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Total Synthesis, Stereochemical Assignment, and Biological Activity of Chamuvarinin and Structural Analogues

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Abstract: A highly stereocontrolled synthesis of (+)-chamuvarinin has been completed in 1.5% overall yield over 20 steps. The key fragment coupling reactions were the addition of alkyne **8** to aldehyde **7** (under Felkin–Anh control), followed by the two step activation/cyclization to close the C20–C23 2,5-*cis*-substituted tetrahydrofuran ring and a Julia–Kocienski olefination at C8–C9 to introduce the terminal butenolide. The inherent flexibility of our coupling strategy led to a streamlined synthesis with 17 steps in the longest sequence (2.2% overall yield), in which the key bond couplings are reversed. In addition, a series of structural analogues of chamuvarinin have been prepared and screened for activity against HeLa cancer cell lines and both the bloodstream and insect forms of *Trypanosoma brucei*, the parasitic agent responsible for African sleeping sickness.

Keywords: acetogenins · natural products · stereochemistry · total synthesis · trypanosomes

Introduction

The *Annonaceae* genera of trees, shrubs and lianas are widely found in tropical and sub-tropical regions of East Africa and South and Central America. The crude extracts of their bark, roots, and leaves are extensively used in traditional medicinal practices for the treatment of bacterial and parasitic infection.[1,2] Interest in the *Annonaceae* intensified with the isolation/discovery of a family of fatty-acid-derived secondary metabolites,[3] termed the annonaceous acetogenins, which currently number in excess of four hundred compounds.[4] Many of these acetogenins display remarkable cytotoxic activity towards human cancer cell lines and a broad spectrum of further biological properties including antifungal and immunosuppressant activities. Their biological activity is primarily attributed to their inhibition of mitochondrial respiratory chain Complex I, of which they are amongst the most potent inhibitors known to date.[5–7]

Isolated in 2004 by Laurens and co-workers from the root extracts of *Uvaria Chamae*, chamuvarinin (**1**, Figure 1) displayed cytotoxicity towards KB 3-1 cervical cancer cell lines with an IC_{50} value of 0.8 nM.[8] Chamuvarinin is unique amongst the acetogenin family of natural products as it is the first reported acetogenin to contain an adjacently linked [bis(tetrahydrofuran)]tetrahydropyran (THF-THF-THP) ring system spanning the C15–C28 region of the carbon backbone.[4] Structurally, the acetogenins are classified according to the number of tetrahydrofuran motifs they contain, that is, monoTHF, bisTHF and trisTHF, and their connectivity, that is, being adjacently or non-adjacently linked. These motifs are located centrally along the 32/34-carbon backbone and account for the vast majority of acetogenin family members.[4] Nonclassical acetogenins containing substituted tetrahydropyran motifs are far less common and to date only eight tetrahydropyran-containing acetogenins have been isolated and include muconin (**2**),[9] bearing an adjacently linked THP-THF ring system and mucocin (**3**) with a non-adjacent THF-THP array.[10]

Given their structural diversity and potent biological profiles acetogenins have been the subject of intense synthetic interest.[11] The majority of this focus has been directed towards the monoTHF and adjacent bisTHF subclasses and has resulted in the development of a range of synthetic methodologies to effectively introduce such stereochemical motifs. These approaches are dominated by the application of intramolecular Williamson etherification reactions, as depicted in Scheme 1.[11–14] The cyclization of activated 1,4-hydroxysulfonate precursors of type **A** or 1,4-epoxyalcohols of type **B** provides efficient access to the corresponding isolated monoTHF compounds of type **C** and **D**, respectively.[12] The former approach has been readily applied in the installation of additional THF motifs in preconstructed systems.[13] Further extension of this tactic has led to the implementation of two-directional cyclization of pseudo-C2-symmetric activated precursors of type **E** and **F**, to assemble the characteristic *anti-threo-anti*-configured bisTHF array of type **G**,[14,15] the predominant structural motif of the adjacent bisTHF acetogenin subclass, typified by squamocin (**4**).[4,16]

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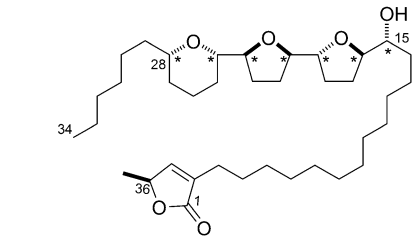
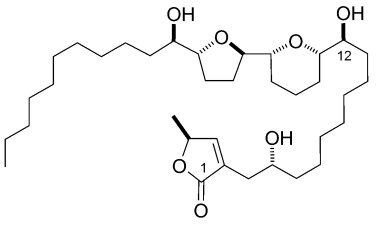
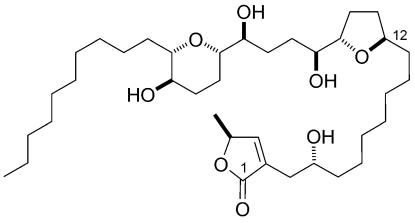


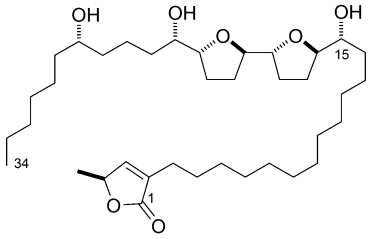
1: chamuvarinin
*relative configuration



2: muconin

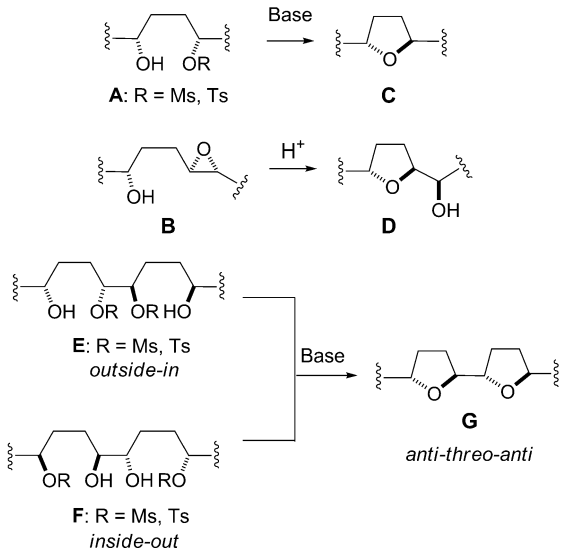


3: mucocin



4: squamocin

Figure 1. Structures of chamuvarinin (**1**) and representative acetogenin family members.

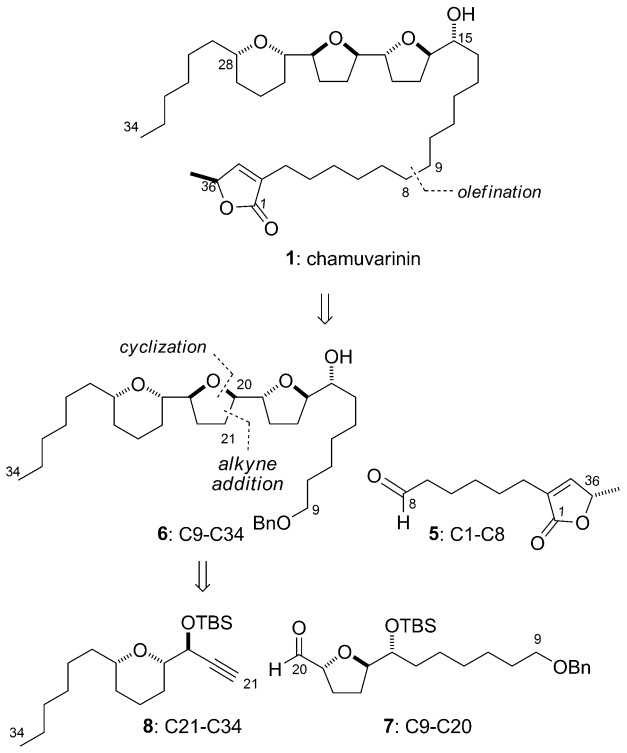


Scheme 1. Application of Williamson-type etherification reactions in acetogenin synthesis. Ms = methylsulfonyl, Ts = 4-methylbenzenesulfonyl.

In common with the majority of acetogenins, chamuvarinin contains a butenolide moiety bearing the 36*S* configuration. The relative stereochemistry of the central C15–C28 ether network initially proved elusive and only the relative configuration of the C15–C19 region was proposed, presenting up to thirty-two possible diastereomeric variations for the actual structure of chamuvarinin.[8a] The stereochemical quandary initially posed by **1** was partially resolved in 2007 by Poupon and co-workers' semi-synthetic study on the biosynthetic origin of chamuvarinin.[8b] It was initially suggested that squamocin (**4**), which was co-isolated from the same crude root extract, could be a plausible biosynthetic precursor of **1** given its structural similarity. However, this proved not to be the case and following a detailed re-evaluation of the ^{1}H and ^{13}C NMR data and structural comparisons with known acetogenins the relative configuration of the C15–C28 region was proposed to be that given in structure **1**, bearing the unusual *threo-anti-threo-syn-threo-syn* adjacently linked [bis(THF)]THP array.[4] Based on a common biogenesis and given that the majority of bioactive acetogenins with a carbinol at C15 bear the *R* configuration, chamuvarinin should share the common 15*R* configuration and we opted to target the diastereomer depicted for the synthesis.[4,17,18] Herein, we provide full details of our initial synthetic route,[19] a revised approach to chamuvarinin employing a reversed-coupling strategy, and report on the trypanocidal activity of a series of analogue structures derived from advanced synthetic intermediates.

