Tetrahedron 66 (2010) 5384–5395

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation and biological evaluation of key fragments and open analogs of scleritodermin A

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ARTICLE INFO

Article history:
Received 8 April 2010
Received in revised form
10 May 2010
Accepted 11 May 2010
Available online 15 May 2010

Keywords:
Scleritodermin A analogs
Key fragments
α-Ketoamide
Azoles

ABSTRACT

The synthesis of key fragments of scleritodermin A, their assembly, and their biological evaluation as cytotoxic and anthelmintic were performed. Highlights of the synthetic route include formation of the α-ketoamide linkage and use of stereocontrolled reactions. Open analogs of this natural product were obtained using a convergent strategy.

1. Introduction

The role of natural products in drug discovery has undergone many changes during the past two decades from a decline in the participation by pharmaceutical companies by the 1990s to a renaissance in the last years.[1] The expectations from combinatorial libraries in drug screening have not been fulfilled and more than 60% of the prescription drugs are of natural product origin.[2] As a consequence, the natural product-inspired drug discovery and development has received renewed attention in recent years.[3]

A large number of natural products, in particular from the marine environment, contain thiazole or oxazole heterocycles. In many cases, promising antiproliferative and anthelmintic activities have been identified for these compounds.[4] Chemotherapy has been a long standing effective instrument for battling parasitic infections in both human and veterinary medicine. It has an important role, not only in the treatment of individual patients but also, in conjunction with public health and vector-control measures, in reducing the transmission of parasitic infections. Unfortunately, resistance to the therapeutic arsenal for the control of helminth infections represented by the benzimidazole, levamizole, and avermectina class of broad-spectrum drugs has become a common and global phenomenon.[5] The loss of income combined with the loss of productivity represents a serious economical problem for countries in South America, Australia, the UK, Holland, and South Africa.

The macrocyclic compound, scleritodermin A (Fig. 1), was isolated by Schmidt et al. from the marine sponge *Scleritoderma nodosum*, showing significant cytotoxic activity against a panel of human tumor cells lines ($IC_{50}<2$ μM).[6] The proposed structure of scleritodermin A (**1**) incorporates a novel conjugated thiazole moiety 2-(1-amino-2-*p*-hydroxyphenylethane)-4-(4-carboxy-2,4-dimethyl-2*Z*,4*E*-propadiene)-thiazole (**ACT**), L-proline, L-serine, and the unusual amino acids keto-*allo*-isoleucine and *O*-methyl-*N*-sulfo-D-serine.

Diverted total synthesis is the most versatile approach to analogs preparation.[7] Danishefsky et al. defined this term as the design of a synthetic route to a given natural product that allows for the de novo introduction of improved structural characteristics en route to the target molecule. The benefit of this approach is that the analogs are usually easier to prepare than the natural product.

Our interest on the synthetic studies of marine natural products with anthelmintic or cytotoxic activity,[8] encouraged us to embark on a general program for the diverted total synthesis of scleritodermin A and analogs. In 2007, our group reported the preparation of the C_1–N_{15} fragment,[9] and recently, Nan et al. reported the total synthesis of the originally proposed and revised structures of scleritodermin A, **1** and **2**, Figure 1.[10]

The present studies allowed us to obtain different key fragments that have been tested for cytotoxic and antihelminthic activity. This information could be essential in order to achieve one of the main aims of analogs synthesis to reduce molecular complexity while maintaining or even improving biological activity. There are many

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doi:10.1016/j.tet.2010.05.040

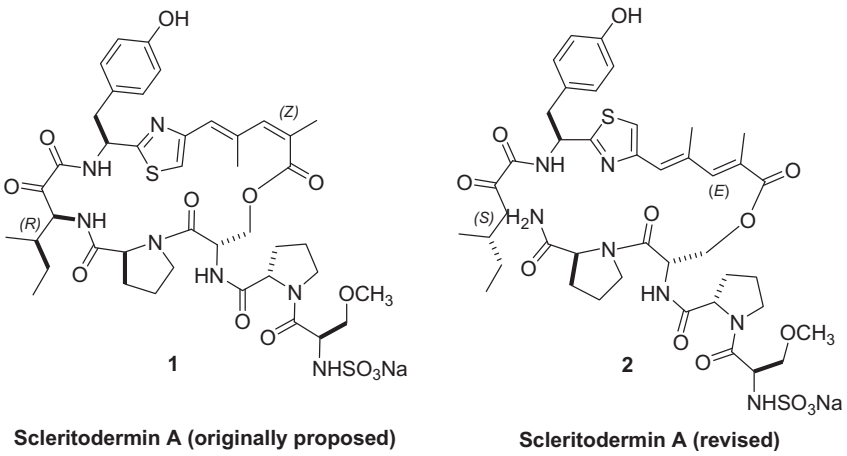


Figure 1. Originally proposed and revised structures of scleritodermin A.

examples of simplified compounds derived from natural products with high biological activity. Danishefsky et al. reached two-migrastatin core derivatives through diverted total synthesis, whose IC_{50} in migration assays were, remarkably, reduced by three orders of magnitude relative to migrastatin.[7] In addition, during their total synthesis of Mycobactin S_{12}, Miller et al. encountered that a small fragment, exhibited similar antituberculosis activity to the whole product.[11] This exemplifies the importance of generating information on the minimal structural requirement for bioactivity.

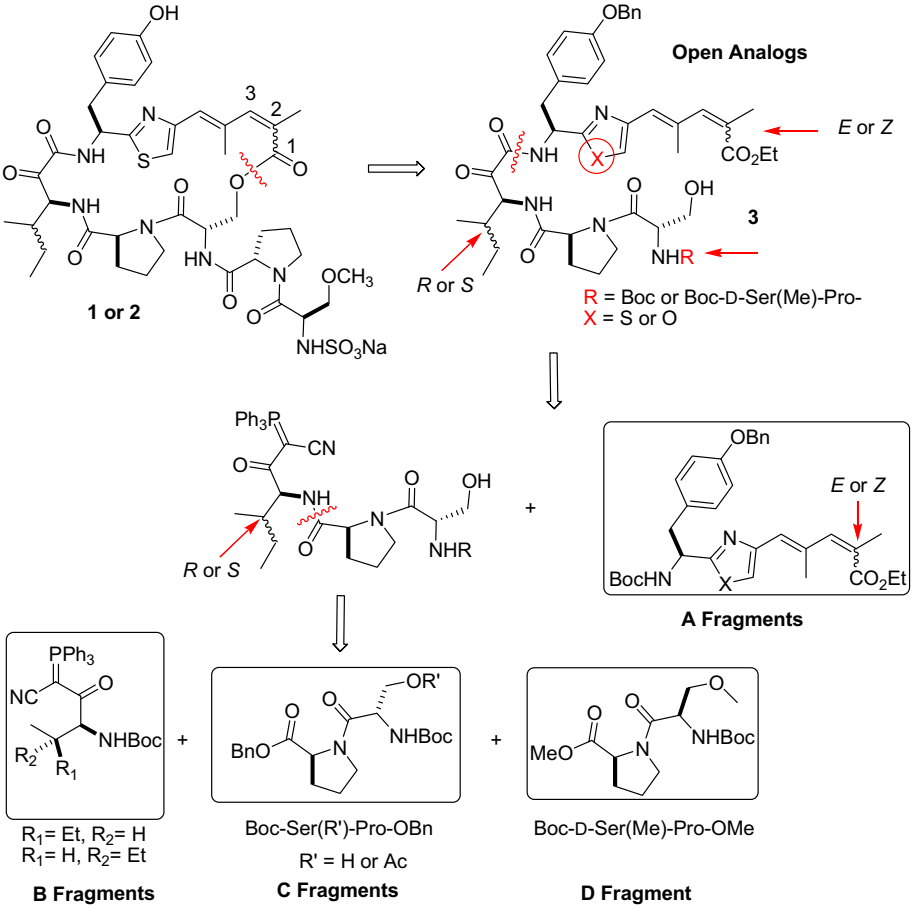
In the present study we propose the synthesis of scleritodermin A fragments containing a thiazole or oxazole ring, L-*allo*-Ile or L-Ile, *E,E* or *E,Z* configurations of the double bonds and different peptides.

We herein describe the synthesis of different key fragments of analogs of scleritodermin A, their assembly, and their biological evaluation. Open analogs of scleritodermin A were obtained using a convergent strategy that allows for structural variations of characteristic parts of the natural product.

2. Results and discussion

2.1. Chemistry

Our retrosynthetic analysis is shown in Scheme 1. Disconnection at the ester group of the macrolactone generates the open analog (**3**). Cleavage at the α-ketoamide bond and at the amide bond between

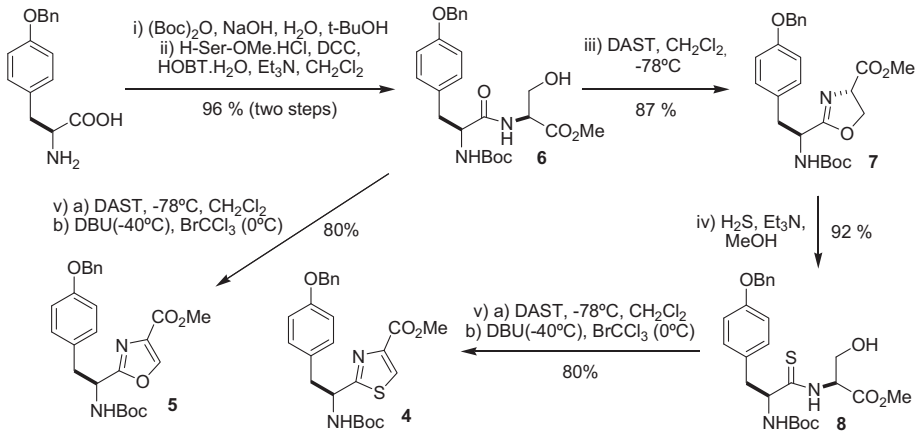


Scheme 1. Retrosynthetic analysis for scleritodermin A and analogs.

