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Total Synthesis of Putative Chagosensine

Marc Heinrich,[+] John J. Murphy,[+] Marina K. Ilg,[+] Aurélien Letort, Jakub Flasz, Petra Philipps, and Alois Fürstner*

Dedicated to Prof. Manfred T. Reetz on the occasion of his 75th birthday

Abstract: *The marine macrolide chagosensine is the only natural product known to date that embodies a Z,Z-configured chloro-1,3-diene unit. This distinguishing substructure was prepared by a sequence of palladium catalyzed 1,2-distannation of an alkyne precursor, regioselective Stille cross coupling at the terminus of the resulting bisstannyl alkene with an elaborated alkenyl iodide, followed by chloro-destannation of the remaining internal site. The preparation of the required substrates centered on cobalt catalyzed oxidative cyclization reactions of hydroxylated olefin precursors, which allowed the 2,5-trans-disubstituted tetrahydrofuran rings embedded into each building block to be formed with excellent selectivity. The highly strained macrolactone could ultimately be closed under forcing Yamaguchi conditions. Comparison of the spectral data of the synthetic sample with those of authentic chagosensine methyl ester proved that the structure of this intriguing compound has been mis-assigned by the isolation team.*

Marine sponges often host highly diverse microbial communities. These symbiotic life forms are arguably amongst the most prolific sources of bioactive secondary metabolites with, in part, unprecedented molecular architectures.[1] A striking example is chagosensine, a highly adorned macrolide isolated from specimens of the calcareous sponge *Leucetta chagosensis* collected off the

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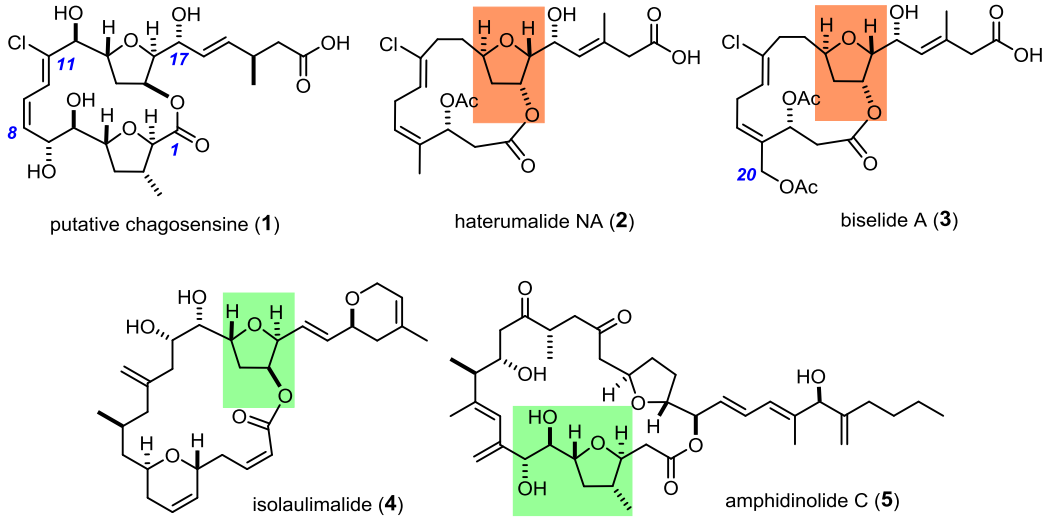
Eilat coastline in the Gulf of Aqaba.[2] The proposed structure **1**, which was elucidated by spectroscopic means and degradation experiments, is noteworthy for the remarkably dense array of 11 stereogenic centers decorating the carbon perimeter; moreover, two 2,5-*trans*-disubstituted tetrahydrofuran rings confer considerable strain onto the encircling 16-membered macrocyclic core. The arguably most salient feature, however, is the (*Z*,*Z*)-configured chloro-1,3-diene motif, which – to the best of our knowledge – is unprecedented in nature.



