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Antiparasite and antimycobacterial activity of passifloricin analogues

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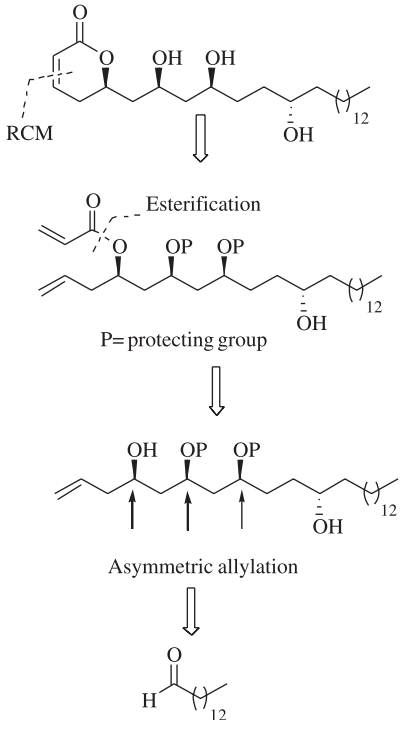
Abstract—Several structural analogues of the polyketide passifloricin lactone were synthesized using asymmetric stereoselective allylations and ring-closing methateses as key reactions. These compounds were active in vitro against intracellular amastigotes of *Leishmania panamensis* (strain UA140), trophozoites of *Plasmodium falciparum* (strain NF54), and *Mycobacterium tuberculosis* (strain $H_{37}Rv$). However, in spite of the significative antiparasitic activity of some synthetic analogues a high cytotoxicity was also observed. Based on these results a lactam derivative was also synthesized. This compound maintained a good level of activity with less toxicity.

1. Introduction

Diseases caused by parasites such as malaria, leishmaniasis, and American trypanosomiasis, and the ones caused by mycobacteria (tuberculosis and leprae) represent approximately a 90% of morbility among the global population, with a higher incidence in developing countries. These ailments affect about 3 billion people, mainly inhabitants of the third world, with very few effective drugs available and with a growing incidence of drug resistant microorganisms. Due to this fact, the World Health Organization through the program 'Tropical Disease Research' (TDR) has classified these diseases as a top priority for research. In this way, it will be possible to find better diagnostic tools, control of vectors, develop vaccines, and alternative treatments.[1] Additionally, it is necessary to search for new molecules using active natural compounds as templates and optimize them through organic synthesis.

It has been reported that natural lactones such as (−)-argentilactone[2] and (+)-boronolide[3] have significant biological activities[4] against some species of *Leishmania* and *Plasmodium*, respectively. Recently, several polyhydroxylated pyrones, named passifloricins, were synthesized[5] and assayed against *Leishmania panamensis* amastigotes.[6] In this article, we describe the synthesis of other passifloricin analogues, their activity against amastigotes of *L. panamensis*



Scheme 1. Retrosynthetic analysis of passifloricin A.

Keywords: Passifloricin; Allylation; Lactone; Antiparasite; Antituberculosis.
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(strain UA140), trophozoites of *Plasmodium falciparum* (strain NF54), and *Mycobacterium tuberculosis* (strain $H_{37}Rv$) as well as their cytotoxic activity.

