN_2O_3$: 296.98453, found 296.98477 $[M+Na]^+$.

Methyl (2*Z*)-3-[4-(3-oxopropyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (22): A solution of diethylamine (52.4 μL, 0.51 mmol, 2.2 equiv) in THF (0.5 mL) was cooled to −78°C, and treated with *n*BuLi (2.5 M solution in hexane, 204.0 μL, 0.51 mmol, 2.2 equiv). After 15 min, a solution of imine[25] **33** (66.1 mg, 0.53 mmol, 2.3 equiv) in THF (0.5 mL) was added to the reaction mixture, immediately followed by HMPA (68.2 mL, 0.393 mmol). The reaction was warmed to 0°C, stirred for 10 min and then cooled to −80°C. The resulting yellow solution of the enolate was transferred via cannula over a period of 5 min into a stirring solution of bromide **32** (63 mg, 0.23 mmol) in THF (0.5 mL) at −30°C. After 20 min at −30°C, the reaction was quenched with a 10% solution of tartaric acid (2 mL), and allowed to warm to room temperature. After the mixture was extracted with EtOAc (3×25 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 98:2→95:5) afforded aldehyde **22** (43 mg, 78%) which was used immediately in the next step. TLC (CH_2Cl_2/MeOH 9:1): R_f=0.48.

Methyl (2*Z*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoate (35): A solution of [18]crown-6, freshly recrystallized from acetonitrile, (269 mg, 1.02 mmol, 6 equiv) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (**34**) (86 μL, 0.41 mmol, 2.4 equiv) in THF (2.5 mL) was cooled to −80°C, and treated with KHMDS (0.5 M solution in toluene, 0.75 mL, 0.37 mmol, 2.2 equiv). After 1 h, the solution of aldehyde **22** (41 mg, 0.17 mmol, 1 equiv) in THF (0.5 mL) was added over a period of 5 min. After 1 h, TLC indicated complete consumption of aldehyde. Then the reaction was quenched with saturated NH_4Cl and warmed to room temperature. After the mixture was extracted with EtOAc (3×20 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 98:2) afforded ester **35** (32 mg, 65% yield, 11:1 mixture of *Z*/*E* isomers by ^{1}H NMR analysis) as a colorless oil. TLC (CH_2Cl_2/MeOH 9:1): R_f=0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.68 (t, J=7.2 Hz, 2H, 5-H), 2.96–3.03 (m, 2H, 4-H), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, CCO_2CH_3), 4.25–4.32 (m, 2H, 3′-H), 5.59 (br s, 1H, NH), 5.80 (d, J=11.6 Hz, 1H, 2-H), 6.03–6.13 (m, 1H, 2′-H), 6.21–6.30 (m, 2H, 3-H, 1′-H), 7.36 ppm (s, 1H, 5″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.6 (C-5), 27.5 (C-4), 39.3 (C-3′), 51.1 (OCH_3), 52.1 (OCH_3), 116.7 (C-1′), 120.2 (C-2), 133.9 (C-5″), 136.2 (C-4″), 141.1 (C-2′), 148.9 (C-5″), 157.1 (CO_2CH_3), 159.9 (C-2″), 166.7 ppm (C-1); HRMS (ESI): m/z: calcd for $C_{14}H_{18}NaN_2O_5$: 317.11079, found 317.11086 $[M+Na]^+$.

Acid 23: A solution of ester **35** (15 mg, 0.05 mmol) in THF (0.5 mL) was treated with LiOH (1 N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 7 h). The reaction was cooled to 0°C and neutralized with aqueous HCl (1 N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4×20 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 95:5→9:1) afforded acid **23** (12.7 mg, 91%) as a colorless oil. TLC (CH_2Cl_2/MeOH 9:1): R_f=0.36; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.69 (t, J=7.3 Hz, 2H, 5-H), 2.98 (m, 2H, 4-H), 3.66 (s, 3H, OCH_3), 4.25–4.32 (m, 2H, 3′-H), 5.52 (br s, 1H, NH), 5.81 (d, J=11.5 Hz, 1H, 2-H), 6.03–6.10 (m, 1H, 2′-H), 6.25–6.32 (m, 2H, 3-H, 1′-H), 7.34 ppm (s, 1H, 5″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.5 (C-5), 27.4 (C-4), 39.3 (C-3′), 52.1 (OCH_3), 116.6 (C-1′), 120.2 (C-2), 133.9 (C-5″), 136.4 (C-4″), 141.0 (C-2′), 148.9 (C-5″), 157.1 (CO_2CH_3), 159.9 (C-2″), 166.7 ppm (C-1); HRMS (ESI): m/z: calcd for $C_{13}H_{16}NaN_2O_5$: 303.09514, found 303.09511 $[M+Na]^+$.

