Pergamon

Tetrahedron 54 (1998) 2227–2242

TETRAHEDRON

Marine Nematocides : Tetrahydrofurans from a Southern Australian Brown Alga, *Notheia Anomala.*

Robert J Capon,* Russell A Barrow, Simone Rochfort, Michael Jobling, Colin Skene,

School of Chemistry, University of Melbourne, Parkville, Victoria, 3052, Australia

Ernest Lacey, Jennifer H Gill,

Microbial Screening Technologies Pty Ltd, Kemps Creek, New South Wales, 2171 Australia

Thomas Friedel and David Wadsworth

Novartis Animal Health Australasia Pty Ltd, Kemps Creek, New South Wales, 2171 Australia

Received 29 October 1997; accepted 18 December 1997

Abstract: Chemical analysis of *N. anomala* collected off rock platforms along the southern coast of Australia yielded a *cis*-dihydroxytetrahydrofuran (**2**), the structure for which was assigned by spectroscopic analysis, chemical derivatization and biomimetic synthesis. Tetrahydrofurans from *Notheia anomala* are reported for the first time as potent and selective inhibitors of the larval development of parasitic nematodes. SAR observations are made on a selection of natural, semi-synthetic and synthetic tetrahydrofurans.

INTRODUCTION

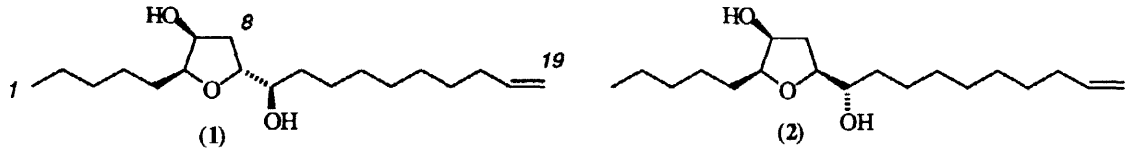
Anthelmintics are drugs used to rid host animals of parasites. Parasitism by nematodes (unsegmented worms which consititute the phylum Nematoda) represents a major source of lost production to the commercial livestock industry. Despite the availability of excellent commercial anthelmintics (*in vivo* effective nematocidal agents), growing levels of resistance to key structure classes (benzimidazoles, macrolides...) necessitates an ever vigilant search for new bioactive agents. This report describes a new *cis*-dihydroxytetrahydrofuran (**2**) from the southern Australian marine brown alga *Notheia anomala*.and reveals for the first time that compounds of this general structure class exhibit potent and selective nematocidal activity against the free-living stages of the parasitic nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis*.

Notheia anomala (Order Notheiales, Family Notheiaceae) is a taxonomically unique alga found along the southern Australia coast as an epiphyte to *Hormosira banksii* (Order Fucales, Family Hormosiraceae).[1] The *trans*-dihydroxytetrahydrofuran (**1**) was first reported from *N. anomala* in 1980 by researchers from the Roche Research Institute of Marine Pharmacology.[2] Although attributed no biological properties at that time, (**1**) has since attracted the attention of chemists as a target molecule capable of illustrating new synthetic strategies to chiral 2,5-disubstituted tetrahydrofurans.[3 plus refs therein] Numerous potent biologically active natural products incorporate the tetrahydrofuran moiety such that efficient synthetic procedures are highly prized. Our detailed re-investigations of *N. anomala* have led to the identification of many new epoxylipids,[4-6] prompting the discovery and characterisation of an efficient acid catalysed transformation of methylene interrupted bisepoxides into tetrahydrofurans,[7] that in turn underpinned a highly convergent biomimetic synthesis.[3]

0040-4020/98/$19.00
PII: S0040-4020(97)10432-X

This report represents an extension of those studies, describing a new *cis*-dihydroxytetrahydrofuran (**2**) and summarizing the nematocidal properties of tetrahydrofurans of this structure class.

RESULTS AND DISCUSSION



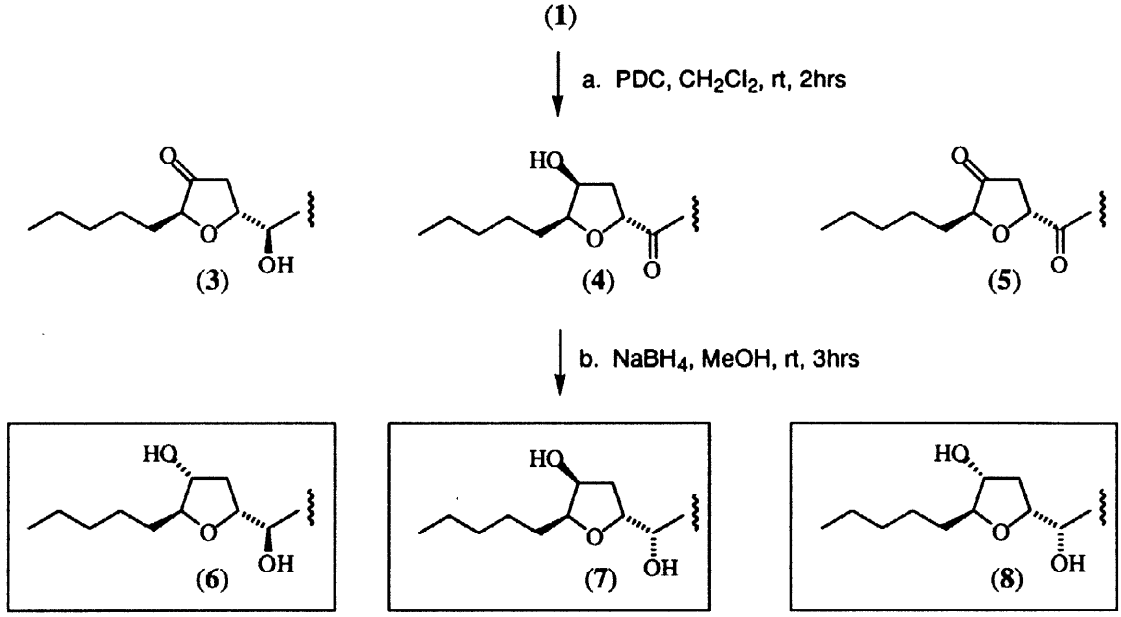
As a consequence of our ongoing research program targeting marine natural products with antiparasitic activity we have examined solvent extracts from several hundred marine alga and invertebrates using amongst others an *in vitro* parasitic nematode larval development assay.[8] Among the earliest leads encountered from this study was the tetrahydrofuran (**1**) from the southern Australian brown alga *N. anomala*. To pursue structure activity relationship (SAR) investigations, samples of *N. anomala* were collected from a variety of geographic locations. Of particular interest was the observation that all collections of *N. anomala* contained an as yet unreported dihydroxytetrahydrofuran (**2**) isomeric with, but at concentrations three orders of magnitude less than that of, the major metabolite (**1**). This report describes the successful isolation, characterisation and identification of (**2**), as well as conclusions drawn from SAR investigations on related tetrahydrofurans.

Large scale extraction of *N. anomala* followed by solvent partitioning and silica chromatography (MPLC and HPLC) yielded the major metabolite (**1**), together with numerous known epoxylipids and a small quantity of an unknown dihydroxytetrahydrofuran (**2**). Collections of *N. anomala* from locations across several hundred kilometres of Victorian and Tasmanian coastline were analysed by HPLC in the hope of identifying a subtype of *N. anomala* yielding higher returns of the target metabolite (**2**). Unfortunately all collections analysed for 5350 ± 400 ppm (**1**), and a meagre 5 ± 1 ppm of (**2**). Extraction of 1.3 kg dry weight of *N. anomala* yielded a pure sample of (**2**) (5 mg).