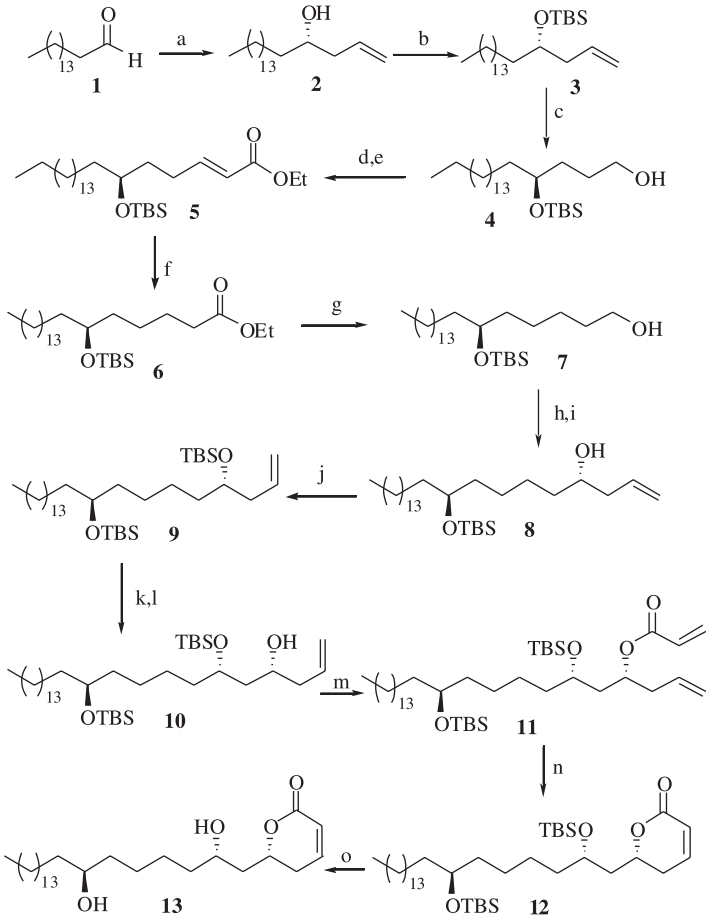
2. Results and discussion

2.1. Synthetic plan

The synthesis of passifloricin analogues was carried out following the methodology described[7] in the literature and according to a retrosynthetic analysis that relied mainly upon asymmetric allylations to create new C–C bonds (Scheme 1).

2.2. Synthesis of δ-lactone of (2*Z*,5*R*,7*S*,12*S*)-trihydroxyheptacos-2-enoic acid (13)

The preparation of passifloricin analogues is exemplified by the synthesis of lactone **13**. Starting with *n*-pentadecanal, an iterative three-step sequence (asymmetric allylation/hydroxyl protection/C=C oxidative cleavage) was proposed to create a new stereogenic carbon atom in each cycle. Acylation of the hydroxyl group generated in the last cycle, followed by ring-closing metathesis, should finally yield the desired unsaturated lactone. Among the existing asymmetric allylation methodologies the Brown chiral allylboranes are the most versatile for the synthesis of this class of compounds due to the relative easy of preparing the allyborane, the efficiency, and the enantiomeric excesses reported.[8] Thus, the synthesis of lactone **13** (Scheme 2) started when *n*-hexadecanal[9] was allowed to react with the B-allyldiisopinocampheylborane (allylBIpc$_2$) prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride).[10] This gave homoallyl alcohol **2** in a 92:8 enantiomeric ratio, as judged from NMR analysis of the Mosher ester.[11] Protection of the hydroxyl group as the *t*-butyldimethylsilyl (TBS)[12] derivative followed by hydroboration[13] yielded the primary alcohol **4**. Swern oxidation[14] of the latter gave an intermediate γ-silyloxy aldehyde, which was subjected to Horner–Wadsworth–Emmons (HWE)[15] reaction. This provided, without further chromatographic purification, α,β-unsaturated ester **5**, which was transformed into saturated ester **6** upon hydrogenation.[16] Reduction of **6** with DIBAL-H[17] resulted in alcohol **7**, which was submitted to Swern oxidation to give an intermediate silyloxy aldehyde, which, without further chromatographic purification, was subjected to



Scheme 2. Reagents and conditions: (a) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (80%, 92:8 enantiomeric mixture); (b) TBSCl, DMF, imidazole, rt, 18 h, 80%; (c) 9-BBN, THF, rt, 20 h, then H_2O_2, NaOH, EtOH, 50 °C, 1 h, 80%; (d) Swern oxidation; (e) $(EtO)_2OPCH_2CO_2Et$, LiCl, DIPEA, CH_3CN, 15 h, 70%; (f) Pd–C 10%, H_2, AcOEt, 94%; (g) DIBAL-H, hexane, 0 °C, 95%; (h) Swern oxidation; (i) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (65% overall for the two steps, 93:7 diastereomeric mixture); (j) TBSOTf, 2,6-lutidine, rt, 1 h, CH_2Cl_2, 88%; (k) O_3, CH_2Cl_2, −78 °C, then PPh_3, 3 h, rt; (l) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (63% overall for the two steps, 91:9 diastereomeric mixture); (m) acryloyl chloride, Et*N*iPr_2, CH_2Cl_2, −78 °C, 1 h, 81%; (n) 10 mol% PhCH=$RuCl_2(PCy_3)_2$, CH_2Cl_2, 60 °C, 83%; (o) PPTS, aqueous MeOH, 70 °C, 18 h, 94%.