L-Ile or L-*allo*-Ile and L-Proline produce different key fragments: **A**, ketophosphorane fragments **B**, and the peptides **C** and **D**.

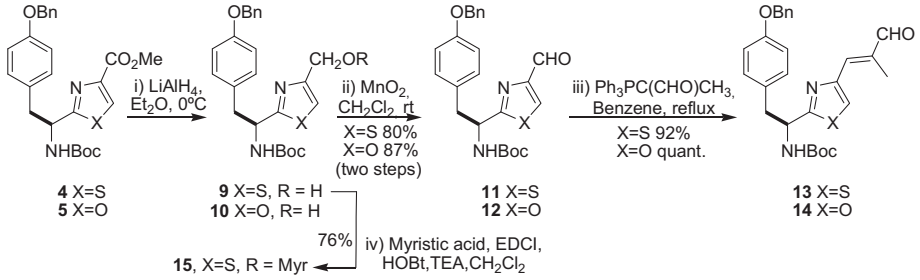
*2.1.1. Synthesis of **A** fragments.* The synthesis of these fragments was based on the methodology previously described by us for the synthesis of **ACT** fragment.[9]

Firstly, we obtained thiazole **4** and oxazole **5** by cyclodehydration of a β-hydroxyamide or thioamide derived from L-serine and L-tyrosine (Scheme 2). The thiolysis of oxazoline **7** in H_2S/MeOH is high-yielding, and offers an alternative to the thionation of peptides using Lawesson's reagent.[12]



Scheme 2. Synthesis of thiazole **4** and oxazole **5** from Tyr and Ser.

Then, the ester groups of **4** or **5** were converted to the corresponding aldehydes with $LiAlH_4$ and activated MnO_2 (Scheme 3).

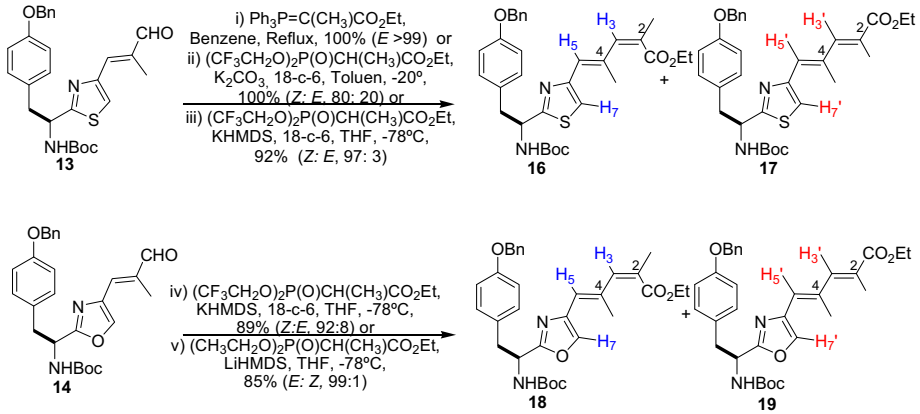


Scheme 3. Synthesis of *E* alkenes **13** and **14**.

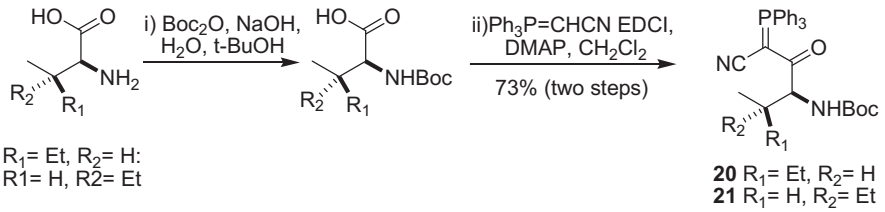
The Wittig reaction between the aldehydes **11** or **12** and 2-(triphenylphosphoranylidene)-propianaldehyde rendered exclusively the *E* alkenes **13** and **14** in excellent yield.

We investigated different conditions for the last coupling reaction (Scheme 4). When **13** and the ylide ethyl 2-(triphenylphosphoranylidene)propionate were refluxed in benzene, the *E* isomer (**17**) was obtained exclusively. Then, we used the modification of Still/Gennari for the HWE reaction,[13] and the fragments **16** and **17** were obtained in ratio, 80:20 using K_2CO_3 or 97:3 using $KN(TMS)_2$ as base. Similarly, the isomers **18** and **19** were obtained in ratio, 92:8 using KHMDS or 99:1 using LiHMDS as base. The configuration of the double bonds in the obtained fragments **16** and **18** was confirmed by NOE correlation between: (1) H_7 of the ring and the methyl group attached to C_4 and (2) H_3 and the methyl group attached to C_2.

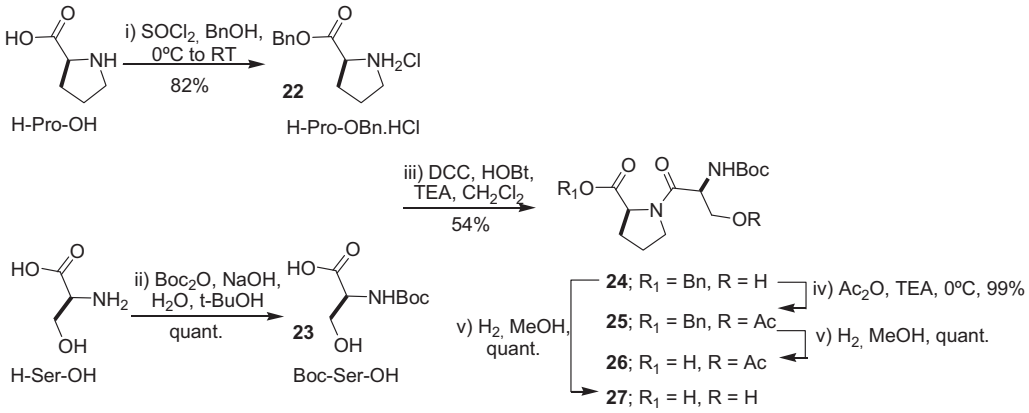
*2.1.2. Synthesis of **B** fragments.* Protection of the amine group of L-isoleucine or L-*allo*-isoleucine with Boc and further reaction of their carboxylic acid with the (triphenylphosphoranylidene)



Scheme 4. Synthesis of fragments **A**.



Scheme 5. Synthesis of fragments **B**.



Scheme 6. Synthesis of fragments **C**.

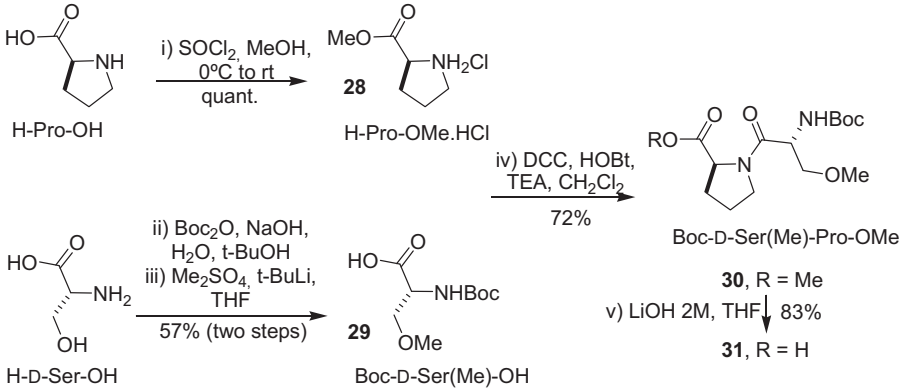
acetonitrile ylide using EDCI as coupling reagent, allowed us to obtain ketophosporanes **20** and **21** (Scheme 5).[10]

*2.1.3. Synthesis of **C** fragments.* The synthesis of **C** fragments was performed from L-serine and L-proline, (Scheme 6). First, the carboxylic acid of L-proline was protected as its methyl ester and then, it was coupled to Boc-Ser. However, using a variety of conditions the basic hydrolysis of the dipeptide Boc-Ser-Pro-Me, was low yielding. In contrast, when we changed the protecting group to a benzyl ester, hydrogenation of the protected dipeptide allowed us to obtain **26** and **27** in excellent yields.

CH_2Cl_2 and LiOH 2 M/THF, respectively (Scheme 8). Dipeptides **32** and **31** were coupled using different conditions. The best result was obtained using PyBrOP as coupling agent (70% yield). Hydrogenation of the resulting ester (**33**) rendered the tetrapeptide **34** in 98% yield.

*2.1.6. Coupling between **B** and **C** fragments.* Tripeptide **35** was obtained in 88% yield from **21** and **26** using EDCI/HOBt or HBTU as coupling reagents (Scheme 9).