The closest relatives of chagosensine are the members of the haterumalide and biselide families which are derived from organisms as different as sponges, ascidians, or even terrestrial bacteria;[3,4] this variety of source organisms highlights the uncertainty as to the actual producer(s) of these secondary metabolites. In structural terms, compounds **2**, **3** and relatives are distinguished by a *skipped* rather than conjugated chlorodiene unit embedded into a molecular framework that is overall less complex than that of **1**. The comparison with chagosensine would be incomplete, however, without noticing some stereochemical subtleties: the "northern" tetrahydrofuran rings of **1** and **2**/**3** are ostensibly enantiomeric,[5,6] whereas the adjacent hydroxylated chiral center on the side chain seems to have the same absolute configuration throughout. Yet, said chagosensine sector finds stereochemical correspondence in isolaulimalide (**4**),[7] while the "southern" *trans*-tetrahydrofuran ring flanked by an *anti*-diol unit is also prominently featured in amphidinolide C (**5**) and F.[8,9]

Members of the haterumalide estate exhibit considerable cytotoxicity against various human cancer cell lines, while esterification of the carboxylate terminus or oxidation at C20 (biselide series) reduces

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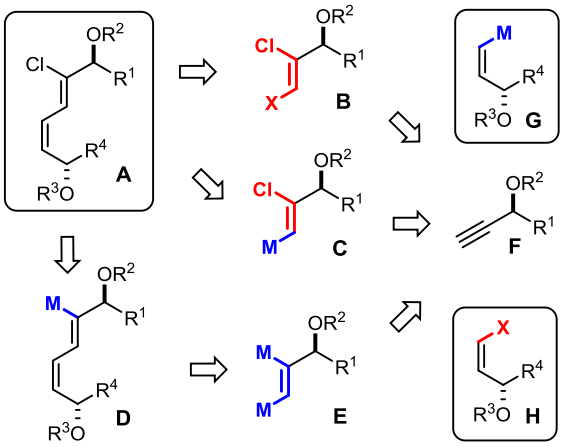
their acute toxicity for brine shrimp.[3] This encouraging profile attests to the notion that chlorine-containing small molecules often exhibit favorable biological properties[10] and is certainly one of the reasons for the numerous studies on compounds of this series, culminating in several total syntheses.[11,12,13,14,15,16,17] In striking contrast, chagosensine remained unappreciated, perhaps because no biodata were reported by the isolation team.[2] This largely disproportional level of attention seems unjustified in view of the truly unique constitution of **1** and the arguably much higher synthetic challenge posed by this particular target. We now present an interim report on our work in this field, which paved a way to putative chagosensine yet showed that the originally assigned structure mandates major revision; to this end, a conceptually new approach to chlorodienes had to be developed which is based on the preparation and serial manipulation of bis(metalated) building blocks.



Scheme 1. Strategic considerations; M = metal or metalloid; X = halogen

Various scenarios for an efficient and stereoselective formation of the distinguishing *Z,Z*-chlorodiene entity of **1** were considered at the outset of the project.[18,19] The ultimately successful pathway was predicated on the strategies summarized in Scheme 1, all of which converge to the same substrate **F**. Of these routes, chloroboration seemed ideal as it would afford a fragment of type **C** amenable to cross coupling with an appropriate reaction partner of type **H**. This tantalizing option, however, could not be reduced to practice even with simple model compounds because the necessary propargylic –OR substituent did not survive under the chosen conditions.[20,21] Likewise, attempted *cis*-carbochlorination or dichlorination to give fragments of type **B** were to no avail.[22] Promising hits,

