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Total Synthesis of Belizentrin Methyl Ester: Report on a Likely Conquest

Felix Anderl,[+] Sylvester Größl,[+] Conny Wirtz, and Alois Fürstner*

Dedicated to Prof. Tohru Fukuyama on the occasion of his 70th birthday

***Abstract**: The assigned structure of the dinoflagellate-derived toxin belizentrin was prepared by total synthesis in form of the corresponding methyl ester for stability reasons. The successful route features an unusual solution for the preparation of a recalcitrant ylid on a C-glycosidic segment; moreover, it involves an asymmetric hetero-Diels/Alder reaction en route to the tertiary hemiacetal substructure, a Negishi cross coupling of two elaborate building blocks, and a macrocyclization based on an intramolecular aminolysis of a spirolactone. A modified Kocienski olefination ultimately allowed the polyol side chain to be attached to the macrocycle, although this transformation faced the exceptional base-sensitivity of this polyunsaturated target compound.*

Many marine dinoflagellates possess disproportionately large genomes that encode for impressive biosynthetic capabilities of these morphologically rather simple organisms.[1] A host of structurally diverse secondary metabolites of utmost complexity was isolated from various members of this taxon, including some of the most potent non-peptidic poisons known to date. Emblematic examples are the alkaloid saxitoxin,[2] an intriguing class of ladder polyethers (maitotoxin, ciguatoxin, brevetoxin etc.),[3] as well as numerous macrolides of polyketide origin, for which the amphidinolide family is deemed representative.[4,5] Because of their intriguing molecular architectures, structural diversity, biological significance and paucity, dinoflagellate-derived natural products served as inspiring yet highly demanding targets for synthesis, and rightfully continue to do so to the present day.

Belizentrin (**1**) is a particularly notable recent addendum to the list.[6] This compound was obtained in low isolation yield (3.1 mg) from a large-scale culture (1000 L) of the benthic dinoflagellate *Prorocentrum belizeanum*.[7] Although the small available quantity and low stability made a detailed

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Supporting Information ##

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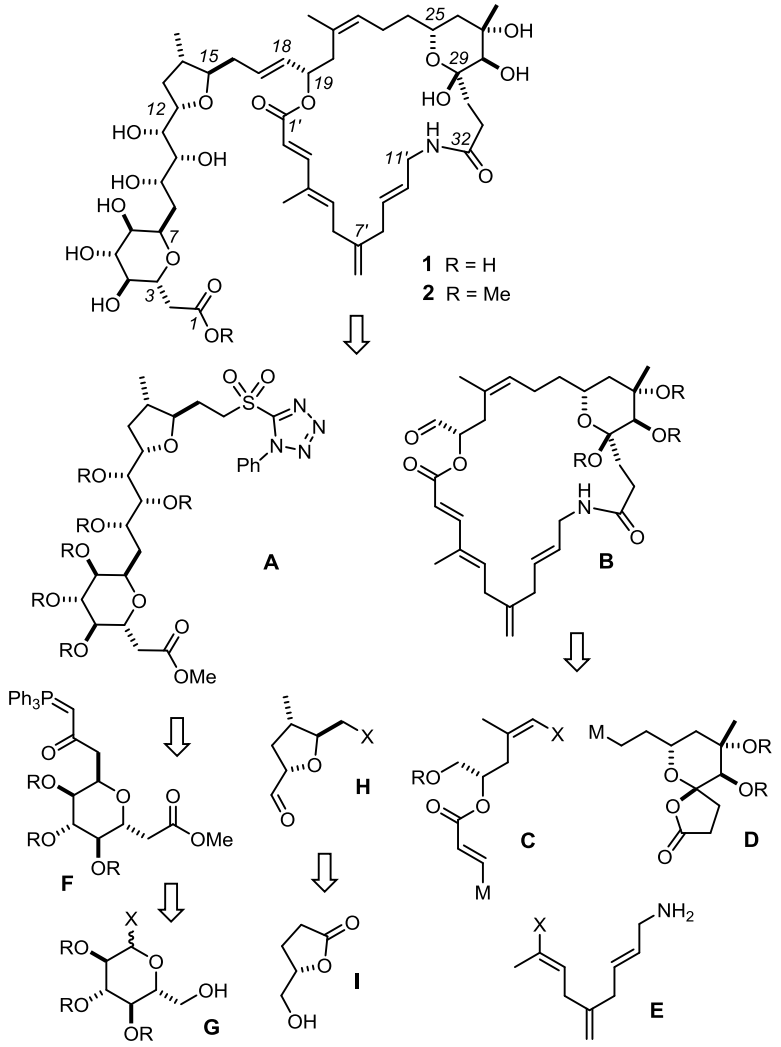
biological assessment impossible, **1** was shown to disrupt the neuronal network of cerebellar cell cultures *in vitro*. Despite a slow onset of action, serious neurite damage was observed at 100 nM and complete degeneration of neuronal somas was induced at 300 nM.[6] Since the compound partly degraded during the course of the bioassay, these data points can only be taken as rough estimates and the inherent activity of **1** might actually be (significantly) higher.