2.1.7. Synthesis of C_1–N_{15} fragments analogs. For the construction of the α-ketoamide function, we used the procedure described by

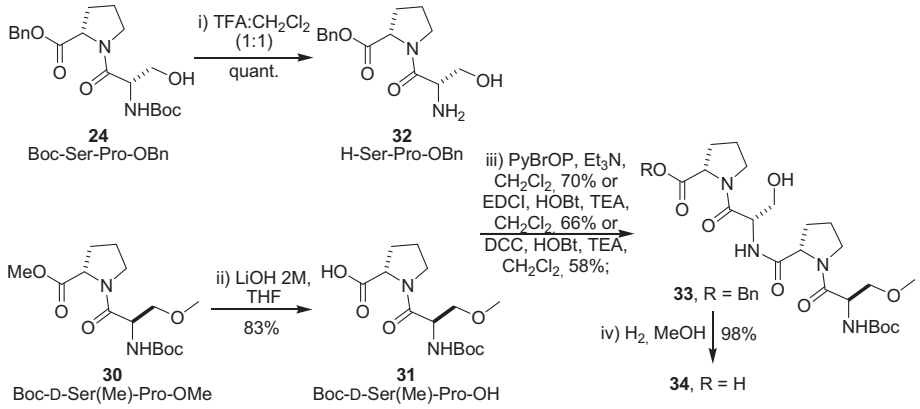


Scheme 7. Synthesis of fragments **D**.

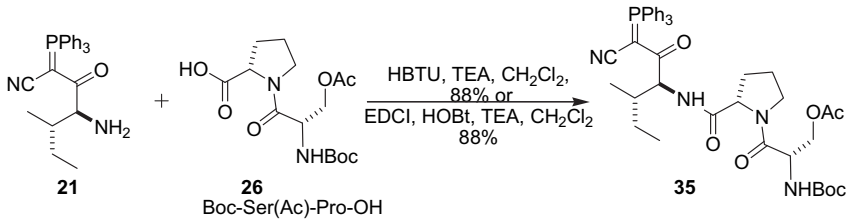
*2.1.4. Synthesis of **D** fragments.* The synthesis of the **D** fragments was performed from D-serine and L-proline as shown in Scheme 7. In contrast with our result for the Boc-Ser-Pro-Me dipeptide, **31** was obtained from **30** in good yield using basic hydrolysis. We conclude that the hydroxyl group on serine must be protected in order to successfully carry out this reaction.

*2.1.5. Coupling between **C** and **D** fragments.* The Boc group of peptide **24** and the methyl ester of **30** were deprotected using TFA/

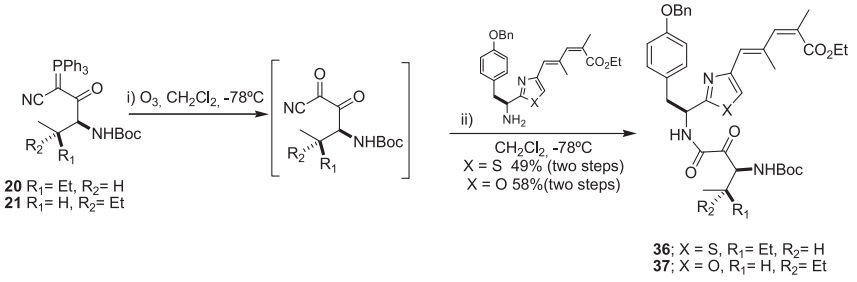
Wasserman in the synthesis of cyclotheonamide **A** and **B**.[14] Ozonolysis of the cyanoketophosporanes **20** and **21**, generated the highly electrophilic not isolables α,β-ketonitriles (Scheme 10). Products **16** or **18** were deprotected using TFA/CH_2Cl_2 and then added, without purification, to the corresponding reaction mixture to obtain **36** and **37** in 49% and 58% yield, respectively. The structures of **36** and **37** were confirmed by the presence of a characteristic ^{13}C signal at 194.5 ppm or at 196.6 ppm, respectively, assignable to the keto function.



Scheme 8. Synthesis of tetrapeptide **34**.



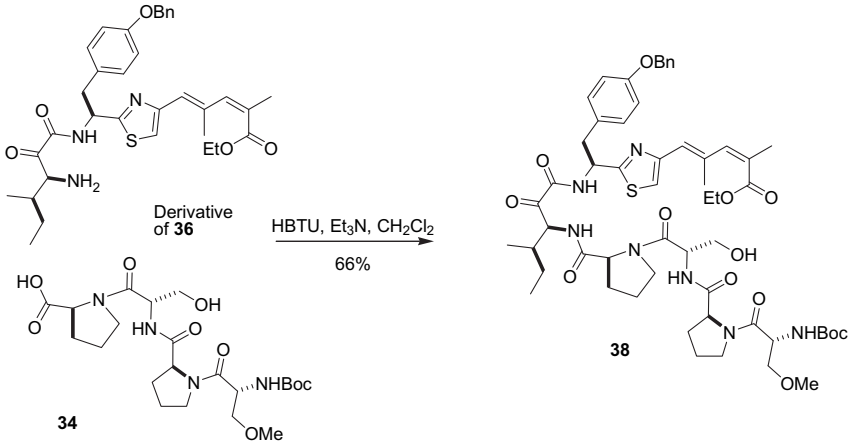
Scheme 9. Synthesis of cyano ketophosphorane tripeptide **35**.



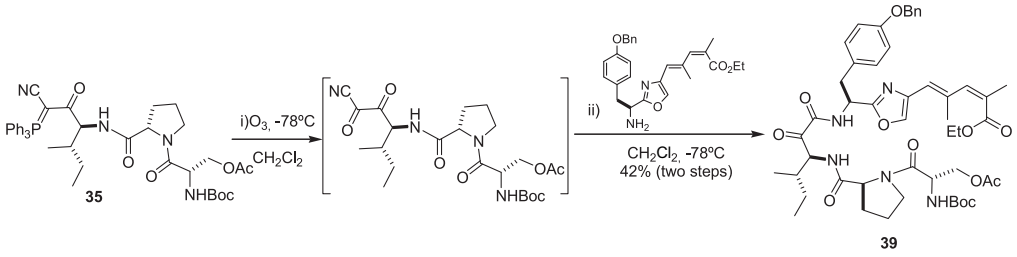
Scheme 10. Synthesis of C_1–N_{15} fragment analogs.

2.1.8. Synthesis of open analogs of scleritodermin A. Product **36** was deprotected in 4 M HCl/dioxane and then coupled without purification to **34** using HBTU. The open analog product of scleritodermin A isomer **38** was obtained in 66% yield (Scheme 11).

One of the advantages of Diverted Total Synthesis is the possibility of obtaining simplified analogs that are easier to synthesize than the parent natural product. Therefore, we have selected the other synthethized A fragment, product **18** that has been obtained in few steps in order to prepare a new analog, (Scheme 12). Ozonolysis of **35** generated the α,β-ketonitrile. Product **18** was deprotected in 4 M HCl/dioxane and then added to the reaction mixture to obtain the open and simplified analog **39**.



Scheme 11. Synthesis of the open analog of scleritodermin A **38**.



Scheme 12. Synthesis of the open analog of scleritodermin A isomer **39**.

2.2. Biological evaluation

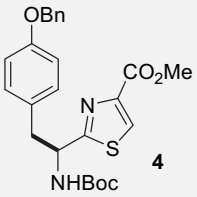
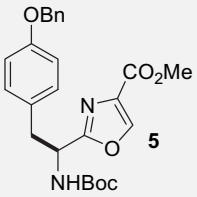
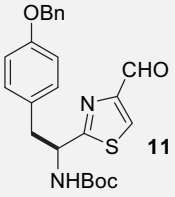
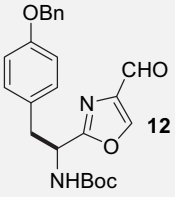
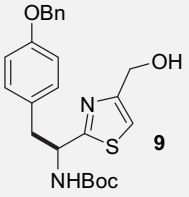
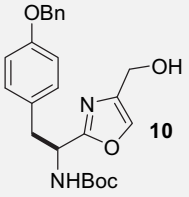
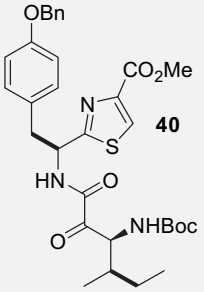
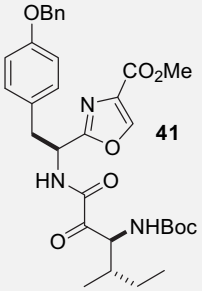
Growth inhibition properties against HCT-15, colon cancer cells were investigated using the sulfurhodamine B (SRB)-assay and mitomycin as control.[15] The anthelmintic effect on the parasitic stage (L_4) of *Nippostrongylus brasiliensis* was evaluated using the protocol of Gordon et al. and albendazole as positive control.[16] The results are summarized in Table 1.

The results of cytotoxic activity show that the type of substituent on the C_4-position of the thiazole or oxazole has different effects. For example, **11** is inactive (GI_{50}>500) and **12** shows a micromolar level GI_{50}. In contrast, thiazole **9** is more active than oxazole **10**.

Compounds **40** and **41** were obtained in order to study the influence of the α,β-ketoamide function coupled to the deprotected derivatives of compounds **4** and **5**, respectively. According with the results, the introduction of the α,β-ketoamide improves the cytotoxic activity.