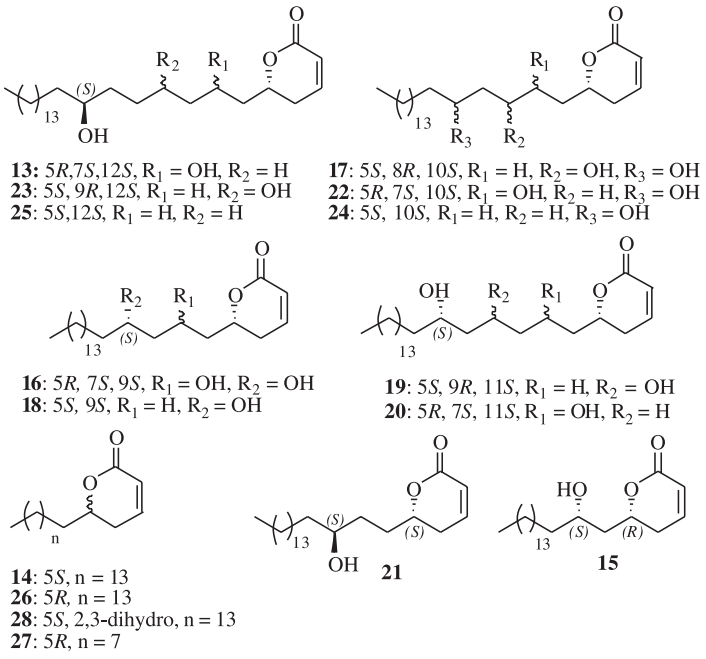


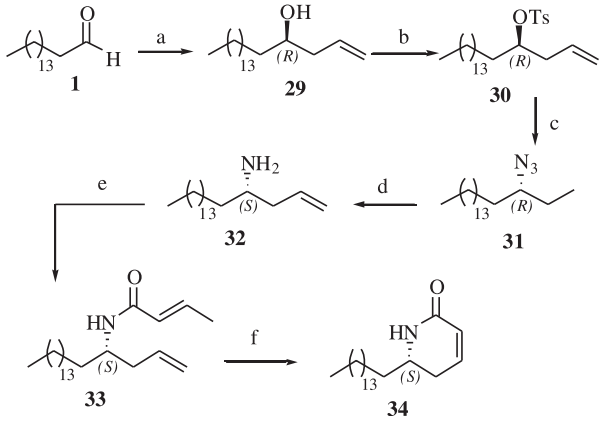
Figure 1. Structures of synthesized lactones.

asymmetric allylation with the same reagent as above. This gave homoallyl alcohol **8**, as a 93:7 diastereomeric mixture, which was then silylated[18] to **9**. Ozonolysis[19] of the olefinic bond in the latter compound was followed by asymmetric allylation with the same reagent as above. This generated the protected triol **10**, which was then treated with acryloyl chloride to produce in good yield the corresponding acrylate.[20] The latter was reactive enough as to undergo RCM with the first generation Grubbs ruthenium catalyst $PhCH{=}RuCl_2(PCy_3)_2$[21] with formation of the unsaturated lactone **12**. Acid-catalyzed cleavage[22] of all the silyl protecting groups in **12** afforded lactone **13** in a 7.3% overall yield from *n*-hexadecanal.

