Tetrahedron 64 (2008) 7106–7111

Contents lists available at ScienceDirect

Tetrahedron

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

Synthetic studies toward paraherquamides E and F and related ^{13}C-labeled putative biosynthetic intermediates: stereocontrolled synthesis of the α-alkyl-β-methylproline ring system

Konrad Sommer [a], Robert M. Williams [a,b,*]

[a] Department of Chemistry, Colorado State University, Fort Collins, CO 80523, United States
[b] University of Colorado Cancer Center, Aurora, CO 80045, United States

ARTICLE INFO

Article history:
Received 19 February 2008
Received in revised form 14 May 2008
Accepted 15 May 2008
Available online 18 May 2008

Keywords:
β-Methylproline
Asymmetric synthesis
Paraherquamide
Asperparaline

ABSTRACT

A substituted 2*R*-allyl-3*S*-methylproline ethyl ester suitable for elaboration to paraherquamides E, F and related ^{13}C-labeled putative biosynthesis intermediates have been prepared efficiently in six steps and 24% overall yield. The key steps are a 5-*exo*-*trig* cyclization of a zinc enolate on an unactivated alkene and a stereocontrolled alkylation of the enolate formed from 3*S*-methyl-pyrrolidine-1,2*R*-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester.

1. Introduction

The paraherquamides constitute part of an unusual family of prenylated indolic natural products derived from various genera of fungi, which contain a common bicyclo[2.2.2]diazaoctane core structure, a spiro-oxindole, and a substituted proline moiety. The parent member, paraherquamide A **1**, was first isolated from cultures of *Penicillium paraherquei* by Yamazaki and co-workers in 1981.[1] Since then, paraherquamides B-I,[2] VM55595, VM55596, and VM55597,[3] SB203105, and SB200437,[4] and sclerotamide[5] have been isolated from various *Penicillium* and *Aspergillus* species. Marcfortines A–C are structurally similar, containing a pipecolic acid unit in place of proline.[6] In addition, VM55599,[3] aspergamides A and B,[7] avrainvillamide (CJ-17,665),[8] and the most recently isolated members of this family, stephacidin A (**10**) and stephacidin B (**11**),[9] and malbrancheamide[10] are closely related members of this rapidly expanding family of prenylated indole alkaloids. This last group of compounds contains a 2,3-disubstituted indole in place of the spiro-oxindole, spiro-indoxyl or spiro-succinimide. Brevianamides A and B (**9**),[11] which contain a spiro-indoxyl rather than a spiro-oxindole, and the asperparalines, which contain a spiro-succinimide,[12] are also structurally comparable (Fig. 1).

This family of prenylated alkaloids has attracted considerable attention due to their molecular complexity, intriguing biogenesis, and biological activities.[13] Some members, most notably paraherquamide A, display potent anthelmintic activity and antinematodal properties.[14] Since, the paraherquamides are unique both structurally and in their mode of action,[15] they represent a potentially promising new class of anthelmintics.[16]

From a biogenetic perspective, the paraherquamides along with the brevianamides, asperparalines, marcfortines, malbrancheamides, notoamides,[17] and sclerotamide comprise an interesting class of structurally related secondary metabolites containing a bicyclo[2.2.2]diazaoctane core. An emerging body of evidence supports the notion that this structural motif is formed by a biosynthetic intramolecular [4+2] cycloaddition of the isoprene-derived olefin across a preformed azadiene moiety derived from an oxidized piperazinedione.[13,18,19]

Everett and co-workers described in 1993 the isolation of VM55599 (**15**, Scheme 1), a minor metabolite from culture extracts of a *Penicillium* sp. (IMI332995) that also produces paraherquamide A (**1**).[3] These authors proposed that VM55599 might indeed be a biosynthetic precursor of paraherquamide A.[3]

Recent experimental observations from this laboratory brought into question the capacity of VM55599 to serve as a biosynthetic precursor to the paraherquamides and we proposed a distinct biosynthesis of the paraherquamides and VM55599.[20] This hypothesis was recently experimentally tested through feeding experiments of racemic, doubly ^{13}C-labeled compounds **15**–**18**.[21]

* Corresponding author. Tel.: +1 970 491 6747; fax: +1 970 491 3944.
E-mail address: rmw@lamar.colostate.edu (R.M. Williams).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.068

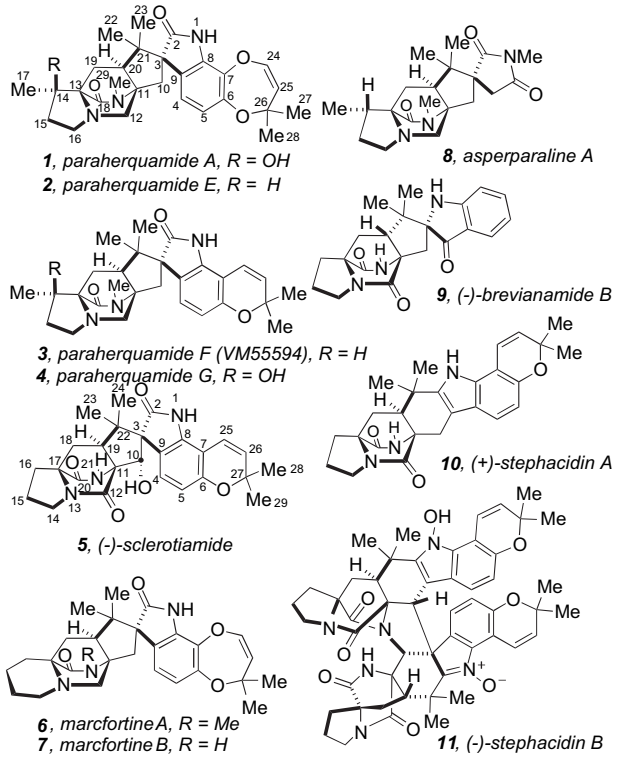
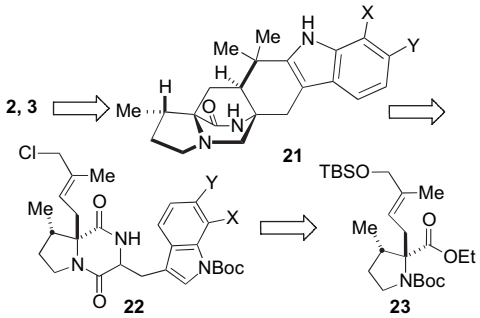


Figure 1. Structures of selected paraherquamides and various related prenylated indole alkaloids.