Results and Discussion

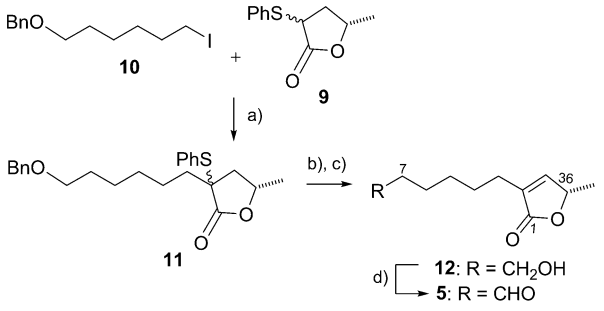
Synthetic strategy: Due to the initial uncertainty surrounding the structure of chamuvarinin at the onset of this synthetic campaign, we devised a modular synthetic strategy based on disconnections at C8–C9 and C20–C21 that would allow the assembly of multiple diastereomeric candidate structures of chamuvarinin.[8a] This requirement was superseded by the stereochemical study by Poupon and co-workers on the biosynthetic relationship between chamuvarinin and squamocin, but our disconnection strategy remained readily applicable to the revised structure with defined relative stereochemistry (Scheme 2).[8b,19] Attachment of the C1–C8 aldehyde **5** containing the butenolide motif in the final coupling enabled our primary focus to be centered on confirming the relative configuration of the adjacently linked tris-tricyclic ether ring system (C15–C28) in **6**. Disconnection of the central C20–C23 THF ring system in **6** gives the C9–C20 aldehyde **7** and the C21–C34 alkyne **8**,[18] in which



Scheme 2. Synthetic strategy for chamuvarinin (**1**).

control over the C20 stereocenter would be reliant upon Felkin–Anh induction from the carbonyl component to enable 5-*exo* cyclization of the C23-hydroxyl to furnish the 2,5-*syn*-configured THF ring system.[13,20]

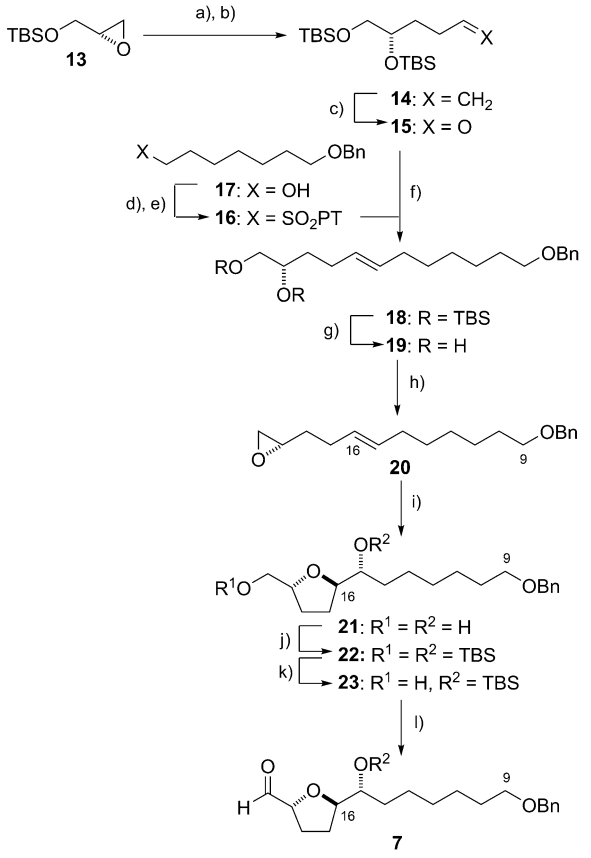
Synthesis of the C1–C8 subunit: The synthesis of the C1–C8 subunit **5** was performed in four steps from lactone **9** through an adaptation of the Marshall butenolide synthesis, as outlined in Scheme 3.[14j] The synthesis began with alkylation of iodide **10**[21] with the lithium enolate of (*S*)-lactone **9**



Scheme 3. Synthesis of C1–C8 aldehyde **5**: a) LDA, DMPU, THF, −78 °C→RT, 75 %; b) mCPBA, CH_2Cl_2, 0 °C; then PhMe, 100 °C, 81 %; c) BCl_3·SMe_2, CH_2Cl_2, −78 °C→RT, 91 %; d) Dess–Martin periodinane, CH_2Cl_2, RT, 93 %. LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, mCPBA = 3-chloroperbenzoic acid, Bn = benzyl.

to provide **11** in 75 % yield.[14j,22] Oxidation and thermal sulfoxide elimination (81 %) was followed by cleavage of the C8-benzyl ether with BCl_3·SMe_2 (91 %)[23] to provide butenolide **12**. Dess–Martin periodinane oxidation of **12** then completed the synthesis of C1–C8 aldehyde **5** (93 %).

Synthesis of the C9–C20 subunit: As shown in Scheme 4, the synthesis of the C9–C20 subunit **7** began with the cop-



Scheme 4. Synthesis of C9–C20 subunit **7**: a) CH_2CHCH_2MgBr, CuI, THF, −40 °C→RT, 82 %; b) TBSCl, ImH, DMAP, DMF, RT, 98 %; c) O_3, Na_2CO_3, CH_2Cl_2, −78 °C, 30 min; then PPh_3, RT, 2 h; d) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DIAD, 0 °C, 98 %; e) $[(NH_4)_6Mo_7O_{24}]$·$4H_2O$, H_2O_2, EtOH, 0 °C→RT, 99 %; f) NaHMDS, DME, −78 °C→−50 °C, 86 % from **14**; g) TBAF, THF, 0 °C→RT, 85 %; h) NaH, TrisIm, THF, 0 °C→RT, 98 %; i) ADmix-β, *t*BuOH/H_2O, 0 °C→RT; then K_2CO_3, MeOH, 0 °C→RT, 89 %, >97:3 d.r.; j) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96 %; k) (±)-CSA (20 mol %), MeOH/CH_2Cl_2 (1:4), 0 °C, 61 % (recovered **22** = 20 % and **21** = 17 %); l) Dess–Martin periodinane, CH_2Cl_2, 0 °C→RT, 70 %. TBS = *tert*-butyldimethylsilyl, ImH = imidazole, DMAP = 4-*N*,*N*′-dimethylaminopyridine, DIAD = diisopropyl azodicarboxylate, NaHMDS = sodium hexamethyldisilylazide, DME = dimethoxyethane, TBAF = tetrabutylammonium fluoride, TrisIm = 2,4,6-triisopropylbenzenesulfonyl imidazole, TfO = triflate, (±)-CSA = (±)-camphorsulfonic acid, PT = phenyl tetrazole.

per(I)-promoted opening of (*S*)-TBS glycidol ether **13** with allylmagnesium bromide (82 %), followed by TBS ether formation (TBSCl, ImH, 98 %) to provide **14**. Ozonolysis of **14**,

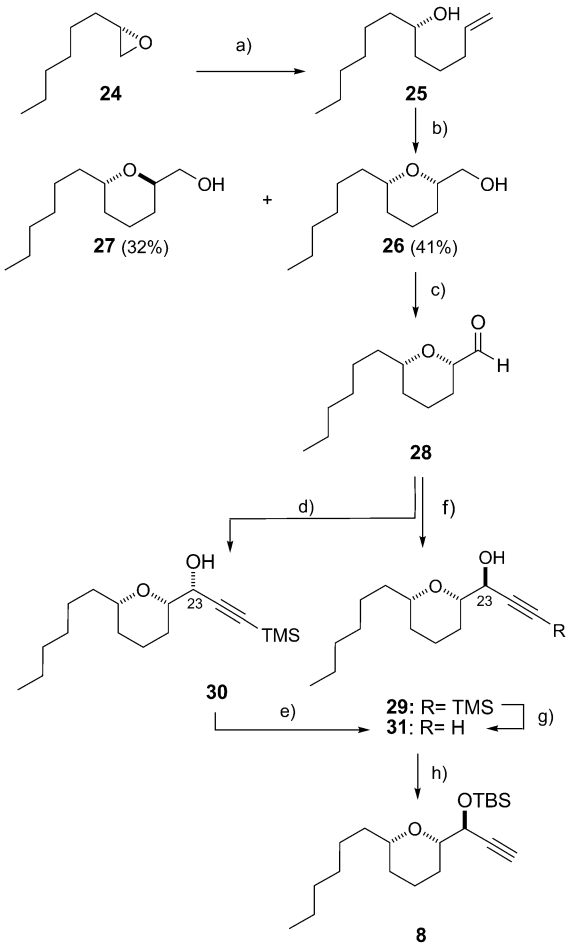
with reductive PPh_3 workup provided aldehyde **15** consistently, which was used directly in the subsequent Julia–Kocienski olefination reaction.[24,25] The phenyltetrazole (PT) sulfone **16** was readily prepared in two steps from known alcohol **17**[26] through a Mitsunobu reaction (DIAD, PPh_3, 1-phenyl-1*H*-tetrazole-5-thiol) and catalytic Mo^{VI} oxidation by using H_2O_2 as a co-oxidant (97% over two steps). Deprotonation of sulfone **16** with NaHMDS in DME at −78°C, followed by addition of aldehyde **15** provided the (*E*)-alkene **18** exclusively in 86% yield from **14**.

With multigram quantities of **18** readily available, installation of the C16–C19 THF ring was addressed. Firstly, TBAF deprotection of the TBS ethers in **18** gave diol **19** in 85% yield, which was readily transformed into epoxide **20** in 98% yield by treatment with NaH and TrisIm.[27] The C15 and C16 hydroxyl stereocenters were then installed by Sharpless asymmetric dihydroxylation[28] and the resulting crude epoxy-diol was treated directly with K_2CO_3 in MeOH to trigger 5-*exo* cyclization, providing the 2,5-*anti*-configured THF diol **21** in 89% yield with >97:3 d.r.[29]

Attempts to selectively oxidize the primary alcohol in **21** proved unsuccessful and a two-step protecting group manipulation was required to differentiate the C15 and C20 hydroxyl groups. Firstly, treatment of **21** with TBSOTf and 2,6-lutidine provided **22**, which underwent selective primary silyl cleavage (CSA (20 mol%) in CH_2Cl_2/MeOH (4:1)) to provide **23** in 61% yield, along with diol **21** (17%) and recovered starting material **22** (20%), which could be recycled accordingly. Finally Dess–Martin oxidation of **23** provided the C9–C20 aldehyde **7** (70%) in preparation for the coupling with the C20–C21 fragment.