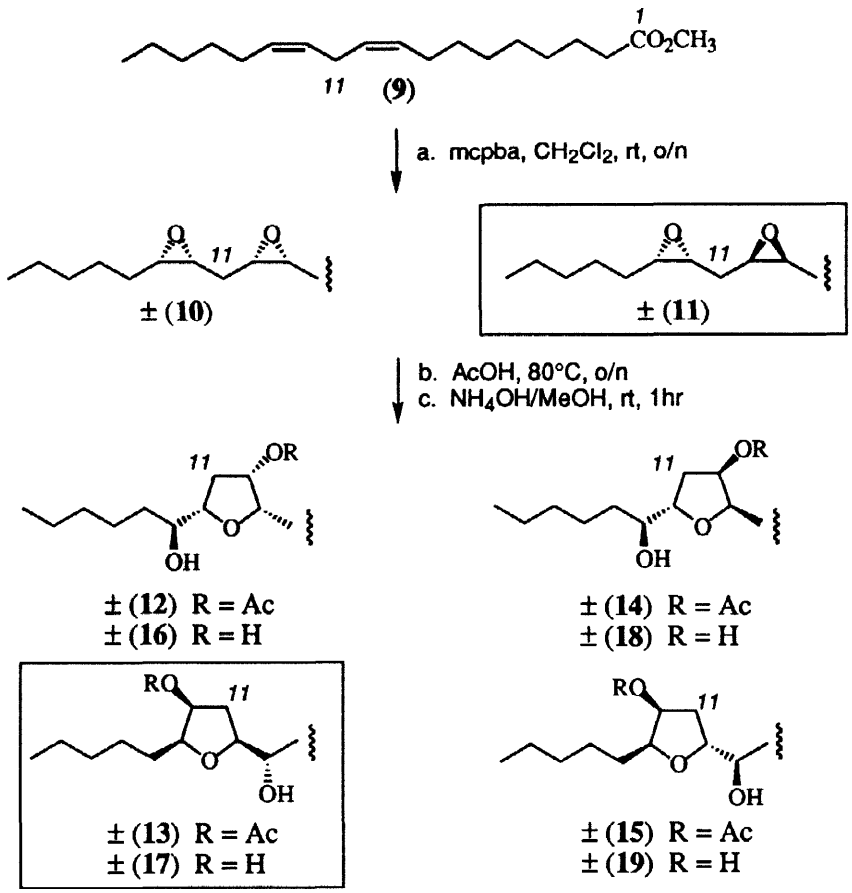
Mass spectral analysis (*m/z* 312, Δmmu -0.6) confirmed (**2**) to be isomeric with the major metabolite (**1**). The NMR data for (**2**) revealed resonances characteristic of a monosubstituted double bond (δ 5.81 (ddt), 139.1 (d) ppm; δ 4.92 (ddt), 4.99 (ddt), 114.1 (t) ppm), a primary methyl (δ 0.88 (t), 14.0 (q) ppm) and four oxymethines (δ 3.47 (ddd), 73.9 (d) ppm; δ 3.62 (dt), 84.3 (d) ppm; δ 3.95 (ddd), 79.0 (d) ppm; δ 4.04 (ddd), 71.5 (d) ppm). Analysis of the COSY NMR data established a connectivity sequence characteristic of the dihydroxytetrahydrofuran moiety in (**1**), which together with a diagnostic fragment ion (*m/z* 157, facile cleavage of the C-9/C-10 bond) in the EIMS confirmed (**2**) as a stereoisomer of (**1**).

In an attempt to assign a relative stereochemistry to (**2**) an authentic sample of (**1**) was subjected to mild oxidation with pyridinium dichromate (PDC) to return a mixture of the two monoketones (**3**) and (**4**), and the diketone (**5**). These ketones were resolved by HPLC and the two monoketones distinguished on the basis of infrared absorptions - the carbonyl for the C-7 ketone (**3**) absorbed at a higher frequency (1755 cm^{-1}) than that for the less strained C-10 ketone (**4**) (1715 cm^{-1}). While (**3**) and (**5**) were stable, the C-10 ketone (**4**) proved susceptible to photo-oxidation and required storage in the dark and/or under nitrogen. Sodium borohydride reduction of (**3**) resulted in stereoselective conversion to the natural product (**1**) and its C-7 epimer (**6**) (1:4.4). Reduction of (**4**) under the same conditions was less stereoselective but successfully returned (**1**) and the C-10

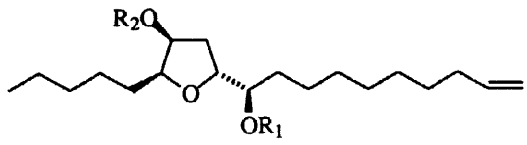
epimer (**7**) (1.2:1). Reduction of the diketone (**5**) yielded a four component mixture that was resolved by HPLC to return (**1**), (**6**), (**7**) and the diastereomer (**8**). None of the *trans*-dihydroxytetrahydrofuran stereoisomers proved identical to (**2**), requiring that (**2**) possess a *cis* relative configuration about C-6 and C-9.



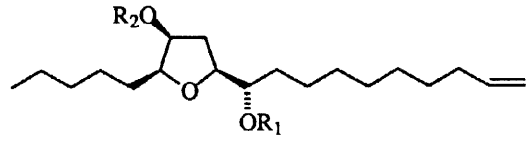
Taking note of the co-occurrence of bisepoxide and tetrahydrofuran metabolites in *N. anomala* , we had previously refined a very efficient synthetic protocol for the conversion of bisepoxides to tetrahydrofurans.[7] In order to determine the relative stereochemistry of (**2**) a sample of methyl linoleate (**9**) was oxidized to the *syn*-bisepoxide ±(**10**) and *anti*-bisepoxide ±(**11**), which were separated by fractional crystallisation. Treatment of ±(**11**) with acetic acid at 80°C returned a near quantitative yield of tetrahydrofuran monoacetates that were resolved by HPLC into four compounds, the *cis* isomers ±(**12**) and ±(**13**) as major products, and the *trans* isomers ±(**14**) and ±(**15**) as minor products. All components were separable by HPLC. As might be expected the NMR data for the structural isomers ±(**12**) versus ±(**13**), and ±(**14**) versus ±(**15**), were virtually identical, however, the structures could be distinguished by diagnostic ions in their respective mass spectra. The mass spectra of ±(**12**) and ±(**14**) featured an intense ion corresponding to cleavage through the C-12/C-13 bond and loss of HOAc (*m/z* 225). On the other hand, the mass spectra of ±(**13**) and ±(**15**) lacked these ions, featuring rather a base peak diagnostic for cleavage through the C-9/C-10 bond and loss of HOAc (*m/z* 139). Treatment of the acetates ±(**12-15**) with methanolic ammonia resulted in quantitative conversion to the respective dihydroxytetrahydrofurans ±(**16-19**). The relative stereochemistry of ±(**12-19**) were initially assigned on the basis of earlier detailed mechanistic investigations of the bisepoxide-tetrahydrofuran transformation,[7] but were readily supported by comparison of the NMR data for ±(**18**) and ±(**19**) with that for the natural product (**1**). Likewise, the NMR data about the key dihydroxytetrahydrofuranyl moiety in ±(**16**) and ±(**17**) proved virtually identical with that of the natural product (**2**), thereby defining the relative stereochemistry as shown. A complete biomimetic synthesis of ±(**1**) and ±(**2**) utilizing this bisepoxide to tetrahydrofuran methodology has recently been reported in a rapid communication.[3]



Although the original determination[2] of absolute stereochemistry for (**1**) had been via Horeau analysis of a monoacetate derivative, given the limited supply of (**2**) we elected to employ the advanced Mosher procedure as a means to determine the absolute stereochemistry of (**2**). In order to establish conditions suitable for preparation of the required C-10 monoacetate and Mosher esters, trials were carried out on the known metabolite (**1**). The optimum procedure involved conversion of (**1**) to the diacetate (**20**), which was then subjected to partial deacetylation with ammonium hydroxide to yield the C-10 acetate (**21**) as the major product after HPLC.



	R_1	R_2
(**20**)	Ac	Ac
(**21**)	Ac	H
(**22**)	Ac	(S)-MTPA ester
(**23**)	Ac	(R)-MTPA ester



	R_1	R_2
(**24**)	Ac	Ac
(**25**)	Ac	H
(**26**)	Ac	(S)-MTPA ester
(**27**)	Ac	(R)-MTPA ester

Preparation of the (S)-MTPA (**22**) and (R)-MTPA (**23**) esters proceeded smoothly, with NMR analysis (δS-δR : H-6, -55.2 Hz; H_a-8, +1.7 Hz; H-9, +28.3 Hz) confirming a 6S,7S,9R,10R absolute stereochemistry for (**1**) - identical with that previously determined by Horeau analysis. More significantly, acetylation of (**2**) yielded the diacetate (**24**), from which deacetylation yielded the C-10 acetate (**25**) as the major product after HPLC. Conversion of (**25**) into the (S)-MTPA ester (**26**) and (R)-MTPA ester (**27**) proceeded smoothly, with NMR analysis (δS-δR : H-6, -2.0 Hz; H_a-8, +14.9 Hz; H-9, +8.8 Hz) confirming a 6S,7S,9S,10S absolute stereochemistry for (**2**).