Scheme 1. Structure of belizentrin (**1**) and retrosynthetic analysis of belizentrin methyl ester (**2**)

The inherent instability also rendered the structure elucidation of belizentrin (**1**) challenging as some desirable NMR data simply could not be acquired. Based on a masterful interplay of spectroscopic analysis, detailed computational studies and careful comparison with literature data, the isolation team proposed the constitution and stereostructure shown in Scheme 1.[6] It was prudently pointed

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out, however, that only the relative configuration within the macrocycle and the sidechain were assigned, whereas the relationship between these domains was arbitrarily assigned.

In any case, belizentrin (**1**) is rather unique in structural terms: it features an odd-numbered 25-membered ring – which in itself is a remarkable structural attribute – that contains an ester as well as an amide linkage and as such seems to be the first example of a dinoflagellate-derived macrolactam. The tetraene subunit in the southern sector is partly skipped, comprises an exocyclic methylene group, and is certainly labile since isomerization of the two remote olefins into conjugation with the ester would entail a considerable enthalpic gain; at the same time, the scattered array of double bonds rigidifies the macrocyclic frame. No less than 16 chiral centers decorate the carbon backbone of **1**, 11 of which reside in the side chain that is highly hydrophilic by virtue of the carboxylic acid terminus, six secondary hydroxy groups and two ether rings. Interestingly, four of the five remaining chiral centers are clustered together to form the unusual tertiary hemiacetal entity embedded into the macrocyclic perimeter. These attributes render belizentrin (**1**) "first in class" in that it stands for an unprecedented type of dinoflagellate-derived secondary metabolites.[6]

Apprehensive of the fact that the limited stability of **1** further augments the synthetic challenges, we deliberately targeted the methyl ester **2** in the hope to improve the lifetime of the compound while not interfering with its biological activity;[8] it is reasonable to believe that hydrolytic enzymes might release the parent compound in a given biological matrix under assay conditions. For the uncertainty concerning the stereochemical correlation between tail and macrocycle, the C17-C18 double bond constituted the obvious assembly site, which mandates an *E*-selective olefination that is compatible with the numerous functionalities in either building block. The Kocienski variant of the Julia reaction was deemed appropriate,[9,10] not least because previous work from this laboratory had shown that a tetrazolyl sulfone carrying a C-H acidic ester group can be successfully engaged in olefination;[11] since the metalated sulfone had not entailed any epimerization of an α-alkoxylated aldehyde either,[11,12] this precedent boded well for the projected coupling of segment **A** with the α-acylated partner **B**, which are of similar complexity yet largely different chemical character.

Various options for macrocyclization were considered, of which macrolactamization was given priority over macrolactonization. Critical for this judgement was our previous experience with a

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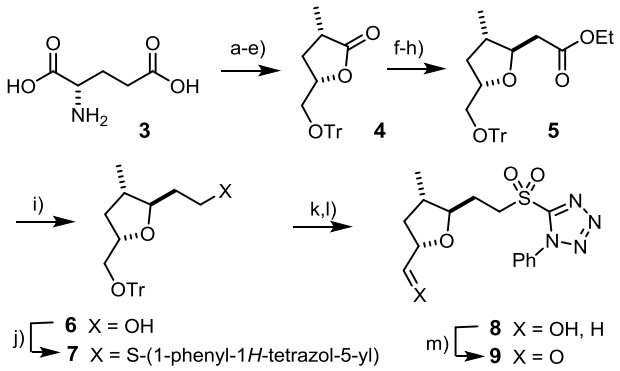
skipped polyunsaturated *seco*-acid, which had been irreparably damaged upon activation as a mixed anhydride.[13] Moreover, it appeared to us that the amide linkage invites an intramolecular aminolysis of a lactone precursor, which is a rather rare tactic for macrocyclization.[14] The required precursor could be assembled via cross coupling from building blocks **C**, **D** and **E** by a convergent route that should allow the number of steps to be minimized where the arguably sensitive polyene motif needs to survive. Symmetry considerations let us trace the tetrahydropyran entity embedded into the polyhydroxylated tail **A** back to D-glucose, whereas the 2,5-*trans*-disubstituted tetrahydrofuran ring **H** seemed accessible from **I** by adaptation of a sequence that had previously served our work in the amphidinolide series well.[15] We were confident that the all-*syn* triol unit connecting the two ether rings could be formed by stereoselective olefination of fragments **F** and **H** followed by a catalyst-controlled dihydroxylation event.