These experiments revealed that only intermediate **17** was incorporated into paraherquamide A, while racemic, doubly ^{13}C-labeled VM55599 (**15**), **16**, and **18** were not incorporated. The lack of incorporation of the diketopiperazine **18** raises interesting questions concerning the timing of the reduction of the tryptophan-derived carbonyl group.

The incorporation of **17** indicates that formation of the bicyclo[2.2.2]diazaoctane occurs at the stage of the non-oxidized tryptophyl moiety. This requires oxidations to the indole ring to form both the catechol-derived dioxepin and spiro-oxindole to occur after the formation of this intermediate. The dioxepin-derived isoprenylation and the *S*-adenosylmethionine-mediated N-methylation reactions probably occur late in the pathway.

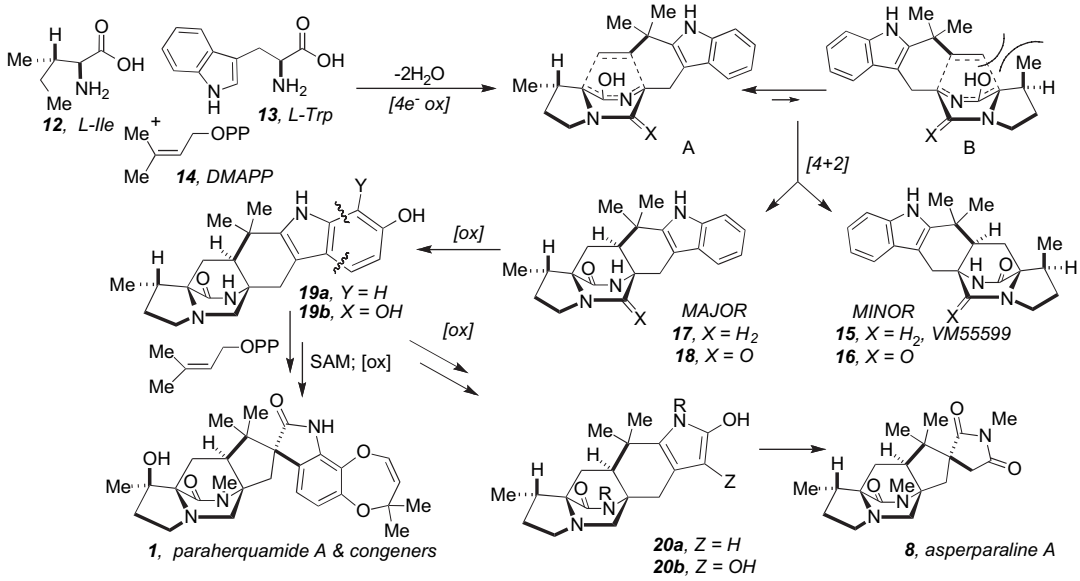
It has been demonstrated that in paraherquamide A biosynthesis, L-tryptophan, L-β-methylproline, and an isoprene moiety are coupled together to provide the hexacyclic indole **17**.[22] Based on the experimental observation that the same three primary biosynthetic building blocks ((*S*)-tryptophan, (*S*)-isoleucine (the biosynthetic precursor to β-methylproline[22]), and dimethylallyl pyrophosphate) constitute asperparaline A, we proposed a unified biogenesis of the paraherquamides and the asperparalines as shown in Scheme 2.[23]



Scheme 2. Retro-synthetic approach to paraherquamides E and F.

As previously reported, coupling of L-tryptophan, L-β-methylproline, and dimethylallyl pyrophosphate (DMAPP) gives, via intramolecular Diels–Alder cycloaddition, compound **17**, which can be oxidized to hypothetical intermediate **19**. Compound **19** is considered to be a key branch-point species for the two respective pathways to paraherquamide A and asperparaline A. In paraherquamide biosynthesis, **19** would suffer prenylation and conversion to the dioxepin.

In asperparaline biosynthesis, **19** would undergo further oxidation ultimately removing four carbon atoms from the benzenoid ring of the tryptophan moiety. In order to test this hypothesis experimentally and to evaluate the late-stage steps in the biosynthesis of paraherquamide A and asperparaline A, we have initiated studies on the synthesis of ^{13}C-labeled functionalized proline derivatives that will be useful to interrogate the structural constitution of putative biosynthetic intermediates in these pathways.



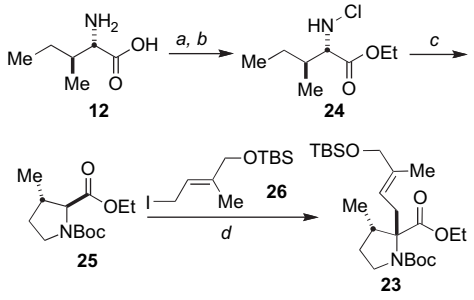
Scheme 1. Proposed unified biogenesis of paraherquamides and asperparalines.

Our synthetic strategy to these β-methylproline-containing natural products, envisions an oxidative spiro-ring contraction of the generic hexacycle **21** that can be constructed via a face-selective intramolecular S_N2' cyclization reaction (Scheme 2).[24] The 3-hydroxy-3-methyl-analogue of compound **23** has recently been prepared for the asymmetric total synthesis of paraherquamide A and has been found to lead to the analogous hexacycle **21** selectively.[24] Our plan thus requires the synthesis of the critical 2-substituted,3-methylproline derivative (**23**), with the desired absolute and relative stereochemistry.