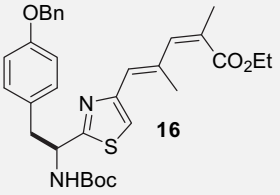
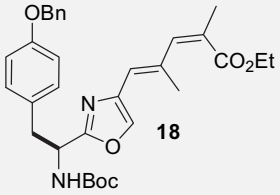
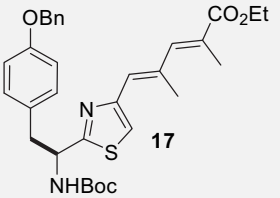
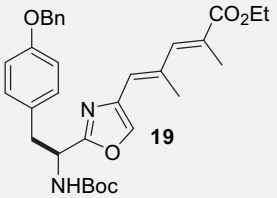
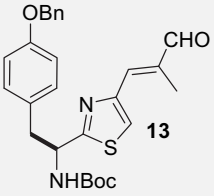
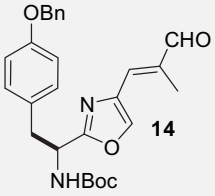
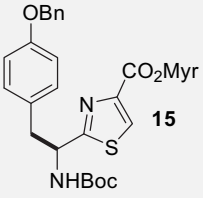
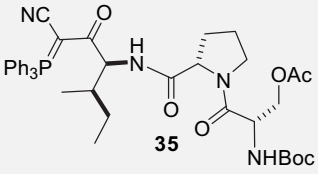
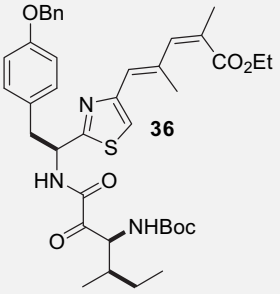
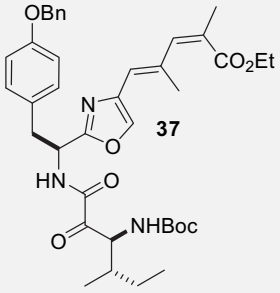
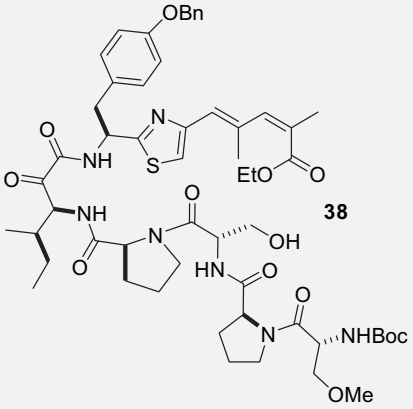
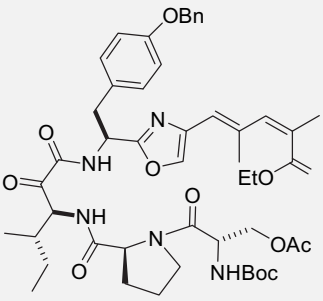
Comparing the results for **36**, **37**, **38**, and **39**, we can conclude that the presence of tetrapeptide Boc-D-Ser(Me)-Pro-Ser-Pro improves the cytotoxic activity.

Table 1
Anthelmintic effect and cytotoxic activity of the obtained products

Compound	Anthelmintic LC_{50} (μM)[a]	HCT-15 GI_{50} (μM)[b]	Compound	Anthelmintic LC_{50} (μM)[a]	HCT-15 GI_{50} (μM)[b]
	500±38	630±30		15±1	>2000
	340±26	>513		170±13	7.6±0.4
	10.0±0.8	10.3±0.4		500±38	54±6
	300±23	54±8		13±1	20±7

(*continued on next page*)

Table 1 (*continued*)

Compound	Anthelmintic LC_{50} (μM)[a]	HCT-15 GI_{50} (μM)[b]	Compound	Anthelmintic LC_{50} (μM)[a]	HCT-15 GI_{50} (μM)[b]
 **16**	100±8	1600±400	 **18**	300±23	135±34
 **17**	30±2	>3000	 **19**	70±5	228±86
 **13**	40±3	21±2	 **14**	15±1	23±1
 **15**	—	>422	 **35**	170±13	>391
 **36**	20±1	>500	 **37**	30±2	192±32
 **38**	9.6±0.7	34±1		16±1	>246

[a] Control: albendazole (ABZ), LC_{50}=0.34±0.02 μM.
[b] Control: mitomycine (Mit), GI_{50}=1.6±0.4 μM.

The compound with the highest antihelminthic activity is the open analog of **1**, compound **38** (LC_{50}=9.6 μM). The open and simplified analog **39** also exhibits considerable activity (LC_{50}=16 μM).

The α,β-ketoamide function has different effects in the anthelmintic activity. For example, compounds **4** and **40** and **5** and **41** have the same order of activity. In contrast, compounds **36** and **37** are more active as anthelmintic than **16** and **18**, respectively.

3. Conclusion

Different key fragments of scleritodermin A and open analogs were prepared in very good yield. The methodology that involves the use of cyanoketophosporanes derivatives allowed us to obtain α-ketoamides in very good yield (42–58%) compared with the previous reported by Nan et al. for the synthesis of scleritodermin A.[10]

All the key fragments that would be used for the synthesis of the revised structure of scleritodermin A were obtained. The developed synthetic strategies could be applied in order to obtain even more structurally diverse molecules.

Some of the products showed cytotoxic activity on HCT-15 cells. Some of the most active products as anthelmintic are the open analogs of scleritodermin A, **38** and **39**.

The biological evaluation revealed some differences that will serve as the basis for further preparations of structurally simplified, bioselective derivatives of this natural product.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8101A spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-400. Chemical shifts are related to TMS as an internal standard. High resolution mass spectra (HRMS) were obtained on a micro Q-TOF (Bruker Daltonics) and on VG AutoSpecQ mass spectrometers. Flash column chromatography was carried out with Silica gel 60 (J.T. Baker, 40 μm average particle diameter). All reactions and chromatographic separations were monitored by TLC, conducted on 0.25 mm Silica gel plastic sheets (Macherey/Nagel, Polygram® SIL G/UV 254). TLC plates were analyzed under 254 nm UV light, by iodine vapor, *p*-hydroxybenzaldehyde spray or ninhydrine spray. All solvents were purified according to literature procedures.[17] All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure compounds.

*4.1.1. Boc-Tyr(Bn)-SerOMe (**6**).* A solution of *O*-benzyl-L-tyrosine (1.96 g, 7.2 mmol) in a mixture of *t*-BuOH (20 mL), water (50 mL), and NaOH (578 mg, 14.5 mmol) was stirred and cooled in an ice-water bath. Di-*tert*-butyl pyrocarbonate (1.58 g, 7.2 mmol) was added and stirring was continued at room temperature overnight. The solution was acidified with 5% HCl. The aqueous phase was extracted with ethyl acetate (3×40 mL). The ethyl acetate was pooled and dried over anhydrous $MgSO_4$ and evaporated in vacuo. *N*-Boc-*O*-benzyl-L-tyrosine (2.46 g, 6.6 mmol) was used without further purification. L-Serine methyl ester hydrochloride (1.03 g, 6.6 mmol), 1-hydroxy-benzotriazole monohydrate (895 mg, 6.6 mmol), Boc-*O*-benzyl-tyrosine (2.46 g, 6.6 mmol), and triethylamine (1.34 g, 13.2 mmol) were dissolved in dry CH_2Cl_2 (30 mL). The solution was cooled in an ice-water bath and stirred while DCC (1.37 g, 6.6 mmol) was added. Stirring was continued for 1 h at 0 °C and an additional hour at room temperature. The precipitated DCU was removed by filtration and the solvent was evaporated in vacuo. Flash column chromatography (SiO_2, EtOAc/*n*-hexane, 2:1) provided **6** (3.3 g, 7.0 mmol) (96% two steps) as a colorless oil. R_f=0.45 (EtOAc/*n*-hexanes, 2:1); $[\alpha]_D^{25}$ +12.3 (*c*1.0, $CHCl_3$); IR (film) 3887, 1741, 1687, 1660, 1512, 1242, 1176, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 2.97 (dd, *J*=7.6, 14.0 Hz, 1H), 3.08 (dd, *J*=6.0, 14.0 Hz, 1H), 3.44 (sa, 1H), 3.75 (s, 3H), 3.92 (s, 2H), 4.38 (m, 1H), 4.64 (m, 1H), 5.04 (s, 2H), 5.27 (d, *J*=7.8 Hz, 1H), 6.92 (d, *J*=8.7 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 1H), 7.14 (d, *J*=8.7 Hz, 2H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 37.8, 53.0, 55.3, 56.4, 63.2, 70.4, 80.8, 115.4, 127.8, 128.3, 129.0, 129.2, 130.8, 137.4, 156, 158.3, 171.0, 172.3; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}N_2O_7$ 472.2210, found 472.2226.

*4.1.2. (S)-Methyl 2-((S)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)-4,5-dihydrooxazole-4-carboxylate (**7**).* Diethylaminosulfur trifluoride (0.91 mL, 6.88 mmol) was added dropwise to a cold (−78 °C) solution of **6** in CH_2Cl_2 (50 mL). After stirring for 1 h at −78 °C, anhydrous K_2CO_3 (0.50 g, 6.88 mmol) was added in one portion and the mixture was allowed to warm to room temperature. The reaction was poured into saturated aqueous $NaHCO_3$, and the biphasic mixture was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, EtOAc/*n*-hexane, 2:1) led to the desired oxazoline **7** (2.46 g, 87%) as a colorless oil. R_f=0.67 (EtOAc/*n*-hexane, 2:1); $[\alpha]_D^{25}$ +5.7 (*c*1.0, $CHCl_3$); IR (film) 2976, 1743, 1716, 1662, 1512, 1367, 1244, 1174, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 3.09 (m, 2H), 3.76 (s, 3H), 4.45 (dd, *J*=10.3, 8.4 Hz, 1H), 4.60 (t, *J*=8.4 Hz, 1H),4.68 (m, 1H), 4.74 (m, 1H), 5.05 (s, 2H), 5.15 (sa, 1H), 6.90 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 2H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 38.4, 50.2, 53.0, 68.2, 70.4, 70.4, 80.1, 115.1, 127.8, 128.3, 128.5, 129.0, 131.0, 137.5, 156.2, 158.3, 169.8, 171.3; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{30}N_2O_6$ (M^+) 454.2104, found 454.2108.