Scheme 2. a) $NaNO_2$, HCl, H_2O, 0 °C → RT, 79%; b) $BH_3{\cdot}SMe_2$, THF, 0 °C → RT, 69%; c) TrCl, pyridine, 73%; d) LDA, MeI, THF, −78 °C → −30 °C, 99%; e) LDA, −78 °C, then H_2O, 96%; f) Dibal-H, CH_2Cl_2, −78 °C, 98%; g) Ph_3P=CHCOOEt, toluene, 80 °C, 69%; h) TBAF·$3H_2O$, THF, 0 °C, 82%; i) $LiAlH_4$, THF, −20 °C → RT, quant.; j) 1-phenyl-1*H*-tetrazolyl-5-thiol, DIAD, PPh_3, THF, 0 °C → RT, 87%; k) $(NH_4)_6Mo_7O_{24}{\cdot}4$ H_2O, aq. H_2O_2, EtOH, 71%; l) TFA, CH_2Cl_2, 0 °C, 98%; m) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, −78 °C → RT, 94%; DIAD = di-isopropyl azodicarboxylate; DIPEA = di-isopropylethylamine; LDA = lithium di-isopropylamide; TBAF = tetra-*n*-butylammonium fluoride; TFA = trifluoroacetic acid; Tr = trityl

In the forward sense, compound **5** was prepared on scale from L-glutamic acid (**3**) by following the route previously described for the enantiomer (Scheme 2).[15] The key step was a fluoride-promoted oxa-Michael reaction, which furnished the 2,5-*trans*-disubstituted tetrahydrofuran ring **5** as the only

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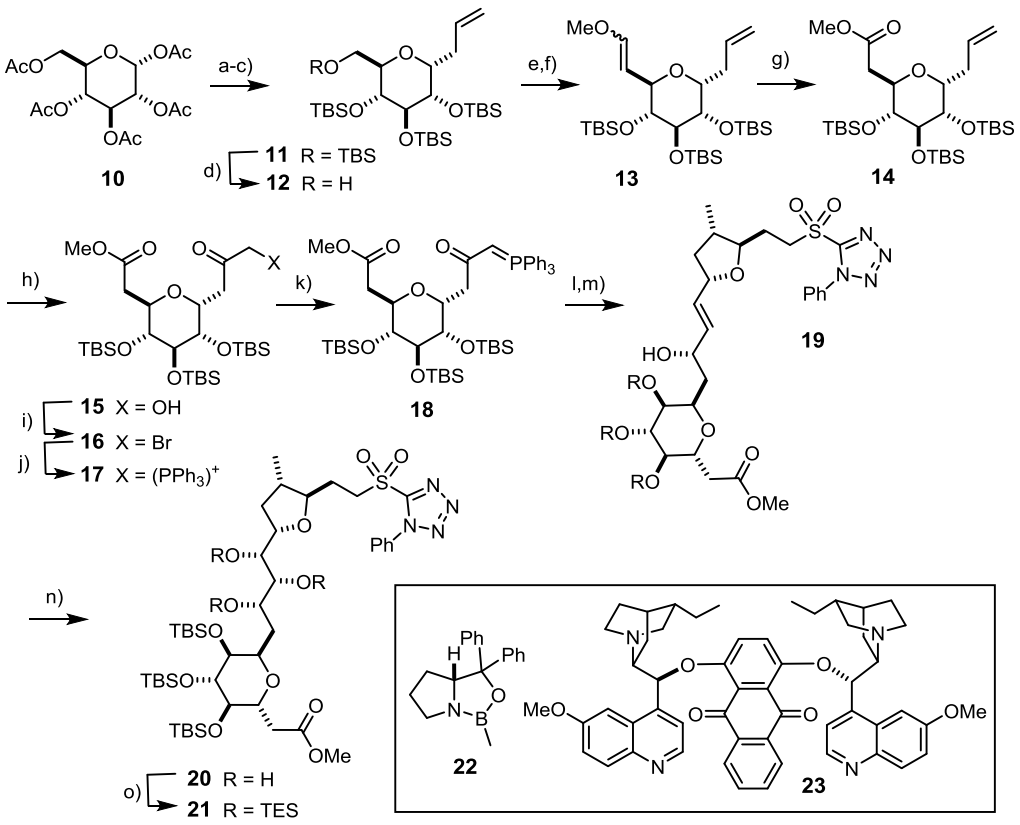
isomer. Elaboration of the ester terminus to the required tetrazolylsulfone was uneventful, as was the conversion of the trityl ether into the labile aldehyde **9**, which had to be used without delay.