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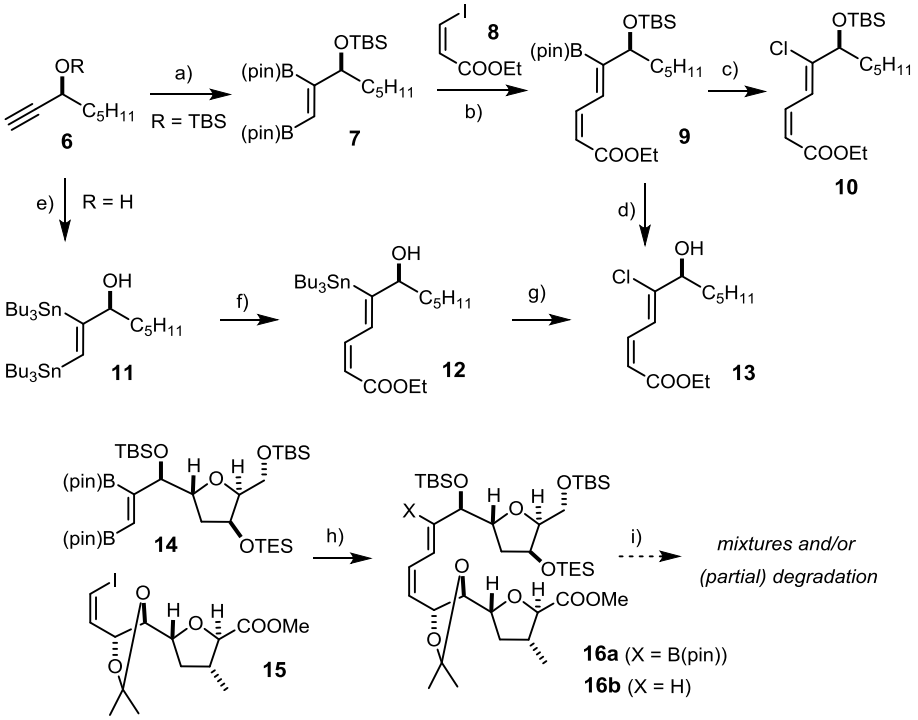
however, were obtained with a sequential strategy commencing with metal catalyzed diboration[23,24] or distannation[25,26,27] of the substrate.[28] It seemed reasonable to expect that the terminal and hence sterically more accessible C–M bond in **E** could be selectively engaged in cross coupling, whereas the remaining internal C–M unit in the resulting product **D** should lend itself to subsequent chlorodemetalation with retention of configuration. In fact, the site-selective Suzuki coupling of 1,2-bisborylalkenes had previously been accomplished with a set of simple coupling partners.[29] In line with this literature precedent, we managed to obtain the model compound **9** in appreciable yield (Scheme 2). However, chlorodeboration under standard conditions[30] proved incompatible with the silyl ether protecting group but required assistance by stoichiometric [Ph_3PAuCl].[31] Encouraged by this result, we went on to engage the much more elaborate building blocks **14** and **15** in the same maneuver.[32] Unfortunately, the site-selective cross coupling was accompanied by substantial protodeboration; truly problematic, however, was the chlorodeboration of **16a** (X = BPin) which furnished rather complex mixtures even in the presence of the gold promoter.



Scheme 2. Model studies: a) $B_2(pin)_2$, $Pt(PPh_3)_4$ (3 mol%), DMF, 80°C, 75%; b) **8**, [(dppf)$PdCl_2$] (3 mol%), K_3PO_4, aq. THF, reflux, 69%; c) (i) Ph_3PAuCl, Cs_2CO_3, *i*PrOH, 3Å MS, 50°C; (ii) NCS, RT, 75%; d) $CuCl_2$, $NaHCO_3$, EtOH/H_2O, 60°C, 75%; e) $(Bu_3Sn)_2$, [(*t*BuNC)$_2PdCl_2$] (10 mol%), THF, 85%; f) **8**, $Pd(PPh_3)_4$ (20 mol%), CuTC, [Ph_2PO_2][NBu_4], DMF, 59%; g) $CuCl_2$, 2,6-lutidine, THF, 74%; h) $Pd_2(dba)_3$

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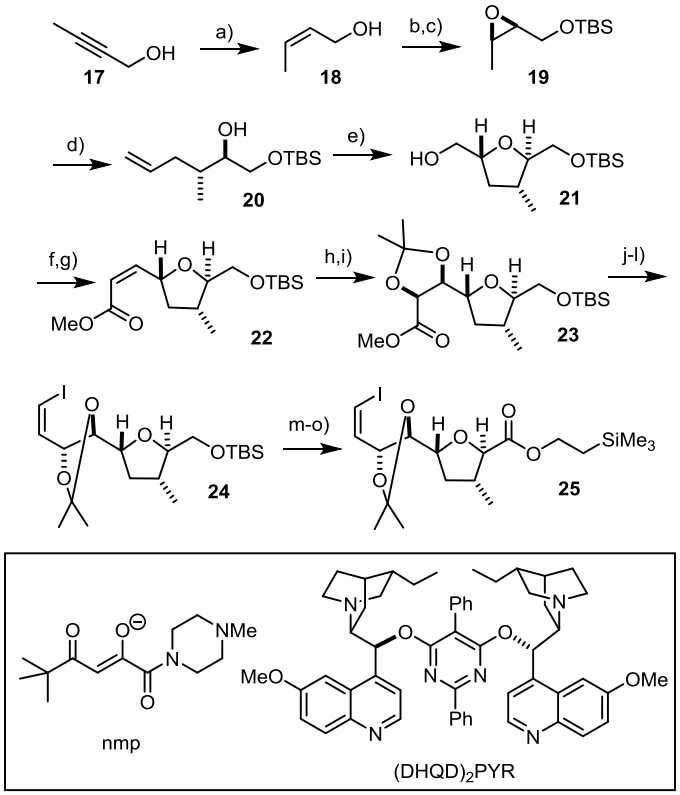
(10 mol%), Ph_3As (40 mol%), Ag_2O, THF/H_2O, 32% (**16a**) + 52% (**16b**); i) Ph_3PAuCl, Cs_2CO_3, MeOH, 3Å MS, 50°C, then NCS, RT; dba = dibenzylideneacetone; dppf = 1,1'-bis(diphenylphosphino)ferrocene; MS = molecular sieves; NCS = *N*-chlorosuccinimide; pin = pinacolato; TC = thiophene-2-carboxylate