We report here, a preparative synthesis of compound **23** that should prove to be a useful substrate from which **2** and **3** as well as asperparaline can be constructed. Significantly, this synthetic strategy offers a rapid and inexpensive means to incorporate ^{13}C-labels into **23** that will prove useful for the evaluation of the biosynthesis of these agents.

2. Results and discussion

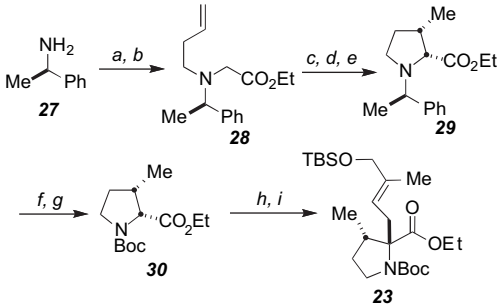
In our initial study, the synthesis of β-methylproline developed by Lavergne and co-workers was applied to access the core of the methylproline derivative **23**.[25,26] Treatment of L-isoleucine (**12**) with thionyl chloride in refluxing ethanol afforded the corresponding ethyl ester, which was then treated with *tert*-butyl hypochlorite to yield the *N*-chloride **24** (Scheme 3). Exposure of **24** to a mercury lamp in 80% sulfuric acid according to the Hofman–Löffler–Freytag protocol, afforded β-methylproline ethyl ester **25** upon neutralization, however, in a disappointingly poor yield of 25% on gram-scale. Nevertheless, with **25** in our hands, we focused our attention on the alkylation of **25** to afford **23**. Thus, enolization with KHMDS at −78 °C followed by addition of allylic iodide **26** gave the desired proline **23**. This highly stereoselective reaction gave a single diastereomer as evidenced by analysis of the ^1H NMR spectrum. The relative and absolute stereochemistry of the alkylation product was secured through ^1H NMR NOE experiments indicating a strong NOE-effect between the allylic and vinyl protons of the introduced side chain and the β-proton of proline ring; conversely, we did not observe an NOE-effect on the protons of the β-methyl group.



Scheme 3. (a) $SOCl_2$, EtOH, 38 h, reflux, 97–100%; (b) *t*-BuOCl, benzene, 0–5 °C, 4 h, 88–98%; (c) (i) hν, 80% H_2SO_4, 3–9 °C, 3 h; (ii) KOH, H_2O; (iii) Boc_2O, THF, H_2O, 0 °C→room temperature, 17 h, 25%; (d) (i) KHMDS, THF, −78 °C, 35 min; (ii) **26**, −78 °C→room temperature, 12 h, 88%.

However, due to high cost of the 1-^{13}C-(*S*)-isoleucine (US$1025/g),[27] the amounts of labeled substrate required for biosynthetic feeding studies, and the low overall yield of this approach, we turned to other more economical alternatives.

For that reason, we decided to examine methodology developed by Chassaing and co-workers as a potentially more practical route to ^{13}C-labeled β-methylproline derivative **23** (Scheme 4).[28] Thus, (*R*)-α-methyl benzyl amine **27** was alkylated with 3-butenyl bromide to give the corresponding secondary amine (66% yield). Subsequent alkylation with ethyl bromoacetate afforded the cyclization substrate **28** (67% yield). Deprotonation of **28** with LDA in diethyl ether/THF followed by transmetalation at −90 °C with zinc bromide, warming to room temperature, and quenching with aqueous NH_4Cl, provided selectively the *N*-protected *cis*-β-methylproline derivative **29** in 80% yield from **28**. Finally, hydrogenolysis of **29** with 5% Pd/C (10 wt %) followed by Boc-protection of the crude material afforded the protected β-methylproline derivative **30** in 84% yield over the two steps. Enolate formation of **30** with KHMDS at −78 °C followed by the addition of allylic iodide **26** gave **23** in 82% yield and was the identical compound to that obtained in Scheme 3 as confirmed by NMR and optical rotation. This route provides for an economical and practical route for the synthesis of the key species **23** in ^{13}C-labeled form starting from 1-^{13}C-ethyl bromoacetate (US$170/g).



Scheme 4. (a) $H_2C{=}CH(CH)_2Br$, K_2CO_3, NaI, DMF, 100 °C, 22 h, 66%; (b) $BrCH_2CO_2Et$, NEt_3, DMSO, 50 °C, 46 h, 67%; (c) LDA, Et_2O, THF, −78 °C→−20 °C; (d) $ZnBr_2$, Et_2O, −90 °C→room temperature; (e) NH_4Cl, H_2O, 80%; (f) 5% Pd/C (10 wt %), H_2, 80 psi, room temperature, 24 h; (g) Boc_2O, K_2CO_3, dioxane/H_2O, 0 °C→room temperature, 19 h, 84%; (h) KHMDS, THF, −78 °C, 35 min; (i) **26**, −78 °C→room temperature, 12 h, 82%.

3. Conclusion

In summary, we have demonstrated an efficient route to the β-methylproline derivative **23** from (*R*)-α-methyl benzyl amine **27**. We are currently deploying this route for use in asymmetric total syntheses of paraherquamides E (**2**) and F (**3**) as well as asperparaline A (**8**). Significantly, this route will prove useful for the preparation of ^{13}C-labeled putative biosynthetic intermediates. Efforts along these lines are currently in progress in our laboratory and will be reported on in due course.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial sources and utilized without purification. All reactions requiring anhydrous conditions were performed under argon using flame-dried glassware. Tetrahydrofuran, dimethylformamide, and toluene were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing alumina or molecular sieves. Dichloromethane was distilled from CaH_2 prior to use. Column chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh). Mass spectra were obtained on Fisons VG Autospec. HPLC data were obtained on a Waters 600 HPLC. ^1H NMR, ^{13}C NMR, and NOE experiments were recorded on a Varian 300 or 400 MHz spectrometer. Chemical shifts were given in parts per million and were recorded relative to the residual solvent peak unless otherwise noted. ^1H NMR signals were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant in hertz, and number of protons. When a signal was deemed 'broad' it was noted as such. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. Optical rotations were determined with a Rudolph

Research Autopol III automatic polarimeter referenced to the D-line of sodium.