Scheme 3. a) allyl(trimethyl)silane, $BF_3{\cdot}OEt_2$, MeCN, RT → 80 °C, 79% (α:β = 7:1); b) NaOEt, MeOH, 98%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 96%; d) HF·pyridine, THF/pyridine, 0 °C → RT, 97% (dr = 8:1); e) ($COCl_2$), DMSO, DIPEA, CH_2Cl_2, −78 °C → RT, 90%; f) [$MeOCH_2PPh_3$]Cl, KOtBu, THF, MS 5Å, −50 °C, then −78 °C → RT, 88%; g) PCC, CH_2Cl_2, 79% (dr = 3:1); h) $KMnO_4$, HOAc, aq. acetone, 77%; i) CBr_4, PPh_3, CH_2Cl_2, 81%; j) PPh_3, benzene, −20 °C, quant.; k) DIPEA, benzene; l) **9**, benzene, 79% (over both steps, *E:Z* = 18:1); m) **22**, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −20 °C, 91% (dr > 30:1); n) K_2OsO_4 (20 mol%), **23** (25 mol%), $MeSO_2NH_2$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*BuOH/H_2O, 59% (dr = 4:1); o) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 82%; MS = molecular sieves; PCC = pyridinium chlorochromate; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Tf = trifluoromethylsulfonyl

The required partner was derived from glucopyranose **10**, which was transformed in three known operations into C-glycoside **11** (Scheme 3).[16] Selective desilylation of the primary –OTBS ether with HF/pyridine furnished alcohol **12**, which held various options for C1-homologation to the required methyl ester **14**. In practical terms, a sequence comprised of Swern oxidation followed by Wittig

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olefination with [MeOCH=PPh_3] and treatment of the resulting enol ether **13** with PCC[17] proved most robust on scale. The subsequent oxidation of the terminal alkene to the corresponding hydroxy ketone **15** with $KMnO_4$ in aqueous acetone/HOAc worked well without noticeable C–C bond cleavage or deprotection of the silyl ethers.[18]

In sharp contrast, the seemingly trivial conversion of **15** into the stabilized ylid **18** was unexpectedly difficult. Because α-bromo ketone **16** is prone to debromination, many attempts at converting this compound into the corresponding phosphonium salt **17** resulted in (partial) degradation. Recourse to a somewhat counterintuitive method allowed this serious problem to be overcome: reminiscent of early studies, which had shown that the N-alkylation of Et_3N is particularly effective in *frozen* benzene,[19] we were hoping that the P-alkylation of PPh_3 with **16** would benefit from the same effect. The observed rate acceleration had been ascribed to phase segregation close to the eutectic temperature, which entails high concentration of any solute reagent in the few remaining liquid regions within an otherwise solid solvent matrix.[19] Indeed, **17** was reliably formed in essentially quantitative yield in benzene glass, simply by storing the reaction mixture at –20 °C.

The fact that the carbonyl group of **17** is notably enolized (NMR) explains why Hünig base sufficed to release ylid **18**, which reacted with aldehyde **9** to give the corresponding enone (*E/Z* = 18:1). For the elaboration of the major *E*-isomer, it proved advantageous to first subject the ketone to CBS-reduction,[20] followed by Sharpless dihydroxylation of the resulting allylic alcohol **19** using $(DHQD)_2AQN$ (**23**) as the ligand.[21] This sequence furnished triol **20** in appreciable yield and selectivity. Its configuration was unambiguously assigned by comparison with the other conceivable diastereomers (prepared by two independent routes), the formation of cyclic derivatives for NMR inspection, as well as on Mosher ester analyses; details will be reported in a future full paper. Final TES-protection gave building block **21** representing the tail region of belizentrin methyl ester (**2**).