Therefore we turned our attention to serial distannation/Stille coupling/chloro-destannation since the inherently higher reactivity of the C–Sn bond almost certainly facilitates the last step of the sequence;[33] in fact, previous work from our group provides encouraging precedent for the chloro-destannation of elaborate compounds.[34,35] Since alkyne 1,2-distannation is also known to be facile,[25-27] the projected gambit seemed promising too. Strikingly, however, site-selective Stille reactions of 1,2-bistannylalkenes are essentially unknown:[36] the only documented examples employed simple hypervalent aryliodonium salts as the electrophilic partner, whereas attempted use of iodobenzene furnished complex mixtures.[37,38] This caveat notwithstanding, we were able to attain proof-of-concept through coupling of **11** with **8** and subsequent chloro-destannation of product **12** thus formed; some competing side reactions in the cross coupling step, however, forecasted the need for careful optimization of the conditions.



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Scheme 3. a) H_2, Pd/$BaSO_4$ (5 mol%), quinoline (10 mol%), MeOH, 65%; b) *t*BuOOH, Ti(O*i*Pr)$_4$ (5 mol%), (+)-DET (6 mol%), CH_2Cl_2, −20°C, 74% (90% ee); c) TBSCl, imidazole, DMAP (5 mol%), CH_2Cl_2, 0°C → RT, 96%; d) allylmagnesium chloride, CuI (15 mol%), THF, −25°C, 77% (pure regioisomer, ratio = 10:1); e) Co(nmp)$_2$ (10 mol%), *t*BuOOH (10 mol%), O_2 (1 atm), *i*PrOH, 55°C, 79%; f) [SO_3·pyridine], (*i*Pr)$_2$NEt, DMSO, CH_2Cl_2, −25°C; g) $(F_3CCH_2O)_2P(=O)CH_2COOMe$, KHMDS, 18-crown-6, THF, −78°C → RT, *Z:E* = 12:1, 63% (of pure *Z*-isomer, over two steps); h) K_2OsO_4·2(H_2O) (6 mol%), (DHQD)$_2$PYR (3 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0°C, dr = 5:1, 67% (of pure isomer); i) 2,2-dimethoxypropane, *p*TsOH (5 mol%), 89%; j) $LiAlH_4$, THF, 0°C → RT, 95%; k) [SO_3·pyridine], (*i*Pr)$_2$NEt, DMSO, CH_2Cl_2, −25°C; l) [Ph_3PCH_2I]I, NaHMDS, HMPA, THF, −78°C, *Z:E* ≥ 20:1, 67% (of pure *Z*-isomer, over two steps); m) HF·pyridine, pyridine, THF, quant.; n) TEMPO (30 mol%), BAIB, aq. MeCN, 98%; o) 2-(trimethylsilyl)ethanol, EDCI, DMAP (20 mol%), CH_2Cl_2, 71% (+ 7% of epimer, see Text); BAIB = bis(acetoxy)iodobenzene; DET = diethyl tartrate; DMAP = 4-(dimethylamino)pyridine; EDCI = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride; HMDS = hexamethyldisilazide; TBS = *tert*-butyldimethylsilyl; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl radical; Ts = *p*-toluenesulfonyl