4.2. 2-Amino-3-methyl-pentanoic acid ethyl ester ((*S*)-isoleucine ethyl ester) (12a)

To a cooled (0 °C) and stirred suspension of (*S*)-isoleucine (**12**) (50.0 g, 381 mmol) in dry ethanol (1500 mL) was added thionyl chloride (317 g, 2.67 mol) dropwise. The mixture was allowed to come to room temperature and refluxed for 38 h until the gas evolution stopped. The solvent was removed under reduced pressure and the crude (*S*)-isoleucine ethyl ester hydrochloride (88 g) was redissolved in cold water (1500 mL). The solution was extracted with diethyl ether (400 mL) and the aqueous phase was made basic (pH=10–12) by the addition of 30% ammonium hydroxide (40 mL). The mixture was extracted with methylene dichloride (5×200 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield 2-amino-3-methyl-pentanoic acid ethyl ester ((*S*)-isoleucine ethyl ester) (60.6 g, 100%) as a colorless oil. $[\alpha]_D^{25}$ +37.2 (*c* 1.0, MeOH). IR (thin film): 3387, 3319, 2964, 2935, 1732, 1464, 1180, 1028, 859 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J*=7.3 Hz, 3H), 0.93 (t, *J*=7.0 Hz, 3H), 1.10–1.32 (m, 1H), 1.27 (t, *J*=7.0 Hz, 3H), 1.36–1.57 (m, 1H), 1.52 (br s, 2H), 1.67–1.82 (m, 1H), 3.33 (d, *J*=5.1 Hz, 1H), 4.08–4.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 60.8, 59.2, 39.3, 24.8, 15.9, 14.5, 11.9. HRMS (FAB^+) calcd for $C_8H_{17}NO_2$ (*m*/*z*) 160.1338 [M^++1]; found (*m*/*z*) 160.1337.

4.3. (2*S*,3*S*)-1-*tert*-butyl 2-ethyl 3-methyl-pyrrolidine-1,2-dicarboxylate (25)

To a stirred and cooled (0 °C) solution of 2-amino-3-methyl-pentanoic acid ethyl ester ((*S*)-isoleucine ethyl ester) (60.5 g, 380 mmol) in benzene (450 mL) was added freshly prepared *tert*-butyl hypochlorite (38.3 mL, 380 mmol) and the reaction mixture was stirred at 0 °C in the dark for 4 h. The mixture was washed with 0.1 N HCl (150 mL), and water (3×150 mL) before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield *N*-chloro-2-amino-3-methyl-pentanoic acid ethyl ester (*N*-chloro-(*S*)-isoleucine ethyl ester) (72.2 g, 98%) as a pale yellow oil. The product was carried on to the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J*=7.3 Hz, 6H), 1.16–1.38 (m, 1H), 1.33 (t, *J*=7.3 Hz, 3H), 1.50–1.66 (m, 1H), 1.67–1.82 (m, 1H), 3.48 (dd, *J*=6.6, 11.4 Hz, 1H), 4.28 (q, *J*=7.0 Hz, 2H), 4.64 (d, *J*=11.4 Hz, 1H), 7.37 (s, 1H). A solution of *N*-chloro-(*S*)-isoleucine ethyl ester (95.8 g, 495 mmol) in 85% H_2SO_4 (475 mL) was prepared in a photochemical reaction vessel fitted with a quartz immersion well and Hg lamp. After purging the system with argon for 15 min, the reaction mixture was then irradiated with a mercury lamp for 3 h under an atmosphere of argon while maintaining the temperature between 3 and 9 °C. The reaction was tested for completion by taking an aliquot (five drops) of the reaction mixture and treating with 5 mL of a 5% KI solution in water and acetone (1:1). When a clear pale yellow color was obtained, the reaction was complete. After an addition of 6 L of an ice/water mixture the reaction was carefully neutralized with aqueous 10 M NaOH solution at 0 °C. The reaction mixture was concentrated under reduced pressure, the residue was taken up in absolute ethanol, and the solids filtered off. Evaporation of the ethanolic solution under reduced pressure left a mixture of L-(2*S*,3*S*)-methylproline ethyl ester and (*S*)-isoleucine ethyl ester (78.9 g total). The mixture was dissolved in 1050 mL of a 1:1 mixture of dioxane and water and cooled to 0 °C. Di-*tert*-butyl dicarbonate (119 g, 545 mmol) and solid K_2CO_3 (68.4 g, 495 mmol) were added. The reaction mixture was slowly brought to room temperature and stirred for 17 h. The solvent was removed under reduced pressure; the reaction was taken up in water (1800 mL), lowered to pH 2 with 10% aqueous $KHSO_4$ solution, and extracted with ethyl acetate (6×150 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude residue was purified via silica gel flash column chromatography as a 1:1 oil mixture with hexanes/diethyl ether and was subjected to gradient elution 9:1, 7:3, 6:4, 0:10 to afford (2*S*,3*S*)-1-*tert*-butyl 2-ethyl 3-methyl-pyrrolidine-1,2-dicarboxylate (**25**) (32.2 g, 25%) as a pale yellow oil. $[\alpha]_D^{25}$ −49.2 (*c* 1.2, MeOH). IR (thin film): 2975, 2933, 2877, 1748, 1701, 1398, 1249, 1174, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): (rotamers) δ 1.17 (d, *J*=7.0 Hz, 3H), 1.29 (t, *J*=7.3 Hz, 3H), 1.42, 1.46 (2s, 9H), 1.50–1.60 (m, 1H), 1.96–2.10 (m, 1H), 2.24–2.40 (m, 1H), 3.40–3.66 (2m, 2H), 3.74, 3.84 (2d, *J*=6.6 Hz, 1H), 4.10–4.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): (rotamers) δ 173.1, 172.8, 154.5, 154.0, 79.9, 79.8, 66.3, 65.9, 60.9, 46.0, 45.8, 39.7, 38.6, 32.7, 32.2, 28.5, 28.4 (2C), 18.7, 18.5, 14.4, 14.3. HRMS (FAB^+) calcd for $C_{13}H_{23}NO_4$ (*m*/*z*) 258.1705 [M^++1]; found (*m*/*z*) 258.1696.