Synthesis of the C21–C34 subunit: As shown in Scheme 5, the synthesis of the C21–C34 subunit **8** began with the Cu^{I}-promoted addition of homoallylmagnesium bromide[30] to (*S*)-1-epoxyoctane **24**[31] to afford **25** in 80% yield. Epoxidation of **25** with mCPBA, followed by addition of a catalytic amount of CSA (20 mol%), cleanly promoted the 6-*exo* cyclization to provide *syn*- and *anti*-THP alcohols **26** (41%) and **27** (32%), which were readily separated by column chromatography on a multigram scale. Swern oxidation of **26** and addition of the lithium anion of trimethylsilylacetylene to aldehyde **28** provided (23*R*) and (23*S*)-propargylic alcohols **29** and **30** in 88% combined yield (**29**:**30**= 12:88 d.r.).[32] Following chromatographic separation the undesired major (23*R*)-diastereomer, **30**, was subjected to Mitsunobu inversion[33] and, following base-mediated methanolysis/desilylation, gave **31** with the correct 23*S* configuration.

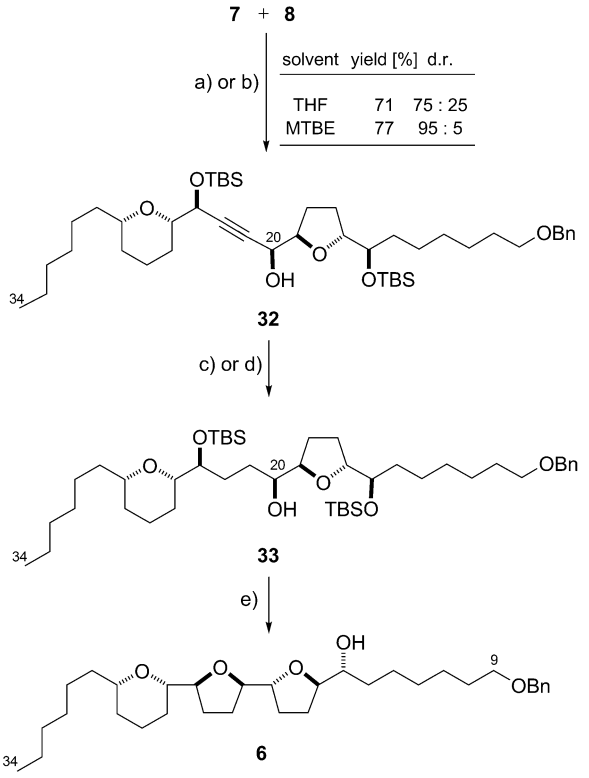
Although this three-step process provided access to **31** in good yield, direct access to **29** from **28** was deemed preferable. This was achieved by employing the Carreira alkynylation protocol to overturn the inherent substrate bias.[34] Thus, treatment of **28** with $Zn(OTf)_2$/*N*-Me-ephedrine and trimethylsilylacetylene provided the (23*S*)-alcohol **29** in 80% yield with >95:5 d.r. Basic methanolysis of the alkynyl TMS group (90%) and subsequent protection of the C23-hydroxyl droup in **31** as its TBS ether (TBSCl/ImH, 91%)



Scheme 5. Synthesis of C21–C34 subunit **8**: a) $CH_2CHCH_2CH_2MgBr$, CuI, THF, −40°C→RT, 80%; b) mCPBA, CH_2Cl_2, 0°C→RT; then (±)-CSA (20 mol%), RT, 73% (**26**=41%, **27**=32%); c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C→RT, 88%; d) HCCTMS, *n*BuLi, THF, −78°C, 88% (**29**/**30**=12:88 d.r.); e) i) 4-$BrC_6H_4CO_2H$, PPh_3, DIAD, 0°C; ii) K_2CO_3, MeOH, RT; f) HCCTMS, (+)-(1*S*,2*R*)-*N*-methylephedrine, Zn-$(OTf)_2$, Et_3N, PhMe, 60°C, 80% (**29**/**30**=>95:5 d.r.; g) K_2CO_3, MeOH, RT, 90%; h) TBSCl, ImH, CH_2Cl_2, RT, 91%. TMS=trimethylsilyl.

completed the C21–C34 subunit **8** in six steps and 13% overall yield from (*S*)-1-epoxyoctane **24**.

Synthesis of the C9–C34 tricyclic ether core: With the C9–C20 and C21–C34 subunits in hand, attention was now focused on their union and assembly of the central C20–C23 THF ring system (Scheme 6). In the event, treatment of alkyne **8** with *n*BuLi in THF at −78°C, followed by addition of aldehyde **7** in THF at −78°C provided the expected adduct **32** in 71% yield with modest diastereoselectivity (75:25 d.r.).[20] Gratifyingly, the level of Felkin–Anh stereoinduction imparted by the aldehyde component could be improved by performing the reaction in MTBE at −100°C, providing **32** in 77% yield with essentially complete diastereoselectivity at C20 (>95:5 d.r.).[20c,32] Reduction of the C21–C22 alkyne under flow hydrogenation by using 5% Pt/C at 100 bar of H_2 provided **33** in 39% yield. However, di-



Scheme 6. Synthesis of the C9–C34 tricyclic ether intermediate **6**: a) compound **8**, *n*BuLi, THF, −78 °C; then **7**, −78 °C, 71 %; or b) compound **8**, *n*BuLi, MTBE, −100 °C; then **7**, −100 °C, 77 %; c) 5 % Pt/C 35 mm Cat-Cart, H-Cube, MeOH, 1 mL min^{-1}, 100 bar H_2, 39 %; or d) $TsNHNH_2$, NaOAc, DME, H_2O, 100 °C, 79 %; e) i) MsCl, Et_3N, 0 °C; ii) TBAF, THF, 0 °C→RT, 90 %. MTBE = methyl *t*-butylether.

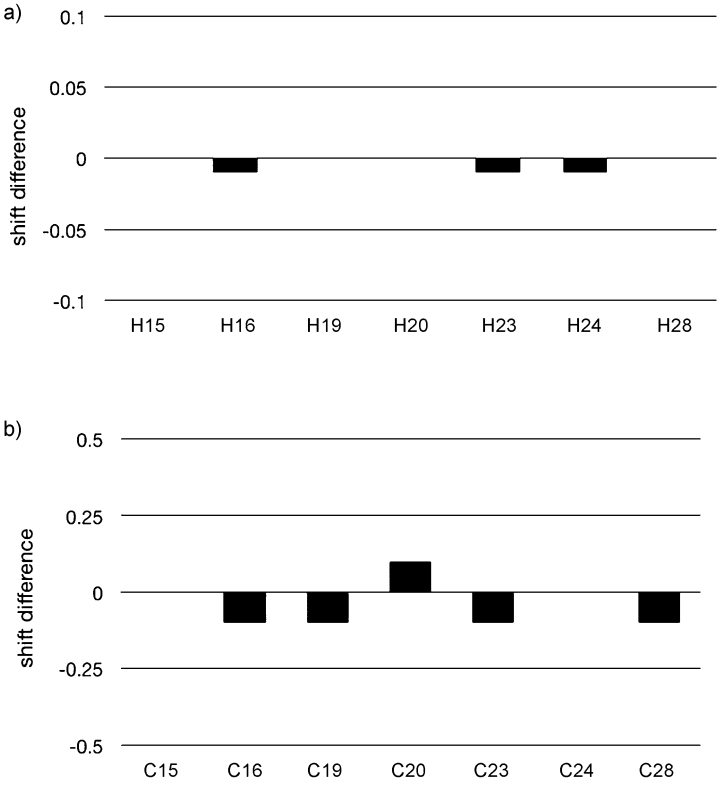


Figure 2. Comparative ^1H and ^{13}C NMR analysis of the synthetic C9–C34 intermediate **6** and natural chamuvarinin. a) Bars represent deviation in ppm between individual proton chemical shifts observed for **6** and those reported for the natural material (400 MHz, $CDCl_3$); b) Bars represent deviation in ppm between individual carbon chemical shifts observed for **6** and those reported for the natural material (100 MHz, $CDCl_3$).

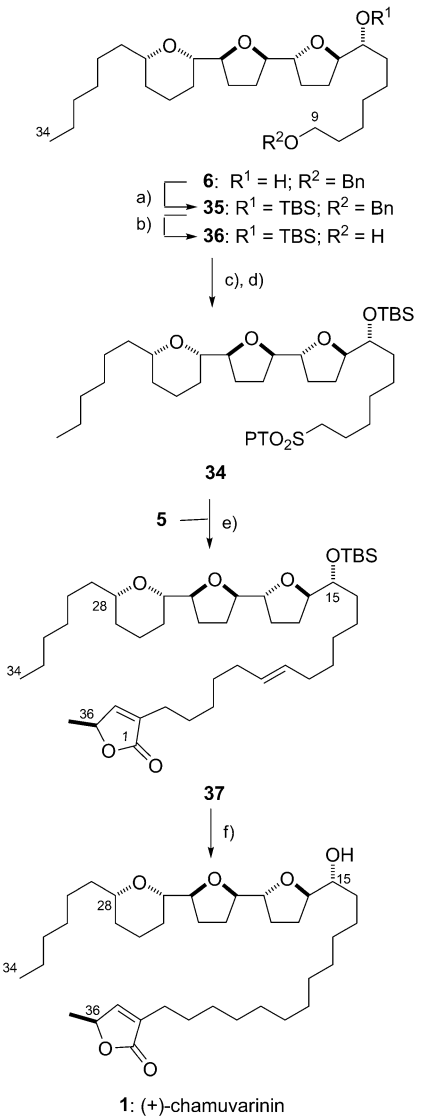
imide reduction ($TsNHNH_2$, NaOAc, DME, H_2O, 100 °C) of **32** proved to be a superior reagent system for the alkyne reduction, providing **33** in 71 % yield.[14d,35]

It now remained to install the central C20–C23 *syn*-configured THF motif. This transformation was readily achieved by activation of the C20 hydroxyl group as its mesylate form ($MsCl/Et_3N$), followed by treatment of the crude reaction mixture with TBAF to promote silyl cleavage at C15 and C23 and in situ 5-*exo* cyclization, providing the C9–C34 intermediate **6** in excellent yield over two steps.[14] At this juncture, comparison of the ^1H and ^{13}C NMR spectra of **6** with those of natural chamuvarinin showed them to be in remarkably close agreement across the C15–C28 stereochemical array (Figure 2), providing confidence in the relative stereochemical assignment proposed by Poupon and coworkers.[8]

Completion of chamuvarinin: With the C9–C34 intermediate **6** in hand, our attention was directed towards the final Julia–Kocienski coupling at C8–C9 and the completion of chamuvarinin, as detailed in Scheme 7. This began with the elaboration of **6** to the corresponding C9–C34 sulfone **34**. Protection of the C15 hydroxyl as its TBS ether provided **35** in 88 % yield. Debenzylation at C9 proceeded smoothly to give **36** in 85 % yield. Finally, treatment of **36** with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions (76 %) and subsequent oxidation of the intermediate sulfide (H_2O_2, cat. Mo^{VI}) provided the sulfone **34** in 76 % yield.