*4.1.3. (S)-Methyl 2-((S)-3-(4-(benzyloxy)phenyl)-2-(tert-butoxycarbonylamino) propanethioamido)-3-hydroxypropanoate (**8**).* A solution of **7** (88 mg, 0.19 mmol) in 14 mL of MeOH/Et_3N (1:1) was saturated with H_2S and stirred at room temperature overnight. CAUTION! H_2S is a toxic gas and has to be handled in a 'well-vented hood'. Excess H_2S, MeOH, and Et_3N were removed by evaporation in vacuo through a solution of bleach, and the residue was chromatographed on SiO_2 (EtOAc/*n*-hexane, 1:1) to yield **8** (87 mg, 92%) as a yellow oil. R_f=0.40 (EtOAc/*n*-hexane, 1:1); IR (film) 2978, 1741, 1689, 1512, 1242, 1174, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 3.14 (d, 2H, *J*=6.8 Hz), 3.77 (s, 3H), 3.96 (m, 1H), 4.14 (m, 1H), 4.59 (m, 1H), 5.06 (s, 2H), 5.17 (m, 1H), 5.26 (sa, 1H), 5.36 (sa, 1H), 6.94 (m, 2H), 7.19 (m, 2H), 7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 41.1, 53.2, 60.0, 61.8, 62.9, 70.4, 81.1, 115.4, 127.8, 128.4, 129.0, 129.1, 130.7, 137.4, 156.1, 158.3, 170.2, 205.0; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}N_2O_6S$ (M^+) 488.1981, found 488.1977.

*4.1.4. (S)-Methyl 2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazole-4-carboxylate (**4**).* Diethylaminosulfur trifluoride (0.43 mL, 3.3 mmol) was added dropwise to a cold (−78 °C) solution of **8** (1.44 g, 2.95 mmol) in CH_2Cl_2. After 30 min, DBU (1.58 mL, 10.6 mmol) was added dropwise to the reaction mixture at −40 °C, followed by bromotrichloromethane (1.04 mL, 10.6 mmol) at 0 °C. The reaction was stirred at room temperature for 8 h and then quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) gave the desired thiazole **4** as a yellow oil (1.10 g, 80%). R_f=0.48 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}$ −7.8 (*c*1.0, $CHCl_3$); IR (film) 3348, 2361, 1716, 1512, 1244, 1221, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 3.28 (m, 2H), 3.97 (s, 3H), 5.04 (s, 2H), 5.26 (sa, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 7.38 (m, 5H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 41.1, 52.8, 54.5 70.4, 80.7, 115.4, 127.9, 128.4, 128.8, 129.0, 130.9,

137.4, 147.3, 155.3, 158.3, 162.2, 173.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_2O_5S$ (M^+) 468.1719, found 468.1732.

*4.1.5. (S)-Methyl 2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)oxazole-4-carboxylate (**5**).* According to the procedure for the conversion of **8** into **4**, **6** (1,37 g, 2,9 mmol) was transformed into **5** (1.05 g, 80%). R_f=0.64 (EtOAc/*n*-hexane, 2:1); $[\alpha]_D^{25}$ −2.0 (*c*1.0, $CHCl_3$); IR (film) 3368, 2980, 1724, 1693, 1583, 1512, 1246, 1167, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.18 (m, 2H), 3.92 (s, 3H), 5.03 (s, 2H), 5.20 (m, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 6.96 (d, *J*=8.5 Hz, 2H), 7.39 (m, 5H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 39.9, 50.7, 52.6, 70.4, 80.6, 115.4, 127.8, 128.2 128.3, 129.0, 130.7, 133.7, 137.4, 144.2, 156.2, 158.4, 161.9, 165.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_2O_6$ (M^+) 452.1947, found 452.1942.

*4.1.6. (S)-tert-Butyl 2-(4-(benzyloxy)phenyl)-1-(4-hydroxymethylthiazol-2-yl)ethylcarbamate (**9**) and (S)-tert-butyl 2-(4-(benzyloxy) phenyl)-1-(4-formylthiazol-2-yl)ethylcarbamate (**11**).* $LiAlH_4$ (17.1 mg, 0.45 mmol) was added in several portions to a solution of ester **4** (211 mg, 0.45 mmol) in dry diethyl ether (5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. The solution was quenched with 20% NaOH solution (20 mL). The mixture was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to obtain the alcohol **9** that was used in the next step without further purification.

MnO_2 (304 mg, 3.5 mmol) was added in five portions over 5 h to a stirred solution of alcohol **9** (154 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resulting reaction mixture was stirred for 15 h until TLC indicated that the reaction was completed. The MnO_2 was removed by filtration, washed with CH_2Cl_2, and the combined organic portions were concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) gave the desired aldehyde **11** as a colorless oil (123 mg, 80%). Compound **9**: R_f=0.19 (EtOAc/*n*-hexane, 2:3); IR (film) 3346, 1688. 1514, 1267, 1248, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 2.69 (s, 1H), 3.25 (m, 2H), 4.77 (s, 2H), 5.04 (s, 2H), 5.28 (m, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 7.08 (s, 1H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 41.5, 54.5, 61.4, 70.4, 80.8, 114.8, 115.5, 127.8, 128.3, 129.0, 129.1, 130.8, 130.8, 137.4, 155.3, 156.7, 158.2, 174.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O_4SNa$ ($(M+Na)^+$) 463.1662, found 463.1672. Compound **11**: R_f=0.58 (EtOAc/*n*-hexane, 2:3); IR (film) 3343, 1701, 1512, 1367, 1246, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 3.28 (m, 2H), 5.05 (s, 2H), 5.28 (m, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 7.03 (d, *J*=8.6 Hz, 2H), 7.36 (m, 5H), 8.08 (s, 1H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 41.0, 54.5, 70.5, 80.8, 115.5, 127.8, 128.2, 128.4, 128.6, 129.0, 131.1, 137.4, 141.2, 155.3, 158.4, 174.5, 185.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}N_2O_4S$ (M^+) 439.1692, found 439.1662.

*4.1.7. (S)-(2-(2-(4-(Benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)methyl myristate (**15**).* Myristic acid (6.6 mg, 0.03 mmol), TEA (4 μL, 0.03 mmol), 1-hydroxy-benzotriazole monohydrate (4.2 mg, 0.03 mmol), EDCI (8.0 mg, 0.04 mmol) were dissolved in dry CH_2Cl_2 (0.5 mL). The solution was cooled in an ice-water bath and stirred while alcohol **9** (12.5 mg, 0.03 mmol) was added. Stirring was continued for 12 h at room temperature. The solution was quenched with water. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, $CHCl_3$) gave the desired ester **15** (14 mg, 76%). R_f=052 (EtOAc/*n*-hexane, 1:3); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J*=6.0 Hz, 3H), 1.27 (m, 20H), 1.43 (s, 9H), 1.66 (m, 2H), 2.40 (m, 2H), 3.24 (d, *J*=8.0 Hz, 2H), 5.05 (s, 2H), 5.19 (m, 4H), 6.89 (d, *J*=8.6 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 7.17 (s, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 24.9, 28.3, 29.2–29.7, 34.2, 40.9, 54.0, 61.6, 70.0, 80.0, 114.8, 117.2, 127.5–128.6, 130.5, 137.0, 151.4, 154.0, 157.8, 173.5, 174.0. HRMS (ESI) *m/z* calcd for $C_{38}H_{54}N_2NaO_5S$ ($(M+Na)^+$) 673.3646, found 673.3663.

*4.1.8. (S)-tert-Butyl 2-(4-(benzyloxy)phenyl)-1-(4-hidroxymethyloxazol-2-yl)ethylcarbamate (**10**) and (S)-tert-butyl 2-(4-(benzyloxy) phenyl)-1-(4-formyloxazol-2-yl)ethylcarbamate (**12**).* According to the procedure for the conversion of **4** into **11**, **5** (118 mg, 3.1 mmol) was transformed into **12** (236 mg, 87%). Compound **10**: R_f=0.10 (EtOAc/*n*-hexane, 1:2); IR (film) 742, 1024, 1170, 1244, 1510, 1699, 2374, 2976, 3354 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.18 (m, 2H), 4.56 (s, 2H), 5.05 (s, 2H), 5.15 (m, 1H), 5.30 (m, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 6.96 (d, *J*=8.6 Hz, 2H), 7.41 (m, 5H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 39.9, 50.7, 57.0, 70.4, 80.4, 115.3, 127.8, 128.3, 128.7, 129.0, 130.7, 135.4, 137.4, 140.7, 154.0, 158.3, 164.7; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O_5Na$ ($(M+Na)^+$) 447.1890, found 447.1872. Compound **12**: R_f=0.7 (EtOAc/*n*-hexane, 1:1); IR (film) 696, 810, 1047, 1165, 1246, 1512, 1691, 3092, 3362 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1,43 (s, 9H), 3,20 (m, 2H), 5.03 (s, 2H), 5.20 (m, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 6.96 (d, *J*=8.5 Hz, 2H), 7.39 (m, 5H), 8.18 (s, 1H), 9,90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 39.7, 50.7, 70.4, 80.7, 115.5, 127.8, 128.4, 128.5, 129.0, 130.7, 137.4, 141.1, 144.8, 155.3, 158.4, 165.8, 184.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}N_2NaO_5$ ($(M+Na)^+$) 445.1734, found 445.1725.