Preparation of tert-butyl hypochlorite: in a 2-L Erlenmeyer flask was placed a commercial bleach solution (1000 mL, Clorox®, 6% NaOCl) and the solution cooled in an ice bath until the temperature dropped below 10 °C. At this point, lights in the vicinity of the apparatus were turned off and a solution of *tert*-butyl alcohol (74 mL) in glacial acetic acid (49 mL) was added in a single portion to the rapidly stirred bleach solution, and stirring was continued for 3 min. The entire reaction mixture was poured into a 2-L separatory funnel. The lower aqueous layer was discarded, and the oily yellow organic layer was washed first with 10% Na_2CO_3 (100 mL) and then with water (100 mL). The oil was dried over anhydrous $CaCl_2$ (2 g) and filtered to yield *tert*-butyl hypochlorite (80 mL, 85%). The product was stored over anhydrous $CaCl_2$.

4.4. Butyl-(4-iodo-2-methyl-but-2*E*-enyloxy)-dimethyl-silane (26)

To a stirred solution of 2-methyl-2-vinyl-oxirane (4.70 g, 55.9 mmol) in CH_2Cl_2 (90 mL) were added $MgSO_4$ (3 g), TBSCl (7.58 g, 50.3 mmol), and TBAI (22.3 g, 60.2) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The solvent was removed under vacuum, hexane was added, and the resulting suspension filtered. The filtrate was concentrated under vacuum and the residue purified by column filtration (silica, hexane/methylene dichloride: 10:0, then 9:1, then 8:2) to give the *tert*-butyl-(4-iodo-2-methyl-but-2*E*-enyloxy)-dimethyl-silane (**26**) (7.43 g, 41%) and the cis-isomer (1.51 g, 8.3%). TLC (SiO_2, hexanes/CH_2Cl_2: 4:1): R_f=0.42. IR (thin film): 2956, 2930, 2886, 2857, 1472, 1463, 1389, 1362, 1254, 1147, 1115, 1078, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): (trans-isomer) δ 0.09 (s, 6H), 0.93 (s, 9H), 1.69 (s, 3H), 4.06 (s, 2H), 4.14 (d, *J*=8.1 Hz, 2H), 5.73 (t, *J*=8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 119.3, 67.4, 40.5, 26.0, 18.5, 13.4, −5.2.

4.5. 2*R*-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3*S*-methyl-but-2*E*-enyl]-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (23)

To a stirred solution of compound **25** (500 mg, 1.94 mmol) in dry THF (10 mL) was added 0.5 M solution of KHMDS (5.06 mL, 2.52 mmol) in toluene at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. A solution of *tert*-butyl-(4-iodo-2-methyl-but-2*E*-enyloxy)-dimethyl-silane (**26**) (824 mg, 2.52 mmol) in dry THF (2 mL) was added at −78 °C and the reaction mixture was allowed to warm slowly to room temperature overnight. The solvent was removed under vacuum, a saturated aqueous solution of potassium sodium tartrate (30 mL) was added and the mixture extracted with ethyl acetate (3×50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was

removed under vacuum, and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 100:0, then 99:1, then 98:2, then 95:5, then 90:10, then 80:20) to yield 2*R*-[4-(*tert*-butyl-dimethyl-silanyloxy)-3*S*-methyl-but-2*E*-enyl]-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (**23**) (780 mg, 88%) as a clear oil. TLC (SiO_2, hexanes/Et_2O: 7:3): R_f=0.43. $[\alpha]_D^{25}$ −63.2 (*c* 1.0, CH_2Cl_2). IR (thin film): 2960, 2927, 2877, 2857, 1738, 1700, 1461, 1392, 1251, 1228, 1065, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): (rotamers) δ 0.06 (s, 6H), 0.86–0.96 (m, 12H), 1.20–1.32 (m, 3H), 1.41, 1.44 (2s, 9H), 1.61, 1.64 (2s, 3H), 1.64–1.80 (m, 2H), 2.16–2.32 (m, 1H), 2.56–2.70 (m, 1H), 2.87, 3.18 (2dd, *J*=5.1, 15.4 Hz, 1H), 3.10–3.24 (m, 1H), 3.70, 3.83 (2t, *J*=8.8 Hz, 1H), 4.03 (s, 2H), 4.06–4.28 (m, 2H), 5.29 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (rotamers) δ 173.2, 153.9, 153.7, 138.1, 137.6, 118.8, 118.3, 80.1, 79.4, 71.3, 71.0, 68.8, 68.4, 60.9, 60.8, 47.8, 47.5, 41.8, 40.5, 31.0, 30.9, 30.5, 29.6, 28.7, 28.6, 26.2, 26.2, 18.7, 14.8, 14.7, 14.7, 14.5, 14.3, 14.2, −4.90, −4.93. HRMS (FAB^+) calcd for $C_{24}H_{45}NO_5Si$ (*m*/*z*) 456.3145 [M^++1]; found (*m*/*z*) 456.3150.