Following similar synthetic strategies a total of 16 lactones, whose structures are shown in Figure 1, were synthesized.[23,24]

2.3. Synthesis of δ-lactam of (2*Z*,5*S*)-hydroxyicos-2-enoic acid (34)

The α,β-unsaturated lactone group is a common feature in many bioactive compounds and it is likely that the electrophilicity of this functional group accounts for their bioactive response. It should be possible to adjust this reactivity through a functional analogue such as a lactam. Therefore we decided to prepare lactam derivative **34**. For the lactam synthesis a similar synthetic strategy was carried out (Scheme 3). Hexadecanal **1** was allowed to react with (−)-B-allyldiisopinocampheylborane, prepared from allylmagnesium bromide and (−)-DIP-Cl, generating homoallyl alcohol **29** as a 90:10 enantiomeric mixture. Tosylation[25] of alcohol **29** following reaction of the corresponding tosylate **30** with sodium azide[26] yielded azide **31**. Reduction of the latter with triphenylphosphine in $THF–H_2O$[27] allowed us to obtain the homoallylic amine **32**, which was subjected to amidation reaction with crotonic acid, DMAP and DCC[28] to yield compound **33**. The latter was reactive enough to undergo RCM using the standard, first generation ruthenium complex with formation of the unsaturated lactam **34**.



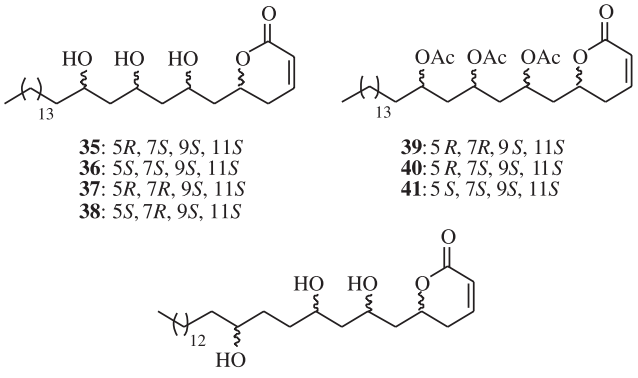
Scheme 3. Reagents and conditions: (a) allylBIpc$_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (78%, 90:10 enantiomeric mixture); (b) TsCl, Py, 12 h, 80%; (c) NaN_3, DMF, 25 °C, 16 h, 74%; (d) PPh_3, $THF–H_2O$, 25 °C, 2 days, 80%; (e) crotonic acid, DCC, DMAP, CH_2Cl_2, 25 °C, 6 h, 81%; (f) 10 mol% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, 60 °C, 82%.

2.4. Antiparasite activity studies

The antiprotozoal and antimycobacterial activities of synthetic compounds, as well as passifloricin A are show in the Figure 1. The other synthetic analogues reported previously[29] are shown in Figure 2.

Below are some conclusions concerning the structure and activity:

- In general, all the compounds had a significant activity against *L. panamensis* amastigotes, exhibiting an EC_{50} lower than 1.0 μg/mL (Fig. 3). Related to the selectivity



35: 5*R*, 7*S*, 9*S*, 11*S*
36: 5*S*, 7*S*, 9*S*, 11*S*
37: 5*R*, 7*R*, 9*S*, 11*S*
38: 5*S*, 7*R*, 9*S*, 11*S*

39: 5*R*, 7*R*, 9*S*, 11*S*
40: 5*R*, 7*S*, 9*S*, 11*S*
41: 5*S*, 7*S*, 9*S*, 11*S*

42: 5*R*, 7*S*, 9*S*, 12*R*
43: 5*S*, 7*S*, 9*S*, 12*R*
44: 5*S*, 7*S*, 9*S*, 12*S*
Passifloricina A,**45** : 5*R*, 7*S*, 9*S*, 11*S*

Figure 2. Passifloricin A analogues reported elsewhere.