*4.1.9. (S,E)-tert-Butyl 2-(4-(benzyloxy)phenyl)-1-(4-(2-methyl-3-oxoprop-1-enyl)thiazol-2-yl)ethylcarbamate (**13**).* A solution of aldehyde **11** (1.26 g, 2.88 mmol) and (α-formylethylidene)triphenyl phosphorane (1.1 g, 3.46 mmol) in benzene (30 mL) was stirred at reflux for 5 h. The reaction mixture was stirred until monitoring by TLC indicated that all starting material had been consumed. The residue obtained after evaporation of the solvent was purified by chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) to afford the α,β-unsaturated aldehyde **13** (1.27 g, 92%). R_f=0.36 (EtOAc/*n*-hexane, 1:3); IR (film) 2977, 1681, 1679, 1512, 1244, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 2.24 (s, 3H), 3.28 (d, *J*=6.2 Hz, 2H), 5.05 (s, 2H), 5.20 (sa, 1H), 5.28 (sa, 1H), 6.89 (d, *J*=8.6 Hz, 2H), 7.04 (d, *J*=8.6 Hz, 2H), 7.27 (s, 1H), 7.40 (m, 5H), 7.56 (s, 1H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5, 28.7, 41.1, 54.5, 70.5, 80.5, 115.4, 123.3, 127.8, 128.4, 128.9, 129.0, 130.9, 137.4, 139.2, 141.2, 152.3, 155.0, 158.3, 173.0, 195.7; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_4S$ (M^+) 479.2005, found 479.2000.

*4.1.10. (S,E)-tert-Butyl 2-(4-(benzyloxy)phenyl)-1-(4-(2-methyl-3-oxoprop-1-enyl)oxazol-2-yl)ethylcarbamate (**14**).* According to the procedure for the conversion of **11** into **13**, **12** (1.1 g, 2.6 mmol) was transformed into **14** (1.04 g, 100%). R_f=0.71 (EtOAc/*n*-hexane, 1:1); IR (film) 696, 1026, 1111, 1167, 1246, 1514, 1693, 1713, 2076 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1,45 (s, 9H), 2.10 (s, 3H), 3.20 (m, 2H), 5.05 (s, 2H), 5.13 (m, 2H), 6.89 (d, 2H, *J*=8.5 Hz), 7.00 (d, 2H, *J*=8.5 Hz), 7.08 (s, 1H), 7.36 (m, 5H), 7,85 (s, 1H), 9,56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5, 28.7, 39.6, 50.6, 70.4, 80.7 115.4, 127.8, 128.4, 128.5, 129.0, 130.0, 130.8, 137.4, 137.8, 139.5, 140.1, 155.3, 158.3, 164.6, 194.6; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_5$ ($(M+H)^+$) 463.2227, found 463.2218; ($(M+Na)^+$) 485.2047, found 485.2049.

*4.1.11. (S,2Z,4E)-Ethyl 5-(2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**16**).* To a solution of $(CF_3CH_2O)_2$ $P(O)CH(CH)_3CO_2Et$ (505 mg, 1.46 mmol) and 18-crown-6 (1.9 g, 7.3 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added KHMDS (2.92 mL, 1.46 mmol). The reaction mixture was stirred at −78 °C, and then aldehyde **13** (700 mg, 1.46 mmol) was added. The mixture was stirred at −78 °C for 4 h and satd NH_4Cl was added, the product was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried with $MgS0_4$ and evaporated, and the residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:6) to afford **16** as a yellow oil (757 mg, 92%) (*Z*/*E*, 97:3). R_f=0.56 (EtOAc/

n-hexane, 1:3); IR (film) 2924, 1749, 1716, 1508, 1265, 1014, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 2.05 (d, J=1.4 Hz, 3H), 2.19 (s, 3H), 3.26 (m, 2H), 4.23 (q, J=7.2 Hz, 2H), 5.04 (s, 2H), 5.25 (m, 2H), 6.30 (s, 1H), 6.50 (br s, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.03 (d, J=8.7 Hz, 2H), 7.4 (s, 1H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 17.8, 22.1, 28.7, 41.3, 54.3, 61.1, 70.4, 80.4, 115.3, 117.3, 124.9, 127.8, 128.3, 128.9, 129.3, 129.6, 130.9, 136.4, 137.5, 138.2, 153.6, 155.4, 158.2, 169.2, 170.6; HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2O_5S$ ($(M+H)^+$) 563.2580, found 563.2600.

*4.1.12. (S,2E,4E)-Ethyl 5-(2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**17**).* A solution of aldehyde **13** (50 mg, 0.1 mmol) and $Ph_3P{=}C(Me)CO_2Et$ (45 mg, 0.13 mmol) in benzene (5 mL) was stirred at reflux. The reaction mixture was stirred until monitoring by TLC indicated that all starting material had been consumed. The residue obtained after evaporation of the solvent was purified by chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) to afford the ester **17** (54 mg, 100%). R_f=0,56 (EtOAc/*n*-hexane, 1:2); IR (film) 2978, 2930, 1711, 1699, 1610, 1516, 1390, 1253, 1111, 1026, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 2.14 (s, 3H), 2.33 (s, 3H), 3.28 (m, 2H), 4.24 (q, J=7.2 Hz, 2H), 5.04 (s, 2H), 5.26 (m, 2H), 6.63 (s, 1H), 6.89 (d, J=8.6 Hz, 2H), 7.04 (d, J=8.6 Hz, 2H), 7.1 (s, 1H), 7.30 (s, 1H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 14.6, 19.3, 28.7, 41.3, 54.4, 61.3, 70.4, 80.5, 115.3, 118.2, 127.1, 127.8, 128.2, 128.4, 129.0, 131.0, 133.8, 136.0, 137.5, 143.3, 153.6, 155.4, 158.2, 169.7, 171.4; HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2O_5S$ ($(M+H)^+$) 563.2574, found 563.2568.

*4.1.13. (S,2Z,4E)-Ethyl 5-(2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)oxazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**18**).* According to the procedure for the conversion of **13** into **16**, **14** (940 mg, 2.03 mmol) was transformed into **18** (984 mg, 89%) (*Z*/*E*, 92:8). R_f=0.4 (EtOAc/*n*-hexane, 1:3); IR (film) 696, 1024, 1111, 1172, 1244, 1367, 1512, 1720, 2980 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H, J=7.2 Hz), 1,44 (s, 9H), 2.03 (m, 6H), 3.19 (m, 2H), 4.22 (q, 2H, J=7.2 Hz), 5.04 (s, 2H), 5.16 (m, 2H), 6.25 (m, 2H), 6.87 (d, 2H, J=8.5 Hz), 6.97 (d, 2H, J=8.5 Hz), 7.39 (m, 5H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 18.0, 22.0, 28.7, 39.8, 50.6, 61.1, 70.4, 80.4, 115.3, 121.2, 127.8, 128.3, 128.7, 128.9, 129.4, 130.8, 136.5, 137.5, 137.7, 139.5, 138.6, 142.5, 158.2, 163.3, 170.4. HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2NaO_6$, ($(M+Na)^+$) 569.2628, found 569.2568.

*4.1.14. (S,2E,4E)-Ethyl 5-(2-(2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)oxazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**19**).* To a solution of $(CH_3CH_2O)_2P(O)CH(CH)_3CO_2Et$ (312 mg, 1.31 mmol) in THF (10 mL) at −78 °C was added LiHMDS (1.2 mL, 1.31 mmol). The reaction mixture was stirred at −78 °C, and then aldehyde **14** (55 mg, 1.31 mmol) was added. The mixture was stirred at −78 °C for 0.5 h and satd NH_4Cl was added, the product was extracted with EtOAc. The EtOAc extracts were dried with $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:6) to afford **19** as a yellow oil (55 mg, 85%). R_f=0.4 (EtOAc/*n*-hexane, 1:3); IR (film) 2980, 2932, 1711, 1512, 1248, 1172, 1022, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 2.07 (s, 3H), 2.17 (s, 3H), 3,22 (m, 2H), 4,22 (q, J=7,2 Hz, 2H), 5.04 (s, 2H), 5.13 (m, 2H), 6.25 (s, 1H), 6.90 (d, J=8.6 Hz, 2H), 7.04 (d, J=8.6 Hz, 2H), 7.25 (s, 1H), 7,41 (m, 5H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 14.7, 19.5, 28.7, 39.8, 50.6, 61.1, 70.4, 80.4, 115.3, 123.3, 127.8, 127.9, 128.3, 128.7, 128.9, 130.8, 136.2, 136.9, 137.5, 138.5, 142.5, 154.0, 158.3, 163.5, 169.1. HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2NaO_6$, ($(M+Na)^+$) 569.2628, found 569.2575.