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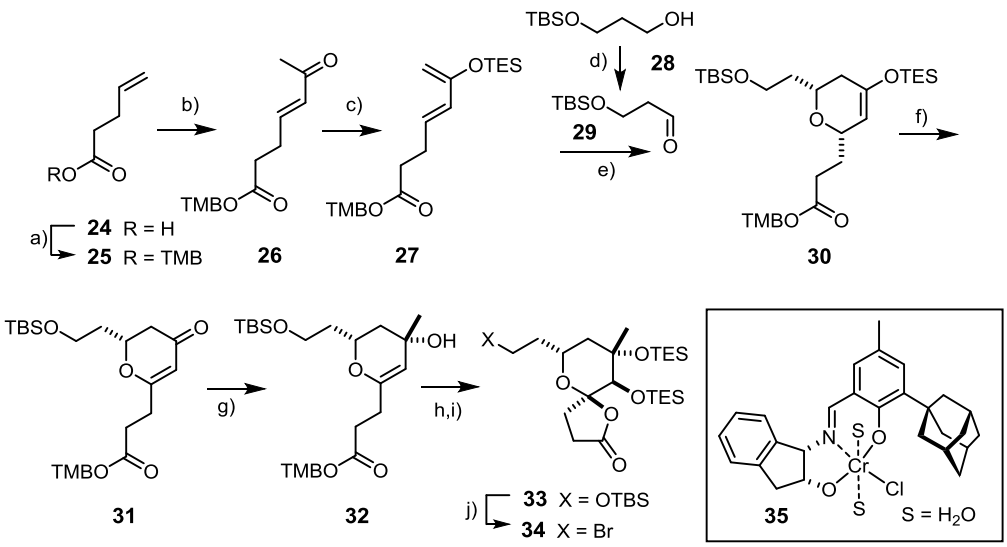

Scheme 4. a) $(COCl)_2$, then TMBOH, DMAP, K_2CO_3, CH_2Cl_2, 91%; b) 3-buten-2-one**,** HG^{II} (0.1 mol%), CH_2Cl_2, reflux, 96%; c) TESOTf, Et_3N, Et_2O, 0 °C, 89%; d) O_2, $[Cu(MeCN)_4]BF_4$ (4.5 mol%), TEMPO (4.5 mol%), 2,2'-bipyridine (4.5 mol%), *N*-methylimidazole (9 mol%), MeCN, quant.; e) **35** (9 mol%), MS 4Å, 76% (95% ee); f) O_2, $Pd(OAc)_2$ (10 mol%), DMSO, 78%; g) MeMgCl, THF, –65°C, 77%; h) AD-mix-β, *t*BuOH/H_2O, 81%; i) TESCl, $AgNO_3$, DMAP, DMF, pyridine, 76%; j) Ph_3PBr_2, CH_2Cl_2, 0 °C, 89%; DMAP = 4-dimethylaminopyridine; TEMPO = 2,2,6,6-tetramethylpiperidinyloxy; TMB = 3,4,5-trimethoxybenzyl

4-Pentenoic acid (**24**) served as point of departure for the preparation of the macrocyclic sector (Scheme 4), which was elaborated into diene **27** by esterification, cross metathesis and enolsilane formation. Compound **27** was subjected to an asymmetric hetero-Diels/Alder reaction with aldehyde **29** catalyzed by the chromium complex **35**,[22,23] which furnished adduct **30** with 95% ee on a multigram scale. A modified Saegusa oxidation then gave enone **31**,[24] which reacted with MeMgCl to provide the tertiary alcohol **32** as a single diastereomer;[25] low temperature was necessary to avoid competing attack of the Grignard reagent onto the ester group. The subsequent asymmetric dihydroxylation under standard conditions[21] was accompanied by spontaneous closure of the butyrolactone ring, which we were hoping would later prove sufficiently electrophilic as to allow for the formation of the macrocyclic ring by intramolecular aminolysis. Protection of the two remaining hydroxy groups mandated in situ activation of TESCl with $AgNO_3$.[26] Treatment of the resulting product **33** with Ph_3PBr_2 engaged only the primary silyl ether into functional group interchange to furnish bromide **34** as an adequate pre-nucleophile for fragment coupling.