The stage was now set for the union of **34** with the C1–C8 aldehyde **5**. Thus, deprotonation of **34** with NaHMDS in THF at −78 °C followed by addition of **5**, with warming to −20 °C over three hours provided the C1–C34 intermediate **37** in 41 % yield.[24,25,36,37] Diimide reduction[14d,35] of the C8–C9 alkene and deprotection of the C15-OTBS ether by acidic methanolysis proceeded smoothly to provide synthetic compound **1** in 73 % yield over two steps.

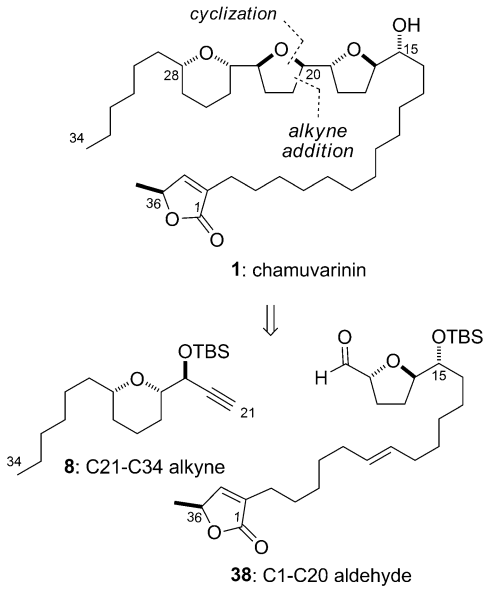
The spectroscopic data obtained for the synthetic material (^1H and ^{13}C NMR spectroscopy, IR spectroscopy and MS), correlated fully with that of natural chamuvarinin, and the measured specific rotation, $[\alpha]_D^{20} = +9.9$ ($c = 0.1$ in $CHCl_3$), for **1** compared with the reported data was consistent with that of the natural material [lit. $[\alpha]_D = +27$ ($c = 0.026$ in $CHCl_3$)].[8] However, in the absence of an authentic sample of **1** for direct NMR spectroscopic, specific rotation and/or HPLC comparison, additional confirmation was sought by qualitative comparison of the biological activity of the synthetic material with the reported activity of the natural material. In screening against the HeLa cervical cancer cell



Scheme 7. Completion of chamuvarinin: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 88%; b) 20% $Pd(OH)_2$/C, H_2 (1 atm), EtOH, RT, 85%; c) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DIAD, 0 °C, 76%; d) $[(NH_4)_6Mo_7O_{24}]\cdot 4H_2O$, H_2O_2, EtOH, 0 °C→RT, 76%; e) **34**, NaHMDS, THF, −78 °C; then **5**, THF −78→−20 °C, 41%; f) $TsNHNH_2$, NaOAc, DME, H_2O, 100 °C; then 3 N HCl, MeOH, RT, 73% from **37**.

line, synthetic compound **1** displayed low micromolar activity ($ED_{50} = 2.88 \pm 0.66$ μM). Additionally, synthetic **1** displayed potent trypanocidal activity towards both the bloodstream and insect form of the parasite *Trypanasoma brucei*, with ED_{50} values of 1.37 ± 0.08 and 1.90 ± 0.11 μM,[38] respectively, which is in line with the trypanocidal activity reported for squamocin **4**.[39]

Revised coupling strategy: Our initial approach to chamuvarinin was designed to resolve the relative and stereochemical configuration of chamuvarinin. Having successfully completed this primary goal,[19] we sought further strategic refinements in an effort to improve synthetic efficiency and enable the synthesis of acetogenin-like analogues to further investigate the activity displayed by **1** towards *T. brucei*. As outlined in Scheme 8, our revised synthetic route uses the common subunits from our first-generation approach and



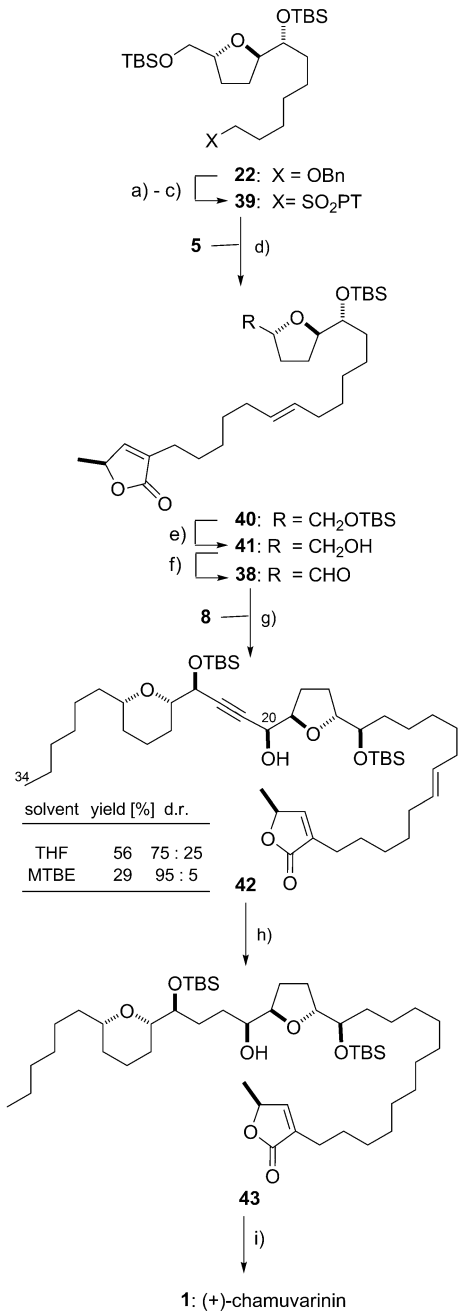
Scheme 8. Revised coupling strategy for chamuvarinin.

maintains key disconnections at C8–C9 and C20–C21, but reverses the order of the bond couplings. Thus, disconnection at C20–C21 gives the C1–C20 aldehyde **38** and the C21–C34 alkyne **8**. In turn, compound **38** could be assembled by adaptation of the C8–C9 Julia–Kocienski olefination developed in our initial synthesis.[19,24,25,36,37]

As shown in Scheme 9, the C9–C20 sulfone **39** was readily prepared in three steps from intermediate **22** in 50% yield, involving C9-debenzylation, Mitsunobu thioetherification, and oxidation to the sulfone. The Julia–Kocienski olefination between aldehyde **5** and sulfone **39** by using NaHMDS in THF proceeded smoothly to provide **40** in excellent yield as a single *E* isomer. At this stage, selective deprotection of the C20-TBS ether with catalytic CSA in $MeOH/CH_2Cl_2$ gave alcohol **41** in 63% yield. Dess–Martin oxidation of **41** gave C1–C20 aldehyde **38** prior to the final coupling reaction with alkyne **8**.

Formation of the lithium anion of alkyne **8** with *n*BuLi at −100 °C in MTBE, followed by addition of aldehyde **38** provided adduct **42** with 95:5 d.r., but only in a modest 29% yield. In contrast, performing the alkynylation of **38** in THF at −78 °C provided **42** in an improved yield albeit with reduced diastereoselectivity (56%, 75:25 d.r.).[20]

Having established the C1–C34 carbon skeleton, all that remained was to close the central C20–C23 THF ring and complete our revised approach. Thus, diimide reduction[35] of the C8-alkene and C21-alkyne in **42** provided **43** in 90% yield. At this point, the minor diasteromer from the previous coupling reaction was readily removed by column chromatography. Activation of the C20-hydroxyl in **43** as its me-