*4.1.15. (Triphenylphosphoranyliden)-(2S)-((tert-butoxicarbonylamino)-3R-methyl-pentanoyl)acetonitrile (**20**)*[10]. A solution of carboxylic acid Boc-L-*allo*-Ile-OH (529 mg, 2.29 mmol), (triphenylphosphoranylidene)acetonitrile (759 mg, 2.52 mmol), 4-DMAP (28 mg, 0.23 mmol), and EDCI (484 mg, 2.52 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was purified by chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:2) was collected. Removal of the solvents gave the product **20** (857 mg, 73%). R_f=(EtOAc/*n*-hexane, 1:2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75 (d, 3H, J=6.86 Hz), 1.03 (t, 3H, J=7.4 Hz), 1.28 (m, 1H), 1.44 (s, 9H), 1.56 (m, 1H), 2.17 (m, 1H), 4.92 (m, 1H), 5.12 (m, 1H), 7.64 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 14.2, 27.6, 28.8, 38.4, 47.6 (d, J=125.5 Hz), 59.4, 79.2, 121.5, 123.6 (d, C_2, J=93.0 Hz), 129.5, 133.5, 134.1, 156.5, 195.5.

*4.1.16. Boc-Ser-Pro-OBn (**24**).* L-Proline benzyl ester hydrochloride (1.29 g, 5.34 mmol), 1-hydroxy-benzotriazole monohydrate (0.79 g, 5.88 mmol), Boc-Ser-OH (1.1 g, 5.34 mmol), and TEA (1.5 mL, 10.8 mmol) were dissolved in dry CH_2Cl_2 (25 mL). The solution was cooled in an ice-water bath and stirred while DCC (1.2 g, 5.88 mmol) was added. Stirring was continued for 1 h at 0 °C and 12 h at room temperature. The precipitated DCU was removed by filtration and the solvent was evaporated in vacuo. Flash column chromatography (SiO_2, EtOAc/*n*-hexane, 3:1) provided **24** (1.13 g, 54%) as a colorless oil. R_f=0.5 (EtOAc/*n*-hexane, 3:1); ^1H NMR (CD_3OD, 400 MHz) δ 1.45 (s, 9H), 2.05 (m, 3H), 2.26 (m, 1H), 3,14 (m, 1H), 3.8 (m, 4H), 4,65 (m, 2H), 5,12 (d, J=16.0 Hz, 1H), 5,25 (d, J=16.0 Hz, 1H), 5.50 (sa, 1H), 7.38 (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 24.8, 28.3, 28.9, 47.2, 53.3, 59.1, 64.2, 67.3, 80.0, 128.1, 128.5, 128.7, 135.3, 155.6, 170.2, 172.2.

*4.1.17. Boc-Ser-Pro-OH (**27**).* The ester **24** (3.74 mg, 0.95 mmol) was dissolved in MeOH (10 mL). Pd/C 10% (37 mg) catalyst was added. The reaction was exposed to an atmosphere of H_2 overnight. The catalyst was removed by filtration. Removal of the solvents gave the product **27** (300 mg, 100%). R_f=0.1 (EtOAc/*n*-hexane, 3:1); ^1H NMR (CD_3OD, 400 MHz) δ 1.41 (s, 9H), 2.05 (m, 3H), 2.30 (m, 1H), 3.74 (m, 4H), 4,76 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.1, 28.0, 29.3, 47.4, 55.0, 53.8, 60.1, 82.1, 158.0, 172.0, 176.4.

*4.1.18. Boc-Ser(Ac)-Pro-OBn (**26**).* To a solution of alcohol **24** (533 mg, 1.36 mmol) in TEA (10 mL), acetic anhydride (10 mL) was added at 0 °C. The mixture was stirred overnight at room temperature. HCl (1 M) was added until pH 3 and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. Flash chromatography (EtOAc/*n*-hexane, 1:1) afforded **25** (582 mg, 99%). R_f=0.5 (EtOAc/*n*-hexane, 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.97−2.2 (m, 6H), 2.23 (m, 1H), 3,72 (m, 1H), 3.84 (m, 1H), 3.98 (dd, J=8.0, 12.0 Hz, 1H), 4.36 (dd, J=4.0, 12.0 Hz, 1H), 4.6 (m, 1H), 4.8 (m, 1H), 5.11 (d, J=12.0 Hz, 1H), 5.19 (d, J=12.0 Hz, 1H), 5.45 (m, 1H), 7.31−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 24.9, 28.3, 29.0, 47.2, 51.2, 59.4, 64.7, 67.0, 79.9, 128.1, 128.3, 128.6, 135.5, 155.6, 167.9, 170.6, 171.3.

*4.1.19. Boc-D-Ser(Me)-Pro-OMe (**30**).* L-Proline methyl ester hydrochloride (1.36 g, 8.2 mmol), 1-hydroxy-benzotriazole monohydrate (1.11 g, 8.2 mmol), Boc-D-Ser(Me)-OH (1.64 g, 7.5 mmol), and triethylamine (2.2 mL, 16 mmol) were dissolved in dry CH_2Cl_2 (20 mL). The solution was cooled in an ice-water bath and stirred while DCC (1.69 g, 8.2 mmol) was added. Stirring was continued for 1 h at 0 °C and 12 h at room temperature. The precipitated DCU was removed by filtration and the solvent was evaporated in vacuo. Flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 1:2) provided **30** (1.8 g, 72%) as an oil. R_f=0.4 (EtOAc/CH_2Cl_2, 1:2); IR (film) 2978, 1747, 1711, 1649, 1437, 1390, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.99 (m, 3H), 2.23 (m, 1H), 3.34 (s, 3H), 3.51 (m, 2H), 3.60 (m, 2H), 3,76 (s, 3H), 4.48 (dd, J=8.7, 4.0 Hz, 1H), 4.67 (m, 1H), 5.36 (d, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 28.7, 29.5, 47.5, 51.2, 52.6, 59.4, 59.7, 73.7, 80.2, 155.5, 169.9, 172.8; HRMS (ESI) m/z calcd for $C_{15}H_{26}N_2NaO_6$ ($(M+Na)^+$) 353.1683, found 353.1687.

*4.1.20. Boc-D-Ser(Me)-Pro-Ser-Pro-OBn (**33**).* Acid **31** (1.41 mmol), TEA (1.41 mmol), and amine **32** (1.41 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled in an ice-water bath and stirred while PyBroP (657 mg, 1.41 mmol) was added. Stirring was continued for 12 h at room temperature. The solution was quenched with 1 M HCl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, $CHCl_3$/MeOH, 10:1) gave the desired tetrapeptide **33** (580 mg, 70%). R_f=0.5 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.97–2.3 (m, 8H), 3.38 (s, 3H), 3.56 (m, 3H), 3.74 (m, 5H), 4.48 (m, 1H), 4.71 (m, 2H), 4.86 (m, 1H), 5.11 (d, J=12.0 Hz, 1H), 5.19 (d, J=12.0 Hz, 1H), 5.43 (m, 1H), 7.28 (s, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 28.7, 28.8, 29.2, 30.1, 47.5, 47.8, 52.0, 53.3, 59.5, 59.7, 60.1, 63.7, 67.5, 73.0, 80.4, 128.6, 128.8, 129.0, 135.8, 155.0, 170.0, 171.1, 171.8, 172.3. HRMS (ESI) m/z calcd for $C_{29}H_{42}N_4NaO_9$ ($(M+Na)^+$) 613.2850, found 613.2867.

*4.1.21. (Triphenylphosphoranyliden)-(2S,3S)-2-((S)-1-((S)-3-acetoxy-2-(tert-butoxycarbonylamino)propanoyl)pyrrolidine-2-carboxamido)-3-methyl-pentanamidoacetonitrile (**35**).* Acid **26** (0.61 mmol), TEA (0.19 mL, 0.68 mmol), amine **21** (0.68 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled in an ice-water bath and stirred while HBTU (254 mg, 0,67 mmol) was added. Stirring was continued for 12 h at room temperature. The solution was quenched with 1 M HCl. The mixture was extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, $CHCl_3$/MeOH, 10:1) gave the desired tripeptide **35** (450 mg, 88%). R_f=0.4 ($CHCl_3$/methanol, 10:1); IR (film) 2968, 2876, 2177, 1743, 1647, 1585, 1439, 1242, 1109, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (m, 3H), 0.97 (m, 3H), 1.45 (s, 9H), 1.75 (m, 2H), 1.97 (m, 1H), 2.03 (s, 3H), 2.12–2.22 (m, 4H), 3.65 (m, 1H), 3.79 (m, 1H), 3.9 (m, 1H), 4.12 (m, 1H), 4.53 (m, 1H), 4.77 (m, 1H), 5.03 (m, 1H), 5.40 (m, 1H), 6.88 (m, 1H), 7.50–7.60 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7, 16.1, 20.7, 23.8, 25.1, 28.1, 28.3, 38.7, 47.5, 50.8, 59.5, 60.4, 64.4, 79.9, 120.8, 122.9 (J=93.0 Hz), 129.1 (J=10.0 Hz), 133.2 (J=2.9 Hz), 133.6 (J=10.3 Hz), 155.2, 168.7, 170.1, 170.7, 193.9 (J=4.0 Hz); HRMS (ESI) m/z calcd for $C_{41}H_{49}N_4NaO_7P$ ($(M+Na)^+$) 763.3231, found 763.3268.

*4.1.22. (2Z,4E)-Ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-((3S,4R)-3-(tert-butoxycarbonylamino)-4-methyl-2-oxohexanamido)ethyl) thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**36**).* Compound **16** (128 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) was added at 0 °C. The reaction mixture was stirred until TLC indicated that all starting material had been consumed. The solvent was evaporated and the residue was dissolved with saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the amine as a yellow oil (103 mg).