As this issue was deemed manageable, we ventured into the preparation of the required building blocks. The southern sector **25** was prepared by adaptation of a literature route directed towards amphidinolide C (Scheme 3).[39] Specifically, Sharpless epoxidation of *Z*-crotyl alcohol (**18**) followed by regioselective opening of the derived epoxide **19** with allylmagnesium chloride in the presence of CuI as the catalyst worked nicely on scale. In line with our expectation, the oxidative Mukaiyama cyclization[40] of the resulting unsaturated alcohol **20** turned out to be exquisitely selective and high yielding when using Co(nmp)$_2$ as the catalyst,[41] furnishing multigram quantities of the required 2,5-*trans*-configured tetrahydrofuran derivative **21**. In contrast, the seemingly trivial oxidation of **21** to the corresponding aldehyde proved delicate: Only a modified Parikh-Doering oxidation[42] using [SO_3·pyridine]/DMSO in combination with (*i*Pr)$_2$NEt rather than Et_3N prevented epimerization of the nascent aldehyde from occurring. The crude product was immediately subjected to Still-Gennari olefination,[43] which afforded **22** (*Z/E* = 12:1). Ligand-controlled Sharpless dihydroxylation of the major isomer closely followed the literature precedent in terms of yield and selectivity.[44] The resulting diol was converted into acetal **23**; this protecting group was chosen not least because the

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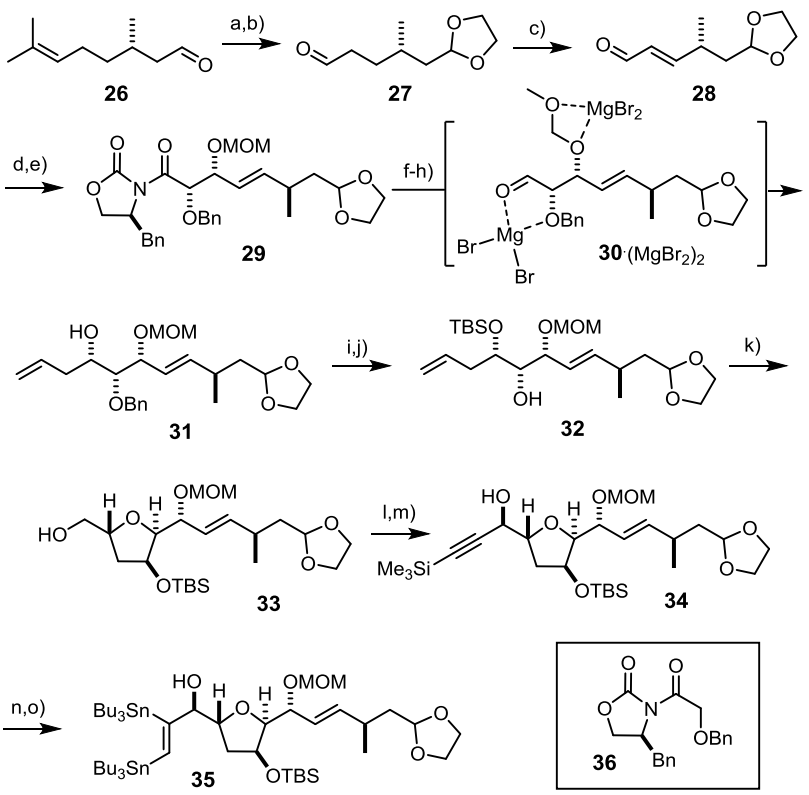
isolation team had managed to convert a sample of authentic chagosensine methyl ester into the corresponding isopropylidene acetal.[2] The further elaboration of **23** involved routine adjustment of the oxidation state followed by Stork/Zhao olefination,[45] which was highly selective (*Z:E* ≥ 20:1) and productive as long as HMPA was used as additive.[46] Finally, the silyl ether terminus of **24** was transformed into the corresponding 2-(trimethylsilyl)ethyl ester **25** as surrogate of the acid functionality to be engaged in the projected macrolactonization.[47] This route proved robust and scalable, furnishing the southern building block **25** in 5.2% overall yield over the 15 steps of the longest linear sequence.



Scheme 4. a) ethylene glycol, $(EtO)_3CH$, camphorsulfonic acid (5 mol%), CH_2Cl_2, 98%; b) O_3, Sudan red, CH_2Cl_2, then Me_2S, −78°C → RT, 97%; c) $Pd(OAc)_2$ (4 mol%), diethyl allyl phosphate, $NaHCO_3$, THF, 86°C, 58%; d) **36**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78°C → −10°C, dr = 12:1, 80% (pure isomer); e) MOMCl, TBAI (1 mol%), $(iPr)_2NEt$, CH_2Cl_2, 0°C, quant.; f) $LiBH_3(OH)$, Et_2O, 0°C → RT, 88%; g) [SO_3·pyridine], $(iPr)_2NEt$, DMSO, CH_2Cl_2, −30°C → −10°C, quant.; h) $MgBr_2·(OEt_2)$, allyltrimethylsilane, CH_2Cl_2, 0°C → RT, dr = 14:1, 92% (pure isomer); i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 88%; j) DDQ, CH_2Cl_2/pH 7.4 buffer (1:1), 50°C, 70%; k) $Co(nmp)_2$ (10 mol%), *t*BuOOH (10 mol%), O_2 (1 atm), *i*PrOH, 55°C, dr ≥ 20:1, 69% (pure isomer); l) [SO_3·pyridine], $(iPr)_2NEt$, DMSO, CH_2Cl_2, −30°C → −20°C; m)