(**28**)

It is tempting to speculate on the biosynthetic pathways leading to (**1**) and (**2**). The bisepoxide (**28**) is a known metabolite in *N. anomala*,[3] and is almost certainly the biosynthetic precursor to the major *trans*-dihydroxytetrahydrofuran (**1**). Synthetic investigations have shown that acid, as opposed to enzyme, mediated conversion of the *syn*-bisepoxide (**28**) can lead to the *trans*-tetrahydrofuran (**1**) together with lesser amounts of the *cis*-tetrahydrofuran (**2**).[7] Given this, enzymatic conversion of (**28**) in *N. anomala* could be stereoselective - leading predominantly to the *trans*-tetrahydrofuran (**1**) but nonetheless returning minor amounts of the *cis*-tetrahydrofuran (**2**). Alternatively, the *cis*-tetrahydrofuran (**2**) could be biosynthetically derived from an as yet undetected *anti*-bisepoxide precursor. In any event *N. anomala* possesses the ability to efficiently convert unsaturated fatty acids to bisepoxides and tetrahydrofurans. To further explore these phenomena efforts are currently in hand to secure cell free enzyme preparations from fresh collections of *N. anomala* , in the hope that oxidase and/or cyclase enzymes can be isolated, studied and possibly applied in stereoselective chemical synthesis.

The natural tetrahydrofuran (**1**), together with a selection of closely related semi-synthetic and synthetic analogues, were submitted for *in vitro* nematocidal screening. Examples of the range of derivatives derived from naturally occurring (**1**), along with their screening code numbers, are shown in Figure 1.The tetrahydrofuran (**1**) exhibited LD_{50} values (concentration required to inhibit 50% of nematode eggs developing to the infective third stage) against *H. contortus* and *T. colubriformis* of 1.8 and 9.9 ppm respectively. This level of nematocidal activity is comparable to that of the commercially available nematocides levamisole and closantel.[8] SAR conclusions drawn from our investigation of tetrahydrofurans from this structure class are summarised as follows;

- stereochemistry about the tetrahydrofuranyl moiety does not significantly influence activity. The most active stereoisomers were the C-10 epimers of (**1**) and (**2**) (LD_{50} = 0.54 and 0.41 respectively).
- while mono and diketone derivatives of (**1**) retained activity, the corresponding acetates were inactive.
- oxidation or reduction of the terminal double bond in (**1**) substantially diminished activity.
- replacement of the terminal double bond in (**1**) with a "styryl" unit retained but did not enhance activity.
- while (**1**) displayed an LD_{50} against *Haemonchus contortus* and *Trichostrongylus colubriformis* of 1.8 and 9.9 ppm respectively, levels for selected synthetic derivatives varied as low as 0.4 and 1.5 ppm.

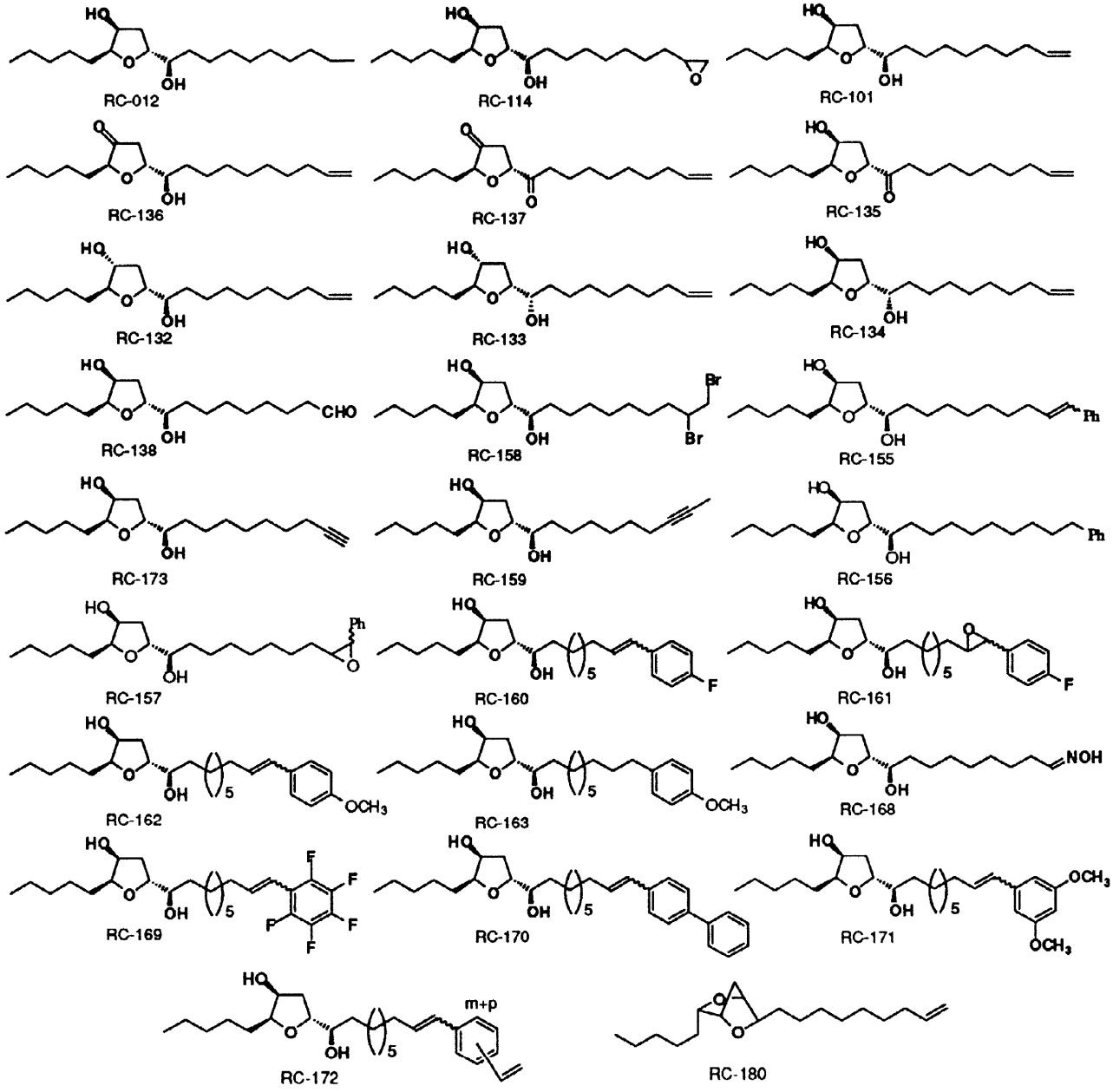


Figure 1 : A selection of SAR derivatives of the natural product (**1**).

Unfortunately, attempts to translate the *in vitro* nematocidal activity elicited by these tetrahydrofurans into an *in vivo* response proved unsuccessful. Although the tetrahydrofurans mentioned in this report are not in themselves useful as commercial anthelmintics, they are a potent and selective class of nematocides with activity against the free living stages of parasitic nematode larvae. An understanding of the *in vitro* mode of action of these tetrahydrofurans may yet contribute to the discovery of new and improved anthelmintics.

EXPERIMENTAL

General experimental details. see ref 9.

Parasitic nematode larval development assay.

Nematode eggs are applied in duplicate to the surface of an agar matrix containing the "test solution" (extract, chromatographic fraction &/or pure compound at a concentration range of ~100 to 0.5 ppm). The eggs are allowed to hatch and develop through to the L3 infective stage (6 days). The extent of larval development is determined quantitatively by counting the number of eggs, L1s, L2s and L3 larvae to determine the proportion of undeveloped larvae (eggs, L1s and L2s) at each concentration. The data is fitted to a log-concentration-logit model to determine the LD_{50} value.

Collection, extraction and isolation.

Notheia anomala (1.3 kg dry weight) was collected by hand off extensive growths of *Hormosira banksii* uncovered at low tide on rock platforms south-west of Bells Beach, Victoria. The fresh alga was air dried away from direct sunlight over a period of three weeks, then steeped in CH_2Cl_2/MeOH (7:3) overnight. The resulting extract was then concentrated *in vacuo*, and the CH_2Cl_2 soluble portion extracted, concentrated *in vacuo* and diluted with hexane to yield the major *trans*-dihydroxytetrahydrofuran (**1**) as a crude white precipitate (6.5 gm, 0.48%). MPLC (silica, 10% stepwise elution from hexane to EtOAc) of the filtrate, followed by HPLC (2.0 mL/min, 40% EtOAc/hexane, Phenomenex 5μ silica column) yielded a mixture of epoxylipids and the pure *cis*-dihydroxytetrahydrofuran (**2**) (5 mg, 0.001%).

(6S,7S,9S,10S)-6,9-epoxynonadec-18-ene-7,10-diol (2).