4.6. But-3-enyl-(1*R*-phenyl-ethyl)-amine

To a stirred solution of *R*-(+)-α-methyl-benzyl amine (**27**) (9.30 g, 76.7 mmol) in dry DMF (90 mL) were added K_2CO_3 (35.0 g, 253 mmol) and NaI (38.0 g, 253 mmol) at room temperature under argon. Finally, 4-bromobut-1-ene (9.42 g, 69.8 mmol) was added and the reaction mixture stirred at 100 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (200 mL), water (200 mL) was added, the organic phase separated, and the aqueous phase extracted with diethyl ether (2×100 mL) and methylene chloride (1×100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, the residue (40 g) taken in water (400 mL), and extracted with diethyl ether (4×100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 95:5, then 80:20, then 60:40, then 40:60) to yield but-3-enyl-(1*R*-phenyl-ethyl)-amine (8.02 g, 66%) as a clear oil. TLC (SiO_2, hexanes/Et_2O: 3:2): R_f=0.26. $[\alpha]_D^{25}$ +49.0 (*c* 1.05, MeOH). IR (thin film): 3352, 3077, 3025, 2974, 2932, 2812, 1450, 1130, 913 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, *J*=6.6 Hz, 3H), 1.45 (br s, 1H), 2.24 (cm, 2H), 2.55 (cm, 2H), 3.78 (q, *J*=6.6 Hz, 1H), 5.03 (d, *J*=10.3 Hz, 1H), 5.08 (d, *J*=17.9 Hz, 1H), 5.76 (ddt, *J*=6.6, 10.3, 17.2 Hz, 1H), 7.20–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 136.6, 128.5 (2C), 127.0, 126.7 (2C), 116.4, 58.4, 46.8, 34.5, 24.5. HRMS (FAB^+) calcd for $C_{12}H_{17}N$ (*m*/*z*) 176.1439 [M^++1]; found (*m*/*z*) 176.1435.

4.7. [But-3-enyl-(1*R*-phenyl-ethyl)-amino]-acetic acid ethyl ester (28)

To a stirred solution of but-3-enyl-(1*R*-phenyl-ethyl)-amine (1.00 g, 5.70 mmol) in dry DMSO (5 mL) was slowly added ethyl bromacetate (524 mg, 3.14 mmol); after 30 min of stirring, dry NEt_3 (317 mg, 3.14 mmol) was slowly added followed by a new addition of ethyl bromacetate (524 mg, 3.14 mmol) and NEt_3 (317 mg, 3.14 mmol). The reaction mixture was heated to 50–60 °C for 46 h, cooled to room temperature, and then diluted with diethyl ether (20 mL). Water (20 mL) was added and the separated organic phase was washed with water (2×10). The combined aqueous phases were extracted with methylene dichloride (1×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 100:0, then 90:10, then 80:20) to yield [but-3-enyl-(1*R*-phenyl-ethyl)-amino]-acetic acid ethyl ester (**28**) (1.00 g, 67%) as a clear oil. TLC (SiO_2, hexanes/Et_2O: 9:1): R_f=0.20. $[\alpha]_D^{25}$ +34.7 (*c* 0.9, MeOH). IR (thin film): 3063, 3027, 2977, 2935, 2847, 1735, 1453, 1370, 1179, 1029, 912 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, *J*=7.0 Hz, 3H), 1.36 (d, *J*=6.6 Hz, 3H), 2.12–2.30 (m, 2H), 2.60–2.78 (m, 2H), 3.30 (1/2 ABq, *J*=17.2 Hz, 1H), 3.45 (1/2 ABq, *J*=17.2 Hz, 1H), 4.06 (q, *J*=7.0 Hz, 1H), 4.15 (q, *J*=7.3 Hz, 2H), 4.97 (dq, *J*=1.2, 10.5 Hz, 1H), 5.01 (dq, *J*=1.8, 17.6 Hz, 1H), 5.76 (ddt, *J*=6.6, 10.3, 17.2 Hz, 1H), 7.23 (t, *J*=7.3 Hz, 1H), 7.31 (t, *J*=7.7 Hz, 2H), 7.37 (t, *J*=7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 144.7, 136.9, 128.4 (2C), 127.7, 127.1 (2C), 115.7, 60.6, 60.4, 51.6, 51.0, 32.6, 19.5, 14.4. HRMS (FAB^+) calcd for $C_{16}H_{23}NO_2$ (*m*/*z*) 262.1807 [M^++1]; found (*m*/*z*) 262.1796.

4.8. 3*S*-Methyl-1-(1*R*-phenyl-ethyl)-pyrrolidine-2*R*-carboxylic acid ethyl ester (29)

To a solution of [but-3-enyl-(1*R*-phenyl-ethyl)-amino]-acetic acid ethyl ester (**28**) (172 mg, 0.659 mmol) in dry diethyl ether (2.5 mL) was added 1.8 M solution of LDA (0.476 mL, 0.857 mmol) in heptane/THF/ethylbenzene at −78 °C. The temperature was raised to −20 °C and then cooled down to −90 °C. Freshly prepared 1 M solution of anhydrous $ZnBr_2$ (2.0 mL, 1.98 mmol) in dry diethyl ether was added dropwise at −90 °C, and the mixture was allowed to warm to room temperature over 3 h, and then stirred for 30 min. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl, stirred overnight, diluted with diethyl ether (20 mL), and 10% aqueous $NaHCO_3$ solution (20 mL) was added. The organic phase was separated and the aqueous phase extracted with diethyl ether (2×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 100:0, then 95:5, then 90:10, then 80:20) to yield 3*S*-methyl-1-(1*R*-phenyl-ethyl)-pyrrolidine-2*R*-carboxylic acid ethyl ester (**29**) (138 mg, 80%) as a clear oil and recovered [but-3-enyl-(1*R*-phenyl-ethyl)-amino]-acetic acid ethyl ester (**28**) (26 mg, 15%). TLC (SiO_2, hexanes/Et_2O: 4:1): R_f=0.25. $[\alpha]_D^{25}$ +68.0 (*c* 1.0, CH_2Cl_2). IR (thin film): 3062, 3027, 2970, 2933, 2874, 1727, 1454, 1372, 1156, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J*=7.0 Hz, 3H), 1.22 (t, *J*=7.3 Hz, 3H), 1.35 (d, *J*=6.9 Hz, 3H), 1.52–1.70 (m, 1H), 1.88–2.02 (m, 1H), 2.32–2.50 (m, 1H), 2.78–2.90 (m, 1H), 2.96–3.08 (m, 1H), 3.31 (d, *J*=8.4 Hz, 1H), 3.71 (q, *J*=8.0 Hz, 1H), 4.09 (q, *J*=7.0 Hz, 2H), 7.18–7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 144.6, 128.3 (2C), 127.6 (2C), 127.2, 67.6, 62.0, 59.8, 50.7, 36.6, 32.1, 22.8, 15.8, 14.5. HRMS (FAB^+) calcd for $C_{16}H_{23}NO_2$ (*m*/*z*) 262.1807 [M^++1]; found (*m*/*z*) 262.1803.