trimethylsilylacetylene, $Zn(OTf)_2$, (−)-*N*-methylephedrine, $(i\text{Pr})_2\text{NEt}$, toluene, dr = 11:1, 65% (over two steps); n) K_2CO_3, MeOH, 85%; o) $(Bu_3Sn)_2$, $[(t\text{BuNC})_2PdCl_2]$ (10 mol%), THF, 93%; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MOM = methoxymethyl; TBAI = tetra-*n*-butylammonium iodide; Tf = trifluoromethanesulfonyl

The northern domain of chagosensine was secured starting from (*S*)-citronellal (**26**) (Scheme 4). Acetalization followed by ozonolysis of the double bond furnished **27** and set the stage for a modified Saegusa oxidation to give enal **28**, which worked nicely on scale using $Pd(OAc)_2$ as catalyst in combination with diethyl allyl phosphate as the terminal oxidant.[48] Parenthetically we note that this sequence is a practical alternative to a literature route that required nine steps for the preparation of the analogous dimethylacetal derivative.[49] An auxiliary-controlled glycolate *syn*-aldol reaction then gave **29** with high selectivity,[50,51] which was processed into aldehyde **30** by standard protecting group- and oxidation state management. Its treatment with allyltrimethylsilane in the presence of $MgBr_2{\cdot}OEt_2$ as promotor set the all-*syn* stereotriad of product **31** (dr ≥ 14:1).[51] This favorable outcome is thought to reflect a 1,2-Cram chelate transition state,[52] in which the directing effect of the proximal benzyl ether outweighs the influence of the distal –OMOM group. To this end, two equivalents of the magnesium salt had to be used to preclude internal competition of the neighboring coordination sites for the Lewis-acid and hence avoid any ambiguity as to which donor substituent steers the addition process.

Compound **31** was readily advanced into alcohol **32**, which was subjected to yet another cobalt catalyzed oxidative Mukaiyama cyclization.[40,41] Although this substrate comprises of two different alkene moieties, the formation of the desired tetrahydrofuran derivative **33** was remarkably selective in regio- as well as stereochemical terms (dr > 20:1, **33**:Σ (other isomers) > 12:1). Epimerization-free oxidation of **33** was again best achieved via the modified Parikh-Doering protocol described above using $(i\text{Pr})_2\text{NEt}$ as the base. The resulting aldehyde, though labile, participated in a diastereoselective Carreira alkynylation with trimethylsilylacetylene (dr = 11:1),[53] although this reaction mandated considerable optimization. The meticulous drying of all reagents and the addition of the aldehyde partner in one portion to the mixture was key to success.[54] With good amounts of **34** in hand,[51] the required building block representing the northern half of chagosensine was well within reach, since

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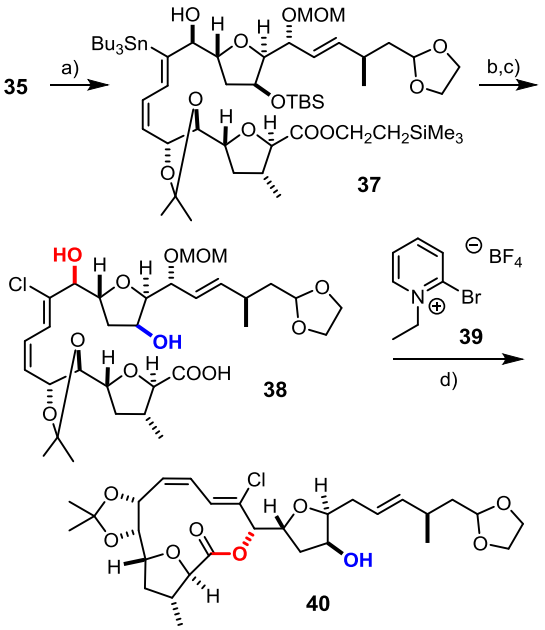
desilylation of the alkyne terminus of **34** and the subsequent palladium catalyzed distannation[25] with formation of **35** both worked exceedingly well. An overall yield of 7.6% over the 15 steps of this sequence attests to the efficacy of the chosen route.