A stable, colorless oil. $[\alpha]_D$ +74.5° (c=0.4, $CHCl_3$); **IR** (film) 3444, 3365, 1642 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 1-H_3), 1.25-1.45 (methylene envelope containing 2, 3, 4, 12, 13, 14, 15 and 16-H_2), 1.21 (m, 11-H_A), 1.62 (m, 11-H_B), 1.64 (m, 5-H_2), 1.84 (dd, *J*=14.2, 3.4 Hz, 8-H_A), 2.03 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.39 (ddd, *J*=14.2, 9.8, 5.4 Hz, 8-H_B), 3.47 (ddd, *J*=7.9, 5.3, 2.5 Hz, 10-H), 3.62 (dt, *J*=2.7, 6.8 Hz, 6-H), 3.95 (ddd, *J*=9.8, 3.4, 2.5 Hz, 9-H), 4.04 (dd, *J*=5.4, 2.7 Hz, 7-H), 4.92 (ddt, *J*=10.3, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.81 (ddt, *J*=17.1, 10.3, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.5 (C-2), 25.9, 26.0 (C-4, C-12), 28.8, 28.9, 29.0, 29.4, 29.6 (C-13, C-14, C-15, C-16, C-5), 32.0 (C-3), 33.8 (C-17), 34.4 (C-11), 38.8 (C-8), 71.5 (C-7), 73.9 (C-10), 79.0 (C-9), 84.3 (C-6), 114.1 (C-19), 139.1 (C-18) ppm; **EIMS** (70eV, *m/z*, %) 312 (M^+, 1), 295 (1), 294 (1), 157 (100), 139 (22), 121 (20), 114 (18), 113 (88), 101 (8), 96 (14), 95 (61), 81 (21), 69 (33), 67 (22), 57 (23), 56 (29), 54 (47); **HRMS** found 312.2670; $C_{19}H_{36}O_3$ requires: 312.2664.

Oxidation of (1).

To the *trans*-dihydroxytetrahydrofuran (**1**) (87 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added freshly prepared PDC (160 mg, 0.42 mmol) and the suspension stirred vigorously at room temperature for 48 hours after which the reaction mixture was filtered through a pad of silica and washed with EtOAc (2 x 20 mL) to return a colorless

mixture of the ketones (3), (4) and (5). Chromatographic resolution of this mixture by HPLC (2 mL/mim, 30% EtOAc/hexane, Phenomenex 5μ silica) provided pure samples of (3) (14 mg, 16%), (4) (29 mg, 33%) and (5) (42 mg, 48%).

(6S,9R,10R)-10-hydroxy-6,9-epoxynonadec-18-en-7-one (3).

A stable colorless oil. $[\alpha]_D$ +33.2° (c=1.0, $CHCl_3$); **IR** (film) 3460, 1755, 1640 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 1-H_3), 1.2-1.6 (methylene envelope, 2, 3, 4, 5, 11, 12, 13, 14, 15 and 16-H_2), 2.03 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.25 (bs, OH), 2.42 (ddd, J=18.3 , 7.1, 0.9 Hz, 8-H_A), 2.52 (dd, *J*=18.3, 7.1 Hz, 8-H_B), 3.54 (bm, 10-H), 3.98 (dd, *J*=8.1, 4.6 Hz, 6-H), 4.18 (ddd, *J*=7.1, 7.1, 5.4 Hz, 9-H), 4.92 (ddt, *J*=10.3, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.81 (ddt, J=17.1, 10.3, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.4 (C-2), 24.9 (C-4), 25.5 (C-12), 28.9, 29.0, 29.3, 29.5 (C-13, C-14, C-15, C-16), 31.0 (C-5), 31.5 (C-3), 33.2 (C-11), 33.8 (C-17), 38.9 (C-8), 73.6 (C-10), 77.8 (C-6), 79.8 (C-9), 114.1 (C-19), 139.1 (C-18), 215.8 (C-7) ppm; **EIMS** (70eV, *m/z*, %) 310 (M^+, 24), 240 (2), 157 (20), 156 (18), 155 (12), 128 (16), 127 (17), 101 (30), 99 (78), 57 (100); **HRMS** found 310.2507; $C_{19}H_{34}O_3$ requires: 310.2507.

(6S,7S,9R)-7-hydroxy-6,9-epoxynonadec-18-en-10-one (4).

An unstable colorless oil. $[\alpha]_D$ +20.4° (c=1.0, $CHCl_3$); **IR** (film) 3445, 1715, 1640 cm^{-1}; **^{1}H NMR** (100 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 1-H_3), 1.2-1.6 (methylene envelope, 2, 3, 4, 5, 12, 13, 14, 15 and 16-H_2), 2.01 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.09 (ddd, *J*=13.7, 8.3, 4.8 Hz, 8-H_A), 2.22 (ddd, *J*=13.7, 8.3, 0.7 Hz, 8-H_B), 2.48 (dt, *J*=17.6, 7.4 Hz, 11-H_A), 2.54 (dt, *J*=17.6, 7.4 Hz, 11-H_B), 3.75 (dt, *J*=2.9, 7.0 Hz, 6-H), 4.22 (dd, *J*=4.8, 2.9 Hz, 7-H), 4.55 (dd, *J*=8.3, 8.3 Hz, 9-H), 4.93 (ddt, *J*=10.3, 2.2, 1.3 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.80 (ddt, *J*=17.1, 10.3, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.5 (C-2), 23.2 (C-4), 25.9 (C-12), 28.6, 28.8, 28.9, 29.1, 29.2, 29.2 (C-5, C-11, C-13, C-14, C-15, C-16), 31.9 (C-3), 33.7 (C-17), 38.3 (C-8), 72.5 (C-7), 81.0 (C-6), 84.1 (C-9), 114.2 (C-19), 139.1 (C-18), 212.5 (C-10) ppm; **EIMS** (70 eV, *m/z*, %) 310 (M^+, 2), 157 (100), 139 (17), 121 (14), 113 (60), 95 (42), 69 (33), 55 (38), 43 (34); **HRMS** found 310.2508; $C_{19}H_{34}O_3$ requires: 310.2507.

(6S,9R)-6,9-epoxynonadec-18-ene-7,10-dione (5).

A moderately stable colorless oil. $[\alpha]_D$ -35.9° (c=1.0, $CHCl_3$); **IR** (film) 1760, 1720 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 1-H_3), 1.3-1.7 (methylene envelope, 2, 3, 4, 5, 12, 13, 14, 15 and 16-H_2), 2.04 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.60 (t, *J*=7.4 Hz, 11-H_2), 2.62 (dd, *J*=18.3, 8.8 Hz, 8-H_A), 2.72 (dd, J=18.3, 5.4 Hz, 8-H_B), 3.90 (dd, *J*=7.8, 4.5 Hz, 6-H), 4.74 (dd, *J*=8.8, 5.4 Hz, 9-H), 4.92 (ddt, *J*=10.3, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.81 (ddt, *J*=17.1, 10.3, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.4 (C-2), 23.1 (C-4), 24.8 (C-12), 28.8, 28.9, 29.1, 29.2, 30.8 (C-5, C-13, C-14, C-15, C-16), 31.3 (C-3), 33.7 (C-17), 37.5 (C-11), 38.7 (C-8), 78.7 (C-6), 79.7 (C-9), 114.2 (C-19), 139.1 (C-18), 209.7 (C-10), 213.7 (C-7) ppm; **EIMS** (70eV, *m/z*, %) 308 (M^+, 2), 266 (2),

237 (1), 209 (8), 181 (29), 151 (52), 135 (39), 127 (71), 111 (47), 99 (23), 83 (81), 69 (57), 55 (100); **HRMS** found 308.2351; $C_{19}H_{32}O_3$ requires: 308.2351.

(6S,7R,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol (6).

To the 7-monoketone (**3**) (10 mg, 0.03 mmol) in MeOH (5 mL) was added $NaBH_4$ (30 mg, excess) and the mixture stirred at room temperature for 2 hours, after which time the MeOH was removed *in vacuo* to yield a colorless solid which was extracted into Et_2O (20 mL). The ethereal extract was washed with H_2O (20 mL), aqueous saturated $NaHCO_3$ (15 mL) and dilute aqueous HCl (15 mL, 2M), then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield a waxy solid (9.6 mg, 95%) that was shown by ^1H NMR spectroscopy to be a 1:4.4 mixture of (**1**) and (**6**). Chromatographic resolution by HPLC (2 mL/min, 40% EtOAc/hexane, Phenomenex 5μ silica) yielded the desired epimer (**6**) as an unstable colorless oil; $[\alpha]_D$ -20.2° (c=0.51, $CHCl_3$); **IR** (film) 3370, 1692 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 1-H_3), 1.3-1.6 (methylene envelope, 2, 3, 4, 5, 11, 12, 13, 14, 15 and 16-H_2), 1.76 (ddd, *J*=13.7, 3.9, 2.5 Hz, 8-H_A), 2.03 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.38 (ddd, *J*=13.7, 9.0, 6.1 Hz, 8-H_B), 3.50 (ddd, *J*=8.1, 4.6, 3.4 Hz, 10-H), 3.89 (dt, *J*=1.7, 4.9 Hz, 6-H), 3.98 (ddd, *J*=9.0, 4.6, 3.9 Hz, 9-H), 4.02 (ddd, *J*=6.1, 1.7, 1.7 Hz, 7-H), 4.93 (ddt, *J*=10.1, 2.2, 1.3 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.80 (ddt, *J*=17.1, 10.1, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.5 (C-2), 25.6, 25.8, 28.8, 29.0, 29.3, 29.5, 31.7, 33.2, 33.7, 34.0 (C-3, C-4, C-5, C-11, C-12 to C-17), 37.2 (C-8), 74.2 (C-10), 75.4 (C-7), 79.4 (C-9), 87.3 (C-6), 114.1 (C-19), 139.1 (C-18) ppm; **EIMS** (70eV, *m/z*, %) 312 (M^+, <1), 157 (100), 139 (18), 121 (20), 113 (72), 95 (53), 69 (36), 55 (42); **HRMS** found 312.2663; $C_{19}H_{36}O_3$ requires: 312.2664.