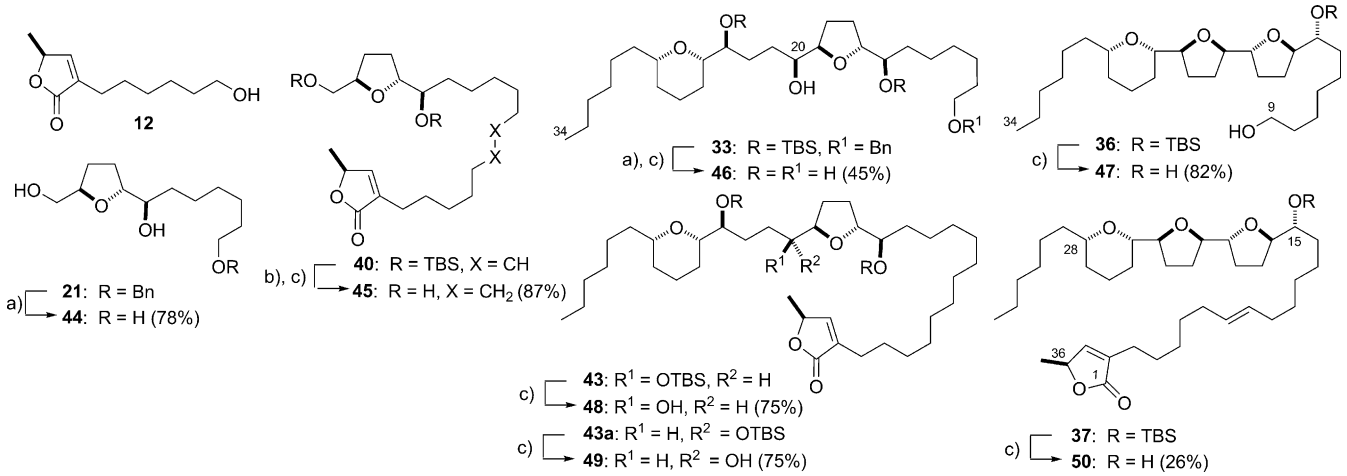
Scheme 9. Revised synthesis of chamuvarinin: a) 20% $Pd(OH)_2/C$, H_2 (1 atm), EtOH, RT, 96%; b) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DIAD, 0°C, 64%; c) $[(NH_4)_6Mo_7O_{24}]\cdot 4H_2O$, H_2O_2, EtOH, HMPA, 0°C→RT, 81%; d) **39**, NaHMDS, THF, −78°C; then **5**, THF, −78→−20°C, 87%; e) (±)-CSA, $MeOH/CH_2Cl_2$ (1:4), 0°C, 63%; f) Dess–Martin periodinane, CH_2Cl_2, 0°C→RT, 69%; g) compound **8**, *n*BuLi, MTBE, −100°C; then **38**, −100°C, 29%; or compound **8**, *n*BuLi, THF, −78°C; then **38**, −78°C, 56%; h) $TsNHNH_2$, NaOAc, DME, H_2O, 100°C, 90%; i) i) MsCl, Et_3N; ii) 3 N HCl, MeOH, RT; iii) pyridine, 70°C, 57% from **43**. HMPA = hexamethylphosphoramide.

sylate ($MsCl/Et_3N$) was followed by deprotection of the C15- and C23-TBS ethers with 3 N HCl in MeOH and exposure of the crude reaction products to pyridine at reflux provided (+)-chamuvarinin in 57% yield over three steps.[13,40] This three-step sequence only required a single chromatographic purification of the final product, which was identical to an authentic sample in all respects.[8,19] By implementation of this revised coupling strategy, we were able to improve the overall step efficiency (the longest linear sequence being 17 steps from **13**, compare with 20 steps in our initial approach), although the overall yield was only slightly improved (2.2% overall yield), in part due to the challenging C20–C21 bond construction. This revised approach also enabled access to a range of advanced structural analogues, which are detailed in the following section.

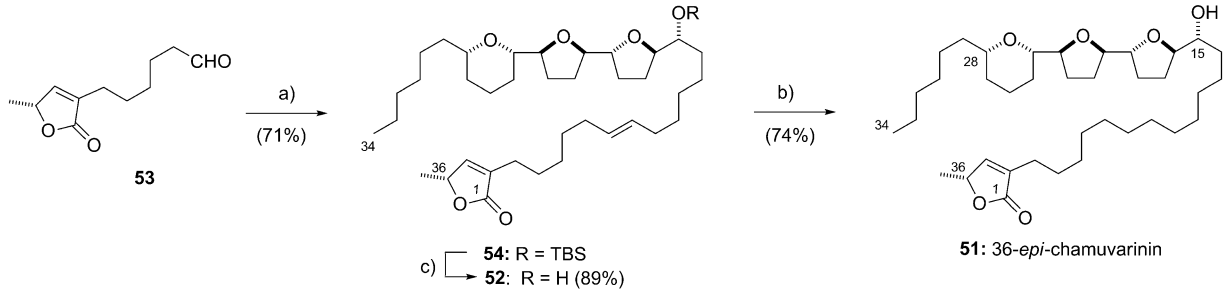
Synthesis and biological evaluation of chamuvarinin analogues: Acetogenins have been the subject of intensive synthetic and biological research, primarily in relation to their development as a new generation of anti-cancer agents. In contrast, their evaluation as potential lead compounds for the treatment of neglected diseases, such as African sleeping sickness, has been largely overlooked. These studies have primarily centered on the screening of crude extracts for trypanocidal activity,[41–43] although Hocquemiller and co-workers have shown squamocin (**4**) to be an effective inhibitor of the bloodstream form of *T. brucei* with an IC_{100} of 16 μM.[39] The low-micromolar activity displayed by our synthetic material towards both the bloodstream and procyclic forms of *T. brucei*, coupled with our modular approach to the synthesis of chamuvarinin, provided an ideal opportunity to access a range of unnatural acetogenin-like analogues to assess their trypanocidal activity.

As shown in Scheme 10, analogues **44–50** were readily prepared from their respective protected precursors by standard deprotection protocols. 36-*epi*-Chamuvarinin (**51**) and 36-*epi*-(8*E*)-alkenyl analogue **52** were prepared from **34** and *R*-configured C1–C8 aldehyde **53**[44] by utilizing our first generation coupling strategy, as outlined in Scheme 11. As expected, compound **51** could not be readily distinguished from **1** by ^1H and ^{13}C NMR spectroscopy and the specific rotation was of the same magnitude, but opposite polarity [**51**: $[\alpha]_D^{20} = -11.9$ ($c = 0.52$ in $CHCl_3$); synthetic **1**: $[\alpha]_D^{20} = +9.9$ ($c = 0.1$ in $CHCl_3$);[19] natural **1**: $[\alpha]_D = +25$ ($c = 0.026$ in $CHCl_3$)[8]].

The synthesized compounds were tested against both the bloodstream and procyclic forms of *T. brucei* and HeLa cells,[38] as a representative mammalian cell line; the results are summarized in Table 1. In all cases, the analogues displayed lower activities towards *T. brucei* than synthetic chamuvarinin, although all were essentially inactive towards HeLa cells. The simple analogues **12** and **44** (Table 1, entries 2 and 3) were devoid of any activity, as was compound **45** (Table 1, entry 4), which corresponds to the C1–C20 fragment of chamuvarinin. The truncated C9–C34 analogues **46** and **47** (Table 1, entries 5 and 6) shared similar activity towards bloodstream *T. brucei*. Incorporation of the butenolide group in **48** and **49** (Table 1, entries 7 and 8) led to increased trypanocidal activity compared with the truncated C9–C34 analogue **46**, but both remained essentially inactive towards HeLa cells. Although **51** (Table 1, entry 10), bearing



Scheme 10. Synthesis of analogues: a) 20% $Pd(OH)_2/C$, H_2 (1 atm), EtOH, RT; b) $TsNHNH_2$, NaOAc, DME, H_2O, 100°C; c) 3N HCl, MeOH, RT.



Scheme 11. Synthesis of 36-*epi*-chamuvarinin: a) **34**, NaHMDS, THF, −78°C; then **53**, THF −78→−20°C, 71%; b) $TsNHNH_2$, NaOAc, DME, H_2O, 100°C; then 3N HCl, MeOH, RT, 74%; c) 3N HCl, MeOH, RT, 89%.

Table 1. Trypanocidal activity of chamuvarinin and analogues.

Entry	Compound[a]	*T. brucei* (BSF)[b] [μM]	*T. brucei* (procyclic) [μM]	HeLa [μM]	SI[c]
1	**1**	1.37±0.08	1.90±0.11	2.88±0.66	2.1
2	**12**	>1000	>1000	>1000	–
3	**44**	528±19.6	>1000	>1000	>1.9
4	**45**	575±35	354±23	132±14	0.23
5	**46**	69.7±2.5	27.6±0.9	>100	>1.4
6	**47**	51.0±3.8	78.9±2.7	>100	>1.9
7	**48**	13.5±0.8	18.6±0.5	>100	>7
8	**49**	27.3±2.0	15.2±2.0	151±7.4	5.5
9	**50**	36.7±2.9	36.5±4.1	>100	>2.7
10	**51**	>100	>100	>100	–
11	**52**	9.6±1.1	18.9±2.8	>100	>10

[a] For structures see Scheme 9; [b] BSF = bloodstream form; [c] Selectivity index = ratio of HeLa ED_{50} versus *T. brucei* (BSF) ED_{50}.

the unnatural (36*R*)-configured butenolide, displayed no activity, the (8*E*)-alkenyl analogue **52** (Table 1, entry 11), which shares the unnatural (36*R*)-configuration, was only 7-fold less active than chamuvarinin and was more potent than the corresponding (36*S*)-diastereomer **50** (Table 1, entry 9).

Conclusion

A highly stereocontrolled synthesis of (+)-chamuvarinin has been completed by a modular coupling strategy in 1.5% overall yield over 20 steps in the longest linear sequence. This enabled the unambiguous confirmation of the relative and absolute stereochemical assignment of this unique acetogenin. Biological screening of our synthetic material against a representative human cell line (HeLa) provided further convincing evidence of the unambiguous stereochemical assignment of **1**, and the trypanocidal activity was in line with the small number of acetogenins that have been screened against *Trypanosoma brucei*. Further refinement of our synthetic strategy led to the reversal of key fragment couplings at C8–C9 and C20–C21, improving the overall synthetic efficiency of our initial approach (2.2% overall yield with 17 steps in the longest linear sequence), while also enabling the preparation of a series of analogues for preliminary structure–activity relationship (SAR) exploration of trypanocidal activity. The selective activity displayed by analogues **48** and **49** towards the bloodstream form of *T. brucei* demonstrates that subtle modifications of the central ether array can retain parasitic activity,

while being essentially inactive towards mammalian cell lines. Studies are currently focused on elucidating the specific parasite protein target(s) of our acetogenin-like analogues because unlike mammalian cells, which are dependent on Complex I for mitochondrial respiration and sensitive to acetogenin inhibition, the bloodstream form of *T. brucei* lacks this multienzyme complex and relies solely on the Trypanosome Alternative Oxidase, a cytochrome-independent terminal oxidase that reduces oxygen to water by the transfer of two electrons from ubiquinol. In conjunction, further structural optimization of our lead compounds as potential new chemotherapeutic agents for the treatment of African sleeping sickness is underway and will be reported in due course.