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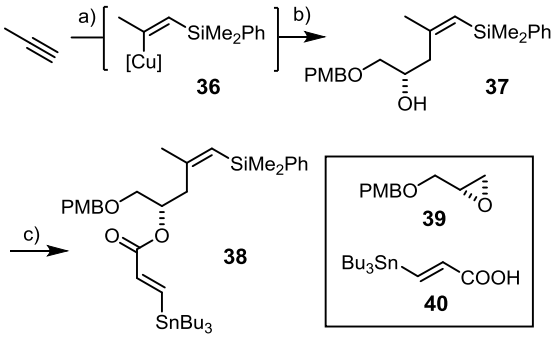

Scheme 5. a) $PhMe_2SiLi$, CuCN, THF, −78 °C; b) **39**, $BF_3{\cdot}OEt_2$, 51%; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **40**, DMAP cat., 0 °C → RT, 63%; PMB = *p*-methoxybenzyl

The second required building block was obtained by silylcupration of propyne,[27] which formed an organocopper reagent of the formal composition **36** that was quenched with **39** in the presence of $BF_3{\cdot}OEt_2$ to give alcohol **37** (Scheme 5). Although the yield was only 51%, the reaction was nicely scalable; therefore this one-step operation was preferred over alternative routes to this compound. Esterification of **37** with the stannylated acrylic acid **40**[28] under Yamaguchi conditions[29] gave product **38** endowed with two orthogonal metalloid sites.

The third segment was secured by regioselective silylmetalation of 2-butyn-1-ol (**41**) (Scheme 6).[30] Conversion of the –OH group of **42** into the corresponding allylic bromide **43** followed by an alkylation/Knoevenagel reaction cascade[31] furnished multigram amounts of **44**, which was transformed into the allylic acetate **45** by standard means. This compound was amenable to an allyl-Suzuki reaction with the boronate derivative **49**,[32] obtained by hydroboration of N-Boc propargyl amine with pinacol borane (see the SI). Since the −NBoc group later proved inadequate for the projected end game, it was transformed at this point into the highly practical –NTsoc group[33] on treatment of **46** with TIPSOTf/2,6-lutidine in CH_2Cl_2.[34] Final iodo-desilylation[35] gave alkenyl iodide **47** as adequate surrogate of the skipped triene motif of belizentrin (**1**).

With all required fragments in hand, the stage was set for the assembly of the macrocycle and the completion of the total synthesis (Scheme 7). To this end, **38** and **47** were engaged in a Stille coupling which was pleasingly productive even though the alkenylstannane **38** is rendered electron-poor by conjugation with the ester group.[36] The polyunsaturated nature of the resulting product **50**

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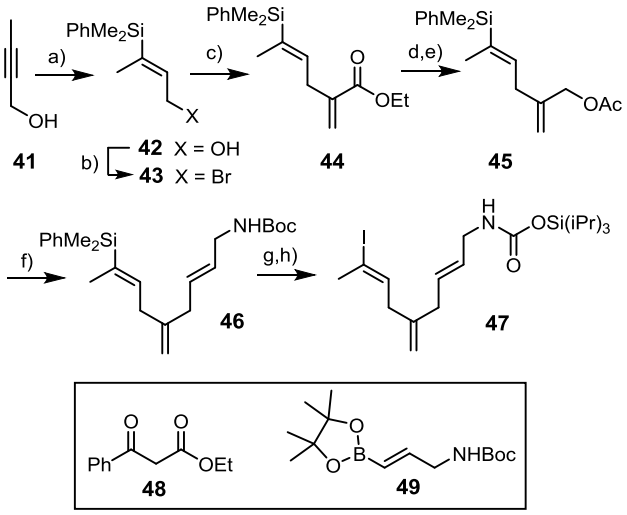
notwithstanding, the alkenyl silane could be selectively iodinated with $[Py_2I]BF_4$, even though partial isomerization of the resulting alkenyl iodide was observed. Compound **51** was then coupled with the highly functionalized organozinc derivative **52** prepared by insertion of Rieke-Zn into bromide **34**.[37] Best results were obtained with a catalyst generated from $[(dppf)PdCl_2]$ and Ph_3As by reduction with Mn metal in DMF prior to use; this procedure is subject to further study in our laboratory. In any case, the advanced Negishi reaction between the two elaborate partners was clean and productive,[38] furnishing product **53** in readiness for the projected macrocyclization.



Scheme 6. a) $PhMe_2SiLi$, $AlEt_3$, CuCN (4 mol%), THF/hexane, 90%; b) CBr_4, PPh_3, CH_2Cl_2, 96%; c) (i) **48**, DBU, toluene; (ii) $(CH_2O)_n$, K_2CO_3, THF, reflux, 77%; d) Dibal-H, CH_2Cl_2; e) Ac_2O, DMAP, Et_3N, 94% (over both steps); f) **49**, $[(tris\text{-}2\text{-}furylphosphine)_2PdCl_2]$ (2.7 mol%), KF, MeOH, 90%; g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 89%; h) NIS, 2,6-lutidine, 1,1,1,3,3,3-hexafluoroisopropanol, 0 °C, 63%; DBU = 1,8-diaza-bicyclo[5.4.0]undec-7-ene; NIS = *N*-iodosuccinimide; TIPS = tri-isopropylsilyl