(6S,7S,9R,10S)-6,9-epoxynonadec-18-ene-7,10-diol (7).

The 10-monoketone (**4**) (25 mg, 0.08 mmol.) was treated in an manner analogous to that described above for (**3**), to yield a 1.2:1 mixture of (**1**) and (**7**) (24.5 mg, 97%). Chromatographic resolution by HPLC (2 mL/min, 40% EtOAc/hexane Phenomenex 5μ silica) returned the desired epimer (**7**) as a stable colorless crystalline solid : **m.p.** 98-99°C (hexane); $[\alpha]_D$ +9.2° (c=0.25, $CHCl_3$); **IR** (film) 3375, 1640 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.8 Hz, 1-H_3), 1.3-1.6 (methylene envelope, 2, 3, 4, 5, 11, 12, 13, 14, 15 and 16-H_2), 1.85 (bdd, *J*=13.2, 6.1 Hz, 8-H_A), 1.96 (bs, OH), 2.03 (bdt, *J*=6.8, 7.1 Hz, 17-H_2), 2.12 (ddd, *J*=13.2, 10.3, 4.4 Hz, 8-H_B), 3.84 (dt, *J*=2.9, 7.1 Hz, 6-H), 3.86 (m, 10-H), 4.16 (ddd, *J*=10.3, 6.1, 3.5 Hz, 9-H), 4.29 (bs, 7-H), 4.94 (ddt, *J*=10.1, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.81 (ddt, *J*=17.1, 10.1, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.6 (C-2), 25.9, 26.0, 28.9, 29.0, 29.2, 29.4, 29.6 (C-4, C-5, C-12, C-13, C-14, C-15, C-16), 32.0 (C-3), 32.3 (C-11), 33.8 (C-17), 34.3 (C-8), 72.1 (C-10), 73.3 (C-7), 80.1 (C-9), 83.5 (C-6), 114.1 (C-19), 139.2 (C-18) ppm; **EIMS** (70eV, *m/z*, %) 312 (M^+, 1), 276 (2), 157 (76), 139 (38), 121 (37), 113 (100), 95 (87), 81 (44), 69 (56), 57 (63), 55 (90); **HRMS** found 312.2666; $C_{19}H_{36}O_3$ requires: 312.2664.

(6S,7R,9R,10S)-6,9-epoxynonadec-18-ene-7,10-diol (8).

The 7,10-diketone (**5**) (25 mg, 0.08 mmol.) was treated in an manner analogous to that described above for (**3**), to yield a 2.3:10:1:3.3 mixture of (**1**), (**6**), (**7**) and (**8**) (23 mg, 91%). Chromatographic resolution by HPLC (2 mL/min, 30% EtOAc/hexane Phenomenex 5μ silica) returned the desired diastereomer (**8**) as a stable colorless amorphous solid : **m.p.** 37-39°C; $[\alpha]_D$ -15.9° (c=0.37, $CHCl_3$); **IR** (film) 3353, 1692 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 1-H_3), 1.3-1.6 (methylene envelope, 2, 3, 4, 5, 11, 12, 13, 14, 15 and 16-H_2), 1.86 (ddd, *J*=14.2, 3.9, 1.5 Hz, 8-H_A), 2.03 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.21 (ddd, *J*=14.2, 9.3, 6.1 Hz, 8-H_B), 3.86 (ddd, *J*=7.9, 5.1, 2.4 Hz, 10-H), 3.96 (bdd, *J*=6.6, 5.9 Hz, 6-H), 4.02 (bd, *J*=6.1 Hz, 7-H), 4.07 (ddd, *J*=9.3, 3.9, 2.4 Hz, 9-H), 4.94 (ddt, *J*=10.1, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.81 (ddt, *J*=17.1 , 10.1, 6.8 Hz, 18-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-1), 22.6 (C-2), 25.6, 25.9, 28.9, 29.0, 29.3, 29.5, 31.7, 32.8, 33.1 (C-3, C-4, C-5, C-11, C-12, C-13, C-14, C-15, C-16), 33.3 (C-8), 33.8 (C-17), 72.5 (C-10), 75.0 (C-7), 80.0 (C-9), 87.5 (C-6), 114.2 (C-19), 139.1 (C-18) ppm; **EIMS** (70eV, *m/z*, %) 312 (M^+, 1), 294 (1), 277 (6), 158 (10), 157 (100), 139 (18), 121 (24), 113 (67), 95 (56), 81 (25), 69 (21), 58 (21), 57 (42), 55 (45); **HRMS** found 312.2666; $C_{19}H_{36}O_3$ requires: 312.2664.

Bisepoxides of methyl linoleate.

Commercially available linoleic acid (190 mg, 0.68 mmol) was methylated with ethereal diazomethane to return a quantitative yield of methyl linoleate (**9**) as a colorless viscous oil. To a vigorously stirred solution of (**9**) (200 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (99%, 250 mg, 1.44 mmol) and the mixture stirred at room temperature for 2 hrs, after which excess *m*-CPBA was destroyed by addition of Na_2SO_3 (5 mL, 10% aqueous solution). The reaction mixture was sequentially washed with aqueous saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), after which the organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a 1:1.8 mixture of the bisepoxides ±(**10**) and ±(**11**) (214 mg, 97%) as a viscous oil. Separation of the diastereomeric bisepoxides was achieved by selective precipitation of the *anti* bisepoxide ±(**11**) (137 mg, 64%) from pentane at -10°C, leaving a filtrate containing the *syn* bisepoxide ±(**10**) (77 mg, 36%) :

methyl (9R,10S*,12R*,13S*)-9,10:12,13-bisepoxy-octadecanoate ±(10).*

A stable, viscous, colorless oil. **IR** (film) 1739 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.0 Hz, 18-H_3), 1.2-1.5 (methylene envelope, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.60 (tt, *J*=7.2, 7.3 Hz, 3-H_2), 1.71 (ddd, *J*=14.7, 5.9, 5.9 Hz, 11-H_A), 1.76 (ddd, *J*=14.7, 6.8, 6.8 Hz, 11-H_B), 2.26 (t, *J*=7.2 Hz, 2-H_2), 2.95 (m, 9-H and 13-H), 3.04 (ddd, *J*=6.8, 5.9, 4.2 Hz, 10-H or 12-H), 3.06. (ddd, *J*=6.8, 5.9, 4.2 Hz, 12-H or 10-H), 3.64 (s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) 13.9 (C-18), 22.5 (C-17), 24.8 (C-3), 26.2, 26.5 (C-8 and C-14), 26.9 (C-11), 27.7, 27.7, 28.9, 29.1, 29.2 (C-15, C-7, C-6, C-5 and C-4), 31.6 (C-16), 34.0 (C-2), 51.4 (OCH_3), 54.1 (C-10 and C-12), 56.6, 56.7 (C-9 and C-13), 174.2 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 295 (M^+-OCH_3, 1), 223 (1), 211 (2), 155 (100), 109 (30), 98 (33), 96 (47), 84 (75); Analysis (%) calc'd for $C_{19}H_{34}O_4$: C 69.9; H 10.5; O 19.6; found: C 70.2; H 10.8; O 19.2.

methyl (9S,10R*,12R*,13S*)-9,10:12,13-bisepoxy-octadecanoate ±(11).*

A stable low melting point waxy solid : **m.p.** 30-31°C; **IR** (film) 1740 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.1 Hz, 18-H_3), 1.2-1.5 (methylene envelope, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.56 (tt, *J*=7.1, 7.1 Hz, 3-H_2), 1.67 (t, *J*=6.2 Hz, 11-H_2), 2.25 (t, *J*=7.3 Hz, 2-H_2), 2.92 (m, 9-H and 13-H), 3.04 (dt, *J*=6.2, 4.4 Hz, 10-H or 12-H), 3.06. dt (*J*=6.2, 4.4 Hz, 12-H or 10-H), 3.61 (s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) 13.9 (C-18), 22.5 (C-17), 24.8 (C-3), 26.1, 26.3 (C-8 and C-14), 27.1 (C-11), 27.9, 27.9, 28.9, 29.1, 29.2 (C-4, C-5, C-6, C-7 and C-15), 31.6 (C-16), 34.0 (C-2), 51.3 (OCH_3), 54.3, 54.3 (C-10 and C-12), 56.9, 56.9 (C-9 and C-13), 174.1 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 295 (M^+-OCH_3, 1), 211 (2), 197 (2), 155 (100), 111 (19), 109 (30), 96 (34), 94 (53), 84 (73), 83 (58), 69 (30); Analysis (%) calc'd for $C_{19}H_{34}O_4$: C 69.9; H 10.5; O 19.6; found: C 70.0; H 10.8 ; O 19.2.