Experimental Section

General: See the Supporting Information for details of instrumentation, purification of reagents and solvents, and chromatography. All non-aqueous reactions were performed under an atmosphere of argon with oven-dried apparatus and standard techniques for handling air-sensitive materials. The Alamar Blue™ viability test[38] was utilized to establish ED_{50} values for all of the analogues, against cultured bloodstream (strain 427) and procyclic (strain 29–13) *T. brucei*, as well as HeLa cells.

Compound 32: *n*BuLi (0.48 mL, 0.67 mmol, 1.6 M in hexane) was added to a solution of alkyne **8** (230 mg, 0.68 mmol) in MTBE (3 mL) at 0 °C. The reaction mixture was cooled to −100 °C and after 10 min a solution of aldehyde **7** (57.9 mg, 0.13 mmol) in MTBE (1 mL) was added through a cannula. After 4 h, saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL) were added. The organic compounds were extracted with CH_2Cl_2 (3×5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/hexanes) provided alkyne **32** (79.3 mg, 77%), as a colorless oil (>95:5 d.r.). R_f=0.10 (5% EtOAc/hexanes); $[\alpha]_D^{20}$=+6.1 (c=0.59 in $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3442, 2929, 2856, 1456, 1363, 1251, 1102, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.38–7.32 (m, 4H; Ar-H), 7.31–7.28 (m, 1H; Ar-H), 4.51 (s, 2H; Ph-CH_2) 4.49–4.45 (m, 1H; H_{20}), 4.33 (dd, J=6.7, 1.6 Hz, 1H; H_{23}), 4.16–4.09 (m, 1H; H_{19}), 4.08–3.89 (m, 1H; H_{16}), 3.68–3.52 (m, 1H; H_{15}), 3.47 (t, J=6.6 Hz, 2H; H_9), 3.31 (ddd, J=11.2, 6.7, 1.9 Hz, 1H; H_{24}), 3.28–3.18 (m, 1H; H_{28}), 2.32 (d, J=6.0 Hz, 1H; OH), 2.03–1.74 (m, 5H; H_{17a}, H_{18}, H_{25a}, H_{26a}), 1.73–1.58 (m, 3H; H_{10}, H_{17b}), 1.57–1.08 (m, 22H; H_{11}–H_{14}, H_{25b}, H_{26b}, H_{27}, H_{29}–H_{33}), 0.97–0.82 (m, 21H; H_{34}, 2×SiC(CH_3)$_3$), 0.13 (s, 3H; $SiCH_3$), 0.12 (s, 3H; $SiCH_3$), 0.08 (s, 3H; $SiCH_3$), 0.06 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.7, 128.4, 127.6, 127.5, 85.2, 83.3, 83.0, 82.5, 82.2, 81.4, 80.70, 80.65, 77.8, 75.2, 74.8, 72.9, 70.5, 66.9, 65.7, 64.5, 36.5, 33.1, 32.9, 31.9, 31.4, 29.8, 29.5, 28.4, 27.9, 27.6, 26.8, 26.7, 26.2, 26.0, 25.8, 25.6, 25.4, 23.3, 22.7, 18.33, 18.28, 14.1, −4.1, −4.5, −4.6, −4.9 ppm; HRMS (ES+): *m/z* calcd for $C_{45}H_{84}O_6Si_2N$: 790.5832 $[M+NH_4]^+$; found: 790.5832.

Compound 33: A solution of alkyne **32** (5.9 mg, 7.6 μmol) and $TsNHNH_2$ (85 mg, 0.46 mmol) in DME (1 mL) was heated at reflux. A solution of NaOAc (62 mg, 0.46 mmol) in H_2O (1 mL) was added to the reaction solution over a period of 4 h. After this time, the reaction solution was cooled and diluted with H_2O (5 mL) and EtOAc (5 mL). The organic compounds were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with HCl (3 M, 3×5 mL), a saturated solution of $NaHCO_3$ (15 mL), and brine (15 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) provided alcohol **33** (3.70 mg, 62%), as a colorless oil. R_f=0.40 (15% EtOAc/hexanes); $[\alpha]_D^{20}$=+2.6 (c=1.1 in $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3442, 2928, 1460, 1363, 1097, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.37–7.32 (m, 4H; Ar-H), 7.31–7.28 (m, 1H; Ar-H), 4.51 (s, 2H; Ph-CH_2), 3.90 (dt, J=8.4, 5.9 Hz, 1H; H_{16}), 3.83 (app. td, J=7.1, 3.7 Hz, 1H; H_{19}), 3.77–3.72 (m, 1H; H_{20}), 3.64 (dt, J=5.6, 5.6 Hz, 1H; H_{23}), 3.57–3.51 (m, 1H; H_{15}), 3.47 (t, J=6.6 Hz, 2H; H_9), 3.30–3.19 (m, 2H; H_{24}, H_{28}), 2.42 (d, J=5.1 Hz, 1H; OH), 1.97–1.76 (m, 4H; H_{17a}, H_{18}, H_{26a}), 1.70–1.49 (m, 8H; H_{10}, H_{17b}, H_{22}, H_{25a}, H_{26b}, H_{27a}), 1.49–1.23 (m, 20H; H_{11}–H_{14}, H_{21}, H_{29}–H_{33}), 1.23–1.05 (m, 2H; H_{25b}, H_{27b}), 0.90–0.83 (m, 21H; H_{34}, 2×SiC(CH_3)$_3$), 0.06 (s, 3H; $SiCH_3$), 0.056 (s, 3H; $SiCH_3$), 0.054 (s, 3H; $SiCH_3$), 0.04 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.7, 128.4, 127.6, 127.5, 82.6, 82.2, 80.8, 78.1, 75.4, 74.5, 72.9, 72.0, 70.5, 36.4, 33.0, 31.9, 31.4, 31.0, 29.8, 29.5, 28.8, 28.5, 28.0, 26.2, 26.00, 25.97, 25.7, 25.6, 25.4, 25.3, 23.6, 22.7, 18.3, 18.2, 14.1, −4.1, −4.2, −4.6 ppm (2C); HRMS (ES+): *m/z* calcd for $C_{45}H_{88}O_6Si_2N$: 794.6147 $[M+NH_4]^+$; found: 794.6145.

Compound 6: Et_3N (176 μL, 1.27 mmol) and MsCl (70 μL, 0.91 mmol) were added to a solution of alcohol **33** (141 mg, 0.181 mmol) in CH_2Cl_2 (9 mL) at 0 °C. After 1 h, saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL) were added. The organic compounds were extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude mesylate was dissolved in THF (7 mL) and cooled to 0 °C with stirring and TBAF (4.53 mL of a 1.0 M solution in THF, 4.53 mmol) was added. The reaction mixture was warmed to RT. After 22 h, the reaction mixture was quenched with H_2O (10 mL) and EtOAc (10 mL). The organic compounds were extracted with EtOAc (3×10 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (20% EtOAc/hexanes) provided tetrahydrofuran alcohol **6** (86 mg, 90%), as a colorless oil. R_f=0.42 (50% EtOAc/hexanes); $[\alpha]_D^{20}$=−1.8 (c=0.5 in $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3453, 2928, 2856, 1454, 1357, 1172, 1092, 1070, 910, 733, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.36–7.32 (m, 4H; Ar-H), 7.31–7.28 (m, 1H; Ar-H), 4.51 (s, 2H; Ph-CH_2), 3.93 (dt, J=7.6, 6.2 Hz, 1H; H_{19}), 3.89 (dt, J=6.8, 5.7 Hz, 1H; H_{23}), 3.87–3.81 (m, 2H; H_{16}, H_{20}), 3.47 (t, J=6.6 Hz, 2H; H_9), 3.41–3.34 (m, 1H; H_{15}), 3.30 (ddd, J=10.1, 5.5, 1.8 Hz, 1H; H_{24}), 3.31–3.27 (m, 1H; H_{28}), 2.53 (br s, 1H; OH), 2.01–1.91 (m, 2H; H_{17a}, H_{18a}), 1.87–1.79 (m, 3H; H_{21a}, H_{22a}, H_{26a}), 1.79–1.70 (m, 2H; H_{18b}, H_{22b}), 1.70–1.45 (m, 8H; H_{10}, H_{14a}, H_{17b}, H_{21b}, H_{25a}, H_{26b}, H_{27a}), 1.43–1.20 (m, 18H; H_{11}–H_{13}, H_{14b}, H_{25b}, H_{29}–H_{33}), 1.20–1.10 (app. dq, J=12.4, 3.8 Hz, 1H; H_{27b}), 0.88 ppm (t, J=6.9 Hz, 3H; H_{34}); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.7, 128.3, 127.6, 127.5, 83.1, 82.1, 82.0, 81.5, 79.9, 77.9, 74.1, 72.9, 70.5, 36.5, 33.4, 31.9, 31.5, 29.7, 29.6, 29.4, 28.9, 28.4, 28.0, 27.4, 26.9, 26.2, 25.7, 25.6, 23.5, 22.7, 14.1 ppm; HRMS (ES+): *m/z* calcd for $C_{33}H_{58}O_5N$: 548.4304 $[M+NH_4]^+$; found: 548.4310.