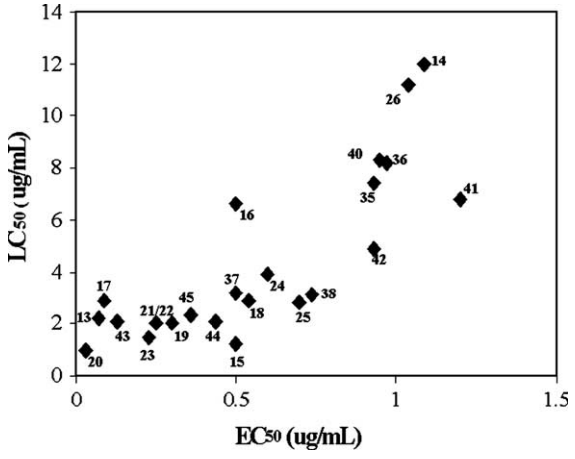


Figure 3. Leishmanicidal activity of passifloricins. Numbering corresponding to structures showed in Figures 1 and 2.

index (SI = $LC_{50}/EC_{50} > 10.0$) compounds **14** (11.0), **16** (13.2), **17** (32,2), **20** (33.7) and **13** (31.4) are the most promising leads, particularly the first one, because simplest structure and lowest LC_{50} (12.0 μg/mL). Passifloricin A, **45**, displayed a SI = 6.4.

Concerning the antiplasmodial activity, compounds with an IC_{50}[†] < 50.0 μg/mL were considered promising.[30] Accordingly, compounds **18** (19.8 μg/mL, 52.1 μM), passifloricin A, **45** (20.9 μg/mL, 47.5 μM), and **23** (26.7 μg/mL, 60.9 μM) exhibit the best activity. Products **20** (39.0 μg/mL, 91.9 μM), **17** (40.1 μg/mL, 97.7 μM), **22** (45.8 μg/mL, 111.6 μM) and **16** (50.1 μg/mL, 126.4 μM) showed marginal activity. The IC_{50} of chloroquine was 1.1 μg/mL (34.5 μM) (Fig. 4).

- Regarding evaluation against *M. tuberculosis* (Table 1) with the green fluorescent protein assay, compounds **13**, **15**, **18**, **19**, **20**, **23** and **24** exhibited an inhibition percentage higher than 90% at 128 μg/mL, while

[†] The IC_{50}: concentration inhibitory dose of the parasite growth in relation to control cultures without compounds.

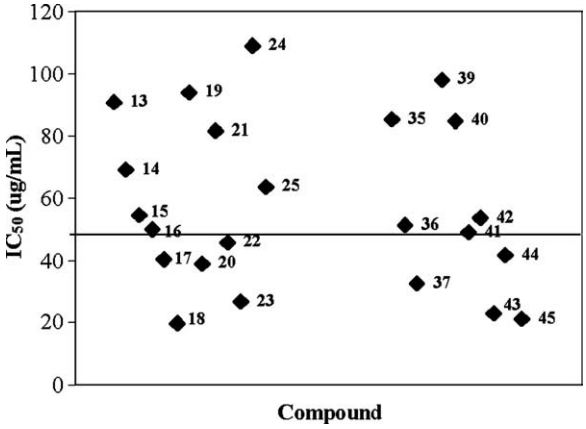


Figure 4. Antiplasmodial activity of passifloricins. Compounds **26**, **27**, **28**, **34**, and **38** were not evaluated.

Table 1. Comparative activity of passifloricins against *M. tuberculosis* $H_{37}Rv$ and Vero cell-line cytotoxicity

Compound	Activity against *M. tuberculosis*		
	Inhibition (%)	MIC (μg/mL, μM)	LC_{50} (μg/mL, μM)
	GFP	MABA	Vero cells
Rifampin	99.6	0.72	117.4
13	97.4	17.31 (39.5)	1.80 (4.1)
14	63.7	> 128	n.e.
15	98.9	35.57 (101.0)	3.07 (8.7)
18	97.4	31.95 (84.0)	2.88 (7.6)
19	95.8	38.04 (89.6)	3.02 (7.2)
20	97.3	48.23 (113.7)	2.20 (5.2)
21	79.1	n.e.	n.e.
22	84.3	n.e.	n.e.
23	98.3	61.47 (140.2)	0.88 (2.0)
24	94.7	24.08 (61.1)	4.60 (12.0)
25	48.1	> 128	n.e.
26	66.3	n.e.	n.e.
27	76.8	n.e.	n.e.
28	53.6	> 128	n.e.
34	74.7	> 128	n.e.
35	81.7	23.4 (53.0)	8.34 (19.0)
45	82.9	29.4 (67.0)	5.61 (13.0)