Acid catalysed rearrangement of the anti bisepoxide ±(11).

The *anti* bisepoxide ±(**11**) (100 mg, 0.31 mmol) was added to glacial acetic acid (5 mL) and the stirred solution heated at 80°C for 20 hours. The acidic solution was then cooled to room temperature, diluted with Et_2O (40 mL), and the ethereal solution washed with H_2O (2 x 50 mL), aqueous saturated $NaHCO_3$ (2 x 20 mL) and finally a second time with H_2O (2 x 50 mL) after which it was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to return a colorless mobile oil in near quantitative yield. Chromatographic resolution (HPLC, silica, 5μ, 25% EtOAc/hexane) returned ±(**12**) (41.4 mg, 35%), ±(**13**) (40.3 mg, 34%), ±(**14**) (14.2 mg, 12%) and ±(**15**) (13.0 mg, 11%).

methyl (9S,10S*,12S*,13S*)-10-acetoxy-9,12-epoxy-13-hydroxyoctadecanoate ±(12).*

A stable colorless oil. **IR** (film) 3480, 1739 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.73 (ddd, *J*=14.4, 6.2, 1.9 Hz, 11-H_A), 2.06 (s, $COCH_3$), 2.29 (t, *J*=7.6 Hz, 2-H_2), 2.38 (ddd, *J*=14.4, 8.3, 6.6 Hz, 11-H_B), 3.47 (m, 13-H), 3.66 (s, OCH_3), 3.72 (ddd, *J*=7.6, 5.9, 3.8 Hz, 9-H), 3.75 (ddd, *J*=8.3, 6.2, 6.0 Hz, 12-H), 5.21 (ddd, *J*=6.6, 3.8, 1.9 Hz, 10-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 21.0 ($CO\underline{C}H_3$), 22.6 (C-17), 24.9, 25.3, 26.1, 28.7, 29.0, 29.1, 29.4, 31.8, 33.6 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.0 (C-2), 35.8 (C-11), 51.4 (OCH_3), 73.8 (C-13), 74.7 (C-10), 80.4 (C-12), 81.7 (C-9), 170.5 ($\underline{C}OCH_3$), 174.3 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 327 (M^+-59, 1), 326 (1), 309 (3), 308 (6), 295 (2), 226 (43), 225 (100), 198 (23), 199 (5), 194 (14), 193 (44), 166 (27), 155 (9), 148 (10), 84 (18); **HRMS** found: 225.1491; $C_{13}H_{21}O_3$ requires: 225.1488; found: 193.1224; $C_{12}H_{17}O_2$ requires: 193.1228; Analysis (%) calc'd for $C_{21}H_{38}O_6$: C 65.2; H 9.9; O 24.8; found: C 64.5 ; H 10.3 ; O 25.2.

methyl (9S,10S*,12S*,13S*)-12-acetoxy-10,13-epoxy-9-hydroxyoctadecanoate ±(13).*

A stable colorless oil. **ir** (film) 3490, 1738 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.73 (ddd, *J*=14.4, 6.4, 1.9 Hz, 11-H_A), 2.06 (s, $COCH_3$), 2.29 (t, *J*=7.6 Hz, 2-H_2), 2.38 (ddd, *J*=14.4, 8.3, 6.6 Hz, 11-H_B), 3.45 (m, 9-H), 3.66 (s, OCH_3), 3.72 (ddd, *J*=7.6, 5.9, 3.8 Hz, 13-H), 3.74 (ddd, *J*=8.3, 6.4, 6.0 Hz, 10-H), 5.22 (ddd, *J*=6.6, 3.8, 1.9 Hz, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 21.1 ($CO\underline{C}H_3$), 22.5 (C-17), 24.9, 25.6, 25.9, 28.7, 29.1, 29.2, 29.4, 31.8, 33.6 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.1 (C-2), 35.9 (C-11), 51.5 (OCH_3), 73.7 (C-9), 74.7 (C-12), 80.4 (C-10), 81.8 (C-13), 170.5 ($\underline{C}OCH_3$), 174.3 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 295 (3), 199 (3), 187 (30), 157 (10), 155 (36), 140 (13), 139 (100), 113 (14), 95 (16), 69 (14), 67 (12), 43 (56); **EIMS** (15eV, *m/z*, %) 327 (M^+-59, 1), 326 (1), 309 (2), 308 (2), 295 (3), 187 (70), 157 (16), 155 (44), 140 (15), 139 (100); **HRMS** found: 187.1332; $C_{10}H_{19}O_3$ requires: 187.1334; found: 139.1119; $C_9H_{15}O$ requires: 139.1123

methyl (9R,10R*,12S*,13S*)-10-acetoxy-9,12-epoxy-13-hydroxyoctadecanoate ±(14).*

A stable colorless oil. **IR** (film) 3480, 1738 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 2.00 (ddd, *J*=13.9, 9.0, 4.6 Hz, 11-H_A), 2.06 (ddd, *J*=13.9, 6.8, 1.5 Hz, 11-H_B), 2.09 (s, $COCH_3$), 2.30 (t, *J*=7.6 Hz, 2-H_2), 3.39 (bm, 13-H), 3.66 (s, CO_2CH_3), 3.89 (ddd, *J*=7.7, 5.8, 3.2 Hz, 9-H), 3.99 (ddd, *J*=9.0, 6.8, 6.8 Hz, 12-H), 5.30 (bm, 10-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 21.0 ($CO\underline{C}H_3$), 22.6 (C-17), 24.9, 25.3, 26.2, 29.0, 29.1, 29.1, 29.4, 31.8, 33.3 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.0 (C-2), 35.5 (C-11), 51.4 (OCH_3), 73.9 (C-13), 75.5 (C-10), 80.4 (C-12), 81.2 (C-9), 170.5 ($\underline{C}OCH_3$), 174.3 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 326 (M^+-CO_2CH_3, 1), 295 (4), 226 (17), 225 (63), 194 (11), 193 (49), 166 (13), 155 (16), 109 (13), 95 (23), 97 (20), 84 (23), 81 (40), 69 (27), 67 (28), 43 (100); **EIMS** (15eV, *m/z*, %) 326 (1), 309 (1), 295 (4), 226 (34), 225 (100), 198 (16), 194 (17), 193 (73), 166 (28), 155 (21), 111 (15), 84 (25); **HRMS** found: 225.1491; $C_{13}H_{21}O_3$ requires: 225.1492; found: 193.1225; $C_{12}H_{17}O_2$ requires: 193.1228.

methyl (9R,10R*,12S*,13S*)-12-acetoxy-10,13-epoxy-9-hydroxyoctadecanoate ±(15).*

A colorless oil. **IR** (film) 3490, 1735 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.87 (t, *J*=6.8 Hz, 18-H_3), 1.2-1.4 (methylene envelope, 4, 5, 6, 7, 15, 16 and 17-H_2), 1.41 (m, 8-H_2), 1.53 (m, 14-H_2), 1.62 (m, 3-H_2), 2.00 (ddd, *J*=13.9, 9.0, 4.6 Hz, 11-H_A), 2.05 (ddd, *J*=13.9, 6.8, 1.5 Hz, 11-H_B), 2.08 (s, $COCH_3$), 2.29 (t, *J*=7.6 Hz, 2-H_2), 3.38 (m, 9-H), 3.66 (s, CO_2CH_3), 3.89 (ddd, *J*=7.6, 5.9, 3.0 Hz, 13-H), 3.98 (ddd, *J*=9.0, 6.8, 6.8 Hz, 10-H), 5.30 (bm, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 21.0 ($CO\underline{C}H_3$), 22.5 (C-17), 24.9, 25.5, 25.9, 29.0, 29.0, 29.1, 29.4, 31.8, 33.2 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.0 (C-2), 35.5 (C-11), 51.4 (OCH_3), 73.8 (C-9), 75.5 (C-12), 80.4 (C-10), 81.3 (C-13), 170.5 ($\underline{C}OCH_3$), 174.3 (C-1) ppm; **EIMS** (15eV, *m/z*, %) 327 (M^+-59, 2), 309 (3), 295 (3), 188 (9), 187 (90), 225 (9), 199 (9), 155 (32), 140 (16), 139 (100); **HRMS** found: 187.1334; $C_{10}H_{19}O_3$ requires: 187.1332; found: 139.1123; $C_9H_{15}O$ requires: 139.1121; Analysis (%) calc'd for $C_{21}H_{38}O_6$: C 65.3; H 9.9; O 24.8; found: C