As expected, the premier implementation of a site-selective Stille coupling of a 1,2-bisstannane derivative into target-oriented synthesis did indeed require careful optimization (Scheme 5). Best results were obtained using copper-free procedures, as this additive evidently favors premature destannation (cf. Scheme 2) and/or coupling at the internal position. Bulky phosphine ligands to the palladium catalyst proved beneficial too,[55,56,57] most likely because they impart selectivity for C–C-bond formation at the sterically more accessible terminal C–Sn site of **35**. At the same time, the P(*t*Bu)$_3$ ligands disfavor competing homocoupling of the alkenyl iodide on steric grounds, which nevertheless remained the most serious side reaction even when **25** was added slowly to the mixture.[55,58] The use of LiCl as promotor and of [Ph_2PO_2][NBu_4] as effective tin scavenger also improved the results.[59,60] These procedural modifications allowed us to obtain the desired diene product **37** in well reproducible 50% yield on a > 100 mg scale (single largest batch).



Scheme 5. a) **25** (slow addition), (tBu$_3$P)$_2$Pd (15 mol%), [Ph_2PO_2][NBu_4], LiCl, NMP, 60°C, 50%; b) $CuCl_2$, 2,6-lutidine, THF, 78%; c) TBAF·(H_2O)$_3$, THF, 80%; d) **39**, $NaHCO_3$, 1,2-dichloroethane, 80°C, 30% (80% brsm); NMP = *N*-methyl-2-pyrrolidone; TBAF = tetra-*n*-butylammonium fluoride

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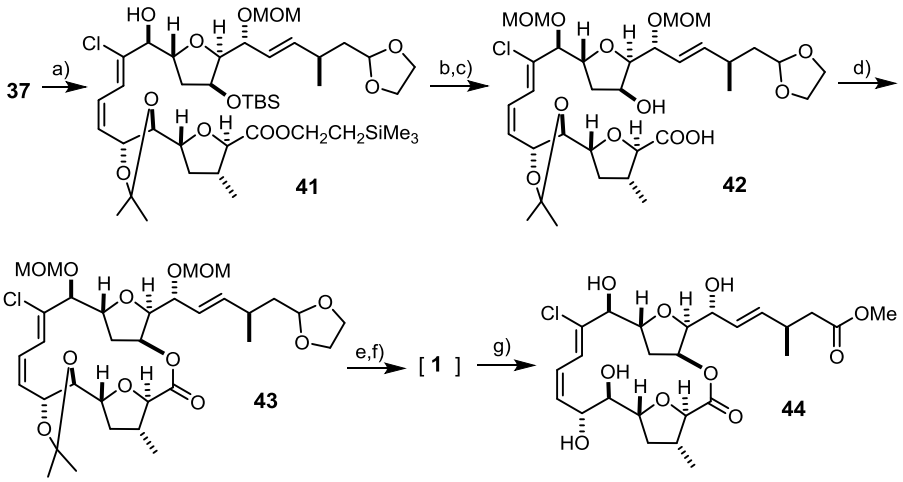
In view of the difficulties with chlorodeborylation encountered during the model studies (vide supra), it was gratifying to find that the chloro-destannation of the densely functionalized derivative **37** proceeded smoothly with $CuCl_2$ in THF under the conditions previously adapted by our group for delicate cases;[34,35] importantly, the stereochemistry of the double bond was strictly preserved. Treatment of the resulting *Z,Z*-chlorodiene with TBAF unveiled *seco*-acid **38** in readiness for macrocyclization. Even though we had anticipated that the two 2,5-*trans*-disubstituted tetrahydrofuran rings would impose considerable strain onto the emerging macrocycle and hence render ring closure challenging, we had to learn that **38** did not engage in macrolactonization at all when subjected to many of the standard protocols.[61] Only a modified Mukaiyama lactonization promoted by **39** afforded a distinct product in modest yield under forcing conditions;[62,63] surprisingly though, detailed NMR analysis showed that the –OH group at C12 rather than the –OH group on the THF-ring had reacted. The formation of a 12-membered macrocycle **40** comprising a single 2,5-*trans*-disubstituted tetrahydrofuran ring is evidently easier than formation of the strained 16-membered lactone of **1**. This somewhat paradoxical outcome highlights the challenge posed by chagosensine.