Compound 37: NaHMDS (160 μL, 0.2 M soln in THF, 32 μmol) was added to a solution of sulfone **34** (18.4 mg, 25 μmol) in THF (4 mL) at −78 °C. After 10 min, a solution of aldehyde **5** (29.0 mg, 148 μmol) in THF (2 mL) was added dropwise through a cannula. The reaction mixture was warmed to −20 °C. After 4 h, saturated aqueous NH_4Cl (2 mL) was added, and the reaction mixture was warmed to RT. The organic compounds were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (15% EtOAc/hexanes) provided **37** (7.2 mg, 41%), as a colorless oil. R_f=0.83 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+10.6 (c=0.36 in $CHCl_3$); IR (NaCl): $\tilde{\nu}$=2929, 2856, 2361, 2342, 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.98 (app. q, J=1.6 Hz, 1H; H_{35}), 5.40–5.35 (m, 2H; H_8, H_9), 4.99 (ddq, J=7.8, 6.8, 1.6 Hz, 1H; H_{36}), 4.00–3.89 (m, 2H; H_{16}, H_{19}), 3.89–3.82 (m, 2H; H_{20}, H_{23}), 3.65–3.59 (m, 1H; H_{15}), 3.29 (ddd, J=9.6, 5.6, 1.9 Hz, 1H; H_{24}), 3.26–3.18 (m, 1H; H_{28}), 2.26 (ddt, J=8.0, 7.5, 1.7 Hz, 2H; H_3), 2.02–1.93 (m, 4H; H_7, H_{10}), 1.93–1.77 (m, 5H; H_{17a}, H_{18a}, H_{21a}, H_{22a}, H_{26a}), 1.77–1.63 (m, 4H; H_{17b}, H_{18b}, H_{21b}, H_{22b}), 1.59–1.06 (m, 29H; H_4–H_6, H_{11}–H_{14}, H_{25}, H_{26b}, H_{27a}, H_{29}–H_{33}), 1.40 (d, J=6.8 Hz, 3H; H_{37}), 1.14 (app. qd, J=11.3, 4.0 Hz, 1H; H_{27b}), 0.91–0.84 (m, 12H; H_{34}, SiC(CH_3)$_3$), 0.06 (s, 3H; $SiCH_3$), 0.04 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.9, 148.9, 134.3, 130.6, 130.0, 82.3, 81.9, 81.8, 81.5, 80.1, 77.8, 77.4, 74.7, 36.5, 32.6, 32.4, 32.2, 31.9, 31.5, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 28.3, 27.9, 27.5, 27.3, 27.2, 27.0, 26.7, 26.0, 25.8, 25.6, 25.1, 23.5, 22.6, 19.2, 18.2, 14.1, −4.2, −4.6 ppm; HRMS (ES+): *m/z* calcd for $C_{43}H_{76}O_6SiNa$: 739.5307 $[M+Na]^+$; found: 739.5309.

Chamuvarinin (1): A solution of alkene **37** (3.4 mg, 4.74 μmol) and $TsNHNH_2$ (53 mg, 284 μmol) in DME (0.5 mL) was heated to reflux. NaOAc (39 mg, 284 μmol) in H_2O (0.5 mL) was added to the reaction solution over 3 h. The reaction mixture was cooled and diluted with H_2O (3 mL) and EtOAc (3 mL). The organic compounds were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with 3 N HCl (3×5 mL), $NaHCO_3$ (10 mL), and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was filtered through a silica plug (20% EtOAc/hexanes), concentrated, and redissolved in MeOH (1.0 mL). A 3 N solution of HCl (0.3 mL) was added to the resulting solution at 0 °C. After 45 min of warming to RT, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL). The organic compounds were extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (35% EtOAc/hexanes) provided chamuvarinin (**1**; 2.1 mg, 73%), as a colorless oil. R_f=0.17 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+9.9 (c=0.1 in $CHCl_3$); IR (NaCl): $\tilde{\nu}$=2926, 2855, 1721, 1438, 1171, 1120, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.98 (q, J=1.6 Hz, 1H; H_{35}), 4.99 (qq, J=6.8, 1.7 Hz, 1H; H_{36}), 3.93 (dt, J=7.9, 6.1 Hz, 1H; H_{19}), 3.88 (dt, J=6.5, 5.6 Hz, 1H; H_{23}), 3.85–3.79 (m, 2H; H_{16}, H_{20}), 3.40–3.33 (m, 1H; H_{15}), 3.28 (ddd, J=11.2, 5.6, 1.9 Hz, 1H; H_{24}), 3.26–3.19 (m, 1H; H_{28}), 2.53 (brs, 1H; OH), 2.28–2.23 (m, 2H; H_3), 2.02–1.89 (m, 2H; H_{17a}, H_{18a}), 1.87–1.78 (m, 3H; H_{21a}, H_{22a}, H_{26a}), 1.78–1.69 (m, 2H; H_{18b}, H_{22b}), 1.69–1.43 (m, 7H; H_4, H_{17b}, H_{21b}, H_{25a}, H_{26b}, H_{27a}), 1.42–1.34 (m, 4H; H_{14}, H_{29}), 1.40 (d, J=6.8 Hz, 3H; H_{37}), 1.33–1.20 (m, 27H; H_5–H_{13}, H_{25b}, H_{30}–H_{33}), 1.13 (qd, J=10.9, 4.1 Hz, 1H; H_{27b}), 0.87 ppm (t, J=7.1 Hz, 3H; H_{34}); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.9, 148.8, 134.3, 83.1, 82.06, 82.02, 81.5, 79.9, 77.9, 77.4, 74.4, 36.5, 33.5, 31.9, 31.4, 29.8, 29.7, 29.6 (2C), 29.5, 29.4 (2C), 29.3, 29.2, 28.8, 28.3, 28.0, 27.4, 26.9, 25.7, 25.5, 25.2, 23.5, 22.6, 19.2, 14.1 ppm; HRMS (ES+): m/z calcd for $C_{37}H_{64}O_6Na$: 627.4601 $[M+Na]^+$; found: 627.4606.

Compound 40: NaHMDS (470 μL, 0.2 M solution in THF, 94 μmol) was added to a solution of sulfone **39** (41.4 mg, 63 μmol) in THF (3 mL) at −78 °C. After 10 min, a solution of aldehyde **5** (48.9 mg, 250 μmol) in THF (2 mL) was added dropwise through a cannula. The reaction mixture was warmed to −20 °C. After 2.5 h, saturated aqueous NH_4Cl (2 mL) was added, and the reaction mixture was warmed to RT. The organic compounds were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (15% EtOAc/hexanes) provided **40** (33.5 mg, 85%), as a colorless oil. R_f=0.53 (15% acetone/hexanes); $[\alpha]_D^{20}$=+19.5 (c=0.81 in $CHCl_3$); IR (thin film): $\tilde{\nu}$=2928, 2857, 1761, 1653, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=6.98 (app. q, J=1.6 Hz, 1H; H_{35}), 5.45–5.32 (m, 2H; H_8, H_9), 5.03–4.95 (qq, J=6.7, 1.7 Hz, 1H; H_{36}), 4.03–3.89 (m, 2H; H_{16}, H_{19}), 3.66–3.49 (m, 3H; H_{15},H_{20}), 2.29–2.23 (ddt, J=8.6, 7.4, 1.6 Hz, 2H; H_3), 2.04–1.80 (m, 6H; H_7, H_{10}, H_{17a}, H_{18a}), 1.75–1.63 (m, 2H; H_{17b}, H_{18b}), 1.55–1.50 (m, 2H; H_4), 1.46–1.25 (m, 12H; H_5, H_6, H_{11}–H_{14}), 1.40 (d, J=6.8 Hz, 3H; H_{37}), 0.89–0.87 (m, 18H; 2×$SiC(CH_3)_3$), 0.06 (s, 3H; $SiCH_3$), 0.049 (s, 3H; $SiCH_3$), 0.048 (s, 3H; $SiCH_3$), 0.04 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.8, 148.8, 134.3, 130.6, 130.0, 82.0, 79.6, 77.2, 74.8, 66.0, 32.5, 32.4, 29.7, 29.6, 29.4, 29.2, 28.6, 28.5, 27.2, 26.0, 25.9, 25.8, 25.1, 19.2, 18.3, 18.2, −4.2, −4.6, −5.3 ppm; HRMS (ES+): m/z calcd for $C_{35}H_{70}O_5Si_2N$: 640.4787 $[M+NH_4]^+$; found: 640.4784.

Compound 41: (±)-CSA (6.80 mg, 0.03 mmol) was added to a solution of bis-*tert*-butyldimethylsilyl ether **40** (184 mg, 0.295 mmol) in MeOH/CH_2Cl_2 (1:4, 3 mL) at 0 °C. After 1.5 h, saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added. The organic compounds were extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (20% EtOAc/hexanes) provided alcohol **41** (94.5 mg, 63%), as a colorless oil. R_f=0.45 (35% EtOAc/hexanes); $[\alpha]_D^{20}$=+16.2 (c=0.87 in $CHCl_3$); IR (thin film): $\tilde{\nu}$=3480, 2928, 2855, 1755, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.97 (q, J=1.5 Hz, 1H; H_{35}), 5.42–5.29 (m, 2H; H_8, H_9), 4.98 (qq, J=6.8, 1.8 Hz, 1H; H_{36}), 4.09–4.02 (m, 1H; H_{19}), 3.91 (dt, J=7.9, 6.3 Hz, 1H; H_{16}), 3.64–3.61 (m, 1H; H_{20a}), 3.58–3.54 (m, 1H; H_{15}), 3.46 (dd, J=11.5, 6.0 Hz, 1H; H_{20b}), 2.25 (ddt, J=8.9, 7.3, 1.7 Hz, 2H; H_3), 2.02–1.86 (m, 6H; H_7, H_{10}, H_{17a}, H_{18a}), 1.73–1.61 (m, 2H; H_{17b}, H_{18b}), 1.59–1.50 (m, 2H; H_4), 1.45–1.27 (m, 12H; H_5, H_6, H_{11}–H_{14}), 1.39 (d, J=6.8 Hz, 3H; H_{37}), 0.88 (s, 9H; $SiC(CH_3)_3$), 0.06 (s, 3H; $SiCH_3$), 0.04 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8, 148.8, 134.2, 130.5, 130.0, 82.0, 79.4, 77.4, 75.0, 64.9, 32.9, 32.5, 32.4, 29.5, 29.3, 29.2, 28.6, 27.8, 27.7, 27.2, 25.9, 25.5, 25.1, 19.2, 18.2, −4.2, −4.6 ppm; HRMS (ES+): m/z calcd for $C_{29}H_{56}O_5SiN$: 526.3922 $[M+NH_4]^+$; found: 526.3920.