65.0; H 10.1; O 24.9.

methyl-(9S,10S*,12S*,13S*)-9,12-epoxy-10,13-dihydroxy-octadecanoate ±(16).*
The acetoxy tetrahydrofuran alcohol ±(**12**) (20 mg, 0.05 mmol) in MeOH (3 mL) with NH_4OH (33% aqueous solution, 2 mL) was stirred at room temperature for 2 hours, after which the mixture was concentrated *in vacuo* to yield the diol ±(**16**) (17.5 mg, 98%) as a stable pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.84 (dd, *J*=14.2, 3.4 Hz, 11-H_A), 2.30 (t, *J*=7.6 Hz, 2-H_2), 2.38 (ddd, *J*=14.2, 10.0, 5.5 Hz, 11-H_B), 3.48 (ddd, *J*=8.3, 5.1, 2.4 Hz, 13-H), 3.62 (dt, *J*=2.7, 6.8 Hz, 9-H), 3.66 (s, OCH_3), 3.95 (ddd, *J*=10.0, 3.4, 2.4 Hz, 12-H), 4.03 (dd, *J*=5.5, 2.7 Hz, 10-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 22.6 (C-17), 24.9, 25.7, 26.1, 28.7, 29.0, 29.1, 29.6, 31.7, 34.4 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.1 (C-2), 38.7 (C-11), 51.5 (OCH_3), 71.5 (C-10), 74.0 (C-13), 79.0 (C-12), 84.3 (C-9), 174.4 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 295 (8), 225 (98), 211 (30), 201 (22), 199 (32), 193 (42), 187 (38), 169 (32), 166 (29), 155 (100), 150 (27), 149 (22), 139 (33), 121 (25), 119 (26), 97 (53), 111 (26), 109 (35), 84 (58), 74 (59), 69 (78), 61 (61); **HRMS** found: 225.1491; $C_{13}H_{21}O_3$ requires: 225.1491; found: 187.1334; $C_{10}H_{19}O_3$ requires: 187.1334; found: 155.1072; $C_9H_{15}O_2$ requires: 155.1072.

methyl (9S,10S*,12S*,13S*)-10,13-epoxy-9,12-dihydroxyoctadecanoate ±(17).*
The acetoxy tetrahydrofuran alcohol ±(**13**) (20 mg, 0.05 mmol) in MeOH (3 mL) with NH_4OH (33% aqueous solution, 2 mL) was stirred at room temperature for 2 hours, after which the mixture was concentrated *in vacuo* to yield the diol ±(**17**) (17.8 mg, 100%) as a stable pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.83 (dd, J=14.2, 3.4 Hz, 11-H_A), 2.30 (t, *J*=7.6 Hz, 2-H_2), 2.38 (ddd, *J*=14.2, 10.0, 5.6 Hz, 11-H_B), 2.70 (bs, OH), 3.47 (ddd, *J*=8.3, 4.9, 2.4 Hz, 9-H), 3.62 (dt, *J*=2.7, 6.8 Hz, 13-H), 3.66 (s, OCH_3), 3.94 (ddd, *J*=10.0, 3.4, 2.4, 10-H), 4.03 (dd, *J*=5.6, 2.7 Hz, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 22.6 (C-17), 24.9, 25.9, 28.7, 29.0, 29.0, 29.1, 29.3, 32.0, 34.3 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.0 (C-2), 38.7 (C-11), 51.5 (OCH_3), 71.5 (C-12), 73.9 (C-9), 79.0 (C-10), 84.3 (C-13), 174.3 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 295 (2), 205 (14), 193 (2), 187 (64), 157 (24), 155 (100), 139 (19), 121 (14), 113 (42), 109 (20), 97 (19), 96 (15), 95 (16), 87 (20), 71 (41), 69 (36), 67 (26), 57 (40), 55 (54), 47 (27); **EIMS** (15eV, *m/z*, %) 310 (2), 295 (1), 220 (11), 205 (10), 188 (10), 187 (100), 185 (17), 157 (32), 155 (79), 140 (12), 139 (27), 113 (23), 111 (10), 99 (11), 96 (10), 95 (12), 71 (14); **HRMS** found: 187.1334; $C_{10}H_{19}O_3$ requires: 187.1334; found: 155.1071; $C_9H_{15}O_2$ requires: 155.1072.

methyl (9R,10R*,12S*,13S*)-9,12-epoxy-10,13-dihydroxy-octadecanoate ±(18).*
The acetoxy tetrahydrofuran alcohol ±(**14**) (20 mg, 0.05 mmol) and NH_4OH (33% aqueous solution, 2 mL) was stirred at room temperature for 2 hours, after which the mixture was concentrated *in vacuo* to yield the diol ±(**18**) (17.5 mg, 98%) as a stable colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.85 (ddd, *J*=13.4, 9.0, 4.4

Hz, 11-H_A), 2.00 (ddd, J=13.4, 6.6, 1.0 Hz, 11-H_B), 2.30 (t, J=7.6 Hz, 2-H_2), 2.35 (bs, OH), 3.39 (m, 13-H), 3.66 (s, OCH_3), 3.73 (dt, J=2.7, 6.8 Hz, 9-H), 4.01 (ddd, J=9.0, 6.6, 6.6 Hz, 12-H), 4.24 (m, 10-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 22.6 (C-17), 24.9, 25.3, 26.2, 28.8, 29.0, 29.1, 29.5, 31.9, 33.1 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.0 (C-2), 37.9 (C-11), 51.4 (OCH_3), 73.4 (C-10), 74.1 (C-13), 80.2 (C-12), 82.4 (C-9), 174.3 (C-1) ppm; **EIMS** (70eV, *m/z*, %) 226 (25), 225 (100), 211 (30), 199 (30), 193 (76), 187 (26), 175 (23), 169 (19), 167 (23), 155 (33), 150 (22), 149 (24), 139 (37), 133 (20), 121 (33), 113 (16), 109 (28), 97 (32), 95 (31), 84 (27), 81 (48), 69 (45), 67 (46), 57 (43), 55 (96); **HRMS** found: 225.1491; $C_{13}H_{21}O_3$ requires: 225.1491; found: 187.1334; $C_{10}H_{19}O_3$ requires: 187.1334; found: 155.1074; $C_9H_{15}O_2$ requires: 155.1072.

methyl (9R,10R*,12S*,13S*)-10,13-epoxy-9,12-dihydroxy-octadecanoate ±(19).*

The acetoxy tetrahydrofuran alcohol ±(**15**) (30 mg, 0.08 mmol) in MeOH (3 mL) and NH_4OH (33% aqueous solution, 2 mL) was stirred at room temperature for 2 hours, after which the mixture was concentrated *in vacuo* to yield the diol ±(**19**) (22.5 mg, 84%) as a stable colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.89 (t, J=6.9 Hz, 18-H_3), 1.3-1.6 (methylene envelope, 3, 4, 5, 6, 7, 8, 14, 15, 16 and 17-H_2), 1.86 (ddd, J=13.4, 9.0, 4.6 Hz, 11-H_A), 2.01 (dd, J=13.4, 6.6 Hz, 11-H_B), 2.30 (t, J=7.6 Hz, 2-H_2), 2.33 (bs, OH), 3.37 (bm, 9-H), 3.66 (s, OCH_3), 3.74 (dt, J=2.7, 6.8 Hz, 13-H), 4.01 (ddd, J=9.0, 6.6, 6.4 Hz, 10-H), 4.25 (bm, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$) 14.0 (C-18), 22.6 (C-17), 24.9, 25.5, 26.0, 28.8, 29.0, 29.1, 29.4, 32.0, 33.1 (C-3, C-4, C-5, C-6, C-7, C-8, C-14, C-15, C-16), 34.1 (C-2), 37.9 (C-11), 51.5 (OCH_3), 73.4 (C-12), 74.0 (C-9), 80.2 (C-10), 82.4 (C-13), 174.3 (C-1) ppm; **EIMS** (15eV, *m/z*, %) 225 (4), 187 (100), 157 (48), 155 (65), 139 (12), 113 (29), 95 (12); **HRMS** found: 187.1334; $C_{10}H_{19}O_3$ requires: 187.1330; found: 155.1072; $C_9H_{15}O_2$ requires: 155.1072.