Scheme 6. a) $CuCl_2$, 2,6-lutidine, THF, 78%; b) MOMCl, TBAI, (*i*Pr)$_2$NEt, 1,2-dichloroethane, 50°C, 92%; c) TBAF·$(H_2O)_3$, THF, 0°C → RT; d) 2,4,6-trichlorobenzoyl chloride, (*i*Pr)$_2$NEt, THF, then DMAP, toluene, reflux, 40% (**43**) + ca. 6% (epimer) + 13% (lactide); e) Me_2BBr, CH_2Cl_2, −78°C; f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0°C; g) CH_2N_2, CH_2Cl_2, 20% (over three steps)

Confronted with this impasse, the C12-OH group in **41** was protected as MOM-acetal prior to release of the *seco*-acid (Scheme 6). Compound **42** thus formed did indeed allow macrolactone **43** to be

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closed, although very harsh conditions were necessary. While the modified Mukaiyama protocol furnished only 27%, Yamaguchi lactonization[64] in boiling toluene gave the desired compound in well reproducible 40% yield after 20 h reaction time; trace amounts of an epimer (presumably at the C2 position) and 13% of the cyclic head-to-tail dimer (lactide) could be separated by flash chromatography (see the Supporting Information). The spectroscopic analysis of **43** was impeded by the presence of (at least) two signal sets, indicative of the presence of two distinct conformers, which interconvert rapidly in solution. This spectral feature was unexpected since the isolation team had not reported any such complication for acetonide derivatives of authentic chagosensine.[2]

The concomitant cleavage of all four acetal units in **43** proceeded under mild conditions with freshly prepared Me_2BBr,[65,66] whereas more common reagents led to degradation. At this stage, the only remaining step for the completion of the total synthesis was the oxidation of the aldehyde to the corresponding carboxylic acid, which should represent chagosensine. While the Pinnick oxidation per se worked well,[67] we found the resulting product to be unexpectedly fragile; several attempts at its isolation resulted in decomposition. In the hope to impart higher stability, the crude acid **1** – which represents putative chagosensine prepared in 22 steps (longest linear sequence) – was treated with diazomethane to give methyl ester **40**; note that the isolated natural product had been treated analogously during the isolation campaign and the data of the resulting ester are well documented.[2]

Although not overly stable either synthetic **44** was manageable and could be fully characterized. Unfortunately, its NMR spectra do not nearly match those of authentic chagosensine methyl ester: the deviations are huge (see the SI), such that there is no doubt that the structure of this enticing natural product has been mis-assigned by the isolation team.[2,68,69] In view of the stereochemical variance reported in the literature for closely related macrolides (see above), it is conceivable that the configuration attributed to the northern tetrahydrofuran ring is incorrect. The fact, however, that the spectral mismatch is scattered over the entire molecular framework does certainly not allow us to exclude other and/or additional mis-assignments at this point. Future work intends to narrow the possible scenarios down, establish the correct structure of chagosensine, make meaningful amounts of this unique macrolide available for biological profiling, and explore the opportunities provided by the newly developed methodology for serial formation of functionalized dienes in more detail.

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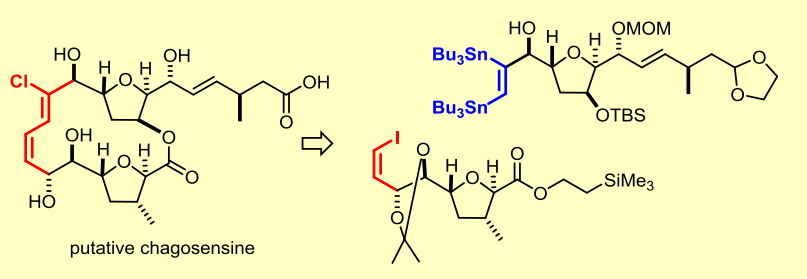

Unique: Chagosensine is the only natural product known to date comprising a *Z,Z*-configured chloro-1,3-diene unit. This distinguishing motif was obtained by serial alkyne 1,2-distannation, regioselective Stille coupling and chloro-destannation. The recorded spectral data showed, however, that the stereostructure of this marine macrolide had been mis-assigned by the isolation team.

Keywords: Chloroalkenes · Macrolides · Organotin Compounds · Stille Coupling · Total Synthesis

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