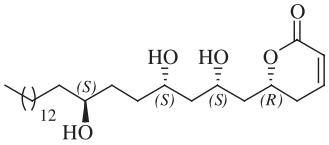
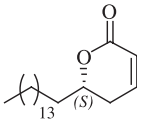
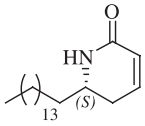
n.e.: no evaluated.

passifloricin A, **45**, reached 82.9%. Additionally, the minimal inhibitory concentration (MIC) of these compounds was lower than 60 μg/mL, except for compound **23**. The other compounds (**14**, **21**, **22**, **25**, **28** and **34**) possesed an inhibition percentage less than 90%. However, the SI of all the compounds was extremely low (0.05–0.36) because their high cytotoxicity levels.

There is not a clear relationship between the antiparasitic activity and other structural facts such as the stereochemistry of the hydroxyl groups and their relative position to the lactone. However, a comparison of the biological profiles of these compounds indicated a tendency to increase the activity against *P. falciparum* and *M. tuberculosis* according to the number of hydroxy groups, but not against *L. panamensis*.

The mechanism of action of these compounds could be originated in the alkylating properties (Michael acceptor) of

Table 2. Comparative activity of lactam **34** against *L. panamensis*

Compound	Structure	Cytotoxicity	Leishmanicidal activity	
		LC $_{50}$ (μg/mL, μM)	EC $_{50}$ (μg/mL, μM)	SI
Glucantime		416.4	6.7	59.6
Passiflorici A, **45**[a]		2.3 (5.2)	0.36 (0.8)	6.4
14		12.0 (39.0)	1.09 (3.5)	11.0
Lactam, **34**		45.1 (146.8)	3.42 (11.1)	13.2

[a] Previous experimental results.

the α,β-unsaturated-δ-lactone; this moiety is widely distributed in nature and have been reported in number bioactivities.[4a,b,31,32]

Lactam **34** exhibited high leishmanicidal activity (3.42 μg/mL, 11.1 μM) versus 0.36 (0.8 μM) and 1.09 (3.5 μM) for passifloricin A and compound **14**, respectively, although it displayed less cytotoxicity (45.1 μg/mL, 146.8 μM vs 2.3 μg/mL, 5.2 μM and 12.0 μg/mL, 39.0 μM) and the SI was almost doubled. However, its profile against *Mycobacterium* was not modified significantly (Table 2).

3. Conclusion

A number of passifloricin analogues have been synthetized and screened. Specific conclusions towards structure–activity relationships point out that the presence of α,β-electrophylic unsaturated lactone moiety is important for the biological actions of these compounds to take place, but the polyhydroxylated side chain seems to have minor influence in their biological profile, as a more simple compound without functionalization on the side chain (compound **14**) is as active as more complex analogues. In addition, this compound displayed a considerable reduction of cytotoxicity. As cytotoxic activity of some synthetic analogues is quite high we intend to screen them as anticancer agents in some cell cancer lines. Work along is in progress and will be the subject of further investigation.

4. Experimental

4.1. General

4.1.1. (*R*)-Nonadec-1-en-4-ol (29). Hexadecanal (1.5 g, 6.25 mmol) was subjected to allyboration with (−)-DIP-Cl as described.[29] Workup as described[29] and column chromatography on silica gel (hexanes/EtOAc, 95:5) provided compound **29** (90:10 mixture of diastereomers, after chromatographic separation 1.37 g, 4.88 mmol, 78%). ^{1}H NMR: δ 0.88 (t, 3H, CH_3, J=6.9 Hz), 1.20–1.36 (m, 26H), 1.40–1.52 (m, 2H, H-5), 2.06 (OH), 2.10–2.19 (m, 1H, H-3′), 2.22–2.31 (m, 1H, H-3), 3.56–3.68 (m, 1H, H-4), 5.09 (d, 1H, H-1, J=9.9 Hz), 5.09 (d, 1H, H-1′, J=17.4 Hz), 5.72–5.92 (m, 1H, H-2); ^{13}C NMR: δ 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.4 (CH_2), 29.7 (×9) (CH_2), 32.0 (CH_2), 36.9 (CH_2), 42.0 (CH_2), 70.8 (CH), 117.7 (CH_2), 135.0 (CH).