It was at this stage that the –NTsoc group proved critically important because it could be selectively removed with excess HF·pyridine without affecting the residual TES-ethers. In contrast, TBAF rapidly decomposed the compound, probably causing instant isomerization of the *exo*-methylene group into conjugation. This observation bore strategic relevance as it implied that basic conditions must be avoided from this point onwards. Moreover, it was noticed that attempted isolation of the released free amine **54** resulted in substantial material loss, which we ascribed to partial oligomerization upon concentration of the mixture. While this finding made a rigorous purification of the macrocyclization

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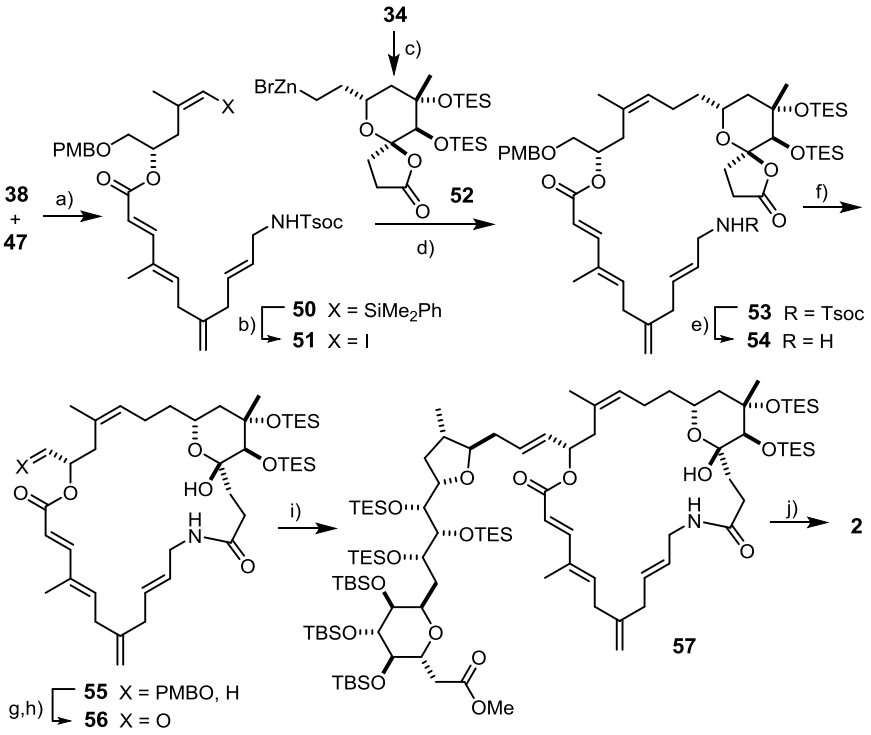
precursor impossible, it augured well for the projected aminolysis. Indeed, heating of the crude amine **54** in dilute toluene solution sufficed to form the desired macrolactam **55**; it proved beneficial to supplement the mixture with excess 2-pyridone which is thought to act as a proton shuttle that accelerates the likely rate-determining breakdown of the tetrahedral intermediate formed upon attack of the amine onto the lactone carbonyl group.[14,39] Somewhat surprisingly though, the reaction invariably stalled at about 60% conversion: it was a control experiment, in which pure **55** was re-subjected to the reaction conditions, which proved that this composition represents the equilibrium mixture: amide formation is obviously reversible by virtue of the favorable disposition of the –OH group in **55** which facilitates re-formation of the spiro-lactone ring.[40]



Scheme 7. a) [$(Ph_3As)_4Pd$] (6 mol%), DMF, 82%; b) $[Py_2I]BF_4$, MeCN, −20 °C, MeCN, 62% (*Z*:*E* = 3:1); c) Rieke-Zn, DMF; d) [(dppf)$PdCl_2$] (20 mol%), Ph_3As, Mn, DMF, then **52**, 70%; e) HF·pyridine, THF, 0°C; f) 2-pyridone, toluene (0.001 M), 90 °C, 45-52% (at ca. 60% conversion, see Text); g) $[Ph_3C]BF_4$, CH_2Cl_2, 0 °C, 44-52%; h) SO_3·pyridine, DMSO, DIPEA, CH_2Cl_2, −20 °C, quant.; i) **21**, lithium hexamethyldisilazide, $ZnCl_2$, then **56**, DMF/DMPU, −40 °C → RT, 25-30%; j) aq. HF, MeCN, then Me_3SiOH, 36%