4.9. (2*R*,3*S*)-1-*tert*-butyl 2-ethyl 3-methyl-pyrrolidine-1,2-dicarboxylate (30)

A solution of 3*S*-methyl-1-(1*R*-phenyl-ethyl)-pyrrolidine-2*R*-carboxylic acid ethyl ester (**29**) (100 mg, 383 μmol) in dry ethanol (2 mL) was stirred under H_2 (80 psi) for 24 h at room temperature in the presence of Pd/C (10 wt %) (20.4 mg, 19.1 μmol). The catalyst was removed by filtration through a pad of Celite, which was washed with ethanol (30 mL), and the majority of solvent was removed under vacuum to yield 3*S*-methyl-pyrrolidine-2*R*-carboxylic acid ethyl ester, which was redissolved in dioxane/H_2O (2 mL, 1:1). The solution was cooled to 0 °C and solid di-*tert*-butyl dicarbonate (91.9 mg, 421 μmol) followed by K_2CO_3 (52.9 mg, 383 μmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 19 h. The solvent was removed under reduced pressure, the residue taken up in water (30 mL), and the mixture was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 10:0, then 9:1, then 8:2, then 7:3) to yield 3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (**30**) (82.5 mg, 84%) as a clear oil. TLC (SiO_2, hexanes/Et_2O: 7:3): R_f=0.20. $[\alpha]_D^{25}$ −9.38

(c 1.3, CH_2Cl_2). IR (thin film): 2974, 2933, 2879, 1743, 1702, 1457, 1396, 1193, 1149, 1116, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): (rotamers) δ 1.00 (t, J=7.0 Hz, 3H), 1.26 (q, J=7.3 Hz, 3H), 1.39, 1.44 (2s, 9H), 1.60–1.83 (m, 1H), 1.88–2.00 (m, 1H), 2.35–2.58 (m, 1H), 3.23–3.40 (1H, m), 3.56–3.74 (m, 1H), 4.08–4.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): (rotamers) δ 172.1, 172.0, 154.6, 154.0, 79.9, 79.8, 63.6, 63.1, 60.8, 60.7, 46.4, 46.0, 37.3, 36.4, 32.2, 31.4, 28.6, 28.5, 28.5, 15.0, 15.0, 14.6, 14.5. HRMS (FAB^+) calcd for $C_{13}H_{23}NO_4$ (m/z) 258.1705 [M^++1]; found (m/z) 258.1693.

4.10. 2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (23)

To a stirred solution of 3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (**30**) (50 mg, 195 μmol) in dry THF (1 mL) was added 0.5 M solution of KHMDS (506 μL, 253 μmol) in toluene at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. A solution of *tert*-butyl-(4-iodo-2-methyl-but-2*E*-enyloxy)-dimethyl-silane (**26**) (82.5 mg, 253 μmol) in dry THF (0.2 mL) was added at −78 °C and the reaction mixture was allowed to warm slowly to room temperature overnight. The solvent was removed under vacuum, a saturated aqueous solution of potassium sodium tartrate (5 mL) was added, and the mixture extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica, hexane/diethyl ether: 100:0, then 99:1, then 98:2, then 95:5, then 90:10, then 80:20, then 70:30, then 60:40) to yield 2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-but-2-enyl]-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (**23**) (88.9 mg, 82%) as a clear oil. TLC (SiO_2, hexanes/Et_2O: 7:3): R_f=0.43. $[\alpha]_D^{25}$ −62.8 (c 1.0, CH_2Cl_2). The NMR and IR spectral properties of this substance matched those for **23** provided above.

Acknowledgements

Financial support from the National Institutes of Health (Grant CA 70375) is gratefully acknowledged. K.M.S. acknowledges the Deutsche Forschungsgemeinschaft Postdoctoral Fellowship (SO 507/1-2).