4.1.2. (*R*)-4-*p*-Toluensulphonate-nonadec-1-en (30). To a solution of compound **29** (800 mg, 2.83 mmol) in pyridine (2 mL) was added tosyl chloride (1.08 g, 5.67 mmol). The mixture was stirred for 12 h and then CH_2Cl_2 (10 mL) was added and washed with HCl 10% (3×15 mL) of saturated aqueous $NaHCO_3$ and water. Column chromatography on silica gel (hexanes/EtOAc, 95:5) provided compound **30** (987 mg, 2.26 mmol, 80%) oil: $[\alpha]^{20}$ +5.4 (c 1.22, $CHCl_3$); ^{1}H NMR: δ 0.87 (t, 3H, CH_3, J=6.9 Hz), 1.11–1.30 (m, 26H), 1.50–1.52 (m, 2H, H-5), 2.31–2.39 (m, 2H, H-3), 2.43 (s, 3H, Ph-CH_3), 4.50–4.61 (m, 2H, H-4), 5.02 (d, 2H, H-1, J=12.3 Hz), 5.53–5.72 (m, 1H, H-2), 7.31 (d, 2H, Ar, J=8.2 Hz), 7.78 (d, 2H, Ar, J=8.2 Hz); ^{13}C NMR: δ 14.5 (CH_3), 22.0 (CH_3), 23.1 (CH_2), 25.1 (CH_2), 29.6–30.1 (×10) (CH_2), 32.4 (CH_2), 34.1 (CH_2), 39.2 (CH_2), 83.5 (CH), 119.0 (CH_2), 128.2 (×2) (CH), 130.0 (×2) (CH), 132.8 (CH).

4.1.3. (*S*)-4-Azide-nonadec-1-en (31). Compound **30** (800 mg, 1.83 mmol) was dissolved in DMF (5 mL) and NaN_3 (954 mg, 14.67 mmol) was added. The mixture was stirred for 16 h and then AcOEt (10 mL) was added and washed with water. Column chromatography on silica gel (hexanes/EtOAc, 95:5) afforded compound **31** (416 mg, 1.35 mmol, 74%) oil: $[\alpha]^{20}$ −10.6 (c 0.80, $CHCl_3$); ^{1}H NMR: δ 0.82 (t, 3H, CH_3, J=6.9 Hz), 1.15–1.26 (m, 26H), 1.40–1.47 (m, 2H, H-5), 2.19–2.27 (m, 2H, H-3), 3.20–3.30 (m, 1H, H-4), 5.01–5.08 (m, 1H, H-1), 5.09–5.12 (m, 1H, H-1′), 5.65–5.83 (m, 1H, H-2); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 26.5 (CH_2), 29.8–30.1 (×10) (CH_2), 32.4 (CH_2), 34.4 (CH_2), 39.2 (CH_2), 62.8 (CH), 118.4 (CH_2), 134.5 (CH).

4.1.4. (*S*)-Nonadec-1-en-4-amine (32). To a solution of azide **31** (800 mg, 2.83 mmol) in THF (5 mL), PPh_3 (445 mg, 1.71 mmol) and water (28 μL) were added. The mixture was stirred for 12 h and then AcOEt (10 mL) was added and washed with saturated $NaHCO_3$ solution. Column chromatography on silica gel (EtOAc) afforded compound **32** (256 mg, 0.91 mmol, 80%) oil: $[\alpha]^{20}$ −8.6 (*c* 0.84, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3255 (N–H); ^1H NMR: δ 0.88 (t, 3H, CH_3, $J=6.9$ Hz), 1.26–1.55 (m, 26H), 2.08–2.25 (m, 2H, H-5), 2.30–2.50 (m, 2H, H-3), 2.81 (s, 2H, N–H), 2.85–3.10 (m, 1H, H-4), 5.27 (d, 1H, H-1′, $J=$ 9.9 Hz), 5.28 (d, 1H, H-1, $J=17.0$ Hz), 5.93–6.01 (m, 1H, H-2); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 29.8–30.1 (×9) (CH_2), 32.3 (CH_2), 37.4 (CH_2), 42.3 (CH_2), 51.1 (CH), 117.9 (CH_2), 135.9 (CH).