(6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol 7,10-diacetate (20).

A solution of (**1**) (50 mg) in Ac_2O (1 mL) and anhydrous pyridine (2 mL) was stirred at room temperature for 24 hrs, after which the reaction was quenched with H_2O (0.5 mL) and extracted with Et_2O (40 mL). The ethereal layer was subsequently washed with cold 1M HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL), and H_2O (2 x 20 mL), then dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the diacetate (**20**) as a colorless oil. Physical and spectroscopic data identical with literature measurements.[2]

(6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol 10-acetate (21).

A sample of the diacetate (**20**) (25 mg) was stirred at room temperature for 10 hrs in an excess of MeOH (20 mL) and NH_4OH (6 mL), after which the solution was concentrated *in vacuo* and purified by silica HPLC to yield as the major product the monoacetate (**21**). Physical and spectroscopic data identical with literature measurements.[2]

(S)-MTPA ester of (21).

A sample of (**21**) (11 mg, 0.031 mmol) in dry CH_2Cl_2 (1 mL) was stirred at room temperature for 24 hrs with (S)-methoxy-trifluoromethyl-phenylacetic acid ((S)-MTPA, 30 mg, 0.128 mmol), 1,3-dicyclohexylcarbodiimide

(30 mg, 0.145 mmol) and 4-dimethylaminopyridine (10 mg, 0.082 mmol), after which the solution was concentrated in vacuo. Elution of the crude product through a silica Sep-Pak (40% EtOAc/hexane) afforded the (S)-MTPA ester (**22**) (16%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) selected resonances : δ 2.02 (m, 8-H_A), 2.08 (s, 10-$OCOCH_3$), 3.92 (dt, *J*= 6.9, 2.8 Hz, 6-H), 4.11 (ddd, *J*= 9.4, 6.6, 6.4 Hz, 9-H), 5.02 (m, 10-H), 5.44 (t, *J*= 3.3 Hz, 7-H); **ESIMS** (+ve) *m/z* 571 (M+H), 588 ($M+NH_4$), 593 (M+Na).

(R)-MTPA ester of (21).

A sample of (**21**) (10 mg, 0.026 mmol) was treated with (R)-MTPA as described above to afford the (R)-MTPA ester (**23**) (24%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) selected resonances : δ 2.01 (m, 8-H_A), 2.08 (s, 10-$OCOCH_3$), 3.76 (dt, *J*= 6.9, 2.7 Hz, 6-H), 4.19 (ddd, *J*= 9.3, 6.6, 6.6 Hz, 9-H), 4.96 (m, 10-H), 5.44 (t, *J*= 2.9 Hz, 7-H); **ESIMS** (+ve) *m/z* 571 (M+H), 588 ($M+NH_4$), 593 (M+Na).

(6S,7S,9S,10S)-6,9-epoxynonadec-18-ene-7,10-diol 7,10-diacetate (24).

A sample of (**2**) was acetylated as described above for (**1**), to return a quantitative yield of the diacetate (**24**). $[\alpha]_D$ +61.3° (c=0.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.0 Hz, 1-H_3), 1.25-1.45 (methylene envelope containing 2, 3, 4, 12, 13, 14, 15 and 16-H_2), 1.21 (m, 11-H_A), 1.62 (m, 11-H_B), 1.64 (m, 5-H_2), 2.04 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.06, 2.07 (2s, 2x$OCOC\underline{H}_3$), 2.37 (m, 8-H_A), 3.69 (dt, *J*=1.8, 6.6 Hz, 6-H), 4.17 (dd, *J*=6.3, 6.2 Hz, 9-H), 4.90 (m, 10-H), 4.92 (ddt, *J*=10.3, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 5.22 (m, 7-H), 5.81 (ddt, *J*=17.1, 10.3, 6.8 Hz, 18-H); **EIMS** (70eV, *m/z*, %) 396 (M^+, 1), 199 (2), 139 (2); **HRMS** found 396.2912; $C_{23}H_{40}O_5$ requires: 396.2876.

(6S,7S,9S,10S)-6,9-epoxynonadec-18-ene-7,10-diol 10-acetate (25).

A sample of the diacetate (**24**) was treated with MeOH and NH_4OH as described above for (**20**) to return as the major product the acetate (**25**) as a colorless oil. $[\alpha]_D$ +72.4° (c=0.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 1-H_3), 1.25-1.45 (methylene envelope containing 2, 3, 4, 12, 13, 14, 15 and 16-H_2), 1.64 (m, 5-H_2), 2.03 (m, 11-H_2), 2.04 (dt, *J*=6.8, 6.8 Hz, 17-H_2), 2.11 (s, $OCOC\underline{H}_3$), 2.22-2.40 (m, 8-H_A and 8-H_B), 3.55 (dt, *J*=2.8, 6.7 Hz, 6-H), 3.98 (m, 9-H), 4.01 (m, 7-H), 4.92 (ddt, *J*=10.3, 2.2, 1.2 Hz, 19-H_{cis}), 4.99 (ddt, *J*=17.1, 2.2, 1.5 Hz, 19-H_{trans}), 4.99 (dt, *J*= 7.3, 4.8 Hz, 10-H), 5.81 (ddt, *J*=17.1, 10.3, 6.8 Hz, 18-H); **EIMS** (70eV, *m/z*, %) 354 (M^+, 3), 303 (5), 157 (89); **HRMS** found 303.0941; $C_{18}H_{33}O_4$ requires: 303.0899.

(S)-MTPA ester of (25).

A sample of (**25**) (3 mg, 0.009 mmol) was treated with (S)-MTPA as described above to afford the (S)-MTPA ester (**26**) (18%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) selected resonances : δ 2.11 (s, 10-Ac), 2.47 (m, 8-H_A), 3.70 (dt, *J*= 6.4, 2.4 Hz, 6-H), 3.89 (m, 9-H), 4.89 (m, 10-$OCOCH_3$), 5.43 (m, 7-H); **ESIMS** (+ve) *m/z* 571 (M+H), 588 ($M+NH_4$), 593 (M+Na).

(R)-MTPA ester of (25).

A sample of (**25**) (4 mg, 0.011 mmol) was treated with (R)-MTPA as described above to afford the (R)-MTPA

ester (27) (38%) as a clear oil. **^{1}H NMR (300 MHz, $CDCl_3$)** selected resonances : δ 2.11 (s, 10-Ac), 2.43 (m, 8-H_A), 3.71 (dt, *J*= 6.5, 2.6 Hz, 6-H), 3.87 (ddd, *J*= 9.4, 2.3, 1.8 Hz, 9-H), 4.88 (m, 10-H), 5.42 (m, 7-H); **ESIMS** (+ve) *m/z* 571 (M+H), 588 (M+NH_4), 593 (M+Na).

REFERENCES

1. *The Marine Benthic Flora of Southern Australian* by H. B. S. Womersley, South Australian Government Printing Division, Adelaide, 1987.
2. Warren, R. G.; Wells, R. J.; Blount, J. F.; *Aust. J. Chem.*, **1980**, *33*, 891-898.
3. Capon, R. J; Barrow, R. A; Skene, C.; Rochfort, S.; *Tet Lett.*, **1997**, *38*, 7609-7612.
4. Barrow, R. A.; Capon, R. J.; *Aust. J. Chem.*, **1990**, *43*, 895-911.
5. Murray, L. M.; Barrow, R. A.; Capon, R. J.; *Aust. J. Chem.*, **1991**, *44*, 843-854.
6. Rochfort, S.; Murray, L. M.; Capon, R. J.; *J. Nat. Prod.*, **1992**, *55*, 1332-1335.
7. Capon, R. J; Barrow, R. A; *J. Org. Chem.*, **1997**, in press.
8. Gill, J. H.; Redwin, J. M.; Van Wyk, J. A.; Lacey, E.; *Int. J. Parasitol.*, **1995**, *25*, 463-470.
9. Murray, L. M.; Lim, T. K.; Currie, G.; Capon, R. J.; *Aust. J. Chem.*, **1995**, *48*, 1253-1266.

ACKNOWLEDGEMENTS

The assistance of D. J. Howse, S. J. Capon and C. J. Capon in the collection of *Notheia anomala* is gratefully acknowledged. *In vivo* screening against commercial livestock was sponsored by Novartis Animal Health Australasia Pty Ltd, and that against companion animals by Mars Inc. in collaboration with J. Parsons of the Victorian Institute of Animal Science. This research was in part funded by the Australian Research Council.