References and notes

1. Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135.
2. (a) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiot.* **1990**, *43*, 1375; (b) Liesch, J. M.; Wichmann, C. F. *J. Antibiot.* **1990**, *43*, 1380; (c) Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1991**, *44*, 492; (d) Pilar Lopez-Gresa, M.; Carmen Gonzalez, M.; Ciavatta, L.; Ayala, I.; Moya, P.; Primo, J. *J. Agric. Food Chem.* **2006**, *54*, 2921.
3. Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Reading, C. *J. Antibiot.* **1993**, *46*, 1355.
4. Banks, R. M.; Blanchflower, S. E.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1997**, *50*, 840.
5. Whyte, A. C.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1996**, *59*, 1093.
6. (a) Polonsky, J.; Merrien, M.-A.; Prangé, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun.* **1980**, 601; (b) Prangé, T.; Billion, M.-A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J.; Moreau, S. *Tetrahedron Lett.* **1981**, *22*, 1977.
7. Fuchser, J. Beeinflussung der Sekundarstoffbildung bei Aspergillusochraceus durch Variation der Kulturbedingungen sowie Isolierung, Strukturaufklarung und Biosynthese der neuen Naturstoffe. Ph.D. Thesis, University of Göttingen, Germany, 1995.
8. (a) Fenical, W.; Jensen, P. R.; Cheng, X.C. U.S. Patent 6,066,635, 2000; (b) Sugie, Y.; Hirai, H.; Inagaki, T.; Ishiguro, M.; Kim, Y.-J.; Kojima, Y.; Sakakibara, T.; Sakemi, S.; Sugiura, A.; Suzuki, Y.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, N. *J. Antibiot.* **2001**, *54*, 911.
9. Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556.
10. Martinez-Luis, S.; Rodriguez, R.; Acevedo, L.; Gonzalez, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron* **2006**, *62*, 1817.
11. (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc. D* **1969**, 644; (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329; (c) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999; (d) Bird, B. A.; Remaley, A. T.; Campbell, I. M. *Appl. Environ. Microbiol.* **1981**, *42*, 521; (e) Bird, B. A.; Campbell, I. M. *Appl. Environ. Microbiol.* **1982**, *43*, 345; (f) Robbers, J. E.; Straus, J. W. *Lloydia* **1975**, *38*, 355; (g) Paterson, R. R. M.; Hawksworth, D. L. *T. Brit. Mycol. Soc.* **1985**, *85*, 95; (h) Wilson, B. J.; Yang, D. T. C.; Harris, T. M. *Appl. Microbiol.* **1973**, *26*, 633; (i) Coetzer, J. *Acta Crystallogr.* **1974**, *B30*, 2254.
12. (a) Hayashi, H.; Nishimoto, Y.; Nozaki, H. *Tetrahedron Lett.* **1997**, *38*, 5655; (b) Hayashi, H.; Nishimoto, Y.; Akiyama, K.; Nozaki, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 111; (c) Banks, R. M.; Blanchflower, S. E.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1998**, *50*, 840.
13. (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127; (b) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711; (c) Williams, R. M.; Stocking, E. M.; Sanz-Cevera, J. F. *Top. Curr. Chem.* **2000**, *209*, 98.
14. (a) Ostlind, D. A.; Mickle, W. G.; Ewanciw, D. V.; Andriuli, F. J.; Campbell, W. C.; Hernandez, S.; Mochales, S.; Munguira, E. *Res. Vet. Sci.* **1990**, *48*, 260; (b) Shoop, W. L.; Egerton, J. R.; Eary, C. H.; Suhayda, D. *J. Parasitol.* **1990**, *76*, 349; (c) Shoop, W. L.; Eary, C. H.; Michael, H. W.; Haines, H. W.; Seward, R. L. *Vet. Parasitol.* **1991**, *40*, 339; (d) Shoop, W. L.; Michael, B. F.; Haines, H. W.; Eary, C. H. *Vet. Parasitol.* **1992**, *43*, 259; (e) Shoop, W. L.; Haines, H. W.; Eary, C. H.; Michael, B. F. *Am. J. Vet. Res.* **1992**, *53*, 2032; (f) Schaeffer, J. M.; Blizzard, T. A.; Ondeyka, J.; Goegelman, R.; Sinclair, P. J.; Mrozik, H. *Biochem. Pharmacol.* **1992**, *43*, 679; For a review, see: (g) Geary, T. G.; Sangster, N. C.; Thompson, D. P. *Vet. Parasitol.* **1999**, *84*, 275.
15. Lee, B. H.; Clothier, M. F.; Dutton, F. E.; Nelson, S. J.; Johnson, S. S.; Thompson, D. P.; Geary, T. G.; Whaley, H. D.; Haber, C. L.; Marshall, V. P.; Kornis, G. I.; McNally, P. L.; Ciadella, J. I.; Martin, D. G.; Bowman, J. W.; Baker, C. A.; Coscarelli, E. M.; Alexander-Bowman, S. J.; Davis, J. P.; Zinser, E. W.; Wiley, V.; Lipton, M. F.; Mauragis, M. A. *Curr. Top. Med. Chem.* **2002**, *2*, 779.
16. Lee, B. H. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 1209.
17. (a) Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2254; (b) Grubbs, A. W.; Artman, G. D., III; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2257; (c) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262.
18. Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 1103.
19. (a) Williams, R. M.; Kwast, E.; Coffman, H.; Glinka, T. *J. Am. Chem. Soc.* **1989**, *111*, 3064; (b) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808; (c) Domingo, L. R.; Sanz-Cervera, J. F.; Williams, R. M.; Picher, M. T.; Marco, J. A. *J. Org. Chem.* **1997**, *62*, 1662; (d) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 347; (e) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471; (f) Williams, R. M.; Sanz-Cervera, J. F.; Sancenon, F.; Marco, J. A.; Halligan, K. *Bioorg. Med. Chem.* **1998**, *6*, 1233.
20. (a) Williams, R. M.; Sanz-Cervera, J. F.; Sancenon, F.; Marco, J. A.; Halligan, K. *J. Am. Chem. Soc.* **1997**, *119*, 1090; (b) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675; (c) Greshock, T. J.; Williams, R. M. *Org. Lett.* **2007**, *9*, 4255; (d) Greshock, T. J.; Grubbs, A. W.; Williams, R. M. *Tetrahedron* **2007**, *63*, 6124; (e) Adams, L. A.; Valente, M. W. N.; Williams, R. M. *Tetrahedron* **2006**, *62*, 5195.
21. Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1296.
22. (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 7008; (b) Stocking, E. M.; Martinez, R. A.; Silks, L. A.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3391; (c) Stocking, M.; Sanz-Cervera, J. F.; Unkefer, C. J.; Williams, R. M. *Tetrahedron* **2001**, *51*, 5303.
23. Gray, C. R.; Sanz-Cervera, J. F.; Silks, L. A.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 14692.
24. (a) Artman, G. D.; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336; (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323; (c) Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540.
25. Williams, R. M.; Cao, J. *Tetrahedron Lett.* **1996**, *37*, 5441.
26. (a) Titouani, S. L.; Lavergne, J.-P.; Vaillefont, P.; Jaqueier. *Tetrahedron* **1980**, *36*, 2961; (b) Stocking, E. M.; Sanz-Cervera, J. F.; Unkefer, C. J.; Williams, R. M. *Tetrahedron* **2001**, *57*, 5303.
27. *Stable Isotopes Catalog*; Cambridge Isotope Laboratories: Andover, MA, 2005; p 60.
28. (a) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85; (b) Karoyan, P.; Chassaing, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2025; (c) Lorthiois, E.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1997**, *38*, 89; (d) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253; (e) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 1221.