4.1.5. (*S*)-*N*-(4-Nonadec-1-en)-crotonamide (33). Amine **32** (200 mg, 0.712 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and treated sequentially with crotonic acid (73.5 mg, 0.855 mmol), DMAP (261 mg, 2.14 mmol) and DCC (193 mg, 0.935 mmol). The reaction mixture was stirred for 6 h and filtered. Then CH_2Cl_2 (10 mL) was added and washed with saturated aqueous $NaHCO_3$. Column chromatography on silica gel (hexanes/EtOAc, 6:4) afforded compound **33** (210 mg, 0.577 mmol, 81%) oil: mp: 87–89 °C; $[\alpha]^{20}$ −10.0 (*c* 0.95, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3285 (N–H), 1630 (C═O), 1551 (C–N); ^1H NMR: δ 0.82 (t, 3H, CH_3, $J=6.9$ Hz), 1.15–1.35 (m, 26H), 1.50–1.60 (m, 2H, H-5), 1.78 (d, 3H, Hc, $J=6.9$ Hz), 2.07–2.29 (m, 2H, H-3), 3.95–4.08 (m, 1H, H-4), 4.95–5.10 (m, 2H, H-1/N–H), 5.63–5.80 (m, 2H, H-a/H-2), 6.68–6.82 (m, 1H, Hb); ^{13}C NMR: δ 14.5 (CH_3), 18.1 (CH_3), 23.1 (CH_2), 26.4 (CH_2), 29.8–30.1 (×9) (CH_2), 31.3 (CH_2), 32.3 (CH_2), 34.9 (CH_2), 39.6 (CH_2), 48.9 (CH), 118.1 (CH_2), 125.8 (CH), 134.9 (CH), 140.0 (CH), 166.9 (C═O).

4.1.6. δ-Lactam of (2*Z*,5*S*)-hydroxyicos-2-enoic acid (34). Compound **33** (160 mg, 0.438 mmol) was dissolved under N_2 in dry, degassed CH_2Cl_2 (50 mL) and treated with ruthenium catalyst $PhCH=RuCl_2(PCy_3)_2$ (36 mg, 0.044 mmol). The mixture was heated at reflux until consumption of the starting material (ca. 3 h, TLC monitoring!). Solvent removal in vacuo and column chromatography on silica gel (hexanes/EtOAc, 1:1) furnished **34** (116 mg, 0.36 mmol, 82%): mp: 74–76 °C; $[\alpha]^{20}$ +37.7 (*c* 3.0, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3210 (N–H), 1687 (C═O), 1550 (C–N); ^1H NMR: δ 0.88 (t, 3H, CH_3, $J=6.9$ Hz), 1.20–1.45 (m, 26H), 1.50–1.60 (m, 2H, H-6), 2.01–2.21 (m, 1H, H-4), 2.30–2.46 (m, 1H, H-4′), 3.50–3.66 (m, 1H, H-5), 5.84–5.98 (m, 2H, H-2/N–H), 6.54–6.64 (m, 1H, H-3); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 25.7 (CH_2), 29.8–30.4 (×11) (CH_2), 32.3 (CH_2), 35.9 (CH_2), 51.5 (CH), 125.0 (CH), 141.0 (CH), 166.9 (C═O). HR EIMS, *m/z* (% rel int.) 307.2805 [M^+] (0.7), 240.2678 (2), 96.0417 (100). Calcd for $C_{20}H_{37}NO$, 307.2875.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.037. Complete antiparasite and antimycobacterial activity data, NMR and Mass spectra, HPLC analysis and synthetic procedures. This material is available free of charge via the Internet at http://www.sciencedirect.com.

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