Compound 38: $NaHCO_3$ (120 mg, 1.40 mmol) followed by Dess–Martin periodinane (360 mg, 0.84 mmol) were added to a solution of alcohol **41** (140 mg, 0.28 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, followed by warming to RT over an additional 1 h. The reaction mixture was re-cooled to 0 °C prior to the addition of cold hexane (5 mL) and cold toluene (5 mL). The resultant white suspension was concentrated in vacuo to remove CH_2Cl_2 and purification by flash column chromatography (15% EtOAc/hexanes) provided aldehyde **38** (98.6 mg, 69%), as a colorless oil. R_f=0.55 (30% EtOAc/hexanes); $[\alpha]_D^{20}$=+30.7 (c=1.08 in $CHCl_3$); IR (thin film): $\tilde{\nu}$=2928, 2855, 1755, 1736, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=9.64 (d, J=2.0 Hz, 1H; H_{20}), 6.98 (app. q, J=1.5 Hz, 1H; H_{35}), 5.43–5.30 (m, 2H; H_8, H_9), 4.98 (qq, J=6.8, 1.8 Hz, 1H; H_{36}), 4.28 (ddd, J=7.7, 6.9, 2.0 Hz, 1H; H_{19}), 4.07–4.00 (m, 1H; H_{16}), 3.61 (app. q, J=5.0 Hz, 1H; H_{15}), 2.25 (ddt, J=8.9, 7.5, 1.6 Hz, 2H; H_3), 2.20–2.11 (m, 1H; H_{18a}), 2.01–1.84 (m, 6H; H_7, H_{10}, H_{17a}, H_{18b}), 1.81–1.69 (m, 1H; H_{17b}), 1.59–1.46 (m, 3H; H_4, H_{14a}), 1.44–1.22 (m, 11H; H_5, H_6, H_{11}–H_{13}, H_{14b}), 1.39 (d, J=6.8 Hz, 3H; H_{37}), 0.87 (s, 9H; $SiC(CH_3)_3$), 0.06 (s, 3H; $SiCH_3$), 0.05 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz ,$CDCl_3$): δ=203.0, 173.8, 148.8, 134.2, 130.4, 130.0, 83.3, 83.0, 77.4, 74.5, 33.1, 32.5, 32.4, 29.5, 29.3, 29.2, 28.6, 27.5, 27.2, 26.9, 25.9, 25.4, 25.1, 19.2, 18.2, −4.3, −4.5 ppm; HRMS (ES+): m/z calcd for $C_{29}H_{54}O_5SiN$: 524.3766 $[M+NH_4]^+$; found: 524.3755.

Compound 42:

Method A: *n*BuLi (430 μL, 0.68 mmol, 1.6 M in hexane) was added to a solution of alkyne **8** (330 mg, 0.97 mmol) in THF (2 mL) at −78 °C. After 10 min, a solution of aldehyde **38** (98.6 mg, 0.19 mmol) in THF (1 mL) was added through a cannula. After 1.5 h, saturated aqueous NH_4Cl (5 mL) and EtOAc (5 mL) were added. The organic compounds were extracted with EtOAc (3×5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/hexanes) provided alkyne **42** as a 75:25 mixture of C20 diastereoisomers (92.7 mg, 56%), as a colorless oil.

Method B: *n*BuLi (160 μL, 0.25 mmol, 1.6 M in hexane) was added to a solution of alkyne **8** (100 mg, 0.29 mmol) in MTBE (1 mL) at 0 °C. The temperature was then lowered to −100 °C and after 10 min a solution of aldehyde **38** (30.2 mg, 59 μmol) in MTBE (1 mL) was added through a cannula. After 4 h, saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL) were added. The organic compounds were extracted with CH_2Cl_2 (3×5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (5–10% EtOAc/hexanes) provided alkyne **42** (14.6 mg, 29%), as a colorless oil (> 95:5 d.r.). R_f=0.53 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+19.4 (c=0.84 in $CHCl_3$); IR (thin film): $\tilde{\nu}$=3486, 2928, 2855, 1759, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=6.98 (app. q, J=1.5 Hz, 1H; H_{35}), 5.45–5.30 (m, 2H; H_8, H_9), 4.99 (qq, J=6.7, 1.6 Hz, 1H; H_{36}), 4.48–4.43 (m, 1H; H_{20}), 4.33–4.28 (m, 1H; H_{23}), 4.15–4.08 (m, 1H; H_{19}), 4.06–3.99 (m, 1H; H_{16}), 3.58–3.51 (m, 1H; H_{15}), 3.30 (ddd, J=11.1, 6.1, 1.8 Hz, 1H; H_{24}), 3.25–3.21 (m, 1H; H_{28}), 2.27 (ddt, J=8.9, 7.6, 1.6 Hz, 2H; H_3), 2.02–1.67 (m, 8H; H_7, H_{10}, H_{17}, H_{18a}, H_{25a}), 1.58–1.49 (m, 3H; H_4, H_{27a}), 1.46–1.24 (m, 25H; H_5, H_6, H_{11}–H_{14}, H_{18b}, H_{26}, H_{29}–H_{33}), 1.40 (d, J=6.8 Hz, 3H; H_{37}), 1.21–1.11 (m, 2H; H_{25b}, H_{27b}), 0.91–0.85 (m, 21H; H_{34}, 2×$SiC(CH_3)_3$), 0.12 (s, 3H; $SiCH_3$), 0.10 (s, 3H; $SiCH_3$), 0.06 (s, 3H; $SiCH_3$), 0.05 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.7, 148.8, 134.2, 130.4, 130.0, 85.1, 83.2, 83.0, 81.4, 80.6 77.7, 77.3, 75.1, 66.8, 64.5, 36.4, 33.0, 32.5, 32.3, 31.8, 31.3, 29.5, 29.4, 29.2, 28.6, 27.8, 27.2, 26.8, 26.6, 25.9, 25.7, 25.4, 25.3, 25.1, 23.2, 22.6, 19.1, 18.23, 18.18, 14.0, −4.2, −4.6, −4.7, −4.9 ppm; HRMS (ES+): m/z calcd for $C_{49}H_{92}O_7Si_2N$: 862.6407 $[M+NH_4]^+$; found: 862.6405.

Compound 43: A solution of alkyne **42** (14.6 mg, 17 μmol) and $TsNHNH_2$ (193 mg, 1.04 mmol) in DME (1 mL) was heated to reflux. NaOAc (141 mg, 1.04 mmol) in H_2O (1 mL) was added to the reaction

solution over 3 h. The reaction mixture was cooled and diluted with H_2O (3 mL) and EtOAc (5 mL). The organic compounds were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with 3N HCl (3×5 mL), $NaHCO_3$ (10 mL), and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (5–10% EtOAc/hexanes) provided alkane **43** (13.3 mg, 90%), as a colorless oil. R_f=0.57 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+7.8 (c=0.98 in $CHCl_3$); IR (thin film): $\tilde{\nu}$=3495, 2928, 2855, 1759, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.99 (app. q, J=1.5 Hz, 1H; H_{35}), 4.99 (qq, J=6.8, 1.6 Hz, 1H; H_{36}), 3.91 (dt, J=8.2, 6.3 Hz, 1H; H_{16}), 3.84 (td, J=7.1, 3.5 Hz, 1H; H_{19}), 3.75–3.71 (m, 1H; H_{20}), 3.64 (app. q, J=5.5 Hz, 1H; H_{23}), 3.55–3.51 (m, 1H; H_{15}), 3.28–3.20 (m, 2H; H_{24}, H_{28}), 2.27 (ddt, J=8.9, 7.2, 1.7 Hz, 2H; H_3), 1.95–1.78 (m, 4H; H_{17a}, H_{18}, H_{26a}), 1.69–1.51 (m, 7H; H_4, H_{17b}, H_{22}, H_{25a}, H_{27a}), 1.49–1.21 (m, 33H; H_5–H_{14}, H_{21}, H_{26b}, H_{29}–H_{33}), 1.40 (d, J=6.8 Hz, 3H; H_{37}), 1.19–1.07 (m, 2H; H_{25b}, H_{27b}), 0.89–0.88 (m, 21H; H_{34}, 2×$SiC(CH_3)_3$), 0.07–0.05 ppm (m, 12H; 2×$SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.9, 148.8, 134.3, 82.5, 82.2, 80.8, 78.0, 77.4, 75.4, 74.5, 72.0, 36.4, 33.0, 31.8, 31.4, 29.8, 29.6, 29.52, 29.46, 29.3, 29.2, 28.8, 28.5, 28.0, 27.4, 26.00, 25.96, 25.7, 25.6, 25.4, 25.3, 25.2, 23.6, 22.6, 19.2, 18.3, 18.2, 14.1, −4.1, −4.2, −4.57, −4.59 ppm; HRMS (ES+): m/z calcd for $C_{49}H_{94}O_7Si_2Na$: 873.6436 $[M+Na]^+$; found: 873.6443.

Compound 1: Et_3N (11.0 μL, 78 μmol) and MsCl (4.30 μL, 56 μmol) were added to a solution of alcohol **43** (9.50 mg, 11.0 μmol) in CH_2Cl_2 (1 mL) at 0°C. After 1.5 h, saturated aqueous NH_4Cl (2 mL) and CH_2Cl_2 (5 mL) were added. The organic compounds were extracted with CH_2Cl_2 (3× 5 mL) and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude mesylate was dissolved in CH_2Cl_2/MeOH (1:4, 2.5 mL), cooled to 0°C, and 3N HCl (0.3 mL) was added. After 2 h of warming to RT, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The organic compounds were extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude diol was dissolved in pyridine (1 mL) and heated to 65°C. After 16 h, H_2O (2 mL) was added and the organic compounds were extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded chamuvarinin **1** (3.8 mg, 57% over 3 steps), as a colorless oil. Spectroscopic data were in full agreement with those of the synthetic material prepared from compound **37**.

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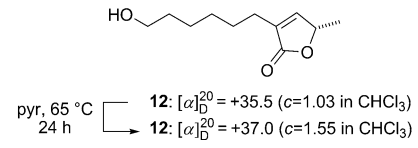

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