With a reliable entry into the macrocyclic fragment **55** secured, we tackled the attachment of the side chain which proved highly demanding. Cleavage of the terminal PMB-ether failed under a variety

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of conditions and could only be achieved with trityl tetrafluoroborate.[41] Considerably more difficult, however, was the actual fragment coupling itself: since all attempts at protecting the sterically hindered tertiary anomeric –OH group were to no avail (at the stage of **55** or before), the Kocienski olefination had to be performed with the α-acylated aldehyde carrying a free -OH group, which, on top, is prone to hemiacetal or hydrate formation.[42] By far most troublesome, however, was the exceptional sensitivity of this polyunsaturated compound towards even moderately basic conditions, which had been foreshadowed during the cleavage of the –NTsoc group: whereas the presence of the ester in **21** did not interfere with the selective deprotonation of the sulfone group, as expected based on prior art,[11] aldehyde **56** got instantly destroyed when exposed to the resulting metalated species; variation of the base, the solvent and/or the temperature remained unsuccessful.[10]

Inspired by a report that the outcome of a Kocienski olefination with an enolizable ketone was much improved upon transmetalation of the lithiated sulfone with $CeCl_3$,[43] we tried to temper the basicity of the nucleophile derived from **21** in an analogous fashion; these conditions did indeed provide a tiny first crop of **57** (≈ 8%). A similar result (≈ 10%) was obtained with TMSCl as the additive, which had previously been recommended for the olefination of a base-sensitive aldehyde.[44] After much experimentation, it was found that $ZnCl_2$ in combination with LiHMDS in DMF/DMPU as the solvent[45] was somewhat more effective, furnishing *E*-**57** as the only detectable isomer in well reproducible 25-30% yield. Although certainly modest, this outcome must be assessed against the chemical challenge that it does address. Global deprotection of all eight silyl ethers in the resulting product **57** mandated the use of aqueous HF in MeCN,[46,47] whereas other commonly used reagents destroyed the valuable compound; to account for the sensitivity and polarity of the resulting product **2**, the work-up procedure was modified by quenching the reaction with Me_3SiOH so as to produce only volatile byproducts (Me_3SiF, H_2O) that could be largely removed in high vacuum.

The recorded ^{13}C NMR spectra of belizentrin methyl ester (**2**) seem to show a systematic drift (≈ –0.4 ppm) relative to the literature data of parent belizentrin (**1**);[6] whether this is due to the fact that the data of the natural product could only be extracted from 2D spectra for the lack of material and are hence likely less accurate, or whether the difference is caused e. g. by different calibration cannot be decided. Upon correction for this apparently systematic difference, almost all positions show a reasonable to excellent match (except for C7, C9, C23), especially if one considers that the natural

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product is a carboxylic acid whereas our synthetic samples are methyl esters. Likewise, the ^{1}H NMR data – including the entire pattern of NOE/ROESY correlations – are in good accord with the reported spectra (for details, see the SI). Therefore we tend to believe that structure **1** describes the correct constitution and relative stereochemistry of belizentrin;[48] it is emphasized, however, that a definitive answer must await the synthesis of the other conceivable diastereomer and release of the carboxylate termini from the corresponding esters.[49] Any such venture is likely to benefit from the intelligence gathered in this report about the Achilles heel of belizentrin and its immediate precursors.

Acknowledgements

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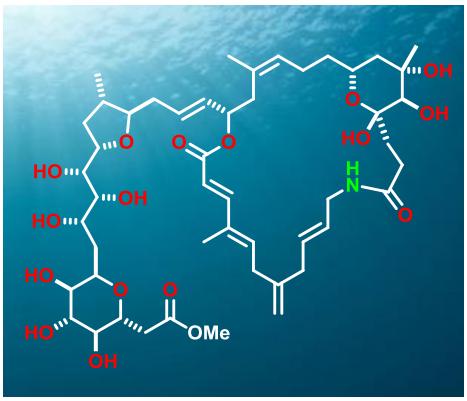

Potent but fragile: The first total synthesis of the provisional structure of belizentrin methyl ester is described. This sizeable metabolite from a tiny marine microorganism potently impacts on the survival of cerebellar cells and the integrity of their neuronal networks at nanomolar concentrations. The successful route had to cope with the sensitivity of this target, which let us recognize the partly skipped polyene region as a veritable Achilles heel.

Keywords: cross coupling · macrocyclization · marine natural products · polyenes · Kocienski olefination

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