A solution of **20** (126 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was ozonized at −78 °C until the color of the solution remained blue (or yellow-blue). After the solution was purged with N_2 to remove the excess O_3, the amine derivative of **16** (103 mg, 0.22 mmol) was introduced at −78 °C. The reaction was stirred at −78 °C for 2 h and then quenched with HCl 1 M and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) gave the desired product **36** as a yellow oil (76 mg, 49%). R_f=0.45 (EtOAc/*n*-hexane, 1:2); IR (film) 2926, 1716, 1699, 1508, 1248, 1016, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (d, J=6.9 Hz, 3H), 1.00 (t, J=6.9 Hz, 3H), 1.31 (m, 5H), 1.44 (s, 9H), 1.96 (m, 1H), 2.06 (s, 3H), 2.20 (s, 3H), 3.29 (m, 2H), 4.23 (q, J=6.9 Hz, 2H), 5.03 (m, 3H), 5.20 (m, 1H), 5.50 (m, 1H), 6.31 (s, 1H), 6.50 (s, 1H), 6.88 (d, 2H, J=8.7 Hz), 7.03 (m, 3H), 7.42 (m, 5H), 7.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0, 14.1, 14.5, 17.8, 22.0, 28.6, 30.0, 36.7, 41.4, 52.5, 58.8, 61.1, 70.4, 79.9, 115.3, 117.5, 124.2, 127.8, 128.3, 128.9, 129.3, 129.6, 130.8, 136.4, 137.5, 137.9, 153.6, 152.4, 158.4, 167.4, 169.2, 170.2, 194.5; HRMS (ESI) m/z calcd for $C_{39}H_{49}N_3O_7S$ (M^+) 703.3291, found 703.3247.

*4.1.23. (2Z,4E)-Ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-((3S,4R)-3-(tert-butoxycarbonylamino)-4-methyl-2-oxohexanamido)ethyl)-oxazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**37**).* Compound **18** (0.36 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) was added at 0 °C. The reaction mixture was stirred until TLC indicated that all starting material had been consumed. The solvent was evaporated and the residue was dissolved with saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the amine as a yellow oil.

A solution of **21** (238 mg, 0.46 mmol) in CH_2Cl_2 (15 mL) was ozonized at −78 °C until the color of the solution remained blue (or yellow-blue). After the solution was purged with N_2 to remove the excess O_3, the amine derivative of **18** (159 mg, 0.36 mmol) was introduced at −78 °C. The reaction was stirred at −78 °C for 2 h and then quenched with HCl 1 M and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:4) gave the desired product **37** as a yellow oil (141 mg, 58%). R_f=0.4 (EtOAc/*n*-hexane, 1:4); IR (film) 1514, 1242, 1172, 1115, 1020, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J=7.4 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.95 (m, 1H), 1.31 (m, 4H), 1.45 (s, 9H), 2.04 (m, 7H), 3.21 (m, 2H), 4.22 (q, J=7.4, 12.0 Hz, 2H,), 5.01 (m, 4H), 5.40 (m, 1H), 6.25 (s, 2H), 6.86 (d, J=8.0 Hz, 2H), 6.96 (d, J=8.0 Hz, 2H), 7.43 (m, 6H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.4, 14.1, 16.1, 17.6, 21.6, 24.3, 28.3, 37.3, 38.8, 48.9, 60.0, 60.7, 70.0, 80.4, 114.9, 120.4, 127.4, 127.6, 128.0, 128.6, 129.2, 130.7, 136.4, 136.6, 136.9, 137.3, 138.5, 154.0, 158.4, 159.1, 161.6, 170.0, 196.6; HRMS (ESI) m/z calcd for $C_{39}H_{49}N_3NaO_8$ ($(M+Na)^+$) 688.3592, found 688.3606.

*4.1.24. (2Z,4E)-Ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-((3S,4R)-3-((S)-1-((S)-2-((S)-1-((R)-2-(tert-butoxycarbonylamino)-3-methoxypropanoyl)pyrrolidine-2-carboxamido)-3-hydroxypropanoyl) pyrrolidine-2-carboxamido)-4-methyl-2-oxohexanamido)ethyl) thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**38**).* Compound **36** (0.025 mmol) was dissolved in 4 M HCl in dioxane. The reaction mixture was stirred until TLC indicated that all starting material had been consumed. The solvent was evaporated in vacuo and the amine was used without further purification.

Acid **34** (0.028 mmol), TEA (0.05 mmol), amine (0.025 mmol) were dissolved in dry CH_2Cl_2 (5 mL). The solution was cooled in an ice-water bath and stirred while HBTU (11 mg, 0,03 mmol) was added. Stirring was continued for 12 h at room temperature. The solution was quenched with HCl 1 M. The mixture was extracted with DCM, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, $CHCl_3$/MeOH, 10:1) gave the desired analog **38** (13.2 mg, 66%). R_f=0.4 (AcOEt/methanol, 10:1); IR (film) 2978, 2932, 1745, 1647, 1512, 1452, 1167, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (m, 3H), 0.92 (m, 3H), 1.1 (m, 1H), 1.26 (t, J=7.2 Hz, 3H), 1.32 (m, 1H), 1.42 (s, 9H), 1.67–2.10 (m, 9H), 2.02 (s, 3H), 2.14 (s, 3H), 3.22 (m, 2H), 3.31 (s, 3H), 3.46–3.82 (m, 8H), 4.19 (q, J=7.2 Hz, 2H), 4.44 (m, 1H), 4.62 (m, 2H), 4.84 (m, 1H), 4.99 (s, 2H), 5.32 (m, 1H), 5.32 (m, 1H), 5.45 (m, 1H), 6.27 (s, 1H), 6.47 (s, 1H), 6.85 (m, 2H), 7.01 (m, 3H), 7.16–7.39 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7, 14.1, 14,2, 17.4, 21.7, 25.0, 25.6, 28.3, 40.1, 47.5, 49.1, 51.9, 53.1, 53.2, 57.4, 59.0, 59.8, 60.2, 60.5, 63.2, 69.5, 72.2, 81.2, 114.7, 117.2, 123.8, 127.5, 128.0, 128.6, 130.1, 137.1, 153.5, 156.9, 157.8, 170.2, 171.3, 197.8; HRMS (ESI) m/z calcd for $C_{56}H_{75}N_7O_{13}SNa$ ($(M+Na)^+$) 1108.5036, found 1108.4997; calcd for ($(M+H)^+$) 1086.5222, found 1086.5101.

*4.1.25. (2Z,4E)-Ethyl 5-(2-((S)-1-((3S,4S)-3-((S)-1-((S)-3-acetoxy-2-(tert-butoxycarbonylamino)propanoyl)pyrrolidine-2-carboxamido)-4-methyl-2-oxohexanamido)-2-(4-(benzyloxy)phenyl)ethyl)oxazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (**39**).* Compound **18** (0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and TFA (1 mL) was added at 0 °C. The reaction mixture was stirred until TLC indicated that all starting material had been consumed. The solvent was evaporated and the residue was dissolved with saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the amine.

A solution of **35** (206 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) was ozonized at −78 °C until the color of the solution remained blue (or yellow-blue). After the solution was purged with N_2 to remove the excess O_3, the amine (0.23 mmol) was introduced at −78 °C. The reaction was stirred at −78 °C for 2 h and then quenched with HCl 1 M and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography ($CHCl_3$/MeOH, 10:1) gave the desired product **39** (80 mg, 42%). R_f=0.6 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, 3H, J=7.2 Hz), 0.88 (d, 3H, J=6.8 Hz), 1.02 (m, 1H), 1.22 (m, 1H), 1.27 (t, 3H, J=7.2 Hz), 1.45 (s, 9H), 1.89 (m, 1H), 2.00–2.20 (m, 3H) 2.00 (s, 3H), 2.06 (s, 3H), 2.19 (s, 3H), 2.3 (m, 1H), 3.2 (m, 2H), 3.7 (m, 2H), 4.06 (dd, J=7.6, 11.1 Hz, 1H), 4.22 (q, J=7,2, 2H), 4.31 (dd, J=5.2, 11.1 Hz, 1H), 4.63 (d, J=10.8 Hz, 1H), 4.80 (m, 1H), 5.02 (s, 2H), 5.19 (dd, J=4.0, 7.6 Hz, 1H), 5.38 (dd, J=5.6, 14.0 Hz, 1H), 5.46 (d, J=8.4 Hz, 1H), 6,25 (s, 1H), 6.27 (s, 1H), 6.85 (d, J=8.0 Hz, 1H,), 6.97 (d, J=8.0 Hz, 1H), 7.41 (m, 7H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.4, 14.1, 16.1, 17.1, 20.7, 21.7, 24.4, 25.1, 28.3, 30.9, 36.8, 38.8, 47.7, 48.8, 51.1, 58.5, 59.9, 60.8, 64.3, 69.9, 80.2, 114.9, 120.4, 127.5, 127.6, 128.0, 128.6, 129.2, 130.3, 136.5, 136.7, 137.0, 138.3, 155.2, 157.9, 158.6, 161.3, 169.5, 170.0, 170.4, 170.7, 196.0; HRMS (ESI) m/z calcd for $C_{49}H_{63}N_5O_{12}$ ($(M+H)^+$) 914.4546, found 914.4536.

Acknowledgements

This work was supported by grants from DICyT (Dirección de Innovación, Ciencia y Tecnología para el Desarrollo) and NIH/FIRCA (Fogarty International Research Collaboration Award).

The authors acknowledge a doctoral fellowship from PEDECIBA (Programa de Desarrollo de Ciencias Básicas) (D.S.).

Supplementary data

Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.040. These data include MOL files and InChIKeys of the most important compounds described in this article.

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