Neopeltolide (2): Diisopropyl azodicarboxylate (88 μL, 0.5 M solution in benzene, 0.044 mmol, 1.76 equiv) was added to a solution of alcohol **16** (8.3 mg, 0.025 mmol, 1 equiv), acid **23** (11.2 mg, 0.04 mmol, 1.6 equiv) and PPh_3 (11.5 mg, 0.044 mmol, 1.76 equiv) in dry benzene (1 mL). After stirring for 1 h at ambient temperature, the reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography (hexane/EtOAC 2:1→1:1→1:2) to afford neopeltolide (**2**) (12.0 mg, 80%) as a colorless oil. TLC (petroleum ether/EtOAc 1:1): R_f=0.36; $[\alpha]_D^{20}$=+23.8 (c = 0.24, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=0.93 (t, J=7.3 Hz, 3H, 16-H), 0.96 (d, J=6.6 Hz, 3H, 17-H), 1.06–1.14 (m, 1H, 10-H), 1.20–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.60 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.63–1.75 (m, 2H, 6-H, 14-H), 1.78–1.89 (m, 2H, 4-H, 12-H), 2.28 (dd, J=14.8, 11.0 Hz, 1H, 2-H), 2.65–2.74 (m, 3H, 2-H, 22-H), 2.96–3.04 (m, 2H, 21-H), 3.27 (s, 3H, 11-OCH_3), 3.55 (apt, J=9.9 Hz, 1H, 7-H), 3.62–3.70 (m, 4H, 29-OCH_3, 11-H), 4.02–4.11 (m, 1H, 3-H), 4.29 (d, J=4.6 Hz, 2H, 28-H), 5.12–5.21 (m, 2H, 13-H, 5-H), 5.87 (d, J=11.4 Hz, 1H, 19-H), 5.98–6.07 (m, 1H, 27-H), 6.26 (dt, J=11.9, 2.0 Hz, 1H, 26-H), 6.36 (dt, J=11.6, 7.4 Hz, 1H, 20-H), 7.65 ppm (s, 1H, 24-H); ^{13}C NMR (100 MHz, CD_3OD): δ=14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 26.4 (C-22), 29.0 (C-21), 32.6 (C-9), 36.2 (C-4), 37.4 (C-6), 37.9 (C-14), 41.0 (C-12), 43.2 (C-2), 43.5 (C-10), 45.2 (C-8), 52.6 (29-OCH_3), 56.4 (11-OCH_3), 69.2 (C-5), 71.3 (C-3), 73.9 (C-13), 77.0 (C-7), 77.1 (C-11), 115.9 (C-26), 121.7 (C-19), 135.9 (C-24), 139.2 (C-27), 142.3 (C-23), 150.0 (C-20), 159.6 (C-29), 161.9 (C-25), 166.9 (C-18), 173.0 ppm (C-1); HRMS (ESI): m/z: calcd for $C_{31}H_{46}NaN_2O_9$: 613.30955, found 613.31039 $[M+Na]^+$.

Biological assays: The viability/toxicity of the compounds with L929 and A549 were tested with an MTT assay after 5 d incubation of serial dilutions of the samples.[34] The cell lines were from DSMZ and kept in DME medium (Dulbecco's Modified Eagle's medium) as reported. Neopeltolide was checked for typical phenotypic effects with L929 cells and Giemsa staining. Giemsa's solution were from Merck. Preparations of submitochondrial particles of bovine heart (SMP) and NADH oxidation assays with SMP were performed as described previously.[33,35] The samples contained 52 μg mL^{-1} of bovine heart protein. The rate of NADH oxidation in the control without inhibitor was 1.8±0.2 μmol mg^{-1} min^{-1}.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (grant Ma 1012/23-1) and the Fonds der Chemischen Industrie is gratefully acknowledged. We also thank Graeme Nicholson (Institute of Organic Chemistry) for measuring the HRMS spectra. In addition, a graduate fellowship for V.V.V. of the state Baden-Württemberg (LGFG) is also acknowledged. We thank Birte Engelhardt, Bettina Hinkelmann, and Lara Hochfeld for excellent technical assistance.

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Received: July 9, 2008
Published online: October 31, 2008

